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Critical appraisal of interventional clinical trials assessing heated tobacco products: a systematic review

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ABSTRACT

Objective To critically assess the methodological characteristics and quality of interventional clinical trials investigating the effects of heated tobacco products (HTPs).

Data sources Web of Science (Core collection and MEDLINE), Scopus, MedRxiv, ClinicalTrials.gov and ICTRP trial databases and transnational HTP manufacturer online publication libraries were searched for clinical trials on HTPs published between January 2010 and April 2022.

Study selection Interventional clinical trials of any design, in which at least one group of adult participants used a currently marketed HTP, were selected by two reviewers with good or very good agreement.

Data extraction Data relating to trial characteristics and effects of intervention on primary outcomes were extracted using a predesigned form. Risk of bias was assessed using Cochrane's Risk of Bias tool v1.

Data synthesis 40 trials were included, 29 of which were tobacco industry affiliated. Methodological characteristics, such as registration, design, setting, comparator interventions, participants, outcomes and analyses, varied between trials, though there were few significant differences between industry-affiliated and independent trials. Of the 40 trials, 33 were judged to be at high risk of bias and 6 at unclear risk of bias. Trial findings were not significantly associated with either affiliation or risk of bias.

Conclusions The conduct and reporting of HTP interventional clinical trials were poor in many respects and limited to investigating effects of short-term exposure. These trials fall short of what is needed to determine whether HTPs are beneficial to public health, meaning they may not be a sound basis for tobacco control policy decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has shown industry-sponsored studies are more likely to have pro-industry results, potentially due to reduced quality and increased bias, yet the quality of interventional clinical trials on heated tobacco products (HTPs) and associations between findings on HTPs and affiliation or risk of bias have not been investigated.

WHAT THIS STUDY ADDS

⇒ Of the 40 identified interventional clinical trials assessing HTPs, 29 were industry affiliated and 11 were independent.

⇒ Many characteristics of these trials, such as short durations, confined settings and choice of comparators and participants, are not representative of real-world use and fail to adequately investigate whether HTPs reduce harm and are beneficial to public health.

⇒ Trial findings on the effect of HTPs relative to cigarettes were not significantly associated with trial affiliation or overall risk of bias.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Existing intervention clinical trials on HTPs are largely inadequate in assessing the impact of HTPs on public health and may not, therefore, be reliable in tobacco control policy decision making.

INTRODUCTION

The harms of inhaling toxicants from combusted tobacco (ie, cigarettes) are well known.[1] Heated tobacco products (HTPs) are designed to heat tobacco to relatively low temperatures. The purpose of this is to produce an inhalable nicotine aerosol which purportedly reduces the amounts of toxicants released and thus reduces health risks compared with cigarettes.[2] The potential to reduce health risks is fundamental to HTP marketing[3] and a contributing factor in their uptake and use by consumers.[4–6] As HTP sales grow globally[7] accurate assessment of their relative risks is essential. However, this assessment currently relies mostly on short-term laboratory research due to a lack of epidemiological studies.[8 9]

Previous reviews have highlighted the difficulties in interpreting the existing clinical evidence. The majority of clinical research into HTPs is conducted by the tobacco industry,[8 9] which has a history of research manipulation.[10] Tobacco industry studies largely show the potential health benefits of HTPs in smokers, while some independent studies have identified potentially harmful effects[8] and found key industry studies do not comprehensively investigate all toxicants present.[11] The association between a conflict of interest and industry-favourable findings has previously been observed in other tobacco and nicotine research.[10 12] Poor or biased study design and reporting have been proposed as possible contributors to this phenomenon.[10] Some methodological shortcomings have already been noted in HTP clinical research, such as short intervention

durations, inconsistent reporting of data and potentially unethical practices, particularly in industry-affiliated studies.[8 9 13–15] However, the quality of all HTP clinical trials has not yet been thoroughly examined.

Before consumers and policy makers make important decisions based on the results of these studies, it is crucial the quality of the evidence is assessed. Therefore, this review sought to critically appraise HTP interventional clinical trials by answering the following questions:

1. What are the methodological characteristics (ie, study details, design, interventions, participants, outcomes and analyses) and affiliations (ie, industry or independent) of interventional clinical trials on HTPs?
2. What is the risk of bias in these trials?
3. Are there differences in the methodological characteristics and risks of bias in industry-affiliated trials compared with trials with no industry affiliation?
4. What is the association between trial findings and: (a) trial risk of bias and (b) trial affiliation?

METHODS

This systematic review followed recommendations set out by PRISMA.[16] The protocol was registered on PROSPERO (CRD42021240676, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021240676).

Search strategy and study selection

Web of Science (core collection and MEDLINE), Scopus, MedRxiv, ClinicalTrials.gov and the International Clinical Trials Registry Platform databases were searched on 28 April 2021. Searches were restricted to studies published from 2010 to exclude those on HTPs no longer marketed. Search terms included HTP terminology, brand names ('IQOS', 'Ploom', 'Glo') and clinical study terms ('trial', 'participant', 'clinical', 'random*'). The online publication libraries of transnational HTP manufacturers (Philip Morris International, PMI; British American Tobacco, BAT; Japan Tobacco International, JTI; Imperial Brands, IB) and the reference lists of included literature were also searched. The full search strategy was reported in the protocol (https://www.crd.york.ac.uk/PROSPEROFILES/240676_STRATEGY_20210429.pdf). The searches were repeated to identify any relevant literature published between 28 April 2021 and 12 April 2022.

Trial publications were managed in Covidence. After duplicates were removed, title and abstract screening was piloted on 10% of the literature. Two reviewers (SB and AvdA) then independently screened all titles and abstracts, followed by full-text assessment against the eligibility criteria. Inter-rater agreement was measured using Cohen's Kappa (k).

Inclusion criteria

Study design: Interventional clinical trials (studies in which human participants are prospectively assigned an intervention to evaluate its effects on health-related outcomes)[17] of any design were included. Eligible studies did not need to be peer-reviewed or formally published.

Population: Adults (≥18 years).

Intervention: Studies were included if at least one arm was assigned a currently marketed HTP.

Comparison: Any comparator interventions.

Outcomes: Any outcomes.

Exclusion criteria

- Studies published before 2010.
- Studies that were not clinical trials.
- Observational clinical studies.
- Studies in which participants were not adults.
- Studies in which an intervention was not a currently marketed brand of HTP.
- Studies for which methodology and results data were not available, for example, ongoing studies.

Data extraction

Trial characteristic data were extracted into a predesigned form in Covidence by one reviewer (SB) and verified by a second reviewer (AvdA). The following data were extracted: study details (citation, country, trial registration date and ID, start and end dates, sponsor and affiliation); trial design (design, duration, comparators, setting); participant characteristics (eligibility criteria, age, sex, ethnicity, smoking history, comorbidities); intervention (type, cointerventions, mode of exposure); analysis (analysis population, unit of analysis, sample size calculation); outcomes (types, outcomes measured and reported, outcome matrices, time points measured) and results (participant flow, direction of effect in primary outcomes between HTP and cigarette groups at last follow-up). Two reviewers (SB and AvdA) independently coded trial affiliation. The full coding scheme is provided in online supplemental appendix 1.

Last follow-up exhaled carbon monoxide means and SD were independently extracted by two reviewers (SB and AvdA). Where SD was not reported, it was calculated as per the Cochrane Handbook for Systematic Reviews of Interventions.[18] Study authors were contacted to request missing data relevant to the meta-regression analysis.

Risk of bias assessment

Risk of bias was assessed using Cochrane's Risk of Bias tool V.1.[19] The assessment consists of six domains: random sequence generation and allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias).

The evident differences between HTPs and comparator interventions means special considerations had to be made when assessing risk of bias. Unblinded trials were rated at low risk of performance bias if they were randomised and used an active comparator of similar intensity (ie, also contains tobacco/nicotine and all arms receive same cointerventions, if any). Unblinded trials were rated at low risk of detection bias if the primary outcome was objectively measured. Selection bias was rated high for all non-randomised trials.

The assessment was piloted on 20% of included trials (SB) and checked by an experienced assessor (JHB). Then, two reviewers (SB and AvdA) independently assessed risk of bias in all trials, resolving disagreements through discussion. The overall risk of bias for each trial was rated as 'low' when there was low risk of bias in all domains, 'unclear' when there was unclear risk of bias in ≥1 domains or 'high' when there was high risk of bias in≥1 domains. Risk of bias plots and graphs were generated using RobVis.[20]

Data synthesis and analysis

Trial characteristics data were summarised using descriptive statistics, distinguished by affiliation and tabulated where possible. Where comparisons involved two categorical variables, Fischer's exact test was used to investigate associations between trial characteristics and affiliation. Due to inconsistent reporting and heterogeneity of available data, we could not conduct the

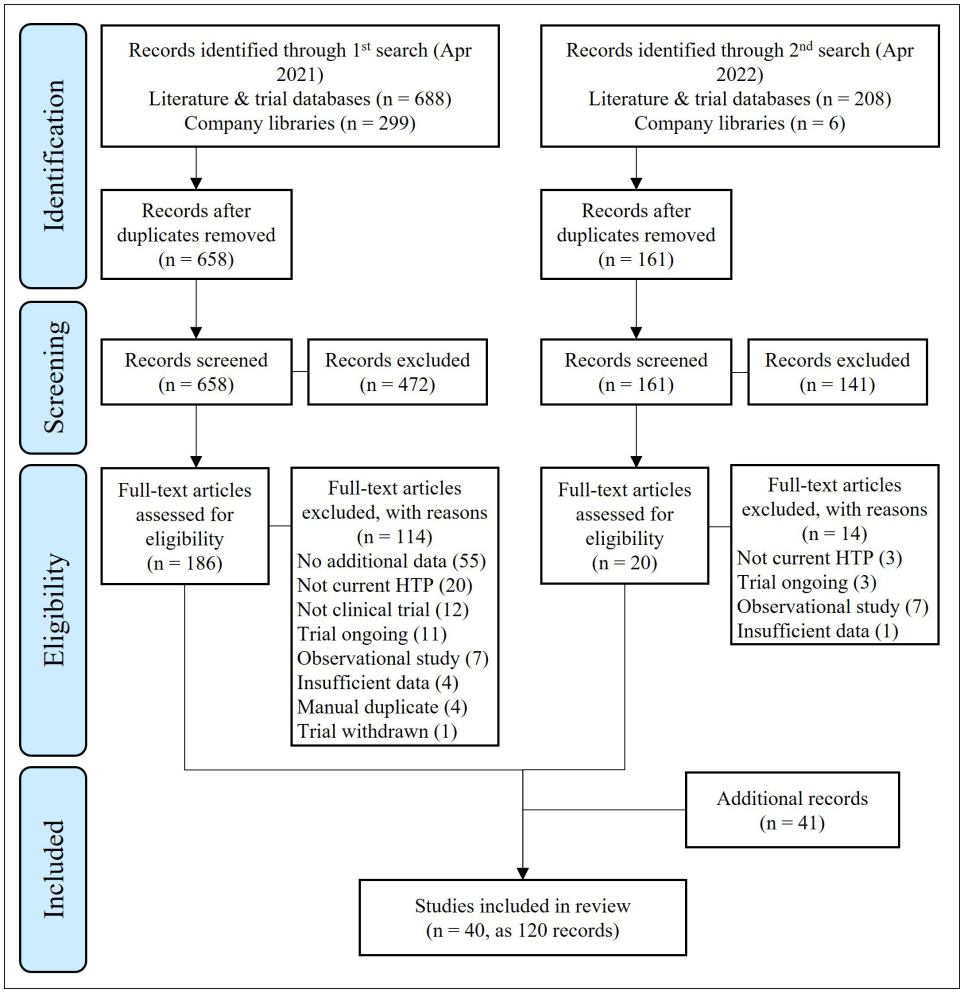

Figure 1 PRISMA flow diagram for study selection. HTP, heated tobacco product.

meta-regression analyses per our protocol. Instead, we created an effect direction plot (as described in the Cochrane Handbook[18] and by Boon and Thomson[21]) and used Fisher's exact test to investigate associations between primary outcomes in each study and affiliation or risk of bias. We excluded studies with mixed effects for primary outcomes and/or were rated unclear risk of bias from these analyses.

Statistical analyses were conducted in Stata V.17. Significance level was 0.05.

RESULTS

Included trials

A total of 987 and 214 records were identified through the first and second searches, respectively, of which 79 were included. There was good or very good agreement[22] between reviewers for screening (first search: k=0.74, second search: k=0.81) and eligibility assessment (first search: k=0.64, second search: k=0.76). The 79 records related to 40 trials. Additional records pertinent to these trials (ie, registrations, protocols, reports and so on) were then collected, meaning 120 total records were included (figure 1). Key trial characteristics are provided in table 1 and full characteristics in online supplemental table 1. Two 'actual use' studies were identified. Typically used in pharmaceutical research, actual use studies investigate how a product is used under simulated real-world conditions.[23] Although usually observational, these two studies met our definition of an interventional clinical trial and were, therefore, included.

Of the 40 trials, 11 (27.5%) had no known industry affiliation and 29 (72.5%) were industry affiliated. PMI conducted 16 trials, BAT conducted 7, JTI conducted 4 and JUUL conducted 1. The first and last authors of one study (Caponnetto, 2018)[24] were funded by the Foundation for a Smoke Free World between 2018 and 2019, which was established with funding from PMI.[25]

Trial registration and reporting

Thirty-one trials (77.5%) were registered (figure 2). Only 12 (30%) were registered prior to enrolment of the first participant (ie, registered a priori). Most trials did not submit results for publication in a peer-reviewed journal (n=23, 57.5%) or post key outcome data on trial registries (n=26, 65%) within 12 months of trial completion (figure 3). Trial completion date was not reported in 12 (30%) trials; thus, timeframe for publishing results was unclear.

There were no significant associations between affiliation and whether the trial was registered (p=0.08), whether it was registered a priori (p=0.70) or published results within 12 months of completion (p=0.07).

Trial design and setting

Thirty trials (75%; 20 industry-affiliated and 10 independent) were conducted in confined settings (ie, controlled environments, like clinics), 4 (11%; all industry-affiliated) in ambulatory settings (ie, uncontrolled environments, like participants'

Table 1 Overview of included trials

Trial*	Country	Sponsor (affiliation)	Design	Interventions (brand/model)
ISRCTN13439529[46 47]	Italy	BAT (Industry-affiliated)	Crossover RCT	HTPs (Glo1.0, Glo1.1) cigarettes (OB), NRT (Nicorette inhaler)
ISRCTN14301360/UMIN000024988[48–51]	Japan	BAT (Industry-affiliated)	Parallel RCT	HTPs (Glo1.0, Glo1.0M, IQOS) cigarettes (Lucky Strike Regular, Lucky Strike Menthol), tobacco and nicotine cessation
ISRCTN80651909[52 53]	UK	BAT (Industry-affiliated)	Parallel RCT	HTPs (Glo1.0, unknown brand HTP) cigarettes (Lucky Strike Regular), e-cigarette (IS1.0(TT)), tobacco and nicotine cessation
ISRCTN81075760[54–60]	UK	BAT (Industry-affiliated)	Parallel RCT	HTPs (Glo1.1, THD2.4T20), cigarettes (OB), smoking cessation
Dalrymple *et al* (2022)[26]	Germany	BAT (Industry-affiliated)	Repeated measures	HTP (Glo), cigarettes (N491), e-cigarette (ePen 3)
Gee *et al* (2018)[61]	Japan	BAT (Industry-affiliated)	Actual use study	HTPs (Glo1.0, Glo1.0M, IQOS) cigarettes (Lucky Strike Regular, Lucky Strike Menthol)
Jones *et al* (2020)[62]	Italy	BAT (Industry-affiliated)	Actual use study	HTPs (Glo1.0, IQOS) cigarettes (Lucky Strike Regular), e-cigarettes (IS1.0(TT))
UMIN000017297[63 64]	Japan	JTI (Industry-affiliated)	Crossover RCT	HTP (Prototype NTVP), cigarettes (unknown brand)
UMIN000025777[65–67]	Japan	JTI (Industry-affiliated)	Parallel RCT	HTP (NTVP), cigarettes (OB), smoking cessation
UMIN000041539[68 69]	Japan	JTI (Industry-affiliated)	Parallel RCT	HTPs (Ploom TECH+, Ploom S2.0, 2 HTPs of unknown brands), cigarettes (OB), smoking cessation
ISRCTN88682435[70 71]	UK	JTI (Industry-affiliated)	Crossover RCT	HTP (HNB2.1), cigarettes (unknown brand)
NCT03700112[72 73]	New Zealand	JUUL Labs (Industry-affiliated)	Crossover RCT	HTP (IQOS), e-cigarettes (JUUL, Myblu, MarkTen Bold Classic, VUSE Solo, PHIX, NJOY Daily), cigarettes (Marlboro Red)
NCT01780688[74 75]	UK	PMI (Industry-affiliated)	Crossover RCT	HTP (IQOS2.1), cigarettes (OB)
NCT01780714[76–78]	Poland	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.1), cigarettes (OB)
NCT01959607[79–82]	Japan	PMI (Industry-affiliated)	Crossover RCT	HTP (IQOS2.2), cigarettes (OB), NRT (Nicorette gum)
NCT01959932[83–89]	Poland	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.2), cigarettes (OB), tobacco and nicotine cessation
NCT01967706[79 90–94]	Japan	PMI (Industry-affiliated)	Crossover RCT	HTP (IQOS2.2M), cigarettes (OB, M), NRT (Nicorette gum)
NCT01967719[95–99]	USA	PMI (Industry-affiliated)	Crossover RCT	HTP (IQOS2.2M), cigarettes (OB, M), NRT (Nicotrol nasal spray)
NCT01967732[100–103]	UK	PMI (Industry-affiliated)	Crossover RCT	HTP (IQOS2.2), cigarettes (OB), NRT (Nicotrol nasal spray)
NCT01970982[104–109]	Japan	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.2), cigarettes (OB), tobacco and nicotine cessation
NCT01970995[110–115]	Japan	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.2M), cigarettes (OB, M), smoking cessation
NCT01989156[116–121]	USA	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.2M), cigarettes (OB, M), smoking cessation
NCT02396381[122–125]	USA	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.2), cigarettes (OB)
NCT02466412[126–128]	Japan	PMI (Industry-affiliated)	Crossover RCT	HTP (CHTP1.1M), cigarettes (OB, M)
NCT02503254[129–134]	Poland	PMI (Industry-affiliated)	Parallel RCT	HTP (CHTP1.0), cigarettes (OB)
NCT02641587[135–138]	Poland	PMI (Industry-affiliated)	Parallel RCT	HTP (CHTP1.2), cigarettes (OB)
NCT02649556[139–141]	USA	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS2.2), cigarettes (OB)
NCT03364751[142–145]	Japan	PMI (Industry-affiliated)	Parallel RCT	HTP (IQOS), cigarettes (OB)
Caponnetto et al (2018)[24]	Unknown	University of Catania (Industry-affiliated)	Crossover RCT	HTPs (IQOS, Glo), cigarettes (OB)
DRKS00012919[146 147]	Germany	University Medical Centre Schleswig-Holstein (Independent)	Crossover RCT	HTP (IQOS2.2), cigarettes (Marlboro Gold), e-cigarettes (eGo-T with and without nicotine)
NCT03301129[148 149]	Italy	University of Roma La Sapienza (Independent)	Crossover RCT	HTP (IQOS2.2), cigarettes (Marlboro Gold), e-cigarette (Blu Pro)
NCT03435562[150 151]	USA	Virginia Commonwealth University and NIDA (Independent)	Crossover RCT	HTP (IQOS), cigarettes (OB), e-cigarette (JUUL)
NCT03452124[152 153]	Greece	National and Kapodistrian University of Athens (Independent)	Crossover RCT+Case Control Study	RCT: HTP (IQOS), cigarettes (Marlboro Red), sham cigarette Case Control: HTPs (IQOS), cigarettes (unknown brand)
NCT03889990/NCT03995329[154–156]	Greece	Aristotle University Of Thessaloniki (Independent)	Single-group assignment	HTP (IQOS)
aspredicted.org #6896[157 158]	Belgium	KU Leuven and Thomas More University of Applied Sciences (Independent)	Crossover RCT	HTP (IQOS), cigarettes (OB), e-cigarette (Eleaf iStick)
Iokeimidis *et al* (2021)[159]	Greece	Athens Medical School, Hippokration Hospital	Crossover RCT	HTP (IQOS), cigarettes (unknown brand), sham cigarette
Lopez *et al* (2016)[160]	USA	NIDA and CTP (Independent)	Crossover RCT	HTP (PAX), CC (OB), e-cigarette (eGo)
Nga *et al* (2020)[161]	Malaysia	International Medical University (Independent)	Quasi-experimental	HTP (IQOS), cigarettes (OB), e-cigarette (Aspire AVP)
Phillips-Waller *et al* (2021)[162]	UK	Tobacco Advisory Group project grant, Cancer Research UK	Non-randomised crossover	HTPS (IQOS), cigarettes (OB), e-cigarettes (JUUL, KangerTech EVOD, Innokin iTaste MVP 2)
Yaman *et al* (2021)[163]	Cyprus	Near East University and Mersin City Training and Research Hospital	Crossover RCT	HTP (IQOS), cigarettes (OB)

*Registration ID for registered trials. Author and date for unregistered trials.
BAT, British American Tobacco; [C]HTP, [carbon] heated tobacco product; CTP, Center for Tobacco Products, U.S. Food and Drug Administration; JTI, Japan Tobacco International; M, menthol; NIDA, National Institute on Drug Abuse; NRT, nicotine replacement therapy; NTVP, novel tobacco vapour product; OB, participant's preferred own brand of cigarettes; PMI, Philip Morris International; RCT, randomised controlled trial.

homes) and 6 (15%; 5 industry-affiliated and 1 independent) in confined followed by ambulatory settings. Intervention duration ranged from single use up to 6 months. One BAT trial (ISRCTN81075760) was 12 months long, but at time of literature, collection results had only been reported for the first 6 months.

Thirty-four trials (85%; 26 industry and 8 independent) were randomised: 15 of parallel design, 18 crossover and 1 crossover followed by a case control study (table 1). The repeated measures study randomised the placement of interventions on participants' skin, but all participants received all interventions and in the same order. Non-randomised designs included: a

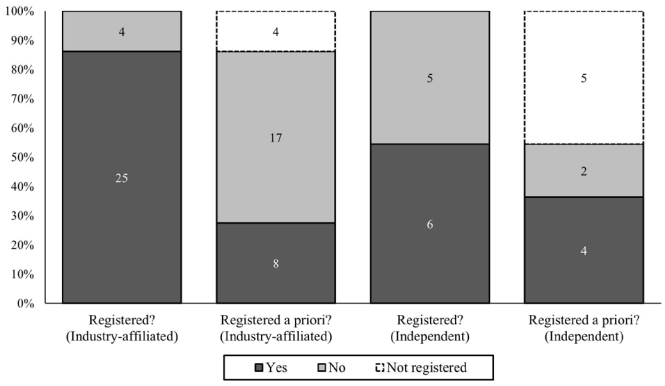

Figure 2 Number of trials that were registered on a clinical trial registry ('Registered?') and whether they were registered prior to enrolment of the first participant ('Registered a priori?'). Size of bar indicates percentage of trials. Number within bar indicates number of trials.

quasiexperimental trial, a non-randomised crossover and a study comprising two single-group assignment trials, one in which smokers used HTPs and one in which non-smokers used HTPs. In the two BAT actual use studies, products were allocated in random order within each group, but subject assignment to groups was not randomised.

There were no significant associations between affiliation and setting (confinement or ambulatory; p=0.25) or randomisation (p=0.32).

Interventions

The minimum number of intervention arms in any one trial was one and the maximum was eight. IQOS was the most common HTP intervention across both industry-affiliated (n=18) and independent trials (n=10). Excluding Caponnetto (2018), who used PMI's IQOS, all industry-affiliated trials used the company's own brand of HTP in at least one arm. Comparators included cigarettes, e-cigarettes, cessation, nicotine replacement therapy and non-smokers (table 1). Independent trials included an e-cigarette group significantly more often than industry-affiliated trials (p=0.0003). Only industry-affiliated trials included nicotine replacement therapies and cessation arms.

In most trials, participants used interventions ad libitum, regardless of confined or ambulatory setting. In seven confined trials, use was restricted (ie, puffing topography restricted). Three trials (9%) implemented both restricted and ad libitum use in confined settings and the mode of exposure was unclear in two (6%) trials. There was no significant association between mode of exposure and affiliation (p=0.27).

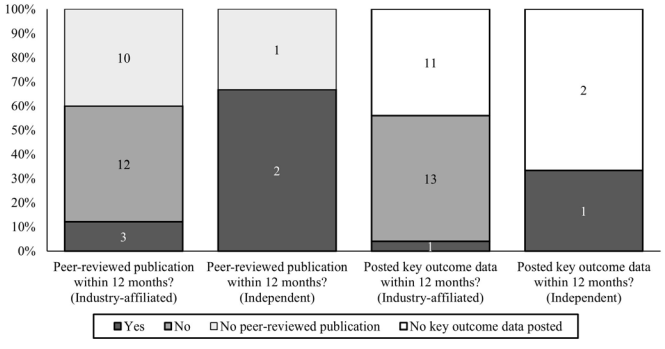

Figure 3 Number of trials that reported results via peer-reviewed publications and posting on trial registrations within 12 months of trial completion. Size of bar indicates percentage of trials. Number within bar indicates number of trials.

Participants

Four trials (10%; 3/29 industry-affiliated and 1/11 independent) failed to report the number of participants enrolled, randomised and/or completed. A total of 4098 participants were randomised (or enrolled in non-randomised trials) across the remaining 36 trials. A total of 3675 participants completed these trials, yielding an attrition rate of 10.3%: 10.5% across 26 industry-affiliated trials and 8.2% across 10 independent trials. Attrition was higher in ambulatory-only trials (average attrition=20%, n=3) than confinement-only trials (2.9%, n=28). Eighteen trials had withdrawals, 15 of which reported reasons for withdrawals and 3 did not.

Twenty-six (65%) trials reported baseline characteristics for the randomised/enrolled population, 8 (20%) reported them for the completed population, 5 (12.5%) reported them for analysis populations and 1 (2.5%) did not report any baseline characteristics. Based on available data, the mean age of participants was 40.1 years old and the ratio of male to female was 1.41:1 (n=4310 across 37 trials). In 35 trials, all participants were described as being in good health or without relevant morbidities. In one PMI trial, some participants had mild or moderate chronic obstructive pulmonary disease (COPD). In another PMI trial, all participants had chronic generalised periodontitis. Three trials did not report whether participants had any relevant morbidities.

Participants were smokers in all but two trials (NCT03889990/NCT03995329 and Dalrymple, 2022). Minimum eligible cigarette consumption across the trials ranged from ≥5 to ≥11 cigarettes per day and having smoked for ≥6 months to ≥10 years. One industry-affiliated and five independent trials did not define eligible smoking history.

Outcomes

A total of 214 different outcomes were measured across the 40 trials (online supplemental table 2). There was a wider variety of biomarkers of potential harm, but biomarkers of exposure were most measured (table 2). Number of outcomes measured in any one trial ranged from 1 to 71. The mean number of outcomes measured in industry-affiliated trials was 27 (mode=19, range=1–71), whereas for independent trials, it was 11 (mode=7, range=1–28). Seventeen trials (42.5%; 14/29 industry-affiliated and 3/11 independent; p=0.29) did not report results data for all outcomes measured.

Analysis characteristics

A total of 275 trials (67.5%; 22/29 industry-affiliated and 5/11 independent; p=0.12) reported sample size calculations. The unit of analysis in 39 trials was individuals and areas of skin in 1 trial.[26] The analysis populations used were: full analysis set (n=5, all industry-affiliated); full analysis set as exposed (n=3, all industry-affiliated); per-protocol population (n=5, all industry-affiliated); pharmacokinetic (PK) population (n=5, all industry-affiliated); per-protocol and PK populations (n=1, industry-affiliated); per-protocol and CEVal-compliant populations (n=1, industry-affiliated); not specified or unclear (n=20, 9 industry-affiliated and 11 independent). Population definitions are provided in online supplemental table 1.

Risk of bias

Thirty-four trials were judged to be at high risk of bias and for six trials risk of bias was judged to be unclear (online supplemental

Table 2 Outcomes measured in heated tobacco product clinical trials

	Number of outcomes		Number of trials	
Outcome type	Measured	Reported in ≥1 trial	Measured outcome	Reported data on outcome
Biomarker of exposure	25	25	32	28
Biomarker of exposure*	2	2	28	24
Biomarker of potential harm	125	104	21	19
Nicotine pharmacokinetics	18	16	17	16
Subjective effects (questionnaire)	20	17	28	22
Other measures	15	12	22	18
Safety profile	9	8	24	23

*Two biomarkers of exposure were also measured as biomarkers of potential harm in one trial.

figure 1). Twenty-seven (93%) industry-affiliated trials were judged to be at high risk of bias and 2 (7%) unclear (figure 4A). Seven (64%) independent trials were judged to be at high risk of bias and 4 (36%) unclear (figure 4B) (significance not estimable as no low ratings). Judgement justifications are provided in online supplemental table 1.

The 5 trials (3/11 independent and 2/29 industry-affiliated) judged to be at high risk of selection bias were due to these being non-randomised trials, meaning there was no random sequence generation or allocation concealment. There was no significant association between affiliation and rating for random sequence generation (p=0.07), but industry-affiliated trials had a significantly higher proportion of low ratings for allocation concealment than independent trials (p=0.0065). Selection bias could not be assessed for Dalrymple 2022 as the unit of randomisation was not individuals.

Risk of performance bias (blinding of participants and personnel) was judged to be high in 25 (86%) industry-affiliated and 2 (18%) independent trials (p=0.11). The numerous high ratings were commonly due to inability to conceal visually distinctive products and the control being non-active (cigarettes). As these factors are expected in HTP clinical research, we also determined overall risk of bias excluding this domain (figure 2; 'Overall (exc. BPP)'). While this had no effect on overall risk of bias judgements across independent trials, 3 industry-affiliated trials went from high to unclear ratings, 10 went from high to low and 1 went from unclear to low. When excluding performance bias, there was evidence that industry-affiliated trials were judged to have low risk of overall bias significantly more often than independent trials (p=0.03).

Risk of detection bias (blinding of outcome assessment) was judged to be high in 3 (10%) industry-affiliated trials and 2 (18%)

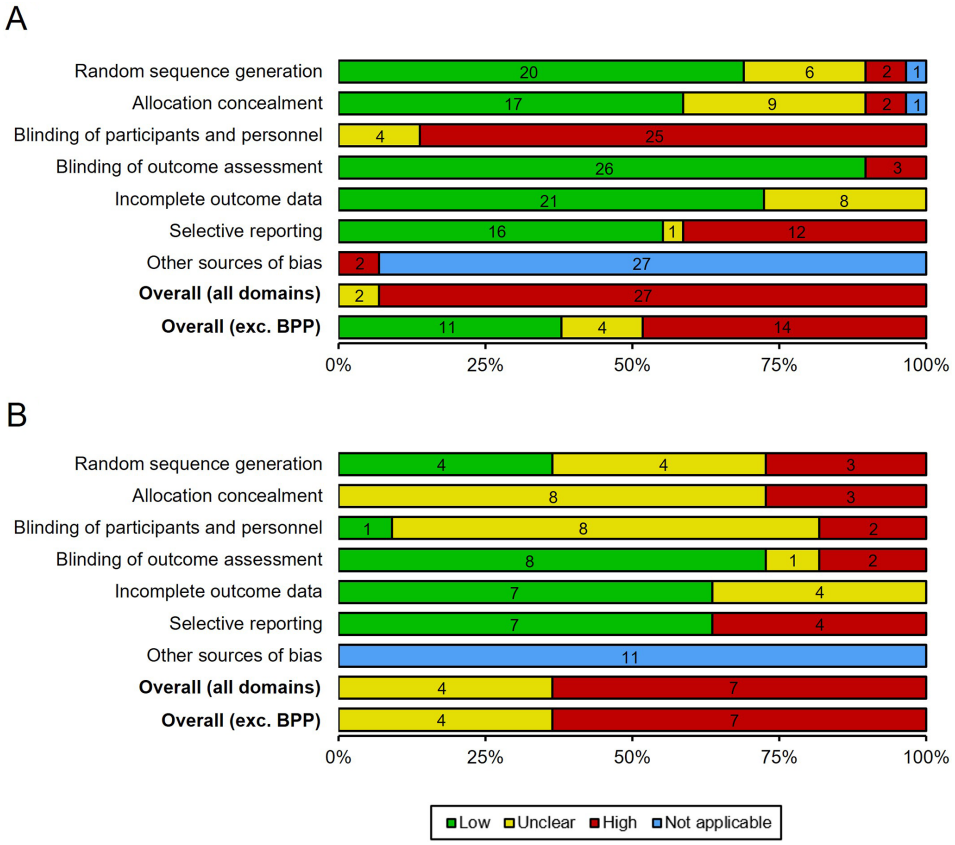

Figure 4 (A) Risk of bias across industry-affiliated trials. (B) Risk of bias across independent trials. Size of bar indicates percentage of trials. Number within bar indicates number of trials. BPP, blinding of participants and personnel.

independent trials (p=0.5875). In all instances, this was due to some primary outcomes being subjectively measured in combination with either the trial being open-label (ie, no blinding) or a lack of information on blinding.

Risk of reporting bias (selective reporting) was high in 12 (41%) industry-affiliated and 4 (36%) independent trials (p=1). In all trials, this was because at least one outcome measured during the trial was not reported on at all in any trial literature.

Other biases were identified in two PMI trials due to all results data being grouped by participant product use (ie, 'full analysis set as exposed' analysis population), not randomisation.

Association between trial findings and affiliation or risk of bias

Table 3 (and online supplemental table 3) shows whether HTPs had a positive, mixed or negative effect on each trials' primary

Table 3 Summary of direction of effect in primary outcomes at last follow-up between heated tobacco product and combustible cigarette arms

Trial	Affiliation	Design	Primary outcomes	RoB (all domains)	RoB (exc. BPP)
ISRCTN13439529	Industry-affiliated	RCT	▼7	High	High
ISRCTN14301360/UMIN000024988	Industry-affiliated	RCT	▲16	High	High
ISRCTN80651909	Industry-affiliated	RCT	▲19	High	High
ISRCTN81075760	Industry-affiliated	RCT	▲1	High	High
Gee *et al* (2018)[61]	Industry-affiliated	NRT	◄►6	High	High
Jones *et al* (2020)[62]	Industry-affiliated	NRT	◄►5	High	High
ISRCTN88682435	Industry-affiliated	RCT	▼3	High	High
NCT03700112	Industry-affiliated	RCT	◄►3	High	High
NCT01780714	Industry-affiliated	RCT	▲4	High	High
NCT02466412	Industry-affiliated	RCT	▼2	High	High
NCT02503254	Industry-affiliated	RCT	▲4	High	High
NCT02641587	Industry-affiliated	RCT	▲5	High	High
NCT02649556	Industry-affiliated	RCT	◄►8	High	High
NCT03364751	Industry-affiliated	RCT	▼1	High	High
UMIN000017297	Industry-affiliated	RCT	◄►3	High	Unclear
UMIN000025777	Industry-affiliated	RCT	▲16	High	Unclear
UMIN000041539	Industry-affiliated	RCT	▲15	High	Unclear
NCT01780688	Industry-affiliated	RCT	▼2	High	Low
NCT01959607	Industry-affiliated	RCT	▲2	High	Low
NCT01959932	Industry-affiliated	RCT	▲4	High	Low
NCT01967706	Industry-affiliated	RCT	▲2	High	Low
NCT01967719	Industry-affiliated	RCT	◄►2	High	Low
NCT01967732	Industry-affiliated	RCT	▲2	High	Low
NCT01970982	Industry-affiliated	RCT	▲4	High	Low
NCT01970995	Industry-affiliated	RCT	▲5	High	Low
NCT01989156	Industry-affiliated	RCT	▲5	High	Low
NCT02396381	Industry-affiliated	RCT	◄►8	High	Low
Dalrymple *et al* (2022)[26]	Industry-affiliated	RMS	▲9	Unclear*	Low*
Caponnetto *et al* (2018)[24]	Industry-affiliated	RCT	▲1	Unclear	Unclear
NCT03889990/NCT03995329	Independent	NRT	NE†	High	High
Nga *et al* (2020)[161]	Independent	NRT	▲1	High	High
Lopez *et al* (2016)[160]	Independent	RCT	◄►6	High	High
DRKS00012919	Independent	RCT	▼1	High	High
NCT03435562	Independent	RCT	▼1	High	High
NCT03452124	Independent	RCT+CCS	▲4	High	High
Phillips-Waller *et al* (2021)[162]	Independent	NRT	▼7	High	High
aspredicted.org #6896	Independent	RCT	◄►5	Unclear	Unclear
NCT03301129	Independent	RCT	▲2	Unclear	Unclear
Ioakeimidis (2021)	Independent	RCT	▲6	Unclear	Unclear
Yaman *et al* (2021)[163]	Independent	RCT	◄►24	Unclear	Unclear

Effect direction: ▲=HTP had a positive effect compared with cigarettes; ▼=HTP had a negative effect compared with cigarettes; ◄►=mixed or conflicting effects.
Numbers next to arrows describe number of primary outcomes within each synthesis.
Trial quality: RoB (all domains)=overall risk of bias based on all domains; RoB (exc. BPP)=overall risk of bias based on all domains except blinding of participants and personnel.
*This is excluding selection bias, which could not be assessed in this study.
†Not estimable due to lack of cigarette arm.
BPP, blinding of participants and personnel; CCS, case-control study; HTP, heated tobacco product; NE, not estimable; NRT, non-randomised trial; RCT, randomised controlled trial; RMS, repeated measures study.

outcomes compared with cigarettes at last follow-up. One independent study (NCT03889990/NCT03995329) had no cigarette arm and therefore direction of effect compared with the HTP was not estimable. Most industry-affiliated trials (59%) found HTPs had positive effects on primary outcomes compared with cigarettes, while most independent trials (60%) found they had mixed or negative effects. However, there was no convincing evidence that the proportion of effect directions was different between industry-affiliated and independent trials ($p>0.05$). We could not investigate associations between overall risk of bias and trial findings because no studies were rated low. Overall risk of bias judgements excluding performance bias were not significantly associated with trial findings ($p=0.18$).

