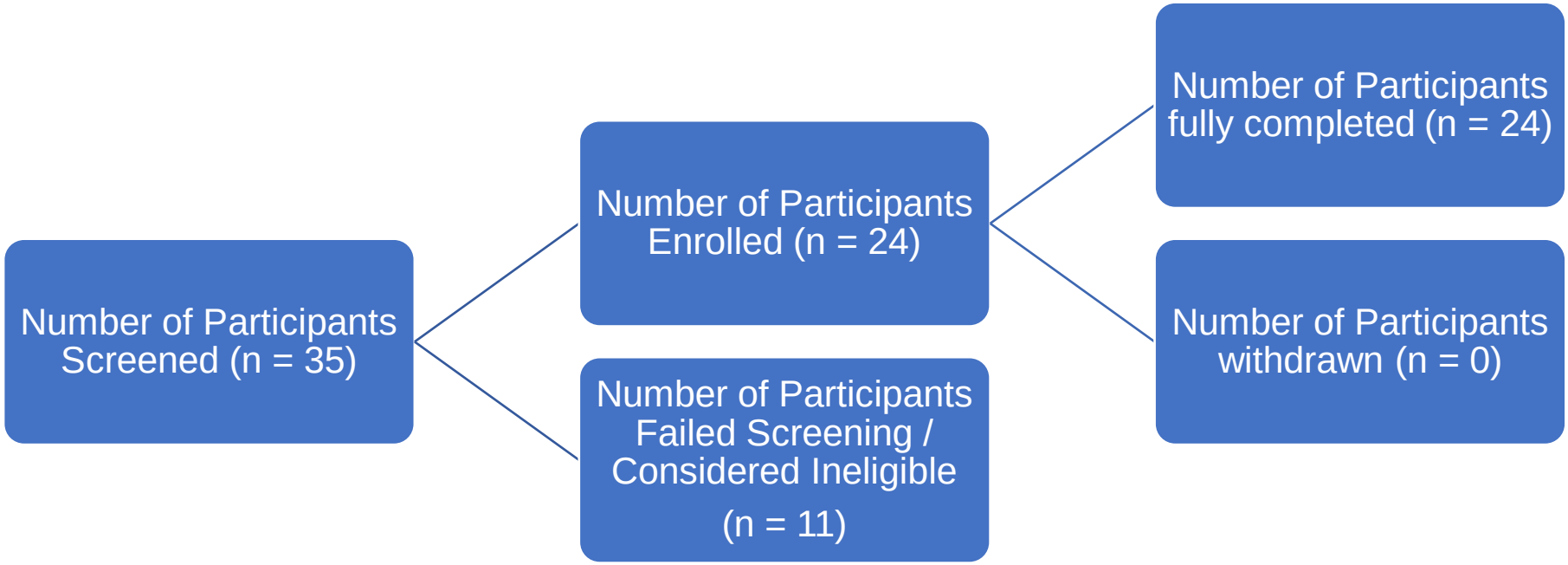
Participant Flow



Baseline Characteristics

Summary of Participant Demographics (Safety Set)

Parameter	Statistic	All Subjects (N=24)
Age (yrs)	N	24
	Mean	37.3
	SD	8.32
Height (m)	N	24
	Mean	1.785
	SD	0.0806
Weight (kg)	N	24
	Mean	82.76
	SD	11.772
BMI (kg/m^2)	N	24
	Mean	25.98
	SD	3.264
Race:		
American Indian or Alaska Native	n (%)	0
Asian	n (%)	0
Black or African American	n (%)	0
Native Hawaiian or Other Pacific Islander	n (%)	0
Other	n (%)	1 (4.2)
White	n (%)	23 (95.8)
Gender:		
Male	n (%)	24 (100.0)

Outcome Measures

Table 1: Summary of Unadjusted Derived Nicotine PK Parameters (PP PK Set)

