Clinical trial results:
Helping Pregnant smokers quit: A multi-centre RCT of electronic cigarettes and nicotine patches

Summary

EudraCT number	2017-001237-65
Trial protocol	GB
Global end of trial date	24 September 2020

Results information

Result version number	v1 (current)
This version publication date	21 November 2021
First version publication date	21 November 2021

Trial information

Trial identification

Sponsor protocol code	011822

Additional study identifiers

ISRCTN number	ISRCTN62025374
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Queen Mary, University of London, Mile end Road, London, United Kingdom, E1 4NS
Public contact	Dr Dunja Przulj, Queen Mary University of London, +44 02078825949, d.przulj@qmul.ac.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to compare abstinence rates at end of pregnancy between the two different treatment arms: nicotine patches and EC.

Protection of trial subjects:

Many women who miscarry can participate in follow up without upset; however, calls can occasionally be distressing. We did not routinely exclude women who miscarried from follow up, but the following minimised potential distress. The co-ordinating trial office sent the local research teams a list of participants to be followed up within the next fortnight; the local research team identified anyone known to have experienced an event which might make follow up distressing. In addition to this, a text reminder was sent to all participants the day before their follow up call was due. Participants could then text back if they did not wish to be called.

Background therapy:

Participants in both arms were provided with up to 6 support calls on a weekly basis. The support provided followed that of usual advice given in the UK Stop-smoking services and was conducted by trained stop-smoking advisors.

Evidence for comparator:

In the UK, nicotine skin patches are currently used routinely with pregnant smokers across the Stop-Smoking Specialist Services.

Actual start date of recruitment	01 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1140
Worldwide total number of subjects	1140
EEA total number of subjects	1140

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1140
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited by research midwives or other appropriately trained staff (such as a specialist pregnancy stop smoking advisor) at NHS hospital sites across England and one stop-smoking service in Scotland. Recruitment ran between January 2018-November 2019.

Pre-assignment

Screening details:

Eligibility criteria: 18 years or over; daily smoker seeking help; 12-24 weeks pregnant; willing to be randomised to NRT or EC and receive follow-up calls; understands English. Exclusion criteria: allergic reaction to nicotine patches; currently using NRT or EC; taking part in a conflicting trial; high-risk pregnancy or serious medical condition.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Period 2

Period 2 title	End of Pregnancy Follow up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Period 3

Period 3 title	3 month post-partum follow up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Period 4

Period 4 title	4 weeks post Target Quit Day
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 4	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Period 5

Period 5 title	1 week post target quit day
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 5	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Period 6

Period 6 title	2 weeks post target quit day
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 6	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Period 7

Period 7 title	3 weeks post target quit day
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nicotine Patch

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Nicorette Invisi Transdermal Patch 15mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Participants were asked to wear one nicotine patch every day for up to 8 weeks. Participants were provided with a supply of 15mg patches but could reduce to 10mg if they wished.

Arm title	E-cig

Arm description:

Electronic cigarette

Arm type	experimental (non-IMP)

No investigational medicinal product assigned in this arm

Number of subjects in period 7	Nicotine Patch	E-cig
Started	569	571
Completed	569	571

Baseline characteristics

Reporting groups

Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	

Reporting group values	Nicotine Patch	E-cig	Total
Number of subjects	569	571	1140
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	27.3	26.6	
inter-quartile range (Q1-Q3)	23.6 to 31.1	22.5 to 30.9	-
Gender categorical			
All participants were female			
Units: Subjects			
Female	569	571	1140
Male	0	0	0
Education level			
Units: Subjects			
Further education/diploma	273	288	561
Higher education	62	54	116
Primary and Secondary School	234	229	463
Employment status			
Units: Subjects			
Employed	257	274	531
Unemployed/other	312	297	609
Ethnicity			
Units: Subjects			
White British	495	513	1008
Other	74	58	132
Past Treatment			
Previous smoking cessation treatment used			
Units: Subjects			

Yes	302	299	601
No	267	272	539

Tried EC			
Number who have tried an e-cigarette in the past			
Units: Subjects			
Tried E-cigarette before	267	288	555
Never tried EC	302	283	585

Lives with a smoker			
Units: Subjects			
Lives with a smoker	328	342	670
Does not live with smoker	241	229	470

Cigarettes per day			
Units: cigarettes per day			
median	10	10	
inter-quartile range (Q1-Q3)	7 to 15	7 to 15	-