Despite attempting to adapt our methods, we were unable to perform the planned analysis. Nonetheless, the issues we encountered provide further insight into the quality of available data. First, there were few objectively measured outcomes which were measured in 10 or more trials (recommended minimum for meta-regression[18]) and measured in both industry-affiliated and independent trials. Data were also highly variable: last follow-up exhaled carbon monoxide (eCO) means ranged from 0.5 to 17.2 ppm across HTP arms and 0.8 to 25.6 ppm across cigarette arms. A possible solution to the issues of variability could have been to compare change in eCO from baseline to last follow-up, but few trials reported this. Moreover, the SD were relatively large compared with the means. This suggests the eCO data were positively skewed, as has been noted in other large population trials,[27 28] yet most trials did not provide log-transformed eCO data.

DISCUSSION

To our knowledge, this is the first study to critically assess the design and reporting of HTP interventional clinical trials and investigate associations between characteristics, affiliations and results. Despite worldwide use increasing,[2] the number of clinical trials assessing HTPs remains low, especially those conducted independently of the tobacco industry, and most HTP trials were judged to be at high risk of bias.

In contrast with existing literature demonstrating industry sponsorship is associated with proindustry findings,[12 29] we found no significant differences between findings from industry-affiliated and independent trials. Further, a 2017 Cochrane review found risk of bias did not differ between industry and independent studies, except for domains regarding blinding, which were more often rated low in industry studies. However, we found most industry-affiliated trials were at high risk of performance bias. When this was omitted, a significantly higher proportion of low overall risk of bias ratings were observed among industry-affiliated compared with independent trials. The differences between our findings and previous reviews' findings may be due to the smaller sample size, most trials being limited laboratory-based studies of short-term exposure and using primary outcome data rather than overall conclusions of each trial to investigate associations. Additionally, selection bias could not be assessed in 1 of the 11 studies rated at low overall risk excluding performance bias. Full study reports were available for the other 10, which provided more information than can be presented in typical trial publications, like journal articles, thus reducing the chances of unclear judgements.

We noted numerous shortcomings in the design and quality of HTP trials. First, most trials were not registered a priori and did not publish results within 12 months, as recommended by the WHO and World Medical Association's Declaration of Helsinki.[30 31] Second, around half the trials did not report data for all prespecified outcomes. Selective reporting compromises the validity of trials, especially if significant outcome results are reported while non-significant results are omitted.[32] It is disconcerting to find safety measures and biomarkers of potential harm particularly neglected given the health impact of HTPs remains uncertain.

Third, three independent and three BAT studies did not use a randomised controlled design and three PMI trials analysed data by exposure rather than random allocation, effectively derandomising the data. Lack of or compromised randomisation may reduce validity of results by creating an imbalance in subject characteristics (ie, possible confounding factors) between groups.[33]

Fourth, there were many characteristics which diminish the representativeness of the findings in real-world populations, including very short follow-up, which may not be long enough for adverse effects to manifest, and use of controlled confined settings. Many trials also used per-protocol or similar analysis populations, which exclude participants who deviated from the protocol or product assigned. In doing this, the trials can only estimate the effects of HTPs in ideal circumstances, that is, when smokers make a complete, or near-complete, switch from cigarettes. This may overestimate their true effects across real-world populations,[34] in which consumers may use HTPs in conjunction with cigarettes or other products.

The choice of participants and products may also not be representative of real-world settings. Most trials included healthy participants, yet 12% of UK smokers report being in 'bad' or 'very bad' health[35] and 15% of US smokers have COPD.[36] Likewise, most trials did not include a 'next best' comparator based on options already available to smokers looking to reduce health risks, such as e-cigarettes, smokeless tobacco and nicotine replacement therapy. Notably, only five industry-affiliated trials included an e-cigarette arm, despite all the companies except PAX, manufacturing both HTPs and e-cigarettes.[37] This could be to avoid directly comparing HTPs to a more established and popular competitor.

Although these short-term, confined trials can provide evidence on exposure to toxicants compared with cigarettes, they fall short of what is needed to determine whether HTPs reduce the risks of tobacco-related diseases and whether they are beneficial to public health in real-world settings. Furthermore, high risks of bias and notable weaknesses in trial conduct and reporting are concerning in regard to existing reviews by governments and health authorities, including in the USA,[38] UK,[39] Netherlands[40] and Belgium,[41] on which regulatory decision have been made. While methodological limitations were noted, most did not include systematic assessments of trial quality.

Although, to our knowledge, BAT's actual use studies have not been reviewed by regulators, similar studies by PMI have.[38 42] However, there is limited guidance on these studies and ethical approval can be complex to obtain.[23 43] Indeed, ethical approval was obtained from BAT's internal Human Research Committee in Jones 2020 and there was no mention of ethical approval in Gee (2018). In the absence of clear guidance, the design and reporting of actual use studies noticeably varies and raises concerns over their consistency and ethicality in tobacco research and regulation.

Strengths and limitations

This review included more trials than previous reviews,[8 9 13 44 45] likely in part due to our less restrictive eligibility criteria. Following

the guidance of the Cochrane Tobacco Addiction Group, we used Risk of Bias V.1 over the newer Risk of Bias V.2 tool because the latter requires an assessment for each outcome. This may have yielded different results, but it would have been impractical to do for all the outcomes we were interested in. Heterogenic data and inconsistent reporting meant the planned meta-regression analyses could not be conducted. Instead, we used direction of effect plots, but these do not consider statistical significance, the magnitude of effects or sample size differences between studies.

CONCLUSION

We found HTP interventional trials to be substandard in many aspects of their design and reporting, with most being at high risk of bias. Though our analyses detected few statistically significant differences between trials of different affiliation and risk of bias, this should only be interpreted as absence of evidence, not evidence of absence. Research in this area remains relatively sparse and results may change as further studies become available. The findings of this review highlight the inadequacy of existing clinical trial data in determining the health impacts of HTPs as used in real-world markets and thus calls into question their utility in regulatory decisions.

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Contributors The study was conceived by SB, who developed its design in conjunction with GMJT, JH-B and CM. SB and AVDA screened, coded and extracted data from study literature. SB and AVDA conducted the risk of bias assessments, checked by JH-B. SB drafted the manuscript, which was edited by all authors. SB is the guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Critical appraisal of interventional clinical trials assessing heated tobacco products: a systematic review and meta-regression.

Supplementary Materials

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:

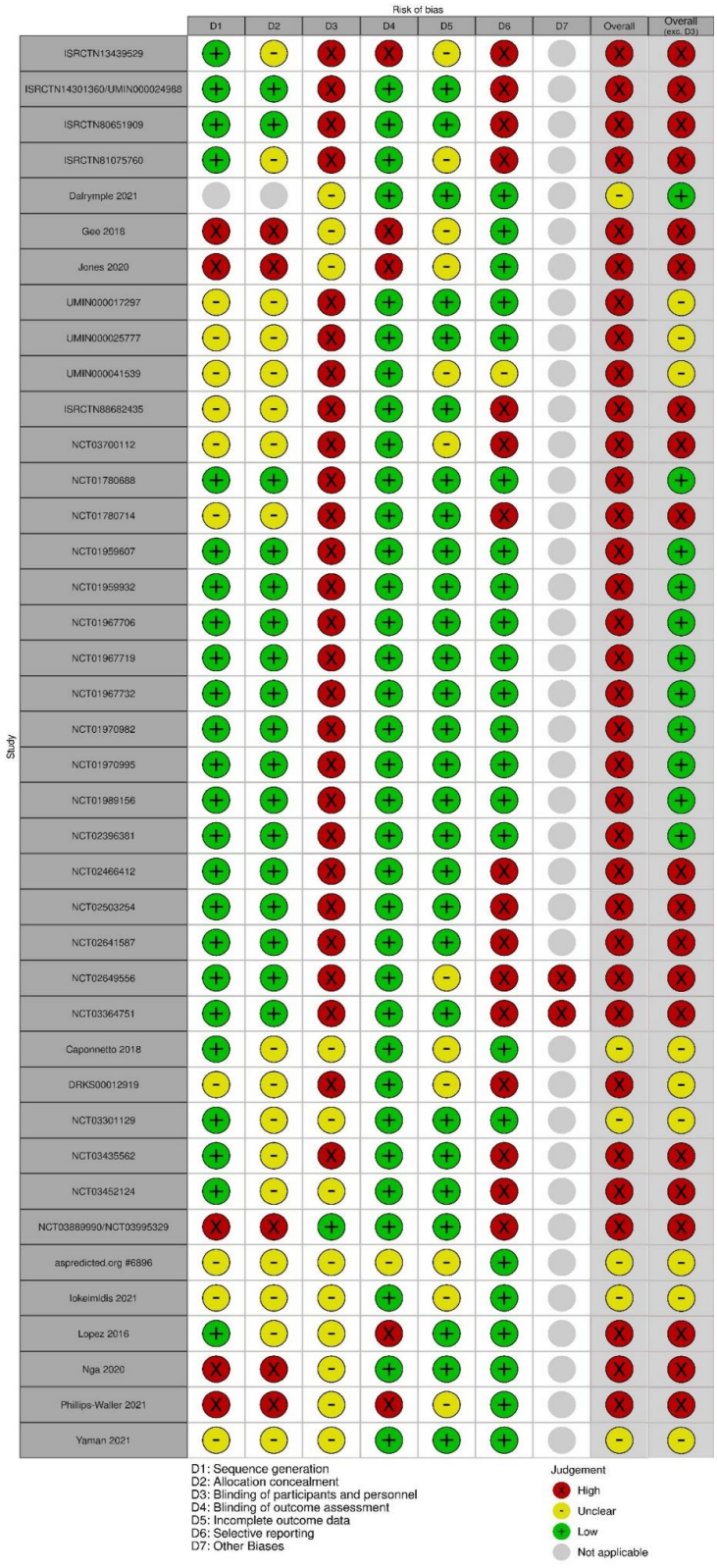
- the sponsor named on the trial registration had no known ties to the tobacco industry; and
- funding statements in any of the trial literature indicated the trial was not funded by a tobacco company or other organisation funded by a tobacco company; and
- author affiliations and conflict of interest 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.

Supplementary Figure 1. Risk of bias summary: Review authors' judgments about risk of bias items for each included study



Supplementary Table 1. Characteristics of included studies.

UMIN000017297		
Methods	**Date of registration:** 27/04/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confinement (Japan) **Study start date; study end date:** 11/05/2015; 27/05/2015 **Intervention duration:** 2 sessions of 10 puffs for 3 mins at approx 20 sec intervals	
Participants	**Number of participants:** 24 randomised, 0 withdrawn, 24 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=24; Mean Age (SD): 39 years (SD not reported); Sex: 100% male; Ethnicity/Nationality: 100% Japanese. **Key inclusion criteria:** Health status: "good health"; ≥11 CPD; smoked for ≥1 year	
Interventions	**Interventions:** HTP (Prototype novel tobacco vapor product), CC (unknown brand) **Co-interventions:** none **Mode of exposure:** direct restricted	
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Adverse Events/Serious Adverse Events, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Terminal half-life of nicotine, Mouth level exposure to nicotine.	
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*completed subjects who completed the study and who did not deviate from the protocol were included in the statistical analysis*" **Unit of analysis:** Individuals	
Study funding	Japan Tobacco International (Industry-affiliated)	
Notes	Not included in meta-regression analysis	
Risk of bias		
Bias	**Authors' judgement**	**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	"Blinding: Open-no one is blinded". Included non-active comparator (cigarettes).
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.
UMIN000025777		
Methods	**Date of registration:** 20/01/2017 **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confinement (Japan) **Study start date; study end date:** 21/01/2017; 22/02/2017 **Intervention duration:** 5 days	

Participants	**Number of participants:** 60 randomised (HTP 20, CC 20, Cess 20), 0 withdrawn, 60 completed (HTP 20, CC 20, Cess 20) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=60; Mean Age (SD): HTP 32.7 (12.3) years, CC 30.9 (12.5) years, Cess 33.3 (14.6); Sex: 70% male; Ethnicity/Nationality: 100% Japanese. **Key inclusion criteria:** Health status: "good health"; ≥11 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (novel tobacco vapor product), CC (own brand), smoking cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, 2-hydroxyethylmercapturic acid, 3-hydroxybenzo[a]pyrene, 1-aminonaphthalene, 4-hydroxybutyl-2-mercapturic acid **Secondary:** Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Minnesota Nicotine Withdrawal Scale, Human Puffing/Smoking Topography (inc. puff count), Product Liking Questionnaire, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*randomized subjects who had at least one BoE assessment after post-randomization*" **Unit of analysis:** Individuals
Study funding	Japan Tobacco International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	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	"Blinding: Open-no one is blinded". Included non-active comparator (cigarettes).
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.

Caponnetto, 2018

Methods	**Date of registration:** Not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (Unknown) **Study start date; study end date:** Not reported **Intervention duration:** 3 sessions of 2x 10 puffs with 30 sec intervals and 5 min inter-round break
Participants	**Number of participants:** 12 randomised, 0 withdrawn, 12 completed **Withdrawal reasons reported:** N/A

	Baseline characteristics: N=12; Mean Age (SD): 28.6 years (SD not reported); Sex: 50% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (IQOS), HTP (Glo), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide **Secondary:** N/A
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified **Unit of analysis:** Individuals
Study funding	University of Catania (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"The randomization sequence was computer-generated"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	Unclear	No information on blinding. Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	No information on blinding, but only outcome was objectively measured.
Incomplete outcome data	Unclear	The authors state 12 subjects "took part" in the study but it is unclear whether more than 12 were initially randomised.
Selective reporting	Low	Only outcome measured (eCO) is reported on in the results.

aspredicted.org #6896

Methods	**Date of registration:** 22/11/2017 **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (Belgium) **Study start date; study end date:** Not reported **Intervention duration:** 3 sessions of single use of one cigarette or tobacco stick
Participants	**Number of participants:** randomised not reported, 0 withdrawn not reported, 34 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=30; Mean Age (SD): 22 (3.09) years; Sex: 67% male; Ethnicity/Nationality: 14 Belgium, 16 Other **Key inclusion criteria:** Health status: cannot have "one or more severe medical conditions"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS), CC (Own brand), EC (Eleaf iStick) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Fagerström Test for Nicotine/Cigarette Dependence, Minnesota Nicotine Withdrawal Scale, A visual analogue scale (VAS) assessing cigarette craving, Product preference **Secondary:** N/A
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals

Study funding	KU Leuven and Thomas More University of Applied Sciences (Independent)
Notes	Although number of participants randomised not reported, the authors stated 46 signed up for intake session. Also 34 completed all sessions, but 4 were excluded from the analyses for not meeting inclusion criteria. Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	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	Unclear	Presence of blinding not described. Included non-active comparator (cigarettes.
Blinding of outcome assessment	Unclear	Presence of blinding not described. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	The authors explained "46 signed up for the intake session, of whom 34 completed all sessions", but number of participants randomised was not reported.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT03435562

Methods	**Date of registration:** 19/02/2018 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** Yes **Design:** Crossover RCT **Setting (Country):** Confined (United States of America) **Study start date; study end date:** 03/03/2018; 16/09/2019 **Intervention duration:** 3 sessions of a 10-puff product use bout and a 90 mins *ad lib* use bout
Participants	**Number of participants:** 22 randomised, 4 withdrawn, 18 completed **Withdrawal reasons reported:** No **Baseline characteristics:** N=18; Mean Age (SD): 36.8 (9.3) years; Sex: 72% male; Ethnicity/Nationality: 7 Black or African America, 8 White, 2 more than one race, 1 unknown or not reported **Key inclusion criteria:** Health status: "healthy"; unspecified CPD; unspecified smoking duration
Interventions	**Interventions:** HTP (IQOS), CC (Own brand), EC (JUUL) **Co-interventions:** None **Mode of exposure:** Direct restricted and direct *ad libitum*
Outcomes	**Primary:** Nicotine **Secondary:** Exhaled Carbon monoxide, Questionnaire of Smoking Urges, Minnesota Nicotine Withdrawal Scale, Heart rate, The Direct Effects of Nicotine Questionnaire, Blood pressure
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Virginia Commonwealth University and National Institute on Drug Abuse, Center for the Study of Tobacco Products (Independent)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Order of the products used in each session will be assigned using Latin-square order procedure"

Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". Primary outcome objectively measured.
Incomplete outcome data	Low	Overall attrition = 18.18%. All participants who completed the study were included in the analysis.
Selective reporting	High	Results data for heart rate and blood pressure have not been reported.

NCT03889990/NCT03995329

Methods	**Date of registration:** 26/03/2019 (NCT03889990); 24/06/2019 (NCT03995329) **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** 2 non-randomised single group assignment trials **Setting (Country):** Confined (Greece) **Study start date; study end date:** 01/01/2018; 01/01/2019 (NCT03889990), 19/06/2019; 10/07/2019 (NCT03995329) **Intervention duration:** 1 session of up to 14 puffs over 5-6 mins
Participants	**Number of participants:** 65 enrolled, 0 withdrawn, 50 completed **Withdrawal reasons reported:** No **Baseline characteristics:** N=50; Mean Age (SD): Smokers 40.3 (13.2) years, Non-smokers 37.4 (10.4) years; Sex: 100% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥5 pack years
Interventions	**Interventions:** HTP (IQOS) in smokers and non-smokers **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide, Forced expiratory volume in one second, Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Total lung capacity, Residual volume, Forced expiratory volume in one second/forced vital capacity, Heart rate, Functional residual capacity, Diffusion Capacity, Peak Expiratory Flow, [Mean] Arterial Blood Pressure, Total respiratory resistances, Respiratory impedance, Oxygen Saturation, Maximal Mid-Expiratory Flow, Expiratory reserve volume **Secondary:** N/A
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Aristotle University Of Thessaloniki (Independent)
Notes	The authors reported enrolling 25 subjects in each trial, but on the registration of one trial (NCT03889990) it was reported that 40 participants had in fact enrolled. It is not clear when or why 15 subjects were removed from the study. Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
Blinding of participants and personnel	Low	Both arms received the same intervention, and the arms were from two separately conducted single-group assignment trials.
Blinding of outcome assessment	Low	All primary outcomes were objectively measured.
Incomplete outcome data	Low	NCT03889990 attrition=37.5%; NCT03995329 attrition =0%, but both arms received the same intervention.
Selective reporting	High	Blood pressure and heart rate were listed as primary outcomes on the non-smoker trial registration (NCT03995329) but results data for these have not been reported.

NCT03301129	
Methods	**Date of registration:** 04/10/2017 **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (Italy) **Study start date; study end date:** 15/10/2017; 25/02/2018 **Intervention duration:** 3 sessions of single use of one cigarette or tobacco stick
Participants	**Number of participants:** 20 randomised, 0 withdrawn, 20 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=20; Mean Age (SD): 35 (13) years; Sex: 30% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: “healthy”; unspecified CPD; unspecified smoking duration
Interventions	**Interventions:** HTP (IQOS2.2), CC (Marlboro Gold), EC (Blu Pro) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Soluble Nox2-derived peptide, Flow-mediated dilation **Secondary:** Cotinine, Vitamin E, Soluble P-selectin, Soluble CD40 ligand, nitric oxide bioavailability, H2O2 production, H2O2 breakdown activity, Systolic blood pressure, Diastolic blood pressure, 8-iso-prostaglandin F2alpha, Product Satisfaction Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	University of Roma La Sapienza (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"The randomization list was computer generated"
Allocation concealment	Unclear	No information provided.
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.

NCT03364751	
Methods	**Date of registration:** 07/12/2017 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Ambulatory (Japan) **Study start date; study end date:** 07/11/2017; 12/06/2019 **Intervention duration:** 6 months
Participants	**Number of participants:** 172 randomised (87 HTP, 85 CC), 2 withdrawn (1 HTP, 1 CC), 170 completed (86 HTP, 84 CC) **Withdrawal reasons reported:** Yes

	Baseline characteristics: N=172; Mean Age (SD): HTP 48.1 years, CC 46.5 years, Dual Use 54.4 years, Other use 54 years (SDs not reported); Sex: 81% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: must have generalized chronic periodontitis; ≥10 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (IQOS), CC (Own brand) **Co-interventions:** Mechanical periodontal therapy **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Mean Periodontal Pocket Depth (PD) reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy **Secondary:** Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Nicotine equivalents, Daily product consumption, Adverse Events/Serious Adverse Events, Mean PD change in sites with initial PD≥4 mm after mechanical periodontal therapy, mean PD change in sites with initial PD<4mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7 mm, Mean clinical attachment level (CAL) change in sites with initial PD≥4mm after mechanical periodontal therapy, mean CAL change in sites with initial PD<4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7mm, change in tooth mobility (grade), change in the number of sites with PD<4 mm, 4-5mm, 5-6 mm, 6-7 mm, and ≥7 mm, change in plague control record, change in mean full-mouth PD, change in mean full-mouth CAL, change in gingival inflammation (GI) score, change in bleeding on probing scores Pro-inflammatory and immuno-regulatory mediators (sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α), Microbiological status, Full transcriptomics profile
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set (as exposed) defined as "*all randomized subjects with at least one product use experience and at least one valid non-safety assessment. Subjects were analyzed based on their actual self-reported product use. Some participants were excluded from analysis for protocol deviations (including, but not limited to, missing measurements)*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization will be done through the Interactive Web and Voice Response System (IXRS)"
Allocation concealment	Low	"Randomization will be done through the Interactive Web and Voice Response System (IXRS)"
Blinding of participants and personnel	High	"Masking: Single (Investigator)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: Single (Investigator)". Primary outcome objectively assessed.
Incomplete outcome data	Low	Attrition: IQOS=1.15% CC=1.18%, overall=1.16%. Exclusion: IQOS=19.54% CC=1.18%, overall=1.74%.
Selective reporting	High	The following outcomes listed in the protocols have not been reported on: measurement of pro-inflammatory and immuno-regulatory mediators; microbiological status; full transcriptomics profile.
Other	High	Only reported data grouped by participant product use not randomisation.

NCT02641587	
Methods	**Date of registration:** 29/12/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined & Ambulatory (Poland) **Study start date; study end date:** January 2016; July 2017 **Intervention duration:** 90 Days (5 days confinement + 85 days ambulatory)
Participants	**Number of participants:** 120 randomised (80 HTP, 40 CC), 5 withdrawn (4 HTP, 1 CC), 115 completed (76 HTP, 39 CC) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=120; Mean Age (SD): HTP 38.9 (8.9) years, CC 39.0 (8.0) years; Sex: 53% male; Ethnicity/Nationality: 100% Caucasian **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥10 years
Interventions	**Interventions:** HTP (carbon heated tobacco product 1.2), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** S-phenylmercapturic acid, monohydroxybutenylmercapturic acid, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin **Secondary:** 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, Exhaled Carbon monoxide, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Cytochrome P450 2A6 activity, Ames mutagenicity test (YG1024+S9), White blood cell count, Systolic blood pressure, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second, Diastolic blood pressure, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Triglycerides, Total cholesterol, Apolipoprotein B, Apolipoprotein A1, Blood glucose, Forced expiratory volume in one second/forced vital capacity, Myeloperoxidase, Intention to use [HTP] Questionnaire, Total anti-oxidant capacity, 8-Hydroxy-2'-deoxyguanosine, Prochaska "Stage of Change" Questionnaire, 4-Hydroxy-2-nonenal, Adverse Events/Serious Adverse Events
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*randomized subjects who fulfilled product adherence criteria and had no major protocol deviations impacting evaluability, such as violation of eligibility criteria or insufficient duration of urine collection. Separate PP populations were defined for the analysis at Day 5 and Day 90. Non-adherence to CHTP was defined as an average cigarette use of > 0.5 cigarettes/day from Day 1 to the end of the respective period (Day 5 or Day 90) or use of > 2 cigarettes on a single day within a week prior to the assessments.*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation	Low	"subjects will be randomized using an interactive web and voice response system (IxRS)"
Allocation concealment	Low	"subjects will be randomized using an interactive web and voice response system (IxRS)"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=5% CC=2.5%, overall=4.17%. 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 "Stage of Change" Questionnaire, MCEQ, and pre- and post-bronchodilator FVC, FEV1/FVC, FEF 25-75 were not reported in any literature sources.

NCT02396381	
Methods	**Date of registration:** 24/03/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Ambulatory (United States of America) **Study start date; study end date:** 12/03/2015; 01/08/2017 **Intervention duration:** 26 weeks
Participants	**Number of participants:** 984 randomised (488 HTP, 496 CC), 127 withdrawn (74 HTP, 53 CC), 857 completed (414 HTP, 443 CC) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=857; Mean Age (SD): HTP 44.2 (9.64) years, CC 45.2 (9.55) years, Dual Use 43.8 (9.77) years, Other use 44.2 (8.14) years; Sex: 58.8% male; Ethnicity/Nationality: 79.2% White, 17.6% Black or African American, 0.7% American Indian or Alaska Native, 0.9% Asian, 0.4% Native Hawaiian or Other Pacific Islander, 1.2% unknown or not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, Carboxyhemoglobin, White blood cell count, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second **Secondary:** 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, Cytochrome P450 2A6 activity, Systolic blood pressure, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Diastolic blood pressure, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Apolipoprotein B, Apolipoprotein A1, Total lung capacity, Residual volume, Forced expiratory volume in one second/forced vital capacity, Myeloperoxidase, Vital capacity, Inspiratory capacity, Functional residual capacity, Intention to use [HTP] Questionnaire, bronchodilator reversibility in FEV1, Albumin

Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set (as exposed) defined as "*Subjects in FAS-AR who had at least 1 record of reported product use diary post-randomization. The exposure assignment was actual product exposure, as defined by the product use pattern categories estimated during the 6 month period: •THS-use: ≥1 THS or CC, and ≥70% THS use over the analysis period, and ≥70% THS use on >50% of days in the analysis period •Dual-use: ≥ 1 THS or CC and, 1% ≤THS<70% over the analysis period, or THS-use and CC-use categories do not apply to 50% of these days •CC-use: ≥1 THS or CC use, and <1% THS use over the entire analysis period and <1% THS use on ≥ 50% of days in the analysis period. •Other-use: Subjects with missing product use, or using e-cigarettes or other tobacco products, quitters, or subjects who switched across different use patterns between consecutive analysis periods*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	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 personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured
Incomplete outcome data	Low	Attrition: IQOS=15.16% CC=10.69%, overall=2.91%. Although not the main analysis population, full analysis set (as randomised) results data were also presented in the published literature.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT02466412

Methods	**Date of registration:** 09/06/2015 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 08/05/2015; November 2015 **Intervention duration:** 2 sessions of single use of one cigarette or tobacco stick
Participants	**Number of participants:** 48 randomised (24 HTP-CC, 24 CC-HTP), 0 withdrawn, 48 completed (24 HTP-CC, 24 CC-HTP) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=47; Mean Age (SD): HTP-CC 44.7 (10.03) years, CC-HTP 40.7 (11.48) years; Sex: 47% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (carbon heated tobacco product 1.1 M), CC (Own brand M) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Spirometry

	Concomitant medications, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC, AUC from start of product use up to 12 hours, Terminal half-life
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations that impact evaluability of the data (to be defined in the SAP) will be included in the PK analysis sets*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	1 subject was excluded from the analyses (sequence HTP-CC) due to all plasma nicotine concentration measurements being below the quantification limit. Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition was 0%. Exclusion: mCHTP-mCC=4.16% mCC-mCHTP=0%, overall=2.1%
Selective reporting	High	Only results data for the two primary outcomes have thus far been published.

NCT02503254

Methods	**Date of registration:** 20/07/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** Yes **Design:** Parallel RCT **Setting (Country):** Confined (Poland) **Study start date; study end date:** 04/07/2015; March 2016 **Intervention duration:** 5 days
Participants	**Number of participants:** 80 randomised (41 HTP, 39 CC), 0 withdrawn, 80 completed (41 HTP, 39 CC) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=80; Mean Age (SD): HTP 34.1 (10.45) years, CC 32.7 (10.97) years; Sex: 49% male; Ethnicity/Nationality: 100% Caucasian **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (carbon heated tobacco product 1.0), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total 1-hydroxypyrene, Adverse Events/Serious Adverse Events, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology

	and urine analysis safety panel, Vital signs, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), Human Puffing/Smoking Topography Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*all the randomized subjects who had at least one post-randomization product use experience, if randomized to CHTP 1.0 or CC, and have at least one valid non safety assessment*." **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"subjects were randomized by an interactive web and voice response system"
Allocation concealment	Low	"subjects were randomized by an interactive web and voice response system"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition and exclusion both 0%.
Selective reporting	High	Several outcomes listed in the study protocol were not reported on in the main results article. Only one was reported on in a poster instead.

NCT02649556

Methods	**Date of registration:** 07/01/2016 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Ambulatory (United States of America) **Study start date; study end date:** 30/09/2015; 20/12/2017 **Intervention duration:** 26 weeks
Participants	**Number of participants:** 857 started (230 HTP, 424 CC, 152 Dual use, 51 Other use), 248 withdrawn (63 HTP, 112 CC, 50 Dual use, 23 Other use), 609 completed (167 HTP, 312 CC, 102 Dual use, 28 Other use) **Withdrawal reasons reported:** No **Baseline characteristics:** N=857; Mean Age (SD): HTP 43.8 (9.68) years, CC 45.2 (9.54) years, Dual use 44.2 (9.76) years, Other use 44.5 (8.21) years; Sex: 58.8% male; Ethnicity/Nationality: 79.2% White, 17.6% Black or African American, 0.7% American Indian or Alaska Native, 0.9% Asian, 0.4% Native Hawaiian or Other Pacific Islander, 1.2% unknown or not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Carboxyhemoglobin, 8-epi-prostaglandin F2alpha, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 11-dehydrothromboxane B2, White blood cell count, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, total N-nitrosonornicotine, Nicotine equivalents, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Nicotine,

	Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Concomitant medications, Cotinine, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Apolipoprotein B, Apolipoprotein A1, Total lung capacity, Forced expiratory volume in one second/forced vital capacity, Myeloperoxidase, Vital capacity, Inspiratory capacity, Functional residual capacity, Intention to use [HTP] Questionnaire, bronchodilator reversibility in FEV1, Albumin, Blood pressure
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set (as exposed) defined as "*The FAS-EX consists of all subjects in FAS-AR who have at least one record of reported product use diary post randomization. The exposure assignment for the FAS-EX will be actual product exposure, as defined by the product use pattern categories estimated during the 12 month period]V4, V16"But note "Some participants were excluded from analysis for protocol deviations (including, but not limited to, missing measurements).*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	This is an extension to NCT02396381. 672 (309 in the THS arm and 363 in the CC arm) subjects enrolled in the extension study; the 857 subjects in the Full Analysis Set - As Exposed (FAS-EX) included subjects for combined analyses from the original six-month study who did not enter the extension study. The analysis was performed according to subjects' exposure over the 12-month period. Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS)."
Allocation concealment	Low	"Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS)."
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	672 subjects enrolled into the extension study (309 THS and 363 CC). However, it is unclear how many completed the study as the data is combined with the previous 6-month trial.
Selective reporting	High	Only results data for the primary outcomes have been published.
Other	High	Only reported data grouped by participant product use not randomisation.

NCT01967706

Methods	**Date of registration:** 23/10/2013 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 01/08/2013; May 2014 **Intervention duration:** 2 sessions of single use of one cigarette, tobacco stick or piece of gum for 35 ± 5 mins
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 1 withdrawn (1 HTP/CC), 61 randomised (43 HTP/CC, 18 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=61; Mean Age (SD): HTP/CC 33.4 (10.03) years, HTP/NRT 30.7 (7.8) years; Sex: 52% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years

Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), NRT (Nicorette Gum) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations (to be defined in the SAP) will be included*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization to product exposure sequence was done through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to product exposure sequence was done through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS-CC=2.27% IQOS-NRT=0%, overall=1.61%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT01780688

Methods	**Date of registration:** 31/01/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** May 2012; December 2012 **Intervention duration:** 2 sessions of single use of one cigarette or tobacco stick and 1 day of *ad lib* use
Participants	**Number of participants:** 28 randomised (14 HTP-CC, 14 CC-HTP), 0 withdrawn, 28 completed (14 HTP-CC, 14 CC-HTP) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=28; Mean Age (SD): HTP-CC 30.0 (4.9) years, CC-HTP 29.1 (4.0) years; Sex: 50% male; Ethnicity/Nationality: 100% Caucasian **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.1), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct restricted and *ad libitum*

Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Questionnaire of Smoking Urges, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Time to reach nicotine Cmax, Terminal half-life of nicotine, Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), Lowest observed plasma concentration during the same sampling interval in which Cpeak was observed, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all randomized subjects who did not deviate from the protocol, who completed at least one of the single use or ad libitum days, and had at least one estimable pharmacokinetic parameter derived from the single or ad libitum days*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization was performed using an Interactive Web Response System"
Allocation concealment	Low	"Randomization was performed using an Interactive Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial and no participants were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT01780714

Methods	**Date of registration:** 31/01/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (Poland) **Study start date; study end date:** June 2012; December 2012 **Intervention duration:** 5 days
Participants	**Number of participants:** 40 randomised (20 HTP, 20 CC), 0 withdrawn, 40 completed (20 HTP, 20 CC) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=40; Mean Age (SD): HTP 37.6 (9.0) years, CC 37.8 (8.3) years; Sex: 50% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.1), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Nicotine, Cotinine, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6

	activity, Human Puffing/Smoking Topography (inc. puff count), Adverse Events/Serious Adverse Events, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*randomized subjects who had record of at least one post-randomization product use and at least one valid biomarker assessment*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**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	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial 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.

ISRCTN88682435

Methods	**Date of registration:** 06/10/2015 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** 06/01/2015; 10/10/2015 **Intervention duration:** 2 sessions of 10 puffs at 20 sec intervals
Participants	**Number of participants:** 25 randomised, 1 withdrawn, 24 completed **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=25; Mean Age (SD): 33.1 (7.34) years; Sex: 52% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "good general health"; ≥10 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (HNB2.1), CC (Unknown) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Mouth level exposure to nicotine, Inhalation to non-inhalation ratios during HTP use, Nicotine
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Japan Tobacco International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias		
Bias	**Authors' judgement**	**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	Study described as "open label". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	Study described as "open label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: NHTP-CC=0%, CC-NHTP=8%. All 24 subjects who completed the study were included in the analyses.
Selective reporting	High	2 outcomes listed on the trial registration (mouth level exposure to nicotine and inhalation to non-inhalation ratios) were not reported.

