Supplemental Material. Auer R *Electronic Nicotine-Delivery Sytems for Smoking Cessation*. In: The New England Journal of Medicine 2024 (in press). Publisher DOI: 10.1056/NEJMoa2308815

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2 ESTxENDS trial organization

Presentation and Publication Committee

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- Jean-Paul Humair, MD, MPH
- Isabelle Jacot-Sadowski, MD
- Ivan Berlin, MD, PhD
- Martin Brutsche, MD, PhD
- Martin Feller, MD, MSc
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- Anna Schöni, PhD (coordinator)
- Reto Auer, MD, MAS, (Chair)

Data management and statistical analysis plan

CTU Bern, University of Bern, Bern, Switzerland

- Sven Trelle, MD
- Sheila Appadoo, MPH
- Andreas Limacher, PhD

BIHAM, University of Bern, Bern, Switzerland

- Anna Schöni, PhD
- Stéphanie Baggio, PhD

Clinical Study coordinator

- Anna Schöni, PhD, main coordinator

Data Safety and Monitoring Board (DSMB)

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- Prof. em. Hans Wedel, PhD, affiliated to University of Gothenburg, Sweden
- Prof. Dr. med. Erich Russi, MD, FCCP, University of Zürich, Switzerland

Independent Adjudication Committee (IAC)

- Baris Gencer, MD, MPH (Board-certified general internist and cardiologist)
- Carole E. Aubert, MD, MSc (Board-certified general internist)

Central laboratory for urinary analyses

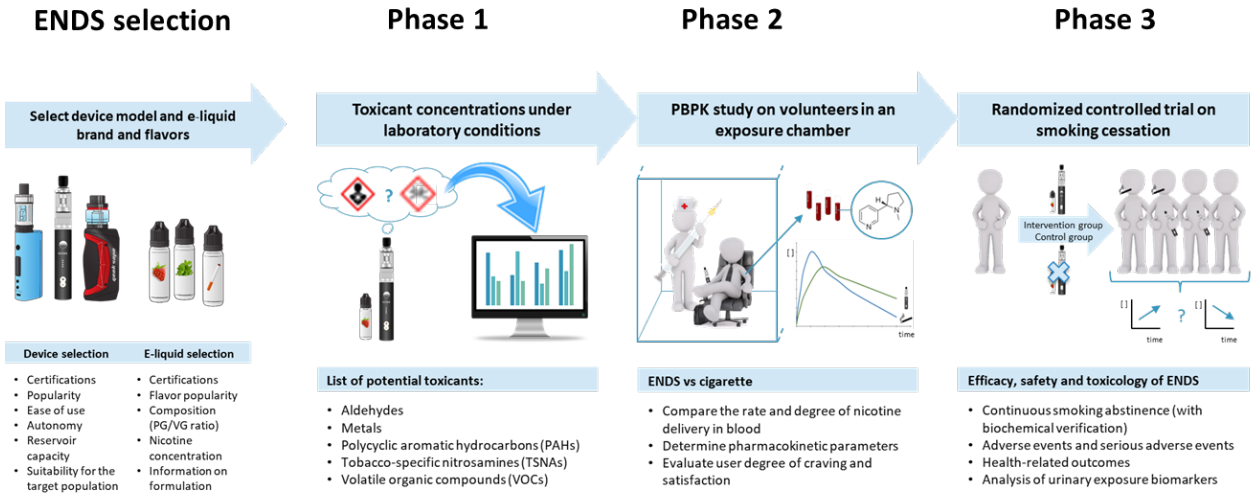
- Aurélie Berthet, PhD (lead)
- Nicolas Sambiagio, PhD
- Nancy Hopf, PhD

3 Supplementary Methods

3.1 Selection and independent pre-clinical evaluation of ENDS and e-liquids

The preparation phase of the ESTxENDS trial comprised three main steps: a) ENDS selection: selecting the device and e-liquids and adapting the intervention based on advice from experienced e-cigarette users who had used ENDS to quit smoking cigarettes, and from experts in the field; b) Phase 1: conducting toxicology tests of the ENDS and e-liquids we selected, in laboratory conditions on a vaping machine; c) Phase 2: conducting a pharmacokinetic/pharmacodynamic study among healthy volunteers to determine if the device and e-liquids deliver enough nicotine to users' blood. Phase 3 was the conduct of the randomized controlled trial (RCT)

3.1.1 Figure S1. Schematic representation of the phases of preparation for testing ENDS and the e-liquids selected for ESTxENDS participants.



3.1.2 Selecting the device

During the trial's preparation phase (2017), we contacted experts in smoking cessation and other scientists conducting clinical studies testing ENDS for smoking cessation for advice on the ENDS they would recommend using in ESTxENDS. We also held two meetings with members of HelveticVape, an advocacy group then active in Switzerland. Written into HelveticVape's statutes is a ban on financial conflicts of interest with the tobacco and vaping industry. At two in-person meetings, we presented our trial's aims and described the population we intended to enroll in the trial (tobacco smokers willing to quit cigarettes). We asked attendees to recommend popular entry devices and they made several suggestions, including the Innokin Endura T20-S. Our first choice was the Innokin Endura T20-S starter kit, based on its range of available colors, and its fixed flow and voltage, which ensured easy use and consistent delivery. The device is

also an opened system, allowing participants to fill the ENDS themselves. The device was authorized for sale in Switzerland and adheres to the CE declaration of Conformity.

3.1.3 Selecting the e-liquids

Consumers from HelveticVape recommended we offer users a range of options for e-liquid flavorings and nicotine concentration so participants could vary and adjust them over time, representing ENDS use in their user community.

We selected "Alphaliquids" by "Gaïatrend," based on the choice investigators planning another RCT in France made, after careful of review of quality standards and an on-site visit by a group of experts.

The research team selected a range of flavorings and nicotine concentration based on the availability of e-liquids sold by the manufacturer. We allowed a range of flavorings and nicotine concentration, restricting it because of logistical challenge with allowing for the full range of available flavorings from the manufacturer. We allowed participants to choose from 4 concentrations of nicotine base (19.6-, 11-, 6- and 0 mg/ml) and 6 flavorings: FR-4 and FR-M tobacco flavors; FRESH MINT (menthol flavor); and RASPBERRY#2, RED FRUITS, and GREEN APPLE fruity flavors (https://www.alfaliquid.com/en). For all e-liquids, the proportion of propylene glycol and vegetable glycerin was 76/24. The e-liquids contained propylene glycol, vegetable glycerin, medical-quality nicotine base, alcohol, and flavorings. The manufacturer provided us with the full list of ingredients for each and their concentrations. According to the documents provided by Gaïatrend, in Alphaliquids, the vegetable glycerin is free of *genetically modified* organisms (GMOs). Alphaliquids are also EP (European Pharmacopoeia) certified. Propylene glycol in Alphaliquids is 99.5% pure, organic, GMO-free of GMOs EP and USP certified. The organic ethyl alcohol in Alphaliquids is made from cereals, Ecocert N° FR-BIO-01 certified, and GMO-free. The nicotine Alphaliquids comes from the only supplier certified by the European Pharmacopoeia. The flavorings in Alphaliquids comply with CE N°1334/2008 quality standards. Gaïatrend e-liquid flasks are ISO8317 certified, so they have child-resistant closures.

3.1.4 Phase 1: pre-clinical laboratory study on chemicals measured in e-liquids and vapors released by the ENDS and e-liquid.

Testing for toxic chemicals released by the selected ENDS device under laboratory conditions was a precursor to interpreting the results of urine quantification of inhaled chemicals in the urine of ESTxENDS study participants. We first performed tests to identify the presence of toxic chemical in the aerosol of our chosen ENDS device. We used a smoking machine developed in our laboratory to generate the aerosol. The machine consists of three ports to add ENDS clearomizers, a piston syringe to simulate the inhaled volume, a pinch-valve system, and silicon tubing to connect the clearomizers to the valves and the valves to the syringe. The puffing regime was based on the CORESTA standard (CRM n°81).[1] Aerosol was sampled to quantify the presence of specific compounds of interest, including several aldehydes, volatile organic compounds (VOCs), tobacco-specific N-nitrosamines (TSNA), and polycyclic aromatic hydrocarbons (PAHs). Because we did not expect to measure PAHs or TSNAs in the aerosol based on the existing literature, we instead measured these compounds in the e-liquids. Of the aldehydes, the results confirmed that only formaldehyde and acetaldehyde were present (in low concentrations) in the aerosol. The manuscript reporting these results is in preparation.

3.1.5 Phase 2: Pharmacokinetics and Pharmacodynamics (PK/PD) volunteer study

We had to ensure that the vaporizer we chose delivered sufficient nicotine to the blood of participants to enable us to validate ESTxENDS study results. To this end, we carried out an exploratory volunteer study (June 2018 to August 2018) do determine nicotine plasma nicotine concentrations during ENDS use and evaluated smoker satisfaction to verify that nicotine uptake was sufficient to satisfy a smoker who wants to quit. Twelve healthy volunteers were divided into two groups: ENDS users and the dual users (ENDS and cigarette use). Each volunteer made two visits to our laboratory and used the ENDS device. ENDS users

vaped nicotine at two concentrations with the Innokin T20S vaporizer and dual users smoked their regular brand of cigarettes and vaped one of the two nicotine concentrations. We used the data we collected to measure the rate of nicotine absorption in plasma, verifying the uptake of nicotine in the blood at each concentration, and comparing the results of vaping to those of a conventional cigarette. Preliminary results showed that the Innokin T20S delivered sufficient nicotine at concentrations of 11 and 19.6 mg/mL, like a conventional cigarette, but cigarette smokers took less time (5 minutes after finishing a cigarette) to reach maximum concentration than ENDS users (10-20 minutes while using ENDS). At the 11 mg/mL e-liquid nicotine concentration, plasma nicotine concentration was higher for ENDS users than for the dual users and dual users had a lower maximum plasma concentration after using ENDS than they did after smoking their own cigarettes. The manuscript reporting these results is in preparation.

3.2 Standards of care smoking cessation counseling

Trained study nurses provided standardized smoking cessation counseling based on cognitive behavior therapy and motivational interviewing, including counseling for drug-supported smoking cessation that applied the principles of shared decision making (see Section 5 below for the standard operating procedures (SOP) for the smoking cessation intervention).[2,3] Recommendation for NRT and further smoking cessation therapy counseling was provided in person at the first clinical visit (baseline visit) and then by phone at target quit date and at Weeks 1, 2, 4, and 8. Counseling was expected to last 30 minutes during the baseline in-person visit and 15 minutes over the phone. Participants willing to use NRT had to purchase them in a pharmacy and pay for it themselves. Participants who wanted prescription drug therapy (varenicline or bupropion) were encouraged to consult their primary care physician or another health professional who could prescribe the drug. Participants received a smoking cessation brochure and were encouraged to go to the www.stop-tabac.ch website to seek additional online smoking cessation support if they wished.

Participants in the control group received SOC smoking cessation counseling as described in Section 5 below. Study nurses adapted the recommendations for NRT and further smoking cessation therapy to participant's nicotine dependence (5.2.2 below for the method to assess dependence to nicotine and 5.2.4, Figure S-B, for the algorithm used for counseling NRT and smoking cessation drug therapy among participants in the control group, based on their nicotine dependence scores). Participants allocated to SOC received a CHF 50 (50 USD) voucher at the baseline visit, which they could use for any purpose, including the purchase of NRT.

Participants in the intervention group also received SOC smoking cessation counseling, as described in Section 5 below. For participants in the intervention group, we adapted SOC smoking cessation counseling so study nurses could provide it in tandem with ENDS and e-liquids. The recommendations for NRT and smoking cessation drug therapy were also adapted to participant's nicotine dependence and the context of nicotine substitution through ENDS (5.2.5, Figure S-C, for the algorithm used for recommending e-liquid dosage and NRT to participants in the intervention group, based on their nicotine dependence scores).

3.3 ENDS and e-liquids and specific counseling provided to the intervention group

We used the Alphaliquid e-liquids produced by Gaïatrend in France (https://www.gaiatrend.fr/en/), which comply with the strict quality criteria set by Agence Française de Normalisation (AFNOR). Available nicotine concentrations were 0 mg/ml, 6 mg/ml, 11 mg/ml, and 19.6 mg/ml. Available flavorings were FR-4 (tobacco flavor) and FR-M (tobacco flavor), FRESH MINT (menthol flavor), RASPBERRY#2 (fruity flavor), RED FRUITS (fruity flavor) or GREEN APPLE (fruity flavor). For all e-liquids, the proportion of propylene glycol to vegetable glycerin was 76/24. E-liquids contained propylene glycol, vegetable glycerin, medical-quality free-base nicotine, alcohol, and flavorings. To avoid financial conflicts of interest with the manufacturer, the study team paid the factory price to Gaïatrend for the e-liquids and paid for the shipping of the e-liquids to the study centers, which were then given for free to study participants.

The Endura T20-S kit, produced in China by "Innokin", came in a user packet with a 1,500 mAh internal Li-Po battery, a Prism S Coil (0.8 ohm, 16-18W) atomizer, a spare drip tip, a micro-USB DC 5V/1A cable and an instruction manual in French or German. Devices came in 5 colors; participants could choose between black, purple, grey, red, and blue. To avoid financial conflicts of interest with the manufacturer, the study team paid the factory price to Innokin for the kits and spare coils and paid for the shipping of the e-liquids to the study centers, which were then given for free to study participants.

At the baseline visit, study nurses explained how to use the ENDS, how to fill the device with e-liquid, charge it, and change the coil every two weeks (5.3 below). Participants could sample from an e-liquid testing board of 24 ENDS (one of each combination of flavor and nicotine concentration) and pick the e-liquid and nicotine concentration they preferred (Appendix Figure 2). Study nurses gave participants no more than 10 e-liquid bottles at the end of this baseline visit and advised them to use only the liquids we provided. During scheduled phone visits, study nurses asked participants what they thought about the e-liquids and took orders for the new e-liquids participants told them they wanted. The provided specific advice based on the self-reported exposure to tobacco smoking and ENDS over time (see 5.4.2, Table S-C. Situation-specific advice for counseling participants in the intervention group). Outside scheduled phone visits, participants could freely contact study nurses during office hours to replace faulty devices, re-order coils, or re-order e-liquids. Participants were allowed to use the ENDS ad libitum and re-order e-liquids whenever they wanted, in whatever amounts they preferred. Replacement devices and e-liquids were shipped by postal mail or made available for pick-up at each study site. See Section 5 at the end of this document for details.

3.3.1 Figure S2. Photograph of the wooden board presenting the ENDS filled with e-liquids and flavors available*

** We designed a wooden cardboard for each study site with pre-filled ENDS with each of the 24 flavors and e-liquids available for selection by participants. Participants could test as many as they wanted and as often as they wanted during the baseline visit.*

3.4 Inclusion/exclusion criteria of participants in the ESTxENDS RCT

Inclusion criteria:

- Informed consent documented by signature;
- Aged 18 or older;
- Currently smoking 5 or more cigarettes per day for at least 12 months;
- Willing to try to quit smoking within the next 3 months;
- A valid phone number, email address, or postal address.

Exclusion criteria:

- Known hypersensitivity or allergy to e-liquid contents;
- Participation in another study with investigational drug within the 30 days before the baseline visit and during the present study if interactions were expected;

- Pregnancy or breast feeding;
- Intention to become pregnant during the scheduled study intervention (within the first 6-months);
- Regular use of ENDS or tobacco heating systems in the 3 months before the baseline visit;
- Nicotine replacement therapy (NRT) or use of other efficacious pharmaceutical smoking cessation aids, (e.g., varenicline or bupropion) within the 3 months before the baseline visit;
- Inability to attend the 6-month follow-up visit;
- Inability to understand instructions delivered in person or by phone, or otherwise unable to participate in study procedures.

3.5 Questionnaires

During the baseline visit, demographics and smoking status and history were assessed and participants completed questionnaires and had health assessments. Tobacco dependence was assessed using the Fagerström Test for Nicotine Dependence, which consists of 6 questions ranging from 0 to 1, 0 to 2 or 0 to 3 that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence; Scores range from 0 to 10, with higher scores indicating greater dependence.[4]. Withdrawal symptoms were assessed with the Minnesota Tobacco Withdrawal Scale (MTWS-R), and respiratory symptoms with the COPD (chronic obstructive pulmonary disease) Assessment Test [CAT]) (see sections 3.7 and 3.8 below).[5-7] Carbon monoxide measurements were done using the Smokerlyzer® from Bedfont, UK. Participants were advised to sit upright and having both feet flat on the floor before pressing all the air out of the lungs into the device.
At the end of the baseline visit, before randomization, participants were asked to rank their preference for group allocation into the intervention and control group on a scale from 0 (control group) to 10 (intervention group).

3.6 Safety outcomes, systematic collection of adverse events and serious adverse events (S(AE))

For the duration of the study, study nurses proactively collected adverse events (AE) and serious adverse events (SAEs) at each follow-up visit; participants could report S(AE) to the research team at any time. We established (S)AE Guidelines to ensure each site would collect medical reports and other documentation the adjudication committee needed to fully adjudicate all SAEs and specific AEs (notable cardiovascular events, respiratory events, new cancer diagnosis). Teams from each study sites followed strict written guidelines and received dedicated training and documentation on collecting (S)AEs.

Definition and assessment of (serious) adverse events were adapted from ICH E6 1.2., which defines an **AE** as any untoward medical occurrence in participants who are administered an intervention during clinical investigation; these events are not necessarily caused by the intervention. AEs include unfavorable and/or unintended signs (including abnormal laboratory findings), symptoms, or diseases temporally associated with the intervention, regardless of their relationship to the intervention.

We classified an **SAE** as any event that:

- required inpatient treatment of at least 24 hours or extended a current hospital stay;
- caused permanent or significant incapacity or disability;
- was life-threatening or caused death;
- caused a congenital anomaly or birth defect.

Notable medical events that did not require hospitalization, were not immediately life-threatening, or did not cause death were also considered to be serious if they could jeopardize the patient's health or might require intervention to prevent one of the outcomes listed above.

Hospitalization or prolongation of current hospitalization for a diagnostic or elective (surgical) procedure planned prior to the participant's enrolment into the study was not classified as an SAE.

Study nurses followed up SAEs until resolved or stabilized. Participants with ongoing SAEs at study end continue to be followed up until they recovered or stabilized, or until the participant was lost to follow-up.

Study nurses systematically queried participants about AE and documented self-reported AE in the centralized database. If participants reported an AE that generated contact with a physician, study nurses attempted to obtain external documentation (e.g., physician's note, discharge letters, laboratory or test results including ECG, angiography report, and lung function tests) to ensure there was enough clinical documentation for AE to be independently adjudicated. Study nurses were given clear standard operating procedures (SOP), including checklists for the documents they needed to collect. We provided separate checklists for "cardiovascular," "respiratory," and "other" AE. For AE for which participants did not contact a physician (e.g., headache without medical consultation), or when participants decided not to contact a physician for an AE, we relied on participant self-reports to collect information; these self-reported AE were not adjudicated.

3.6.1 Data Safety and Monitoring Board (DSMB)

Since the Ethics Committee did not require us to set up a DSMB before we started the trial in 2017. We set the DSMD in 2020, after the trial began, in the context of the EVALI epidemic in the USA and the serious concerns health authorities in the USA had expressed about the ENDS safety. Our DSMB was designed to independently evaluate our procedures for collecting adverse events (AE) and serious adverse events (SAE) and to review the SAE collected over time, stratified by group allocation. The DSMB met in October 2020, January 2022, and November 2022 and wrote independent reports on the conduct of the study.

3.6.2 Independent Adjudication Committee (IAC)

Two clinician-researchers reviewed independently reviews of all SAE based on the available medical documentation. They determined the correctness of the diagnosis of each SAE and its reliability. The IAC did not do imputation, i.e. did not pronounce about the potential association between the SAE and ENDS.

3.7 Withdrawal symptoms at baseline and 6-months follow-up

3.7.1 Withdrawal symptoms measures:

We used the Minnesota Tobacco Withdrawal Scale (MTWS-R) to assess withdrawal symptoms to tobacco.[6,7] The MTWS-R consists of 15 questions; users rated symptoms on a scale from 0 to 4. To calculate the total withdrawal discomfort score, we summed the following items: 1. Angry, irritable, frustrated; 2. Anxious, nervous; 3. Depressed mood, sad; 4. Difficulty concentrating; 5. Increased appetite, hungry, weight gain; 6. Insomnia, sleep problems, awakening at night; 7. Restless; and 8. Desire or craving to smoke. Total withdrawal discomfort score ranged from 0 to 32; higher scores indicate more withdrawal symptoms.

3.7.2 Statistical analyses for withdrawal symptoms:

The association between the intervention and the continuous MTWS-R-score at 6-month follow-up was analyzed by linear regression with robust standard errors. WFe adjusted the model for baseline covariates (age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström test score, study site and baseline MTWS-R-score). We used stabilized inverse probability censoring weights to account for potential selective attrition.

3.8 Respiratory symptoms at baseline and 6-months follow-up

3.8.1 Respiratory symptoms measures:

We used the Chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) to assess respiratory symptoms.[8] The CAT was designed for persons with COPD and measures the association of COPD with COPD-related quality of life and the way interventions may change COPD symptoms. The questionnaire comprises 8 questions, each formatted as a semantic six-point differential scale, covering domains of symptoms including cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence about leaving home, sleep, and energy.[5] Though we queried study participants if they had been diagnosed with COPD at the baseline visit, prior studies suggest COPD is underdiagnosed in adult smokers. We also used CAT because there are no guidelines recommending which questionnaire researchers should use to survey changes in respiratory symptoms among participants in a smoking cessation trial. RCTs that tested the effect of ENDS on smoking cessation used different questionnaires to assess changes in respiratory symptoms over time.[9,10] A large trial reported significant differences between the intervention and control group for changes in cough and phlegm, but not for shortness of breath and wheezing.[10]
When filling out the CAT questionnaire, participants are asked to rank each of the 8 queried symptoms in a Likert scale ranging from 0 to 5 (0 [cough/phlegm/breathless]: not at all; energy: lots of energy) to 5 (cough/phlegm/breathless: all the time/completely; energy: no energy at all). To compute the overall CAT, one sums the numbers from each item (min 0, max 40).

3.8.2 Statistical analyses for respiratory symptoms:

The association between the intervention and the continuous CAT score at 6-month follow-up was analyzed by linear regression with robust standard errors. The model was adjusted for baseline covariates (age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström test score, study site and baseline CAT-score). We used stabilized inverse probability censoring weights to account for potential selective attrition.

4 Supplementary Results

4.1 Selection process and studied sample

4.1.1 Table S1. Reasons for ineligibility

Reasons 399/2027 screened potential participants were ineligible:

Reason for ineligibility	**N**	%
- Under 18	1	0.3
- Had not smoked 5 or more cigarettes a day for at least the last 12 months	41	10.3
- Not willing to try to quit smoking within the next 3 months	109	27.3
- Did not provide a valid phone number, a valid email address and/or a valid postal address	1	0.3
- Had been enrolled in another investigational drug study within the 30 days before the baseline visit or during the present study where interactions would be expected	1	0.3
- Pregnant / breastfeeding or intended to become pregnant during the scheduled study intervention	15	3.8
- Had regularly used ENDS or tobacco heating systems in the 3 months before the baseline visit	76	19.0

- Had used nicotine replacement therapy (NRT) or other efficacious smoking cessation medications, e.g., varenicline or bupropion, within the 3 months before the baseline visit	29	7.3
- Would not be able to attend the 6-month follow-up visit	10	2.5
- Could not understand instructions	13	3.3
- Did not want to set a TQD	19	4.8
- Was unwilling to delay using ENDS until after 6 months if randomized into the control group	68	17.0
- Had a guardianship	4	1.0
- Did not want to use an ENDS	1	0.3
Total ineligible with reason	388	97.2
- Missing data on reason for ineligibility	11	2.8
Total ineligible	**399**	100

4.1.2 Table S2. Reasons eligible persons were not randomized

Although they met the eligibility criteria at screening, 382/2027 participants were not randomized for the following reasons:

Reason for declining to participate	**N**	**%**
Changed their mind about participating / personal decision	109	28.5
Contact lost with person lost, no reason collected	69	18.1
Were afraid or not ready to participate	30	7.9
Died or contracted a disease before their baseline visit	17	4.5
Were prevented by professional obligations	9	2.4
Stopped smoking just before baseline visit	16	4.2
Transferred to other study site	4	1.0
Got pregnant	1	0.0
Had COVID-19 or feared catching COVID-19	6	1.6
Felt participation would take too much effort / time	3	0.8
Moved away	1	0.3
Wanted to quit on their own	1	0.3
Physician / psychologist opposed their participation	1	0.3
Other	11	2.9
Total with reason for declining to participate	278	72.8
Missing data on reason for declining to participate	104	27.2
Total not randomized, though eligible	**382**	100

4.1.3 Table S3. Number of participants with efficacy and safety outcome data at 6-month follow-up.

	Control group	Intervention group	Total
Total number of participants included in the main analyses	N=624	N=622	N=1246
Data on **smoking status and (S)AE**, N/N included (%)*	556/624 (89.1%)	575/622 (92.4%)	1131/1246 (90.8%)
Data collection for **smoking status and (S)AE**, N/N included (%):			
- In person visit	350/624 (56.1%)	446/622 (71.7%)	796/1246 (63.9%)
- Not in person visit:	206/624 (33.0%)	129/622 (20.7%)	335/1246 (26.9%)

- By phone / e-mail directly from participant	172/624 (27.6%)	117/622 (18.8%)	289/1246 (23.2%)
- By questionnaire sent home to participant	2/624 (0.3%)	1/622 (0.2%)	3/1246 (0.2%)
- By phone from relative or close person	26/624 (4.2%)	9/622 (1.4%)	35/1246 (2.8%)
- By phone from general practitioner	1/624 (0.2%)	1/622 (0.2%)	2/1246 (0.2%)
- Missing data on how data was collected	5/624 (0.8%)	1/622 (0.2%)	6/1246 (0.5%)
Data on **smoking status and (S)AE** among those who did not withdrew, N/N included who did not withdrew (%) †	556/595 (93.4%)	575/618 (93.0%)	1131/1212 (93.3%)
Data on **past 7 days tobacco cigarette smoking**, N/N included (%)	523/624 (83.8%)	561/622 (90.2%)	1084/1246 (87.0%)
Data on **past 7 days ENDS use**, N/N included (%)	515/624 (82.5%)	557/622 (89.5%)	1072/1246 (86.0%)
Data on past **7 days tobacco cigarette smoking and ENDS use, past 24 hours NRT** use, N/N included (%)	504/624 (80.8%)	552/622 (88.7%)	1056/1246 (84.8%)
Data on **exhaled CO**, N/N included (%)	335/624 (53.7%)	433/622 (69.6%)	768/1246 (61.6%)
Data on **anabasine**, N/N included (%) §	138/624 (22.1%)	228/622 (36.7%)	366/1246 (29.4%)
Data on **anabasine, or CO if anabasine missing**, among participants reporting continuous tobacco smoking abstinence, N/N with continuous tobacco smoking abstinence (%) ¶	110/146 (75.3%)	198/237 (83.5%)	308/383 (80.4%)
Data on **anabasine**, among participants reporting continuous tobacco smoking abstinence, N/N with continuous tobacco smoking abstinence (%)¶	75/146 (51.4%)	130/237 (54.9%)	205/383 (53.5%)
Data on **exhaled CO**, among participants reporting continuous tobacco smoking abstinence, N/N with continuous tobacco smoking abstinence (%)¶	110/146 (75.3%)	194/237 (83.1%)	304/383 (79.4%)

* Outcome data on smoking status was collected in person at the study site, over the phone, via mailed questionnaire or by proxy.
† In the control group, 29 withdrew participation and 4 in the intervention group. One participant in the control group died.
‡ CO, exhaled carbon monoxide performed in all participants at clinical visits, regardless of smoking status
§ Anabasine in urine performed in all participants coming in in-person visits, restricted to those reporting not smoking cigarettes in the 7-days prior to the clinical visit.
¶ Continuous tobacco smoking abstinence (primary outcome) was defined as self-report of smoking no cigarettes from target quit date (TQD) to 6-months follow-up visit

4.1.4 Table S4. Additional sample characteristics

	Control group		Intervention group		Total	
	N=624	(%)	N=622	(%)	N=1246	(%)
Study site						
Bern	221	(35.4)	217	(35.0)	438	(35.2)
Geneva	161	(25.8)	170	(27.3)	331	(26.6)
Lausanne	83	(13.3)	73	(11.7)	156	(12.5)
St. Gallen	82	(13.1)	90	(14.5)	172	(13.8)
Zürich	77	(12.3)	72	(11.6)	149	(12.0)
Smoking cessation aids used previously*						
ENDS†	96	(15.4)	107	(17.2)	203	(16.3)
Nicotine replacement therapy‡	206	(33.0)	215	(34.6)	421	(33.8)
Smoking cessation medication§	69	(11.1)	60	(9.7)	129	(10.4)
Other methods¶	183	(29.3)	159	(25.6)	342	(27.5)
Spouse or partner smokes - no. (%)#	325	(52.1)	330	(53.1)	655	(52.6)

* Previously used were defined as any use over the lifetime reported by participants. During the initial pre-screening over the phone and again at the beginning of the baseline visit, study nurses asked participants if they had used NRT or other smoking cessation drug therapy (e.g., varenicline or bupropion) over the last 3 months. Participants that did so were excluded.
† missing data for N=26

‡ nicotine replacement therapy includes nicotine gum, nicotine inhaler, nicotine lozenge, nicotine patch and nicotine oral spray; missing data for N=24

§ Smoking cessation medication includes bupropion and varenicline; missing data for N=21

¶ Other methods include acupuncture, books, hypnosis, support groups, etc.; missing data for N=44

Missing data for N=3

4.1.5 Table S5: Representativeness of Study Participants[23]

Characteristic	Example
Disease, problem, or condition under investigation	Tobacco smoking, the first preventable cause of death and disabilities in most countries.
Special considerations related to	
Sex and gender	Tobacco smoking prevalence is prevalent in both men and women. While the proportion of women smoking was lower than men smoking, a gender gap in smoking is tightening.
Age	Most adult smokers have started smoking when they were <18. Prevalence is higher in young adults, decreasing gradually over the years. While some can quit in young adulthood, people smoking in middle age tend to have more issues quitting. The proportion of people with psychiatric co-morbidities and disabilities that smoke in middle age is higher than among younger adults.
Race or ethnic group	In the USA, smoking prevalence is higher among Black people and Hispanic people. Tobacco smoking, especially tobacco smoking initiation is strongly linked to the social network people live in. Outside the USA, tobacco prevalence varies greatly between countries and between communities within each country.
Geography	Tobacco smoking is prevalent in virtually all counties around the world. In other parts of the world than the USA, tobacco prevalence varies greatly between countries and between communities within each countries.
Overall representativeness of this trial	In ESTxENDS, 53% identified as men and 47% identified as women. While we let participants choose another gender identity, no participant identified as non-binary. The prevalence of daily smoking in Switzerland among 40 years old (the mean age of participants in ESTxENDS) is 17.2%, while 26.8% declare themselves as cigarette smokers (includes occasional smoking) according to the Swiss Health and Lifestyle Study 2022. We included participants in five study site, three located in the German part and two in the French part of Switzerland. No study site recruited in the Italian part of Switzerland. Participants could participate is they spoke French, German or English. Unlike the USA, participants typically do not identify themselves as White, Black, Hispanic, or Asian, so we did not query participants about their race or ethnicity. We asked participants about their highest education level. In total, 7% had finalized obligatory school as highest education, 46% a secondary education and 47% a tertiary education. In Switzerland, among the general population, 13.9% have finalized obligatory school, 41.3% a secondary education and 44.7% a tertiary education. We restricted the exclusion criteria to the minimum to enable participants with psychiatric comorbidities and further substance use disorder such as alcohol use disorder and illicit drug use to participate. We excluded women pregnant or planning pregnancy because dedicated trials should be conducted in this population.

4.2 Secondary efficacy outcomes and sensitivity analyses

4.2.1 Table S6. Additional tobacco smoking abstinence rates outcomes at 6-month follow-up*

Secondary outcome[†]	Control group, N included in analyses=624	Intervention group, N included in analyses =622	Crude relative Risk (95% CI) [‡]	Sensitivity analysis, Adjusted relative risk (95% CI) [§]	Absolute risk reduction (95%CI) [¶]
Continuous abstinence, only validated by CO, N (%)	105 (16.8)	186 (29.9)	1.78 (1.44 - 2.20)	1.73(1.41 - 2.13)	13.1 (8.4 - 17.7)
Continuous abstinence, only validated by anabasine, N (%)	69 (11.1)	118 (19.0)	1.72 (1.30 - 2.26)	1.67 (1.27 - 2.19)	7.9 (4.0 - 11.9)
Sustained abstinence allowing a 2-week' grace period, without validation, N (%)	170 (27.2)	258 (41.5)	1.52 (1.30 - 1.78)	1.48 (1.27 - 1.72)	14.2 (9.0 - 19.5)
Sustained abstinence allowing a 2-week' grace period, only validated by CO, N (%)	113 (18.1)	196 (31.5)	1.74 (1.42 - 2.13)	1.71 (1.40 - 2.08)	13.4 (8.7 - 18.1)
Sustained abstinence allowing a 2-week' grace period, only validated by anabasine	73 (11.7)	126 (20.3)	1.73 (1.33 - 2.26)	1.70 (1.31 - 2.21)	8.6 (4.5 - 12.6)
Sustained abstinence allowing up to 5 cig in total, without validation, N (%)	168 (26.9)	291 (46.8)	1.74 (1.49 - 2.03)	1.68 (1.45 - 1.95)	19.9 (14.6 - 25.1)
Sustained abstinence allowing up to 5 cig in total, only validated by CO, N (%)	113 (18.1)	226 (36.3)	2.01 (1.65 - 2.44)	1.96 (1.62 - 2.37)	18.3 (13.4 - 23.1)
Sustained abstinence allowing up to 5 cig in total, only validated by anabasine, N (%)	74 (11.9)	137 (22.0)	1.86 (1.43 - 2.41)	1.81 (1.40 - 2.34)	10.2 (6.0 - 14.3)
7 days point prevalence abstinence, only validated by CO, N (%)	137 (22.0)	251 (40.4)	1.84 (1.54 - 2.19)	1.74 (1.47 - 2.07)	18.4 (13.4 - 23.4)
7 days point prevalence abstinence, only validated by anabasine, N (%)	87 (13.9)	157 (25.2)	1.81 (1.43 - 2.30)	1.72 (1.36 - 2.18)	11.3 (6.9 - 15.7)

* Tobacco smoking abstinence at 6-months follow up for the secondary outcome were not validated, or validated either only by CO or only by anabasine. More participants met the definition of tobacco smoking abstinence with these secondary outcome definitions since the definition for the primary outcome was a more stringent (for the primary outcome, continuous tobacco smoking abstinence at 6-months follow up was defined as a self-report of smoking no cigarettes from target quit date (TQD) to 6-months follow-up, validated biochemically by urinary anabasine level of less than 3 ng/ml and if not available, by expired carbon monoxide level of ≤ 9 ppm at 6-months).

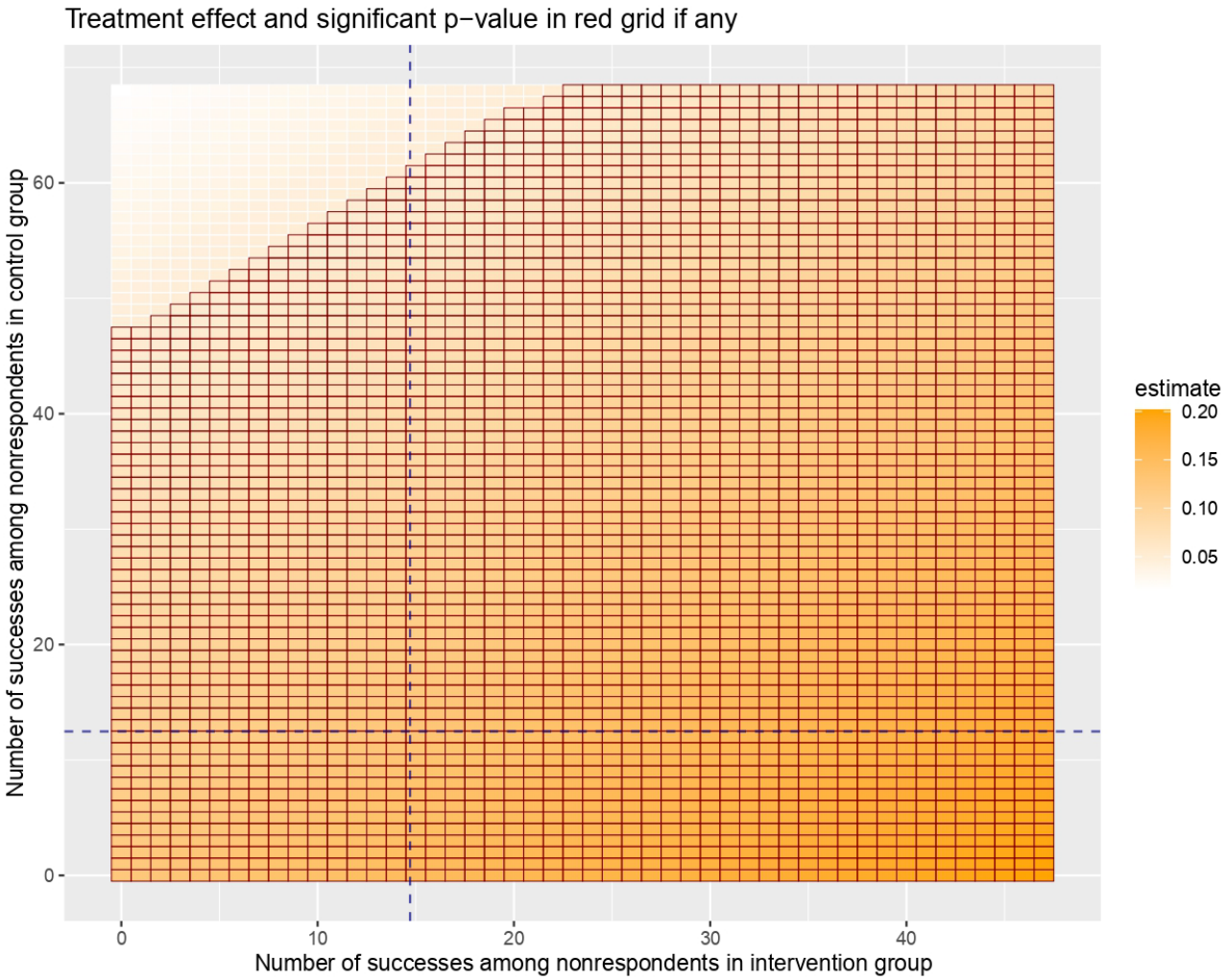
[†] Confidence interval widths for secondary outcomes were no adjusted for multiplicity and may not be used in place of hypothesis testing.

[‡] Relative risk with 95% Koopman confidence interval

[§] Multivariable adjusted model, adjusted for study site, age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström score with stabilized inverse probability of censoring weights (IPCW).

[¶] Risk reduction with 95% Newcombe-hybrid-score confidence interval.

4.2.2 Figure S3. Tipping point analysis for continuous tobacco smoking abstinence, validated by anabasine and by CO if anabasine missing (primary outcome)[24]



Horizontal and vertical axes indicate the number of successes (defined as a participant with continuous tobacco smoking abstinence from target quit date to 6-months follow-up, validated by anabasine, or CO if anabasine not available (primary outcome)) that could have occurred among nonrespondents (defined as those without data on the primary outcome) in the intervention (x axis, n=47) and control (y axis, n=68) groups. Colors correspond to the treatment effect, with magnitude changing from dark (large positive values) to white (zero estimate effect). Significant p-values (0.05 level) for the comparison between the two proportions are represented with the grid. Horizontal and vertical dashed lines indicate the observed number of successes in the intervention (x axis) and control (y axis) groups. The stair-case region indicates the tipping points that modify the study's conclusion. Simulation of potential successes among nonrespondents showed that it is unlikely that rate of nonrespondents influenced the results. For example, if there was no success among nonrespondents in the intervention group and 48 successes among nonrespondents in the control group, the test would have become statistically not significant.

4.2.3 Preferred allocation group at baseline and association between group allocation preference and efficacy outcome

At the end of the baseline visit, all participants ranked their preference for group allocation on a scale from 0 (control group) to 10 (intervention group). This preference scale was added after the trial began, in July 2019, 838/1246 (67%) filled it out. Table S7 presents the distribution of participants allocated to control or

intervention based on their rank on the scale 0-10 scale and categorized in those with rank 3-7, (suggesting no strong preference for any of both groups) and those with rank 0-2 or 8-10 (suggesting strong preference).

4.2.4 Table S7. Distribution of participants according to rank of preference for group allocation before randomization and group allocation after randomization

	Group allocation		
Preferred group	Control	Intervention	Total
0 (control group)	40	54	94
1	5	6	11
2	9	11	20
3	15	16	31
4	10	8	18
5	130	116	246
6	23	24	47
7	48	37	85
8	44	44	88
9	16	23	39
10 (intervention group)	81	78	158
3-7 (No strong preference)	226	201	427
0-2 or 8-10 (strong preference)	195	216	411
Total	421	417	838

The coefficient for the interaction term of preference for group allocation modeled as a continuous linear outcome when added to the main model was 1.01 (95% CI: 0.93 to 1.10); when modeled as a dichotomous variable of low or high preference (scale values 0-2 and 8-10 vs 3-7) the coefficient was 0.99 (95% CI: 0.57 to 1.73). Confidence interval widths for sensitivity analyses such as testing for interaction were not adjusted for multiplicity and may not be used in place of hypothesis testing.

4.3 Adherence to study products and further smoking cessation aid during study conduct

4.3.1 Table S8. Participants' self-reported intention to use ENDS and other smoking cessation drug therapies, measured at the end of their baseline clinical visit (inclusion) and at each follow-up phone visit

Adherence to products	Control group	Intervention group
Intention to use product at the end of baseline visit (in person), N (% of included at baseline):	624 (100%)	622 (100%)
- Nicotine replacement therapy, N (% of included at baseline)	512 (82.1%)	225 (36.2%)
- Missing information, N (% of included at baseline)	*14 (2.2%)*	*15 (2.4%)*
- Smoking cessation drug therapy*, N (% of included at baseline)	37 (5.9%)	7 (1.1%)
- Missing information, N (% of included at baseline)	*26 (4.2%)*	*23 (3.7%)*
Self-reported use **at target quit date** (phone follow-up), N (% of included at baseline):	566 (91%)	580 (93%)
- ENDS use since last visit, N (% of contacted during visit)	10 (1.8%)	544 (93.8%)
- Missing information on ENDS use, N (% of contacted during visit)	-	-
- Use of nicotine replacement therapy since last visit*, N (% of contacted during visit)	287 (50.7%)	23 (4.0%)
- Missing information on NRT use, N (% of contacted during visit)	*1 (0.2%)*	-
- Smoking cessation drug therapy*, N (% of included at baseline)	24 (4.2%)	3 (0.5%)
- Missing information on drug therapy, N (% of contacted during visit)*	*1 (0.2%)*	*1 (0.2%)*
Self-reported use at **Week 1 after target quit date** (phone follow-up), N (% of included at baseline):	536 (86%)	561 (90%)
- ENDS use since last visit, N (% of contacted during visit)	21 (3.9%)	538 (95.9%)
- Missing information on ENDS use, N (% of contacted during visit)	-	-
- Use of nicotine replacement therapy since last visit, N (% of contacted during visit)	341 (63.6%)	38 (6.8%)
- Missing information on NRT use, N (% of contacted during visit)	*1 (0.2%)*	*2 (0.4%)*
- Smoking cessation drug therapy*, N (% of included at baseline)	22 (4.1%)	3 (0.5%)
- Missing information on drug therapy, N (% of contacted during visit)*	-	*2 (0.4%)*
Self-reported use at **Week 2 after target quit date** (phone follow-up), N (% of included at baseline):	520 (83%)	550 (88%)
- ENDS use since last visit, N (% of contacted during visit)	24 (4.6%)	520 (94.6%)
- Missing information on ENDS use, N (% of contacted during visit)	-	-
- Use of nicotine replacement therapy since last visit, N (% of contacted during visit)	307 (59.0%)	37 (6.7%)
- Missing information on NRT use, N (% of contacted during visit)	-	-
- Smoking cessation drug therapy*, N (% of included at baseline)	22 (4.2%)	4 (0.7%)
- Missing information on drug therapy, N (% of contacted during visit)*	*1 (0.2%)*	-
Self-reported use at **week 4 after target quit date** (phone follow-up), N (% of included at baseline):	495 (79%)	546 (88%)
- ENDS use since last visit, N (% of contacted during visit)	22 (4.4%)	507 (92.9%)
- Missing information on ENDS use, N (% of contacted during visit)	-	-
- Use of nicotine replacement therapy since last visit, N (% of contacted during visit)	252 (50.9%)	28 (5.1%)
- Missing information on NRT use, N (% of contacted during visit)	*1 (0.2%)*	*2 (0.4%)*
- Smoking cessation drug therapy*, N (% of included at baseline)	25 (5.1%)	1 (0.2%)
- Missing information on drug therapy, N (% of contacted during visit)*	*1 (0.2%)*	*2 (0.4%)*
Self-reported use at **week 8 after target quit date** (phone follow-up), N (% of included at baseline):	472 (76%)	539 (87%)

- ENDS use since last visit, N (% of contacted during visit)	24 (5.1%)	479 (88.9%)
- Missing information on ENDS use, N (% of contacted during visit)	-	-
- Use of nicotine replacement therapy since last visit, N (% of contacted during visit)	162 (34.3%)	25 (4.6%)
- Missing information on NRT use, N (% of contacted during visit)	-	-
- Smoking cessation drug therapy*, N (% of included at baseline)	24 (5.1%)	3 (0.2%)
- Missing information on drug therapy, N (% of contacted during visit)*	-	*1 (0.2%)*

* Smoking cessation drug therapy: bupropion or varenicline

4.3.2 Table S9. Self-reported ENDS e-liquid nicotine concentration, quantity of e-liquids used per week, and computed total amount of nicotine delivered via ENDS among participants of the intervention group at target quit date, at phone follow-ups 1-, 2-, 4-, and 8-weeks after target quit date, and at the 6-month follow-up.

Product	Intervention group, N=622
Phone follow-up **at target quit date**, N contacted/N included (%):	580/622 (93)
- N reporting ENDS use since last visit/N contacted (%)	544/580 (94)
- N reporting ENDS use in the last 7 days/N contacted (%)	542/580 (93)
- N with data on e-liquids use/N reporting ENDS use in the last 7 days (%)	523/542 (96)
-- self-reported ml e-liquids used per week, median (IQR)	3 (2; 8)
-- self-reported mg/ml nicotine concentration in e-liquids*, median (IQR)	11 (11; 19.6)
-- computed mg nicotine per week†, median (IQR)	39 (22; 98)
Phone follow-up **1 week** after target quit date: N contacted/N included (%):	561/622 (90)
- N reporting ENDS use since last visit/N contacted (%)	538/561 (96)
- N reporting ENDS use in the last 7 days/N contacted (%)	538/561 (96)
- N with data on e-liquids use/N reporting ENDS use in the last 7 days (%)	534/538 (99)
-- self-reported ml e-liquids used per week, median (IQR)	10 (7; 17)
-- self-reported mg/ml nicotine concentration in e-liquids*, median (IQR)	11 (8.5; 19.6)
-- computed mg nicotine per week†, median (IQR)	122 (60; 220)
Phone follow-up **2 weeks** after target quit date: N contacted/N included (%):	550/622 (88)
- N reporting ENDS use since last visit/N contacted (%)	520/550 (95)
- N reporting ENDS use in the last 7 days/N contacted (%)	517/550 (94)
- N with data on e-liquids use/N reporting ENDS use in the last 7 days (%)	507/517 (98)
-- self-reported ml e-liquids used per week, median (IQR)	10 (7; 20)
-- self-reported mg/ml nicotine concentration in e-liquids*, median (IQR)	11 (8.5; 15.3)
-- computed mg nicotine per week†, median (IQR)	132 (60; 231)
Phone follow-up **4 weeks** after target quit date: N contacted/N included (%):	546/622 (88)
- N reporting ENDS use since last visit/N contacted (%)	507/546 (93)
- N reporting ENDS use in the last 7 days/N contacted (%)	495/546 (91)
- N with data on e-liquids use/N reporting ENDS use in the last 7 days (%)	487/495 (98)
-- self-reported ml e-liquids used per week, median (IQR)	10.5 (7; 20)
-- self-reported mg/ml nicotine concentration in e-liquids*, median (IQR)	11 (6; 15.3)
-- computed mg nicotine per week†, median (IQR)	124 (60; 238)
Phone follow-up **8 weeks** after target quit date: N contacted/N included (%):	539/622 (87)
- N reporting ENDS use since last visit/N contacted (%)	479/539 (89)
- N reporting ENDS use in the last 7 days/N contacted (%)	457/539 (85)
- N with data on e-liquids use/N reporting ENDS use in the last 7 days (%)	448/457 (98)
-- self-reported ml e-liquids used per week, median (IQR)	14 (8; 23)
-- self-reported mg/ml nicotine concentration in e-liquids*, median (IQR)	11 (6; 11)
-- computed mg nicotine per week†, median (IQR)	119 (60; 231)
Phone follow-up **6 months** after target quit date: N contacted/N included (%):	575/622 (92)
- N reporting ENDS use since last visit/N contacted (%)	472/575 (82)
- N reporting ENDS use in the last 7 days/N contacted (%)	370/575 (64)
- N with data on e-liquids use/N reporting ENDS use in the last 7 days (%)	346/370 (94)
-- self-reported ml e-liquids used per week, median (IQR)	13 (5; 23.5)

-- self-reported mg/ml nicotine concentration in e-liquids*, median (IQR)	6 (3; 11)
-- computed mg nicotine per week†, median (IQR)	84 (18; 154)

* In ESTxENDS, we gave participants a choice of e-liquids with 19.6-, 11-, 6- and 0- mg/ml nicotine; participants could order as many of each as they liked. When participants reported using e-liquids with different nicotine concentrations, e.g., 6 mg/ml and 11 mg/ml, we averaged them and coded the value as, e.g., 8.5 mg/ml.

† mg/week computed by multiplying the amount (in ml) of e-liquid used per week by the nicotine concentration (in mg/ml) in the e-liquid.

4.4 Adverse events and serious adverse events

4.4.1 Table S10. Serious adverse events.

In total, 56 (4.5%) participants reported 60 SAE; 34 SAE in 31 (5.0%) participants in the control group and 26 SAE in 25 (4.0 %) participants in the intervention group (RR 0.81; 95%CI: 0.48 to 1.35; unadjusted p-value 0.49). Confidence interval widths for secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing. Data available on SAE available for 1131/1246 (90.8%) of all participants; 556/624 (89.1%) of participants in the control group and 575/622 (92.4%) of participants in the intervention group.

	Total N=1246 participants included		**Control group N=624 participants included**		**Intervention group N=622 participants included**	
	N Events	**N Participants**	**N Events**	**N Participants**	**N Events**	**N Participants**
All serious adverse events	**60**	**56**	**34**	**31**	**26**	**25**
Cardiovascular	7	7	4	4	3	3
Respiratory	3	3	1	1	2	2
Gastrointestinal	7	6	2	2	5	4
Urology	1	1	1	1	0	0
Gynecology	1	1	0	0	1	1
Musculoskeletal system and soft tissue injury	14	13	10	9	4	4
Endocrinology	1	1	0	0	1	1
Neurology/Neurosurgery	4	4	2	2	2	2
Psychiatry	11	11	6	6	5	5
Dermatology	2	2	2	2	0	0
Ophthalmology	1	1	0	0	1	1
Otorhinolaringology	1	1	1	1	0	0
Neoplasia	4	4	3	3	1	1
Hematology	1	1	1	1	0	0
Deaths*	1	1	1	1	0	0
Unclassified	1	1	0	0	1	1

*One participant died during follow-up in the control group. Four months after randomization, he was diagnosed with Stage IV pulmonary adenocarcinoma. After three cycles of pembrolizumab over two months in ambulatory care, the patient was hospitalized for deteriorating health. He died three weeks after this hospitalization.

4.4.2 Table S11. Detailed presentation of serious adverse events (SAE).

	Total N=1246 participants included		**Control group N=624 participants included**		**Intervention group N=622 participants included**	
	N Events	**N Participants**	**N Events**	**N Participants**	**N Events**	**N Participants**
Cardiovascular	7	7	4	4	3	3
Cardiovascular symptoms	1	1	0	0	1	1

Ischemic heart disease (ACS, angina)	1	1	1	1	0	0
Vascular diseases	5	5	3	3	2	2
Thrombosis (also pulmonary embolism)	*1*	*1*	*0*	*0*	*1*	*1*
Peripheral arterial disease	*2*	*2*	*2*	*2*	*0*	*0*
Cerebrovascular events	*2*	*2*	*1*	*1*	*1*	*1*
Respiratory	3	3	1	1	2	2
Covid-19, hospitalized	1	1	1	1	0	0
Pneumonia	1	1	0	0	1	1
Surgery of respiratory tract	1	1	0	0	1	1
Gastrointestinal	7	6	2	2	5	4
Diseases related to the teeth	2	1	0	0	2	1
Tooth extraction, with infection	*1*	*1*	*0*	*0*	*1*	*1*
Other tooth-related diseases including toothache	*1*	*1*	*0*	*0*	*1*	*1*
Gastrointestinal diseases	2	2	1	1	1	1
Gastrointestinal bleeding	*1*	*1*	*1*	*1*	*0*	*0*
Inflammatory bowel disease: Crohn's disease	*1*	*1*	*0*	*0*	*1*	*1*
Gastrointestinal surgery / intervention	2	2	0	0	2	2
Other diseases concerning the gastroint. System	1	1	1	1	0	0
Urology	1	1	1	1	0	0
Urolithiasis	1	1	1	1	0	0
Gynecology	1	1	0	0	1	1
Gynecological surgery	1	1	0	0	1	1
Musculoskeletal system and soft tissue injury	14	13	10	9	4	4
Concerning muscles including muscle pain / tensions	1	1	1	1	0	0
Concerning bones	6	5	3	2	3	3
Concerning ligaments (incl. Distortion)	2	2	2	2	0	0
Concerning other soft tissue structures	3	3	3	3	0	0
Infection of the bones, joints and/or soft tissues	2	2	1	1	1	1
Endocrinology	1	1	0	0	1	1
Other endocrinologic diseases	1	1	0	0	1	1
Neurology/Neurosurgery	4	4	2	2	2	2
Spinal disc herniation	2	2	1	1	1	1
Diseases concerning the peripheral nerves incl. nerve compression syndromes, sensitivity disorders	1	1	0	0	1	1
Multiple sclerosis	1	1	1	1	0	0
Psychiatry	11	11	6	6	5	5
Affective disorders	6	6	2	2	4	4
Depression	*3*	*3*	*0*	*0*	*3*	*3*
Suicide thoughts, active thoughts	*1*	*1*	*1*	*1*	*0*	*0*
Suicide attempt	*2*	*2*	*1*	*1*	*1*	*1*
Addictions apart from smoking	3	3	3	3	0	0
Other / unclear psychiatric disorders incl. ADHD	2	2	1	1	1	1

Dermatology	2	2	2	2	0	0
Eczema / allergic skin reactions	1	1	1	1	0	0
Other skin-related diseases such as fistula, etc.	1	1	1	1	0	0
Ophthalmology	1	1	0	0	1	1
Ophthalmological surgery	1	1	0	0	1	1
Otorhinolaringology	1	1	1	1	0	0
Otitis: media	1	1	1	1	0	0
Neoplasia	4	4	3	3	1	1
Benign alterations	1	1	0	0	1	1
Pulmonary cancer	2	2	2	2	0	0
Other cancer	1	1	1	1	0	0
Hematology	1	1	1	1	0	0
Hypochromic anemia	1	1	1	1	0	0
Deaths	1	1	1	1	0	0
Other/unclear	1	1	1	1	0	0
Unclassified	1	1	0	0	1	1

In italics: Numbers of subgroups do not add to the total number of events.

4.4.3 Table S12. Adverse events

From baseline to the 6-month follow-up visit, 501 (40.2%) participants reported 791 AE; 272 (43.7%) participants reported 425 AE in the intervention group, and 229 (36.7%) participants reported 366 AE in the control group (RR: 1.19; 95%CI: 1.04 to 1.37; unadjusted p-value: 0.01). Confidence interval widths for secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing. Data available on SAE available for 1131/1246 (90.8%) of all participants; 556/624 (89.1%) of participants in the control group and 575/622 (92.4%) of participants in the intervention group.

	Total N=1246 participants included		**Control group N=624 participants included**		**Intervention group N=622 participants included**	
	N Events	**N Participants**	**N Events**	**N Participants**	**N Events**	**N Participants**
All adverse events	**791**	**501**	**366**	**229**	**425**	**272**
Cardiovascular	27	23	10	9	17	14
Respiratory	232	200	105	93	127	107
Gastrointestinal	158	137	68	58	90	79
Nephrology	1	1	1	1	0	0
Urology	35	35	14	14	21	21
Gynecology	26	23	10	9	16	14
Rheumatology	8	8	5	5	3	3
Musculoskeletal system and soft tissue injury	115	106	50	44	65	62
Endocrinology	7	6	3	2	4	4
Neurology/Neurosurgery	54	53	25	25	29	28
Psychiatry	66	61	38	34	28	27
Dermatology	32	32	18	18	14	14
Ophthalmology	7	7	6	6	1	1
Otorhinolaringology	10	9	4	3	6	6
Neoplasia	12	12	8	8	4	4

Unclassified	1	1	1	1	0	0

4.4.4 Table S13. Detailed presentation of adverse events (AE)

	Total N=1246		Control group N=624		Intervention group N=622	
	N Events	N Participants	N Events	N Participants	N Events	N Participants
Cardiovascular	**27**	**23**	**10**	**9**	**17**	**14**
Cardiovascular symptoms	14	14	7	7	7	7
Chest pain / feeling of pressure on the chest	*10*	*10*	*3*	*3*	*7*	*7*
Palpitations / sensation of tachycardia	*4*	*4*	*4*	*4*	*0*	*0*
Cardiac arrhythmias (tachycardia, bradycardia, flutter, fibrillation)	1	1	0	0	1	1
Ischemic heart disease (ACS, Angina)	2	2	1	1	1	1
Vascular diseases	6	5	2	1	4	4
Thrombosis (also pulmonary embolism)	*1*	*1*	*0*	*0*	*1*	*1*
Peripheral arterial disease)	*4*	*3*	*2*	*1*	*2*	*2*
Varicosis/ chronic venous insufficiency	*1*	*1*	*0*	*0*	*1*	*1*
Intervention / surgery of the cardiovascular system	2	2	0	0	2	2
Other cardiovascular events (cardiomyopathy, valvular disease etc.)	2	1	0	0	2	1
Respiratory	**232**	**200**	**105**	**93**	**127**	**107**
Respiratory symptoms (cough, phlegm, wheezing, sore throat)	49	45	20	18	29	27
Cough	*12*	*12*	*7*	*7*	*5*	*5*
Phlegm	*3*	*3*	*1*	*1*	*2*	*2*
Shortness of breath / dyspnea	*7*	*7*	*3*	*3*	*4*	*4*
Wheezing	*1*	*1*	*0*	*0*	*1*	*1*
Sore throat / throat irritation	*13*	*12*	*4*	*3*	*9*	*9*
Other respiratory symptoms (feeling of pressure on the lung, dysphagia, hoarseness, nasal breathing impairment)	*13*	*13*	*5*	*5*	*8*	*8*
Acute bronchitis	14	13	10	9	4	4
Sinusitis	12	11	5	5	7	6
Group A streptococcal angina	5	4	4	3	1	1
Other upper resp. tract infection (mononucleosis, tonsillopharyngitis)	9	9	3	3	6	6
Covid-19	29	29	8	8	21	21
Suspected infection (no confirmation test)	*3*	*3*	*0*	*0*	*3*	*3*
Symptomatic and positive confirmation test	*26*	*26*	*8*	*8*	*18*	*18*
Pneumonia	1	1	1	1	0	0
Bronchial asthma	10	10	7	7	3	3
Newly diagnosed	*2*	*2*	*1*	*1*	*1*	*1*
Asthma attack/ exacerbation	*8*	*8*	*6*	*6*	*2*	*2*
COPD exacerbation	1	1	0	0	1	1
Sleep-related respiratory disorders: obstructive sleep apnea	7	7	2	2	5	5
Allergic rhinoconjunctivitis	5	5	3	3	2	2
Olfactory or gustatory disorders not associated with Covid-19	6	4	0	0	6	4
Surgery of the respiratory tract	1	1	0	0	1	1
Common cold / rhinitis	80	76	41	39	39	37
Other respiratory events	3	3	1	1	2	2
Gastrointestinal	**158**	**137**	**68**	**58**	**90**	**79**
Gastrointestinal symptoms (mouth ulcers, gingivitis, nausea, diarrhea, etc.)	101	90	39	34	62	56
Symptoms concerning the lips	*8*	*8*	*1*	*1*	*7*	*7*
Dry mouth	*2*	*2*	*0*	*0*	*2*	*2*
Mouth and tongue irritation / change of the oral mucosa	*6*	*6*	*1*	*1*	*5*	*5*
Mouth ulcers	*8*	*8*	*5*	*5*	*3*	*3*
Gingivitis	*14*	*13*	*4*	*4*	*10*	*9*
Gingival bleeding	*7*	*7*	*3*	*3*	*4*	*4*
Dyspepsia / gastritis	*16*	*16*	*7*	*7*	*9*	*9*
Nausea	*10*	*10*	*6*	*6*	*4*	*4*
Emesis	*13*	*13*	*8*	*8*	*5*	*5*
Abdominal pain	*3*	*3*	*1*	*1*	*2*	*2*
Indigestion	*3*	*3*	*1*	*1*	*2*	*2*
Diarrhea	*5*	*5*	*0*	*0*	*5*	*5*
Constipation	*6*	*6*	*2*	*2*	*4*	*4*
Reported weight gain	*2*	*2*	*1*	*1*	*1*	*1*
Reported weight loss	*1*	*1*	*0*	*0*	*1*	*1*
Other gastrointestinal symptoms such as hiccups, meteorism, abscess in the mouth	*4*	*4*	*2*	*2*	*2*	*2*
Diseases related to the teeth	26	24	17	15	9	9
Tooth inflammation / infection (without extraction) incl. periodontitis	*9*	*9*	*6*	*6*	*3*	*3*
Tooth extraction	*13*	*13*	*8*	*8*	*5*	*5*
With infection	*5*	*5*	*4*	*4*	*1*	*1*
Other tooth-related diseases including toothache	*4*	*4*	*3*	*3*	*1*	*1*
Gastrointestinal diseases (bleeding, gastroenteritis, infl. Bowel disease, etc.)	23	22	7	7	16	15
Gastrointestinal bleeding	*1*	*1*	*1*	*1*	*0*	*0*

Infectious bowel disease such as gastroenteritis, h.pylori, C. diff	*16*	*15*	*3*	*3*	*13*	*12*
Inflammatory bowel disease	*2*	*2*	*1*	*1*	*1*	*1*
Ulcerative colitis	*1*	*1*	*0*	*0*	*1*	*1*
Diverticulitis	*1*	*1*	*1*	*1*	*0*	*0*
Irritable bowel syndrome	*2*	*2*	*1*	*1*	*1*	*1*
Other diseases affecting the intestine such as hernias, gastric ulcer	*2*	*2*	*1*	*1*	*1*	*1*
Liver or biliary system	2	2	1	1	1	1
Cholelithiasis / cholecystitis / cholangitis	*1*	*1*	*0*	*0*	*1*	*1*
Hepatitis: unspecified	*1*	*1*	*1*	*1*	*0*	*0*
Pancreas: Pancreatitis	1	1	0	0	1	1
Gastrointestinal surgery / intervention	2	2	2	2	0	0
Other diseases concerning the gastroint. System as anal fistula etc.	3	3	2	2	1	1
Nephrology	**1**	**1**	**1**	**1**	**0**	**0**
Other diseases concerning the kidney	1	1	1	1	0	0
Urology	**35**	**35**	**14**	**14**	**21**	**21**
Urological symptoms such as dysuria, urge to urinate, flank/side pain	4	4	2	2	2	2
Urocystitis / urethritis	21	21	9	9	12	12
Pyelonephritis	2	2	0	0	2	2
Sexually transmitted diseases	5	5	2	2	3	3
Infections / Inflammation of the male genital organs	1	1	1	1	0	0
Urological surgery	1	1	0	0	1	1
Other urological diseases	1	1	0	0	1	1
Gynecology	**26**	**23**	**10**	**9**	**16**	**14**
Pregnancy / delivery	7	7	2	2	5	5
Abortion	3	3	1	1	2	2
Induced abortion	*2*	*2*	*1*	*1*	*1*	*1*
Spontaneous abortion	*1*	*1*	*0*	*0*	*1*	*1*
Infections of the female genital organs apart from STDs	2	2	0	0	2	2
Endometriosis / myoma	4	3	3	2	1	1
Gynecological surgery (Breast & surgery of female genital organs)	5	4	1	1	4	3
Other gynecological diseases like menopause problems	5	5	3	3	2	2
Rheumatology	**8**	**8**	**5**	**5**	**3**	**3**
Arthrosis	3	3	1	1	2	2
Arthritis	3	3	2	2	1	1
Other rheumatologic diseases like gout, vasculitides, or collagenosis	2	2	2	2	0	0
Musculoskeletal system and soft tissue injury	**115**	**106**	**50**	**44**	**65**	**62**
Concerning muscles including muscle pain / tensions	14	14	6	6	8	8
Concerning bones	13	13	6	6	7	7
Concerning tendons and tendon sheaths (incl. epicondylitis)	17	17	5	5	12	12
Concerning ligaments (incl. Distortion)	9	9	4	4	5	5
Concerning other soft tissue structures (joint pain, cutting, animal bite)	48	46	24	22	24	24
Infection of the bones, joints and/or soft tissues	14	13	5	4	9	9
Endocrinology	**7**	**6**	**3**	**2**	**4**	**4**
Diabetes Mellitus	1	1	0	0	1	1
Hyper/ hypothyroidism	4	4	2	2	2	2
Other endocrinologic diseases	2	2	1	1	1	1
Neurology/Neurosurgery	**54**	**53**	**25**	**25**	**29**	**28**
Headache	26	26	12	12	14	14
Dizziness	1	1	0	0	1	1
Vertigo	10	10	2	2	8	8
Spinal disc herniation	7	7	5	5	2	2
Diseases concerning the peripheral nerves incl. nerve compression syndromes, sensitivity disorders	5	5	3	3	2	2
Multiple sclerosis	1	1	1	1	0	0
Other neurologic diseases such as craniocerebral injury, syncope	4	4	2	2	2	2
Psychiatry	**66**	**61**	**38**	**34**	**28**	**27**
Affective disorders	41	40	20	20	21	20
Mood deterioration	*11*	*11*	*7*	*7*	*4*	*4*
Depression	*16*	*16*	*7*	*7*	*9*	*9*
Suicide thoughts	*12*	*12*	*6*	*6*	*6*	*6*
Suicidal ideation	*3*	*3*	*1*	*1*	*2*	*2*
Tired of life	*9*	*9*	*5*	*5*	*4*	*4*
Other affective disorders	*2*	*2*	*0*	*0*	*2*	*2*
Anxiety disorders including panic and phobia	4	4	2	2	2	2
Addictions apart from smoking	4	4	4	4	0	0
Sleeping disorders	15	15	10	10	5	5
Due to nicotine abstinence /reduction	*9*	*9*	*6*	*6*	*3*	*3*
Other / unclear psychiatric disorders incl. ADHD	2	2	2	2	0	0
Dermatology	**32**	**32**	**18**	**18**	**14**	**14**
Eczema / allergic skin reactions	12	12	10	10	2	2
Due to nicotine patch	*7*	*7*	*7*	*7*	*0*	*0*
Acne	3	3	2	2	1	1
Dermatologic intervention	3	3	1	1	2	2

Other skin-related diseases such as fistula, cysts, psoriasis etc.	8	8	3	3	5	5
Other allergies apart from allergic rhinoconjunctivitis, skin reactions	6	6	2	2	4	4
Ophthalmology	**7**	**7**	**6**	**6**	**1**	**1**
Eye infection / inflammation	4	4	3	3	1	1
Conjunctivitis	3	3	2	2	1	1
Other	1	1	1	1	0	0
Other ophthalmologic diseases such as corneal injury, visual loss, hyposphagma, retinal tear	3	3	3	3	0	0
Otorhinolaringology	**10**	**9**	**4**	**3**	**6**	**6**
Earache	2	2	1	1	1	1
Otitis	6	5	3	2	3	3
Externa	*2*	*2*	*2*	*2*	*0*	*0*
Media	*1*	*1*	*1*	*1*	*0*	*0*
Unspecified	*3*	*3*	*0*	*0*	*3*	*3*
Hearing loss	2	2	0	0	2	2
Acute	*1*	*1*	*0*	*0*	*1*	*1*
Chronic	*1*	*1*	*0*	*0*	*1*	*1*
Neoplasia	**12**	**12**	**8**	**8**	**4**	**4**
Benign alterations	7	7	5	5	2	2
Benign mammary alterations	*1*	*1*	*0*	*0*	*1*	*1*
Intestinal polyps	*2*	*2*	*2*	*2*	*0*	*0*
Other benign alterations	*4*	*4*	*3*	*3*	*1*	*1*
Metaplasia/ Precancerosis	1	1	1	1	0	0
Other cancer	3	3	2	2	1	1
Malignancies related conditions	1	1	0	0	1	1
Unclassified	**1**	**1**	**1**	**1**	**0**	**0**

In italics: Numbers of subgroups do not add to the total number of events.

4.4.5 Table S14. Number of self-reported antibiotics use and reason for use

Between baseline and 6-month follow-up, 54 (8.7%) participants in the intervention group reported 61 episodes of antibiotic use; 43 (6.9%) of those in the control group reported 56 episodes of antibiotic use (RR of participants with antibiotic use: 1.26; 95%CI: 0.86 to 1.85).

	Total N=1246 participants included		**Control group N=624 participants included**		**Intervention group N=622 participants included**	
	N events with antibiotics	**N participants**	**N events with antibiotics**	**N participants**	**N events with antibiotics**	**N participants**
All events with antibiotics	**117**	**97**	**56**	**43**	**61**	**54**
Group A Streptococcal angina	5	3	5	3	0	0
Skin and soft tissues	23	20	12	10	11	10
Gastrointestinal, incl. gall bladder	2	2	1	1	1	1
Sinusitis	11	8	3	3	8	5
Acute bronchitis	7	7	4	4	3	3
Other upper respiratory tract	4	4	2	2	2	2
COPD exacerbation	1	1	0	0	1	1
Bones and joints	6	5	3	2	3	3
STI (sexually transmitted infections)	2	2	1	1	1	1
Lower urinary tract	20	19	8	7	12	12
Upper urinary tract	4	4	2	2	2	2
Pneumonia	2	2	1	1	1	1
Otitis media	2	2	1	1	1	1
Gynecological infections (endometritis, mastitis)	2	2	0	0	2	2
Invasive infections (meningitis, sepsis)	0	0	0	0	0	0
Oral cavity and teeth	13	12	8	7	5	5
Other	12	11	4	4	8	7
Not classified	1	1	1	1	0	0

4.4.6 Table S15. Distribution of withdrawal symptoms by allocated group at 6-months follow-up.

	Control group	Intervention group
N reporting on withdrawal symptoms/N included (%)	409/624 (66%)	506/622 (81%)
Total withdrawal score* - mean (SD)	**6.2 (5.3)**	**5.3 (4.9)**
Angry, irritable, frustrated - mean (SD)	**0.91 (1.22)**	**0.83 (1.15)**
None (0)	221 (54%)	287 (57%)
Slight (1)	81 (20%)	98 (19%)
Mild (2)	52 (13%)	62 (12%)
Moderate (3)	31 (8%)	40 (8%)
Severe (4)	24 (6%)	19 (4%)
Anxious, nervous - mean (SD)	**0.73 (1.07)**	**0.67 (1.02)**
None (0)	243 (59%)	314 (62%)
Slight (1)	83 (20%)	95 (19%)
Mild (2)	46 (11%)	59 (12%)
Moderate (3)	25 (6%)	26 (5%)
Severe (4)	12 (3%)	12 (2%)
Depressed mood, sad - mean (SD)	**0.56 (0.95)**	**0.46 (0.9)**
None (0)	274 (67%)	370 (73%)
Slight (1)	69 (17%)	73 (14%)
Mild (2)	42 (10%)	36 (7%)
Moderate (3)	18 (4%)	19 (4%)
Severe (4)	6 (1%)	8 (2%)
Difficulty concentrating - mean (SD)	**0.54 (0.93)**	**0.52 (0.92)**
None (0)	284 (69%)	348 (69%)
Slight (1)	56 (14%)	92 (18%)
Mild (2)	45 (11%)	32 (6%)
Moderate (3)	21 (5%)	29 (6%)
Severe (4)	3 (1%)	5 (1%)
Increased appetite, hungy, weight gain - mean (SD)	**0.6 (1.03)**	**0.58 (1.04)**
None (0)	280 (68%)	354 (70%)
Slight (1)	54 (13%)	69 (14%)
Mild (2)	44 (11%)	42 (8%)
Moderate (3)	21 (5%)	26 (5%)
Severe (4)	10 (2%)	15 (3%)
Insomnia, sleep problems, awakening at night - mean (SD)	**0.68 (1.2)**	**0.61 (1.06)**
None (0)	287 (70%)	347 (69%)
Slight (1)	38 (9%)	64 (13%)
Mild (2)	29 (7%)	53 (10%)
Moderate (3)	36 (9%)	27 (5%)
Severe (4)	19 (5%)	15 (3%)
Restless - mean (SD)	0.59 (0.98)	0.51 (0.93)
None (0)	274 (67%)	355 (70%)
Slight (1)	66 (16%)	87 (17%)
Mild (2)	40 (10%)	31 (6%)
Moderate (3)	22 (5%)	24 (5%)

Severe (4)	7 (2%)	9 (2%)
Desire or craving to smoke - mean (SD)	1.63 (1.5)	1.17 (1.45)
None (0)	147 (36%)	259 (51%)
Slight (1)	59 (14%)	78 (15%)
Mild (2)	69 (17%)	52 (10%)
Moderate (3)	68 (17%)	58 (11%)
Severe (4)	66 (16%)	59 (12%)

* Total withdrawal score ranges from 0-32. the higher the total score, the more withdrawal symptoms are present.

4.4.7 Table S16. Difference in mean total withdrawal score by allocated group at 6-months follow-up

Continuous withdrawal score	Difference in mean MTWS-R-score (95%CI)	Adjusted difference in mean MTWS-R-score (95%CI)*
Intervention vs control	-0.90 (-1.56 to -0.23)	-0.85 (-1.48 to -0.22)*

* Multivariable adjusted linear regression with robust standard errors. Model adjusted for baseline covariates (age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström test score, study site and baseline withdrawal-score). We used stabilized inverse probability censoring weights to account for potential selective attrition. Confidence interval widths for secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing.

4.5 Secondary outcomes

4.5.1 Table S17. Assessments listed in the protocol whose results are published in the present manuscript and the assessments planned to be reported in subsequent manuscripts.

Assessments at 6-months follow-up	**Presented in manuscript**	**Planned other manuscript**	**Publication of early results available Separately registered in Clinicaltrials.gov***
Demographics	X		
Medical History		X	
Smoking history	X		
Main smoking cessation outcome	**X**		**Main entry on Clinicaltrials.gov: NCT03589989**
Adverse events, serious AE	X		
Nicotine dependence	X		
Withdrawal symptoms	X		
Environmental pollution (e.g. secondhand smoke)		X	
Alcohol and illicit drug use		X	
Anxiety		X	
Depression symptoms		X	Separate entry on Clinicaltrials.gov: NCT03603340
Sleep quality		X	Separate entry on Clinicaltrials.gov: NCT03603353
Quality of life		X	
Pulmonary function tests and MBW (Multiple breath washout parameters, Bern site)		X	Separate entry on Clinicaltrials.gov: NCT03938298 Performed at baseline and follow-up in a selected subgroup of participants at the study site of Bern. Results from MBW assessed among 44 participants in the study site of Bern coming for the 6-months visit published in the study on lung MRI study.[25] Analyses of changes in MBW planned.
MRI of the lung (Parameters of ventilation, perfusion and structural changes of the lung, Bern site)			Only preformed in a selected subgroup of 44 participants in the study site of Bern coming for the 6-months visit. Only one cross sectional analysis with experimental design assessing outcomes before and

			right after exposure to ENDS, tobacco smoke, or ambient air.[25]
Micronuclei assessment in buccal epithelium		X	Separate entry on Clinicaltrials.gov: NCT04244773
Olfactory function		X	Separate entry on Clinicaltrials.gov: NCT04617444
"Dry-hit" recognition			Dropped after COVID-19 pandemic and for safety reason
Inflammatory biomarkers		X	Separate entry on Clinicaltrials.gov: NCT03603340
Tobacco use	X		
Estimated ENDS use (ml e-liquids used)	X		
Exhaled CO	X		
Urinary nicotine, cotinine, anabasine	X		
Urinary metabolites of nitrosamines (TSNAs), VOC and PAH		X	Separate entry on Clinicaltrials.gov: NCT03612544 Results from urinary analyses of subsample of study participants for urine collected at baseline published.[26]
Oxidative stress markers in urine		X	Separate entry on Clinicaltrials.gov: NCT03612375 Methods and results from urinary analyses of study participants at baseline published.[26,27]
Oxidative stress in exhaled breath (Lausanne site only)		X	Separate entry on Clinicaltrials.gov: NCT03612453
Blood pressure, heart rate, height, weight (BMI), waist circumference		X	Separate entry on Clinicaltrials.gov: NCT03603340
Blood lipids, HbA1c (only for participants with diabetes)		X	Separate entry on Clinicaltrials.gov: NCT03603340
Respiratory symptoms	X		Separate entry on Clinicaltrials.gov: NCT03632421
Physical activity		X	
Assessments at 12- and 24-months follow-up		**X**	**Separate entry on Clinicaltrials.gov: NCT04236791**
Assessments at 60-months follow-up		**X**	**Funding approved in May 2023, adaptation to the protocol in process**

* To ensure planned secondary analyzes get published, we registered secondary outcomes separately in Clinicaltrials.gov. In recent years, this approach is not recommended anymore, with most trialists only registering the main trial and list the secondary outcomes within only one entry in Clinicaltrials.gov registration. We decided to keep the multiple clinicaltrials.gov entries and continue the focus of announcing results of the secondary analyses as such and not as primary analyses of the secondary outcomes.

4.5.2 Table S18. Distribution of respiratory symptoms by allocated group at 6-months follow-up.

	Control group	**Intervention group**
N Reporting on respiratory symptom/N included (%)	412/624 (66%)	506/622 (81%)
CAT total score – mean (SD)	5.7 (4.5)	4.8 (3.9)
CAT total score – categories		
0-5	231 (56%)	339 (67%)
6-9	108 (26%)	104 (21%)
10-20	69 (17%)	61 (12%)
21-40	4 (1%)	2 (0%)
Cough		
I have never cough (0)	141 (34%)	207 (41%)
(1)	132 (32%)	194 (38%)
(2)	66 (16%)	60 (12%)
(3)	56 (14%)	30 (6%)
(4)	12 (3%)	10 (2%)
I cough all the time (5)	5 (1%)	5 (1%)
Phlegm		

I have no phlegm (mucus) in my chest at all (0)	210 (51%)	312 (62%)
(1)	87 (21%)	125 (25%)
(2)	74 (18%)	41 (8%)
(3)	28 (7%)	19 (4%)
(4)	10 (2%)	9 (2%)
My chest is completely full of phlegm (mucus) (5)	3 (1%)	0 (0%)
Chest tight		
My chest does not feel tight at all (0)	296 (72%)	367 (73%)
(1)	69 (17%)	86 (17%)
(2)	26 (6%)	29 (6%)
(3)	16 (4%)	14 (3%)
(4)	5 (1%)	8 (2%)
My chest feels very tight (5)	0 (0%)	2 (0%)
Breathless		
When I walk up a hill or one flight of stairs I am not breathless (0)	124 (30%)	173 (34%)
(1)	103 (25%)	142 (28%)
(2)	86 (21%)	102 (20%)
(3)	60 (15%)	56 (11%)
(4)	28 (7%)	24 (5%)
When I walk up a hill or one flight of stairs I am very breathless (5)	11 (3%)	9 (2%)
Activity at home		
I am not limited doing any activities at home (0)	384 (93%)	482 (95%)
(1)	14 (3%)	12 (2%)
(2)	7 (2%)	7 (1%)
(3)	6 (1%)	3 (1%)
(4)	0 (0%)	1 (0%)
I am very limited doing activities at home (5)	1 (0%)	1 (0%)
Leaving home		
I am confident leaving my home despite my lung condition (0)	393 (95%)	485 (96%)
(1)	8 (2%)	13 (3%)
(2)	6 (1%)	2 (0%)
(3)	2 (0%)	4 (1%)
(4)	2 (0%)	2 (0%)
I am not at all confident leaving my home because of my lung condition (5)	1 (0%)	0 (0%)
Sleep		
I sleep soundly (0)	369 (90%)	466 (92%)
(1)	30 (7%)	19 (4%)
(2)	8 (2%)	13 (3%)
(3)	3 (1%)	4 (1%)
(4)	1 (0%)	4 (1%)
I don’t sleep soundly because of my lung condition (5)	1 (0%)	0 (0%)
Energy		
I have lots of energy (0)	162 (39%)	202 (40%)
(1)	103 (25%)	132 (26%)
(2)	64 (16%)	80 (16%)
(3)	59 (14%)	66 (13%)
(4)	18 (4%)	21 (4%)
I have no energy at all (5)	6 (1%)	5 (1%)

4.5.3 Table S19. Difference in mean overall CAT-score by allocated group at 6-months follow-up.

	Difference in mean CAT-score (95%CI)	Adjusted difference in mean CAT-score (95%CI)*

Intervention vs control	-0.96 (-1.52 to -0.41)	-0.66 (-1.13 to -0.18)

* Multivariable adjusted linear regression with robust standard errors. Model adjusted for baseline covariates (age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström test score, study site and baseline CAT-score). We used stabilized inverse probability censoring weights to account for potential selective attrition. Confidence interval widths for secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing.

5 Standard Operating Procedures (SOP) for the smoking cessation intervention

Study nurses followed standard operating procedures (SOP) for the smoking cessation intervention. These were provided in French and German. Since these procedures have not yet been published, we share them here, translated into English.

5.1 Principles of the clinical intervention

The clinical intervention is based on the model described in the reference document "Medical advice for smokers" from the 2015 Swiss program *Vivre sans tabac*.[33,34] This approach is based on a synthesis of the medical literature and international recommendations, and its efficacy for tobacco smoking abstinence of at least 6 months has been well-documented.[35,36]

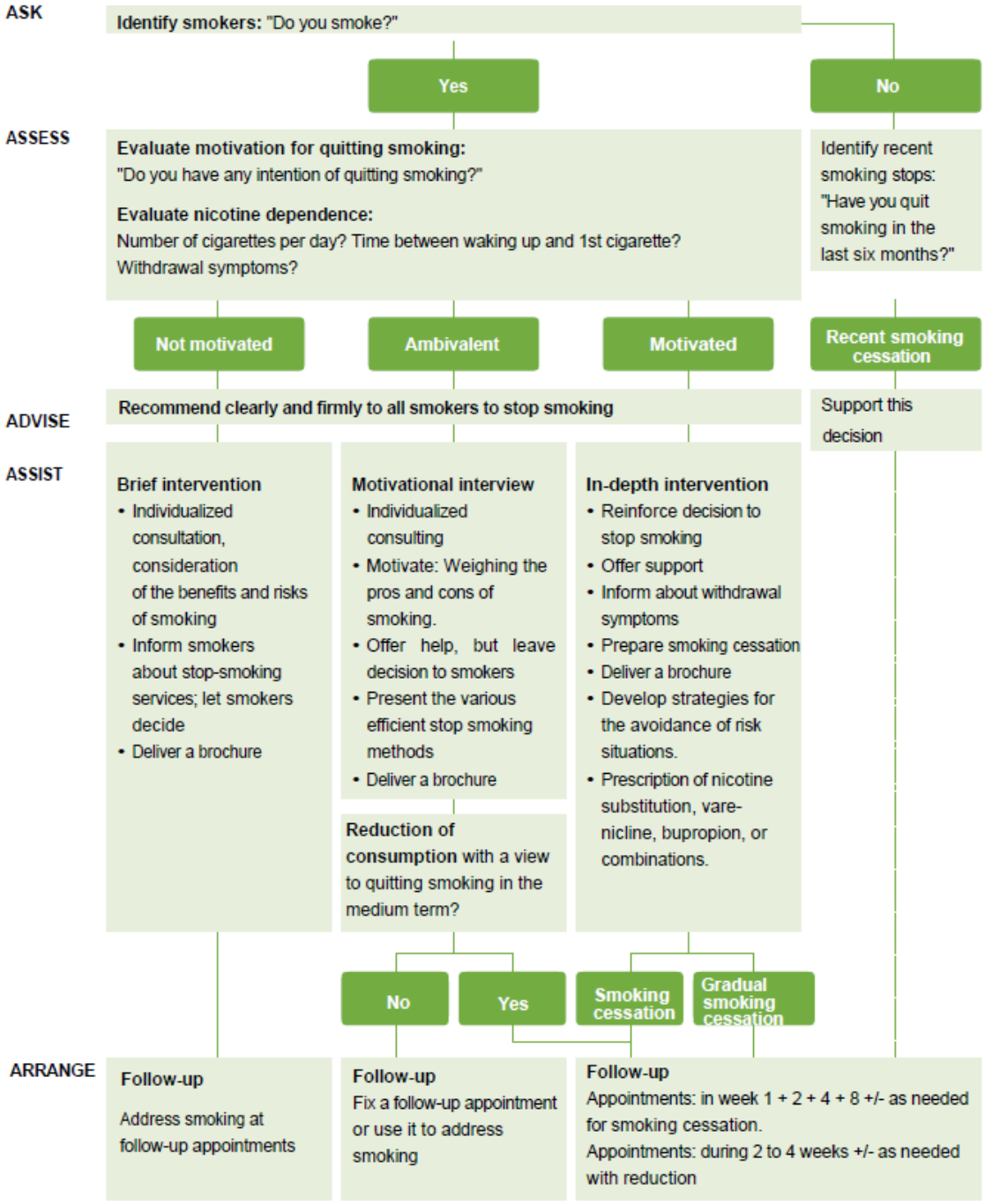
The intervention, which is tailored to the patient's level motivation to quit smoking, relies on behavioral and motivational interviewing techniques (Figure A). Since participants were included only if they were determined to stop smoking within 3 months, we adopted the smoking cessation model for smokers motivated to quit at the baseline visit and for smokers who recently quit or relapsed at follow-up.

At the baseline visit, these behavioral interventions will support tobacco smoking abstinence, will last around 30 minutes and will be delivered by a trained study nurse.

The intervention described in the document "Medical advice for smokers" from the Swiss program *Vivre sans tabac* recommends using pharmacological treatments (NRT, varenicline or bupropion). The study will give participants in the intervention group an ENDS and recommend NRT to both groups but will not supply participants with NRT. To enable participants select a smoking cessation aid that fits their preference and values, the clinical encounter support tool presenting the options for NRT, varenicline and bupropion will be used.[3] Participants will receive information about these smoking cessation aids, can choose to use them or not, and will inform the study personnel of their choice. If participants wish to use varenicline or bupropion, they will be advised to get a prescription from their general practitioner.

The smoking cessation process in the intervention group will be supported by ENDS, which will be given to participants. The clinical intervention will therefore include information on the ENDS and practical advice about how to use it.

5.1.1 Figure S-A. General algorithm to support smoking cessation in both groups[34]



5.2 Baseline visit

5.2.1 General advice for smoking cessation

(strategies for smokers motivated to quit according to Figure S-A)

- Inform participants about the smoking cessation process:
  - Smoking cessation leads to withdrawal symptoms
  - Withdrawal symptoms are most marked during the first 3 days of abstinence, then gradually diminish over a period from about 10 days to 4 weeks
  - Withdrawal symptoms include cravings, dizziness, headaches, fatigue, coughing, tightness, sleep disturbances, constipation, hunger, lack of concentration, irritability, depressed mood.
  - Support from a healthcare professional increases the chances of success
  - Nicotine replacement therapy, varenicline and bupropion reduce withdrawal symptoms and increase the chance a quit attempt will be successful.
- Set a quit date
  - Planning a quit date allows the participant to implement the decision and make a personal commitment to the caregiver.
  - The participant chooses a convenient quit date within the next 12 weeks.
  - If the participant wishes to gradually reduce their consumption before the quit date, encourage them to set cigarettes-per-day goals, set their duration, and use NRT or ENDS during the reduction phase.
- Seek support in the social network
  - Inform their relatives
  - Identify a closely-connected person who can provide support (preferably a non-smoker or ex-smoker)
  - Create a smoke-free home environment
- Offer smoking cessation documentation
  - Stop smoking brochure: "I've made up my mind to stop smoking!"
  - stop-tabac.ch website
  - Application stop-tabac.ch (only in French) and/or smokefree.ch (French and German)
- Preventing relapse
  - Identify situations that put participants at risk of relapse: major withdrawal symptoms; stress; boredom; depressed mood; conflicts; other smokers; alcohol consumption; end of meals; coffee; habits; etc.
  - Plan appropriate strategies, e.g., temporarily avoid risky situations (other smokers, alcohol overuse), wait for the craving to pass, divert attention with alternative activities or thoughts, leave the place or situation.
  - Inform participants that cravings are short-lived (about 5 minutes)
  - Prepare a sentence they can say to refuse a cigarette
  - Briefly explain how to limit weight gain when quitting smoking: 3 balanced meals; avoid nibbling; snack with low-calorie foods; regular moderate physical activity.

5.2.2 Determination of nicotine dependence

Determine the patient's nicotine dependence using the table below. The level of dependence is defined by the criterion corresponding to the highest degree of dependence:

5.2.3 Table S-A. Nicotine dependence assessment

Nicotine dependence	**low**	**moderate**	**strong**	**very strong**
Number of cigarettes/day	1 - 9	10 - 19	20 - 30	> 30
Time between waking up and smoking 1 ère	> 60 min	31 - 60 min	5 - 30 min	< 5 min
Withdrawal symptoms	absent/minor	moderate	High	Very high

5.2.4 Figure S-B. Algorithm for counseling NRT and smoking cessation drug therapy among participants in the control group, based on their nicotine dependence scores [34]

Indication for pharmacological treatment
- Motivation for smoking cessation or temporary substitution.
- Nicotine addiction

Contraindications/caution
- **Nicotine Substitution**
  - **Caution with:** Myocardial infarction < 2 weeks, unstable angina, severe arrhythmia, pregnancy/breastfeeding.
- **Varenicline**
  - **Contraindications:** severe renal insufficiency, pregnancy/breastfeeding, < 18-year-old.
  - **Caution with:** mental disorders.
- **Bupropion**
  - **Risk in case of overdose:** hepatic and renal insufficiency.
  - **Contraindications:** Epilepsy, anorexia/bulimia, alcohol withdrawal or sedatives, liver cirrhosis, brain tumor, MAO inhibitors, bipolar disorder, pregnancy/breastfeeding, < 18-year-old.
  - **Caution with:** Lowering of seizure threshold, neuroleptics, antidepressants, tramadol, quinolones, antimalarials, systemic steroids, alcohol dependence, use of stimulants or appetite suppressants, diabetes with antidiabetic drugs or insulin treatment, history of traumatic brain injury.
  - **Interaction:** CYP2D6.

Low dependence	Medium dependence	Strong dependence	Very strong dependence
• < 10 cig. per day or • 1st cigarette > 60 min. after waking up	• 10-19 cig. per day or • 1st cigarette 31-60 min. after waking up	• 20-30 cig. per day or • 1st cigarette 5-30 min. after waking up	• > 30 cig. per day or • 1st cigarette < 5 min. after waking up

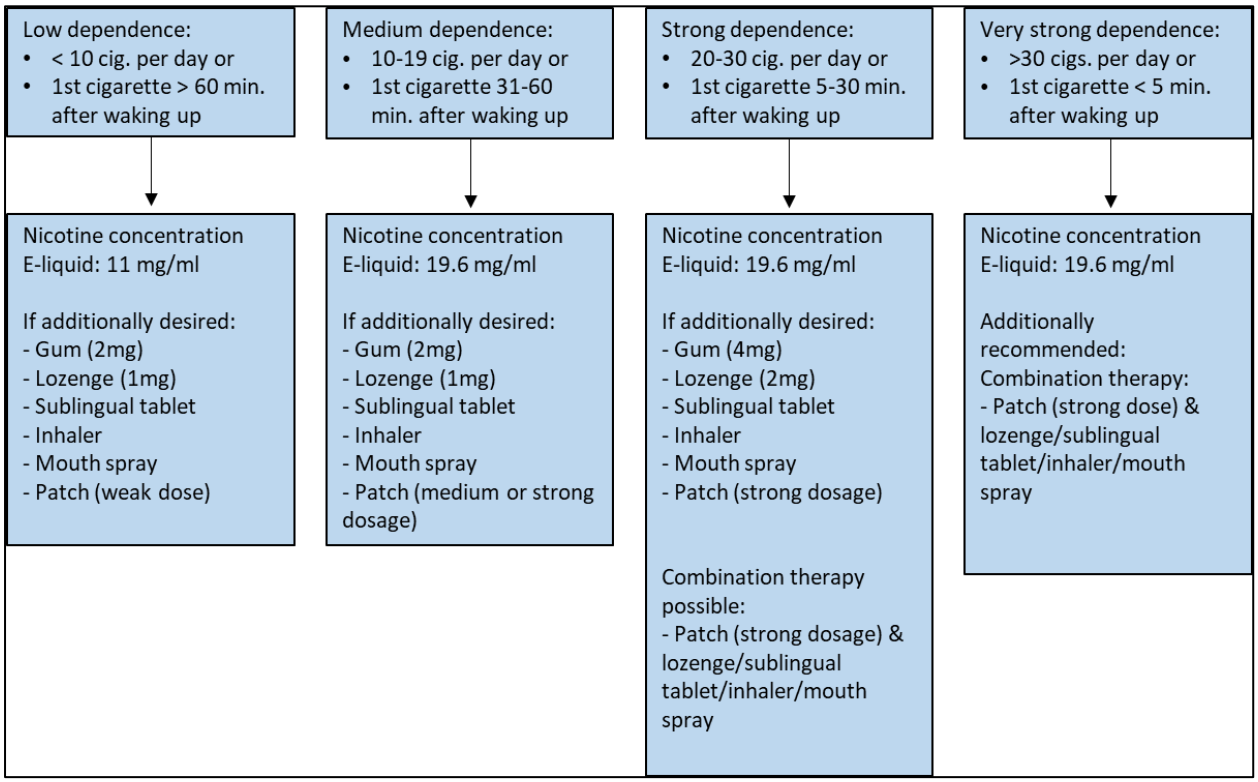
Selection depending on: Patient preference, experience, contraindications, co-morbidities, episodes of depression, other substance use, additional medications

Low dependence	Medium dependence	Strong dependence	Very strong dependence
Nicotine Substitution • **Chewing gum** 2 mg • **Nicotine lozenge** 1 mg • **Sublingual tablet** • **Inhaler** • **Mouth spray** • **Patch** weak dose	**Nicotine Substitution** • **Chewing gum** 2 mg • **Nicotine lozenge** 1 mg • **Sublingual tablet** • **Inhaler** • **Mouth spray** • **Patch** medium or strong dose **Varenicline** **Bupropion**	**Nicotine Substitution** • **Monotherapy:** patch strong dose/chewing gum 4 mg/tablet 2 mg/sublingual tbl/inhaler/mouth spray. • **Combination therapy:** patch strong dose + short-acting nicotine substitution *. **Varenicline** **Bupropion** **Bupropion + nicotine substitution** (short-acting nicotine substitutes*/patches)	**Nicotine Substitution** • **Combination therapy:** patch strong dose + short-acting nicotine substitution *. **Varenicline** **Bupropion** **Bupropion + nicotine subst.** (short-acting nicotine substit. */patch) **Bupropion + nicotine substit. in combination therapy** (patch + short-acting nicotine substit. *)

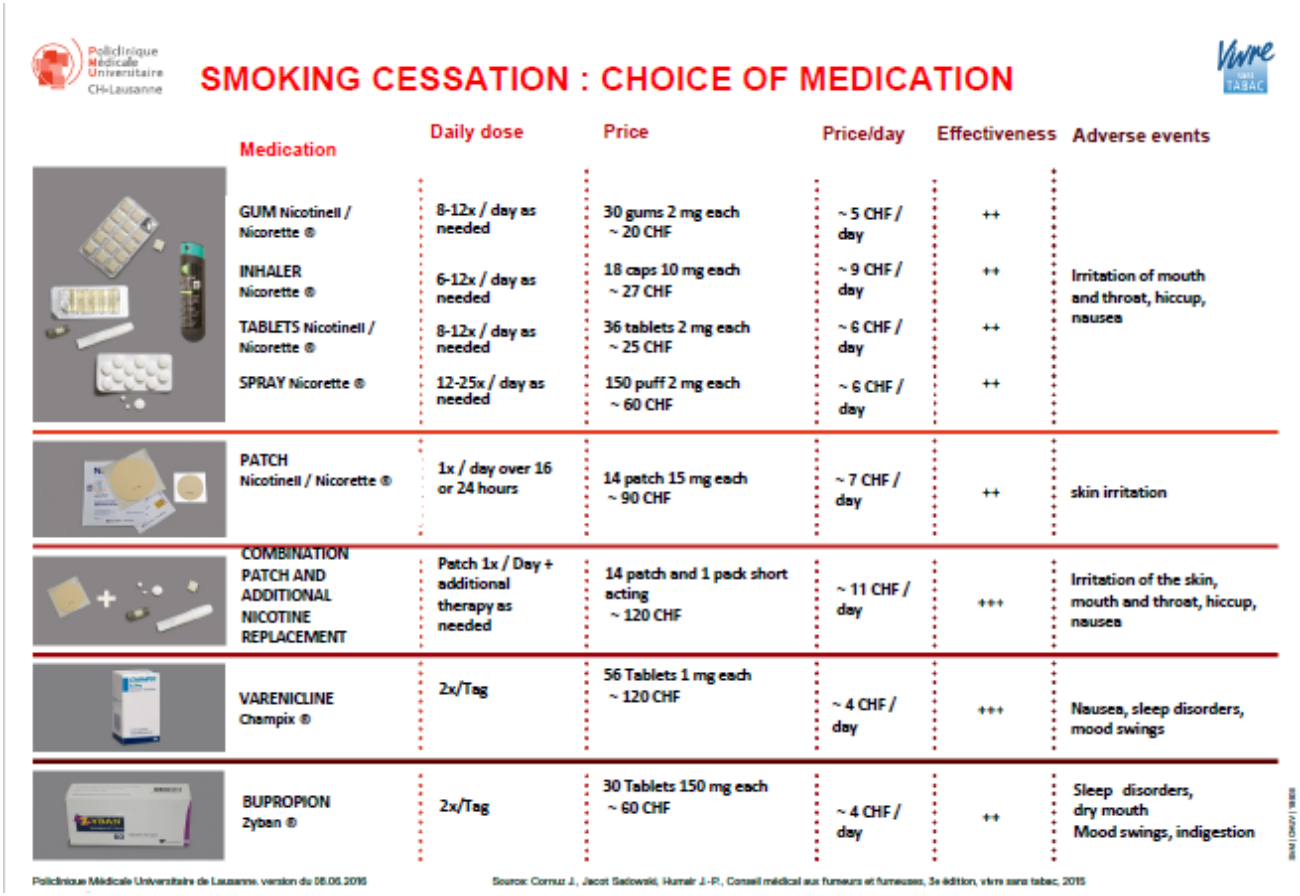
- **Temporary substitution:** short-acting nicotine substitution * prefer, if insufficient: add patch
- **Gradual smoking cessation:** consumption reduction during a few weeks before complete smoking cessation. Option: short-acting nicotine substitution * during this period.
- **Pretreatment:** nicotine substitution 2 to 3 weeks before smoking cessation. Efficacy controversial. Patches preferable.
- **E-cigarette:** The e-cigarette is not currently recommended for smoking cessation. However, its use as a cigarette substitute might reduces health risks

* **Short-acting nicotine substitution:** nicotine lozenge/sublingual tablet/inhaler/mouth spray.

5.2.5 Figure S-C. Algorithm for recommending e-liquid dosage and NRT to participants in the intervention group, based on their nicotine dependence scores.



5.2.6 Figure S-D. Clinical encounter decision support tool enabling participants in both groups to select NRT or smoking cessation drug support [3]



5.2.7 Table S-B. Specific recommendations for NRT.[34]

Patch 4 p.m. Nicorette ® patch 25 mg /15 mg /10 mg	• High dose: 25mg x 8 weeks, then 15mg x 2 weeks, then 10mg x 2 weeks. Duration: 2-3 months, up to 6-12 months if necessary. • Average dose: 15 mg x 4 weeks, then 10 mg x 2 (4) weeks. Duration: 6-8 weeks, up to 6-12 months if necessary. • Low dose: 10 mg. Duration: 4-8 weeks, up to 6-12 months if necessary. Apply to hairless skin. Change place daily.
Patch 24 h Nicotinell ® patch 21mg /14mg /7 mg	• High dose: 21 mg x 4 weeks, then 14 mg x 2 (4) weeks, then 7 mg x 2 (4) weeks. Duration: 2-3 months, up to 6-12 months if necessary. • Average dose: 14mg x 4 weeks, then 7 mg x 2 (4) weeks. Duration: 6-8 weeks, up to 6-12 months if necessary. • Low dose: 7 mg. Duration: 4-8 weeks, up to 6-12 months if necessary. Apply to hairless skin. Change place daily.
Gum Nicorette® / Nicotinell ® 2mg /4mg	8-12 gums / day x 4 weeks (max.15 / day) to be adapted. Gradual reduction. Duration: 2-3 months, up to 6-12 months if necessary. If dual therapy with patch: max. 6 x 2 mg gums / day. Chew for 20-30 sec. Then press alternately against gums for 30 min.
Sucking tablet Nicotinell ® 1mg /2mg	8-12 cpr / day x 4 weeks (max. 15 / day) to be adapted. Gradual reduction. Duration: 2-3 months, up to 6-12 months if necessary. If dual therapy with patch: max. 6 pcs 1 mg / day. Leave to melt in the mouth without crunching or swallowing.
Sublingual tablet Nicorette Microtab ® 2mg	8-12 cpr / day x 4 weeks, to be adapted. Can be increased to 2 cpr per dose in case of heavy dependence (max 30 cpr / day). Gradual reduction. Duration: 2-3 months, up to 6-12 months if necessary.

	If dual therapy with patch: max. 6 cpr / day. Melt under the tongue.
Inhaler Nicorette Inhaler ® 10mg	6-12 cartridges / day x 4 weeks (max 16 / day) to be adapted. Gradual reduction. Duration: 2-3 months, up to 6-12 months if necessary. If dual therapy with patch: max. 4 cartridges / day. Repeated brief inhalations for 30 min.
Mouth spray Nicorette® oral spray solution 1 mg /dose	1 bis 2 sprays every 30 to 60 minutes (max. 64 / day) x 6 weeks, to be adapted. Gradual reduction. Duration: 2-3 months, up to 6-12 months if required. If dual therapy with patch: max. 30 sprays / day. Spray the solution into the mouth, avoid breathing when administering, and do not swallow for a few seconds after spraying.

5.3 Advice on using ENDS

5.3.1 General information about ENDS

- ENDS is a device for producing nicotine-containing vapor.
- ENDS vapor reduces exposure to harmful substances to well below that of cigarette smoke.
- ENDS does not contain tobacco.
- ENDS is not a medication.
- The ENDS consists of a battery, coil, tank, mouthpiece, and charger.
- The liquid is composed of propylene glycol, glycerol, flavorings, alcohol (for preservation) and nicotine in varying concentrations.
- The liquids come from a company in France that follows rigorous quality criteria and uses pharmaceutical-grade products.
- The quality of the liquids used in this study was assessed by independent laboratories; the study's research laboratory rechecked the contents of test liquids.
- The vapor generated by the ENDS was evaluated by the study's research laboratory to ensure inhaling the vapor is safe.
- E-liquid bottles are designed to prevent them from being opened by children; they must be kept out of reach of children and pets, and the contents must not be swallowed.
- If the contents of the vials are accidentally ingested, participants must immediately contact the investigators or call Tox Info Suisse on 145 if the investigators cannot be reached right away.
- ENDS could help smokers quit, but its effectiveness in smoking cessation has not been clearly demonstrated.
- Currently known adverse reactions associated with ENDSare short- to medium-term symptoms of low severity: coughing; irritation/dryness of the mouth and throat; mouth ulcers; transient loss of taste.
- In the event of nicotine overdose, the symptoms are mainly nausea, perhaps vomiting, headaches, dizziness, and an unpleasant taste in the mouth.
- Long-term effects of ENDS on health-related outcomes are unknown.

5.3.2 Explain how ENDS work

- Show the different elements of ENDS
- Explain how to load ENDS
- Show how to switch ENDS on and off
- Show how to change the ENDS coil.
- Tell participants they must change the coil every 2-3 weeks, depending on use, or after about 30 ml of liquid, or if the taste changes (in case of a "dry hit").
- Show them how to fill the fluid tank
- Link to an explanatory video and the STOP-Tabac.ch website

5.3.3 Explanations about e-liquids

5.3.3.1 Inform participants of choice of e-liquids

- Choice of 4 nicotine concentrations: 19.6 mg/ml; 11 mg/ml; 6 mg/ml; and 0 mg/ml
- Choice of 6 flavors: 2 tobacco (FR-M; FR-4); fresh mint; 2 fruit (red fruit; raspberry; green apple).

5.3.3.2 Enable participants to test the e-liquids

- Choice available to participants (24 total)
    - 19.6 mg/ml tobacco flavor, fresh mint, fruit
    - 11 mg/ml tobacco flavor, fresh mint, fruit
    - 6 mg/ml tobacco flavor, fresh mint, fruit
    - 0 mg/ml tobacco flavor, fresh mint, fruit
- If the participant asks for advice: propose 19.6 mg/ml in the case of strong or very strong dependence, based on the dependence test (see 1.2); 11 mg/ml for medium and low dependence.
- The experience of smokers who switch to ENDS suggests that they start with tobacco flavors and, over time, as they regain their sense of smell and taste after quitting, prefer menthol or fruit-based flavors.

5.3.4 Practical aspects of providing ENDS and E-liquids to participants

- Hand over the ENDS to participant at the baseline visit, with the leaflet in its packaging.
- Have participants change the coils themselves and when the ENDS is not yet full of liquid, to ensure that they know how to change them regularly.
- Have participants fill in the ENDS with the liquid of their choice during the baseline visit to ensure that they know how to use the device on their planned quit date.
- Hand over 2 ENDS, 5 coils and up to 10 bottles at the baseline visit.
- Inform participants that each order will include bottles of liquids with a different flavor and nicotine concentration for them to try out, if they wish, in advance of their next order.

5.3.5 Instructions for use to be given to participants

- Vape on demand, based on nicotine withdrawal symptoms (ad libitum).
- Inhale slowly, holding the vapor in the mouth for about 3 seconds before inhaling it into the lungs (mouth to lung, MTL).
- Vaping must be learned. Experienced vapers tend to be more successful in delivering the nicotine they need through ENDS than inexperienced vapers. Try ENDS a few times before your planned quit date. Study nurse can be contacted to discuss strategies for ways to improve nicotine delivery or visit the stop-tabac.ch website for further advice.
- Remember to charge the battery.
- Estimate daily e-liquid intake (usually 2-4 ml).
- Plan e-liquid orders based on estimated use and available e-liquids.
- Fill the tank before leaving home.
- Do not vape if liquid level is too low.
- When changing the coil, first empty the tank.
- When using the ENDS for the first time, wait about 5 minutes after filling the tank before vaping. You must wait for the cotton in the coil to soak up the liquid, otherwise you risk "frying" the coil.
- Order e-liquids 2 weeks before you will run out; contact the study nurse.
- If you have any questions, the study nurse can be reached by telephone or e-mail during working hours.
- You can also consult the vaping forum on the stop-tabac.ch website.
- In the event e-liquid leaks from the ENDS, check that the e-liquid cartridge is correctly inserted, that the ENDS components are in good condition and correctly assembled (in particular, that the plastic strap on the cap is in place and that the coil is correctly positioned in the ENDS), and contact the study nurse for more detailed technical advice (to dismantle and completely clean the atomizer and, if leaks persist, replace the device).

5.3.6 Information about adverse reactions associated with ENDS given to participants

Give advice in the event of adverse reactions associated with ENDS use (see detailed adverse reactions associated with ENDScollection sheet)

- Coughing and throat irritation: favor slow inhalations, holding vapor in the mouth for about 3 seconds in the mouth before inhaling into the lungs (mouth-to-lung method, MTL). If adverse reactions associated with ENDS do not improve, try a lower nicotine concentration, bearing in mind that the nicotine substitution may be less effective for smoking cessation. Remember that these symptoms tend to fade over time. Throat irritation, also known as "throat hit," is mainly because nicotine directly stimulates the nerves in the throat. “Throat hit" is well known to cigarette smokers. It's the same phenomenon as in ENDS use, but without the smoke.
- Dry mouth: drink regularly, remembering that this is an expected adverse reaction associated with propylene glycol and glycerol and that symptoms tend to abate over time.
- “Dry hit”: In the event of a “dry hit,” it is essential to change the coil before starting to vape again. “Dry hit" is a change in the taste of the vapor—a "burnt" taste. Dry hit occurs when the coil is clogged or overheated, which releases unpleasant toxic substances into the vapor. This occurs when the heating element is not changed regularly, when consumption is resumed after replacing the element without waiting the 5 minutes required to humidify the cotton in the coil, or when the ENDS is switched on with insufficient liquid in the tank.
- Loss of taste: change flavor, suggest mint flavor. Loss of taste is a transitory symptom; generally speaking, smoking cessation is associated with rediscovery of taste and smell.
- Mouth ulcers: symptomatic treatment. Mouth ulcers occur regularly in people who stop smoking. A direct link to ENDS has not been demonstrated.

5.4 Phone follow-up

5.4.1 Anamnesis

- Smoking behavior, including forms of tobacco other than cigarettes
- Use of ENDS (proposed in the study or other), quantity of liquid, type of liquid (nicotine concentration, flavor)
- Adverse reactions associated with ENDS
- Use of smoking cessation medication
- Withdrawal symptoms
- Motivation to quit smoking
- Desire to change liquid nicotine flavor or concentration

5.4.2 Table S-C. Situation-specific advice for counseling participants in the intervention group.

Smoking		
Complete tobacco smoking abstinence	No withdrawal symptoms	Praise the abstinence. Continue vaping at the same dosage. If ENDS not appreciated/tolerated and they wish to discontinue use, follow the algorithm to advise on NRT
	Withdrawal symptoms	Praise the abstinence. Recommend increasing nicotine concentration and/or frequency and duration of ENDS use. If they don't want to change their habits, suggest short-acting NRT. If ENDS not appreciated/tolerated and they wish to discontinue use, follow the algorithm to advise on NRT

Reduction in number of tobacco cigarettes	No withdrawal symptoms	Support the reduction approach while encouraging complete abstinence. Recommend higher nicotine concentration, more frequent and longer ENDS use to stop or further reduce cigarette consumption. If they don't want to change their habits, suggest short-NRT. If ENDS not appreciated/tolerated and they wish to discontinue use, follow the algorithm to advise on NRT
	Withdrawal symptoms	Ditto, with encouraging a greater increase in nicotine use.
Consumption of tobacco cigarettes unchanged		Explore motivation for stopping. Evaluate ENDS use. Recommend higher nicotine concentration, more frequent and longer ENDS use to stop or further reduce cigarette consumption. If ENDS not appreciated/tolerated and they wish to discontinue use, follow the algorithm to advise on NRT
Relapse	Not related to withdrawal symptoms	Assess the circumstances of relapse. Explore motivation to quit. Encourage a new quit attempt with ENDS in the same liquid dosage and quantity. If ENDS not appreciated/tolerated and they wish to discontinue use, follow the algorithm to advise on NRT Strategize to prevent relapse, particularly for the situation that led to the relapse.
	Linked to withdrawal symptoms	Assess the circumstances of relapse. Explore motivation to quit. Encourage a new quit attempt with ENDS. Recommend higher nicotine concentration, more frequent and longer ENDS use to stop or further reduce cigarette consumption. If they don't want to change their smoking habits, suggest short-acting NRT. If ENDS not appreciated/tolerated and they wish to discontinue use, follow the algorithm to advise on NRT. Strategize to prevent relapse, particularly for the situation that led to the relapse.

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