FTCD			
Fagestrome Test of Cigarette Dependence			
Units: N/A			
arithmetic mean	4.3	4.0	
standard deviation	± 2.1	± 2.1	-

Cotinine			
Units: ng/ml			
median	118	111	
inter-quartile range (Q1-Q3)	73.9 to 176.0	75.8 to 165.0	-

End points

End points reporting groups

Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	
Subject analysis set title	Abstainers using EC
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were abstinent from smoking and regularly using the EC (regardless of randomisation arm).	
Subject analysis set title	Abstainers not using nicotine
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were abstinent from smoking and not using any form of nicotine.	
Subject analysis set title	Abstainers using NRT
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants who were abstinent from smoking and regularly using NRT (regardless of randomisation	

arm).

Primary: Validated prolonged abstinence

End point title	Validated prolonged abstinence
End point description:	
End point type	Primary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	25	39		

Statistical analyses

Statistical analysis title	Validated prolonged abstinence at EoP
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.53

Primary: Validated prolonged abstinence- per protocol

End point title	Validated prolonged abstinence- per protocol
End point description:	
Sensitivity analysis of primary outcome (per protocol)	
End point type	Primary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	483		
Units: Number of participants				
Abstinent	23	39		

Statistical analyses

Statistical analysis title	Per protocol sensitivity analysis
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	865
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.21

Primary: Validated prolonged abstinence- multiple imputation

End point title	Validated prolonged abstinence- multiple imputation

End point description:

Sensitivity analysis of primary outcome- multiple imputation.
The counts given are an estimate obtained by averaging results from the 50 imputed datasets using Rubin's rules. They are only reported as a reference and should be interpreted with caution.

End point type	Primary

End point timeframe:

End of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	41	58		

Statistical analyses

Statistical analysis title	Sensitivity analysis- multiple imputation
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.21

Primary: Validated prolonged abstinence- excluding abstinent contaminators

End point title	Validated prolonged abstinence- excluding abstinent contaminators
End point description:	
Sensitivity analysis of primary outcome- excludes abstainers who were using a non-allocated product	
End point type	Primary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	564	571		
Units: Number of participants				
Abstinent	20	39		

Statistical analyses

Statistical analysis title	Sensitivity analysis excluding contaminators
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	3.26

Secondary: Self-reported prolonged abstinence at EOP

End point title	Self-reported prolonged abstinence at EOP
End point description:	
End point type	Secondary
End point timeframe:	
End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	44	63		

Statistical analyses

Statistical analysis title	Self-reported prolonged abstinence at EoP
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	2.06

Secondary: Validated point prevalence abstinence at EOP

End point title	Validated point prevalence abstinence at EOP
End point description:	
End point type	Secondary
End point timeframe:	
End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	40	58		

Statistical analyses

Statistical analysis title	Validated point prevalence abstinence at EOP
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.13

Secondary: Self-reported point prevalence abstinence at EOP

End point title	Self-reported point prevalence abstinence at EOP
End point description:	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	78	118		

Statistical analyses

Statistical analysis title	Self-reported point prevalence abstinence at EOP
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	1.96

Secondary: Validated abstinence for the past two months at EOP

End point title	Validated abstinence for the past two months at EOP

End point description:

End point type	Secondary

End point timeframe:

End of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	35	46		

Statistical analyses

Statistical analysis title	Validated abstinence for past two months at EOP
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2

Secondary: Self-reported abstinence for the past two months at EOP

End point title	Self-reported abstinence for the past two months at EOP
End point description:	
End point type	Secondary
End point timeframe:	
End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	59	68		

Statistical analyses

Statistical analysis title	Self-reported abstinence for the past two months
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.6

Secondary: Self-reported abstinence at 4 weeks

End point title	Self-reported abstinence at 4 weeks
End point description:	
End point type	Secondary
End point timeframe:	
4 wees post Target Quit Day	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	61	89		

Statistical analyses

Statistical analysis title	Self-reported abstinence at 4 weeks	
Comparison groups	Nicotine Patch v E-cig	
Number of subjects included in analysis	1140	
Analysis specification	Pre-specified	
Analysis type	superiority	
Parameter estimate	Risk ratio (RR)	
Point estimate	1.45	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	1.07	
upper limit	1.97	

Secondary: Validate 50% smoking reduction at EOP in non-abstainers

End point title	Validate 50% smoking reduction at EOP in non-abstainers
End point description:	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	453		
Units: Number of participants				
Reduced	12	12		