Parameter	Statistic	ENHALE Electronic Inhaler (N=24)		Nicorette Inhalator (N=24)		Nicorette QuickMist (N=23)	
		1st Admin.	5th Admin.	1st Admin.	5th Admin.	1st Admin.	5th Admin.
C_{max} (ng/mL)	n	24	24	24	24	23	23
	Geo.Mean	4.01	7.53	1.51	2.81	4.26	8.88
	CV%	59.4	45.8	55.1	57.2	32.9	23.2
T_{max} (min)	n	24	24	24	24	23	23
	Median	2.00	3.00	12.0	10.0	15.0	12.0
	Min-Max	2.0-30.0	2.0-10.0	5.9-51.8	6.0-20.0	6.0-30.0	8.0 – 30.3
$pAUC_{0-50}$ (min*ng/mL)	n	21	24	23	23	23	23
	Geo.Mean	113	242	51.2	127	147	370
	CV%	49.8	33.4	68.0	54.2	22.8	21.6
$t_{1/2}$ (min)	n		22		21		23
	Geo.Mean	N/A	172	N/A	157	N/A	188
	CV%		57.1		38.5		50.0
$pAUC_{0-60}$ (min*ng/mL)	n		24		23		23
	Geo.Mean	N/A	278	N/A	149	N/A	436
	CV%		33.6		54.2		21.8
AUC_{0-t} (min*ng/mL)	n		24		24		23
	Geo.Mean	N/A	862	N/A	336	N/A	1600
	CV%		68.4		75.2		45.9

Table 2: Summary of Statistical Analysis of Bioavailability of Derived Unadjusted Plasma Nicotine Cmax and AUC PK Data – ENHALE Electronic Inhaler vs Nicorette Inhalator (PP PK Set)

	Parameter	Test	Reference	No. in Comparison	Geometric LSMeans (95% CI)		Geometric LSMean Ratio (%) (90% CI) [Within-Subject CV%]
					Test	Reference	Test / Reference
1st Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	4.04 (3.26 - 5.00)	1.50 (1.21 - 1.86)	268.67 (208.52 - 346.18) [53.3]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	20[1]	111. (87.4 - 140)	52.6 (41.5 - 66.7)	210.13 (159.82 - 276.26) [51.5]
5th Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	7.56 (6.48 - 8.82)	2.80 (2.40 - 3.27)	269.63 (224.64 - 323.62) [37.2]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	23[2]	246 (220 - 275)	126 (112 - 141)	195.40 (171.14 - 223.10) [26.0]
	$pAUC_{0-60}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	23[2]	283 (253 - 316)	148 (132 - 165)	191.63 (168.07 - 218.51) [25.8]
	AUC_{0-t} (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	858 (573 - 1280)	338 (226 - 506)	253.75 (157.63 - 408.47) [118.9]

1. 1st administration: n=20 as $pAUC_{0-50}$ was non-calculable for Subjects 001, 005 and 007 for the ENHALE and Subject 008 Nicorette Inhalator, was excluded from analysis due to sample time deviation > 5 mins at 50 mins.

2. 5th administration: n=23 as $pAUC_{0-50}$ and $pAUC_{0-60}$ was non-calculable for Subject 021, Nicorette Inhalator.

Results obtained using an ANCOVA with fixed effects for treatment, period, sequence and subject nested within sequence with baseline (pre-1st hourly administration) nicotine concentration as a covariate.

Table 3: Summary of Statistical Analysis of Plasma Nicotine Tmax PK Data - ENHALE Electronic Inhaler vs Nicorette Inhalator (PP PK Set)

	Parameter	Test	Reference	No.in Comparison	Median (Min, Max)		Median Difference (95% C.I.[a]) (p-value[b])
					Test	Reference	Test vs Reference
1st Admin.	T_{max} (min)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	2.00 (2.00 - 30.00)	12.00 (5.90 - 51.82)	-7.50 (-10.0 - -5.00) (p<0.0001)
5th Admin.	T_{max} (min)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	3.00 (2.00 - 10.00)	10.00 (6.00 - 20.00)	-7.00 (-8.00 - -6.00) (p<0.0001)

Table 4: Summary of Statistical Analysis of Bioavailability of Derived Unadjusted Plasma Nicotine Cmax and AUC PK Data – ENHALE Electronic Inhaler vs Nicorette QuickMist (PP PK Set)

	Parameter	Test	Reference	No. in Comparison	Geometric LSMeans (95% CI)		Geometric LSMean Ratio (%) (90% CI) [Within-Subject CV%]
					Test	Reference	Test / Reference
1st Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23	3.85 (3.11 - 4.77)	4.26 (3.44 - 5.29)	90.25 (70.18 - 116.06) [51.7]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	20[1]	110 (99.3 - 122)	152 (137 - 168)	72.52 (64.48 - 81.55) [21.2]
5th Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23[2]	7.63 (6.68 - 8.73)	8.94 (7.82 - 10.2)	85.39 (72.97 - 99.92) [31.1]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23[2]	241 (216 - 268)	371 (333 - 413)	64.99 (57.29 - 73.73) [24.8]
	$pAUC_{0-60}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23[2]	277 (249 - 308)	437 (393 - 486)	63.44 (56.03 - 71.84) [24.4]
	AUC_{0-t} (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23[2]	861 (754 - 983)	1590 (1390 - 1820)	54.16 (46.36 - 63.29) [30.8]

1. 1st administration: n=20 as $pAUC_{0-50}$ was non-calculable for Subjects 001, 005 and 007 for the ENHALE and Subject 024 was excluded from the PP PK Set.