Nga, 2020	
Methods	**Date of registration:** Not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Non-randomised quasi-experimental (Parallel) **Setting (Country):** Confined (Malaysia) **Study start date; study end date:** Not reported **Intervention duration:** 1 session of 2 10-puff rounds at 30 sec intervals and 5 min inter-round break
Participants	**Number of participants:** 45 enrolled (15 HTP, 15 CC, 15 EC), 0 withdrawn, 45 completed (15 HTP, 15 CC, 15 EC) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=45; Mean Age (SD): 43.6 years (SDs not reported); Sex: 87% male; Ethnicity/Nationality: 51% Chinese, 22% Malay, 20% Indian, 7% Other **Key inclusion criteria:** Health status: not specified; ≥10 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (IQOS), CC (Own brand), EC (Aspire AVP) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	International Medical University (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
Blinding of participants and personnel	Unclear	No information provided on blinding. Included a non-active comparator (cigarettes).
Blinding of outcome assessment	Low	No information provided on blinding. Primary outcome objectively measured.
Incomplete outcome data	Low	All participants enrolled completed the trial and no participants were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

Lopez, 2016

Methods	**Date of registration:** Not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (United States of America) **Study start date; study end date:** Not reported **Intervention duration:** 3 sessions of 2 10-puff bouts at 30 sec intervals and 60 min inter-bout break
Participants	**Number of participants:** 24 randomised, 9 withdrawn, 15 completed **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=15; Mean Age (SD): 33.6 (11.8) years; Sex: 80% male; Ethnicity/Nationality: 47% White or Caucasian, 40% Black or African American, 7% Asian, 7% unknown **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; unspecified smoking duration
Interventions	**Interventions:** HTP (PAX), CC (Own brand), EC (eGo) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide, Questionnaire of Smoking Urges, Nicotine, Minnesota Nicotine Withdrawal Scale, The Direct Effects of Nicotine Questionnaire, The Direct Effects of Product scale **Secondary:** Fagerström Test for Nicotine/Cigarette Dependence, Heart rate
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the U.S. Food and Drug Administration (Independent)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Participants completed each of the three, Latin-square ordered, ~2.5-h sessions"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	Unclear	No information provided on blinding. Included a non-active comparator (cigarettes).
Blinding of outcome assessment	High	No information provided on blinding. Some primary outcomes subjectively measured.
Incomplete outcome data	Low	Overall attrition = 37.5%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

ISRCTN81075760

Methods	**Date of registration:** 31/01/2018 **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Ambulatory (United Kingdom) **Study start date; study end date:** 15/02/2018; 31/03/2020 **Intervention duration:** 12-months (day 90 interim analysis)
Participants	**Number of participants:** 411 enrolled (Glo 105, CC 42, Cess 190, NS 40, THD 34) **Withdrawal reasons reported:** Unclear **Baseline characteristics:** N=280 (baseline characteristics for THD arm not reported); Mean Age (SD): Glo 39 (8.8) years, CC 38 (9.3) years, Cess 38 (9.0) years, NS 40 (9.9)

	years; Sex: 55% male; Ethnicity/Nationality: 90.7% White, 3.6% Asian, 2.5% Black or African American, 3.2% Other **Key inclusion criteria:** Health status: "good health"; 10-30 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (Glo1.1), CC (Own brand), smoking cessation (aided if necessary), NS, HTP (THD2.4T20) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Augmentation index, 8-epi-prostaglandin F2alpha, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol **Secondary:** 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Spirometry, 11-dehydrothromboxane B2, White blood cell count, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Triglycerides, Total cholesterol, N-(2-cyanoethyl)valine haemoglobin adducts, Pulse wave velocity, Peak Expiratory Flow, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Product Satisfaction Questionnaire, 4-Hydroxy-2-nonenal, Blood pressure, Tissue plasminogen activator, Plasminogen activator inhibitor-1, Nitric oxide, Monocyte chemotactic protein 1/C-C motif chemokine ligand 2, Glucose, E-selectin, Endothelin-1, 3-nitrotyrosine, Finger plethysmography, 6-minute walking test, Smoking cessation quality of life questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all subjects who had a valid assessment of a biomarker variable and completed the study (to day 90) according to the protocol. This population excludes subjects in Groups B and D who had major protocol deviations or a significant level of self-reported smoking*" and CEVal-compliant population defined as "*excludes subjects in Groups B and D who were considered noncompliant with smoking restrictions, based on CEVal levels above predetermined thresholds*" **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	The published data was from an interim analysis at day 90. Data for the full 12-months has not yet been published. The number of participants randomised/withdrawn/completed at Day 90 was only reported for one arm (THD2.4T20) in which all 34 randomised participants were excluded from the study without explanation. Included in meta-regression analysis. Data obtained from study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"randomised using blocks of computer-generated random number sequences"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"This study will not be blinded". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"This study will not be blinded". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	Number of subjects randomised, attrition and exclusions were not reported, neither were reasons for exclusion.
Selective reporting	High	The 90-day interim publication is the only reporting of results from this 12-month trial. In this publication, only a small selection of outcomes listed in the trial registration and protocol are reported, including only 1 primary outcome.

ISRCTN13439529	
Methods	**Date of registration:** 07/08/2018 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (Italy) **Study start date; study end date:** 01/01/2018; 30/09/2018 **Intervention duration:** 4 sessions of single use of one cigarette, tobacco stick or cartridge
Participants	**Number of participants:** 32 randomised, withdrawn/completed not reported **Withdrawal reasons reported:** N/A **Baseline characteristics:** N= 32; Mean Age (SD): 35.8 (9.66) years; Sex: 72% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: normal biochemistry, haematology, urinalysis, ECG and physical; ≥10 CPD; smoked for ≥ 1 year
Interventions	**Interventions:** HTP (Glo1.0), HTP (Glo1.1), CC (Own brand), NRT (Nicorette inhaler) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration, Intention to use [HTP] Questionnaire, Product Liking Questionnaire, Urge To Smoke questionnaire, Urge For Product questionnaire **Secondary:** Product Evaluation Scale, Human Puffing/Smoking Topography (inc. puff count), Adverse events
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"The order of use will be assigned by a pre-defined computer-generated randomisation schedule"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"open-label". Included non-active comparator.
Blinding of outcome assessment	High	"open-label". Some primary outcomes subjectively measured.
Incomplete outcome data	Unclear	While the number of participants randomised is reported, the number withdrawn/completed and included in the analysis was not reported.
Selective reporting	High	The two secondary outcomes (Puff count during 5 minute investigational product use session and Product evaluation using the Product Evaluation Scale (PES)) were not reported.

ISRCTN14301360/UMIN000024988	
Methods	**Date of registration:** 14/12/2016 (ISRCTN), 24/11/2016 (UMIN) **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 01/08/2016; 30/06/2017 **Intervention duration:** 5 days

Participants	**Number of participants:** 182 (30 Glo R, 30 Glo M, 30 CC R, 30 CC M, 30 Cess, 30 IQOS R, 2 unknown), 2 withdrawn (2 unknown), 180 completed (30 Glo R, 30 Glo M, 30 CC R, 30 CC M, 30 Cess, 30 IQOS R) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 180; Mean Age (SD): Glo R 34 (10.1) years, Glo M 31 (7.7) years, CC R 32 (8.2) years, CC M 33 (8.6) years, Cess 35 (10.0) years, IQOS R 33 (9.5) years; Sex: 50% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "good health"; 10-30CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (Glo 1.0 R), HTP (Glo 1.0 M), HTP (IQOS R), CC (Lucky Strike R), CC (Lucky Strike M), tobacco and nicotine cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine, N-acetyl-S-(2-carba-moylethyl)cysteine **Secondary:** Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Electrocardiogram, Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration, Spirometry, 8-epi-prostaglandin F2alpha, Human Puffing/Smoking Topography (inc. puff count), White blood cell count, Nicotine molar metabolic ratio, Product Satisfaction Questionnaire, Medical history, Adverse Events/Serious Adverse Events, Daily product consumption, Vital signs
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per protocol population defined as "*All subjects who had valid assessment of a biomarker variable and completed study according to the protocol will be used for biomarker analyses*" and pharmacokinetic population defined as "*All subjects who had sufficient data to calculate at least 1 pharmacokinetic parameter and completed study according to the protocol will be used for PK data analyses*". **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	2 participants were randomised but withdrew before the exposure period. The groups these 2 belonged to were not reported. Included in meta-regression analysis. Data obtained from published literature and study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"The randomisation will be performed by Covance"
Allocation concealment	Low	"The randomisation will be performed by Covance and the clinics will enrol the participants and assign them to interventions"
Blinding of participants and personnel	High	"open-label". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"open-label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Overall attrition = 1.1%. No subjects who completed the study were excluded from the primary analyses.
Selective reporting	High	There were several outcomes listed in the protocol, namely biomarkers of effect and pharmacokinetic measures, that were not reported on.

DRKS00012919

Methods	**Date of registration:** 29/08/2017

	Submitted to peer-reviewed journal within 12 months: Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (Germany) **Study start date; study end date:** 01/06/2016; not reported **Intervention duration:** 4 sessions of single use of one cigarette or tobacco stick at 1 puff every 30 secs for 10 puffs
Participants	**Number of participants:** 20 randomised, 0 withdrawn, 20 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N= 20; Mean Age (SD): 21.9 (2.6) years; Sex: 50% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: no disorders or diseases; CPD and smoking duration not reported
Interventions	**Interventions:** HTP (IQOS2.2), CC (Marlboro Gold), EC (eGo nicotine), EC (eGo no nicotine) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Nicotine, Systolic blood pressure **Secondary:** Heart rate, Pulse wave velocity, Augmentation index, [Mean] Arterial Blood Pressure
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Universitätsklinikum Schleswig-Holstein Campus Lübeck (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**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	Only the e-cigarette arms were blinded. Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	Only the e-cigarette arms were blinded. All primary outcomes objectively measured.
Incomplete outcome data	Unclear	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.
Selective reporting	High	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.

ISRCTN80651909

Methods	**Date of registration:** 09/03/2017 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** 01/08/2016; 03/10/2017 **Intervention duration:** 5 days
Participants	**Number of participants:** 148 randomised (30 Glo, 30 CC, 30 EC, 29 Cess, 29 HTP), 7 withdrawn (2 Glo, 2 EC, 2 Cess, 1 HTP), 143 (28 Glo, 30 CC, 28 EC, 29 Cess, 28 HTP) **Withdrawal reasons reported:** Yes

	Baseline characteristics: N= 148; Mean Age (SD): Glo 37.4 (11.48) years, CC 35.6 (8.93) years, EC 36.7 (9.1) years, Cess 37.2 (9.09) years, HTP (32.8 (8.78) years; Sex: 59% male; Ethnicity/Nationality: 100% White **Key inclusion criteria:** Health status: "good health"; 10-30CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (Glo1.0), CC (Lucky Strike Regular), EC (prototype IS1.0[TT]), tobacco and nicotine cessation, HTP (unknown) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid , total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine, N-acetyl-S-(2-carba-moylethyl)cysteine, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, 8-epi-prostaglandin F2alpha, White blood cell count, Nicotine molar metabolic ratio **Secondary:** Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration, Spirometry, Product Satisfaction Questionnaire, Adverse Events/Serious Adverse Events, Daily product consumption
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	According to the published study literature, 29 participants were randomised to the cessation and 29 completed this study, yet 2 were said to have withdrawn. It is not clear if these 2 were replaced or if this was a mistake. Data from the unknown HTP arm was excluded from the analysis because the authors "*wished to focus on the exposure continuum*". Included in meta-regression analysis. Data obtained from published literature and study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"The randomization will be computer-generated using SAS Version 9.3"
Allocation concealment	Low	"A randomisation scheme was provided for the clinical site to recruit 30 participants for each arm, giving a total of 150 participants"
Blinding of participants and personnel	High	"open-label". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"open-label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: Glo=6.67% CC=0% EC=6.67% Cess=0% HTP=3.45%, overall=3.38%. Exclusion: Glo=6.67% CC=0% EC=6.67% Cess=0% HTP=N/A, overall=3.34%.
Selective reporting	High	No data reported for an entire study arm (C: "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

UMIN000041539

Methods	**Date of registration:** 25/08/2020 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (Japan)

	Study start date; study end date: September 2020; October 2020 **Intervention duration:** 5 days
Participants	**Number of participants:** 90 randomised (15 Ploom Tech+, 15 Ploom S2.0, 15 unknown HTP, 15 unknown HTP, 15 CC, 15 Cess), withdrawn/completed not reported **Withdrawal reasons reported:** N/A **Baseline characteristics:** not reported **Key inclusion criteria:** Health status: "good health"; unspecified CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (Ploom Tech+), HTP (Ploom S2.0), HTP (unknown), HTP (unknown), CC (Own brand), smoking cessation **Co-interventions:** None **Mode of exposure:** Unclear
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, 3-hydroxybenzo[a]pyrene, 1-aminonaphthalene **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Japan Tobacco International (Industry-affiliated)
Notes	Data requested from study authors, but no data received. Therefore, not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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	"Open -no one is blinded". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Open -no one is blinded". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	While the number of participants randomised was reported, the number completed and included in the analysis was not.
Selective reporting	Unclear	As the trial registration does not explicitly list all outcomes measured in this trial and there is no publicly available protocol, it is difficult to determine whether the 15 biomarkers of exposure were the only measures of the study. Moreover, data is thus far only presented in a graph.

NCT03700112

Methods	**Date of registration:** 09/10/2018 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (New Zealand) **Study start date; study end date:** 04/12/2018; 09/04/2019 **Intervention duration:** 8 sessions of 10 puffs at 30 second intervals and 8 sessions of *ad lib* use for 4.5 minutes
Participants	**Number of participants:** 25 randomised, 0 withdrawn, 25 completed **Withdrawal reasons reported:** N/A

	Baseline characteristics: N= 25; Mean Age (SD): 30.44 (10.18) years; Sex: 72% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥8 CPD; smoked for ≥1 year
Interventions	**Interventions:** EC (JUUL), EC (myblu Original 2.4%), EC (MarkTen Bold Classic 4.0%), EC (VUSE Solo Original 4.8%), EC (PHIX Original Tobacco 5.0%), EC (NJOY Daily EXTRA Rich Tobacco 6.0%), HTP (IQOS), CC (Marlboro Red) **Co-interventions:** None **Mode of exposure:** Direct restricted and *ad libitum*
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Baseline adjusted Cmax, Baseline adjusted AUC1hour, Area under the concentration curve from start of product use to 60 minutes **Secondary:** Exhaled Carbon monoxide, Modified Cigarette/Product Evaluation Questionnaire, Human Puffing/Smoking Topography (inc. puff count), Rate of plasma nicotine rise (speed of absorption)
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	JUUL Labs Inc. (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	Attrition was 0%. Exclusion=0-8% as the analysis population stated under the tables on poster was "N=24-25" or "N=23-25". However, the exact N for each outcome analysis is not specified and reasons for excluding some subjects from the analyses are not provided.
Selective reporting	High	Total number of puffs during exposure session and exhaled CO - both measures listed on the trial registration - were not reported.

NCT01970995

Methods	**Date of registration:** 28/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined and Ambulatory (Japan) **Study start date; study end date:** 01/08/2013; November 2014 **Intervention duration:** 90 Days (5 days confinement + 85 days ambulatory)
Participants	**Number of participants:** 160 randomised (78 HTP, 42 CC, 40 Cess), 5 withdrawn (2 HTP, 1 CC, 2 Cess), 155 (76 HTP, 41 CC, 38 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 37.1 (10.58) years, CC 37.4 (11.23) years, Cess 37 (9.96) years; Sex: 57.5% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), smoking cessation (aided if necessary) **Co-interventions:** None

	Mode of exposure: Direct restricted and *ad libitum*
Outcomes	**Primary:** Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), White blood cell count, Systolic blood pressure, Soluble intercellular adhesion molecule-1. High-density lipoprotein cholesterol, Diastolic blood pressure, Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Potential combustion occurances in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire, Triglycerides Total cholesterol, Blood glucose
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all randomized subjects who - have had compliance to their randomized arm if randomized to THS 2.2 Menthol or SA arms. Non-compliance will be defined over a period (confinement period,] Day6-Day 30 Visit],]Day 30 Visit-Day 60 Visit],]Day 60 Visit-Day 90 Visit] and will be defined as having smoked than 3 CC during a single day in that period or having smoked on average over that period more that, not including 0.5 cigarettes per day. - have not been misrandomized. - and have no major protocol deviation*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**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 personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	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%.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01989156

Methods	**Date of registration:** 20/11/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined and Ambulatory (United States of America) **Study start date; study end date:** 17/12/2013; May 2015

	Intervention duration: 91 Days (5 days confinement + 86 days ambulatory)
Participants	**Number of participants:** 160 (80 HTP, 41 CC, 39 Cess), 21 withdrawn (7 HTP, 6 CC, 8 Cess), 139 completed (73 HTP, 35 CC, 31 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 39.2 (11.72) years, CC 33.7 (10.17) years, Cess 38.8 (11.42) years; Sex: 60% male; Ethnicity/Nationality: 62% White, 32% Black or African American, 6% other, 1% missing **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), smoking cessation (aided if necessary) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, 2-cyanoethylmercapturic acid , Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), White blood cell count, Systolic blood pressure, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second, Diastolic blood pressure, Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Potential combustion occurances in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire, Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Triglycerides, Total cholesterol, Apolipoprotein B, Apolipoprotein A1, Total lung capacity, Blood glucose, Residual volume, Vital capacity, Inspiratory capacity, Diffusion Capacity, Carbon monoxide transfer coefficient, Oxysterols (6α-hydroxy-5α-cholestanol, 7α-hydroxycholesterol, 5α,6αepoxycholestanol, 7-ketocholesterol, 7β-hydroxycholesterol, 5β,6β-epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 22(R)-hydroxycholesterol, 4ßhydroxycholesterol, and 27-hydroxycholesterol), Prochaska "Stage of Change" Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all randomized subjects who: Have had compliance to their randomized arm; Have not been misrandomized; and Have no major protocol deviation*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
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". Included non-active comparator (cigarettes).
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	
Methods	**Date of registration:** 28/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 23/07/2013; July 2014 **Intervention duration:** 5 days
Participants	**Number of participants:** 160 randomised (80 HTP, 40 CC, 40 Cess), 2 withdrawn (2 Cess), 158 completed (80 HTP, 40 CC, 38 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 37.6 (11.7) years, CC 37.2 (11.7) years, Cess 35.9 (10.6) years; Sex: 50% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), tobacco and nicotine cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Potential combustion occurrences in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*all the randomized subjects who had at least one post-randomization product use experience, if randomized to THS 2.2 or CC, and have at least one valid nonsafety assessment*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Data requested from study authors, but no data received. Therefore, not included in meta-regression analysis.

Risk of bias		
Bias	**Authors' judgement**	**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)". Included non-active comparator (cigarettes).
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	
Methods	**Date of registration:** 10/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined (Poland) **Study start date; study end date:** 29/06/2013; June 2014 **Intervention duration:** 5 days
Participants	**Number of participants:** 160 randomised (80 HTP, 41 CC, 39 Cess), 2 withdrawn (1 HTP), 158 completed (79 HTP, 41 CC, 39 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 35.4 (9.4) years CC 32.6 (10.06) years, Cess 33.6 (11.51) years; Sex: 50% male; Ethnicity/Nationality: 100% White **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), tobacco and nicotine cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Potential combustion occurances in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*all randomized participants who used the allocated product at least once after randomization and with at least one valid value for a biomarker of exposure*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Data requested from study authors, but no data received. Therefore, not included in meta-regression analysis.
Risk of bias	

Bias	Authors' judgement	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)". Included non-active comparator (cigarettes).
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 study were included in the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01959607

Methods	**Date of registration:** 10/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 31/07/2013; April 2014 **Intervention duration:** 2 sessions of 14 puffs (6 minutes)
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 2 withdrawn (2 HTP/CC), 60 completed (42 HTP/CC, 18 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 60; Mean Age (SD): HTP/CC 33.2 (8.61) years, HTP/NRT 35.8 (10.44) years; Sex: 55% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), NRT (Nicorette gum) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all randomised subjects who gave informed consent, completed at least 1 of the single-use days (Day 1 or 3), and for whom at least 1 PK parameter was derived. Subjects with major protocol deviations that impacted the evaluability of the results were excluded from the PK analysis sets*." **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System."

Allocation concealment	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System."
Blinding of participants and personnel	High	"This was an open-label study". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"This was an open-label study". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS-CC=5%, IQOS-NRT=0%. No participants who completed the trial were excluded from the analyses.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01967732	
Methods	**Date of registration:** 23/10/2013 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** 01/11/2013; July 2014 **Intervention duration:** 2 sessions of single use of one cigarette, tobacco stick or 1 nasal spray in each nostril
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 2 withdrawn (2 HTP/CC), 60 completed (42 HTP/CC, 18 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 60; Mean Age (SD): HTP/CC 32.1 (8.98) years, HTP/NRT 30.6 (5.8) years; Sex: 58% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), NRT (Nicotrol nasal spray) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization to product exposure sequence was performed through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to product exposure sequence was performed through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).

Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS/CC=4.55% IQOS/NRT=5.56%, overall=4.84%. Exclusion: IQOS/CC=6.81% IQOS/NRT=5.5%, overall=6.45%.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01967719	
Methods	**Date of registration:** 23/10/2013 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (United States of America) **Study start date; study end date:** 02/10/2013; May 2014 **Intervention duration:** 2 sessions of single use of one cigarette, tobacco stick or 1 nasal spray in each nostril
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 3 withdrawn (2 HTP/CC, 1 HTP/NRT), 60 completed (42 HTP/CC, 17 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 62; Mean Age (SD): HTP/CC 37.2 (10.2) years, HTP/NRT 33.1 (7.3) years; Sex: 53% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), NRT (Nicotrol nasal spray) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Cotinine, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations will be included in the PK analysis sets*." **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS/CC=4.55% IQOS/NRT=0%, overall=3.23%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.

Gee et al., 2018 (Actual Use Study)	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Actual use study. **Setting (Country):** Confined and Ambulatory (Japan) **Study start date; study end date:** not reported **Intervention duration:** Group 1 = 13 days, Groups 2 and 3 = 9 days, Group 4 = 1 day
Participants	**Number of participants:** 208 (52 Group 1, 52 Group 2, 52 Group 3, 52 Group 4) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=208; Age, n participants: 21-29=58, 30-44=109, 45-65=40; Sex: 52% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: not specified; smokers ≥5 CPD, smoked for ≥6 months; THS users ≥5 product use sessions per day, using for ≥3 months
Interventions	**Interventions:** Group 1 (smokers): CC (T189 R), HTP (Glo1.0 R), HTP (IQOS R) Group 2 (smokers): CC (322 M), HTP (Glo1.0 M) Group 3 (THS users): HTP (Glo1.0 R), HTP (IQOS R) Group 4 (smokers): HTP (Glo1.0 R) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Puffing topography, Mouth level exposure to nicotine free dry particulate matter, nicotine and menthol, Daily product consumption, Mouth insertion depth **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. Non-active (CC) comparator.
Blinding of outcome assessment	High	No information is provided in the text regarding blinding. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	Number of participants enrolled, completed and withdrawn was not reported.
Selective reporting	Low	All outcomes listed in methods were reported on in the main results.

Jones et al., 2020 (Actual Use Study)	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Actual use study. **Setting (Country):** Confined and Ambulatory (Italy) **Study start date; study end date:** not reported **Intervention duration:** Group 1 = 15 days, Group 2 = 10 days, Group 3 = 5 days
Participants	**Number of participants:** 152 (50 Group 1, 50 Group 2, 52 Group 3)

	Withdrawal reasons reported: N/A **Baseline characteristics:** N=152; Age, n participants: 25-29=21, 30-44=67, 45-65=64; Sex: 50% male; Ethnicity/Nationality: 100% Italian **Key inclusion criteria:** Health status: not specified; smokers ≥8 CPD, smoked for ≥7 years; vapers ≥1 product use per day, using for ≥6 months
Interventions	**Interventions:** Group 1 (smokers): EC (IS1.0[T]), HTP (IQOS2.4), CC (C651) Group 2 (vapers): EC (Is1.0[T]) Group 3 (smokers): HTP (Glo1.0), CC (C651) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Puffing topography, Mouth level exposure to nicotine free dry particulate matter and nicotine, Daily product consumption, Sensory questionnaire **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
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	High	No information is provided in the text regarding blinding. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	Number of participants enrolled, completed and withdrawn was not reported.
Selective reporting	Low	All outcomes listed in methods were reported on in the main results.

Dalrymple, 2022

Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** repeated measures **Setting (Country):** Confined (Germany) **Study start date; study end date:** not reported **Intervention duration:** 3 sessions of 32 puffs of Glo, ePen 3 or N491 cigarette
Participants	**Number of participants:** 10 enrolled, 0 withdrawn, 10 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=10; Age, n participants: 52.8; Sex: 30% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; non-smokers
Interventions	**Interventions:** HTP (Glo), CC (N491), EC (ePen 3) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Malondialdehyde; Catalase; Squalene; Squalene monohydroperoxide; Squalene monohydroperoxide/Squalene ratio; L* (lightness); a* (green-red); b* (blue-yellow); Total difference in colour from control (ΔE) **Secondary:** Adverse Events/Serious Adverse Events
Analyses	**Sample size calculation reported:** No

	Primary analysis population: Not specified or unclear **Unit of analysis:** areas of skin
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	N/A	Cochrane RoB tools designed to assess trials in which the unit of randomisation is people, rather than multiple sites on one individual, selection bias cannot be fairly assessed using this tool on this study.
Allocation concealment	N/A	
Blinding of participants and personnel	Unclear	There is insufficient information 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, but all primary outcomes objectively measured.
Incomplete outcome data	Low	All participants completed the study and none withdrew.
Selective reporting	Low	All outcomes were reported on.

NCT03452124

Methods	**Date of registration:** 02/03/2018 **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Randomised controlled crossover followed by case control study **Setting (Country):** Confined and ambulatory (Greece) **Study start date; study end date:** 30/03/2018; not reported **Intervention duration:** acute: 3x 7 minute sessions of sham cigarette, IQOS or cigarette Chronic: 1 month
Participants	**Number of participants:** acute: 50 randomised, 0 withdrawn, 50 completed Chronic: 25 enrolled, 0 withdrawn, 25 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=75; Age, n participants: 48 (acute) 26 (chronic); Sex: 48% (acute & chronic) male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; smokers ≥5 CPD
Interventions	**Interventions:** Acute: HTP (IQOS), CC (Marlboro Red), sham cigarette Chronic: HTPs (IQOS), CC (unknown brand) **Co-interventions:** None **Mode of exposure:** Direct ad libitum
Outcomes	**Primary:** Pulse wave velocity; Exhaled Carbon Monoxide; Perfused boundary region of sublinqual arterial microvessels; Global longitudinal strain of left ventricle; Coronary flow reserve **Secondary:** 11-dehydrothromboxane B2; Systolic blood pressure; Central Systolic blood pressure; Heart rate; Diastolic blood pressure; Protein carbonyls; Malondialdehyde; Myocardial work; Total arterial compliance; Augmentation index; Vital signs; Electrocardiogram; High-sensitivity C-reactive protein; Transforming growth factor-b; lipoprotein associated phospholipase A2; Tumor necrosis factor-a; Interleukin 6; Interleukin 10; Procollagen propeptide type III; Matrix metalloproteinase 2; Matrix metalloproteinase 9; Macrophage-colony stimulating factor; Flow-mediated dilation
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	National and Kapodistrian University of Athens (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization was performed by an attending research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm"
Allocation concealment	Unclear	There is insufficient information provided to determine whether intervention allocation was concealed
Blinding of participants and personnel	Unclear	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.
Blinding of outcome assessment	Low	"examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures.
Incomplete outcome data	Low	All participants completed the study and none withdrew.
Selective reporting	High	Not all outcomes measured were reported on.

Iokeimidis, 2021

Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** Randomised controlled crossover **Setting (Country):** Confined (Greece) **Study start date; study end date:** note reported; not reported **Intervention duration:** 3 sessions of 5 minutes use of IQOS, cigarette or cham cigarette
Participants	**Number of participants:** 22 randomised, 0 withdrawn, 22 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=22; Age, n participants: 33, n=22; Sex: 45% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; smoking history criteria not defined
Interventions	**Interventions:** HTP (IQOS), CC (unknown brand), sham cigarette **Co-interventions:** none **Mode of exposure:** direct ad libitum
Outcomes	**Primary:** Heart rate; Brachial systolic blood pressure; Aortic systolic blood pressure; Augmentation index; Carotid–femoral pulse wave velocity; Brachial-ankle pulse wave velocity **Secondary:** none
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** not specified or unclear **Unit of analysis:** individuals
Study funding	Athens Medical School, Hippokration Hospital (ndependent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear	Whether or how participants were randomised is unclear.
Allocation concealment	Unclear	How interventions were allocated is not described.
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 objectively measured.
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	Low	Results data for all outcomes were reported.

Yaman, 2021	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** randomised controlled crossover **Setting (Country):** confined (Cyprus) **Study start date; study end date:** Not reported; not reported **Intervention duration:** 3 sessions of 5 minutes use of IQOS or cigarettes
Participants	**Number of participants:** 27 randomised, 0 withdrawn, 27 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=27; Age, n participants: 39.2, n=27; Sex: 59% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; smoking history criteria not reported
Interventions	**Interventions:** HTP (IQOS), CC (own brand) **Co-interventions:** none **Mode of exposure:** Direct restricted
Outcomes	**Primary:** A wave velocity; Diastolic blood pressure; E wave velocity; E/A ratio; Em/Am ratio; Heart rate; Left atrium diameter; Left ventricle ejection fraction; Left ventricle global circumferential strain; Left ventricle global longitudinal strain; Left ventricular end-diastolic diameter; Peak early diastolic velocity of the left ventricle; Peak late diastolic velocity of the left ventricle; Right atrium diameter; Right ventricle diameter; Right ventricle free wall strain; Right ventricle global longitudinal strain; Right ventricle peak early diastolic velocity; Right ventricle peak late diastolic velocity; Right ventricle systolic myocardial velocity; Right ventricle Em/Am ratio; Systolic blood pressure; Systolic myocardial velocity of the left ventricle; Tricuspid annular plane systolic excursion **Secondary:** none
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** individuals
Study funding	Near East University and Mersin City Training and Research Hospital (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Despite explaining the subjects were randomised, the sequence generation was not described in any of the study literature.
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	Low	All outcomes were reported on.

Phillips-Waller, 2021	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** Non-randomised controlled crossover **Setting (Country):** confined (UK) **Study start date; study end date:** not reported; not reported

	Intervention duration: 5 sessions of single use of IQOS, cigarette, JUUL, KangerTech EVOD, Innokin iTaste MVP 2
Participants	**Number of participants:** 22 enrolled, 0 withdrawn, 22 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=22; Age, n participants: 31, n=22; Sex: 82% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "No serious illnesses"; smokers & vapers <1 CPD
Interventions	**Interventions:** HTPS (IQOS), CC (own brand), EC (JUUL, KangerTech EVOD, Innokin iTaste MVP 2) **Co-interventions:** none **Mode of exposure:** direct ad libitum
Outcomes	**Primary:** Human Puffing/Smoking Topography (inc. puff count); Maximal nicotine concentration; Time to reach nicotine Cmax; Area under the concentration curve from start of product use to 30 minutes; Nicotine; Nicotine boost effect; Urge To Smoke questionnaire; Non-standard questionnaire on user experience **Secondary:** none
Analyses	**Sample size calculation reported:** no **Primary analysis population:** not specified or unclear **Unit of analysis:** individuals
Study funding	Tobacco Advisory Group project grant, Cancer Research UK (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial
Allocation concealment	High	Non-randomised trial
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	High	No information is provided in the text regarding blinding. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	The authors state they "studied 22 current smokers" but it is unclear whether more than 22 were initially enrolled.
Selective reporting	Low	All outcomes were reported on.

Abbreviations: HTP=heated tobacco product; CC=combustible cigarette; EC=electronic cigarette; Cess=cessation; NS=non-smoker; NRT=nicotine replacement therapy; R=regular, M=menthol; CPD=cigarettes per day

Supplementary Table 2. Outcomes measured and reported in heated tobacco product interventional trials.