Statistical analyses

Statistical analysis title	validated reduction at EOP in non-abstainers
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	944
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.39

Secondary: Self-reported 50% smoking reduction at EoP in non-abstainers

End point title	Self-reported 50% smoking reduction at EoP in non-abstainers
End point description:	

End point type	Secondary
End point timeframe:	
End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	453		
Units: Number of participants				
Reduced	166	192		

Statistical analyses

Statistical analysis title	self-reported reduction at EOP in non-abstainers
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	944
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.48

Secondary: Self-reported 50% smoking reduction at EoP (abstainers included as

reducers)

End point title	Self-reported 50% smoking reduction at EoP (abstainers included as reducers)
End point description:	
End point type	Secondary
End point timeframe:	
End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Reduced	198	248		

Statistical analyses

Statistical analysis title	self-reported reduction at EOP
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.44

Secondary: Change in cotinine levels in abstainers using nicotine

End point title	Change in cotinine levels in abstainers using nicotine
End point description:	
Abstainers are defined as 7-day point prevalence	
End point type	Secondary
End point timeframe:	
Change from baseline to End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	37		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	-7 (-108.2 to -0.2)	-5.3 (-77.6 to 44.6)		

Statistical analyses

Statistical analysis title	Change in cotinine levels
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-123.3
upper limit	110.3

Secondary: Change in cotinine levels in 50% reducers using nicotine

End point title	Change in cotinine levels in 50% reducers using nicotine
End point description:	
50% reducers are those who reduced their smoking by 50%	
End point type	Secondary
End point timeframe:	
Change from baseline to End of Pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	99		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	6 (-44 to 59.0)	6 (-27.2 to 82)		

Statistical analyses

Statistical analysis title	Change in cotinine levels
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.9
upper limit	28.9

Secondary: Change in cotinine levels in dual users

End point title	Change in cotinine levels in dual users

End point description:

Dual users are those who have smoked in last 7 days and are still using nicotine products

End point type	Secondary

End point timeframe:

Change from baseline to End of Pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	87		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	10 (-4.5 to 59)	8 (-31 to 105)		

Statistical analyses

Statistical analysis title	Change in cotinine levels
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.8
upper limit	51.8

Secondary: Number who set Target Quit Day

End point title	Number who set Target Quit Day
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Set TQD	394	418		

Statistical analyses

Statistical analysis title	Number setting quit day
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.14

Secondary: Support sessions completed

End point title	Support sessions completed
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks post Target Quit Day	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: number of sessions				
median (inter-quartile range (Q1-Q3))	1 (0 to 2)	1 (0 to 3)		

Statistical analyses

Statistical analysis title	Support sessions completed
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.31

Secondary: Accessed local stop smoking services

End point title	Accessed local stop smoking services
End point description:	

End point type	Secondary
End point timeframe:	
From baseline to end of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Accessed services	34	29		

Statistical analyses

Statistical analysis title	Accessed local stop smoking services
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.38

Secondary: Current use of allocated product at EOP

End point title	Current use of allocated product at EOP

End point description:

End point type	Secondary

End point timeframe:

End of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Currently using	32	193		

Statistical analyses

Statistical analysis title	Current use of allocated product at EOP
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	6.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.21
upper limit	8.58

Secondary: Current use of non-allocated product at EOP

End point title	Current use of non-allocated product at EOP
End point description:	
non-allocated product refers to participants in the EC arm using NRT and vice versa.	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Currently using	49	4		

Statistical analyses

Statistical analysis title	Current use of non-allocated product at EOP
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.22

Secondary: Used allocated product since last contact

End point title	Used allocated product since last contact
End point description:	
End point type	Secondary
End point timeframe:	
1 week post target quit day to end of pregnancy	

End point values	Nicotine Patch	E-cig	Nicotine Patch	E-cig
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	569	571	569	571
Units: Number of participants				
Used product	236	371	128	228

End point values	Nicotine Patch	E-cig	Nicotine Patch	E-cig
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	569	571	569	571
Units: Number of participants				
Used product	169	232	139	213

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Used product	103	187		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of regular allocated product use

End point title	Duration of regular allocated product use
End point description:	

End point type	Secondary
End point timeframe:	
From start of treatment to end of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	465		
Units: weeks				
median (inter-quartile range (Q1-Q3))	1 (0 to 5)	8 (2 to 19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of occasional allocated product use