2. 5th administration: n=23 due to Subject 024 being excluded from the PP PK set.

Results obtained using an ANCOVA with fixed effects for treatment, period, sequence and subject nested within sequence with baseline (pre-1st hourly administration) nicotine concentration as a covariate. Subject 024 Nicorette QuickMist data is excluded from the PP PK Set.

Table 5: Summary of Statistical Analysis of Plasma Nicotine Tmax PK Data - ENHALE Electronic Inhaler vs Nicorette QuickMist (PP PK Set)

	Parameter	Test	Reference	No.in Comparison	Median (Min, Max)		Median Difference (95% C.I.[a]) (p-value[b])
					Test	Reference	Test vs Reference
1st Admin.	T_{max} (min)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23	2.00 (2.00 - 30.00)	15.00 (6.00 - 30.00)	-9.50 (-13.0 - -6.00) (p<0.0001)
5th Admin	T_{max} (min)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23	2.00 (2.00 - 10.00)	12.00 (8.00 - 30.30)	-9.00 (-11.0 - -7.00) (p<0.0001)

Table 6: Summary of Baseline-Adjusted Derived Nicotine PK Parameters (PP PK Set)

Parameter	Statistic	ENHALE Electronic Inhaler (N=24)		Nicorette Inhalator (N=24)		Nicorette QuickMist (N=23)	
		1st Admin.	5th Admin.	1st Admin.	5th Admin.	1st Admin.	5th Admin.
C_{max} (ng/mL)	n	24	24	24	24	23	23
	Geo.Mean	3.21	3.75	1.04	0.785	4.00	2.40
	CV%	65.4	71.5	43.6	76.9	34.5	54.3
T_{max} (min)	n	24	24	24	24	23	23
	Median	2.0	3.00	12.0	10.0	15.0	12.0
	Min-Max	2.0-30.0	2.0-10.0	5.9-51.8	6.0-20.0	6.0-30.0	8.0-30.3
$pAUC_{0-50}$ (min*ng/mL)	n	22	23	23	13	23	20
	Geo.Mean	92.8	67.8	32.6	32.4	133	58.8
	CV%	46.8	53.9	48.0	65.2	26.0	49.5
$t_{1/2}$ (min)	n		21		10		12
	Geo.Mean	N/A	13.0	N/A	20.2	N/A	14.6
	CV%		87.5		44.7		61.9
$pAUC_{0-60}$ (min*ng/mL)	n		23		13		20
	Geo.Mean	N/A	70.2	N/A	35.4	N/A	64.1
	CV%		55.3		64.6		47.8
AUC_{0-t} (min*ng/mL)	n		24		24		23
	Geo.Mean	N/A	67.0	N/A	13.5	N/A	51.1
	CV%		61.7		102		59.5

LLOQ = 0.495 ng/mL. For the purposes of PK parameter calculation, BLQ values were set to zero.Baseline-adjustment performed by subtracting the pre dose concentration value for a particular administration from the associated post-dose timepoints. Any negative values occurring as a result of baseline-adjustment were set to 0 prior to PK parameter derivation. The low "n" is the result of not being able to derive many of the parameters using baseline adjusted data either due to exclusions or where baseline adjustment resulted in a more limited profile which then did not support the derivation of parameters reliant on linear regression. Subject 024 Nicorette QuickMist data is excluded from the Per Protocol PK Set.

Table 7: Summary of Statistical Analysis of Bioavailability of Derived Baseline-Adjusted Plasma Nicotine Cmax and AUC PK Data - ENHALE Electronic Inhaler vs Nicorette Inhalator (PP PK Set)

	Parameter	Test	Reference	No. in Comparison	Geometric LSMeans (95% CI)		Geometric LSMean Ratio (%) (90% CI) [Within-Subject CV%]
					Test	Reference	Test / Reference
1st Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	3.18 (2.17 - 4.68)	1.05 (0.717 - 1.55)	302.16 (191.95 - 475.66) [110.7]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	21[1]	87.4 (59.3 - 129)	33.5 (22.8 - 49.4)	260.58 (165.37 - 410.59) [99.4]
5th Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	3.750 (2.92 - 4.83)	0.784 (0.609 - 1.01)	478.91 (355.58 - 645.01) [64.1]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	13[2]	80.7 (55.7 - 117)	35.4 (24.4 - 51.2)	228.03 (150.71 - 345.01) [57.0]
	$pAUC_{0-60}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	13[2]	83.4 (56.9 - 122)	38.8 (26.5 - 56.8)	215.06 (140.22 - 329.83) [59.2]
	AUC_{0-t} (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	24	65.9 (44.6 - 97.4)	13.7 (9.27 - 20.2)	481.62 (303.97 - 763.10) [113.0]

1. 1st administration: n=21 as $pAUC_{0-50}$ was non-calculable for Subjects 001 and 007 for the ENHALE and Subject 008 Nicorette Inhalator, was excluded from analysis due to sample time deviation > 5 mins at 50 mins.
2. 5th administration: n=13 as $pAUC_{0-50}$ and $pAUC_{0-60}$ were non-calculable for Subjects 001, 005, 011, 012, 014, 015, 017, 020, 021, 023. Subject 024 was excluded.

Results obtained using an ANCOVA with fixed effects for treatment, period, sequence and subject nested within sequence with baseline (pre-1st hourly administration) nicotine concentration as a covariate. Subject 024 Nicorette QuickMist data is excluded from the PP PK Set.

Table 8: Summary of Statistical Analysis of Bioavailability of Derived Baseline-Adjusted Plasma Nicotine Cmax and AUC PK Data - ENHALE Electronic Inhaler vs Nicorette QuickMist (PP PK Set)

	Parameter	Test	Reference	No. in Comparison	Geometric LSMeans (95% CI)		Geometric LSMean Ratio (%) (90% CI) [Within-Subject CV%]
					Test	Reference	Test / Reference
1st Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23	3.11 (2.23 - 4.33)	3.96 (2.84 - 5.52)	78.50 (53.23 - 115.78) [87.2]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	21[1]	90.3 (78.1 - 104)	136 (117 - 157)	66.59 (56.34 - 78.71) [31.5]
5th Admin.	C_{max} (ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23	3.87 (3.16 - 4.73)	2.44 (2.00 - 2.99)	158.31 (124.99 - 200.51) [48.2]
	$pAUC_{0-50}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	20[2]	68.6 (54.8 - 85.9)	57.5 (45.9 - 71.9)	119.45 (92.25 - 154.67) [48.7]
	$pAUC_{0-60}$ (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	20[2]	71.4 (56.8 - 89.7)	62.7 (49.9 - 78.7)	113.92 (87.48 - 148.34) [49.9]
	AUC_{0-t} (min*ng/mL)	ENHALE Electronic Inhaler (N=24)	Nicorette QuickMist (N=23)	23	69.3 (54.2 - 88.7)	50.6 (39.5 - 64.8)	137.06 (102.61 - 183.09) [60.7]

1. 1st administration: n=21 as $pAUC_{0-50}$ was non-calculable for Subjects 001 and 007 for the ENHALE and Subject 024 was excluded.
2. 5th administration: n=20 as $pAUC_{0-50}$ and $pAUC_{0-60}$ were non-calculable for Subjects 009, 016 and 017 for the QuickMist and Subject 024 was excluded.

Results obtained using an ANCOVA with fixed effects for treatment, period, sequence and subject nested within sequence with baseline (pre-1st hourly administration) nicotine concentration as a covariate. Subject 024 Nicorette QuickMist data is excluded from the PP PK Set.

Table 9: Summary of VAS of Nicotine Craving Change from Pre-Dose of each Administration (PP PD Set)

Treatment	Visit/Timepoint	n	Mean	SD	Min	Median	Max
ENHALE Electronic Inhaler (N=24)	Dose 1: 10 Min	24	-26.6	27.17	-100	-19.9	-1
	Dose 2: 10 Min	24	-18.6	18.21	-55	-18.4	25
	Dose 3: 10 Min	24	-17.0	17.69	-67	-12.5	3
	Dose 4: 10 Min	24	-19.5	19.17	-78	-14.3	-1
	Dose 5: 10 Min	24	-15.7	13.14	-44	-14.0	5
	Dose 5: 30 Min	24	-12.2	9.50	-36	-9.5	1
Nicorette Inhalator (N=24)	Dose 1: 10 Min	24	-17.9	22.71	-75	-12.5	16
	Dose 2: 10 Min	24	-15.4	19.88	-81	-10.5	8
	Dose 3: 10 Min	24	-16.8	16.50	-56	-12.8	2
	Dose 4: 10 Min	24	-11.6	17.22	-54	-9.5	23
	Dose 5: 10 Min	24	-8.7	16.02	-54	-6.1	21
	Dose 5: 30 Min	24	-4.4	12.06	-41	-4.5	28
Nicorette QuickMist (N=23)	Dose 1: 10 Min	23	-24.7	18.46	-58	-26.0	5
	Dose 2: 10 Min	23	-17.6	16.62	-62	-18.8	16
	Dose 3: 10 Min	23	-14.5	16.73	-69	-11.0	3
	Dose 4: 10 Min	23	-12.5	17.14	-70	-9.0	6
	Dose 5: 10 Min	23	-15.6	15.97	-54	-9.0	1
	Dose 5: 30 Min	23	-10.5	14.26	-51	-6.0	8

Change calculated by subtracting the pre-dose concentration value for a particular administration from the associated post-dose timepoints.

VAS scores range from 0 (no craving) to 100 (strong craving).

Adverse Events

A total of 9 TEAEs were reported by 7 (29.2%) subjects during the study. All subjects reported mild events, the majority of which were of no reasonable possibility of relationship to study product. Events considered to be of reasonable possibility of relationship to study product included dyspepsia, nausea and headache.

One (1) subject reported reasonable possibly related dyspepsia (mild) following Nicorette QuickMist. The event occurred 2 h 34 min post-dose, lasted 9 h 01 min, no action was taken, and the subject completely recovered.

One (1) subject reported reasonable possibly related nausea (mild) following Nicorette QuickMist. The events occurred 7 min and 4 h 06 min post-dose, lasted between 7-10 min, no action was taken, and the subject completely recovered.

One (1) subject reported reasonable possibly related headache (mild) following ENHALE Electronic Inhaler. The event occurred 1 h 08 min post-dose, lasted 16 min, no action was taken, and the subject completely recovered with sequelae.

There were no severe or SAEs reported and the most commonly occurring TEAE was headache (12.5%), followed by nausea (8.3%). There were no observed trends in TEAE profiles and all TEAEs resolved.

Table 10: Overall Summary of TEAEs by Severity and Relationship (Safety Set)

	ENHALE Electronic Inhaler (N=24)	Nicorette Inhalator (N=24)	Nicorette QuickMist (N=24)	Overall (N=24)
Number of TEAEs	4	1	4	9
Number (%) of subjects reporting at least one:				
TEAE	3 (12.5%)	1 (4.2%)	3 (12.5%)	7 (29.2%)
Serious TEAE	0	0	0	0
TEAE Leading to Withdrawal of IMP	0	0	0	0
TEAE Leading to Death	0	0	0	0
Number (%) of subjects with TEAE by severity:				
Mild	3 (12.5%)	1 (4.2%)	3 (12.5%)	7 (29.2%)
Moderate	0	0	0	0
Severe	0	0	0	0
Number (%) of subjects with TEAE by relationship to IMP:				
Reasonable Possibility	1 (4.2%)	0	2 (8.3%)	3 (12.5%)
No Reasonable Possibility	2 (8.3%)	1 (4.2%)	1 (4.2%)	4 (16.7%)

A subject with multiple AEs is counted only once at the maximum level of severity or the highest association to study drug.
Percentages are calculated from the number of subjects in the Safety Set within a treatment.

Table 11: TEAEs in each Treatment Group by SOC and Preferred Term (Safety Set)

SYSTEM ORGAN CLASS Preferred Term	Number of Events / Subjects (%)			
	ENHALE Electronic Inhaler (N=24)	**Nicorette Inhalator (N=24)**	**Nicorette QuickMist (N=24)**	**Overall (N=24)**
GASTROINTESTINAL DISORDERS:	1 / 1 (4.2%)	0	3 / 2 (8.3%)	4 / 3 (12.5%)
Nausea	1 / 1 (4.2%)	0	2 / 1 (4.2%)	3 / 2 (8.3%)
Dyspepsia	0	0	1 / 1 (4.2%)	1 / 1 (4.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:	0	1 / 1 (4.2%)	0	1 / 1 (4.2%)
Influenza like illness	0	1 / 1 (4.2%)	0	1 / 1 (4.2%)
INFECTIONS AND INFESTATIONS:	1 / 1 (4.2%)	0	0	1 / 1 (4.2%)
Upper respiratory tract infection	1 / 1 (4.2%)	0	0	1 / 1 (4.2%)
NERVOUS SYSTEM DISORDERS:	2 / 2 (8.3%)	0	1 / 1 (4.2%)	3 / 3 (12.5%)
Headache	2 / 2 (8.3%)	0	1 / 1 (4.2%)	3 / 3 (12.5%)

A subject is counted only once per system organ class and preferred term.
Percentages are calculated from the number of subjects in the Safety Set within a treatment.
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