Outcome	Number of trials (measured)	Number of trials (reported)
Biomarkers of exposure		
Exhaled Carbon monoxide	26	21
2-cyanoethylmercapturic acid	14	14
Nicotine	14	11
Nicotine equivalents (molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide)	14	13
total N-nitrosonornicotine	14	13
3-hydroxypropylmercapturic acid	13	13

monohydroxybutenylmercapturic acid	13	13
S-phenylmercapturic acid	13	12
total 1-hydroxypyrene	13	13
2-aminonaphthalene	12	12
4-aminobiphenyl	12	12
o-toluidine	12	12
2-hydroxyethylmercapturic acid	11	11
3-hydroxy-1-methylpropylmercapturic acid	11	11
Cotinine	10	8
3-hydroxybenzo[a]pyrene	9	9
1-aminonaphthalene	8	8
Cytochrome P450 2A6 activity	8	7
Ames mutagenicity test (YG1024+S9)	6	6
S-benzylmercepturic acid	4	4
N-acetyl-S-(2-carba-moylethyl)cysteine	2	2
N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine	2	2
4-hydroxybutyl-2-mercapturic acid	1	1
Cotinine	1	1
N-(2-cyanoethyl)valine haemoglobin adducts	1	1
Carboxyhemoglobin*	14	13
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol*	15	15
Biomarkers of potential harm		
11-dehydrothromboxane B2	10	10
8-epi-prostaglandin F2alpha	9	9
Systolic blood pressure	8	8
White blood cell count	8	7
Diastolic blood pressure	7	7
Heart rate	7	5
High-sensitivity C-reactive protein	7	5
Fibrinogen	6	4
Forced expiratory flow at 25–75% of forced vital capacity (aka Maximal mid-expiratory flow)	6	3
Forced expiratory volume in one second	6	6
Forced vital capacity	6	3
High-density lipoprotein cholesterol	6	6
Homocysteine	6	4
Low-density lipoprotein cholesterol	6	4
Soluble intercellular adhesion molecule-1	6	6
Waist circumference	6	4
Weight	6	4
Hemoglobin glycosylated (Hemoglobin A1C)	5	4
Platelet count	5	4
Apolipoprotein A1	4	3
Apolipoprotein B	4	3
Augmentation index	4	2

Forced expiratory volume in one second/forced vital capacity	4	2
Total cholesterol	4	3
Total lung capacity	4	3
Triglycerides	4	3
Blood glucose	3	3
Blood pressure	3	0
Functional residual capacity	3	2
Inspiratory capacity	3	2
Myeloperoxidase	3	2
Pulse wave velocity	3	2
Residual volume	3	3
Vital capacity	3	2
[Mean] Arterial Blood Pressure	2	1
4-Hydroxy-2-nonenal	2	0
Albumin	2	1
bronchodilator reversibility in FEV1	2	1
Carbon monoxide transfer coefficient	2	2
Diffusion Capacity	2	2
Flow-mediated dilation	2	2
Malondialdehyde	2	2
Peak Expiratory Flow	2	1
3-nitrotyrosine	1	0
8-Hydroxy-2’-deoxyguanosine	1	1
8-iso-prostaglandin F2alpha	1	1
A wave velocity	1	1
Aortic systolic blood pressure	1	1
Brachial systolic blood pressure	1	1
Brachial-ankle pulse wave velocity	1	1
Carotid–femoral pulse wave velocity	1	1
Catalase	1	1
Central Systolic blood pressure	1	1
change in bleedng on probing scores	1	1
change in gingival inflammation (GI) score	1	1
Change in mean full-mouth CAL	1	1
change in mean full-mouth PD	1	1
change in plaque control record	1	1
change in the number of sites with PD<4 mm, 4-5mm, 5-6 mm, 6-7 mm, and ≥7 mm	1	1
change in tooth mobility (grade)	1	1
Coronary flow reserve	1	1
E wave velocity	1	1
E/A ratio	1	1
Em/Am ratio	1	1
Endothelin-1	1	0
E-selectin	1	0

Expiratory reserve volume	1	1
Forced expiratory flow at X%	1	1
Global longitudinal strain of left ventricle	1	1
Glucose	1	0
H2O2 breakdown activity	1	1
H2O2 production	1	1
Interleukin 10	1	0
Interleukin 6	1	0
Left atrium diameter	1	1
Left ventricle ejection fraction	1	1
Left ventricle global circumferential strain	1	1
Left ventricle global longitudinal strain	1	1
Left ventricular end-diastolic diameter	1	1
lipoprotein associated phospholipase A2	1	0
Macrophage-colony stimulating factor	1	0
Matrix metalloproteinase 2	1	0
Matrix metalloproteinase 9	1	0
mean CAL change in sites with initial PD<4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7mm	1	1
Mean clinical attachment level (CAL) change in sites with initial PD≥4mm after mechanical periodontal therapy	1	1
mean PD change in sites with initial PD<4mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7 mm	1	1
Mean PD change in sites with initial PD≥4 mm after mechanical periodontal therapy	1	1
Mean Periodontal Pocket Depth (PD) reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy	1	1
Microbiological status	1	0
Monocyte chemotactic protein 1/C-C motif chemokine ligand 2	1	0
Myocardial work	1	1
Nitric oxide	1	1
nitric oxide bioavailability	1	1
Oxygen Saturation	1	1
Peak early diastolic velocity of the left ventricle	1	1
Peak late diastolic velocity of the left ventricle	1	1
Perfused boundary region of sublinqual arterial microvessels	1	0
Plasminogen activator inhibitor-1	1	0
Procollagen propeptide type III	1	0
Pro-inflammatory and immuno-regulatory mediators (sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α)	1	0
Protein carbonyls	1	1
Respiratory impedance	1	1
Right atrium diameter	1	1

Right ventricle diameter	1	1
Right ventricle Em/Am ratio	1	1
Right ventricle free wall strain	1	1
Right ventricle global longitudinal strain	1	1
Right ventricle peak early diastolic velocity	1	1
Right ventricle peak late diastolic velocity	1	1
Right ventricle systolic myocardial velocity	1	1
Soluble CD40 ligand	1	1
Soluble Nox2-derived peptide	1	1
Soluble P-selectin	1	1
Squalene	1	1
Squalene monohydroperoxide	1	1
Squalene monohydroperoxide/Squalene ratio	1	1
Systolic myocardial velocity of the left ventricle	1	1
Tissue plasminogen activator	1	0
Total anti-oxidant capacity	1	1
Total arterial compliance	1	1
Total respiratory resistances	1	1
Transforming growth factor-b	1	0
Tricuspid annular plane systolic excursion	1	1
Tumor necrosis factor-a	1	0
Vitamin E	1	1
Pharmacokinetic outcomes		
Time to reach nicotine Cmax	13	10
Maximal nicotine concentration	12	10
Area under the concentration curve from start of product use to time of last quantifiable concentration	11	9
Terminal half-life of nicotine	8	7
Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity	6	5
Maximum observed nicotine concentration (following ad lib use)	5	5
Partial AUC	5	4
Time to nicotine Cpeak	5	5
Weighted average nicotine concentration over 24 hours	4	4
Nicotine molar metabolic ratio	2	1
Area under the concentration curve from start of product use to 60 minutes	1	0
Area under the concentration curve from start of product use to 60 minutes	1	1
AUC from start of product use up to 12 hours	1	0
Baseline adjusted AUC1hour	1	1
Baseline adjusted Cmax	1	1
Lowest observed plasma concentration during the same sampling interval in which Cpeak was observed	1	1
Nicotine boost effect	1	1
Rate of plasma nicotine rise (speed of absorption)	1	1
Questionnaires/Subjective effects		
Modified Cigarette/Product Evaluation Questionnaire	18	14
Questionnaire of Smoking Urges	17	14
Fagerström Test for Nicotine/Cigarette Dependence	14	12
Minnesota Nicotine Withdrawal Scale	10	8
Human Puffing/Smoking Topography Questionnaire	5	4

Intention to use [HTP] Questionnaire	4	2
Product Satisfaction Questionnaire	4	1
Prochaska “Stage of Change” Questionnaire	2	1
Product Liking Questionnaire	2	2
The Direct Effects of Nicotine Questionnaire	2	2
Urge To Smoke questionnaire	2	2
A visual analogue scale (VAS) assessing cigarette craving	1	1
Inhalation to non-inhalation ratios during HTP use	1	0
Product Evaluation Scale	1	0
Product preferene	1	1
Questionnaire (Other)	1	1
Sensory questionnaire	1	1
Smoking cessation quality of life questionnaire	1	0
The Direct Effects of Product scale	1	1
Urge For Product questionnaire	1	1
Safety Profile		
Adverse Events/Serious Adverse Events	23	23
Vital signs	19	11
Clinical chemistry, hematology and urine analysis safety panel	18	10
Physical examination	18	10
Electrocardiogram	16	10
Respiratory symptoms (inc. cough assessment)	16	11
Spirometry	14	9
Concomitant medications	13	9
Medical history	1	0
Other outcomes		
Daily product consumption	16	14
Human Puffing/Smoking Topography (inc. puff count)	13	10
Mouth level exposure to nicotine	4	3
Potential combustion occurances in tobacco plugs	4	4
Mouth level exposure to NFDPM	2	2
6-minute walking test	1	0
a* (green-red)	1	1
b* (blue-yellow)	1	1
Finger plethysmography	1	0
Full transcriptomics profile	1	0
L* (lightness)	1	1
Mouth insertion depth	1	1
Mouth level exposure to menthol	1	1
Oxysterols (6α-hydroxy-5α-cholestanol, 7α-hydroxycholesterol, 5α,6αepoxycholestanol, 7-ketocholesterol, 7β-hydroxycholesterol, 5β,6β-epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 22(R)-hydroxycholesterol, 4ßhydroxycholesterol, and 27-hydroxycholesterol)	1	1
Total difference in colour from control (ΔE)	1	1

*Also measured as biomarkers of potential harm in one study

Supplementary Table 3. Direction of effect in primary outcomes compared between heated tobacco and cigarette arms.

Trial ID	Primary Outcome(s)	Time point	Data	EoE between group difference*
UMIN000017297	Time to reach nicotine Cmax (min)	N/A	PNTV (median, range): 3.83, 2.83-7.83) CC (median, range): 3.83, 2.83-4.83	↔ (Positive)
	Maximal nicotine concentration (ng/mL)	N/A	PNTV (mean, 95% CI): 5.39, 4.34;6.69 CC (mean, 95% CI): 11.8, 9.49;14.6	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	PNTV (mean, 95% CI): 4.12, 3.43;4.95 CC (mean, 95% CI): 6.03, 5.02;7.25	↓ (Negative)
UMIN000025777	3-hydroxypropylmercapturic acid (ug/24hr)	Day 5	NTV=484 ± 256 CC=1579 ± 696	↓ (Positive)
	2-cyanoethylmercapturic acid (ug/24hr)	Day 5	NTV=12.4 ± 6.6 CC=118.1 ± 64.7	↓ (Positive)
	4-aminobiphenyl (ng/24hr)	Day 5	NTV=1.8 ± 1.0 CC=12.3 ± 5.7	↓ (Positive)
	1-aminonaphthalene (ng/24hr)	Day 5	NTV=5.7 ± 3.2 CC=93.6 ± 45.8	↓ (Positive)
	2-aminonaphthalene (ng/24hr)	Day 5	NTV=2.5 ± 0.8 CC=26.3 ± 12.2	↓ (Positive)
	S-phenylmercapturic acid (ng/24hr)	Day 5	NTV=276 ± 102 CC=2741 ± 1939	↓ (Positive)
	3-hydroxybenzo[a]pyrene (pg/24hr)	Day 5	NTV=48.7 ± 29.5 CC=156.3 ± 82.2	↓ (Positive)
	monohydroxybutenylmercapturic acid (ng/24hr)	Day 5	NTV=219 ± 85 CC=1921 ± 1588	↓ (Positive)
	Exhaled Carbon Monoxide (ppm)	Day 5	NTV=3.7 ± 1.8 CC=25.6 ± 10.6	↓ (Positive)
	4-hydroxybutyl-2-mercapturic acid (ug/24hr)	Day 5	NTV=75.7 ± 22.0 CC=346.3 ± 160.9	↓ (Positive)
	2-hydroxyethylmercapturic acid (ng/24hr)	Day 5	NTV=844 ± 364 CC=3023 ± 2252	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24hr)	Day 5	NTV=41.5 ± 30.3 CC=116.6 ± 75.1	↓ (Positive)

	Total N-nitrosonornicotine (pg/24hr)	Day 5	NTV=955 ± 604 CC=4986 ± 6644	↓ (Positive)
	o-Toluidine (ng/24hr)	Day 5	NTV=50.8 ± 20.2 CC=154.0 ± 41.0	↓ (Positive)
	Total 1-hydroxypyrene (ng/24hr)	Day 5	NTV=208.7 ± 89.0 CC=332.4 ± 135.1	↓ (Positive)
	Nicotine equivalents (mg/24hr)	Day 5	NTV=5.0 ± 3.0 CC=10.5 ± 4.8	↓ (Negative)
Caponnetto , 2018	Exhaled Carbon monoxide (ppm)	45 mins	Specific quantitative data was not provided, however based on the graph provided eCO was substantially lower in the HTP arms compared to the CC arm at all time points past baseline, with no overlapping error bars. Moreover, "repeated-measures ANOVA post-hoc comparisons showed significant differences between-product effect (iQOS/GLO vs own brand cigarette; P < 0.0001"	↓ (Positive)
aspredicted.org #6896	Exhaled Carbon monoxide (ppm)	55 mins	IQOS(mean, SE)=3.07, 0.32 CC(mean, SE)=6.47, 0.41	↓ (Positive)
	Modified Cigarette/Product Evaluation Questionnaire	5 mins	All subscales of the mCEQ (“Smoking satisfaction”, “Psychological reward”, “Aversion”, “Enjoyment of respiratory tract sensations”, and “Craving reduction”) were rated lower for the IQOSTM than for the tobacco cigarette.	↓ (Negative)
	Questionnaire of Smoking Urges	55 mins	"At T1 and T5, smoking resulted in lower craving scores compared to vaping (all ps < 0.01) and compared to using the IQOSTM (all ps < 0.01)"	↑ (Negative)
	Fagerström Test for Nicotine/Cigarette Dependence		No relevant comparison (only reported at baseline)	N/A
	Minnesota Nicotine Withdrawal Scale	55 mins	"At T5, no differences in withdrawal symptoms were present between smoking and using the IQOS […] ps>0.11"	↔ (Positive)
	A visual analogue scale (VAS) assessing cigarette craving	55 mins	IQOS(mean, SE)=58.20, 3.89 CC(mean, SE)=45.33, 4.05	↑ (Negative)
	Product preference		No relevant comparison (no HTP v CC comparison for outcome)	N/A
NCT03435562	Nicotine (ng/mL)	5 mins post restricted use and 1-hour post *ad lib* use	Post-puff bout (mean, SD): IQOS=10.65 (6.20), CC=18.31 (11.39) Post ad lib (mean, SD): IQOS=5.97 (7.70), CC=12.23 (9.26)	↓ (Negative)

NCT03889990/ NCT03995329	No relevant comparison (no HTP v CC comparison for outcome)			N/A
NCT03301129	Soluble Nox2-derived peptide (pg/mL)	Immediately after product use	IQOS (mean, SD)= 29.9 ± 5.0 CC (mean, SD)=44.1 ± 17.1	↓ (Positive)
	Flow-mediated dilation (%)	Immediately after product use	IQOS (mean, SD)= 3.79 ± 2.68 CC (mean, SD)= 2.40 ± 1.89	↑ (Positive)
NCT03364751	Mean Periodontal Pocket Depth (PD) reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy (mm)	Month 6	IQOS (mean 95%CI)=-1.046, -1.194;-0.898 CC (mean, 95%CI)=-1.114, -1.258;-0.970. Mean difference=0.068 (-0.06; 0.196), p=0.297	↔ (Negative)
NCT02641587	S-phenylmercapturic acid (pg/mg creat)	Day 90	CHTP (mean, 95%CI)=467, 365;597 CC (mean, 95%CI)=2652, 1853;3795	↓ (Positive)
	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 90	CHTP(mean, 95%CI)=420, 365;483 CC (mean, 95%CI)=2552, 1802;3612	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Day 90	CHTP(mean, 95%CI)=39.7, 29.3;53.7 CC (mean, 95%CI)=196.7, 117;245.0	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 90	CHTP(mean, 95%CI)=378.2, 334.6;427.6 CC (mean, 95%CI)=966.0, 786.4;1187	↓ (Positive)
	Carboxyhemoglobin (%)	Day 90	CHTP(mean, 95%CI)=1.94, 1.78;2.13 CC (mean, 95%CI)=4.33, 3.69; 5.07	↓ (Positive)
NCT02396381	8-epi-prostaglandin F2alpha (pg/mg creat)	Month 6	FAS-AR (mean 95%CI): IQOS=330 (316;345) CC=349 (335;364) FAS-EX (mean 95%CI): IQOS=326 (309;345) CC=350 (336;365) [p=0.018]	↔ ↔ (Negative)
	11-dehydrothromboxane B2 (pg/mg creat)	Month 6	FAS-AR (mean 95%CI): IQOS=511 (475;549) CC=527 (492;565) FAS-EX (mean 95%CI): IQOS=502 (458;550) CC=527 (491;564) [p=0.193]	↔ ↔ (Negative)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	Month 6	FAS-AR (mean 95%CI): IQOS=198 (178;220) CC=282 (254;312) FAS-EX (mean 95%CI): IQOS=159 (140;181) CC=281 (254;311) [p<0.001*]	↓ ↓ (Favourable)
	Carboxyhemoglobin (%)	Month 6	FAS-AR (mean 95%CI): IQOS=3.46 (3.18;3.77) CC=4.40 (4.06;4.78) FAS-EX (mean 95%CI): IQOS=2.95 (2.69;3.24) CC=4.35 (4.03;4.70) [p<0.001*]	↓ ↓ (Positive)
	White blood cell count (GI/L)	Month 6	FAS-AR (mean 95%CI): IQOS=7.26 (7.05;7.48) CC=7.53 (7.33;7.74)	↔ ↓

			FAS-EX (mean 95%CI): IQOS=7.06 (6.81;7.31) CC=7.48 (7.28;7.68) [p=0.001*]	(Unclear)
	Soluble intercellular adhesion molecule-1 (ng/mL)	Month 6	FAS-AR (mean 95%CI): IQOS=260 (253;266) CC=264 (257;271) FAS-EX (mean 95%CI): IQOS=257 (249;265) CC=265 (258;271) [p0.030]	↔ ↔ (Negative)
	High-density lipoprotein cholesterol (mg/dL)	Month 6	FAS-AR (mean 95%CI): IQOS=54.6 (53.5;55.8) CC=51.8 (50.6;52.9) FAS-EX (mean 95%CI): IQOS=54.6 (53.1;56.2) CC=51.6 (50.4;52.7) [p<0.001*]	↑ ↑ (Positive)
	Forced expiratory volume in one second (% pred)	Month 6	FAS-AR (mean 95%CI): IQOS=94.4 (93.6;95.1) CC=93.1 (92.4;93.9) FAS-EX (mean 95%CI): IQOS=94.4 (93.4;95.3) CC=93.1 (92.3;93.9) [p=0.008*]	↔ ↑ (Unclear)
NCT02466412	Maximal nicotine concentration (ng/mL)	N/A	CHTP(mean, 95% CI)=6.2950, 5.2610;7.5322 CC(mean, 95%CI)=9.8463, 8.2290;11.7815 Mean ratio=63.9326% (49.6045;82.3991 [95%])	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	CHTP(mean, 95% CI)=8.5311, 6.9550;10.4642 CC(mean, 95%CI)=14.2172, 11.5908;17.4388 Mean ratio=60.0052% (44.9517;80.0997 [95%])	↓ (Negative)
NCT02503254	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	CHTP (mean, 95%CI)=339.73 (301.82;382.42) CC(mean, 95%CI)=1840.61 (1275.38;2656.32)	↓ (Positive)
	3-hydroxypropylmercapturic acid (pg/mg creat)	Day 5	CHTP (mean, 95%CI)=494.70 (417.53;586.12) CC(mean, 95%CI)=1187.97 (1026.63;1374.65)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	CHTP (mean, 95%CI)=2.7 (2.2; 3.2) CC(mean, 95%CI)=6.4 (5.7; 7.1)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	CHTP (mean, 95%CI)=361.48 (289.26; 451.74) CC(mean, 95%CI)=2898.46 (2172.62; 3866.79)	↓ (Positive)
NCT02649556	Carboxyhemoglobin (%)	Week 52	IQOS (mean, 95%CI)=2.59, 2.24;3.01 CC (mean, 95%CI)=4.06, 3.77;4.38 % relative reduction=31.7 (23.3;39.1[95%])	↓ (Positive)
	8-epi-prostaglandin F2alpha (pg/mg creat)	Week 52	IQOS (mean, 95%CI)=307, 279;338 CC (mean, 95%CI)=327, 307;348 % relative reduction=7.15 (-1.03;14.7[95%])	↔ (Negative)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Week 52	IQOS (mean, 95%CI)=133, 105;168 CC (mean, 95%CI)=269, 238;305 % relative reduction=46.3 (36.2;54.8[95%])	↓ (Positive)
	11-dehydrothromboxane B2 (pg/mg creat)	Week 52	IQOS (mean, 95%CI)=582, 518;654 CC (mean, 95%CI)=586, 538;638 % relative reduction=3.44 (-8.74;14.3[95%])	↔ (Negative)
	White blood cell count (GI/L)	Week 52	IQOS (mean, 95%CI)=6.73, 6.47;6.99 CC (mean, 95%CI)=7.31, 7.07;7.54 LS mean diff=-0.413 (-0.694;-0.131[95%])	↓ (Positive)

	Soluble intercellular adhesion molecule-1 (ng/mL)	Week 52	IQOS (mean, 95%CI)=246, 230;263 CC (mean, 95%CI)=258, 244;272 % relative reduction=3.11 (0.0231;6.10[95%])	↔ (Negative)
	High-density lipoprotein cholesterol (mg/dL)	Week 52	IQOS (mean, 95%CI)=52.2, 49.5;54.8 CC (mean, 95%CI)=50.6, 48.9;52.3 Mean diff=1.75 (-0.160;3.65[95%])	↔ (Negative)
	Forced expiratory volume in one second (% pred)	Week 52	IQOS (mean, 95%CI)=93.2, 91.1;95.2 CC (mean, 95%CI)=92.3, 90.7;94.0 Mean diff=0.914 (-0.339;2.17[95%])	↔ (Negative)
NCT01967706	Maximal nicotine concentration (ng/mL)	N/A	IQOS (mean, 95%CI)=10.70, 8.94;12.8 CC (mean, 95%CI)=12.09, 10.10;14.47 Mean ratio=88.47 (68.64;114.03[95%])	↔ (Positive)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	IQOS (mean, 95%CI)=23.99, 20.87;27.57 CC (mean, 95%CI)=24.45, 21.27;28.10 Mean ratio=98.13 (80.61;119.46[95%])	↔ (Positive)
NCT01780688	Maximal nicotine concentration (ng/mL)	N/A	IQOS (mean, 95%CI)=8.4, 6.8;10.3 CC (mean, 95%CI)=11.9, 9.5;14.9 Mean ratio=70.3% (60.0;82.2[90%])	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	IQOS (mean, 95%CI)=17.7, 15.0;20.8 CC (mean, 95%CI)=22.8, 19.4;26.8 Mean ratio=77.4% (70.5;85.0[90%])	↓ (Negative)
NCT01780714	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	% reduction IQOS/CC mean (95%CI)=88.5 (84.7–91.4) [p<0.001]	↓ (Positive)
	3-hydroxypropylmercapturic acid (pg/mg creat)	Day 5	% reduction IQOS/CC mean (95%CI)=72.1 (67.4–76.1) [p<0.001]	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	% reduction IQOS/CC mean (95%CI)=76.7 (74.3–78.9) [p<0.001]	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	% reduction IQOS/CC mean (95%CI)=93.0 (90.6–94.9) [p<0.001]	↓ (Positive)
ISRCTN88682435	Maximal nicotine concentration (ng/mL)	N/A	HTP (mean, SD)=1.18±1.13 CC (mean, SD)=7.76±4.65 [p<0.05]	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	HTP (mean, SD)=1.07±0.75 CC (mean, SD)=5.97±2.15 [p<0.05]	↓ (Negative)

	Time to reach nicotine Cmax (min)	N/A	HTP (median, min-max)=9.02, 2.05-31.0 CC (median, min-max)=5.02, 3.90-20.0 [p<0.05]	↑ (Negative)
Nga, 2020	Exhaled Carbon monoxide (ppm)	45 mins post product use	IQOS mean=4.67 CC mean=16.47 (no variance values provided but error bars do not overlap in graph presented) Between product effect significant difference (repeated-measures ANOVA, p<0.001)	↓ (Positive)
Lopez, 2016	Exhaled Carbon monoxide (ppm)	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	Bout 1, mean (SD): CC=12.1 (3.4) LLTV=not reported [CC sig higher than LLTV, cohens d=2.4] Bout 2, mean (SD): CC= 16.9 (5.8) LLTV=4.5 (2.1) [CC sig higher than LLTV, cohens d=2.9]	↓ (Positive)
	Questionnaire of Smoking Urges	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	"There were no significant differences between any of the conditions immediately following either bout"	↔ (Positive)
	Nicotine (ng/mL)	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	Bout 1, mean (SD): CC=24.4 (12.6) LLTV=14.3 (8.1) [CC sig higher than LLTV, cohens d=1.0] Bout 2, mean (SD): CC= 23.7 (14.5) LLTV=16.4 (11.3) [CC higher than LLTV but not significantly]	↓ (Negative)
	Minnesota Nicotine Withdrawal Scale	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	"There were no significant differences between any of the conditions immediately following either bout."	↔ (Positive)
	The Direct Effects of Nicotine Questionnaire	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	"there were no differences between the [CC] and LLTV conditions at that same time point [Bout 1]. There were no significant differences between any of the conditions immediately following bout 2."	↔ (Negative)
	The Direct Effects of Product scale	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	“Was the product satisfying?”: "Immediately following bout 1, the mean score for the OB condition of 93.3 (10.51) was significantly higher compared to the scores of 51.2 (30.9) for the LLTV condition (d = 1.8) [...] There was a similar pattern following bout 2" “Did the product taste good?”: "immediately following bout 1, the mean score for the OB condition of 92.9 (11.4) was significantly higher compared to the score of 43.7 (31.8) for the LLTV condition [t(14) = 5.2, p < 0.017; d = 2.1] “Did the product calm you down?”: "immediately following bout 1, the mean score for the OB condition of 68.4 (28.9) was significantly higher compared to the LLTV score of 41.8 (31.2; [t(14) = 4.1, p < 0.017; d = 0.9]) [...] There were no significant differences between any of the conditions immediately following bout 2”	↓ (Negative)

ISRCTN81075760	Augmentation index	No results reported		Not reported
	8-epi-prostaglandin F2alpha	No results reported		Not reported
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24h)	Day 90	Graph shows levels were equivalent at baseline PP-population mean change baseline-day 90: Glo=-120 CC=-12 Diff (99.94% CI)=-108 (-168;-48) [p<0.0001] CEVal-population mean change baseline-day 90: Glo=-110 CC=-5 Diff (99.94% CI)=-105 (-193; -17)	↓ (Positive)
ISRCTN13439529	Time to reach nicotine Cmax (min)	N/A	Median (range): Glo1.0=4.1, 1.1-45.0 Glo1.1=4.1, 1.2-15.4 CC=6.0, 3.0-9.1	↔ (Positive)
	Maximal nicotine concentration (ng/mL)	N/A	Mean (90%CI): Glo1.0=8.7 (6.93;10.95) Glo1.1=10.9 (8.63;13.70) CC=23.3 (18.46;29.33)	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (min*ng/mL)	N/A	Mean (90%CI): Glo1.0=527 (438.7;633.3) Glo1.1=695 (577.6;835.6) CC=1374 (1142.4;1653.1)	↓ (Negative)
	Intention to use [HTP] Questionnaire	240 min post 1st puff	Mean±SD, median: Glo1.0=2.5 ± 2.67, 2.0 Glo1.1=3.1 ± 2.84, 2.0 CC=9.1 ± 1.37, 10	↓ (Negative)
	Product Liking Questionnaire	3-240min	Mean±SD, median: Glo1.0=720 ± 733, 640 Glo1.1=820 ± 724, 675 CC=2107 ± 403, 2281	↓ (Negative)
	Urge To Smoke questionnaire	5 min post 1st puff	Mean±SD, median: Glo1.0=5.0 ± 3.33, 5.0 Glo1.1=4.8 ± 3.27, 5.0 CC=2.6 ± 3.50, 1.0	↓ (Negative)
	Urge For Product questionnaire	No comparison to cigarette arm		N/A
ISRCTN14301360/ UMIN000024988	Exhaled Carbon monoxide (ppm)	Day 7	CC(mean)=20.30, Glo(mean)=3.40, IQOS(mean)=3.40, mCC(mean)=20.07, mGlo(mean)=2.80	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24h)	Day 7	CC(mean)=197.85, Glo(mean)=128.63, IQOS(mean)=80.35, mCC(mean)=167.02, mGlo(mean)=149.38	↓ (Positive)
	2-cyanoethylmercapturic acid (ug/24h)	Day 7	CC(mean)=159.04, Glo(mean)=17.84, IQOS(mean)=16.54, mCC(mean)=165.62, mGlo(mean)=21.03	↓ (Positive)
	total N-nitrosonornicotine (ng/24h)	Day 7	CC(mean)=15.36, Glo(mean)=5.85, IQOS(mean)=1.06, mCC(mean)=9.62, mGlo(mean)=5.57	↓ (Positive)
	Nicotine equivalents (mg/24h)	Day 7	CC(mean)=8.33, Glo(mean)=6.15, IQOS(mean)=7.58, mCC(mean)=9.77, mGlo(mean)=5.75	↓ (Negative)
	monohydroxybutenylmercapturic acid (ng/24h)	Day 7	CC(mean)=770.64, Glo(mean)=49.87, IQOS(mean)=118.38, mCC(mean)=1010.18, mGlo(mean)=98.40	↓ (Positive)
	3-hydroxypropylmercapturic acid (ug/24h)	Day 7	CC(mean)=1448.93, Glo(mean)=568.66, IQOS(mean)=639.21, mCC(mean)=1422.37, mGlo(mean)=656.99	↓ (Positive)

	total 1-hydroxypyrene (ng/24h)	Day 7	CC(mean)=172.86, Glo(mean)=75.58, IQOS(mean)=50.18, mCC(mean)=195.19, mGlo(mean)=63.46	↓ (Positive)
	S-phenylmercapturic acid (ug/24h)	Day 7	CC(mean)=2.25, Glo(mean)=0.20, IQOS(mean)=0.19 mCC(mean)=2.81, mGlo(mean)=0.20	↓ (Positive)
	o-toluidine (ng/24h)	Day 7	CC(mean)=153.21, Glo(mean)=58.52, IQOS(mean)=54.81, mCC(mean)=119.04, mGlo(mean)=39.39	↓ (Positive)
	4-aminobiphenyl (ng/24h)	Day 7	CC(mean)=10.86, Glo(mean)=2.45, IQOS(mean)=2.25, mCC(mean)=10.44, mGlo(mean)=2.31	↓ (Positive)
	2-aminonaphthalene (ng/24h)	Day 7	CC(mean)=17.80, Glo(mean)=1.74, IQOS(mean)=1.72, mCC(mean)=17.65, mGlo(mean)=1.92	↓ (Positive)
	3-hydroxy-1-methylpropylmercapturic acid (ug/24h)	Day 7	CC(mean)=385.50, Glo(mean)=79.00, IQOS(mean)=79.63, mCC(mean)=362.45, mGlo(mean)=73.23	↓ (Positive)
	2-hydroxyethylmercapturic acid (ug/24h)	Day 7	CC(mean)=5.08, Glo(mean)=2.46, IQOS(mean)=2.60 mCC(mean)=7.13, mGlo(mean)=2.84	↓ (Positive)
	N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine (ug/24h)	Day 7	CC(mean)=17.24, Glo(mean)=15.68, IQOS(mean)=13.75, mCC(mean)=16.40, mGlo(mean)=15.36	↓ (Positive)
	N-acetyl-S-(2-carba-moylethyl)cysteine (ug/24h)	Day 7	CC(mean)=111.65, Glo(mean)=91.75, IQOS(mean)=65.76, mCC(mean)=114.96, mGlo(mean)=88.82	↓ (Positive)
DRKS00012919	Nicotine	Not reported		Not reported
	Systolic blood pressure (mm Hg)	120 min	Based on graph presenting data throughout study period, SPB at end of exposure was not substantially different between the HTP and CC arms	↔ (Negative)
ISRCTN80651909	Exhaled Carbon monoxide (ppm)	Day 7	CC(mean)=25.3 Glo(mean)=4.4	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24h)	Day 7	CC(mean)=289.54 Glo(mean)=195.71	↓ (Positive)
	2-cyanoethylmercapturic acid (mg/24h)	Day 7	CC(mean)=0.24 Glo(mean)=0.03	↓ (Positive)
	total N-nitrosonornicotine (ng/24h)	Day 7	CC(mean)=10.85 Glo(mean)=6.10	↓ (Positive)
	Nicotine equivalents (mg/24h)	Day 7	CC(mean)=14.88 Glo(mean)=7.37	↓ (Positive)
	monohydroxybutenylmercapturi c acid (ng/24h)	Day 7	CC(mean)=2552.74 Glo(mean)=240.28	↓ (Positive)

	3-hydroxypropylmercapturic acid (mg/24h)	Day 7	CC(mean)=1.37 Glo(mean)=0.27	↓ (Positive)
	total 1-hydroxypyrene (ng/24h)	Day 7	CC(mean)=313.33 Glo(mean)=106.71	↓ (Positive)
	S-phenylmercapturic acid (ng/24h)	Day 7	CC(mean)=5572.79 Glo(mean)=231.36	↓ (Positive)
	o-toluidine (ng/24h)	Day 7	CC(mean)=146.60 Glo(mean)=38.40	↓ (Positive)
	4-aminobiphenyl (ng/24h)	Day 7	CC(mean)=22.36 Glo(mean)=3.36	↓ (Positive)
	2-aminonaphthalene (ng/24h)	Day 7	CC(mean)=32.38 Glo(mean)=3.03	↓ (Positive)
	N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine (ng/24h)	Day 7	CC(mean)=33554.88 Glo(mean)=24749.07	↓ (Positive)
	N-acetyl-S-(2-carba-moylethyl)cysteine (mg/24h)	Day 7	CC(mean)=0.18 Glo(mean)=0.12	↓ (Positive)
	3-hydroxy-1-methylpropylmercapturic acid (mg/24h)	Day 7	CC(mean)=0.54 Glo(mean)=0.07	↓ (Positive)
	2-hydroxyethylmercapturic acid (ng/24h)	Day 7	CC(mean)=9673.61 Glo(mean)=3954.5	↓ (Positive)
	8-epi-prostaglandin F2alpha (no units reported)	Day 7	"8-epi-PGF2α Type III, there was no significant change in all arms except the glo THP arm, which showed a significant decrease in the urinary levels of this BoBE" Without baseline data there is no way to know whether the end of exposure levels differed between study arms.	Unclear
	White blood cell count (no units reported)	Day 7	"white blood cell count was significantly reduced between baseline and Day 7 for the glo THP and the prototype EC arms. However, there was no significant change in the nicotine cessation or in the control cigarette arm." Without baseline data there is no way to know whether the end of exposure levels differed between study arms.	Unclear
	Nicotine molar metabolic ratio (no units reported)	Day 7	CC(mean)=2.74 Glo(mean)=3.31	↑ (Unclear)

UMIN000041539	Exhaled Carbon monoxide (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	2-cyanoethylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	total N-nitrosonornicotine (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	monohydroxybutenylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group" This is substantiated by the graph presented	↓ (Positive)
	3-hydroxypropylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	total 1-hydroxypyrene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	S-phenylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	o-toluidine (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	4-aminobiphenyl (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	2-aminonaphthalene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	3-hydroxy-1-methylpropylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)

	2-hydroxyethylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	3-hydroxybenzo[a]pyrene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	1-aminonaphthalene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
NCT03700112	Time to reach nicotine Cmax (mins)	N/A	Controlled (mean(SD)): CC=6.71 (5.11) IQOS=5.41 (1.36) Ad lib (mean(SD)): CC=5.84 (1.36) IQOS=6.38 (5.06)	↔ (Positive)
	Maximal nicotine concentration	Not reported		Not reported
	Baseline adjusted Cmax (ng/mL)	N/A	Controlled (mean(SD)): CC=21.2 (11.7) IQOS=16.1 (7.7) Ad lib (mean(SD)): CC=27.9 (19.6) IQOS=17.4 (7.3)	↓ (Negative)
	Baseline adjusted AUC1hour (hrs*ng/mL)	N/A	Controlled (mean(SD)): CC=7.67 (3.56) IQOS=5.15 (2.32) Ad lib (mean(SD)): CC=9.76 (5.69) IQOS=5.72 (1.88)	↓ (Negative)
	Area under the concentration curve from start of product use to 60 minutes	Not reported		Not reported
NCT01970995	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=23.23 (19.34;27.91) CC (mean, 95%CI)=95.03 (77.31;116.82)	↓ (Positive)
	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=141.74 (120.62;166.57) CC (mean, 95%CI)=785.27 (576.82;1069.04)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 90	mIQOS (mean, 95%CI)=386.37 (356.30;418.97) CC (mean, 95%CI)=695.58 (602.43;803.13)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 90	mIQOS (mean, 95%CI)=2.97 (2.88;3.06) CC (mean, 95%CI)=5.73 (5.24;6.25)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=145.58 (121.67;174.18) CC (mean, 95%CI)=1157.25 (848.59;1578.17)	↓ (Positive)
NCT01989156	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=47.53 (34.80;64.91) CC (mean, 95%CI)=152.11 (108.38;213.47)	↓ (Positive)
	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=260.98 (205.28;331.79) CC (mean, 95%CI)=1040.71 (677.79;1597.94)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 90	mIQOS (mean, 95%CI)=314.05 (281.51;350.34) CC (mean, 95%CI)=606.10 (468.27;784.48)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 90	mIQOS (mean, 95%CI)=2.66 (2.40;2.94)	↓

			CC (mean, 95%CI)=5.62 (5.00;6.32)	(Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=314.02 (219.66;448.93) CC (mean, 95%CI)=1218.56 (822.54;1805.25)	↓ (Positive)
NCT01970982	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=107.39 (97.24;118.60) CC (mean, 95%CI)=450.19 (300.07;675.42)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 5	IQOS (mean, 95%CI)=311.08 (279.59;346.12) CC (mean, 95%CI)=599.67 (511.70;702.76)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	IQOS (mean, 95%CI)=2.39 (2.32;2.46) CC (mean, 95%CI)=5.14 (4.66;5.66)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=143.77 (126.08;163.93) CC (mean, 95%CI)=850.02 (620.40;1164.63)	↓ (Positive)
NCT01959932	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=192.93 (174.90; 212.83) CC (mean, 95%CI)=2399.40 (1884.60; 3054.83)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 5	IQOS (mean, 95%CI)=402.26 (366.55; 441.45) CC (mean, 95%CI)=931.01 (825.73; 1049.72)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	IQOS (mean, 95%CI)=1.06 (1.03; 1.08) CC (mean, 95%CI)=4.51 (4.05; 5.01)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=164.45 (144.45; 187.22) CC (mean, 95%CI)=2922.81 (2362.80; 3615.54)	↓ (Positive)
NCT01959607	Maximal nicotine concentration (ng/mL)	N/A	IQOS (geo mean, 95%CI)=14.30 (11.41;17.91) CC (geo mean, 95%CI)=13.82 (11.00;17.35)	↔ (Positive)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	IQOS (geo mean, 95%CI)=23.75 (19.74;28.58) CC (geo mean, 95%CI)=24.66 (20.24;30.03)	↔ (Positive)
NCT01967732	Maximal nicotine concentration (ng/mL)	N/A	IQOS (mean, 95%CI)=9.60 (7.64;12.07) CC (mean, 95%CI)=12.34 (10.47;14.54)	↔ (Positive)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	IQOS (mean, 95%CI)=15.20 (12.01;19.23) CC (mean, 95%CI)=20.13 (17.72;22.88)	↔ (Positive)
NCT01967719	Maximal nicotine concentration (ng/mL)	N/A	mIQOS (mean, 95%CI)=7.39 (5.68;9.62) CC (mean, 95%CI)=13.02 (10.06;16.85)	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	mIQOS (mean, 95%CI)=16.56 (12.46;22.01) CC (mean, 95%CI)=29.47 (21.35;40.67)	↔ (Positive)

Jones, 2020	Human Puffing/Smoking Topography (inc. puff count)	During single-use session on Day 5	**Group 1** (mean, ±SD) Puff number: IQOS=15.0 (±5.5), CC=17.3(±5.9) Total puff volume: IQOS=730.9mL (±350.4), CC=682.8mL (±224.7) Mean puff volume: IQOS=48.8mL (±17.9), CC=41.3mL (±12.7) Puff duration: IQOS=1.4s (±0.5), CC=1.5s (±0.5) Puff interval: IQOS=17.1s (±20.7), CC=18.8s (±10.6) Session length: IQOS=195.6s (±87.2), CC=289.5s (±85.7) **Group 3** (mean, ±SD) Puff number: Glo=15.4 (±7.4), CC=16.0 (±5.6) Total puff volume: Glo=731.3mL (±437.6), CC=596.8mL (±197.1) Mean puff volume: Glo=46.6mL (±16.8), CC=39.3mL (±12.4) Puff duration: Glo=1.6s (±0.5), CC=1.6s (±0.5) Puff interval: Glo=11.1s (±5.8), CC=18.8s (±10.6) Session length: Glo=150.4s (±40.5), CC=269.3s (±88.0)	↓ (Positive) ↑ (Negative) ↑ (Negative) ↓[IQOS] ↔ [Glo] (Positive) ↓ (Negative) ↓ (Positive)
	Daily product consumption	Ambulatory average	IQOS (mean, ±SD)=8.5 (±5.2) Glo (mean, ±SD)=7.0 (±5.5) CC (mean, ±SD)=13.2 (±4.4) [Group 1], 12.6 (±4.7) [Group 3]	↓ (Positive)
	Mouth level exposure to NFDPM (mg/session)	During single-use session on Day 5	IQOS (mean, ±SD)=9.6 (±5.0) Glo (mean, ±SD)=4.7 (±2.9) CC (mean, ±SD)=19.0 (±7.7) [Group 1], 16.7 (±7.6) [Group 3]	↓ (Positive)
	Mouth level exposure to nicotine (mg/session)	During single-use session on Day 5	IQOS (mean, ±SD)=0.98 (±0.51) Glo (mean, ±SD)=0.34 (±0.21) CC (mean, ±SD)=1.55 (±0.63) [Group 1], 1.36 (±0.62) [Group 3]	↓ (Negative)
	Sensory questionnaire (magnitude scale [1-7], 'just right' scale [Low, Just right, High])	During single-use session on Day 5	**Group 1** (mean (±SD) magnitude score, just right score) Immediate smoke/aerosol delivery: IQOS=3.7 (± 1.7), Low; CC=5.4 (± 1.3), Just right Draw effort: IQOS=4.1 (± 1.7), High; CC=3.5 (± 1.7), High Mouthful: IQOS=3.8 (± 1.3), Low; CC=4.8 (± 1.0), Just right Irritation: IQOS=3.4 (± 2.0), Just right; CC=2.9 (± 1.8), Just right Intensity of kick/hit: IQOS=3.6 (± 1.7), Just right; CC=3.4 (± 1.8), Just right Taste - likeability: IQOS=3.4 (± 2.0); CC=5.2 (± 1.3) Taste - amount: IQOS=4.2 (± 1.4), Just right; CC=5.0 (± 1.2), Just right Overall likeability: IQOS=3.6 (± 1.9); CC=5.3 (± 1.2) **Group 3** (mean (±SD) magnitude score, just right score) Immediate smoke/aerosol delivery: Glo=3.3 (± 1.6), Low; CC=5.0 (± 1.3), Just right Draw effort: Glo=4.9 (± 1.6), High; CC=3.8 (± 1.5), High Mouthful: Glo=3.2 (± 1.3), Low; CC= 4.5 (± 1.2), Just right Irritation: Glo=3.6 (± 1.9), Just right; CC=3.3 (± 1.4), Just right	↓ (Negative) ↑ (Negative) ↓ (Negative) ↑↔ (Unclear) ↑↔ (Positive) ↓ (Negative) ↓↔ (Unclear) ↓

			Intensity of kick/hit: Glo=3.9 (± 1.8), Just right; CC=3.8 (± 1.3), Just right Taste - likeability: Glo=2.8 (± 2.0); CC=5.1 (± 1.6) Taste - amount: Glo=4.0 (± 1.8), Just right; CC=4.6 (± 1.3), Just right Overall likeability: Glo=3.1 (± 1.9); CC=5.2 (± 1.4)	(Negative)
Gee, 2018	Human Puffing/Smoking Topography (inc. puff count)	During single-use session on day 5	**Group 1** (mean, ±SD) Total puff volume (mL): IQOS=668.1 ± 322.6, Glo=736.4 ± 415.8, CC=489.0 ± 177.7 Mean puff volume (mL): IQOS=63.5 ± 20.3, Glo=66.7 ± 23.7, CC=48.9 ± 14.8 Puff number: IQOS=10.3. ± 3.6, Glo=10.9 ± 5.6, CC=10.7 ± 5.0 Puff duration (s): IQOS=1.8 ± 0.6, Glo=1.8 ± 0.6, CC=1.8 ± 0.6 Puff interval (s): IQOS=8.3 ± 3.0, Glo=7.4 ± 2.7, CC=9.7 ± 3.4 **Group 2** (mean, ±SD) Total puff volume (mL): mGlo=618.2 ± 389.6, mCC=493.7 ± 192.4 Mean puff volume (mL): mGlo=62.2 ± 32.8, mCC=51.1 ± 16.0 Puff number: mGlo=10.0 ± 4.5, mCC=10.0 ± 3.7 Puff duration (s): mGlo=1.8 ± 0.5, mCC=2.0 ± 0.5 Puff interval (s): mGlo=8.1 ± 3.0, mCC=9.9 ± 3.4	↑ (Negative) ↑ (Negative) ↓[IQOS] ↑[Glo] ↔[mGlo] (Unclear) ↓[mGlo]↔[IQOS/Glo] (Positive) ↓ (Negative)
	Daily product consumption	Ambulatory average	IQOS (mean, ±SD)=12.2 ± 6.2 Glo (mean, ±SD)=10.3 ± 5.5 CC (mean, ±SD)=16.0 ± 8.1 mGlo (mean, ±SD)=11.4 ± 5.7 mCC (mean, ±SD)=15.3 ± 6.9	↓ (Positive)
	Mouth level exposure to NFDPM (mg/stick)	During single-use session on day 5	IQOS (mean, ±SD)=8.4 ± 4.5 Glo (mean, ±SD)=5.2 ± 3.4 CC (mean, ±SD)=13.5 ± 6.2 mGlo (mean, ±SD)=6.2 ± 3.8 mCC (mean, ±SD)=14.8 ± 7.4	↓ (Positive)
	Mouth level exposure to menthol (mg/stick)	During single-use session on day 5	mGlo (mean, ±SD)=1.4 ± 0.8 mCC (mean, ±SD)=1.2 ± 0.5	↑ (Unclear)
	Mouth level exposure to nicotine (mg/stick)	During single-use session on day 5	IQOS (mean, ±SD)=1.0 ± 0.5 Glo (mean, ±SD)=0.3 ± 0.2 CC (mean, ±SD)=1.3 ± 0.5 mGlo (mean, ±SD)=0.3 ± 0.2 mCC (mean, ±SD)=1.3 ± 0.6	↓ (Negative)
	Mouth insertion depth	Post product use	No comparison to cigarette arm	N/A

NCT03452124	Pulse wave velocity (m/s)	Acute=post single use Chronic=1 month	Acute: IQOS (mean, ±SD)=10.2 ± 1.7; CC (mean, ±SD)=10.8 ± 2.4 Chronic: IQOS (mean, ±SD)=10.1 ± 1.5; CC (mean, ±SD)=10.2 ± 2.3	↓ (Positive)
	Exhaled Carbon monoxide (ppm)	Acute=post single use Chronic=1 month	Acute: IQOS (mean, ±SD)=14.1±7.3; CC (mean, ±SD)=17.5±7.8 Chronic: IQOS (mean, ±SD)=6.7±6.4; CC (mean, ±SD)=17.4±4.8	↓ (Positive)
	Perfused boundary region of sublinqual arterial microvessels	N/A	Not reported	N/A
	Global longitudinal strain of left ventricle (%)	1 month	Chronic: IQOS (mean, ±SD)=−20.9±2.5; CC (mean, ±SD)=−20±0.7 GLS was improved in the HNBC compared to the control group at follow-up (diference=2.35%; 95% CI 0.23–4.48, p=0.03)	↑ (Positive)
	Coronary flow reserve (no units)	1 month	Chronic: IQOS (mean, ±SD)=3.5±0.8; CC (mean, ±SD)=2.6±0.2	↑ (Positive)
Dalrymple, 2022	Catalase (UI/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=12.87, 7.77 CC (mean, SD)=10.01, 3.63	↑ (Positive)
	Malondialdehyde (ng/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=46.10, 6.46 CC (mean, SD)=62.80, 12.02	↓ (Positive)
	Squalene (µg/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=36.97, 24.29 CC (mean, SD)=34.95, 22.54	↑ (Positive)
	Squalene monohydroperoxide (ng/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=73.80, 49.34 CC (mean, SD)=159.45, 67.26	↓ (Positive)
	Squalene monohydroperoxide/Squalene ratio (ng/µg)	Post exposure to 32 puffs of product	Glo (mean, SD)=2.07, 0.65 CC (mean, SD)=5.19, 1.38	↓ (Positive)
	L* (lightness) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=69.30, 3.56 CC (mean, SD)=66.79, 2.57	↑ (Positive)
	a* (green-red) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=7.32, 1.88 CC (mean, SD)=8.23, 0.95	↓ (Positive)

	b* (blue-yellow) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=15.72, 2.72 CC (mean, SD)=20.72, 1.91	↓ (Positive)
	Total difference in colour from control (ΔE) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=2.61, 1.14 CC (mean, SD)=5.39, 1.54	↓ (Positive)
Ioakeimidis, 2021	Augmentation index (%)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Compared with sham smoking, cfPWV (Figure 1(b)), baPWV and AIx@75 (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in cfPWV, baPWV and AIx@75 (by 0.30 m/s, 86 cm/s and 3.5%, respectively)."	↓ (Positive)
	Heart rate (bpm)	Post use	"There were no differences in all baseline measurements between the three sessions." "HR increased similarly in both the tobacco cigarette and HNBC sessions (maximum increase by 10 beats/min)"	↔ (Negative)
	Brachial systolic blood pressure (mmHg)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Both brachial (Figure 1(a)) and aortic systolic BP increased immediately after the end of smoking by tobacco cigarette (by 11.5 and 10.5 mmHg, $p < 0.001$ and $p < 0.01$, respectively) and by HNBC (by 7.5 and 6 mmHg, all $p < 0.01$)"	↓ (Positive)
	Aortic systolic blood pressure (mmHg)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Both brachial (Figure 1(a)) and aortic systolic BP increased immediately after the end of smoking by tobacco cigarette (by 11.5 and 10.5 mmHg, $p < 0.001$ and $p < 0.01$, respectively) and by HNBC (by 7.5 and 6 mmHg, all $p < 0.01$)"	↓ (Positive)
	Carotid–femoral pulse wave velocity (m/s)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Compared with sham smoking, cfPWV (Figure 1(b)), baPWV and AIx@75 (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in cfPWV, baPWV and AIx@75 (by 0.30 m/s, 86 cm/s and 3.5%, respectively)."	↓ (Positive)
	Brachial-ankle pulse wave velocity (cm/s)	Post use	"There were no differences in all baseline measurements between the three sessions." "Compared with sham smoking, cfPWV (Figure 1(b)), baPWV and AIx@75 (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in cfPWV, baPWV and AIx@75 (by 0.30 m/s, 86 cm/s and 3.5%, respectively)."	↓ (Positive)

Yaman, 2021	A wave velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=55.8 (14.2), n=27 CC [mean, (SD)]=57.9 (15.5), n=27	↓ (Positive)
	Diastolic blood pressure (mmHg)	10 minutes post-use	IQOS [mean, (SD)]=71.9 (10.1), n=27 CC [mean, (SD)]=75.5 (10), n=27	↓ (Positive)
	E wave velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=66.8 (12), n=27 CC [mean, (SD)]=67.3 (14.1), n=27	↓ (Negative)
	E/A ratio (no units)	10 minutes post-use	IQOS [mean, (SD)]=1.2 (0.3), n=27 CC [mean, (SD)]=1.2 (0.4), n=27	↔ (Negative)
	Em/Am ratio (no units)	10 minutes post-use	IQOS [mean, (SD)]=1.2 (0.5), n=27 CC [mean, (SD)]=1.3 (1.0), n=27	↓ (Negative)
	Heart rate (bpm)	10 minutes post-use	IQOS [mean, (SD)]=1.8 (8.7), n=27 CC [mean, (SD)]=82.6 (8.8), n=27	↓ (Positive)
	Left atrium diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=38.8 (4.8), n=27 CC [mean, (SD)]=38.3 (5.2), n=27	↑ (Negative)
	Left ventricle ejection fraction (%)	10 minutes post-use	IQOS [mean, (SD)]=64.5 (3.8), n=27 CC [mean, (SD)]=64.4 (3.9), n=27	↑ (Positive)
	Left ventricle global circumferential strain (%)	10 minutes post-use	IQOS [mean, (SD)]=18.3 (3.9), n=27 CC [mean, (SD)]=17.5 (3.9), n=27	↑ (Positive)
	Left ventricle global longitudinal strain (%)	10 minutes post-use	IQOS [mean, (SD)]=17.9 (2.4), n=27 CC [mean, (SD)]=17.9 (2.8), n=27	↔ (Negative)
	Left ventricular end-diastolic diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=46.1 (4.1), n=27 CC [mean, (SD)]=46.3 (4.5), n=27	↓ (Positive)
	Peak early diastolic velocity of the left ventricle (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=11.6 (3.6), n=27 CC [mean, (SD)]=10.7 (3.8), n=27	↑ (Positive)
	Peak late diastolic velocity of the left ventricle (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=9.5 (2.2), n=27 CC [mean, (SD)]=10 (2.9), n=27	↓ (Positive)
	Right atrium diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=38.2 (4.0), n=27 CC [mean, (SD)]=38.3 (3.9), n=27	↓ (Positive)
	Right ventricle diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=34.2 (3.2), n=27 CC [mean, (SD)]=34.2 (3.3), n=27	↔ (Negative)
	Right ventricle free wall strain (%)	10 minutes post-use	IQOS [mean, (SD)]=23.9 (6.2), n=27 CC [mean, (SD)]=21.2 (5.6), n=27	↑ (Positive)
	Right ventricle global longitudinal strain (%)	10 minutes post-use	IQOS [mean, (SD)]=21.4 (4.1), n=27 CC [mean, (SD)]=19.4 (4.1), n=27	↑ (Positive)
	Right ventricle peak early diastolic velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=10.7 (2.4), n=27 CC [mean, (SD)]=10.5 (2.4), n=27	↑ (Positive)

	Right ventricle peak late diastolic velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=15 (4.5), n=27 CC [mean, (SD)]=14.5 (3.4), n=27	↑ (Negative)
	Right ventricle systolic myocardial velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]= 13.1 (2.1), n=27 CC [mean, (SD)]=12.8 (2.5), n=27	↑ (Negative)
	Right ventricle Em/Am ratio (no units)	10 minutes post-use	IQOS [mean, (SD)]= 0.7 (0.2), n=27 CC [mean, (SD)]=0.7 (0.2), n=27	↔ (Negative)
	Systolic blood pressure (mmHg)	10 minutes post-use	IQOS [mean, (SD)]=114.1 (16.8), n=27 CC [mean, (SD)]=120.5 (12.7), n=27	↓ (Positive)
	Systolic myocardial velocity of the left ventricle (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=9.8 (2.4), n=27 CC [mean, (SD)]=9.1 (2.3), n=27	↑ (Negative)
	Tricuspid annular plane systolic excursion (mm)	10 minutes post-use	IQOS [mean, (SD)]=20.9 (2.5), n=27 CC [mean, (SD)]=20.2 (2.9), n=27	↑ (Positive)
Phillips-Waller, 2021	Human Puffing/Smoking Topography (inc. puff count)	During single-use	IQOS (median, IQR)=14.0, 13.5-14.0 CC (median, IQR)=13.0, 10.8-16.3	↑ (Negative)
	Maximal nicotine concentration	N/A	IQOS (median, IQR)=8.3, 4.5-19.3 CC (median, IQR)=12.9, 7.2-28.6 Mean maximal nicotine concentration also lower in IQOS group than CC group based on graph (Figure 1)	↓ (Negative)
	Nicotine	30 minutes	"IQOS delivered about half as much nicotine over 30 minutes (AUC0–>30) as a cigarette"	↓ (Negative)
	Time to reach nicotine Cmax	N/A	IQOS (median, IQR)=4.0, 4.0-6.0 CC (median, IQR)=6.0, 4.0-8.0	↓ (Positive)
	Urge To Smoke questionnaire	Post product use	"OBC reduced urges to smoke more than IQOS"	↑ (Negative)
	Area under the concentration curve from start of product use to 60 minutes	N/A	IQOS (median, IQR)=152.0, 91.2-254.5 CC (median, IQR)=314, 136.4-465.6 "IQOS delivered about half as much nicotine over 30 minutes (AUC0–>30) as a cigarette"	↓ (Negative)
	Nicotine boost effect score	N/A	IQOS (median, IQR)=5.4, 2.6-10.8 CC (median, IQR)=12.7, 6.7-26.8	↓ (Negative)
	Questionnaire (Other)	Post product use	No comparison to cigarette arm	NE

* ↑ = higher in HTP arm; ↔ = equivocal; ↓ = lower in HTP arm
Abbreviations: Positive=HTP has positive impact compared to CC; Negative=HTP has negative impact compared to CC; N/A=not applicable; HTP=heated tobacco product; CHTP=carbon HTP; CC=combustible cigarette; [P]NTV=[prototype] novel tobacco vapor; LLTV=loose leaf tobacco vaporiser; create=creatinine; FAS-AR=Full analysis set – as randomised; FAS-EX=Full analysis set – as exposed; Cmax=maximal concentration; mean=arithmetic mean; geo mean=geometric mean

Critical appraisal of interventional clinical trials assessing heated tobacco products: a systematic review and meta-regression.

Supplementary Materials

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:

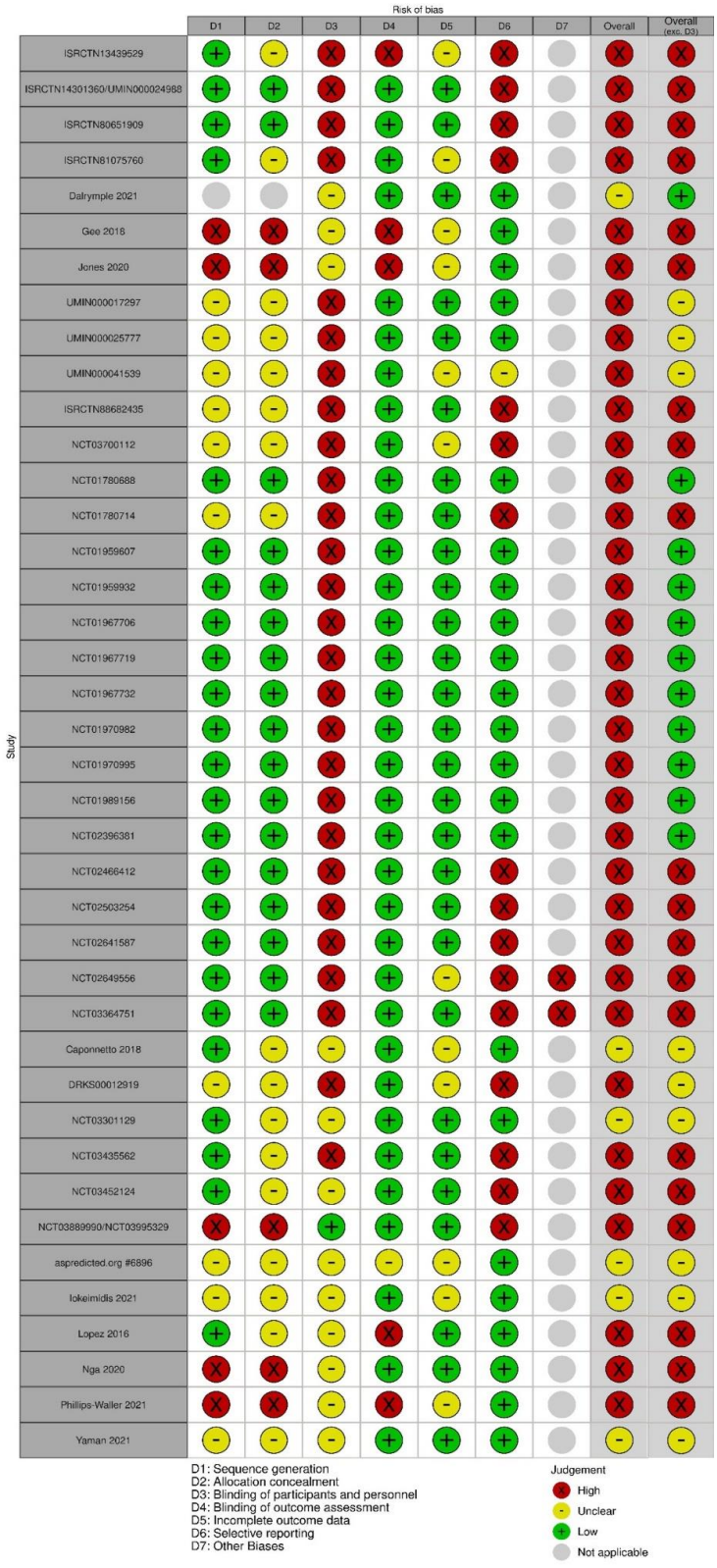
- the sponsor named on the trial registration had no known ties to the tobacco industry; and
- funding statements in any of the trial literature indicated the trial was not funded by a tobacco company or other organisation funded by a tobacco company; and
- author affiliations and conflict of interest 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.

Supplementary Figure 1. Risk of bias summary: Review authors' judgments about risk of bias items for each included study



Supplementary Table 1. Characteristics of included studies.

UMIN000017297			
Methods	**Date of registration:** 27/04/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confinement (Japan) **Study start date; study end date:** 11/05/2015; 27/05/2015 **Intervention duration:** 2 sessions of 10 puffs for 3 mins at approx 20 sec intervals		
Participants	**Number of participants:** 24 randomised, 0 withdrawn, 24 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=24; Mean Age (SD): 39 years (SD not reported); Sex: 100% male; Ethnicity/Nationality: 100% Japanese. **Key inclusion criteria:** Health status: "good health"; ≥11 CPD; smoked for ≥1 year		
Interventions	**Interventions:** HTP (Prototype novel tobacco vapor product), CC (unknown brand) **Co-interventions:** none **Mode of exposure:** direct restricted		
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Adverse Events/Serious Adverse Events, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Terminal half-life of nicotine, Mouth level exposure to nicotine.		
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*completed subjects who completed the study and who did not deviate from the protocol were included in the statistical analysis*" **Unit of analysis:** Individuals		
Study funding	Japan Tobacco International (Industry-affiliated)		
Notes	Not included in meta-regression analysis		
Risk of bias			
Bias		**Authors' judgement**	**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	"Blinding: Open-no one is blinded". Included non-active comparator (cigarettes).
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.
UMIN000025777			
Methods	**Date of registration:** 20/01/2017 **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confinement (Japan) **Study start date; study end date:** 21/01/2017; 22/02/2017 **Intervention duration:** 5 days		

Participants	**Number of participants:** 60 randomised (HTP 20, CC 20, Cess 20), 0 withdrawn, 60 completed (HTP 20, CC 20, Cess 20) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=60; Mean Age (SD): HTP 32.7 (12.3) years, CC 30.9 (12.5) years, Cess 33.3 (14.6); Sex: 70% male; Ethnicity/Nationality: 100% Japanese. **Key inclusion criteria:** Health status: "good health"; ≥11 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (novel tobacco vapor product), CC (own brand), smoking cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, 2-hydroxyethylmercapturic acid, 3-hydroxybenzo[a]pyrene, 1-aminonaphthalene, 4-hydroxybutyl-2-mercapturic acid **Secondary:** Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Minnesota Nicotine Withdrawal Scale, Human Puffing/Smoking Topography (inc. puff count), Product Liking Questionnaire, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*randomized subjects who had at least one BoE assessment after post-randomization*" **Unit of analysis:** Individuals
Study funding	Japan Tobacco International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	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	"Blinding: Open-no one is blinded". Included non-active comparator (cigarettes).
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.

Caponnetto, 2018

Methods	**Date of registration:** Not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (Unknown) **Study start date; study end date:** Not reported **Intervention duration:** 3 sessions of 2x 10 puffs with 30 sec intervals and 5 min inter-round break
Participants	**Number of participants:** 12 randomised, 0 withdrawn, 12 completed **Withdrawal reasons reported:** N/A

	Baseline characteristics: N=12; Mean Age (SD): 28.6 years (SD not reported); Sex: 50% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (IQOS), HTP (Glo), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide **Secondary:** N/A
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified **Unit of analysis:** Individuals
Study funding	University of Catania (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"The randomization sequence was computer-generated"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	Unclear	No information on blinding. Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	No information on blinding, but only outcome was objectively measured.
Incomplete outcome data	Unclear	The authors state 12 subjects "took part" in the study but it is unclear whether more than 12 were initially randomised.
Selective reporting	Low	Only outcome measured (eCO) is reported on in the results.

aspredicted.org #6896

Methods	**Date of registration:** 22/11/2017 **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (Belgium) **Study start date; study end date:** Not reported **Intervention duration:** 3 sessions of single use of one cigarette or tobacco stick
Participants	**Number of participants:** randomised not reported, 0 withdrawn not reported, 34 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=30; Mean Age (SD): 22 (3.09) years; Sex: 67% male; Ethnicity/Nationality: 14 Belgium, 16 Other **Key inclusion criteria:** Health status: cannot have "one or more severe medical conditions"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS), CC (Own brand), EC (Eleaf iStick) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Fagerström Test for Nicotine/Cigarette Dependence, Minnesota Nicotine Withdrawal Scale, A visual analogue scale (VAS) assessing cigarette craving, Product preference **Secondary:** N/A
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals

Study funding	KU Leuven and Thomas More University of Applied Sciences (Independent)
Notes	Although number of participants randomised not reported, the authors stated 46 signed up for intake session. Also 34 completed all sessions, but 4 were excluded from the analyses for not meeting inclusion criteria. Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	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	Unclear	Presence of blinding not described. Included non-active comparator (cigarettes.
Blinding of outcome assessment	Unclear	Presence of blinding not described. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	The authors explained "46 signed up for the intake session, of whom 34 completed all sessions", but number of participants randomised was not reported.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT03435562

Methods	**Date of registration:** 19/02/2018 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** Yes **Design:** Crossover RCT **Setting (Country):** Confined (United States of America) **Study start date; study end date:** 03/03/2018; 16/09/2019 **Intervention duration:** 3 sessions of a 10-puff product use bout and a 90 mins *ad lib* use bout
Participants	**Number of participants:** 22 randomised, 4 withdrawn, 18 completed **Withdrawal reasons reported:** No **Baseline characteristics:** N=18; Mean Age (SD): 36.8 (9.3) years; Sex: 72% male; Ethnicity/Nationality: 7 Black or African America, 8 White, 2 more than one race, 1 unknown or not reported **Key inclusion criteria:** Health status: "healthy"; unspecified CPD; unspecified smoking duration
Interventions	**Interventions:** HTP (IQOS), CC (Own brand), EC (JUUL) **Co-interventions:** None **Mode of exposure:** Direct restricted and direct *ad libitum*
Outcomes	**Primary:** Nicotine **Secondary:** Exhaled Carbon monoxide, Questionnaire of Smoking Urges, Minnesota Nicotine Withdrawal Scale, Heart rate, The Direct Effects of Nicotine Questionnaire, Blood pressure
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Virginia Commonwealth University and National Institute on Drug Abuse, Center for the Study of Tobacco Products (Independent)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Order of the products used in each session will be assigned using Latin-square order procedure"

Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". Primary outcome objectively measured.
Incomplete outcome data	Low	Overall attrition = 18.18%. All participants who completed the study were included in the analysis.
Selective reporting	High	Results data for heart rate and blood pressure have not been reported.

NCT03889990/NCT03995329

Methods	**Date of registration:** 26/03/2019 (NCT03889990); 24/06/2019 (NCT03995329) **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** 2 non-randomised single group assignment trials **Setting (Country):** Confined (Greece) **Study start date; study end date:** 01/01/2018; 01/01/2019 (NCT03889990), 19/06/2019; 10/07/2019 (NCT03995329) **Intervention duration:** 1 session of up to 14 puffs over 5-6 mins
Participants	**Number of participants:** 65 enrolled, 0 withdrawn, 50 completed **Withdrawal reasons reported:** No **Baseline characteristics:** N=50; Mean Age (SD): Smokers 40.3 (13.2) years, Non-smokers 37.4 (10.4) years; Sex: 100% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥5 pack years
Interventions	**Interventions:** HTP (IQOS) in smokers and non-smokers **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide, Forced expiratory volume in one second, Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Total lung capacity, Residual volume, Forced expiratory volume in one second/forced vital capacity, Heart rate, Functional residual capacity, Diffusion Capacity, Peak Expiratory Flow, [Mean] Arterial Blood Pressure, Total respiratory resistances, Respiratory impedance, Oxygen Saturation, Maximal Mid-Expiratory Flow, Expiratory reserve volume **Secondary:** N/A
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Aristotle University Of Thessaloniki (Independent)
Notes	The authors reported enrolling 25 subjects in each trial, but on the registration of one trial (NCT03889990) it was reported that 40 participants had in fact enrolled. It is not clear when or why 15 subjects were removed from the study. Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
Blinding of participants and personnel	Low	Both arms received the same intervention, and the arms were from two separately conducted single-group assignment trials.
Blinding of outcome assessment	Low	All primary outcomes were objectively measured.
Incomplete outcome data	Low	NCT03889990 attrition=37.5%; NCT03995329 attrition =0%, but both arms received the same intervention.
Selective reporting	High	Blood pressure and heart rate were listed as primary outcomes on the non-smoker trial registration (NCT03995329) but results data for these have not been reported.

NCT03301129	
Methods	**Date of registration:** 04/10/2017 **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (Italy) **Study start date; study end date:** 15/10/2017; 25/02/2018 **Intervention duration:** 3 sessions of single use of one cigarette or tobacco stick
Participants	**Number of participants:** 20 randomised, 0 withdrawn, 20 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=20; Mean Age (SD): 35 (13) years; Sex: 30% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: “healthy”; unspecified CPD; unspecified smoking duration
Interventions	**Interventions:** HTP (IQOS2.2), CC (Marlboro Gold), EC (Blu Pro) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Soluble Nox2-derived peptide, Flow-mediated dilation **Secondary:** Cotinine, Vitamin E, Soluble P-selectin, Soluble CD40 ligand, nitric oxide bioavailability, H2O2 production, H2O2 breakdown activity, Systolic blood pressure, Diastolic blood pressure, 8-iso-prostaglandin F2alpha, Product Satisfaction Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	University of Roma La Sapienza (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"The randomization list was computer generated"
Allocation concealment	Unclear	No information provided.
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.

NCT03364751	
Methods	**Date of registration:** 07/12/2017 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Ambulatory (Japan) **Study start date; study end date:** 07/11/2017; 12/06/2019 **Intervention duration:** 6 months
Participants	**Number of participants:** 172 randomised (87 HTP, 85 CC), 2 withdrawn (1 HTP, 1 CC), 170 completed (86 HTP, 84 CC) **Withdrawal reasons reported:** Yes

	Baseline characteristics: N=172; Mean Age (SD): HTP 48.1 years, CC 46.5 years, Dual Use 54.4 years, Other use 54 years (SDs not reported); Sex: 81% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: must have generalized chronic periodontitis; ≥10 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (IQOS), CC (Own brand) **Co-interventions:** Mechanical periodontal therapy **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Mean Periodontal Pocket Depth (PD) reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy **Secondary:** Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Nicotine equivalents, Daily product consumption, Adverse Events/Serious Adverse Events, Mean PD change in sites with initial PD≥4 mm after mechanical periodontal therapy, mean PD change in sites with initial PD<4mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7 mm, Mean clinical attachment level (CAL) change in sites with initial PD≥4mm after mechanical periodontal therapy, mean CAL change in sites with initial PD<4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7mm, change in tooth mobility (grade), change in the number of sites with PD<4 mm, 4-5mm, 5-6 mm, 6-7 mm, and ≥7 mm, change in plague control record, change in mean full-mouth PD, change in mean full-mouth CAL, change in gingival inflammation (GI) score, change in bleeding on probing scores Pro-inflammatory and immuno-regulatory mediators (sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α), Microbiological status, Full transcriptomics profile
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set (as exposed) defined as "*all randomized subjects with at least one product use experience and at least one valid non-safety assessment. Subjects were analyzed based on their actual self-reported product use. Some participants were excluded from analysis for protocol deviations (including, but not limited to, missing measurements)*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization will be done through the Interactive Web and Voice Response System (IXRS)"
Allocation concealment	Low	"Randomization will be done through the Interactive Web and Voice Response System (IXRS)"
Blinding of participants and personnel	High	"Masking: Single (Investigator)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: Single (Investigator)". Primary outcome objectively assessed.
Incomplete outcome data	Low	Attrition: IQOS=1.15% CC=1.18%, overall=1.16%. Exclusion: IQOS=19.54% CC=1.18%, overall=1.74%.
Selective reporting	High	The following outcomes listed in the protocols have not been reported on: measurement of pro-inflammatory and immuno-regulatory mediators; microbiological status; full transcriptomics profile.
Other	High	Only reported data grouped by participant product use not randomisation.

NCT02641587	
Methods	**Date of registration:** 29/12/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined & Ambulatory (Poland) **Study start date; study end date:** January 2016; July 2017 **Intervention duration:** 90 Days (5 days confinement + 85 days ambulatory)
Participants	**Number of participants:** 120 randomised (80 HTP, 40 CC), 5 withdrawn (4 HTP, 1 CC), 115 completed (76 HTP, 39 CC) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=120; Mean Age (SD): HTP 38.9 (8.9) years, CC 39.0 (8.0) years; Sex: 53% male; Ethnicity/Nationality: 100% Caucasian **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥10 years
Interventions	**Interventions:** HTP (carbon heated tobacco product 1.2), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** S-phenylmercapturic acid, monohydroxybutenylmercapturic acid, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin **Secondary:** 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, Exhaled Carbon monoxide, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Cytochrome P450 2A6 activity, Ames mutagenicity test (YG1024+S9), White blood cell count, Systolic blood pressure, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second, Diastolic blood pressure, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Triglycerides, Total cholesterol, Apolipoprotein B, Apolipoprotein A1, Blood glucose, Forced expiratory volume in one second/forced vital capacity, Myeloperoxidase, Intention to use [HTP] Questionnaire, Total anti-oxidant capacity, 8-Hydroxy-2'-deoxyguanosine, Prochaska "Stage of Change" Questionnaire, 4-Hydroxy-2-nonenal, Adverse Events/Serious Adverse Events
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*randomized subjects who fulfilled product adherence criteria and had no major protocol deviations impacting evaluability, such as violation of eligibility criteria or insufficient duration of urine collection. Separate PP populations were defined for the analysis at Day 5 and Day 90. Non-adherence to CHTP was defined as an average cigarette use of > 0.5 cigarettes/day from Day 1 to the end of the respective period (Day 5 or Day 90) or use of > 2 cigarettes on a single day within a week prior to the assessments.*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation	Low	"subjects will be randomized using an interactive web and voice response system (IxRS)"
Allocation concealment	Low	"subjects will be randomized using an interactive web and voice response system (IxRS)"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=5% CC=2.5%, overall=4.17%. 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 "Stage of Change" Questionnaire, MCEQ, and pre- and post-bronchodilator FVC, FEV1/FVC, FEF 25-75 were not reported in any literature sources.

NCT02396381	
Methods	**Date of registration:** 24/03/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Ambulatory (United States of America) **Study start date; study end date:** 12/03/2015; 01/08/2017 **Intervention duration:** 26 weeks
Participants	**Number of participants:** 984 randomised (488 HTP, 496 CC), 127 withdrawn (74 HTP, 53 CC), 857 completed (414 HTP, 443 CC) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=857; Mean Age (SD): HTP 44.2 (9.64) years, CC 45.2 (9.55) years, Dual Use 43.8 (9.77) years, Other use 44.2 (8.14) years; Sex: 58.8% male; Ethnicity/Nationality: 79.2% White, 17.6% Black or African American, 0.7% American Indian or Alaska Native, 0.9% Asian, 0.4% Native Hawaiian or Other Pacific Islander, 1.2% unknown or not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, Carboxyhemoglobin, White blood cell count, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second **Secondary:** 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, Cytochrome P450 2A6 activity, Systolic blood pressure, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Diastolic blood pressure, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Apolipoprotein B, Apolipoprotein A1, Total lung capacity, Residual volume, Forced expiratory volume in one second/forced vital capacity, Myeloperoxidase, Vital capacity, Inspiratory capacity, Functional residual capacity, Intention to use [HTP] Questionnaire, bronchodilator reversibility in FEV1, Albumin

Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set (as exposed) defined as "*Subjects in FAS-AR who had at least 1 record of reported product use diary post-randomization. The exposure assignment was actual product exposure, as defined by the product use pattern categories estimated during the 6 month period: •THS-use: ≥1 THS or CC, and ≥70% THS use over the analysis period, and ≥70% THS use on >50% of days in the analysis period •Dual-use: ≥ 1 THS or CC and, 1% ≤THS<70% over the analysis period, or THS-use and CC-use categories do not apply to 50% of these days •CC-use: ≥1 THS or CC use, and <1% THS use over the entire analysis period and <1% THS use on ≥ 50% of days in the analysis period. •Other-use: Subjects with missing product use, or using e-cigarettes or other tobacco products, quitters, or subjects who switched across different use patterns between consecutive analysis periods*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	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 personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured
Incomplete outcome data	Low	Attrition: IQOS=15.16% CC=10.69%, overall=2.91%. Although not the main analysis population, full analysis set (as randomised) results data were also presented in the published literature.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT02466412

Methods	**Date of registration:** 09/06/2015 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 08/05/2015; November 2015 **Intervention duration:** 2 sessions of single use of one cigarette or tobacco stick
Participants	**Number of participants:** 48 randomised (24 HTP-CC, 24 CC-HTP), 0 withdrawn, 48 completed (24 HTP-CC, 24 CC-HTP) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=47; Mean Age (SD): HTP-CC 44.7 (10.03) years, CC-HTP 40.7 (11.48) years; Sex: 47% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (carbon heated tobacco product 1.1 M), CC (Own brand M) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Spirometry

	Concomitant medications, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC, AUC from start of product use up to 12 hours, Terminal half-life
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations that impact evaluability of the data (to be defined in the SAP) will be included in the PK analysis sets*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	1 subject was excluded from the analyses (sequence HTP-CC) due to all plasma nicotine concentration measurements being below the quantification limit. Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition was 0%. Exclusion: mCHTP-mCC=4.16% mCC-mCHTP=0%, overall=2.1%
Selective reporting	High	Only results data for the two primary outcomes have thus far been published.

NCT02503254

Methods	**Date of registration:** 20/07/2015 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** Yes **Design:** Parallel RCT **Setting (Country):** Confined (Poland) **Study start date; study end date:** 04/07/2015; March 2016 **Intervention duration:** 5 days
Participants	**Number of participants:** 80 randomised (41 HTP, 39 CC), 0 withdrawn, 80 completed (41 HTP, 39 CC) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=80; Mean Age (SD): HTP 34.1 (10.45) years, CC 32.7 (10.97) years; Sex: 49% male; Ethnicity/Nationality: 100% Caucasian **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (carbon heated tobacco product 1.0), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total 1-hydroxypyrene, Adverse Events/Serious Adverse Events, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology

	and urine analysis safety panel, Vital signs, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), Human Puffing/Smoking Topography Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*all the randomized subjects who had at least one post-randomization product use experience, if randomized to CHTP 1.0 or CC, and have at least one valid non safety assessment*." **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"subjects were randomized by an interactive web and voice response system"
Allocation concealment	Low	"subjects were randomized by an interactive web and voice response system"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition and exclusion both 0%.
Selective reporting	High	Several outcomes listed in the study protocol were not reported on in the main results article. Only one was reported on in a poster instead.

NCT02649556

Methods	**Date of registration:** 07/01/2016 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Ambulatory (United States of America) **Study start date; study end date:** 30/09/2015; 20/12/2017 **Intervention duration:** 26 weeks
Participants	**Number of participants:** 857 started (230 HTP, 424 CC, 152 Dual use, 51 Other use), 248 withdrawn (63 HTP, 112 CC, 50 Dual use, 23 Other use), 609 completed (167 HTP, 312 CC, 102 Dual use, 28 Other use) **Withdrawal reasons reported:** No **Baseline characteristics:** N=857; Mean Age (SD): HTP 43.8 (9.68) years, CC 45.2 (9.54) years, Dual use 44.2 (9.76) years, Other use 44.5 (8.21) years; Sex: 58.8% male; Ethnicity/Nationality: 79.2% White, 17.6% Black or African American, 0.7% American Indian or Alaska Native, 0.9% Asian, 0.4% Native Hawaiian or Other Pacific Islander, 1.2% unknown or not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Carboxyhemoglobin, 8-epi-prostaglandin F2alpha, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 11-dehydrothromboxane B2, White blood cell count, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, total N-nitrosonornicotine, Nicotine equivalents, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Nicotine,

	Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Concomitant medications, Cotinine, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Apolipoprotein B, Apolipoprotein A1, Total lung capacity, Forced expiratory volume in one second/forced vital capacity, Myeloperoxidase, Vital capacity, Inspiratory capacity, Functional residual capacity, Intention to use [HTP] Questionnaire, bronchodilator reversibility in FEV1, Albumin, Blood pressure
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set (as exposed) defined as "*The FAS-EX consists of all subjects in FAS-AR who have at least one record of reported product use diary post randomization. The exposure assignment for the FAS-EX will be actual product exposure, as defined by the product use pattern categories estimated during the 12 month period]V4, V16"But note "Some participants were excluded from analysis for protocol deviations (including, but not limited to, missing measurements).*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	This is an extension to NCT02396381. 672 (309 in the THS arm and 363 in the CC arm) subjects enrolled in the extension study; the 857 subjects in the Full Analysis Set - As Exposed (FAS-EX) included subjects for combined analyses from the original six-month study who did not enter the extension study. The analysis was performed according to subjects' exposure over the 12-month period. Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS)."
Allocation concealment	Low	"Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS)."
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	672 subjects enrolled into the extension study (309 THS and 363 CC). However, it is unclear how many completed the study as the data is combined with the previous 6-month trial.
Selective reporting	High	Only results data for the primary outcomes have been published.
Other	High	Only reported data grouped by participant product use not randomisation.

NCT01967706

Methods	**Date of registration:** 23/10/2013 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 01/08/2013; May 2014 **Intervention duration:** 2 sessions of single use of one cigarette, tobacco stick or piece of gum for 35 ± 5 mins
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 1 withdrawn (1 HTP/CC), 61 randomised (43 HTP/CC, 18 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=61; Mean Age (SD): HTP/CC 33.4 (10.03) years, HTP/NRT 30.7 (7.8) years; Sex: 52% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years

Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), NRT (Nicorette Gum) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations (to be defined in the SAP) will be included*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization to product exposure sequence was done through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to product exposure sequence was done through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS-CC=2.27% IQOS-NRT=0%, overall=1.61%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT01780688

Methods	**Date of registration:** 31/01/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** May 2012; December 2012 **Intervention duration:** 2 sessions of single use of one cigarette or tobacco stick and 1 day of *ad lib* use
Participants	**Number of participants:** 28 randomised (14 HTP-CC, 14 CC-HTP), 0 withdrawn, 28 completed (14 HTP-CC, 14 CC-HTP) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=28; Mean Age (SD): HTP-CC 30.0 (4.9) years, CC-HTP 29.1 (4.0) years; Sex: 50% male; Ethnicity/Nationality: 100% Caucasian **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.1), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct restricted and *ad libitum*

Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Questionnaire of Smoking Urges, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Time to reach nicotine Cmax, Terminal half-life of nicotine, Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), Lowest observed plasma concentration during the same sampling interval in which Cpeak was observed, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all randomized subjects who did not deviate from the protocol, who completed at least one of the single use or ad libitum days, and had at least one estimable pharmacokinetic parameter derived from the single or ad libitum days*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization was performed using an Interactive Web Response System"
Allocation concealment	Low	"Randomization was performed using an Interactive Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial and no participants were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

NCT01780714

Methods	**Date of registration:** 31/01/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (Poland) **Study start date; study end date:** June 2012; December 2012 **Intervention duration:** 5 days
Participants	**Number of participants:** 40 randomised (20 HTP, 20 CC), 0 withdrawn, 40 completed (20 HTP, 20 CC) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=40; Mean Age (SD): HTP 37.6 (9.0) years, CC 37.8 (8.3) years; Sex: 50% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.1), CC (Own brand) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Nicotine, Cotinine, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6

	activity, Human Puffing/Smoking Topography (inc. puff count), Adverse Events/Serious Adverse Events, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*randomized subjects who had record of at least one post-randomization product use and at least one valid biomarker assessment*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial 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.

ISRCTN88682435

Methods	**Date of registration:** 06/10/2015 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** 06/01/2015; 10/10/2015 **Intervention duration:** 2 sessions of 10 puffs at 20 sec intervals
Participants	**Number of participants:** 25 randomised, 1 withdrawn, 24 completed **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=25; Mean Age (SD): 33.1 (7.34) years; Sex: 52% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "good general health"; ≥10 CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (HNB2.1), CC (Unknown) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Mouth level exposure to nicotine, Inhalation to non-inhalation ratios during HTP use, Nicotine
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Japan Tobacco International (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias		
Bias	**Authors' judgement**	**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	Study described as "open label". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	Study described as "open label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: NHTP-CC=0%, CC-NHTP=8%. All 24 subjects who completed the study were included in the analyses.
Selective reporting	High	2 outcomes listed on the trial registration (mouth level exposure to nicotine and inhalation to non-inhalation ratios) were not reported.

Nga, 2020	
Methods	**Date of registration:** Not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Non-randomised quasi-experimental (Parallel) **Setting (Country):** Confined (Malaysia) **Study start date; study end date:** Not reported **Intervention duration:** 1 session of 2 10-puff rounds at 30 sec intervals and 5 min inter-round break
Participants	**Number of participants:** 45 enrolled (15 HTP, 15 CC, 15 EC), 0 withdrawn, 45 completed (15 HTP, 15 CC, 15 EC) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=45; Mean Age (SD): 43.6 years (SDs not reported); Sex: 87% male; Ethnicity/Nationality: 51% Chinese, 22% Malay, 20% Indian, 7% Other **Key inclusion criteria:** Health status: not specified; ≥10 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (IQOS), CC (Own brand), EC (Aspire AVP) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	International Medical University (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
Blinding of participants and personnel	Unclear	No information provided on blinding. Included a non-active comparator (cigarettes).
Blinding of outcome assessment	Low	No information provided on blinding. Primary outcome objectively measured.
Incomplete outcome data	Low	All participants enrolled completed the trial and no participants were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

Lopez, 2016

Methods	**Date of registration:** Not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (United States of America) **Study start date; study end date:** Not reported **Intervention duration:** 3 sessions of 2 10-puff bouts at 30 sec intervals and 60 min inter-bout break
Participants	**Number of participants:** 24 randomised, 9 withdrawn, 15 completed **Withdrawal reasons reported:** Yes **Baseline characteristics:** N=15; Mean Age (SD): 33.6 (11.8) years; Sex: 80% male; Ethnicity/Nationality: 47% White or Caucasian, 40% Black or African American, 7% Asian, 7% unknown **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; unspecified smoking duration
Interventions	**Interventions:** HTP (PAX), CC (Own brand), EC (eGo) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Exhaled Carbon monoxide, Questionnaire of Smoking Urges, Nicotine, Minnesota Nicotine Withdrawal Scale, The Direct Effects of Nicotine Questionnaire, The Direct Effects of Product scale **Secondary:** Fagerström Test for Nicotine/Cigarette Dependence, Heart rate
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the U.S. Food and Drug Administration (Independent)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Participants completed each of the three, Latin-square ordered, ~2.5-h sessions"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	Unclear	No information provided on blinding. Included a non-active comparator (cigarettes).
Blinding of outcome assessment	High	No information provided on blinding. Some primary outcomes subjectively measured.
Incomplete outcome data	Low	Overall attrition = 37.5%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.

ISRCTN81075760	
Methods	**Date of registration:** 31/01/2018 **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Ambulatory (United Kingdom) **Study start date; study end date:** 15/02/2018; 31/03/2020 **Intervention duration:** 12-months (day 90 interim analysis)
Participants	**Number of participants:** 411 enrolled (Glo 105, CC 42, Cess 190, NS 40, THD 34) **Withdrawal reasons reported:** Unclear **Baseline characteristics:** N=280 (baseline characteristics for THD arm not reported); Mean Age (SD): Glo 39 (8.8) years, CC 38 (9.3) years, Cess 38 (9.0) years, NS 40 (9.9)

	years; Sex: 55% male; Ethnicity/Nationality: 90.7% White, 3.6% Asian, 2.5% Black or African American, 3.2% Other **Key inclusion criteria:** Health status: "good health"; 10-30 CPD; smoked for ≥5 years
Interventions	**Interventions:** HTP (Glo1.1), CC (Own brand), smoking cessation (aided if necessary), NS, HTP (THD2.4T20) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Augmentation index, 8-epi-prostaglandin F2alpha, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol **Secondary:** 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Spirometry, 11-dehydrothromboxane B2, White blood cell count, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Triglycerides, Total cholesterol, N-(2-cyanoethyl)valine haemoglobin adducts, Pulse wave velocity, Peak Expiratory Flow, Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Product Satisfaction Questionnaire, 4-Hydroxy-2-nonenal, Blood pressure, Tissue plasminogen activator, Plasminogen activator inhibitor-1, Nitric oxide, Monocyte chemotactic protein 1/C-C motif chemokine ligand 2, Glucose, E-selectin, Endothelin-1, 3-nitrotyrosine, Finger plethysmography, 6-minute walking test, Smoking cessation quality of life questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all subjects who had a valid assessment of a biomarker variable and completed the study (to day 90) according to the protocol. This population excludes subjects in Groups B and D who had major protocol deviations or a significant level of self-reported smoking*" and CEVal-compliant population defined as "*excludes subjects in Groups B and D who were considered noncompliant with smoking restrictions, based on CEVal levels above predetermined thresholds*" **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	The published data was from an interim analysis at day 90. Data for the full 12-months has not yet been published. The number of participants randomised/withdrawn/completed at Day 90 was only reported for one arm (THD2.4T20) in which all 34 randomised participants were excluded from the study without explanation. Included in meta-regression analysis. Data obtained from study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"randomised using blocks of computer-generated random number sequences"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"This study will not be blinded". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"This study will not be blinded". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	Number of subjects randomised, attrition and exclusions were not reported, neither were reasons for exclusion.
Selective reporting	High	The 90-day interim publication is the only reporting of results from this 12-month trial. In this publication, only a small selection of outcomes listed in the trial registration and protocol are reported, including only 1 primary outcome.

ISRCTN13439529	
Methods	**Date of registration:** 07/08/2018 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (Italy) **Study start date; study end date:** 01/01/2018; 30/09/2018 **Intervention duration:** 4 sessions of single use of one cigarette, tobacco stick or cartridge
Participants	**Number of participants:** 32 randomised, withdrawn/completed not reported **Withdrawal reasons reported:** N/A **Baseline characteristics:** N= 32; Mean Age (SD): 35.8 (9.66) years; Sex: 72% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: normal biochemistry, haematology, urinalysis, ECG and physical; ≥10 CPD; smoked for ≥ 1 year
Interventions	**Interventions:** HTP (Glo1.0), HTP (Glo1.1), CC (Own brand), NRT (Nicorette inhaler) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration, Intention to use [HTP] Questionnaire, Product Liking Questionnaire, Urge To Smoke questionnaire, Urge For Product questionnaire **Secondary:** Product Evaluation Scale, Human Puffing/Smoking Topography (inc. puff count), Adverse events
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"The order of use will be assigned by a pre-defined computer-generated randomisation schedule"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"open-label". Included non-active comparator.
Blinding of outcome assessment	High	"open-label". Some primary outcomes subjectively measured.
Incomplete outcome data	Unclear	While the number of participants randomised is reported, the number withdrawn/completed and included in the analysis was not reported.
Selective reporting	High	The two secondary outcomes (Puff count during 5 minute investigational product use session and Product evaluation using the Product Evaluation Scale (PES)) were not reported.

ISRCTN14301360/UMIN000024988	
Methods	**Date of registration:** 14/12/2016 (ISRCTN), 24/11/2016 (UMIN) **Submitted to peer-reviewed journal within 12 months:** Yes **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 01/08/2016; 30/06/2017 **Intervention duration:** 5 days

Participants	**Number of participants:** 182 (30 Glo R, 30 Glo M, 30 CC R, 30 CC M, 30 Cess, 30 IQOS R, 2 unknown), 2 withdrawn (2 unknown), 180 completed (30 Glo R, 30 Glo M, 30 CC R, 30 CC M, 30 Cess, 30 IQOS R) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 180; Mean Age (SD): Glo R 34 (10.1) years, Glo M 31 (7.7) years, CC R 32 (8.2) years, CC M 33 (8.6) years, Cess 35 (10.0) years, IQOS R 33 (9.5) years; Sex: 50% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "good health"; 10-30CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (Glo 1.0 R), HTP (Glo 1.0 M), HTP (IQOS R), CC (Lucky Strike R), CC (Lucky Strike M), tobacco and nicotine cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine, N-acetyl-S-(2-carba-moylethyl)cysteine **Secondary:** Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Electrocardiogram, Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration, Spirometry, 8-epi-prostaglandin F2alpha, Human Puffing/Smoking Topography (inc. puff count), White blood cell count, Nicotine molar metabolic ratio, Product Satisfaction Questionnaire, Medical history, Adverse Events/Serious Adverse Events, Daily product consumption, Vital signs
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per protocol population defined as "*All subjects who had valid assessment of a biomarker variable and completed study according to the protocol will be used for biomarker analyses*" and pharmacokinetic population defined as "*All subjects who had sufficient data to calculate at least 1 pharmacokinetic parameter and completed study according to the protocol will be used for PK data analyses*". **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	2 participants were randomised but withdrew before the exposure period. The groups these 2 belonged to were not reported. Included in meta-regression analysis. Data obtained from published literature and study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"The randomisation will be performed by Covance"
Allocation concealment	Low	"The randomisation will be performed by Covance and the clinics will enrol the participants and assign them to interventions"
Blinding of participants and personnel	High	"open-label". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"open-label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Overall attrition = 1.1%. No subjects who completed the study were excluded from the primary analyses.
Selective reporting	High	There were several outcomes listed in the protocol, namely biomarkers of effect and pharmacokinetic measures, that were not reported on.

DRKS00012919

Methods	**Date of registration:** 29/08/2017

	Submitted to peer-reviewed journal within 12 months: Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Crossover RCT **Setting (Country):** Confined (Germany) **Study start date; study end date:** 01/06/2016; not reported **Intervention duration:** 4 sessions of single use of one cigarette or tobacco stick at 1 puff every 30 secs for 10 puffs
Participants	**Number of participants:** 20 randomised, 0 withdrawn, 20 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N= 20; Mean Age (SD): 21.9 (2.6) years; Sex: 50% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: no disorders or diseases; CPD and smoking duration not reported
Interventions	**Interventions:** HTP (IQOS2.2), CC (Marlboro Gold), EC (eGo nicotine), EC (eGo no nicotine) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Nicotine, Systolic blood pressure **Secondary:** Heart rate, Pulse wave velocity, Augmentation index, [Mean] Arterial Blood Pressure
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Universitätsklinikum Schleswig-Holstein Campus Lübeck (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**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	Only the e-cigarette arms were blinded. Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	Only the e-cigarette arms were blinded. All primary outcomes objectively measured.
Incomplete outcome data	Unclear	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.
Selective reporting	High	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.

ISRCTN80651909

Methods	**Date of registration:** 09/03/2017 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** 01/08/2016; 03/10/2017 **Intervention duration:** 5 days
Participants	**Number of participants:** 148 randomised (30 Glo, 30 CC, 30 EC, 29 Cess, 29 HTP), 7 withdrawn (2 Glo, 2 EC, 2 Cess, 1 HTP), 143 (28 Glo, 30 CC, 28 EC, 29 Cess, 28 HTP) **Withdrawal reasons reported:** Yes

	Baseline characteristics: N= 148; Mean Age (SD): Glo 37.4 (11.48) years, CC 35.6 (8.93) years, EC 36.7 (9.1) years, Cess 37.2 (9.09) years, HTP (32.8 (8.78) years; Sex: 59% male; Ethnicity/Nationality: 100% White **Key inclusion criteria:** Health status: "good health"; 10-30CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (Glo1.0), CC (Lucky Strike Regular), EC (prototype IS1.0[TT]), tobacco and nicotine cessation, HTP (unknown) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid , total N-nitrosonornicotine, Nicotine equivalents, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine, N-acetyl-S-(2-carba-moylethyl)cysteine, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, 8-epi-prostaglandin F2alpha, White blood cell count, Nicotine molar metabolic ratio **Secondary:** Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration, Spirometry, Product Satisfaction Questionnaire, Adverse Events/Serious Adverse Events, Daily product consumption
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	According to the published study literature, 29 participants were randomised to the cessation and 29 completed this study, yet 2 were said to have withdrawn. It is not clear if these 2 were replaced or if this was a mistake. Data from the unknown HTP arm was excluded from the analysis because the authors "*wished to focus on the exposure continuum*". Included in meta-regression analysis. Data obtained from published literature and study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"The randomization will be computer-generated using SAS Version 9.3"
Allocation concealment	Low	"A randomisation scheme was provided for the clinical site to recruit 30 participants for each arm, giving a total of 150 participants"
Blinding of participants and personnel	High	"open-label". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"open-label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: Glo=6.67% CC=0% EC=6.67% Cess=0% HTP=3.45%, overall=3.38%. Exclusion: Glo=6.67% CC=0% EC=6.67% Cess=0% HTP=N/A, overall=3.34%.
Selective reporting	High	No data reported for an entire study arm (C: "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

UMIN000041539

Methods	**Date of registration:** 25/08/2020 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Parallel RCT **Setting (Country):** Confined (Japan)

	Study start date; study end date: September 2020; October 2020 **Intervention duration:** 5 days
Participants	**Number of participants:** 90 randomised (15 Ploom Tech+, 15 Ploom S2.0, 15 unknown HTP, 15 unknown HTP, 15 CC, 15 Cess), withdrawn/completed not reported **Withdrawal reasons reported:** N/A **Baseline characteristics:** not reported **Key inclusion criteria:** Health status: "good health"; unspecified CPD; smoked for ≥1 year
Interventions	**Interventions:** HTP (Ploom Tech+), HTP (Ploom S2.0), HTP (unknown), HTP (unknown), CC (Own brand), smoking cessation **Co-interventions:** None **Mode of exposure:** Unclear
Outcomes	**Primary:** Exhaled Carbon monoxide, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, total N-nitrosonornicotine, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, total 1-hydroxypyrene, S-phenylmercapturic acid, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, 3-hydroxybenzo[a]pyrene, 1-aminonaphthalene **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	Japan Tobacco International (Industry-affiliated)
Notes	Data requested from study authors, but no data received. Therefore, not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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	"Open -no one is blinded". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Open -no one is blinded". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	While the number of participants randomised was reported, the number completed and included in the analysis was not.
Selective reporting	Unclear	As the trial registration does not explicitly list all outcomes measured in this trial and there is no publicly available protocol, it is difficult to determine whether the 15 biomarkers of exposure were the only measures of the study. Moreover, data is thus far only presented in a graph.

NCT03700112	
Methods	**Date of registration:** 09/10/2018 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No results posted **Design:** Crossover RCT **Setting (Country):** Confined (New Zealand) **Study start date; study end date:** 04/12/2018; 09/04/2019 **Intervention duration:** 8 sessions of 10 puffs at 30 second intervals and 8 sessions of *ad lib* use for 4.5 minutes
Participants	**Number of participants:** 25 randomised, 0 withdrawn, 25 completed **Withdrawal reasons reported:** N/A

	Baseline characteristics: N= 25; Mean Age (SD): 30.44 (10.18) years; Sex: 72% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥8 CPD; smoked for ≥1 year
Interventions	**Interventions:** EC (JUUL), EC (myblu Original 2.4%), EC (MarkTen Bold Classic 4.0%), EC (VUSE Solo Original 4.8%), EC (PHIX Original Tobacco 5.0%), EC (NJOY Daily EXTRA Rich Tobacco 6.0%), HTP (IQOS), CC (Marlboro Red) **Co-interventions:** None **Mode of exposure:** Direct restricted and *ad libitum*
Outcomes	**Primary:** Time to reach nicotine Cmax, Maximal nicotine concentration, Baseline adjusted Cmax, Baseline adjusted AUC1hour, Area under the concentration curve from start of product use to 60 minutes **Secondary:** Exhaled Carbon monoxide, Modified Cigarette/Product Evaluation Questionnaire, Human Puffing/Smoking Topography (inc. puff count), Rate of plasma nicotine rise (speed of absorption)
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	JUUL Labs Inc. (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	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	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	Attrition was 0%. Exclusion=0-8% as the analysis population stated under the tables on poster was "N=24-25" or "N=23-25". However, the exact N for each outcome analysis is not specified and reasons for excluding some subjects from the analyses are not provided.
Selective reporting	High	Total number of puffs during exposure session and exhaled CO - both measures listed on the trial registration - were not reported.

NCT01970995

Methods	**Date of registration:** 28/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined and Ambulatory (Japan) **Study start date; study end date:** 01/08/2013; November 2014 **Intervention duration:** 90 Days (5 days confinement + 85 days ambulatory)
Participants	**Number of participants:** 160 randomised (78 HTP, 42 CC, 40 Cess), 5 withdrawn (2 HTP, 1 CC, 2 Cess), 155 (76 HTP, 41 CC, 38 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 37.1 (10.58) years, CC 37.4 (11.23) years, Cess 37 (9.96) years; Sex: 57.5% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), smoking cessation (aided if necessary) **Co-interventions:** None

	Mode of exposure: Direct restricted and *ad libitum*
Outcomes	**Primary:** Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), White blood cell count, Systolic blood pressure, Soluble intercellular adhesion molecule-1. High-density lipoprotein cholesterol, Diastolic blood pressure, Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Potential combustion occurances in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire, Triglycerides Total cholesterol, Blood glucose
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all randomized subjects who - have had compliance to their randomized arm if randomized to THS 2.2 Menthol or SA arms. Non-compliance will be defined over a period (confinement period,] Day6-Day 30 Visit],]Day 30 Visit-Day 60 Visit],]Day 60 Visit-Day 90 Visit] and will be defined as having smoked than 3 CC during a single day in that period or having smoked on average over that period more that, not including 0.5 cigarettes per day. - have not been misrandomized. - and have no major protocol deviation*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**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 personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	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%.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01989156

Methods	**Date of registration:** 20/11/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined and Ambulatory (United States of America) **Study start date; study end date:** 17/12/2013; May 2015

	Intervention duration: 91 Days (5 days confinement + 86 days ambulatory)
Participants	**Number of participants:** 160 (80 HTP, 41 CC, 39 Cess), 21 withdrawn (7 HTP, 6 CC, 8 Cess), 139 completed (73 HTP, 35 CC, 31 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 39.2 (11.72) years, CC 33.7 (10.17) years, Cess 38.8 (11.42) years; Sex: 60% male; Ethnicity/Nationality: 62% White, 32% Black or African American, 6% other, 1% missing **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), smoking cessation (aided if necessary) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, 2-cyanoethylmercapturic acid , Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), White blood cell count, Systolic blood pressure, Soluble intercellular adhesion molecule-1, High-density lipoprotein cholesterol, Forced expiratory volume in one second, Diastolic blood pressure, Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Weight, Waist circumference, Low-density lipoprotein cholesterol, Homocysteine, High-sensitivity C-reactive protein, Fibrinogen, Platelet count, Hemoglobin glycosylated (Hemoglobin A1C), Potential combustion occurances in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire, Forced vital capacity, Forced expiratory flow at 25–75% of forced vital capacity, Triglycerides, Total cholesterol, Apolipoprotein B, Apolipoprotein A1, Total lung capacity, Blood glucose, Residual volume, Vital capacity, Inspiratory capacity, Diffusion Capacity, Carbon monoxide transfer coefficient, Oxysterols (6α-hydroxy-5α-cholestanol, 7α-hydroxycholesterol, 5α,6αepoxycholestanol, 7-ketocholesterol, 7β-hydroxycholesterol, 5β,6β-epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 22(R)-hydroxycholesterol, 4ßhydroxycholesterol, and 27-hydroxycholesterol), Prochaska "Stage of Change" Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Per-protocol population defined as "*all randomized subjects who: Have had compliance to their randomized arm; Have not been misrandomized; and Have no major protocol deviation*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
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". Included non-active comparator (cigarettes).
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	
Methods	**Date of registration:** 28/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 23/07/2013; July 2014 **Intervention duration:** 5 days
Participants	**Number of participants:** 160 randomised (80 HTP, 40 CC, 40 Cess), 2 withdrawn (2 Cess), 158 completed (80 HTP, 40 CC, 38 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 37.6 (11.7) years, CC 37.2 (11.7) years, Cess 35.9 (10.6) years; Sex: 50% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), tobacco and nicotine cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, Fagerström Test for Nicotine/Cigarette Dependence, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine Withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Potential combustion occurrences in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*all the randomized subjects who had at least one post-randomization product use experience, if randomized to THS 2.2 or CC, and have at least one valid nonsafety assessment*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Data requested from study authors, but no data received. Therefore, not included in meta-regression analysis.

Risk of bias		
Bias	**Authors' judgement**	**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)". Included non-active comparator (cigarettes).
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	
Methods	**Date of registration:** 10/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Parallel RCT **Setting (Country):** Confined (Poland) **Study start date; study end date:** 29/06/2013; June 2014 **Intervention duration:** 5 days
Participants	**Number of participants:** 160 randomised (80 HTP, 41 CC, 39 Cess), 2 withdrawn (1 HTP), 158 completed (79 HTP, 41 CC, 39 Cess) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 160; Mean Age (SD): HTP 35.4 (9.4) years CC 32.6 (10.06) years, Cess 33.6 (11.51) years; Sex: 50% male; Ethnicity/Nationality: 100% White **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), tobacco and nicotine cessation **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** monohydroxybutenylmercapturic acid, 3-hydroxypropylmercapturic acid, Carboxyhemoglobin, S-phenylmercapturic acid **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 2-cyanoethylmercapturic acid, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, total N-nitrosonornicotine, Nicotine equivalents, total 1-hydroxypyrene, o-toluidine, 4-aminobiphenyl, 2-aminonaphthalene, Daily product consumption, 3-hydroxy-1-methylpropylmercapturic acid, 2-hydroxyethylmercapturic acid, Respiratory symptoms (inc. cough assessment), Nicotine, Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, 3-hydroxybenzo[a]pyrene, Spirometry, Concomitant medications, Cotinine, 1-aminonaphthalene, 8-epi-prostaglandin F2alpha, 11-dehydrothromboxane B2, Minnesota Nicotine withdrawal Scale, Cytochrome P450 2A6 activity, Human Puffing/Smoking Topography (inc. puff count), Ames mutagenicity test (YG1024+S9), Time to nicotine Cpeak, Maximum observed nicotine concentration (following ad lib use), S-benzylmercepturic acid, Potential combustion occurances in tobacco plugs, Weighted average nicotine concentration over 24 hours, Human Puffing/Smoking Topography Questionnaire
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Full analysis set defined as "*all randomized participants who used the allocated product at least once after randomization and with at least one valid value for a biomarker of exposure*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Data requested from study authors, but no data received. Therefore, not included in meta-regression analysis.
Risk of bias	

Bias	Authors' judgement	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)". Included non-active comparator (cigarettes).
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 study were included in the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01959607

Methods	**Date of registration:** 10/10/2013 **Submitted to peer-reviewed journal within 12 months:** No **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (Japan) **Study start date; study end date:** 31/07/2013; April 2014 **Intervention duration:** 2 sessions of 14 puffs (6 minutes)
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 2 withdrawn (2 HTP/CC), 60 completed (42 HTP/CC, 18 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 60; Mean Age (SD): HTP/CC 33.2 (8.61) years, HTP/NRT 35.8 (10.44) years; Sex: 55% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), NRT (Nicorette gum) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all randomised subjects who gave informed consent, completed at least 1 of the single-use days (Day 1 or 3), and for whom at least 1 PK parameter was derived. Subjects with major protocol deviations that impacted the evaluability of the results were excluded from the PK analysis sets*." **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System."

Allocation concealment	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System."
Blinding of participants and personnel	High	"This was an open-label study". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"This was an open-label study". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS-CC=5%, IQOS-NRT=0%. No participants who completed the trial were excluded from the analyses.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01967732	
Methods	**Date of registration:** 23/10/2013 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (United Kingdom) **Study start date; study end date:** 01/11/2013; July 2014 **Intervention duration:** 2 sessions of single use of one cigarette, tobacco stick or 1 nasal spray in each nostril
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 2 withdrawn (2 HTP/CC), 60 completed (42 HTP/CC, 18 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 60; Mean Age (SD): HTP/CC 32.1 (8.98) years, HTP/NRT 30.6 (5.8) years; Sex: 58% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2), CC (Own brand), NRT (Nicotrol nasal spray) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Fagerström Test for Nicotine/Cigarette Dependence, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations*" **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization to product exposure sequence was performed through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to product exposure sequence was performed through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).

Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS/CC=4.55% IQOS/NRT=5.56%, overall=4.84%. Exclusion: IQOS/CC=6.81% IQOS/NRT=5.5%, overall=6.45%.
Selective reporting	Low	All outcomes reported in at least one literature source.

NCT01967719	
Methods	**Date of registration:** 23/10/2013 **Submitted to peer-reviewed journal within 12 months:** No publication **Published key outcomes on trial registration within 12 months:** No **Design:** Crossover RCT **Setting (Country):** Confined (United States of America) **Study start date; study end date:** 02/10/2013; May 2014 **Intervention duration:** 2 sessions of single use of one cigarette, tobacco stick or 1 nasal spray in each nostril
Participants	**Number of participants:** 62 randomised (44 HTP/CC, 18 HTP/NRT), 3 withdrawn (2 HTP/CC, 1 HTP/NRT), 60 completed (42 HTP/CC, 17 HTP/NRT) **Withdrawal reasons reported:** Yes **Baseline characteristics:** N= 62; Mean Age (SD): HTP/CC 37.2 (10.2) years, HTP/NRT 33.1 (7.3) years; Sex: 53% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; ≥10 CPD; smoked for ≥3 years
Interventions	**Interventions:** HTP (IQOS2.2 M), CC (Own brand M), NRT (Nicotrol nasal spray) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Maximal nicotine concentration, Area under the concentration curve from start of product use to time of last quantifiable concentration **Secondary:** Exhaled Carbon monoxide, Adverse Events/Serious Adverse Events, Modified Cigarette/Product Evaluation Questionnaire, Questionnaire of Smoking Urges, Carboxyhemoglobin, Respiratory symptoms (inc. cough assessment), Physical examination, Clinical chemistry, haematology and urine analysis safety panel, Vital signs, Electrocardiogram, Time to reach nicotine Cmax, Spirometry, Concomitant medications, Cotinine, Terminal half-life of nicotine, Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity, Partial AUC
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Pharmacokinetic population defined as "*all the randomized subjects who give informed consent, completed at least one of the single use Day 1 or Day 3, and for whom at least one PK parameter can been derived. Only subjects without major protocol deviations will be included in the PK analysis sets*." **Unit of analysis:** Individuals
Study funding	Philip Morris International (Industry-affiliated)
Notes	Included in meta-regression analysis. Data obtained from published literature.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS/CC=4.55% IQOS/NRT=0%, overall=3.23%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.

Gee et al., 2018 (Actual Use Study)	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Actual use study. **Setting (Country):** Confined and Ambulatory (Japan) **Study start date; study end date:** not reported **Intervention duration:** Group 1 = 13 days, Groups 2 and 3 = 9 days, Group 4 = 1 day
Participants	**Number of participants:** 208 (52 Group 1, 52 Group 2, 52 Group 3, 52 Group 4) **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=208; Age, n participants: 21-29=58, 30-44=109, 45-65=40; Sex: 52% male; Ethnicity/Nationality: 100% Japanese **Key inclusion criteria:** Health status: not specified; smokers ≥5 CPD, smoked for ≥6 months; THS users ≥5 product use sessions per day, using for ≥3 months
Interventions	**Interventions:** Group 1 (smokers): CC (T189 R), HTP (Glo1.0 R), HTP (IQOS R) Group 2 (smokers): CC (322 M), HTP (Glo1.0 M) Group 3 (THS users): HTP (Glo1.0 R), HTP (IQOS R) Group 4 (smokers): HTP (Glo1.0 R) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Puffing topography, Mouth level exposure to nicotine free dry particulate matter, nicotine and menthol, Daily product consumption, Mouth insertion depth **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. Non-active (CC) comparator.
Blinding of outcome assessment	High	No information is provided in the text regarding blinding. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	Number of participants enrolled, completed and withdrawn was not reported.
Selective reporting	Low	All outcomes listed in methods were reported on in the main results.

Jones et al., 2020 (Actual Use Study)	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Actual use study. **Setting (Country):** Confined and Ambulatory (Italy) **Study start date; study end date:** not reported **Intervention duration:** Group 1 = 15 days, Group 2 = 10 days, Group 3 = 5 days
Participants	**Number of participants:** 152 (50 Group 1, 50 Group 2, 52 Group 3)

	Withdrawal reasons reported: N/A **Baseline characteristics:** N=152; Age, n participants: 25-29=21, 30-44=67, 45-65=64; Sex: 50% male; Ethnicity/Nationality: 100% Italian **Key inclusion criteria:** Health status: not specified; smokers ≥8 CPD, smoked for ≥7 years; vapers ≥1 product use per day, using for ≥6 months
Interventions	**Interventions:** Group 1 (smokers): EC (IS1.0[T]), HTP (IQOS2.4), CC (C651) Group 2 (vapers): EC (Is1.0[T]) Group 3 (smokers): HTP (Glo1.0), CC (C651) **Co-interventions:** None **Mode of exposure:** Direct *ad libitum*
Outcomes	**Primary:** Puffing topography, Mouth level exposure to nicotine free dry particulate matter and nicotine, Daily product consumption, Sensory questionnaire **Secondary:** None
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	High	Non-randomised trial.
Allocation concealment	High	Non-randomised trial.
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	High	No information is provided in the text regarding blinding. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	Number of participants enrolled, completed and withdrawn was not reported.
Selective reporting	Low	All outcomes listed in methods were reported on in the main results.

Dalrymple, 2022

Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** repeated measures **Setting (Country):** Confined (Germany) **Study start date; study end date:** not reported **Intervention duration:** 3 sessions of 32 puffs of Glo, ePen 3 or N491 cigarette
Participants	**Number of participants:** 10 enrolled, 0 withdrawn, 10 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=10; Age, n participants: 52.8; Sex: 30% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; non-smokers
Interventions	**Interventions:** HTP (Glo), CC (N491), EC (ePen 3) **Co-interventions:** None **Mode of exposure:** Direct restricted
Outcomes	**Primary:** Malondialdehyde; Catalase; Squalene; Squalene monohydroperoxide; Squalene monohydroperoxide/Squalene ratio; L* (lightness); a* (green-red); b* (blue-yellow); Total difference in colour from control (ΔE) **Secondary:** Adverse Events/Serious Adverse Events
Analyses	**Sample size calculation reported:** No

	Primary analysis population: Not specified or unclear **Unit of analysis:** areas of skin
Study funding	British American Tobacco (Industry-affiliated)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	N/A	Cochrane RoB tools designed to assess trials in which the unit of randomisation is people, rather than multiple sites on one individual, selection bias cannot be fairly assessed using this tool on this study.
Allocation concealment	N/A	
Blinding of participants and personnel	Unclear	There is insufficient information 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, but all primary outcomes objectively measured.
Incomplete outcome data	Low	All participants completed the study and none withdrew.
Selective reporting	Low	All outcomes were reported on.

NCT03452124

Methods	**Date of registration:** 02/03/2018 **Submitted to peer-reviewed journal within 12 months:** Unclear **Published key outcomes on trial registration within 12 months:** Unclear **Design:** Randomised controlled crossover followed by case control study **Setting (Country):** Confined and ambulatory (Greece) **Study start date; study end date:** 30/03/2018; not reported **Intervention duration:** acute: 3x 7 minute sessions of sham cigarette, IQOS or cigarette Chronic: 1 month
Participants	**Number of participants:** acute: 50 randomised, 0 withdrawn, 50 completed Chronic: 25 enrolled, 0 withdrawn, 25 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=75; Age, n participants: 48 (acute) 26 (chronic); Sex: 48% (acute & chronic) male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; smokers ≥5 CPD
Interventions	**Interventions:** Acute: HTP (IQOS), CC (Marlboro Red), sham cigarette Chronic: HTPs (IQOS), CC (unknown brand) **Co-interventions:** None **Mode of exposure:** Direct ad libitum
Outcomes	**Primary:** Pulse wave velocity; Exhaled Carbon Monoxide; Perfused boundary region of sublinqual arterial microvessels; Global longitudinal strain of left ventricle; Coronary flow reserve **Secondary:** 11-dehydrothromboxane B2; Systolic blood pressure; Central Systolic blood pressure; Heart rate; Diastolic blood pressure; Protein carbonyls; Malondialdehyde; Myocardial work; Total arterial compliance; Augmentation index; Vital signs; Electrocardiogram; High-sensitivity C-reactive protein; Transforming growth factor-b; lipoprotein associated phospholipase A2; Tumor necrosis factor-a; Interleukin 6; Interleukin 10; Procollagen propeptide type III; Matrix metalloproteinase 2; Matrix metalloproteinase 9; Macrophage-colony stimulating factor; Flow-mediated dilation
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** Not specified or unclear **Unit of analysis:** Individuals
Study funding	National and Kapodistrian University of Athens (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low	"Randomization was performed by an attending research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm"
Allocation concealment	Unclear	There is insufficient information provided to determine whether intervention allocation was concealed
Blinding of participants and personnel	Unclear	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.
Blinding of outcome assessment	Low	"examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures.
Incomplete outcome data	Low	All participants completed the study and none withdrew.
Selective reporting	High	Not all outcomes measured were reported on.

Iokeimidis, 2021

Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** Randomised controlled crossover **Setting (Country):** Confined (Greece) **Study start date; study end date:** note reported; not reported **Intervention duration:** 3 sessions of 5 minutes use of IQOS, cigarette or cham cigarette
Participants	**Number of participants:** 22 randomised, 0 withdrawn, 22 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=22; Age, n participants: 33, n=22; Sex: 45% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; smoking history criteria not defined
Interventions	**Interventions:** HTP (IQOS), CC (unknown brand), sham cigarette **Co-interventions:** none **Mode of exposure:** direct ad libitum
Outcomes	**Primary:** Heart rate; Brachial systolic blood pressure; Aortic systolic blood pressure; Augmentation index; Carotid–femoral pulse wave velocity; Brachial-ankle pulse wave velocity **Secondary:** none
Analyses	**Sample size calculation reported:** Yes **Primary analysis population:** not specified or unclear **Unit of analysis:** individuals
Study funding	Athens Medical School, Hippokration Hospital (ndependent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear	Whether or how participants were randomised is unclear.
Allocation concealment	Unclear	How interventions were allocated is not described.
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 objectively measured.
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	Low	Results data for all outcomes were reported.

Yaman, 2021	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** randomised controlled crossover **Setting (Country):** confined (Cyprus) **Study start date; study end date:** Not reported; not reported **Intervention duration:** 3 sessions of 5 minutes use of IQOS or cigarettes
Participants	**Number of participants:** 27 randomised, 0 withdrawn, 27 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=27; Age, n participants: 39.2, n=27; Sex: 59% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "healthy"; smoking history criteria not reported
Interventions	**Interventions:** HTP (IQOS), CC (own brand) **Co-interventions:** none **Mode of exposure:** Direct restricted
Outcomes	**Primary:** A wave velocity; Diastolic blood pressure; E wave velocity; E/A ratio; Em/Am ratio; Heart rate; Left atrium diameter; Left ventricle ejection fraction; Left ventricle global circumferential strain; Left ventricle global longitudinal strain; Left ventricular end-diastolic diameter; Peak early diastolic velocity of the left ventricle; Peak late diastolic velocity of the left ventricle; Right atrium diameter; Right ventricle diameter; Right ventricle free wall strain; Right ventricle global longitudinal strain; Right ventricle peak early diastolic velocity; Right ventricle peak late diastolic velocity; Right ventricle systolic myocardial velocity; Right ventricle Em/Am ratio; Systolic blood pressure; Systolic myocardial velocity of the left ventricle; Tricuspid annular plane systolic excursion **Secondary:** none
Analyses	**Sample size calculation reported:** No **Primary analysis population:** Not specified or unclear **Unit of analysis:** individuals
Study funding	Near East University and Mersin City Training and Research Hospital (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Despite explaining the subjects were randomised, the sequence generation was not described in any of the study literature.
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	Low	All outcomes were reported on.

Phillips-Waller, 2021	
Methods	**Date of registration:** not registered **Submitted to peer-reviewed journal within 12 months:** unclear **Published key outcomes on trial registration within 12 months:** unclear **Design:** Non-randomised controlled crossover **Setting (Country):** confined (UK) **Study start date; study end date:** not reported; not reported

	Intervention duration: 5 sessions of single use of IQOS, cigarette, JUUL, KangerTech EVOD, Innokin iTaste MVP 2
Participants	**Number of participants:** 22 enrolled, 0 withdrawn, 22 completed **Withdrawal reasons reported:** N/A **Baseline characteristics:** N=22; Age, n participants: 31, n=22; Sex: 82% male; Ethnicity/Nationality: not reported **Key inclusion criteria:** Health status: "No serious illnesses"; smokers & vapers <1 CPD
Interventions	**Interventions:** HTPS (IQOS), CC (own brand), EC (JUUL, KangerTech EVOD, Innokin iTaste MVP 2) **Co-interventions:** none **Mode of exposure:** direct ad libitum
Outcomes	**Primary:** Human Puffing/Smoking Topography (inc. puff count); Maximal nicotine concentration; Time to reach nicotine Cmax; Area under the concentration curve from start of product use to 30 minutes; Nicotine; Nicotine boost effect; Urge To Smoke questionnaire; Non-standard questionnaire on user experience **Secondary:** none
Analyses	**Sample size calculation reported:** no **Primary analysis population:** not specified or unclear **Unit of analysis:** individuals
Study funding	Tobacco Advisory Group project grant, Cancer Research UK (Independent)
Notes	Not included in meta-regression analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High	Non-randomised trial
Allocation concealment	High	Non-randomised trial
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	High	No information is provided in the text regarding blinding. Some primary outcomes were subjectively measured.
Incomplete outcome data	Unclear	The authors state they "studied 22 current smokers" but it is unclear whether more than 22 were initially enrolled.
Selective reporting	Low	All outcomes were reported on.

Abbreviations: HTP=heated tobacco product; CC=combustible cigarette; EC=electronic cigarette; Cess=cessation; NS=non-smoker; NRT=nicotine replacement therapy; R=regular, M=menthol; CPD=cigarettes per day

Supplementary Table 2. Outcomes measured and reported in heated tobacco product interventional trials.

Outcome	Number of trials (measured)	Number of trials (reported)
Biomarkers of exposure		
Exhaled Carbon monoxide	26	21
2-cyanoethylmercapturic acid	14	14
Nicotine	14	11
Nicotine equivalents (molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide)	14	13
total N-nitrosonornicotine	14	13
3-hydroxypropylmercapturic acid	13	13

monohydroxybutenylmercapturic acid	13	13
S-phenylmercapturic acid	13	12
total 1-hydroxypyrene	13	13
2-aminonaphthalene	12	12
4-aminobiphenyl	12	12
o-toluidine	12	12
2-hydroxyethylmercapturic acid	11	11
3-hydroxy-1-methylpropylmercapturic acid	11	11
Cotinine	10	8
3-hydroxybenzo[a]pyrene	9	9
1-aminonaphthalene	8	8
Cytochrome P450 2A6 activity	8	7
Ames mutagenicity test (YG1024+S9)	6	6
S-benzylmercepturic acid	4	4
N-acetyl-S-(2-carba-moylethyl)cysteine	2	2
N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine	2	2
4-hydroxybutyl-2-mercapturic acid	1	1
Cotinine	1	1
N-(2-cyanoethyl)valine haemoglobin adducts	1	1
Carboxyhemoglobin*	14	13
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol*	15	15
Biomarkers of potential harm		
11-dehydrothromboxane B2	10	10
8-epi-prostaglandin F2alpha	9	9
Systolic blood pressure	8	8
White blood cell count	8	7
Diastolic blood pressure	7	7
Heart rate	7	5
High-sensitivity C-reactive protein	7	5
Fibrinogen	6	4
Forced expiratory flow at 25–75% of forced vital capacity (aka Maximal mid-expiratory flow)	6	3
Forced expiratory volume in one second	6	6
Forced vital capacity	6	3
High-density lipoprotein cholesterol	6	6
Homocysteine	6	4
Low-density lipoprotein cholesterol	6	4
Soluble intercellular adhesion molecule-1	6	6
Waist circumference	6	4
Weight	6	4
Hemoglobin glycosylated (Hemoglobin A1C)	5	4
Platelet count	5	4
Apolipoprotein A1	4	3
Apolipoprotein B	4	3
Augmentation index	4	2

Forced expiratory volume in one second/forced vital capacity	4	2
Total cholesterol	4	3
Total lung capacity	4	3
Triglycerides	4	3
Blood glucose	3	3
Blood pressure	3	0
Functional residual capacity	3	2
Inspiratory capacity	3	2
Myeloperoxidase	3	2
Pulse wave velocity	3	2
Residual volume	3	3
Vital capacity	3	2
[Mean] Arterial Blood Pressure	2	1
4-Hydroxy-2-nonenal	2	0
Albumin	2	1
bronchodilator reversibility in FEV1	2	1
Carbon monoxide transfer coefficient	2	2
Diffusion Capacity	2	2
Flow-mediated dilation	2	2
Malondialdehyde	2	2
Peak Expiratory Flow	2	1
3-nitrotyrosine	1	0
8-Hydroxy-2’-deoxyguanosine	1	1
8-iso-prostaglandin F2alpha	1	1
A wave velocity	1	1
Aortic systolic blood pressure	1	1
Brachial systolic blood pressure	1	1
Brachial-ankle pulse wave velocity	1	1
Carotid–femoral pulse wave velocity	1	1
Catalase	1	1
Central Systolic blood pressure	1	1
change in bleedng on probing scores	1	1
change in gingival inflammation (GI) score	1	1
Change in mean full-mouth CAL	1	1
change in mean full-mouth PD	1	1
change in plaque control record	1	1
change in the number of sites with PD<4 mm, 4-5mm, 5-6 mm, 6-7 mm, and ≥7 mm	1	1
change in tooth mobility (grade)	1	1
Coronary flow reserve	1	1
E wave velocity	1	1
E/A ratio	1	1
Em/Am ratio	1	1
Endothelin-1	1	0
E-selectin	1	0

Expiratory reserve volume	1	1
Forced expiratory flow at X%	1	1
Global longitudinal strain of left ventricle	1	1
Glucose	1	0
H2O2 breakdown activity	1	1
H2O2 production	1	1
Interleukin 10	1	0
Interleukin 6	1	0
Left atrium diameter	1	1
Left ventricle ejection fraction	1	1
Left ventricle global circumferential strain	1	1
Left ventricle global longitudinal strain	1	1
Left ventricular end-diastolic diameter	1	1
lipoprotein associated phospholipase A2	1	0
Macrophage-colony stimulating factor	1	0
Matrix metalloproteinase 2	1	0
Matrix metalloproteinase 9	1	0
mean CAL change in sites with initial PD<4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7mm	1	1
Mean clinical attachment level (CAL) change in sites with initial PD≥4mm after mechanical periodontal therapy	1	1
mean PD change in sites with initial PD<4mm, 4-5 mm, 5-6 mm, 6-7 mm, and ≥7 mm	1	1
Mean PD change in sites with initial PD≥4 mm after mechanical periodontal therapy	1	1
Mean Periodontal Pocket Depth (PD) reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy	1	1
Microbiological status	1	0
Monocyte chemotactic protein 1/C-C motif chemokine ligand 2	1	0
Myocardial work	1	1
Nitric oxide	1	1
nitric oxide bioavailability	1	1
Oxygen Saturation	1	1
Peak early diastolic velocity of the left ventricle	1	1
Peak late diastolic velocity of the left ventricle	1	1
Perfused boundary region of sublinqual arterial microvessels	1	0
Plasminogen activator inhibitor-1	1	0
Procollagen propeptide type III	1	0
Pro-inflammatory and immuno-regulatory mediators (sCD40L, CRP, EGF, Eotaxin/CCL11, Flt3 ligand, GM-CSF, GRO, IFNα2, IL-1α, IL-1β, IL-1Ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A/CTLA8, IP10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MDC/CCL22, MIP-1α/CCL3, MIP-1β/CCL4, MMP-1, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13, osteoprotegerin, PDGF-AA, PDGF-AB/BB, RANKL, RANTES/CCL5, TGFα, TIMP-1, TNFα, TNFβ / LT-α)	1	0
Protein carbonyls	1	1
Respiratory impedance	1	1
Right atrium diameter	1	1

Right ventricle diameter	1	1
Right ventricle Em/Am ratio	1	1
Right ventricle free wall strain	1	1
Right ventricle global longitudinal strain	1	1
Right ventricle peak early diastolic velocity	1	1
Right ventricle peak late diastolic velocity	1	1
Right ventricle systolic myocardial velocity	1	1
Soluble CD40 ligand	1	1
Soluble Nox2-derived peptide	1	1
Soluble P-selectin	1	1
Squalene	1	1
Squalene monohydroperoxide	1	1
Squalene monohydroperoxide/Squalene ratio	1	1
Systolic myocardial velocity of the left ventricle	1	1
Tissue plasminogen activator	1	0
Total anti-oxidant capacity	1	1
Total arterial compliance	1	1
Total respiratory resistances	1	1
Transforming growth factor-b	1	0
Tricuspid annular plane systolic excursion	1	1
Tumor necrosis factor-a	1	0
Vitamin E	1	1
Pharmacokinetic outcomes		
Time to reach nicotine Cmax	13	10
Maximal nicotine concentration	12	10
Area under the concentration curve from start of product use to time of last quantifiable concentration	11	9
Terminal half-life of nicotine	8	7
Area under the plasma concentration-time curve from start of product use extrapolated from time of last quantifiable concentration to infinity	6	5
Maximum observed nicotine concentration (following ad lib use)	5	5
Partial AUC	5	4
Time to nicotine Cpeak	5	5
Weighted average nicotine concentration over 24 hours	4	4
Nicotine molar metabolic ratio	2	1
Area under the concentration curve from start of product use to 60 minutes	1	0
Area under the concentration curve from start of product use to 60 minutes	1	1
AUC from start of product use up to 12 hours	1	0
Baseline adjusted AUC1hour	1	1
Baseline adjusted Cmax	1	1
Lowest observed plasma concentration during the same sampling interval in which Cpeak was observed	1	1
Nicotine boost effect	1	1
Rate of plasma nicotine rise (speed of absorption)	1	1
Questionnaires/Subjective effects		
Modified Cigarette/Product Evaluation Questionnaire	18	14
Questionnaire of Smoking Urges	17	14
Fagerström Test for Nicotine/Cigarette Dependence	14	12
Minnesota Nicotine Withdrawal Scale	10	8
Human Puffing/Smoking Topography Questionnaire	5	4

Intention to use [HTP] Questionnaire	4	2
Product Satisfaction Questionnaire	4	1
Prochaska “Stage of Change” Questionnaire	2	1
Product Liking Questionnaire	2	2
The Direct Effects of Nicotine Questionnaire	2	2
Urge To Smoke questionnaire	2	2
A visual analogue scale (VAS) assessing cigarette craving	1	1
Inhalation to non-inhalation ratios during HTP use	1	0
Product Evaluation Scale	1	0
Product preferene	1	1
Questionnaire (Other)	1	1
Sensory questionnaire	1	1
Smoking cessation quality of life questionnaire	1	0
The Direct Effects of Product scale	1	1
Urge For Product questionnaire	1	1
Safety Profile		
Adverse Events/Serious Adverse Events	23	23
Vital signs	19	11
Clinical chemistry, hematology and urine analysis safety panel	18	10
Physical examination	18	10
Electrocardiogram	16	10
Respiratory symptoms (inc. cough assessment)	16	11
Spirometry	14	9
Concomitant medications	13	9
Medical history	1	0
Other outcomes		
Daily product consumption	16	14
Human Puffing/Smoking Topography (inc. puff count)	13	10
Mouth level exposure to nicotine	4	3
Potential combustion occurances in tobacco plugs	4	4
Mouth level exposure to NFDPM	2	2
6-minute walking test	1	0
a* (green-red)	1	1
b* (blue-yellow)	1	1
Finger plethysmography	1	0
Full transcriptomics profile	1	0
L* (lightness)	1	1
Mouth insertion depth	1	1
Mouth level exposure to menthol	1	1
Oxysterols (6α-hydroxy-5α-cholestanol, 7α-hydroxycholesterol, 5α,6αepoxycholestanol, 7-ketocholesterol, 7β-hydroxycholesterol, 5β,6β-epoxycholestanol, 24(R)-hydroxycholesterol, 25-hydroxycholesterol, 22(R)-hydroxycholesterol, 4ßhydroxycholesterol, and 27-hydroxycholesterol)	1	1
Total difference in colour from control (ΔE)	1	1

*Also measured as biomarkers of potential harm in one study

Supplementary Table 3. Direction of effect in primary outcomes compared between heated tobacco and cigarette arms.

Trial ID	Primary Outcome(s)	Time point	Data	EoE between group difference*
UMIN000017297	Time to reach nicotine Cmax (min)	N/A	PNTV (median, range): 3.83, 2.83-7.83) CC (median, range): 3.83, 2.83-4.83	↔ (Positive)
	Maximal nicotine concentration (ng/mL)	N/A	PNTV (mean, 95% CI): 5.39, 4.34;6.69 CC (mean, 95% CI): 11.8, 9.49;14.6	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	PNTV (mean, 95% CI): 4.12, 3.43;4.95 CC (mean, 95% CI): 6.03, 5.02;7.25	↓ (Negative)
UMIN000025777	3-hydroxypropylmercapturic acid (ug/24hr)	Day 5	NTV=484 ± 256 CC=1579 ± 696	↓ (Positive)
	2-cyanoethylmercapturic acid (ug/24hr)	Day 5	NTV=12.4 ± 6.6 CC=118.1 ± 64.7	↓ (Positive)
	4-aminobiphenyl (ng/24hr)	Day 5	NTV=1.8 ± 1.0 CC=12.3 ± 5.7	↓ (Positive)
	1-aminonaphthalene (ng/24hr)	Day 5	NTV=5.7 ± 3.2 CC=93.6 ± 45.8	↓ (Positive)
	2-aminonaphthalene (ng/24hr)	Day 5	NTV=2.5 ± 0.8 CC=26.3 ± 12.2	↓ (Positive)
	S-phenylmercapturic acid (ng/24hr)	Day 5	NTV=276 ± 102 CC=2741 ± 1939	↓ (Positive)
	3-hydroxybenzo[a]pyrene (pg/24hr)	Day 5	NTV=48.7 ± 29.5 CC=156.3 ± 82.2	↓ (Positive)
	monohydroxybutenylmercapturic acid (ng/24hr)	Day 5	NTV=219 ± 85 CC=1921 ± 1588	↓ (Positive)
	Exhaled Carbon Monoxide (ppm)	Day 5	NTV=3.7 ± 1.8 CC=25.6 ± 10.6	↓ (Positive)
	4-hydroxybutyl-2-mercapturic acid (ug/24hr)	Day 5	NTV=75.7 ± 22.0 CC=346.3 ± 160.9	↓ (Positive)
	2-hydroxyethylmercapturic acid (ng/24hr)	Day 5	NTV=844 ± 364 CC=3023 ± 2252	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24hr)	Day 5	NTV=41.5 ± 30.3 CC=116.6 ± 75.1	↓ (Positive)

	Total N-nitrosonornicotine (pg/24hr)	Day 5	NTV=955 ± 604 CC=4986 ± 6644	↓ (Positive)
	o-Toluidine (ng/24hr)	Day 5	NTV=50.8 ± 20.2 CC=154.0 ± 41.0	↓ (Positive)
	Total 1-hydroxypyrene (ng/24hr)	Day 5	NTV=208.7 ± 89.0 CC=332.4 ± 135.1	↓ (Positive)
	Nicotine equivalents (mg/24hr)	Day 5	NTV=5.0 ± 3.0 CC=10.5 ± 4.8	↓ (Negative)
Caponnetto , 2018	Exhaled Carbon monoxide (ppm)	45 mins	Specific quantitative data was not provided, however based on the graph provided eCO was substantially lower in the HTP arms compared to the CC arm at all time points past baseline, with no overlapping error bars. Moreover, "repeated-measures ANOVA post-hoc comparisons showed significant differences between-product effect (iQOS/GLO vs own brand cigarette; P < 0.0001"	↓ (Positive)
aspredicted.org #6896	Exhaled Carbon monoxide (ppm)	55 mins	IQOS(mean, SE)=3.07, 0.32 CC(mean, SE)=6.47, 0.41	↓ (Positive)
	Modified Cigarette/Product Evaluation Questionnaire	5 mins	All subscales of the mCEQ (“Smoking satisfaction”, “Psychological reward”, “Aversion”, “Enjoyment of respiratory tract sensations”, and “Craving reduction”) were rated lower for the IQOSTM than for the tobacco cigarette.	↓ (Negative)
	Questionnaire of Smoking Urges	55 mins	"At T1 and T5, smoking resulted in lower craving scores compared to vaping (all ps < 0.01) and compared to using the IQOSTM (all ps < 0.01)"	↑ (Negative)
	Fagerström Test for Nicotine/Cigarette Dependence		No relevant comparison (only reported at baseline)	N/A
	Minnesota Nicotine Withdrawal Scale	55 mins	"At T5, no differences in withdrawal symptoms were present between smoking and using the IQOS […] ps>0.11"	↔ (Positive)
	A visual analogue scale (VAS) assessing cigarette craving	55 mins	IQOS(mean, SE)=58.20, 3.89 CC(mean, SE)=45.33, 4.05	↑ (Negative)
	Product preference		No relevant comparison (no HTP v CC comparison for outcome)	N/A
NCT03435562	Nicotine (ng/mL)	5 mins post restricted use and 1-hour post *ad lib* use	Post-puff bout (mean, SD): IQOS=10.65 (6.20), CC=18.31 (11.39) Post ad lib (mean, SD): IQOS=5.97 (7.70), CC=12.23 (9.26)	↓ (Negative)

NCT03889990/ NCT03995329	No relevant comparison (no HTP v CC comparison for outcome)			N/A
NCT03301129	Soluble Nox2-derived peptide (pg/mL)	Immediately after product use	IQOS (mean, SD)= 29.9 ± 5.0 CC (mean, SD)=44.1 ± 17.1	↓ (Positive)
	Flow-mediated dilation (%)	Immediately after product use	IQOS (mean, SD)= 3.79 ± 2.68 CC (mean, SD)= 2.40 ± 1.89	↑ (Positive)
NCT03364751	Mean Periodontal Pocket Depth (PD) reduction in all sites with initial PD ≥ 4 mm after mechanical periodontal therapy (mm)	Month 6	IQOS (mean 95%CI)=-1.046, -1.194;-0.898 CC (mean, 95%CI)=-1.114, -1.258;-0.970. Mean difference=0.068 (-0.06; 0.196), p=0.297	↔ (Negative)
NCT02641587	S-phenylmercapturic acid (pg/mg creat)	Day 90	CHTP (mean, 95%CI)=467, 365;597 CC (mean, 95%CI)=2652, 1853;3795	↓ (Positive)
	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 90	CHTP(mean, 95%CI)=420, 365;483 CC (mean, 95%CI)=2552, 1802;3612	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Day 90	CHTP(mean, 95%CI)=39.7, 29.3;53.7 CC (mean, 95%CI)=196.7, 117;245.0	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 90	CHTP(mean, 95%CI)=378.2, 334.6;427.6 CC (mean, 95%CI)=966.0, 786.4;1187	↓ (Positive)
	Carboxyhemoglobin (%)	Day 90	CHTP(mean, 95%CI)=1.94, 1.78;2.13 CC (mean, 95%CI)=4.33, 3.69; 5.07	↓ (Positive)
NCT02396381	8-epi-prostaglandin F2alpha (pg/mg creat)	Month 6	FAS-AR (mean 95%CI): IQOS=330 (316;345) CC=349 (335;364) FAS-EX (mean 95%CI): IQOS=326 (309;345) CC=350 (336;365) [p=0.018]	↔ ↔ (Negative)
	11-dehydrothromboxane B2 (pg/mg creat)	Month 6	FAS-AR (mean 95%CI): IQOS=511 (475;549) CC=527 (492;565) FAS-EX (mean 95%CI): IQOS=502 (458;550) CC=527 (491;564) [p=0.193]	↔ ↔ (Negative)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	Month 6	FAS-AR (mean 95%CI): IQOS=198 (178;220) CC=282 (254;312) FAS-EX (mean 95%CI): IQOS=159 (140;181) CC=281 (254;311) [p<0.001*]	↓ ↓ (Favourable)
	Carboxyhemoglobin (%)	Month 6	FAS-AR (mean 95%CI): IQOS=3.46 (3.18;3.77) CC=4.40 (4.06;4.78) FAS-EX (mean 95%CI): IQOS=2.95 (2.69;3.24) CC=4.35 (4.03;4.70) [p<0.001*]	↓ ↓ (Positive)
	White blood cell count (GI/L)	Month 6	FAS-AR (mean 95%CI): IQOS=7.26 (7.05;7.48) CC=7.53 (7.33;7.74)	↔ ↓

			FAS-EX (mean 95%CI): IQOS=7.06 (6.81;7.31) CC=7.48 (7.28;7.68) [p=0.001*]	(Unclear)
	Soluble intercellular adhesion molecule-1 (ng/mL)	Month 6	FAS-AR (mean 95%CI): IQOS=260 (253;266) CC=264 (257;271) FAS-EX (mean 95%CI): IQOS=257 (249;265) CC=265 (258;271) [p0.030]	↔ ↔ (Negative)
	High-density lipoprotein cholesterol (mg/dL)	Month 6	FAS-AR (mean 95%CI): IQOS=54.6 (53.5;55.8) CC=51.8 (50.6;52.9) FAS-EX (mean 95%CI): IQOS=54.6 (53.1;56.2) CC=51.6 (50.4;52.7) [p<0.001*]	↑ ↑ (Positive)
	Forced expiratory volume in one second (% pred)	Month 6	FAS-AR (mean 95%CI): IQOS=94.4 (93.6;95.1) CC=93.1 (92.4;93.9) FAS-EX (mean 95%CI): IQOS=94.4 (93.4;95.3) CC=93.1 (92.3;93.9) [p=0.008*]	↔ ↑ (Unclear)
NCT02466412	Maximal nicotine concentration (ng/mL)	N/A	CHTP(mean, 95% CI)=6.2950, 5.2610;7.5322 CC(mean, 95%CI)=9.8463, 8.2290;11.7815 Mean ratio=63.9326% (49.6045;82.3991 [95%])	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	CHTP(mean, 95% CI)=8.5311, 6.9550;10.4642 CC(mean, 95%CI)=14.2172, 11.5908;17.4388 Mean ratio=60.0052% (44.9517;80.0997 [95%])	↓ (Negative)
NCT02503254	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	CHTP (mean, 95%CI)=339.73 (301.82;382.42) CC(mean, 95%CI)=1840.61 (1275.38;2656.32)	↓ (Positive)
	3-hydroxypropylmercapturic acid (pg/mg creat)	Day 5	CHTP (mean, 95%CI)=494.70 (417.53;586.12) CC(mean, 95%CI)=1187.97 (1026.63;1374.65)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	CHTP (mean, 95%CI)=2.7 (2.2; 3.2) CC(mean, 95%CI)=6.4 (5.7; 7.1)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	CHTP (mean, 95%CI)=361.48 (289.26; 451.74) CC(mean, 95%CI)=2898.46 (2172.62; 3866.79)	↓ (Positive)
NCT02649556	Carboxyhemoglobin (%)	Week 52	IQOS (mean, 95%CI)=2.59, 2.24;3.01 CC (mean, 95%CI)=4.06, 3.77;4.38 % relative reduction=31.7 (23.3;39.1[95%])	↓ (Positive)
	8-epi-prostaglandin F2alpha (pg/mg creat)	Week 52	IQOS (mean, 95%CI)=307, 279;338 CC (mean, 95%CI)=327, 307;348 % relative reduction=7.15 (-1.03;14.7[95%])	↔ (Negative)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Week 52	IQOS (mean, 95%CI)=133, 105;168 CC (mean, 95%CI)=269, 238;305 % relative reduction=46.3 (36.2;54.8[95%])	↓ (Positive)
	11-dehydrothromboxane B2 (pg/mg creat)	Week 52	IQOS (mean, 95%CI)=582, 518;654 CC (mean, 95%CI)=586, 538;638 % relative reduction=3.44 (-8.74;14.3[95%])	↔ (Negative)
	White blood cell count (GI/L)	Week 52	IQOS (mean, 95%CI)=6.73, 6.47;6.99 CC (mean, 95%CI)=7.31, 7.07;7.54 LS mean diff=-0.413 (-0.694;-0.131[95%])	↓ (Positive)

	Soluble intercellular adhesion molecule-1 (ng/mL)	Week 52	IQOS (mean, 95%CI)=246, 230;263 CC (mean, 95%CI)=258, 244;272 % relative reduction=3.11 (0.0231;6.10[95%])	↔ (Negative)
	High-density lipoprotein cholesterol (mg/dL)	Week 52	IQOS (mean, 95%CI)=52.2, 49.5;54.8 CC (mean, 95%CI)=50.6, 48.9;52.3 Mean diff=1.75 (-0.160;3.65[95%])	↔ (Negative)
	Forced expiratory volume in one second (% pred)	Week 52	IQOS (mean, 95%CI)=93.2, 91.1;95.2 CC (mean, 95%CI)=92.3, 90.7;94.0 Mean diff=0.914 (-0.339;2.17[95%])	↔ (Negative)
NCT01967706	Maximal nicotine concentration (ng/mL)	N/A	IQOS (mean, 95%CI)=10.70, 8.94;12.8 CC (mean, 95%CI)=12.09, 10.10;14.47 Mean ratio=88.47 (68.64;114.03[95%])	↔ (Positive)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	IQOS (mean, 95%CI)=23.99, 20.87;27.57 CC (mean, 95%CI)=24.45, 21.27;28.10 Mean ratio=98.13 (80.61;119.46[95%])	↔ (Positive)
NCT01780688	Maximal nicotine concentration (ng/mL)	N/A	IQOS (mean, 95%CI)=8.4, 6.8;10.3 CC (mean, 95%CI)=11.9, 9.5;14.9 Mean ratio=70.3% (60.0;82.2[90%])	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	IQOS (mean, 95%CI)=17.7, 15.0;20.8 CC (mean, 95%CI)=22.8, 19.4;26.8 Mean ratio=77.4% (70.5;85.0[90%])	↓ (Negative)
NCT01780714	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	% reduction IQOS/CC mean (95%CI)=88.5 (84.7–91.4) [p<0.001]	↓ (Positive)
	3-hydroxypropylmercapturic acid (pg/mg creat)	Day 5	% reduction IQOS/CC mean (95%CI)=72.1 (67.4–76.1) [p<0.001]	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	% reduction IQOS/CC mean (95%CI)=76.7 (74.3–78.9) [p<0.001]	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	% reduction IQOS/CC mean (95%CI)=93.0 (90.6–94.9) [p<0.001]	↓ (Positive)
ISRCTN88682435	Maximal nicotine concentration (ng/mL)	N/A	HTP (mean, SD)=1.18±1.13 CC (mean, SD)=7.76±4.65 [p<0.05]	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (h*ng/mL)	N/A	HTP (mean, SD)=1.07±0.75 CC (mean, SD)=5.97±2.15 [p<0.05]	↓ (Negative)

	Time to reach nicotine Cmax (min)	N/A	HTP (median, min-max)=9.02, 2.05-31.0 CC (median, min-max)=5.02, 3.90-20.0 [p<0.05]	↑ (Negative)
Nga, 2020	Exhaled Carbon monoxide (ppm)	45 mins post product use	IQOS mean=4.67 CC mean=16.47 (no variance values provided but error bars do not overlap in graph presented) Between product effect significant difference (repeated-measures ANOVA, p<0.001)	↓ (Positive)
Lopez, 2016	Exhaled Carbon monoxide (ppm)	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	Bout 1, mean (SD): CC=12.1 (3.4) LLTV=not reported [CC sig higher than LLTV, cohens d=2.4] Bout 2, mean (SD): CC= 16.9 (5.8) LLTV=4.5 (2.1) [CC sig higher than LLTV, cohens d=2.9]	↓ (Positive)
	Questionnaire of Smoking Urges	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	"There were no significant differences between any of the conditions immediately following either bout"	↔ (Positive)
	Nicotine (ng/mL)	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	Bout 1, mean (SD): CC=24.4 (12.6) LLTV=14.3 (8.1) [CC sig higher than LLTV, cohens d=1.0] Bout 2, mean (SD): CC= 23.7 (14.5) LLTV=16.4 (11.3) [CC higher than LLTV but not significantly]	↓ (Negative)
	Minnesota Nicotine Withdrawal Scale	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	"There were no significant differences between any of the conditions immediately following either bout."	↔ (Positive)
	The Direct Effects of Nicotine Questionnaire	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	"there were no differences between the [CC] and LLTV conditions at that same time point [Bout 1]. There were no significant differences between any of the conditions immediately following bout 2."	↔ (Negative)
	The Direct Effects of Product scale	Immediately after bout 1 (at 5mins) and 2 (at 65mins)	“Was the product satisfying?”: "Immediately following bout 1, the mean score for the OB condition of 93.3 (10.51) was significantly higher compared to the scores of 51.2 (30.9) for the LLTV condition (d = 1.8) [...] There was a similar pattern following bout 2" “Did the product taste good?”: "immediately following bout 1, the mean score for the OB condition of 92.9 (11.4) was significantly higher compared to the score of 43.7 (31.8) for the LLTV condition [t(14) = 5.2, p < 0.017; d = 2.1] “Did the product calm you down?”: "immediately following bout 1, the mean score for the OB condition of 68.4 (28.9) was significantly higher compared to the LLTV score of 41.8 (31.2; [t(14) = 4.1, p < 0.017; d = 0.9]) [...] There were no significant differences between any of the conditions immediately following bout 2”	↓ (Negative)

ISRCTN81075760	Augmentation index	No results reported		Not reported
	8-epi-prostaglandin F2alpha	No results reported		Not reported
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24h)	Day 90	Graph shows levels were equivalent at baseline PP-population mean change baseline-day 90: Glo=-120 CC=-12 Diff (99.94% CI)=-108 (-168;-48) [p<0.0001] CEVal-population mean change baseline-day 90: Glo=-110 CC=-5 Diff (99.94% CI)=-105 (-193; -17)	↓ (Positive)
ISRCTN13439529	Time to reach nicotine Cmax (min)	N/A	Median (range): Glo1.0=4.1, 1.1-45.0 Glo1.1=4.1, 1.2-15.4 CC=6.0, 3.0-9.1	↔ (Positive)
	Maximal nicotine concentration (ng/mL)	N/A	Mean (90%CI): Glo1.0=8.7 (6.93;10.95) Glo1.1=10.9 (8.63;13.70) CC=23.3 (18.46;29.33)	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (min*ng/mL)	N/A	Mean (90%CI): Glo1.0=527 (438.7;633.3) Glo1.1=695 (577.6;835.6) CC=1374 (1142.4;1653.1)	↓ (Negative)
	Intention to use [HTP] Questionnaire	240 min post 1st puff	Mean±SD, median: Glo1.0=2.5 ± 2.67, 2.0 Glo1.1=3.1 ± 2.84, 2.0 CC=9.1 ± 1.37, 10	↓ (Negative)
	Product Liking Questionnaire	3-240min	Mean±SD, median: Glo1.0=720 ± 733, 640 Glo1.1=820 ± 724, 675 CC=2107 ± 403, 2281	↓ (Negative)
	Urge To Smoke questionnaire	5 min post 1st puff	Mean±SD, median: Glo1.0=5.0 ± 3.33, 5.0 Glo1.1=4.8 ± 3.27, 5.0 CC=2.6 ± 3.50, 1.0	↓ (Negative)
	Urge For Product questionnaire	No comparison to cigarette arm		N/A
ISRCTN14301360/ UMIN000024988	Exhaled Carbon monoxide (ppm)	Day 7	CC(mean)=20.30, Glo(mean)=3.40, IQOS(mean)=3.40, mCC(mean)=20.07, mGlo(mean)=2.80	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24h)	Day 7	CC(mean)=197.85, Glo(mean)=128.63, IQOS(mean)=80.35, mCC(mean)=167.02, mGlo(mean)=149.38	↓ (Positive)
	2-cyanoethylmercapturic acid (ug/24h)	Day 7	CC(mean)=159.04, Glo(mean)=17.84, IQOS(mean)=16.54, mCC(mean)=165.62, mGlo(mean)=21.03	↓ (Positive)
	total N-nitrosonornicotine (ng/24h)	Day 7	CC(mean)=15.36, Glo(mean)=5.85, IQOS(mean)=1.06, mCC(mean)=9.62, mGlo(mean)=5.57	↓ (Positive)
	Nicotine equivalents (mg/24h)	Day 7	CC(mean)=8.33, Glo(mean)=6.15, IQOS(mean)=7.58, mCC(mean)=9.77, mGlo(mean)=5.75	↓ (Negative)
	monohydroxybutenylmercapturic acid (ng/24h)	Day 7	CC(mean)=770.64, Glo(mean)=49.87, IQOS(mean)=118.38, mCC(mean)=1010.18, mGlo(mean)=98.40	↓ (Positive)
	3-hydroxypropylmercapturic acid (ug/24h)	Day 7	CC(mean)=1448.93, Glo(mean)=568.66, IQOS(mean)=639.21, mCC(mean)=1422.37, mGlo(mean)=656.99	↓ (Positive)

	total 1-hydroxypyrene (ng/24h)	Day 7	CC(mean)=172.86, Glo(mean)=75.58, IQOS(mean)=50.18, mCC(mean)=195.19, mGlo(mean)=63.46	↓ (Positive)
	S-phenylmercapturic acid (ug/24h)	Day 7	CC(mean)=2.25, Glo(mean)=0.20, IQOS(mean)=0.19 mCC(mean)=2.81, mGlo(mean)=0.20	↓ (Positive)
	o-toluidine (ng/24h)	Day 7	CC(mean)=153.21, Glo(mean)=58.52, IQOS(mean)=54.81, mCC(mean)=119.04, mGlo(mean)=39.39	↓ (Positive)
	4-aminobiphenyl (ng/24h)	Day 7	CC(mean)=10.86, Glo(mean)=2.45, IQOS(mean)=2.25, mCC(mean)=10.44, mGlo(mean)=2.31	↓ (Positive)
	2-aminonaphthalene (ng/24h)	Day 7	CC(mean)=17.80, Glo(mean)=1.74, IQOS(mean)=1.72, mCC(mean)=17.65, mGlo(mean)=1.92	↓ (Positive)
	3-hydroxy-1-methylpropylmercapturic acid (ug/24h)	Day 7	CC(mean)=385.50, Glo(mean)=79.00, IQOS(mean)=79.63, mCC(mean)=362.45, mGlo(mean)=73.23	↓ (Positive)
	2-hydroxyethylmercapturic acid (ug/24h)	Day 7	CC(mean)=5.08, Glo(mean)=2.46, IQOS(mean)=2.60 mCC(mean)=7.13, mGlo(mean)=2.84	↓ (Positive)
	N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine (ug/24h)	Day 7	CC(mean)=17.24, Glo(mean)=15.68, IQOS(mean)=13.75, mCC(mean)=16.40, mGlo(mean)=15.36	↓ (Positive)
	N-acetyl-S-(2-carba-moylethyl)cysteine (ug/24h)	Day 7	CC(mean)=111.65, Glo(mean)=91.75, IQOS(mean)=65.76, mCC(mean)=114.96, mGlo(mean)=88.82	↓ (Positive)
DRKS00012919	Nicotine	Not reported		Not reported
	Systolic blood pressure (mm Hg)	120 min	Based on graph presenting data throughout study period, SPB at end of exposure was not substantially different between the HTP and CC arms	↔ (Negative)
ISRCTN80651909	Exhaled Carbon monoxide (ppm)	Day 7	CC(mean)=25.3 Glo(mean)=4.4	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (ng/24h)	Day 7	CC(mean)=289.54 Glo(mean)=195.71	↓ (Positive)
	2-cyanoethylmercapturic acid (mg/24h)	Day 7	CC(mean)=0.24 Glo(mean)=0.03	↓ (Positive)
	total N-nitrosonornicotine (ng/24h)	Day 7	CC(mean)=10.85 Glo(mean)=6.10	↓ (Positive)
	Nicotine equivalents (mg/24h)	Day 7	CC(mean)=14.88 Glo(mean)=7.37	↓ (Positive)
	monohydroxybutenylmercapturi c acid (ng/24h)	Day 7	CC(mean)=2552.74 Glo(mean)=240.28	↓ (Positive)

	3-hydroxypropylmercapturic acid (mg/24h)	Day 7	CC(mean)=1.37 Glo(mean)=0.27	↓ (Positive)
	total 1-hydroxypyrene (ng/24h)	Day 7	CC(mean)=313.33 Glo(mean)=106.71	↓ (Positive)
	S-phenylmercapturic acid (ng/24h)	Day 7	CC(mean)=5572.79 Glo(mean)=231.36	↓ (Positive)
	o-toluidine (ng/24h)	Day 7	CC(mean)=146.60 Glo(mean)=38.40	↓ (Positive)
	4-aminobiphenyl (ng/24h)	Day 7	CC(mean)=22.36 Glo(mean)=3.36	↓ (Positive)
	2-aminonaphthalene (ng/24h)	Day 7	CC(mean)=32.38 Glo(mean)=3.03	↓ (Positive)
	N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine (ng/24h)	Day 7	CC(mean)=33554.88 Glo(mean)=24749.07	↓ (Positive)
	N-acetyl-S-(2-carba-moylethyl)cysteine (mg/24h)	Day 7	CC(mean)=0.18 Glo(mean)=0.12	↓ (Positive)
	3-hydroxy-1-methylpropylmercapturic acid (mg/24h)	Day 7	CC(mean)=0.54 Glo(mean)=0.07	↓ (Positive)
	2-hydroxyethylmercapturic acid (ng/24h)	Day 7	CC(mean)=9673.61 Glo(mean)=3954.5	↓ (Positive)
	8-epi-prostaglandin F2alpha (no units reported)	Day 7	"8-epi-PGF2α Type III, there was no significant change in all arms except the glo THP arm, which showed a significant decrease in the urinary levels of this BoBE" Without baseline data there is no way to know whether the end of exposure levels differed between study arms.	Unclear
	White blood cell count (no units reported)	Day 7	"white blood cell count was significantly reduced between baseline and Day 7 for the glo THP and the prototype EC arms. However, there was no significant change in the nicotine cessation or in the control cigarette arm." Without baseline data there is no way to know whether the end of exposure levels differed between study arms.	Unclear
	Nicotine molar metabolic ratio (no units reported)	Day 7	CC(mean)=2.74 Glo(mean)=3.31	↑ (Unclear)

UMIN000041539	Exhaled Carbon monoxide (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	2-cyanoethylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	total N-nitrosonornicotine (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	monohydroxybutenylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group" This is substantiated by the graph presented	↓ (Positive)
	3-hydroxypropylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	total 1-hydroxypyrene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	S-phenylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	o-toluidine (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	4-aminobiphenyl (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	2-aminonaphthalene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	3-hydroxy-1-methylpropylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)

	2-hydroxyethylmercapturic acid (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	3-hydroxybenzo[a]pyrene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
	1-aminonaphthalene (no units reported)	Day 5	"After the five-day study period, the levels of Biomarkers of Exposure (BoEs) of the selected HPHCs observed in the four heated tobacco product groups were significantly reduced to that observed in the CC group"	↓ (Positive)
NCT03700112	Time to reach nicotine Cmax (mins)	N/A	Controlled (mean(SD)): CC=6.71 (5.11) IQOS=5.41 (1.36) Ad lib (mean(SD)): CC=5.84 (1.36) IQOS=6.38 (5.06)	↔ (Positive)
	Maximal nicotine concentration	Not reported		Not reported
	Baseline adjusted Cmax (ng/mL)	N/A	Controlled (mean(SD)): CC=21.2 (11.7) IQOS=16.1 (7.7) Ad lib (mean(SD)): CC=27.9 (19.6) IQOS=17.4 (7.3)	↓ (Negative)
	Baseline adjusted AUC1hour (hrs*ng/mL)	N/A	Controlled (mean(SD)): CC=7.67 (3.56) IQOS=5.15 (2.32) Ad lib (mean(SD)): CC=9.76 (5.69) IQOS=5.72 (1.88)	↓ (Negative)
	Area under the concentration curve from start of product use to 60 minutes	Not reported		Not reported
NCT01970995	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=23.23 (19.34;27.91) CC (mean, 95%CI)=95.03 (77.31;116.82)	↓ (Positive)
	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=141.74 (120.62;166.57) CC (mean, 95%CI)=785.27 (576.82;1069.04)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 90	mIQOS (mean, 95%CI)=386.37 (356.30;418.97) CC (mean, 95%CI)=695.58 (602.43;803.13)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 90	mIQOS (mean, 95%CI)=2.97 (2.88;3.06) CC (mean, 95%CI)=5.73 (5.24;6.25)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=145.58 (121.67;174.18) CC (mean, 95%CI)=1157.25 (848.59;1578.17)	↓ (Positive)
NCT01989156	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=47.53 (34.80;64.91) CC (mean, 95%CI)=152.11 (108.38;213.47)	↓ (Positive)
	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=260.98 (205.28;331.79) CC (mean, 95%CI)=1040.71 (677.79;1597.94)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 90	mIQOS (mean, 95%CI)=314.05 (281.51;350.34) CC (mean, 95%CI)=606.10 (468.27;784.48)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 90	mIQOS (mean, 95%CI)=2.66 (2.40;2.94)	↓

			CC (mean, 95%CI)=5.62 (5.00;6.32)	(Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 90	mIQOS (mean, 95%CI)=314.02 (219.66;448.93) CC (mean, 95%CI)=1218.56 (822.54;1805.25)	↓ (Positive)
NCT01970982	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=107.39 (97.24;118.60) CC (mean, 95%CI)=450.19 (300.07;675.42)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 5	IQOS (mean, 95%CI)=311.08 (279.59;346.12) CC (mean, 95%CI)=599.67 (511.70;702.76)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	IQOS (mean, 95%CI)=2.39 (2.32;2.46) CC (mean, 95%CI)=5.14 (4.66;5.66)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=143.77 (126.08;163.93) CC (mean, 95%CI)=850.02 (620.40;1164.63)	↓ (Positive)
NCT01959932	monohydroxybutenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=192.93 (174.90; 212.83) CC (mean, 95%CI)=2399.40 (1884.60; 3054.83)	↓ (Positive)
	3-hydroxypropylmercapturic acid (ng/mg creat)	Day 5	IQOS (mean, 95%CI)=402.26 (366.55; 441.45) CC (mean, 95%CI)=931.01 (825.73; 1049.72)	↓ (Positive)
	Carboxyhemoglobin (%)	Day 5	IQOS (mean, 95%CI)=1.06 (1.03; 1.08) CC (mean, 95%CI)=4.51 (4.05; 5.01)	↓ (Positive)
	S-phenylmercapturic acid (pg/mg creat)	Day 5	IQOS (mean, 95%CI)=164.45 (144.45; 187.22) CC (mean, 95%CI)=2922.81 (2362.80; 3615.54)	↓ (Positive)
NCT01959607	Maximal nicotine concentration (ng/mL)	N/A	IQOS (geo mean, 95%CI)=14.30 (11.41;17.91) CC (geo mean, 95%CI)=13.82 (11.00;17.35)	↔ (Positive)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	IQOS (geo mean, 95%CI)=23.75 (19.74;28.58) CC (geo mean, 95%CI)=24.66 (20.24;30.03)	↔ (Positive)
NCT01967732	Maximal nicotine concentration (ng/mL)	N/A	IQOS (mean, 95%CI)=9.60 (7.64;12.07) CC (mean, 95%CI)=12.34 (10.47;14.54)	↔ (Positive)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	IQOS (mean, 95%CI)=15.20 (12.01;19.23) CC (mean, 95%CI)=20.13 (17.72;22.88)	↔ (Positive)
NCT01967719	Maximal nicotine concentration (ng/mL)	N/A	mIQOS (mean, 95%CI)=7.39 (5.68;9.62) CC (mean, 95%CI)=13.02 (10.06;16.85)	↓ (Negative)
	Area under the concentration curve from start of product use to time of last quantifiable concentration (ng.h/mL)	N/A	mIQOS (mean, 95%CI)=16.56 (12.46;22.01) CC (mean, 95%CI)=29.47 (21.35;40.67)	↔ (Positive)

Jones, 2020	Human Puffing/Smoking Topography (inc. puff count)	During single-use session on Day 5	**Group 1** (mean, ±SD) Puff number: IQOS=15.0 (±5.5), CC=17.3(±5.9) Total puff volume: IQOS=730.9mL (±350.4), CC=682.8mL (±224.7) Mean puff volume: IQOS=48.8mL (±17.9), CC=41.3mL (±12.7) Puff duration: IQOS=1.4s (±0.5), CC=1.5s (±0.5) Puff interval: IQOS=17.1s (±20.7), CC=18.8s (±10.6) Session length: IQOS=195.6s (±87.2), CC=289.5s (±85.7) **Group 3** (mean, ±SD) Puff number: Glo=15.4 (±7.4), CC=16.0 (±5.6) Total puff volume: Glo=731.3mL (±437.6), CC=596.8mL (±197.1) Mean puff volume: Glo=46.6mL (±16.8), CC=39.3mL (±12.4) Puff duration: Glo=1.6s (±0.5), CC=1.6s (±0.5) Puff interval: Glo=11.1s (±5.8), CC=18.8s (±10.6) Session length: Glo=150.4s (±40.5), CC=269.3s (±88.0)	↓ (Positive) ↑ (Negative) ↑ (Negative) ↓[IQOS] ↔ [Glo] (Positive) ↓ (Negative) ↓ (Positive)
	Daily product consumption	Ambulatory average	IQOS (mean, ±SD)=8.5 (±5.2) Glo (mean, ±SD)=7.0 (±5.5) CC (mean, ±SD)=13.2 (±4.4) [Group 1], 12.6 (±4.7) [Group 3]	↓ (Positive)
	Mouth level exposure to NFDPM (mg/session)	During single-use session on Day 5	IQOS (mean, ±SD)=9.6 (±5.0) Glo (mean, ±SD)=4.7 (±2.9) CC (mean, ±SD)=19.0 (±7.7) [Group 1], 16.7 (±7.6) [Group 3]	↓ (Positive)
	Mouth level exposure to nicotine (mg/session)	During single-use session on Day 5	IQOS (mean, ±SD)=0.98 (±0.51) Glo (mean, ±SD)=0.34 (±0.21) CC (mean, ±SD)=1.55 (±0.63) [Group 1], 1.36 (±0.62) [Group 3]	↓ (Negative)
	Sensory questionnaire (magnitude scale [1-7], 'just right' scale [Low, Just right, High])	During single-use session on Day 5	**Group 1** (mean (±SD) magnitude score, just right score) Immediate smoke/aerosol delivery: IQOS=3.7 (± 1.7), Low; CC=5.4 (± 1.3), Just right Draw effort: IQOS=4.1 (± 1.7), High; CC=3.5 (± 1.7), High Mouthful: IQOS=3.8 (± 1.3), Low; CC=4.8 (± 1.0), Just right Irritation: IQOS=3.4 (± 2.0), Just right; CC=2.9 (± 1.8), Just right Intensity of kick/hit: IQOS=3.6 (± 1.7), Just right; CC=3.4 (± 1.8), Just right Taste - likeability: IQOS=3.4 (± 2.0); CC=5.2 (± 1.3) Taste - amount: IQOS=4.2 (± 1.4), Just right; CC=5.0 (± 1.2), Just right Overall likeability: IQOS=3.6 (± 1.9); CC=5.3 (± 1.2) **Group 3** (mean (±SD) magnitude score, just right score) Immediate smoke/aerosol delivery: Glo=3.3 (± 1.6), Low; CC=5.0 (± 1.3), Just right Draw effort: Glo=4.9 (± 1.6), High; CC=3.8 (± 1.5), High Mouthful: Glo=3.2 (± 1.3), Low; CC= 4.5 (± 1.2), Just right Irritation: Glo=3.6 (± 1.9), Just right; CC=3.3 (± 1.4), Just right	↓ (Negative) ↑ (Negative) ↓ (Negative) ↑↔ (Unclear) ↑↔ (Positive) ↓ (Negative) ↓↔ (Unclear) ↓

			Intensity of kick/hit: Glo=3.9 (± 1.8), Just right; CC=3.8 (± 1.3), Just right Taste - likeability: Glo=2.8 (± 2.0); CC=5.1 (± 1.6) Taste - amount: Glo=4.0 (± 1.8), Just right; CC=4.6 (± 1.3), Just right Overall likeability: Glo=3.1 (± 1.9); CC=5.2 (± 1.4)	(Negative)
Gee, 2018	Human Puffing/Smoking Topography (inc. puff count)	During single-use session on day 5	**Group 1** (mean, ±SD) Total puff volume (mL): IQOS=668.1 ± 322.6, Glo=736.4 ± 415.8, CC=489.0 ± 177.7 Mean puff volume (mL): IQOS=63.5 ± 20.3, Glo=66.7 ± 23.7, CC=48.9 ± 14.8 Puff number: IQOS=10.3. ± 3.6, Glo=10.9 ± 5.6, CC=10.7 ± 5.0 Puff duration (s): IQOS=1.8 ± 0.6, Glo=1.8 ± 0.6, CC=1.8 ± 0.6 Puff interval (s): IQOS=8.3 ± 3.0, Glo=7.4 ± 2.7, CC=9.7 ± 3.4 **Group 2** (mean, ±SD) Total puff volume (mL): mGlo=618.2 ± 389.6, mCC=493.7 ± 192.4 Mean puff volume (mL): mGlo=62.2 ± 32.8, mCC=51.1 ± 16.0 Puff number: mGlo=10.0 ± 4.5, mCC=10.0 ± 3.7 Puff duration (s): mGlo=1.8 ± 0.5, mCC=2.0 ± 0.5 Puff interval (s): mGlo=8.1 ± 3.0, mCC=9.9 ± 3.4	↑ (Negative) ↑ (Negative) ↓[IQOS] ↑[Glo] ↔[mGlo] (Unclear) ↓[mGlo]↔[IQOS/Glo] (Positive) ↓ (Negative)
	Daily product consumption	Ambulatory average	IQOS (mean, ±SD)=12.2 ± 6.2 Glo (mean, ±SD)=10.3 ± 5.5 CC (mean, ±SD)=16.0 ± 8.1 mGlo (mean, ±SD)=11.4 ± 5.7 mCC (mean, ±SD)=15.3 ± 6.9	↓ (Positive)
	Mouth level exposure to NFDPM (mg/stick)	During single-use session on day 5	IQOS (mean, ±SD)=8.4 ± 4.5 Glo (mean, ±SD)=5.2 ± 3.4 CC (mean, ±SD)=13.5 ± 6.2 mGlo (mean, ±SD)=6.2 ± 3.8 mCC (mean, ±SD)=14.8 ± 7.4	↓ (Positive)
	Mouth level exposure to menthol (mg/stick)	During single-use session on day 5	mGlo (mean, ±SD)=1.4 ± 0.8 mCC (mean, ±SD)=1.2 ± 0.5	↑ (Unclear)
	Mouth level exposure to nicotine (mg/stick)	During single-use session on day 5	IQOS (mean, ±SD)=1.0 ± 0.5 Glo (mean, ±SD)=0.3 ± 0.2 CC (mean, ±SD)=1.3 ± 0.5 mGlo (mean, ±SD)=0.3 ± 0.2 mCC (mean, ±SD)=1.3 ± 0.6	↓ (Negative)
	Mouth insertion depth	Post product use	No comparison to cigarette arm	N/A

NCT03452124	Pulse wave velocity (m/s)	Acute=post single use Chronic=1 month	Acute: IQOS (mean, ±SD)=10.2 ± 1.7; CC (mean, ±SD)=10.8 ± 2.4 Chronic: IQOS (mean, ±SD)=10.1 ± 1.5; CC (mean, ±SD)=10.2 ± 2.3	↓ (Positive)
	Exhaled Carbon monoxide (ppm)	Acute=post single use Chronic=1 month	Acute: IQOS (mean, ±SD)=14.1±7.3; CC (mean, ±SD)=17.5±7.8 Chronic: IQOS (mean, ±SD)=6.7±6.4; CC (mean, ±SD)=17.4±4.8	↓ (Positive)
	Perfused boundary region of sublinqual arterial microvessels	N/A	Not reported	N/A
	Global longitudinal strain of left ventricle (%)	1 month	Chronic: IQOS (mean, ±SD)=−20.9±2.5; CC (mean, ±SD)=−20±0.7 GLS was improved in the HNBC compared to the control group at follow-up (diference=2.35%; 95% CI 0.23–4.48, p=0.03)	↑ (Positive)
	Coronary flow reserve (no units)	1 month	Chronic: IQOS (mean, ±SD)=3.5±0.8; CC (mean, ±SD)=2.6±0.2	↑ (Positive)
Dalrymple, 2022	Catalase (UI/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=12.87, 7.77 CC (mean, SD)=10.01, 3.63	↑ (Positive)
	Malondialdehyde (ng/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=46.10, 6.46 CC (mean, SD)=62.80, 12.02	↓ (Positive)
	Squalene (µg/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=36.97, 24.29 CC (mean, SD)=34.95, 22.54	↑ (Positive)
	Squalene monohydroperoxide (ng/cm2)	Post exposure to 32 puffs of product	Glo (mean, SD)=73.80, 49.34 CC (mean, SD)=159.45, 67.26	↓ (Positive)
	Squalene monohydroperoxide/Squalene ratio (ng/µg)	Post exposure to 32 puffs of product	Glo (mean, SD)=2.07, 0.65 CC (mean, SD)=5.19, 1.38	↓ (Positive)
	L* (lightness) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=69.30, 3.56 CC (mean, SD)=66.79, 2.57	↑ (Positive)
	a* (green-red) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=7.32, 1.88 CC (mean, SD)=8.23, 0.95	↓ (Positive)

	b* (blue-yellow) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=15.72, 2.72 CC (mean, SD)=20.72, 1.91	↓ (Positive)
	Total difference in colour from control (ΔE) (no units)	Post exposure to 32 puffs of product	Glo (mean, SD)=2.61, 1.14 CC (mean, SD)=5.39, 1.54	↓ (Positive)
Ioakeimidis, 2021	Augmentation index (%)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Compared with sham smoking, cfPWV (Figure 1(b)), baPWV and AIx@75 (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in cfPWV, baPWV and AIx@75 (by 0.30 m/s, 86 cm/s and 3.5%, respectively)."	↓ (Positive)
	Heart rate (bpm)	Post use	"There were no differences in all baseline measurements between the three sessions." "HR increased similarly in both the tobacco cigarette and HNBC sessions (maximum increase by 10 beats/min)"	↔ (Negative)
	Brachial systolic blood pressure (mmHg)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Both brachial (Figure 1(a)) and aortic systolic BP increased immediately after the end of smoking by tobacco cigarette (by 11.5 and 10.5 mmHg, $p < 0.001$ and $p < 0.01$, respectively) and by HNBC (by 7.5 and 6 mmHg, all $p < 0.01$)"	↓ (Positive)
	Aortic systolic blood pressure (mmHg)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Both brachial (Figure 1(a)) and aortic systolic BP increased immediately after the end of smoking by tobacco cigarette (by 11.5 and 10.5 mmHg, $p < 0.001$ and $p < 0.01$, respectively) and by HNBC (by 7.5 and 6 mmHg, all $p < 0.01$)"	↓ (Positive)
	Carotid–femoral pulse wave velocity (m/s)	30 mins post use	"There were no differences in all baseline measurements between the three sessions." "Compared with sham smoking, cfPWV (Figure 1(b)), baPWV and AIx@75 (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in cfPWV, baPWV and AIx@75 (by 0.30 m/s, 86 cm/s and 3.5%, respectively)."	↓ (Positive)
	Brachial-ankle pulse wave velocity (cm/s)	Post use	"There were no differences in all baseline measurements between the three sessions." "Compared with sham smoking, cfPWV (Figure 1(b)), baPWV and AIx@75 (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in cfPWV, baPWV and AIx@75 (by 0.30 m/s, 86 cm/s and 3.5%, respectively)."	↓ (Positive)

Yaman, 2021	A wave velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=55.8 (14.2), n=27 CC [mean, (SD)]=57.9 (15.5), n=27	↓ (Positive)
	Diastolic blood pressure (mmHg)	10 minutes post-use	IQOS [mean, (SD)]=71.9 (10.1), n=27 CC [mean, (SD)]=75.5 (10), n=27	↓ (Positive)
	E wave velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=66.8 (12), n=27 CC [mean, (SD)]=67.3 (14.1), n=27	↓ (Negative)
	E/A ratio (no units)	10 minutes post-use	IQOS [mean, (SD)]=1.2 (0.3), n=27 CC [mean, (SD)]=1.2 (0.4), n=27	↔ (Negative)
	Em/Am ratio (no units)	10 minutes post-use	IQOS [mean, (SD)]=1.2 (0.5), n=27 CC [mean, (SD)]=1.3 (1.0), n=27	↓ (Negative)
	Heart rate (bpm)	10 minutes post-use	IQOS [mean, (SD)]=1.8 (8.7), n=27 CC [mean, (SD)]=82.6 (8.8), n=27	↓ (Positive)
	Left atrium diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=38.8 (4.8), n=27 CC [mean, (SD)]=38.3 (5.2), n=27	↑ (Negative)
	Left ventricle ejection fraction (%)	10 minutes post-use	IQOS [mean, (SD)]=64.5 (3.8), n=27 CC [mean, (SD)]=64.4 (3.9), n=27	↑ (Positive)
	Left ventricle global circumferential strain (%)	10 minutes post-use	IQOS [mean, (SD)]=18.3 (3.9), n=27 CC [mean, (SD)]=17.5 (3.9), n=27	↑ (Positive)
	Left ventricle global longitudinal strain (%)	10 minutes post-use	IQOS [mean, (SD)]=17.9 (2.4), n=27 CC [mean, (SD)]=17.9 (2.8), n=27	↔ (Negative)
	Left ventricular end-diastolic diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=46.1 (4.1), n=27 CC [mean, (SD)]=46.3 (4.5), n=27	↓ (Positive)
	Peak early diastolic velocity of the left ventricle (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=11.6 (3.6), n=27 CC [mean, (SD)]=10.7 (3.8), n=27	↑ (Positive)
	Peak late diastolic velocity of the left ventricle (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=9.5 (2.2), n=27 CC [mean, (SD)]=10 (2.9), n=27	↓ (Positive)
	Right atrium diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=38.2 (4.0), n=27 CC [mean, (SD)]=38.3 (3.9), n=27	↓ (Positive)
	Right ventricle diameter (mm)	10 minutes post-use	IQOS [mean, (SD)]=34.2 (3.2), n=27 CC [mean, (SD)]=34.2 (3.3), n=27	↔ (Negative)
	Right ventricle free wall strain (%)	10 minutes post-use	IQOS [mean, (SD)]=23.9 (6.2), n=27 CC [mean, (SD)]=21.2 (5.6), n=27	↑ (Positive)
	Right ventricle global longitudinal strain (%)	10 minutes post-use	IQOS [mean, (SD)]=21.4 (4.1), n=27 CC [mean, (SD)]=19.4 (4.1), n=27	↑ (Positive)
	Right ventricle peak early diastolic velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=10.7 (2.4), n=27 CC [mean, (SD)]=10.5 (2.4), n=27	↑ (Positive)

	Right ventricle peak late diastolic velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=15 (4.5), n=27 CC [mean, (SD)]=14.5 (3.4), n=27	↑ (Negative)
	Right ventricle systolic myocardial velocity (cm/s)	10 minutes post-use	IQOS [mean, (SD)]= 13.1 (2.1), n=27 CC [mean, (SD)]=12.8 (2.5), n=27	↑ (Negative)
	Right ventricle Em/Am ratio (no units)	10 minutes post-use	IQOS [mean, (SD)]= 0.7 (0.2), n=27 CC [mean, (SD)]=0.7 (0.2), n=27	↔ (Negative)
	Systolic blood pressure (mmHg)	10 minutes post-use	IQOS [mean, (SD)]=114.1 (16.8), n=27 CC [mean, (SD)]=120.5 (12.7), n=27	↓ (Positive)
	Systolic myocardial velocity of the left ventricle (cm/s)	10 minutes post-use	IQOS [mean, (SD)]=9.8 (2.4), n=27 CC [mean, (SD)]=9.1 (2.3), n=27	↑ (Negative)
	Tricuspid annular plane systolic excursion (mm)	10 minutes post-use	IQOS [mean, (SD)]=20.9 (2.5), n=27 CC [mean, (SD)]=20.2 (2.9), n=27	↑ (Positive)
Phillips-Waller, 2021	Human Puffing/Smoking Topography (inc. puff count)	During single-use	IQOS (median, IQR)=14.0, 13.5-14.0 CC (median, IQR)=13.0, 10.8-16.3	↑ (Negative)
	Maximal nicotine concentration	N/A	IQOS (median, IQR)=8.3, 4.5-19.3 CC (median, IQR)=12.9, 7.2-28.6 Mean maximal nicotine concentration also lower in IQOS group than CC group based on graph (Figure 1)	↓ (Negative)
	Nicotine	30 minutes	"IQOS delivered about half as much nicotine over 30 minutes (AUC0–>30) as a cigarette"	↓ (Negative)
	Time to reach nicotine Cmax	N/A	IQOS (median, IQR)=4.0, 4.0-6.0 CC (median, IQR)=6.0, 4.0-8.0	↓ (Positive)
	Urge To Smoke questionnaire	Post product use	"OBC reduced urges to smoke more than IQOS"	↑ (Negative)
	Area under the concentration curve from start of product use to 60 minutes	N/A	IQOS (median, IQR)=152.0, 91.2-254.5 CC (median, IQR)=314, 136.4-465.6 "IQOS delivered about half as much nicotine over 30 minutes (AUC0–>30) as a cigarette"	↓ (Negative)
	Nicotine boost effect score	N/A	IQOS (median, IQR)=5.4, 2.6-10.8 CC (median, IQR)=12.7, 6.7-26.8	↓ (Negative)
	Questionnaire (Other)	Post product use	No comparison to cigarette arm	NE

* ↑ = higher in HTP arm; ↔ = equivocal; ↓ = lower in HTP arm
Abbreviations: Positive=HTP has positive impact compared to CC; Negative=HTP has negative impact compared to CC; N/A=not applicable; HTP=heated tobacco product; CHTP=carbon HTP; CC=combustible cigarette; [P]NTV=[prototype] novel tobacco vapor; LLTV=loose leaf tobacco vaporiser; create=creatinine; FAS-AR=Full analysis set – as randomised; FAS-EX=Full analysis set – as exposed; Cmax=maximal concentration; mean=arithmetic mean; geo mean=geometric mean