End point title	Duration of occasional allocated product use

End point description:

End point type	Secondary

End point timeframe:

From start of treatment to end of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	465		
Units: weeks				
median (inter-quartile range (Q1-Q3))	2 (1 to 4)	0 (0 to 1)		

Statistical analyses

Statistical analysis title	Weeks of occasional product use
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.16
upper limit	1.84

Secondary: Duration of regular non-allocated product use

End point title	Duration of regular non-allocated product use

End point description:

End point type	Secondary

End point timeframe:

From start of treatment to end of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	21		
Units: weeks				
median (inter-quartile range (Q1-Q3))	1 (0 to 2)	1 (0 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of occasional non-allocated product use

End point title	Duration of occasional non-allocated product use
End point description:	

End point type	Secondary
End point timeframe:	
From start of treatment to end of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	21		
Units: week				
median (inter-quartile range (Q1-Q3))	1 (0 to 1)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Type of NRT used

End point title	Type of NRT used
End point description:	

End point type	Secondary
End point timeframe:	
from target quit day to end of pregnancy	

End point values	Nicotine Patch			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: Number of participants				
Nicotine Patch	220			
Combination NRT	16			
Mouthspray	1			
Inhaler	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Type of EC used

End point title	Type of EC used
End point description:	

End point type	Secondary
End point timeframe:	
from target quit day to end of pregnancy	

End point values	E-cig	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	344		
Units: Number of participants				
Refillable	330	324		
Cig-a-like	0	1		
Cartridge/Pod	2	1		
Missing	39	18		

Statistical analyses

No statistical analyses for this end point

Secondary: E-liquid nicotine strength used

End point title	E-liquid nicotine strength used
End point description:	

End point type	Secondary
End point timeframe:	
from target quit day to end of pregnancy	

End point values	E-cig	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	344		
Units: Number of participants				
0 mg/mL	8	7		
1-10 mg/mL	77	47		
11-20 mg/mL	61	199		
Missing	225	91		

Statistical analyses

No statistical analyses for this end point

Secondary: E-liquid flavours used

End point title	E-liquid flavours used

End point description:

End point type	Secondary

End point timeframe:

from target quit day to end of pregnancy

End point values	E-cig	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	344		
Units: Number of participants				
Fruit	97	180		
Tobacco	38	24		
Mint/menthol	19	22		
chcocolate/dessert/candy	17	11		
Other	24	21		
Missing	176	86		

Statistical analyses

No statistical analyses for this end point

Secondary: Birth Outcomes- singleton birth

End point title	Birth Outcomes- singleton birth

End point description:
Birth outcomes in singleton births

End point type	Secondary

End point timeframe:
End of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	546		
Units: Number of participants				
Miscarraige	3	2		
Still birth	0	3		
Neonatal Death	3	2		
Post-neonatal death	3	0		
Maternal death	0	0		
Pre-term birth	63	46		
NICU admission	46	51		
Congenital abnormalities	15	25		
Terminations (due to abnormalities)	2	1		
Terminations (due to PROM)	0	2		
C-section delivery	148	131		

Statistical analyses

Statistical analysis title	Miscarriage
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	4

Statistical analysis title	Neonatal death
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	4

Statistical analysis title	Preterm birth
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.05

Statistical analysis title	NICU admission
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.63

Statistical analysis title	Congenital abnormalities
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	3.14

Statistical analysis title	Terminations due to Congenital abnormalities
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	9

Statistical analysis title	C-section
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1095
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.09

Secondary: Gestational age- singleton births	
End point title	Gestational age- singleton births
End point description:	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	547	545		
Units: week				
arithmetic mean (standard deviation)	38.2 (± 3.1)	38.4 (± 3.0)		

Statistical analyses

Statistical analysis title	Gestational age
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.59

Secondary: Birth-weight- singleton births

End point title	Birth-weight- singleton births
End point description:	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	541	541		
Units: kilogram(s)				
arithmetic mean (standard deviation)	3.1 (± 0.62)	3.1 (± 0.60)		

Statistical analyses

Statistical analysis title	Birthweight
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.1

Secondary: Birth Outcomes- including multiple births

End point title	Birth Outcomes- including multiple births
End point description:	
Sensitivity analysis inlcuding twin births	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	564		
Units: Number of participants				
Miscarriage	3	3		
Stillbirth	0	2		
Neonatal death	3	2		
Post-neonatal death	3	0		
Maternal death	0	0		
Preterm Birth	69	56		
NICU admission	46	58		
Congenital abnormalities	15	26		
Terminations (due to abnormalities)	2	1		
Terminations (due to PROM)	0	2		
C-section delivery	152	145		

Statistical analyses

Statistical analysis title	Miscarriage
Comparison groups	E-cig v Nicotine Patch

Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	4.87

Statistical analysis title	Neonatal death
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	3.93

Statistical analysis title	Preterm birth
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.14

Statistical analysis title	NICU admission
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.81

Statistical analysis title	Congenital abnormalities
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	3.2

Statistical analysis title	Terminations due to Congenital abnormalities
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	8.84

Statistical analysis title	C-section
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1121
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.15

Secondary: Gestational age- multiple births included

End point title	Gestational age- multiple births included

End point description:

End point type	Secondary

End point timeframe:

End of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	555	562		
Units: week				
arithmetic mean (standard deviation)	38.2 (± 3.1)	38.3 (± 3.1)		

Statistical analyses

Statistical analysis title	Gestational age- multiple births included
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1117
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.49

Secondary: Birth-weight- multiple births

End point title	Birth-weight- multiple births
End point description:	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	558		
Units: kilogram(s)				
arithmetic mean (standard deviation)	3.1 (± 0.63)	3.1 (± 0.63)		

Statistical analyses

Statistical analysis title	Birth-weight- multiple births
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1107
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.08

Secondary: Nicotine use and birth-weight

End point title	Nicotine use and birth-weight
End point description:	
Effect of nicotine use on birth-weight, controlling for time since last cigarette.	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Abstainers using EC	Abstainers not using nicotine	Abstainers using NRT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62	9	18	
Units: kilogram(s)				
arithmetic mean (standard deviation)	3.4 (± 0.57)	3.1 (± 0.62)	3.2 (± 0.55)	

Statistical analyses

Statistical analysis title	Birthweight
Comparison groups	Abstainers using EC v Abstainers not using nicotine
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.66

Statistical analysis title	Birthweight
Comparison groups	Abstainers using EC v Abstainers using NRT
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.53

Secondary: Nicotine use and gestational age

End point title	Nicotine use and gestational age
End point description:	
Effect of nicotine use on gestational age, controlling for time since last cigarette.	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Abstainers using EC	Abstainers not using nicotine	Abstainers using NRT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	9	18	
Units: week				
arithmetic mean (standard deviation)	39 (± 1.7)	38.4 (± 2.3)	38.9 (± 1.6)	

Statistical analyses

Statistical analysis title	Nicotine use and gestational age
Comparison groups	Abstainers using EC v Abstainers not using nicotine
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	2.56

Statistical analysis title	Nicotine use and gestational age
Comparison groups	Abstainers using EC v Abstainers using NRT
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	1.56

Secondary: New respiratory symptoms

End point title	New respiratory symptoms
End point description:	

Reports of new respiratory symptoms since start of treatment

End point type	Secondary

End point timeframe:

From baseline to end of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	64		
Units: Number of participants				
New symptoms	63	54		

Statistical analyses

Statistical analysis title	New respiratory symptoms
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.23

Secondary: Severe respiratory symptoms

End point title	Severe respiratory symptoms
End point description:	
Number of participants experiencing severe respiratory symptoms	
End point type	Secondary
End point timeframe:	
From baseline to end of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	53		
Units: Number of participants				
Severe symptoms	12	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Validated prolonged abstinence- effect of COVID

End point title	Validated prolonged abstinence- effect of COVID

End point description:

Sensitivity analysis of primary outcome to check whether COVID had any effect on saliva sample return rate. In total, 5 saliva kits were posted to self-reported abstainers between 1st March and 5th May, during the period of pandemic lock-down in the UK (3 EC arm and 2 NRT arm). Of these, 2 were returned. The rate of sample return in pre-Covid period was 73.6% and 66.7% in the EC and NRT arms, respectively. The rate of passed validation observed pre-Covid was 92.1% and 100% in EC and NRT arms, respectively. Therefore, we assumed that 66.0% in the EC arm and 66.7% in NRT arm would be returned and pass validation. We estimated validation status (pass/fail) for the 3 non-responders for each arm separately and found that 2 could be expected to pass validation (1 in each arm).

End point type	Secondary

End point timeframe:

End of pregnancy

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Abstinent	26	40		

Statistical analyses

Statistical analysis title	Validated prolonged abstinence- effect of COVID
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.48

Secondary: Validate 50% smoking reduction at EOP (abstainers included as reducers)

End point title	Validate 50% smoking reduction at EOP (abstainers included as reducers)

End point description:

End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	569	571		
Units: Number of participants				
Reduced	22	22		

Statistical analyses

Statistical analysis title	validated reduction at EOP
Comparison groups	E-cig v Nicotine Patch
Number of subjects included in analysis	1140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.78

Secondary: Low birthweight- singleton birth

End point title	Low birthweight- singleton birth
End point description:	

End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	541	541		
Units: Number of participants				
Low birthweight	80	52		

Statistical analyses

Statistical analysis title	Low birthweight- singleton births
Comparison groups	Nicotine Patch v E-cig
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.91

Secondary: Low birthweight- multiple births

End point title	Low birthweight- multiple births
End point description:	
End point type	Secondary
End point timeframe:	
End of pregnancy	

End point values	Nicotine Patch	E-cig		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	558		
Units: Number of participants				
Low birthweight	86	63		

Statistical analyses

Statistical analysis title	Low birthweight- multiple births
Comparison groups	Nicotine Patch v E-cig

Number of subjects included in analysis	1107
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.99

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from when participants were posted out their products until the end of the study.

Adverse event reporting additional description:

Adverse events were collected for participants and their infants. Although infant deaths occurred, these are not counted in the 'fatalities' count as no participants died during the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Nicotine Patch
Reporting group description: -	
Reporting group title	E-cig
Reporting group description:	
Electronic cigarette	

Serious adverse events	Nicotine Patch	E-cig	
Total subjects affected by serious adverse events			
subjects affected / exposed	222 / 569 (39.02%)	209 / 571 (36.60%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Spinal cord neoplasm			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ceasarean section			
subjects affected / exposed	150 / 569 (26.36%)	138 / 571 (24.17%)	
occurrences causally related to treatment / all	0 / 150	0 / 138	
deaths causally related to treatment / all	0 / 0	0 / 0	

termination of pregnancy		
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hospitalisation for further diagnosis		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystectomy		
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions		
Miscarriage		
subjects affected / exposed	3 / 569 (0.53%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Stillbirth		
subjects affected / exposed	0 / 569 (0.00%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Premature baby		
subjects affected / exposed	35 / 569 (6.15%)	18 / 571 (3.15%)
occurrences causally related to treatment / all	0 / 35	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0
Birthweight low		
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Premature rupture of membranes		
subjects affected / exposed	5 / 569 (0.88%)	5 / 571 (0.88%)
occurrences causally related to treatment / all	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0

Pre-eclampsia		
subjects affected / exposed	3 / 569 (0.53%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Threatened labour		
subjects affected / exposed	3 / 569 (0.53%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage in pregnancy		
subjects affected / exposed	2 / 569 (0.35%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Premature labour		
subjects affected / exposed	2 / 569 (0.35%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Jaundice neonatal		
subjects affected / exposed	2 / 569 (0.35%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Foetal growth restriction		
subjects affected / exposed	2 / 569 (0.35%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypothermia neonatal		
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Foetal hypokinesia		
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Poor weight gain neonatal		

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Shoulder dystocia

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Postpartum haemorrhage

subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Eclampsia

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Gestational diabetes

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Hyperemesis gravidarum

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Premature separation of placenta

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Preterm premature rupture of membranes

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Retained products of conception

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Foetal Cardiac disorder

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

General disorders and administration site conditions

Death neonatal

subjects affected / exposed	3 / 569 (0.53%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

death of child

subjects affected / exposed	3 / 569 (0.53%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Drug withdrawal syndrome neonatal

subjects affected / exposed	1 / 569 (0.18%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0

Dehydration

subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Reproductive system and breast disorders

Vaginal haemorrhage

subjects affected / exposed	4 / 569 (0.70%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Cervix inflammation

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
neonatal respiratory disorders			
subjects affected / exposed	7 / 569 (1.23%)	9 / 571 (1.58%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium aspiration syndrome			
subjects affected / exposed	1 / 569 (0.18%)	3 / 571 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infantile apnoea			
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Childhood asthma			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal pneumothorax			
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Injury, poisoning and procedural complications

Skull fracture

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Ureteric injury

subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Congenital, familial and genetic disorders

Congenital abnormality NOS

subjects affected / exposed	1 / 569 (0.18%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0

Ankyloglossia congenital

subjects affected / exposed	0 / 569 (0.00%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Developmental hip dysplasia

subjects affected / exposed	0 / 569 (0.00%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Heart disease congenital

subjects affected / exposed	2 / 569 (0.35%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0

Hypospadias

subjects affected / exposed	1 / 569 (0.18%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Talipes		
subjects affected / exposed	1 / 569 (0.18%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cleft lip		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
cleft palate		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Congenital aortic anomaly		
subjects affected / exposed	0 / 569 (0.00%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Deafness congenital		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fallot's tetralogy		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroschisis		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Inborn error of metabolism		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hernia congenital		

subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Laryngomalacia				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Otospondylomegaepiphyseal dysplasia				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Polydactyly				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Trisomy 13				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Anal atresia				
subjects affected / exposed	2 / 569 (0.35%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Congenital arterial malformation				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Congenital hydronephrosis				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Holoprosencephaly				

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple congenital abnormalities			
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spina bifida			
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal cardiac arrest			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest neonatal			
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	2 / 569 (0.35%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal seizure			

subjects affected / exposed	0 / 569 (0.00%)	2 / 571 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hypoxic-ischaemic encephalopathy				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
hypnagogic myoclonus				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intraventricular haemorrhage neonatal				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Perinatal stroke				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebral haemorrhage				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sciatica				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebral ventricle dilatation				
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Epilepsy				

subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Blood and lymphatic system disorders		
Immune thrombocytopenia		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ear and labyrinth disorders		
Neonatal deafness		
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal disorders		
Abdominal pain		
subjects affected / exposed	1 / 569 (0.18%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Infantile vomiting		
subjects affected / exposed	2 / 569 (0.35%)	2 / 571 (0.35%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal distension		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal pain upper		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Necrotising enterocolitis neonatal		
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Diarrhoea				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastritis				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal wall cyst				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Skin and subcutaneous tissue disorders				
Skin discolouration				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal and urinary disorders				
Genitourinary tract infection				
subjects affected / exposed	4 / 569 (0.70%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nephrolithiasis				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal pain				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal cyst				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Musculoskeletal and connective tissue disorders				
Hypertonia neonatal				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infections and infestations				
Sepsis neonatal				
subjects affected / exposed	0 / 569 (0.00%)	4 / 571 (0.70%)		
occurrences causally related to treatment / all	0 / 0	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Tonsillitis				
subjects affected / exposed	1 / 569 (0.18%)	2 / 571 (0.35%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Viral infection				
subjects affected / exposed	0 / 569 (0.00%)	2 / 571 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Beta haemolytic streptococcal infection				
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Neonatal infection				
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchiolitis				
subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchitis				

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puerperal pyrexia			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 569 (0.18%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 569 (0.00%)	1 / 571 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Endometritis decidual

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Lower respiratory tract infection

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pyelonephritis acute

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Tooth infection

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Upper respiratory tract infection

subjects affected / exposed	1 / 569 (0.18%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Metabolism and nutrition disorders

Hypoglycaemia neonatal

subjects affected / exposed	0 / 569 (0.00%)	3 / 571 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0

Poor feeding infant

subjects affected / exposed	2 / 569 (0.35%)	0 / 571 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nicotine Patch	E-cig	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 569 (18.45%)	81 / 571 (14.19%)	
General disorders and administration site conditions			
Application site irritation			
subjects affected / exposed	50 / 569 (8.79%)	2 / 571 (0.35%)	
occurrences (all)	51	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	47 / 569 (8.26%)	29 / 571 (5.08%)	
occurrences (all)	48	30	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 569 (1.41%)	50 / 571 (8.76%)	
occurrences (all)	8	51	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2018	Update to paper CRF storage; update to Sponsor representative; addition of questions to CRF.
04 July 2019	Replacement of ineligible participants; update to SAE procedure; addition of new outcomes; addition of CO measurement to verify abstinence.
30 January 2020	Add Professor Christopher Griffiths as new CI; update to saliva sample payments.
12 May 2020	Update to protocol to reflect statistical analysis plan. Inclusion of data analysis at completion of end of pregnancy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Validation of smoking status via postal saliva sampling proved problematic. Almost half of participants did not provide usable samples, which led to low primary outcome abstinence rates and reduced the study power.

Notes: