VOLUME 9

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27	Vector Tobacco, Inc. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of Quest alone and in combination with nicotine replacement therapy as a smoking cessation aid, protocol number Vector-201, IND Number 69,185. Clinical Study Report dated October 13, 2006 continued	9	1
28	Hatsukami DK, Kotlyar M, Hertsgaar LA, *et al*. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction* 2010; 105:343-355	9	346

APPENDIX A - SUPPLEMENTAL TABLES

Table S1.1 Summary of Subject Demographics
(Site = 01)

	Group 1 (N = 26)	Group 2 (N = 28)	Group 3 (N = 26)	Total (N = 80)	p-value*
Gender - n (%)					0.8484
Female	10 (38.5%)	13 (46.4%)	12 (46.2%)	35 (43.8%)	
Male	16 (61.5%)	15 (53.6%)	14 (53.8%)	45 (56.3%)	
Race - n (%)					0.6500
Black, not of Hispanic Origin	1 (3.8%)	0	0	1 (1.3%)	
Caucasian, not of Hispanic Origin	25 (96.2%)	28 (100.0%)	26 (100.0%)	79 (98.8%)	
Age at Randomization					0.1689
Number of available subjects	26	28	26	80	
Mean (SD)	39.0 (11.8)	43.4 (9.5)	44.6 (12.0)	42.4 (11.2)	
Median	35.9	42.9	46.1	42.5	
Minimum, maximum	21, 64	25, 65	24, 66	21, 66	
Weight (lbs)					0.4035
Number of available subjects	26	28	26	80	
Mean (SD)	185.6 (51.9)	196.7 (50.3)	179.8 (35.5)	187.6 (46.6)	
Median	186.0	189.8	185.6	187.5	
Minimum, maximum	106, 312	123, 298	120, 254	106, 312	

Table S1.2 Summary of Subject Demographics
(Site = 02)

	Group 1 (N = 16)	Group 2 (N = 19)	Group 3 (N = 17)	Total (N = 52)	p-value[a]
Gender – n (%)					0.6092
Female	9 (56.3%)	11 (57.9%)	7 (41.2%)	27 (51.9%)	
Male	7 (43.8%)	8 (42.1%)	10 (58.8%)	25 (48.1%)	
Race – n (%)					0.2317
Asian or Pacific Islander	0	1 (5.3%)	0	1 (1.9%)	
Black, not of Hispanic Origin	1 (6.3%)	2 (10.5%)	0	3 (5.8%)	
Caucasian, not of Hispanic Origin	13 (81.3%)	13 (68.4%)	10 (58.8%)	36 (69.2%)	
Hispanic	2 (12.5%)	3 (15.8%)	7 (41.2%)	12 (23.1%)	
Age at Randomization					0.7229
Number of available subjects	16	19	17	52	
Mean (SD)	49.0 (11.1)	51.1 (9.3)	48.4 (11.5)	49.6 (10.5)	
Median	51.7	52.1	51.7	51.9	
Minimum, maximum	28, 63	35, 63	24, 64	24, 64	
Weight (lbs)					0.3032
Number of available subjects	16	19	17	52	
Mean (SD)	160.3 (37.9)	178.3 (54.5)	185.3 (46.2)	175.0 (47.4)	
Median	157.5	180.0	190.0	180.0	
Minimum, maximum	100, 220	105, 284	102, 268	100, 284	

Table S1.2 Summary of Subject Demographics
(Site = 02)

	Group 1 (N = 16)	Group 2 (N = 19)	Group 3 (N = 17)	Total (N = 52)	p-value*
Height (in)					0.7821
Number of available subjects	16	19	17	52	
Mean (SD)	66.1 (4.6)	66.9 (4.8)	67.1 (4.4)	66.7 (4.6)	
Median	65.5	65.0	68.0	66.5	
Minimum, maximum	59, 74	59, 76	58, 72	58, 76	

N = number of randomized subjects
% was based on the number of available subjects.
* Fisher's Exact Test for categorical variables and F-test for continuous variables.

Table S1.3 Summary of Subject Demographics
(Site = 03)

	Group 1 (N = 25)	Group 2 (N = 20)	Group 3 (N = 23)	Total (N = 68)	p-value[a]
Gender – n (%)					0.4438
Female	9 (36.0%)	11 (55.0%)	11 (47.8%)	31 (45.6%)	
Male	16 (64.0%)	9 (45.0%)	12 (52.2%)	37 (54.4%)	
Race – n (%)					0.8241
Black, not of Hispanic Origin	1 (4.0%)	1 (5.0%)	0	2 (2.9%)	
Caucasian, not of Hispanic Origin	23 (92.0%)	19 (95.0%)	23 (100.0%)	65 (95.6%)	
Other, specify	1 (4.0%)	0	0	1 (1.5%)	
Age at Randomization					0.3008
Number of available subjects	25	20	23	68	
Mean (SD)	46.2 (9.7)	41.4 (12.6)	42.7 (10.1)	43.6 (10.8)	
Median	46.1	42.1	42.2	43.1	
Minimum, maximum	27, 63	23, 65	27, 64	23, 65	
Weight (lbs)					0.5176
Number of available subjects	25	20	23	68	
Mean (SD)	182.4 (38.6)	190.6 (44.0)	176.2 (40.5)	182.7 (40.7)	
Median	181.8	188.2	178.3	183.9	
Minimum, maximum	122, 268	119, 273	118, 277	118, 277	
Height (in)					0.5050

Table S1.3 Summary of Subject Demographics
(Site = 03)

	Group 1 (N = 25)	Group 2 (N = 20)	Group 3 (N = 23)	Total (N = 68)	*p-value**
Number of available subjects	25	20	23	68	
Mean (SD)	68.5 (4.1)	67.1 (4.2)	67.7 (3.7)	67.8 (4.0)	
Median	70.0	68.3	66.5	68.0	
Minimum, maximum	62, 76	60, 75	63, 74	60, 76	

N = number of randomized subjects
% was based on the number of available subjects.
* Fisher's Exact Test for categorical variables and F-test for continuous variables.

Table S1.4 Summary of Subject Demographics
(Site = 04)

	Group 1 (N = 19)	Group 2 (N = 22)	Group 3 (N = 20)	Total (N = 61)	p-value[a]
Gender – n (%)					0.0003
Female	3 (15.8%)	17 (77.3%)	8 (40.0%)	28 (45.9%)	
Male	16 (84.2%)	5 (22.7%)	12 (60.0%)	33 (54.1%)	
Race – n (%)					0.5132
Black, not of Hispanic Origin	1 (5.3%)	0	2 (10.0%)	3 (4.9%)	
Caucasian, not of Hispanic Origin	18 (94.7%)	21 (95.5%)	18 (90.0%)	57 (93.4%)	
Native American or Alaska Native	0	1 (4.5%)	0	1 (1.6%)	
Age at Randomization					0.8450
Number of available subjects	19	22	20	61	
Mean (SD)	50.0 (9.0)	48.3 (10.4)	49.7 (10.1)	49.3 (9.8)	
Median	49.1	51.3	49.8	49.6	
Minimum, maximum	36, 66	23, 62	28, 63	23, 66	
Weight (lbs)					0.0074
Number of available subjects	19	22	20	61	
Mean (SD)	202.9 (42.4)	161.7 (45.4)	200.5 (49.4)	187.3 (49.1)	
Median	201.5	149.8	185.0	178.0	
Minimum, maximum	114, 280	111, 302	125, 312	111, 312	
Height (in)					0.0006

Table S1.4 Summary of Subject Demographics
(Site = 04)

	Group 1 (N = 19)	Group 2 (N = 22)	Group 3 (N = 20)	Total (N = 61)	*p-value**
Number of available subjects	18	22	20	60	
Mean (SD)	69.9 (3.6)	65.2 (3.3)	68.3 (4.3)	67.7 (4.2)	
Median	71.0	64.0	67.9	67.0	
Minimum, maximum	60, 75	61, 73	63, 79	60, 79	

N = number of randomized subjects
% was based on the number of available subjects.
* Fisher's Exact Test for categorical variables and F-test for continuous variables.

Table S1.5 Summary of Subject Demographics
(Site = 05)

	Group 1 (N = 30)	Group 2 (N = 27)	Group 3 (N = 28)	Total (N = 85)	p-value[a]
Gender – n (%)					0.2224
Female	10 (33.3%)	15 (55.6%)	14 (50.0%)	39 (45.9%)	
Male	20 (66.7%)	12 (44.4%)	14 (50.0%)	46 (54.1%)	
Race – n (%)					0.4613
Asian or Pacific Islander	0	0	1 (3.6%)	1 (1.2%)	
Black, not of Hispanic Origin	0	1 (3.7%)	1 (3.6%)	2 (2.4%)	
Caucasian, not of Hispanic Origin	30 (100.0%)	26 (96.3%)	26 (92.9%)	82 (96.5%)	
Age at Randomization					0.8715
Number of available subjects	30	27	28	85	
Mean (SD)	45.8 (11.0)	47.0 (9.2)	47.1 (10.7)	46.6 (10.2)	
Median	43.4	44.4	48.8	44.4	
Minimum, maximum	27, 66	31, 62	31, 64	27, 66	
Weight (lbs)					0.2411
Number of available subjects	30	27	28	85	
Mean (SD)	193.8 (38.4)	178.9 (46.2)	175.9 (45.0)	183.2 (43.4)	
Median	189.2	170.2	175.6	183.0	
Minimum, maximum	115, 268	119, 311	87, 291	87, 311	
Height (in)					0.6623

Table S1.5 Summary of Subject Demographics
(Site = 05)

	Group 1 (N = 30)	Group 2 (N = 27)	Group 3 (N = 28)	Total (N = 85)	p-value*
Number of available subjects	30	27	28	85	
Mean (SD)	67.4 (4.0)	67.0 (4.1)	66.4 (4.0)	67.0 (4.0)	
Median	67.5	66.0	66.0	66.5	
Minimum, maximum	59, 75	60, 76	60, 75	59, 76	

N = number of randomized subjects
% was based on the number of available subjects.
* Fisher's Exact Test for categorical variables and F-test for continuous variables.

Table S2 Subgroup Analysis of 4-Week Abstinence Proportions Using Treatment Failure Imputation

				p-value[1]	
Baseline Covariate	Group 1	Group 2	Group 3	Group 1 vs Group 3	Group 2 vs Group 3
Patient Sex					
---Female	15/41 (36.6%)	13/67 (19.4%)	8/52 (15.4%)	0.0175	0.3741
---Male	23/75 (30.7%)	6/49 (12.2%)	17/62 (27.4%)	0.4111	0.9874
---Homogeneity				0.1114	0.0720
Race					
---Caucasian	35/109 (32.1%)	18/107 (16.8%)	24/103 (23.3%)	0.1006	0.9110
---Non-Caucasian	3/7 (42.9%)	1/9 (11.1%)	1/11 (9.1%)	0.1373	0.7105
---Homogeneity				0.2197	0.6777
Age at Randomization					
---≤ 45	20/55 (36.4%)	12/57 (21.1%)	13/52 (25.0%)	0.1439	0.7636
---> 45	18/61 (29.5%)	7/59 (11.9%)	12/62 (19.4%)	0.1354	0.9173
---Homogeneity				0.9771	0.6056
Baseline Weight (lbs)					
---≤ 180	20/55 (36.4%)	7/62 (11.3%)	10/55 (18.2%)	0.0265	0.9064
---> 180	18/61 (29.5%)	12/54 (22.2%)	15/59 (25.4%)	0.3838	0.7316
---Homogeneity				0.2225	0.5822
Brand Type					
---Other	29/96 (30.2%)	17/94 (18.1%)	18/90 (20.0%)	0.0757	0.6980

Table S2 Subgroup Analysis of 4-Week Abstinence Proportions Using Treatment Failure Imputation

				p-value	
Baseline Covariate	Group 1	Group 2	Group 3	Group 1 vs Group 3	Group 2 vs Group 3
---Ultra-light	9/20 (45.0%)	2/22 (9.1%)	7/24 (29.2%)	0.2199	0.9841
---Homogeneity				0.8489	0.1613
First attempt to quit?					
---No	34/104 (32.7%)	17/109 (15.6%)	23/102 (22.5%)	0.0704	0.9284
---Yes	4/12 (33.3%)	2/7 (28.6%)	2/12 (16.7%)	0.3202	0.4750
---Homogeneity				0.6957	0.3261
Number of Previous Attempts					
---≤ 3	21/68 (30.9%)	14/72 (19.4%)	18/77 (23.4%)	0.2033	0.7831
---> 3	17/48 (35.4%)	5/43 (11.6%)	7/37 (18.9%)	0.0749	0.8896
---Homogeneity				0.4587	0.6516
Years of Smoking					
---≤ 25	21/61 (34.4%)	14/57 (24.6%)	15/52 (28.8%)	0.3336	0.7651
---> 25	17/55 (30.9%)	5/59 (8.5%)	10/62 (16.1%)	0.0469	0.9412
---Homogeneity				0.3352	0.4795
Cigarettes per day					
---≤ 20	16/52 (30.8%)	13/65 (20.0%)	17/62 (27.4%)	0.4255	0.8836
---> 20	22/64 (34.4%)	6/51 (11.8%)	8/52 (15.4%)	0.0164	0.7944
---Homogeneity				0.1488	0.8861

Table S2 Subgroup Analysis of 4-Week Abstinence Proportions Using Treatment Failure Imputation

Baseline Covariate	Group 1	Group 2	Group 3	*p-value** Group 1 vs Group 3	*p-value** Group 2 vs Group 3
Corrected CO Measurement					
---≤ 24	19/56 (33.9%)	10/53 (18.9%)	10/54 (18.5%)	0.0523	0.5795
---> 24	19/60 (31.7%)	9/63 (14.3%)	15/60 (25.0%)	0.2719	0.9583
---Homogeneity				0.4230	0.2919
Baseline Saliva Cotinine Level					
---≤ 2000	8/39 (20.5%)	5/60 (8.3%)	8/51 (15.7%)	0.3739	0.9329
---> 2000	30/77 (39.0%)	14/56 (25.0%)	17/63 (27.0%)	0.0942	0.6748
---Homogeneity				0.7411	0.4035
Most Often Smoking Location					
---At Work	11/38 (28.9%)	4/27 (14.8%)	10/35 (28.6%)	0.5887	0.9465
---Home	20/57 (35.1%)	13/72 (18.1%)	10/60 (16.7%)	0.0189	0.5102
---Other	7/21 (33.3%)	2/17 (11.8%)	5/19 (26.3%)	0.4462	0.9387
---Homogeneity				0.3386	0.3727
Reproductive Status					
--- Contraceptive measures	8/15 (53.3%)	6/26 (23.1%)	3/21 (14.3%)	0.0161	0.3525
---Not applicable	23/75 (30.7%)	6/49 (12.2%)	17/62 (27.4%)	0.4111	0.9874

Table S2 Subgroup Analysis of 4-Week Abstinence Proportions Using Treatment Failure Imputation

				p-value	
Baseline Covariate	Group 1	Group 2	Group 3	Group 1 vs Group 3	Group 2 vs Group 3
---Post-menopausal for one year	4/11 (36.4%)	3/19 (15.8%)	3/12 (25.0%)	0.4445	0.8633
---Surgically sterilized specify	3/15 (20.0%)	4/22 (18.2%)	2/19 (10.5%)	0.3836	0.4061
---Homogeneity				0.2448	0.2281
Used Prohibited Drugs					
---No	30/99 (30.3%)	17/106 (16.0%)	22/103 (21.4%)	0.0980	0.8780
---Yes	8/17 (47.1%)	2/10 (20.0%)	3/11 (27.3%)	0.2596	0.8151
---Homogeneity				0.6602	0.9613
Baseline FTND Addiction Level					
---High	17/43 (39.5%)	5/37 (13.5%)	13/42 (31.0%)	0.2742	0.9841
---Low	8/17 (47.1%)	2/21 (9.5%)	7/21 (33.3%)	0.2989	0.9898
---Medium	2/17 (11.8%)	8/21 (38.1%)	1/14 (7.1%)	0.5749	0.0445
---Very High	8/32 (25.0%)	2/32 (6.3%)	2/31 (6.5%)	0.0456	0.7057
---Very Low	3/7 (42.9%)	2/5 (40.0%)	2/6 (33.3%)	0.5874	0.6515
---Homogeneity				0.7907	0.0404

Table S3.1 Summary of Baseline Characteristics
(Site = 01)

	Group 1 (N = 26)	Group 2 (N = 28)	Group 3 (N = 26)	Total (N = 80)
Usual Cigarette Brand – n (%)				
100 Cigarette	0	0	1 (3.8%)	1 (1.3%)
Full Flavor	11 (42.3%)	9 (32.1%)	5 (19.2%)	25 (31.3%)
King Size	1 (3.8%)	0	0	1 (1.3%)
Light	8 (30.8%)	15 (53.6%)	12 (46.2%)	35 (43.8%)
Ultra-Light	6 (23.1%)	4 (14.3%)	8 (30.8%)	18 (22.5%)
First Attempt to Quit – n (%)				
No	19 (73.1%)	22 (78.6%)	20 (76.9%)	61 (76.3%)
Yes	7 (26.9%)	6 (21.4%)	6 (23.1%)	19 (23.8%)
Number of Previous Quit Attempts – n (%)				
0	7 (26.9%)	6 (21.4%)	6 (23.1%)	19 (23.8%)
1	4 (15.4%)	7 (25.0%)	7 (26.9%)	18 (22.5%)
2	6 (23.1%)	4 (14.3%)	4 (15.4%)	14 (17.5%)
3	3 (11.5%)	4 (14.3%)	5 (19.2%)	12 (15.0%)
4	3 (11.5%)	3 (10.7%)	1 (3.8%)	7 (8.8%)
5	1 (3.8%)	1 (3.6%)	2 (7.7%)	4 (5.0%)
6	1 (3.8%)	2 (7.1%)	0	3 (3.8%)
10	0	1 (3.6%)	1 (3.8%)	2 (2.5%)
15	1 (3.8%)	0	0	1 (1.3%)
Number of Previous Quit Attempts				
Number of available subjects	26	28	26	80

Table S3.1 Summary of Baseline Characteristics
(Site = 01)

	Group 1 (N = 26)	Group 2 (N = 28)	Group 3 (N = 26)	Total (N = 80)
Mean (SD)	2.4 (3.1)	2.4 (2.3)	2.1 (2.2)	2.3 (2.5)
Median	2.0	2.0	1.5	2.0
Minimum, maximum	0, 15	0, 10	0, 10	0, 15
Years of Smoking				
Number of available subjects	26	28	26	80
Mean (SD)	21.2 (10.2)	22.8 (12.1)	25.4 (11.9)	23.1 (11.4)
Median	20.0	25.0	25.3	21.6
Minimum, maximum	4, 45	2, 51	6, 46	2, 51
Current Number of Cigarettes per Day				
Number of available subjects	26	28	26	80
Mean (SD)	30.1 (9.8)	28.7 (11.2)	25.2 (8.0)	28.0 (9.9)
Median	30.0	25.0	20.0	30.0
Minimum, maximum	15, 55	18, 60	15, 45	15, 60
Corrected CO Measurement (ppm)				
Number of available subjects	26	28	26	80
Mean (SD)	25.5 (12.1)	22.6 (6.1)	20.9 (6.1)	23.0 (8.6)
Median	19.0	21.5	18.0	19.0
Minimum, maximum	15, 54	15, 36	15, 34	15, 54
Saliva Cotinine Level (ng/mL) – n (%)				
200 – 500	1 (3.8%)	0	0	1 (1.3%)
500 – 2000	2 (7.7%)	4 (14.3%)	5 (19.2%)	11 (13.8%)

Table S3.1 Summary of Baseline Characteristics
(Site = 01)

	Group 1 (N = 26)	Group 2 (N = 26)	Group 3 (N = 26)	Total (N = 80)
> 2000	23 (88.5%)	24 (85.7%)	21 (80.8%)	68 (85.0%)
Most Often Smoking Location – n (%)				
At Work (anywhere)	7 (26.9%)	4 (14.3%)	7 (26.9%)	18 (22.5%)
At Work (in designated area)	1 (3.8%)	1 (3.6%)	1 (3.8%)	3 (3.8%)
Home	12 (46.2%)	19 (67.9%)	13 (50.0%)	44 (55.0%)
Other, specify	6 (23.1%)	4 (14.3%)	5 (19.2%)	15 (18.8%)
Reproductive Status / Birth Control Method – n (%)				
Post-menopausal for one year	2 (7.7%)	4 (14.3%)	3 (11.5%)	9 (11.3%)
Surgically sterilized	2 (7.7%)	5 (17.9%)	3 (11.5%)	10 (12.5%)
Contraceptive measures	6 (23.1%)	4 (14.3%)	6 (23.1%)	16 (20.0%)
Hormonal Contraceptive	1 (3.8%)	1 (3.6%)	2 (7.7%)	4 (5.0%)
Barrier Method with Spermicide	4 (15.4%)	2 (7.1%)	3 (11.5%)	9 (11.3%)
Abstinence	1 (3.8%)	1 (3.6%)	1 (3.8%)	3 (3.8%)
Not applicable	16 (61.5%)	15 (53.6%)	14 (53.8%)	45 (56.3%)

N = number of randomized subjects
% was based on the number of available subjects.

Table S3.2 Summary of Baseline Characteristics
(Site = 02)

	Group 1 (N = 16)	Group 2 (N = 19)	Group 3 (N = 17)	Total (N = 52)
Usual Cigarette Brand – n (%)				
100 Cigarette	1 (6.3%)	2 (10.5%)	3 (17.6%)	6 (11.5%)
Full Flavor	2 (12.5%)	3 (15.8%)	7 (41.2%)	12 (23.1%)
King Size	0	0	1 (5.9%)	1 (1.9%)
Light	12 (75.0%)	11 (57.9%)	5 (29.4%)	28 (53.8%)
Ultra-Light	1 (6.3%)	3 (15.8%)	1 (5.9%)	5 (9.6%)
First Attempt to Quit – n (%)				
No	15 (93.8%)	19 (100.0%)	15 (88.2%)	49 (94.2%)
Yes	1 (6.3%)	0	2 (11.8%)	3 (5.8%)
Number of Previous Quit Attempts – n (%)				
0	1 (6.3%)	0	2 (11.8%)	3 (5.8%)
1	3 (18.8%)	7 (36.8%)	4 (23.5%)	14 (26.9%)
2	2 (12.5%)	1 (5.3%)	4 (23.5%)	7 (13.5%)
3	3 (18.8%)	6 (31.6%)	4 (23.5%)	13 (25.0%)
4	3 (18.8%)	3 (15.8%)	0	6 (11.5%)
5	1 (6.3%)	1 (5.3%)	1 (5.9%)	3 (5.8%)
6	2 (12.5%)	0	0	2 (3.8%)
8	0	0	1 (5.9%)	1 (1.9%)
10	1 (6.3%)	1 (5.3%)	1 (5.9%)	3 (5.8%)
Number of Previous Quit Attempts				
Number of available subjects	16	19	17	52

Table S3.2 Summary of Baseline Characteristics (Site = 02)

	Group 1 (N = 16)	Group 2 (N = 19)	Group 3 (N = 17)	Total (N = 52)
Mean (SD)	3.4 (2.5)	2.8 (2.2)	2.8 (2.7)	3.0 (2.4)
Median	3.0	3.0	2.0	3.0
Minimum, maximum	0, 10	1, 10	0, 10	0, 10
Years of Smoking				
Number of available subjects	16	19	17	52
Mean (SD)	28.7 (12.8)	27.5 (10.9)	31.3 (11.5)	29.1 (11.6)
Median	31.5	27.0	32.0	31.0
Minimum, maximum	4, 46	1, 45	12, 50	1, 50
Current Number of Cigarettes per Day				
Number of available subjects	16	19	17	52
Mean (SD)	25.6 (9.5)	24.4 (7.0)	28.4 (9.4)	26.1 (8.6)
Median	20.0	20.0	30.0	20.0
Minimum, maximum	15, 50	20, 40	18, 50	15, 50
Corrected CO Measurement (ppm)				
Number of available subjects	16	19	17	52
Mean (SD)	24.0 (9.3)	24.8 (6.3)	24.2 (6.5)	24.4 (7.3)
Median	19.5	24.0	22.0	22.0
Minimum, maximum	18, 53	16, 40	16, 40	16, 53
Saliva Cotinine Level (ng/mL) – n (%)				
200 – 500	1 (6.3%)	3 (15.8%)	1 (5.9%)	5 (9.6%)
500 – 2000	7 (43.8%)	11 (57.9%)	5 (29.4%)	23 (44.2%)

Table S3.2 Summary of Baseline Characteristics
(Site = 02)

	Group 1 (N = 16)	Group 2 (N = 19)	Group 3 (N = 17)	Total (N = 52)
> 2000	8 (50.0%)	5 (26.3%)	11 (64.7%)	24 (46.2%)
Most Often Smoking Location – n (%)				
At Work (anywhere)	6 (37.5%)	4 (21.1%)	4 (23.5%)	14 (26.9%)
At Work (in designated area)	0	1 (5.3%)	0	1 (1.9%)
Bar	1 (6.3%)	1 (5.3%)	2 (11.8%)	4 (7.7%)
Home	7 (43.8%)	12 (63.2%)	9 (52.9%)	28 (53.8%)
Other, specify	2 (12.5%)	1 (5.3%)	2 (11.8%)	5 (9.6%)
Reproductive Status / Birth Control Method – n (%)				
Post-menopausal for one year	6 (37.5%)	5 (26.3%)	3 (17.6%)	14 (26.9%)
Surgically sterilized	2 (12.5%)	2 (10.5%)	2 (11.8%)	6 (11.5%)
Contraceptive measures	1 (6.3%)	4 (21.1%)	2 (11.8%)	7 (13.5%)
Hormonal Contraceptive	1 (6.3%)	1 (5.3%)	1 (5.9%)	3 (5.8%)
Barrier Method with Spermicide	0	3 (15.8%)	0	3 (5.8%)
Intra-Uterine Device	0	0	1 (5.9%)	1 (1.9%)
Not applicable	7 (43.8%)	8 (42.1%)	10 (58.8%)	25 (48.1%)

N = number of randomized subjects
% was based on the number of available subjects.

Table S3.3 Summary of Baseline Characteristics (Site = 03)

	Group 1 (N = 25)	Group 2 (N = 20)	Group 3 (N = 23)	Total (N = 68)
Usual Cigarette Brand – n (%)				
100 Cigarette	3 (12.0%)	2 (10.0%)	3 (13.0%)	8 (11.8%)
Full Flavor	6 (24.0%)	1 (5.0%)	3 (13.0%)	10 (14.7%)
Light	10 (40.0%)	11 (55.0%)	12 (52.2%)	33 (48.5%)
Ultra-Light	6 (24.0%)	6 (30.0%)	5 (21.7%)	17 (25.0%)
First Attempt to Quit – n (%)				
No	25 (100.0%)	19 (95.0%)	22 (95.7%)	66 (97.1%)
Yes	0	1 (5.0%)	1 (4.3%)	2 (2.9%)
Number of Previous Quit Attempts – n (%)				
0	0	1 (5.0%)	1 (4.3%)	2 (2.9%)
1	4 (16.0%)	4 (20.0%)	3 (13.0%)	11 (16.2%)
2	4 (16.0%)	4 (20.0%)	5 (21.7%)	13 (19.1%)
3	5 (20.0%)	2 (10.0%)	4 (17.4%)	11 (16.2%)
4	2 (8.0%)	2 (10.0%)	2 (8.7%)	6 (8.8%)
5	4 (16.0%)	3 (15.0%)	2 (8.7%)	9 (13.2%)
6	0	0	2 (8.7%)	2 (2.9%)
7	1 (4.0%)	1 (5.0%)	0	2 (2.9%)
10	2 (8.0%)	1 (5.0%)	2 (8.7%)	5 (7.4%)
12	0	0	1 (4.3%)	1 (1.5%)
20	2 (8.0%)	1 (5.0%)	0	3 (4.4%)
30	1 (4.0%)	0	0	1 (1.5%)
50	0	0	1 (4.3%)	1 (1.5%)

Table S3.3 Summary of Baseline Characteristics
(Site = 03)

	Group 1 (N = 25)	Group 2 (N = 20)	Group 3 (N = 23)	Total (N = 68)
Unknown	0	1 (5.0%)	0	1 (1.5%)
Number of Previous Quit Attempts				
Number of available subjects	25	19	23	67
Mean (SD)	6.1 (7.1)	4.1 (4.6)	6.0 (10.1)	5.5 (7.7)
Median	3.0	3.0	3.0	3.0
Minimum, maximum	1, 30	0, 20	0, 50	0, 50
Years of Smoking				
Number of available subjects	25	20	23	68
Mean (SD)	26.7 (9.3)	25.6 (12.1)	25.2 (11.9)	25.9 (10.9)
Median	25.0	22.5	25.0	25.0
Minimum, maximum	12, 45	8, 53	6, 49	6, 53
Current Number of Cigarettes per Day				
Number of available subjects	25	20	23	68
Mean (SD)	26.0 (10.1)	25.6 (8.6)	26.1 (8.3)	25.9 (9.0)
Median	25.0	22.5	24.0	24.5
Minimum, maximum	15, 60	15, 50	15, 50	15, 60
Corrected CO Measurement (ppm)				
Number of available subjects	25	20	23	68
Mean (SD)	29.3 (15.3)	29.5 (7.6)	30.1 (11.5)	29.6 (12.0)
Median	24.0	28.5	27.0	27.0
Minimum, maximum	16, 72	16, 42	14, 60	14, 72

Table S3.3 Summary of Baseline Characteristics
(Site = 03)

	Group 1 (N = 25)	Group 2 (N = 20)	Group 3 (N = 23)	Total (N = 68)
Saliva Cotinine Level (ng/mL) – n (%)				
100 – 200	0	0	2 (8.7%)	2 (2.9%)
200 – 500	1 (4.0%)	0	1 (4.3%)	2 (2.9%)
500 – 2000	5 (20.0%)	7 (35.0%)	8 (34.8%)	20 (29.4%)
> 2000	19 (76.0%)	13 (65.0%)	12 (52.2%)	44 (64.7%)
Most Often Smoking Location – n (%)				
At Work (anywhere)	5 (20.0%)	4 (20.0%)	9 (39.1%)	18 (26.5%)
At Work (in designated area)	1 (4.0%)	3 (15.0%)	0	4 (5.9%)
Home	14 (56.0%)	8 (40.0%)	12 (52.2%)	34 (50.0%)
Other, specify	3 (12.0%)	4 (20.0%)	2 (8.7%)	9 (13.2%)
Restaurant	2 (8.0%)	0	0	2 (2.9%)
Unknown	0	1 (5.0%)	0	1 (1.5%)
Reproductive Status / Birth Control Method – n (%)				
Post-menopausal for one year	2 (8.0%)	3 (15.0%)	2 (8.7%)	7 (10.3%)
Surgically sterilized	5 (20.0%)	3 (15.0%)	4 (17.4%)	12 (17.6%)
Contraceptive measures	2 (8.0%)	5 (25.0%)	5 (21.7%)	12 (17.6%)
Hormonal Contraceptive	0	0	1 (4.3%)	1 (1.5%)
Barrier Method with Spermicide	2 (8.0%)	4 (20.0%)	4 (17.4%)	10 (14.7%)
Intra-Uterine Device	0	1 (5.0%)	0	1 (1.5%)

Table S3.3 Summary of Baseline Characteristics
(Site = 03)

	Group 1 (N = 25)	Group 2 (N = 20)	Group 3 (N = 23)	Total (N = 68)
Not applicable	16 (64.0%)	9 (45.0%)	12 (52.2%)	37 (54.4%)

N = number of randomized subjects
% was based on the number of available subjects.

Table S3.4 Summary of Baseline Characteristics
(Site = 04)

	Group 1 (N = 19)	Group 2 (N = 22)	Group 3 (N = 20)	Total (N = 61)
Usual Cigarette Brand – n (%)				
100 Cigarette	1 (5.3%)	2 (9.1%)	0	3 (4.9%)
Full Flavor	4 (21.1%)	4 (18.2%)	6 (30.0%)	14 (23.0%)
Light	11 (57.9%)	12 (54.5%)	9 (45.0%)	32 (52.5%)
Ultra-Light	3 (15.8%)	4 (18.2%)	5 (25.0%)	12 (19.7%)
First Attempt to Quit – n (%)				
No	17 (89.5%)	22 (100.0%)	18 (90.0%)	57 (93.4%)
Yes	2 (10.5%)	0	2 (10.0%)	4 (6.6%)
Number of Previous Quit Attempts – n (%)				
0	2 (10.5%)	0	2 (10.0%)	4 (6.6%)
1	2 (10.5%)	3 (13.6%)	4 (20.0%)	9 (14.8%)
2	1 (5.3%)	2 (9.1%)	3 (15.0%)	6 (9.8%)
3	4 (21.1%)	5 (22.7%)	2 (10.0%)	11 (18.0%)
4	4 (21.1%)	8 (36.4%)	1 (5.0%)	13 (21.3%)
5	1 (5.3%)	1 (4.5%)	2 (10.0%)	4 (6.6%)
6	0	1 (4.5%)	2 (10.0%)	3 (4.9%)
10	3 (15.8%)	2 (9.1%)	2 (10.0%)	7 (11.5%)
12	1 (5.3%)	0	0	1 (1.6%)
20	0	0	1 (5.0%)	1 (1.6%)
30	1 (5.3%)	0	0	1 (1.6%)
50	0	0	1 (5.0%)	1 (1.6%)

Table S3.4 Summary of Baseline Characteristics
(Site = 04)

	Group 1 (N = 19)	Group 2 (N = 22)	Group 3 (N = 20)	Total (N = 61)
Number of Previous Quit Attempts				
Number of available subjects	19	22	20	61
Mean (SD)	5.7 (6.9)	3.9 (2.4)	6.6 (11.2)	5.3 (7.6)
Median	4.0	4.0	3.0	4.0
Minimum, maximum	0, 30	1, 10	0, 50	0, 50
Years of Smoking				
Number of available subjects	19	22	20	61
Mean (SD)	31.3 (8.5)	27.6 (11.3)	31.8 (10.9)	30.1 (10.4)
Median	30.0	30.0	30.0	30.0
Minimum, maximum	15, 48	6, 46	5, 50	5, 50
Current Number of Cigarettes per Day				
Number of available subjects	19	22	20	61
Mean (SD)	31.1 (10.5)	25.2 (8.2)	27.0 (9.7)	27.6 (9.6)
Median	30.0	20.0	20.0	25.0
Minimum, maximum	15, 50	15, 50	20, 50	15, 50
Corrected CO Measurement (ppm)				
Number of available subjects	19	22	20	61
Mean (SD)	33.0 (11.1)	27.2 (8.2)	28.2 (9.9)	29.3 (9.9)
Median	31.0	27.5	27.0	28.0
Minimum, maximum	16, 54	16, 49	17, 52	16, 54
Saliva Cotinine Level (ng/mL) – n (%)				

Table S3.4 Summary of Baseline Characteristics (Site = 04)

	Group 1 (N = 19)	Group 2 (N = 22)	Group 3 (N = 20)	Total (N = 61)
100 – 200	0	1 (4.5%)	1 (5.0%)	2 (3.3%)
200 – 500	0	1 (4.5%)	1 (5.0%)	2 (3.3%)
500 – 2000	13 (68.4%)	18 (81.8%)	16 (80.0%)	47 (77.0%)
> 2000	6 (31.6%)	2 (9.1%)	2 (10.0%)	10 (16.4%)
Most Often Smoking Location – n (%)				
At Work (anywhere)	5 (26.3%)	3 (13.6%)	4 (20.0%)	12 (19.7%)
At Work (in designated area)	3 (15.8%)	2 (9.1%)	2 (10.0%)	7 (11.5%)
Home	9 (47.4%)	15 (68.2%)	12 (60.0%)	36 (59.0%)
Other, specify	2 (10.5%)	2 (9.1%)	2 (10.0%)	6 (9.8%)
Reproductive Status / Birth Control Method – n (%)				
Post-menopausal for one year	0	2 (9.1%)	0	2 (3.3%)
Surgically sterilized	1 (5.3%)	8 (36.4%)	7 (35.0%)	16 (26.2%)
Contraceptive measures	2 (10.5%)	7 (31.8%)	1 (5.0%)	10 (16.4%)
Hormonal Contraceptive	0	2 (9.1%)	0	2 (3.3%)
Barrier Method with Spermicide	1 (5.3%)	3 (13.6%)	0	4 (6.6%)
Abstinence	1 (5.3%)	2 (9.1%)	1 (5.0%)	4 (6.6%)
Not applicable	16 (84.2%)	5 (22.7%)	12 (60.0%)	33 (54.1%)

N = number of randomized subjects
% was based on the number of available subjects.

Table S3.5 Summary of Baseline Characteristics
(Site = 05)

	Group 1 (N = 30)	Group 2 (N = 27)	Group 3 (N = 28)	Total (N = 85)
Usual Cigarette Brand – n (%)				
100 Cigarette	2 (6.7%)	1 (3.7%)	1 (3.6%)	4 (4.7%)
Full Flavor	7 (23.3%)	7 (25.9%)	6 (21.4%)	20 (23.5%)
Light	16 (53.3%)	12 (44.4%)	12 (42.9%)	40 (47.1%)
Ultra-Light	5 (16.7%)	7 (25.9%)	9 (32.1%)	21 (24.7%)
First Attempt to Quit – n (%)				
No	28 (93.3%)	27 (100.0%)	27 (96.4%)	82 (96.5%)
Yes	2 (6.7%)	0	1 (3.6%)	3 (3.5%)
Number of Previous Quit Attempts – n (%)				
0	2 (6.7%)	0	1 (3.6%)	3 (3.5%)
1	4 (13.3%)	4 (14.8%)	4 (14.3%)	12 (14.1%)
2	2 (6.7%)	4 (14.8%)	7 (25.0%)	13 (15.3%)
3	9 (30.0%)	8 (29.6%)	5 (17.9%)	22 (25.9%)
4	1 (3.3%)	6 (22.2%)	6 (21.4%)	13 (15.3%)
5	3 (10.0%)	2 (7.4%)	0	5 (5.9%)
6	3 (10.0%)	0	2 (7.1%)	5 (5.9%)
7	1 (3.3%)	0	1 (3.6%)	2 (2.4%)
8	1 (3.3%)	0	1 (3.6%)	2 (2.4%)
10	3 (10.0%)	1 (3.7%)	0	4 (4.7%)
12	1 (3.3%)	1 (3.7%)	0	2 (2.4%)
24	0	0	1 (3.6%)	1 (1.2%)
30	0	1 (3.7%)	0	1 (1.2%)

Table S3.5 Summary of Baseline Characteristics (Site = 05)

	Group 1 (N = 30)	Group 2 (N = 27)	Group 3 (N = 28)	Total (N = 85)
Number of Previous Quit Attempts				
Number of available subjects	30	27	28	85
Mean (SD)	4.3 (3.2)	4.5 (5.7)	3.9 (4.4)	4.2 (4.4)
Median	3.0	3.0	3.0	3.0
Minimum, maximum	0, 12	1, 30	0, 24	0, 30
Years of Smoking				
Number of available subjects	30	27	28	85
Mean (SD)	25.8 (13.3)	29.1 (9.5)	27.3 (10.1)	27.3 (11.1)
Median	20.5	29.0	24.5	25.0
Minimum, maximum	4, 51	12, 50	10, 46	4, 51
Current Number of Cigarettes per Day				
Number of available subjects	30	27	28	85
Mean (SD)	23.3 (6.4)	22.9 (5.9)	24.3 (8.0)	23.5 (6.8)
Median	20.0	20.0	20.0	20.0
Minimum, maximum	15, 40	15, 35	15, 40	15, 40
Corrected CO Measurement (ppm)				
Number of available subjects	30	27	28	85
Mean (SD)	30.8 (14.9)	29.5 (11.5)	32.0 (8.9)	30.8 (12.0)
Median	27.0	28.0	31.0	28.0
Minimum, maximum	16, 82	16, 56	16, 55	16, 82

Table S3.5 Summary of Baseline Characteristics
(Site = 05)

	Group 1 (N = 30)	Group 2 (N = 27)	Group 3 (N = 28)	Total (N = 85)
Saliva Cotinine Level (ng/mL) – n (%)				
30 – 100	0	0	1 (3.6%)	1 (1.2%)
100 – 200	0	0	1 (3.6%)	1 (1.2%)
200 – 500	0	1 (3.7%)	1 (3.6%)	2 (2.4%)
500 – 2000	9 (30.0%)	14 (51.9%)	8 (28.6%)	31 (36.5%)
> 2000	21 (70.0%)	12 (44.4%)	17 (60.7%)	50 (58.8%)
Most Often Smoking Location – n (%)				
At Work (anywhere)	6 (20.0%)	3 (11.1%)	7 (25.0%)	16 (18.8%)
At Work (in designated area)	4 (13.3%)	2 (7.4%)	1 (3.6%)	7 (8.2%)
Bar	0	0	2 (7.1%)	2 (2.4%)
Home	15 (50.0%)	18 (66.7%)	14 (50.0%)	47 (55.3%)
Other, specify	5 (16.7%)	4 (14.8%)	4 (14.3%)	13 (15.3%)
Reproductive Status / Birth Control Method – n (%)				
Post-menopausal for one year	1 (3.3%)	5 (18.5%)	4 (14.3%)	10 (11.8%)
Surgically sterilized	5 (16.7%)	4 (14.8%)	3 (10.7%)	12 (14.1%)
Contraceptive measures	4 (13.3%)	6 (22.2%)	7 (25.0%)	17 (20.0%)
Hormonal Contraceptive	1 (3.3%)	2 (7.4%)	1 (3.6%)	4 (4.7%)
Barrier Method with Spermicide	2 (6.7%)	3 (11.1%)	5 (17.9%)	10 (11.8%)
Abstinence	1 (3.3%)	1 (3.7%)	1 (3.6%)	3 (3.5%)
Not applicable	20 (66.7%)	12 (44.4%)	14 (50.0%)	46 (54.1%)

N = number of randomized subjects
% was based on the number of available subjects.

Table S4 Summary of Study and Regular Cigarettes Smoked (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 2			
Number of regular cigarettes smoked			
Number of available subjects	116	116	114
Mean (SD)	181.9 (70.0)	179.9 (74.0)	183.3 (64.0)
Median	161.5	156.0	164.5
Minimum, maximum	61, 402	59, 415	91, 345
Visit 3			
Number of study cigarettes smoked			
Number of available subjects	112	113	109
Mean (SD)	396.9 (152.7)	407.4 (157.9)	390.5 (154.0)
Median	372.5	378.0	356.0
Minimum, maximum	14, 800	135, 829	14, 800
Number of regular cigarettes smoked			
Number of available subjects	112	114	109
Mean (SD)	19.5 (52.7)	13.3 (34.2)	9.1 (28.1)
Median	1.0	0.0	0.0
Minimum, maximum	0, 410	0, 240	0, 252
Visit 4			
Number of study cigarettes smoked			
Number of available subjects	107	107	107
Mean (SD)	450.3 (169.8)	440.7 (174.5)	424.5 (174.2)
Median	431.0	426.0	379.0
Minimum, maximum	7, 800	7, 811	90, 800

Table S4 Summary of Study and Regular Cigarettes Smoked (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Number of regular cigarettes smoked			
Number of available subjects	108	107	107
Mean (SD)	17.8 (116.9)	6.6 (28.0)	2.7 (11.9)
Median	0.0	0.0	0.0
Minimum, maximum	0, 1120	0, 225	0, 83
Visit 5			
Number of study cigarettes smoked			
Number of available subjects	99	97	103
Mean (SD)	363.2 (207.2)	385.2 (208.0)	408.3 (176.1)
Median	328.0	351.0	385.0
Minimum, maximum	16, 800	0, 811	14, 839

N = number of randomized subjects who received study treatment

Table S5 Summary of Change From Visit 2 in Total Cigarettes Smoked Per Day (Safety Population)

	Group 1 (N = 113)	Group 2 (N = 114)	Group 3 (N = 109)
Visit 3			
Number of total cigarettes smoked per day			
Number of available subjects	112	113	109
Mean (SD)	29.7 (10.4)	29.9 (11.8)	28.3 (10.6)
Median	26.7	27.5	26.2
Minimum, maximum	7, 60	10, 76	6, 60
Change from Visit 2			
Number of available subjects	112	113	109
Mean (SD)	3.8 (6.3)	4.6 (6.7)	2.0 (6.5)
Median	3.0	3.6	0.7
Minimum, maximum	-11, 20	-9, 24	-15, 20
Visit 4			
Number of total cigarettes smoked per day			
Number of available subjects	107	107	107
Mean (SD)	32.9 (11.8)	31.6 (12.1)	30.1 (11.9)
Median	31.7	30.4	26.4
Minimum, maximum	10, 62	10, 69	10, 68
Change from Visit 2			
Number of available subjects	107	107	107
Mean (SD)	7.1 (8.3)	6.5 (8.4)	3.9 (7.6)
Median	6.2	5.4	2.8
Minimum, maximum	-22, 32	-19, 26	-18, 31

Table S5 Summary of Change From Visit 2 in Total Cigarettes Smoked Per Day (Safety Population)

	Group 1 (N = 113)	Group 2 (N = 114)	Group 3 (N = 109)
Visit 5			
Number of total cigarettes smoked per day			
Number of available subjects	99	97	103
Mean (SD)	25.6 (13.8)	27.6 (13.3)	28.4 (12.0)
Median	23.9	25.1	26.6
Minimum, maximum	1, 57	0, 57	5, 66
Change from Visit 2			
Number of available subjects	99	97	103
Mean (SD)	0.3 (11.4)	3.2 (11.5)	2.3 (8.7)
Median	-0.3	2.6	1.2
Minimum, maximum	-29, 35	-25, 32	-27, 31

N = number of randomized subjects who received study treatment
Total cigarettes smoked per day = total number of study and regular cigarettes smoked / number of days in the last visit

Table S6 Reasons for Missing 3-Month Abstinence Status

	Group 1 (N = 30) n (%)	Group 2 (N = 40) n (%)	Group 3 (N = 23) n (%)	Total (N = 93) n (%)
Discontinued on or before Visit 11	28 (93.3%)	39 (97.5%)	22 (95.7%)	89 (95.7%)
Adverse Event	2 (6.7%)	2 (5.0%)	2 (8.7%)	6 (6.5%)
Lost to Follow-Up	9 (30.0%)	14 (35.0%)	11 (47.8%)	34 (36.6%)
Non-Compliance	3 (10.0%)	3 (7.5%)	1 (4.3%)	7 (7.5%)
Other, specify	1 (3.3%)	0	0	1 (1.1%)
Sponsor's Request	0	0	1 (4.3%)	1 (1.1%)
Subject failed to quit smoking	3 (10.0%)	4 (10.0%)	1 (4.3%)	8 (8.6%)
Subject's Request / Withdrawal of consent	10 (33.3%)	16 (40.0%)	6 (26.1%)	32 (34.4%)
Discontinued after Visit 11	2 (6.7%)	1 (2.5%)	1 (4.3%)	4 (4.3%)
Missing CO or smoking status at any visits from 6 to 11	2 (6.7%)	1 (2.5%)	1 (4.3%)	4 (4.3%)

N = number of randomized subjects whose 3-month abstinence status was missing
n = number of subjects
% = n / N x 100%

Table S7 Reasons for Missing 6-Month Abstinence Status

	Group 1 (N = 35) n (%)	Group 2 (N = 41) n (%)	Group 3 (N = 27) n (%)	Total (N = 103) n (%)
Discontinued on or before Visit 12	35 (100.0%)	41 (100.0%)	27 (100.0%)	103 (100.0%)
Adverse Event	3 (8.6%)	2 (4.9%)	2 (7.4%)	7 (6.8%)
Lost to Follow-Up	10 (28.6%)	15 (36.6%)	13 (48.1%)	38 (36.9%)
Non-Compliance	3 (8.6%)	3 (7.3%)	1 (3.7%)	7 (6.8%)
Other, specify	1 (2.9%)	0	0	1 (1.0%)
Sponsor's Request	0	0	1 (3.7%)	1 (1.0%)
Subject failed to quit smoking	7 (20.0%)	5 (12.2%)	3 (11.1%)	15 (14.6%)
Subject's Request / Withdrawal of consent	11 (31.4%)	16 (39.0%)	6 (22.2%)	33 (32.0%)
Completed Study	0	0	1 (3.7%)	1 (1.0%)
Missing CO or smoking status at Visits from 6 to 12	0	0	1 (3.7%)	1 (1.0%)

N = number of randomized subjects whose 6-month abstinence status was missing
n = number of subjects
% = n / N x 100%

Table S8 Three-Month and Six-Month Abstinence Proportions Using Treatment Failure Imputation (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 6 to Visit 11			
Corrected exhaled CO < 10ppm – n (%)	23 (19.8%)	17 (14.7%)	24 (21.1%)
No cigarettes smoked since last visit – n (%)	28 (24.1%)	19 (16.4%)	22 (19.3%)
Three-month abstinence – n (%)	20 (17.2%)	12 (10.3%)	17 (14.9%)
95% CI for 3-month abstinence rate	(10.9%, 25.4%)	(5.5%, 17.4%)	(8.9%, 22.8%)
p-value compared with Group 3*	0.3819	0.8931	
Visit 6 to Visit 12			
Corrected exhaled CO < 10ppm – n (%)	16 (13.8%)	11 (9.5%)	17 (14.9%)
No cigarettes smoked since last visit – n (%)	18 (15.5%)	13 (11.2%)	12 (10.5%)
Six-month abstinence – n (%)	13 (11.2%)	9 (7.8%)	11 (9.6%)
95% CI for 6-month abstinence rate	(6.1%, 18.4%)	(3.6%, 14.2%)	(4.9%, 16.6%)
p-value compared with Group 3*	0.4326	0.7709	

Subjects whose criterion cannot be determined were treated as not meeting the criterion
N = number of randomized subjects
% = n / N x 100%
Exact 95% CI are given
* One-sided Fisher's exact test for 3-month and 6-month abstinence proportions compared with Group 3

Table S9 Three-Month (Visits 6 to 11) Abstinence Proportions Using Treatment Failure Imputation, Stratified by Study Site (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Site 1			
Corrected exhaled CO < 10ppm – n (%)	9 / 26 (34.6%)	6 / 28 (21.4%)	8 / 26 (30.8%)
No cigarettes smoked since last visit – n (%)	9 / 26 (34.6%)	5 / 28 (17.9%)	5 / 26 (19.2%)
Three-month abstinence – n (%)	8 / 26 (30.8%)	5 / 28 (17.9%)	5 / 26 (19.2%)
95% CI for 3-month abstinence rate	(14.3%, 51.8%)	(6.1%, 36.9%)	(6.6%, 39.4%)
Site 2			
Corrected exhaled CO < 10ppm – n (%)	0 / 16 (0.0%)	0 / 19 (0.0%)	0 / 17 (0.0%)
No cigarettes smoked since last visit – n (%)	7 / 16 (43.8%)	6 / 19 (31.6%)	4 / 17 (23.5%)
Three-month abstinence – n (%)	0 / 16 (0.0%)	0 / 19 (0.0%)	0 / 17 (0.0%)
95% CI for 3-month abstinence rate	(0.0%, 20.6%)	(0.0%, 17.6%)	(0.0%, 19.5%)
Site 3			
Corrected exhaled CO < 10ppm – n (%)	7 / 25 (28.0%)	5 / 20 (25.0%)	5 / 23 (21.7%)
No cigarettes smoked since last visit – n (%)	6 / 25 (24.0%)	4 / 20 (20.0%)	3 / 23 (13.0%)
Three-month abstinence – n (%)	6 / 25 (24.0%)	4 / 20 (20.0%)	3 / 23 (13.0%)
95% CI for 3-month abstinence rate	(9.4%, 45.1%)	(5.7%, 43.7%)	(2.8%, 33.6%)
Site 4			

Table S9 Three-Month (Visits 6 to 11) Abstinence Proportions Using Treatment Failure Imputation, Stratified by Study Site (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Corrected exhaled CO < 10ppm – n (%)	0 / 19 (0.0%)	0 / 22 (0.0%)	2 / 20 (10.0%)
No cigarettes smoked since last visit – n (%)	0 / 19 (0.0%)	0 / 22 (0.0%)	1 / 20 (5.0%)
Three-month abstinence – n (%)	0 / 19 (0.0%)	0 / 22 (0.0%)	1 / 20 (5.0%)
95% CI for 3-month abstinence rate	(0.0%, 17.6%)	(0.0%, 15.4%)	(0.1%, 24.9%)
Site 5			
Corrected exhaled CO < 10ppm – n (%)	7 / 30 (23.3%)	6 / 27 (22.2%)	9 / 28 (32.1%)
No cigarettes smoked since last visit – n (%)	6 / 30 (20.0%)	4 / 27 (14.8%)	9 / 28 (32.1%)
Three-month abstinence – n (%)	6 / 30 (20.0%)	3 / 27 (11.1%)	8 / 28 (28.6%)
95% CI for 3-month abstinence rate	(7.7%, 38.6%)	(2.4%, 29.2%)	(13.2%, 48.7%)
Site Main Effect*			0.0242
Treatment-by-site interactions*			0.9123

Subjects whose criterion cannot be determined were treated as not meeting the criterion
N = number of randomized subjects
Exact 95% CI are given
* *p-values* were based on a logistic regression with the covariates treatment group, site, and their interactions.

Table S10 Six-Month (Visits 6 to 12) Abstinence Proportions Using Treatment Failure Imputation, Stratified by Study Site (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Site 1			
Corrected exhaled CO < 10ppm – n (%)	8 / 26 (30.8%)	4 / 28 (14.3%)	7 / 26 (26.9%)
No cigarettes smoked since last visit – n (%)	7 / 26 (26.9%)	3 / 28 (10.7%)	5 / 26 (19.2%)
Six-month abstinence – n (%)	6 / 26 (23.1%)	3 / 28 (10.7%)	5 / 26 (19.2%)
95% CI for 6-month abstinence rate	(9.0%, 43.6%)	(2.3%, 28.2%)	(6.6%, 39.4%)
Site 2			
Corrected exhaled CO < 10ppm – n (%)	0 / 16 (0.0%)	0 / 19 (0.0%)	0 / 17 (0.0%)
No cigarettes smoked since last visit – n (%)	3 / 16 (18.8%)	3 / 19 (15.8%)	0 / 17 (0.0%)
Six-month abstinence – n (%)	0 / 16 (0.0%)	0 / 19 (0.0%)	0 / 17 (0.0%)
95% CI for 6-month abstinence rate	(0.0%, 20.6%)	(0.0%, 17.6%)	(0.0%, 19.5%)
Site 3			
Corrected exhaled CO < 10ppm – n (%)	4 / 25 (16.0%)	3 / 20 (15.0%)	5 / 23 (21.7%)
No cigarettes smoked since last visit – n (%)	4 / 25 (16.0%)	3 / 20 (15.0%)	2 / 23 (8.7%)
Six-month abstinence – n (%)	4 / 25 (16.0%)	3 / 20 (15.0%)	2 / 23 (8.7%)
95% CI for 6-month abstinence rate	(4.5%, 36.1%)	(3.2%, 37.9%)	(1.1%, 28.0%)
Site 4			

Table S10 Six-Month (Visits 6 to 12) Abstinence Proportions Using Treatment Failure Imputation, Stratified by Study Site (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Corrected exhaled CO < 10ppm – n (%)	0 / 19 (0.0%)	0 / 22 (0.0%)	0 / 20 (0.0%)
No cigarettes smoked since last visit – n (%)	0 / 19 (0.0%)	0 / 22 (0.0%)	0 / 20 (0.0%)
Six-month abstinence – n (%)	0 / 19 (0.0%)	0 / 22 (0.0%)	0 / 20 (0.0%)
95% CI for 6-month abstinence rate	(0.0%, 17.6%)	(0.0%, 15.4%)	(0.0%, 16.8%)
Site 5			
Corrected exhaled CO < 10ppm – n (%)	4 / 30 (13.3%)	4 / 27 (14.8%)	5 / 28 (17.9%)
No cigarettes smoked since last visit – n (%)	4 / 30 (13.3%)	4 / 27 (14.8%)	5 / 28 (17.9%)
Six-month abstinence – n (%)	3 / 30 (10.0%)	3 / 27 (11.1%)	4 / 28 (14.3%)
95% CI for 6-month abstinence rate	(2.1%, 26.5%)	(2.4%, 29.2%)	(4.0%, 32.7%)
Site Main Effect*			0.1788
Treatment-by-site interactions*			0.9856

Subjects whose criterion cannot be determined were treated as not meeting the criterion
N = number of randomized subjects
Exact 95% CI are given
* *p-values* were based on a logistic regression with the covariates treatment group, site, and their interactions.

Table S11 Significant Baseline Covariates in Logistic Regression Model for 3-Month Abstinence Rates Using Treatment Failure Imputation (ITT Population)

Effect	*p-value*	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Baseline Saliva Cotinine Level (1 – 2000 vs > 2000 ng/mL)	0.0079	0.389	0.194	0.781
Treatment Group (Group 1 vs Group 3)	0.5375	1.084	0.530	2.218
Treatment Group (Group 2 vs Group 3)		0.705	0.317	1.567

Covariates selected by a backward elimination procedure at a significance level of 0.1. Treatment group was always included in the model.

Table S12 Significant Baseline Covariates in Logistic Regression Model for 6-Month Abstinence Rates Using Treatment Failure Imputation (ITT Population)

Effect	*p-value*	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Baseline Saliva Cotinine Level (1 – 2000 vs > 2000 ng/mL)	0.0660	0.470	0.210	1.051
Treatment Group (Group 1 vs Group 3)	0.8424	1.096	0.466	2.578
Treatment Group (Group 2 vs Group 3)		0.837	0.331	2.118

Covariates selected by a backward elimination procedure at a significance level of 0.1. Treatment group was always included in the model.

Table S13 Three-Month and Six-Month Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 6 to Visit 11			
Corrected exhaled CO < 10ppm – n (%)	23 / 87 (26.4%)	17 / 78 (21.8%)	24 / 88 (27.3%)
No cigarettes smoked since last visit – n (%)	28 / 84 (33.3%)	19 / 80 (23.8%)	22 / 91 (24.2%)
Three-month abstinence – n (%)	20 / 89 (22.5%)	12 / 81 (14.8%)	17 / 92 (18.5%)
95% CI for 3-month abstinence rate	(14.3%, 32.6%)	(7.9%, 24.4%)	(11.1%, 27.9%)
*p-value**	0.3150	0.8013	
Visit 6 to Visit 12			
Corrected exhaled CO < 10ppm – n (%)	16 / 86 (18.6%)	11 / 76 (14.5%)	17 / 86 (19.8%)
No cigarettes smoked since last visit – n (%)	18 / 83 (21.7%)	13 / 79 (16.5%)	12 / 89 (13.5%)
Six-month abstinence – n (%)	13 / 88 (14.8%)	9 / 80 (11.3%)	11 / 90 (12.2%)
95% CI for 6-month abstinence rate	(8.1%, 23.9%)	(5.3%, 20.3%)	(6.3%, 20.8%)
*p-value**	0.3903	0.6666	

Subjects whose criterion cannot be determined were treated as not meeting the criterion
N = number of randomized subjects
Exact 95% CI are given
* One-sided Fisher's exact test for 3-month and 6-month abstinence proportions compared with Group 3

Table S14 Three-Month (Visits 6 to 11) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined), Stratified by Study Site

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Site 1			
Corrected exhaled CO < 10ppm – n (%)	9 / 20 (45.0%)	6 / 23 (26.1%)	8 / 24 (33.3%)
No cigarettes smoked since last visit – n (%)	9 / 20 (45.0%)	5 / 23 (21.7%)	5 / 24 (20.8%)
Three-month abstinence – n (%)	8 / 20 (40.0%)	5 / 23 (21.7%)	5 / 24 (20.8%)
95% CI for 3-month abstinence rate	(19.1%, 63.9%)	(7.5%, 43.7%)	(7.1%, 42.2%)
Site 2			
Corrected exhaled CO < 10ppm – n (%)	0 / 13 (0.0%)	0 / 12 (0.0%)	0 / 14 (0.0%)
No cigarettes smoked since last visit – n (%)	7 / 12 (58.3%)	6 / 12 (50.0%)	4 / 13 (30.8%)
Three-month abstinence – n (%)	0 / 13 (0.0%)	0 / 12 (0.0%)	0 / 14 (0.0%)
95% CI for 3-month abstinence rate	(0.0%, 24.7%)	(0.0%, 26.5%)	(0.0%, 23.2%)
Site 3			
Corrected exhaled CO < 10ppm – n (%)	7 / 15 (46.7%)	5 / 9 (55.6%)	5 / 13 (38.5%)
No cigarettes smoked since last visit – n (%)	6 / 15 (40.0%)	4 / 12 (33.3%)	3 / 16 (18.8%)
Three-month abstinence – n (%)	6 / 16 (37.5%)	4 / 12 (33.3%)	3 / 16 (18.8%)
95% CI for 3-month abstinence rate	(15.2%, 64.6%)	(9.9%, 65.1%)	(4.0%, 45.6%)
Site 4			

Table S14 Three-Month (Visits 6 to 11) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined), Stratified by Study Site

	Group 1 (N = 116)	Group 2 (N = 110)	Group 3 (N = 114)
Corrected exhaled CO < 10ppm – n (%)	0 / 13 (0.0%)	0 / 10 (0.0%)	2 / 15 (13.3%)
No cigarettes smoked since last visit – n (%)	0 / 12 (0.0%)	0 / 10 (0.0%)	1 / 15 (6.7%)
Three-month abstinence – n (%)	0 / 13 (0.0%)	0 / 10 (0.0%)	1 / 15 (6.7%)
95% CI for 3-month abstinence rate	(0.0%, 24.7%)	(0.0%, 30.8%)	(0.2%, 31.9%)
Site 5			
Corrected exhaled CO < 10ppm – n (%)	7 / 26 (26.9%)	6 / 24 (25.0%)	9 / 22 (40.9%)
No cigarettes smoked since last visit – n (%)	6 / 25 (24.0%)	4 / 23 (17.4%)	9 / 23 (39.1%)
Three-month abstinence – n (%)	6 / 27 (22.2%)	3 / 24 (12.5%)	8 / 23 (34.8%)
95% CI for 3-month abstinence rate	(8.6%, 42.3%)	(2.7%, 32.4%)	(16.4%, 57.3%)
Site Main Effect*			0.0413
Treatment-by-site interactions*			0.6841

Subjects whose criterion cannot be determined were treated as not meeting the criterion
N = number of randomized subjects
Exact 95% CI are given
* *p-values* were based on a logistic regression with the covariates treatment group, site, and their interactions

Table S15 Six-Month (Visits 6 to 12) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined), Stratified by Study Site

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Site 1			
Corrected exhaled CO < 10ppm – n (%)	8 / 20 (40.0%)	4 / 23 (17.4%)	7 / 24 (29.2%)
No cigarettes smoked since last visit – n (%)	7 / 20 (35.0%)	3 / 23 (13.0%)	5 / 24 (20.8%)
Six-month abstinence – n (%)	6 / 20 (30.0%)	3 / 23 (13.0%)	5 / 24 (20.8%)
95% CI for 6-month abstinence rate	(11.9%, 54.3%)	(2.8%, 33.6%)	(7.1%, 42.2%)
Site 2			
Corrected exhaled CO < 10ppm – n (%)	0 / 13 (0.0%)	0 / 12 (0.0%)	0 / 14 (0.0%)
No cigarettes smoked since last visit – n (%)	3 / 12 (25.0%)	3 / 12 (25.0%)	0 / 13 (0.0%)
Six-month abstinence – n (%)	0 / 13 (0.0%)	0 / 12 (0.0%)	0 / 14 (0.0%)
95% CI for 6-month abstinence rate	(0.0%, 24.7%)	(0.0%, 26.5%)	(0.0%, 23.2%)
Site 3			
Corrected exhaled CO < 10ppm – n (%)	4 / 14 (28.6%)	3 / 7 (42.9%)	5 / 13 (38.5%)
No cigarettes smoked since last visit – n (%)	4 / 14 (28.6%)	3 / 11 (27.3%)	2 / 16 (12.5%)
Six-month abstinence – n (%)	4 / 15 (26.7%)	3 / 11 (27.3%)	2 / 16 (12.5%)
95% CI for 6 month abstinence rate	(7.8%, 55.1%)	(6.0%, 61.0%)	(1.6%, 38.3%)
Site 4			

Table S15 Six-Month (Visits 6 to 12) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined), Stratified by Study Site

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Corrected exhaled CO < 10ppm – n (%)	0 / 13 (0.0%)	0 / 10 (0.0%)	0 / 14 (0.0%)
No cigarettes smoked since last visit – n (%)	0 / 12 (0.0%)	0 / 10 (0.0%)	0 / 14 (0.0%)
Six-month abstinence – n (%)	0 / 13 (0.0%)	0 / 10 (0.0%)	0 / 14 (0.0%)
95% CI for 6-month abstinence rate	(0.0%, 24.7%)	(0.0%, 30.8%)	(0.0%, 23.2%)
Site 5			
Corrected exhaled CO < 10ppm – n (%)	4 / 26 (15.4%)	4 / 24 (16.7%)	5 / 21 (23.8%)
No cigarettes smoked since last visit – n (%)	4 / 25 (16.0%)	4 / 23 (17.4%)	5 / 22 (22.7%)
Six-month abstinence – n (%)	3 / 27 (11.1%)	3 / 24 (12.5%)	4 / 22 (18.2%)
95% CI for 6-month abstinence rate	(2.4%, 29.2%)	(2.7%, 32.4%)	(5.2%, 40.3%)
Site Main Effect*			0.2452
Treatment-by-site interactions*			0.9237

Subjects whose criterion cannot be determined were treated as not meeting the criterion
N = number of randomized subjects
Exact 95% CI are given
* *p-values* were based on a logistic regression with the covariates treatment group, site, and their interactions.

Table S16 Three-Month and Six-Month Abstinence Proportions (Per-Protocol Population)

	Group 1 (N = 67)	Group 2 (N = 65)	Group 3 (N = 79)
Visit 6 to Visit 11			
Corrected exhaled CO < 10ppm – n (%)	20 / 61 (32.8%)	13 / 56 (23.2%)	21 / 70 (30.0%)
No cigarettes smoked since last visit – n (%)	24 / 61 (39.3%)	13 / 62 (21.0%)	19 / 75 (25.3%)
Three-month abstinence – n (%)	17 / 65 (26.2%)	8 / 63 (12.7%)	16 / 76 (21.1%)
95% CI for 3-month abstinence rate	(16.0%, 38.5%)	(5.6%, 23.5%)	(12.5%, 31.9%)
*p-value**	0.3032	0.9375	
Visit 6 to Visit 12			
Corrected exhaled CO < 10ppm – n (%)	13 / 56 (23.2%)	7 / 50 (14.0%)	14 / 63 (22.2%)
No cigarettes smoked since last visit – n (%)	14 / 54 (25.9%)	8 / 61 (13.1%)	11 / 70 (15.7%)
Six-month abstinence – n (%)	10 / 60 (16.7%)	5 / 62 (8.1%)	10 / 72 (13.9%)
95% CI for 6-month abstinence rate	(8.3%, 28.5%)	(2.7%, 17.8%)	(6.9%, 24.1%)
*p-value**	0.4192	0.9115	

N = number of randomized subjects in the per-protocol population
Exact 95% CI are given
* One-sided Fisher's exact test for 3-month and 6-month abstinence proportions compared with Group 3

Table S17 Three-Month (Visits 6 to 11) Abstinence Proportions, Stratified by Study Site (Per-Protocol Population)

	Group 1 (N = 67)	Group 2 (N = 65)	Group 3 (N = 70)
Site 1			
Corrected exhaled CO < 10ppm – n (%)	8 / 15 (53.3%)	3 / 15 (20.0%)	5 / 20 (25.0%)
No cigarettes smoked since last visit – n (%)	7 / 15 (46.7%)	2 / 15 (13.3%)	4 / 20 (20.0%)
Three-month abstinence – n (%)	7 / 15 (46.7%)	2 / 15 (13.3%)	4 / 20 (20.0%)
95% CI for 3-month abstinence rate	(21.3%, 73.4%)	(1.7%, 40.5%)	(5.7%, 43.7%)
Site 2			
Corrected exhaled CO < 10ppm – n (%)	0 / 12 (0.0%)	0 / 8 (0.0%)	0 / 11 (0.0%)
No cigarettes smoked since last visit – n (%)	7 / 11 (63.6%)	4 / 8 (50.0%)	2 / 10 (20.0%)
Three-month abstinence – n (%)	0 / 12 (0.0%)	0 / 8 (0.0%)	0 / 11 (0.0%)
95% CI for 3-month abstinence rate	(0.0%, 26.5%)	(0.0%, 36.9%)	(0.0%, 28.5%)
Site 3			
Corrected exhaled CO < 10ppm – n (%)	5 / 10 (50.0%)	4 / 7 (57.1%)	5 / 10 (50.0%)
No cigarettes smoked since last visit – n (%)	4 / 10 (40.0%)	3 / 11 (27.3%)	3 / 14 (21.4%)
Three-month abstinence – n (%)	4 / 11 (36.4%)	3 / 11 (27.3%)	3 / 14 (21.4%)
95% CI for 3-month abstinence rate	(10.9%, 69.2%)	(6.0%, 61.0%)	(4.7%, 50.8%)
Site 4			

Table S17 Three-Month (Visits 6 to 11) Abstinence Proportions, Stratified by Study Site (Per-Protocol Population)

	Group 1 (N = 67)	Group 2 (N = 65)	Group 3 (N = 79)
Corrected exhaled CO < 10ppm – n (%)	0 / 9 (0.0%)	0 / 7 (0.0%)	2 / 11 (18.2%)
No cigarettes smoked since last visit – n (%)	0 / 8 (0.0%)	0 / 8 (0.0%)	1 / 12 (8.3%)
Three-month abstinence – n (%)	0 / 9 (0.0%)	0 / 8 (0.0%)	1 / 12 (8.3%)
95% CI for 3-month abstinence rate	(0.0%, 33.6%)	(0.0%, 36.9%)	(0.2%, 38.5%)
Site 5			
Corrected exhaled CO < 10ppm – n (%)	7 / 15 (46.7%)	6 / 19 (31.6%)	9 / 18 (50.0%)
No cigarettes smoked since last visit – n (%)	6 / 17 (35.3%)	4 / 20 (20.0%)	9 / 19 (47.4%)
Three-month abstinence – n (%)	6 / 18 (33.3%)	3 / 21 (14.3%)	8 / 19 (42.1%)
95% CI for 3-month abstinence rate	(13.3%, 59.0%)	(3.0%, 36.3%)	(20.3%, 66.5%)
Site Main Effect*			0.1719
Treatment-by-site interactions*			0.6785

N = number of randomized subjects in the per-protocol population
Exact 95% CI are given
* *p-values* were based on a logistic regression with the covariates treatment group, site, and their interactions.

Table S18 Six-Month (Visits 6 to 12) Abstinence Proportions, Stratified by Study Site
(Per-Protocol Population)

	Group 1 (N = 67)	Group 2 (N = 65)	Group 3 (N = 39)
Site 1			
Corrected exhaled CO < 10ppm – n (%)	7 / 14 (50.0%)	1 / 13 (7.7%)	4 / 19 (21.1%)
No cigarettes smoked since last visit – n (%)	5 / 14 (35.7%)	0 / 15 (0.0%)	4 / 20 (20.0%)
Six-month abstinence – n (%)	5 / 14 (35.7%)	0 / 15 (0.0%)	4 / 20 (20.0%)
95% CI for 6-month abstinence rate	(12.8%, 64.9%)	(0.0%, 21.8%)	(5.7%, 43.7%)
Site 2			
Corrected exhaled CO < 10ppm – n (%)	0 / 12 (0.0%)	0 / 8 (0.0%)	0 / 11 (0.0%)
No cigarettes smoked since last visit – n (%)	3 / 9 (33.3%)	2 / 8 (25.0%)	0 / 9 (0.0%)
Six-month abstinence – n (%)	0 / 12 (0.0%)	0 / 8 (0.0%)	0 / 11 (0.0%)
95% CI for 6-month abstinence rate	(0.0%, 26.5%)	(0.0%, 36.9%)	(0.0%, 28.5%)
Site 3			
Corrected exhaled CO < 10ppm – n (%)	2 / 8 (25.0%)	2 / 5 (40.0%)	5 / 10 (50.0%)
No cigarettes smoked since last visit – n (%)	2 / 8 (25.0%)	2 / 10 (20.0%)	2 / 14 (14.3%)
Six-month abstinence – n (%)	2 / 9 (22.2%)	2 / 10 (20.0%)	2 / 14 (14.3%)
95% CI for 6-month abstinence rate	(2.8%, 60.0%)	(2.5%, 55.6%)	(1.8%, 42.8%)
Site 4			

Table S18 Six-Month (Visits 6 to 12) Abstinence Proportions, Stratified by Study Site
(Per-Protocol Population)

	Group 1 (N = 67)	Group 2 (N = 65)	Group 3 (N = 79)
Corrected exhaled CO < 10ppm – n (%)	0 / 9 (0.0%)	0 / 7 (0.0%)	0 / 9 (0.0%)
No cigarettes smoked since last visit – n (%)	0 / 8 (0.0%)	0 / 8 (0.0%)	0 / 11 (0.0%)
Six-month abstinence – n (%)	0 / 9 (0.0%)	0 / 8 (0.0%)	0 / 11 (0.0%)
95% CI for 6-month abstinence rate	(0.0%, 33.6%)	(0.0%, 36.9%)	(0.0%, 28.5%)
Site 5			
Corrected exhaled CO < 10ppm – n (%)	4 / 13 (30.8%)	4 / 17 (23.5%)	5 / 14 (35.7%)
No cigarettes smoked since last visit – n (%)	4 / 15 (26.7%)	4 / 20 (20.0%)	5 / 16 (31.3%)
Six-month abstinence – n (%)	3 / 16 (18.8%)	3 / 21 (14.3%)	4 / 16 (25.0%)
95% CI for 6-month abstinence rate	(4.0%, 45.6%)	(3.0%, 36.3%)	(7.3%, 52.4%)
Site Main Effect*			0.7454
Treatment-by-site interactions*			0.9093

N = number of randomized subjects in the per-protocol population
Exact 95% CI are given
* *p-values* were based on a logistic regression with the covariates treatment group, site, and their interactions

Table S19 Summary of Corrected Exhaled CO Levels (ppm) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	116	116	114
Mean (SD)	26.3 (8.6)	26.5 (9.9)	25.6 (9.7)
Median	24.0	24.0	23.0
Minimum, maximum	16, 53	16, 68	16, 68
p-value compared with Group 3*	0.2621	0.3923	
Visit 2			
Number of available subjects	116	116	114
Mean (SD)	28.7 (13.3)	26.6 (8.6)	27.3 (9.7)
Median	25.5	25.0	25.5
Minimum, maximum	15, 82	15, 56	14, 60
p-value compared with Group 3*	0.9557	0.7911	
Visit 3			
Number of available subjects	113	114	109
Mean (SD)	30.2 (12.2)	29.1 (11.4)	26.6 (11.1)
Median	29.0	28.0	24.0
Minimum, maximum	11, 80	9, 64	11, 72
p-value compared with Group 3*	0.0135	0.0489	
Visit 4			
Number of available subjects	108	110	107
Mean (SD)	32.1 (13.6)	29.6 (12.3)	27.0 (10.6)

**Table S19 Summary of Corrected Exhaled CO Levels (ppm)
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	28.5	28.5	25.0
Minimum, maximum	6, 73	1, 57	8, 66
p-value compared with Group 3*	0.0065	0.0882	
Visit 5			
Number of available subjects	101	98	104
Mean (SD)	23.2 (14.1)	23.1 (13.7)	24.4 (10.8)
Median	21.0	23.0	22.5
Minimum, maximum	0, 65	0, 89	3, 67
p-value compared with Group 3*	0.3851	0.4023	
Visit 6			
Number of available subjects	87	79	95
Mean (SD)	11.2 (12.1)	12.3 (11.0)	12.2 (10.7)
Median	7.0	12.0	10.0
Minimum, maximum	0, 56	0, 60	0, 43
p-value compared with Group 3*	0.1635	0.9024	
Visit 7			
Number of available subjects	70	56	70
Mean (SD)	8.4 (10.2)	9.1 (8.6)	8.9 (8.3)
Median	4.0	5.0	6.0
Minimum, maximum	0, 50	0, 40	0, 28
p-value compared with Group 3*	0.3026	0.8631	

Table S19 Summary of Corrected Exhaled CO Levels (ppm) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 8			
Number of available subjects	60	45	60
Mean (SD)	7.4 (9.9)	7.8 (6.9)	6.9 (6.5)
Median	4.0	5.0	5.0
Minimum, maximum	0, 49	0, 25	0, 24
p-value compared with Group 3*	0.4125	0.5116	
Visit 9			
Number of available subjects	54	43	56
Mean (SD)	7.2 (9.3)	8.1 (8.0)	7.4 (6.1)
Median	4.0	5.0	6.0
Minimum, maximum	0, 40	0, 29	0, 22
p-value compared with Group 3*	0.1601	0.9099	
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	6.2 (6.1)	7.3 (7.5)	7.5 (7.1)
Median	4.0	5.0	4.5
Minimum, maximum	0, 32	0, 39	0, 27
p-value compared with Group 3*	0.4996	0.7261	
Visit 11			
Number of available subjects	45	37	45
Mean (SD)	6.7 (7.6)	6.5 (6.2)	6.1 (5.1)

**Table S19 Summary of Corrected Exhaled CO Levels (ppm)
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	4.0	6.0	5.0
Minimum, maximum	1, 39	0, 24	0, 18
p-value compared with Group 3*	0.9321	0.9851	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	5.4 (8.4)	4.0 (3.5)	5.1 (4.3)
Median	3.0	3.0	4.0
Minimum, maximum	0, 43	0, 12	0, 17
p-value compared with Group 3*	0.3760	0.3991	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S20 Summary of Change From Baseline in Corrected Exhaled CO Levels (ppm)
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	113	114	109
Mean (SD)	1.5 (11.3)	2.5 (10.7)	-0.2 (10.2)
Median	1.0	1.0	0.0
Minimum, maximum	-43, 39	-27, 29	-48, 31
p-value compared with Group 3*	0.1296	0.1256	
Visit 4			
Number of available subjects	108	110	107
Mean (SD)	2.9 (11.3)	2.9 (10.8)	0.2 (10.6)
Median	3.0	2.0	0.0
Minimum, maximum	-50, 36	-25, 31	-40, 25
p-value compared with Group 3*	0.0308	0.0904	
Visit 5			
Number of available subjects	101	98	104
Mean (SD)	-5.4 (14.4)	-3.0 (12.5)	-2.5 (11.3)
Median	-5.0	-4.0	-2.0
Minimum, maximum	-53, 32	-27, 64	-52, 40
p-value compared with Group 3*	0.0934	0.3291	
Visit 6			
Number of available subjects	87	79	95
Mean (SD)	-17.4 (15.6)	-13.4 (13.2)	-14.9 (14.4)

Table S20 Summary of Change From Baseline in Corrected Exhaled CO Levels (ppm) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	-16.0	-12.0	-14.0
Minimum, maximum	-69, 22	-54, 21	-55, 21
p-value compared with Group 3*	0.2503	0.4308	
Visit 7			
Number of available subjects	70	56	70
Mean (SD)	-19.3 (13.9)	-16.0 (12.2)	-19.3 (14.4)
Median	-17.0	-14.0	-17.5
Minimum, maximum	-71, 12	-53, 11	-59, 11
p-value compared with Group 3*	0.9900	0.2140	
Visit 8			
Number of available subjects	60	45	60
Mean (SD)	-19.8 (13.6)	-18.2 (11.3)	-21.3 (13.2)
Median	-17.0	-14.0	-19.5
Minimum, maximum	-63, 17	-53, 0	-58, 4
p-value compared with Group 3*	0.7269	0.2169	
Visit 9			
Number of available subjects	54	43	56
Mean (SD)	-19.5 (13.0)	-17.5 (12.5)	-20.5 (12.0)
Median	-16.5	-16.0	-18.5
Minimum, maximum	-59, 3	-56, 8	-53, 0
p-value compared with Group 3*	0.6687	0.1959	

Table S20 Summary of Change From Baseline in Corrected Exhaled CO Levels (ppm)
(ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	-19.3 (10.5)	-18.6 (10.0)	-20.1 (12.8)
Median	-16.0	-16.0	-17.0
Minimum, maximum	-45, -1	-53, 2	-54, 7
p-value compared with Group 3*	0.8542	0.6910	
Visit 11			
Number of available subjects	45	37	45
Mean (SD)	-18.1 (10.9)	-18.9 (10.5)	-21.2 (12.1)
Median	-15.0	-18.0	-18.0
Minimum, maximum	-45, 13	-53, 2	-53, -2
p-value compared with Group 3*	0.2414	0.4871	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	-20.1 (10.4)	-22.8 (10.2)	-21.1 (12.7)
Median	-17.0	-20.0	-16.5
Minimum, maximum	-43, 6	-54, -10	-54, -5
p-value compared with Group 3*	0.7316	0.2788	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S21 Summary of Saliva Cotinine Concentration Levels (ng/mL) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	116	116	114
10 – 30 ng/mL	0	0	1 (0.9%)
30 – 100 ng/mL	0	0	1 (0.9%)
100 – 200 ng/mL	0	2 (1.7%)	2 (1.8%)
200 – 500 ng/mL	8 (6.9%)	8 (6.9%)	3 (2.6%)
500 - 2000 ng/mL	33 (28.4%)	41 (35.3%)	34 (29.8%)
> 2000 ng/mL	75 (64.7%)	65 (56.0%)	73 (64.0%)
p-value compared with Group 3*	0.9315	0.2159	
Visit 2			
Number of available subjects	116	116	113
30 – 100 ng/mL	0	0	1 (0.9%)
100 – 200 ng/mL	0	1 (0.9%)	4 (3.5%)
200 – 500 ng/mL	3 (2.6%)	5 (4.3%)	4 (3.5%)
500 – 2000 ng/mL	36 (31.0%)	54 (46.6%)	42 (37.2%)
> 2000 ng/mL	77 (66.4%)	56 (48.3%)	62 (54.9%)
p-value compared with Group 3*	0.0454	0.4949	
Visit 3			
Number of available subjects	113	113	108
1 – 10 ng/mL	1 (0.9%)	0	0
30 – 100 ng/mL	1 (0.9%)	1 (0.9%)	0
100 – 200 ng/mL	0	3 (2.7%)	1 (0.9%)

Table S21 Summary of Saliva Cotinine Concentration Levels (ng/mL) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
200 - 500 ng/mL	8 (7.1%)	6 (5.3%)	12 (11.1%)
500 - 2000 ng/mL	50 (44.2%)	55 (48.7%)	43 (39.8%)
> 2000 ng/mL	53 (46.9%)	48 (42.5%)	52 (48.1%)
p-value compared with Group 3*	0.9536	0.6009	
Visit 4			
Number of available subjects	107	109	107
10 - 30 ng/mL	0	2 (1.8%)	0
30 - 100 ng/mL	1 (0.9%)	0	1 (0.9%)
100 - 200 ng/mL	2 (1.9%)	2 (1.8%)	2 (1.9%)
200 - 500 ng/mL	5 (4.7%)	11 (10.1%)	9 (8.4%)
500 - 2000 ng/mL	59 (55.1%)	56 (51.4%)	49 (45.8%)
> 2000 ng/mL	40 (37.4%)	38 (34.9%)	46 (43.0%)
p-value compared with Group 3*	0.6777	0.2225	
Visit 5			
Number of available subjects	101	98	104
1 - 10 ng/mL	0	0	1 (1.0%)
10 - 30 ng/mL	1 (1.0%)	2 (2.0%)	1 (1.0%)
100 - 200 ng/mL	4 (4.0%)	9 (9.2%)	4 (3.8%)
200 - 500 ng/mL	11 (10.9%)	13 (13.3%)	12 (11.5%)
500 - 2000 ng/mL	47 (46.5%)	55 (56.1%)	38 (36.5%)
> 2000 ng/mL	38 (37.6%)	19 (19.4%)	48 (46.2%)
p-value compared with Group 3*	0.4096	0.0005	

Table S21 Summary of Saliva Cotinine Concentration Levels (ng/mL) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 119)
Visit 6			
Number of available subjects	87	79	96
10 – 30 ng/mL	1 (1.1%)	1 (1.3%)	0
30 – 100 ng/mL	2 (2.3%)	3 (3.8%)	3 (3.1%)
100 – 200 ng/mL	6 (6.9%)	16 (20.3%)	5 (5.2%)
200 – 500 ng/mL	9 (10.3%)	13 (16.5%)	9 (9.4%)
500 – 2000 ng/mL	39 (44.8%)	31 (39.2%)	45 (46.9%)
> 2000 ng/mL	30 (34.5%)	15 (19.0%)	34 (35.4%)
p-value compared with Group 3*	0.7243	0.0003	
Visit 7			
Number of available subjects	70	56	70
1 – 10 ng/mL	1 (1.4%)	0	0
10 – 30 ng/mL	0	1 (1.8%)	0
30 –100 ng/mL	1 (1.4%)	3 (5.4%)	1 (1.4%)
100 – 200 ng/mL	9 (12.9%)	12 (21.4%)	14 (20.0%)
200 – 500 ng/mL	12 (17.1%)	9 (16.1%)	9 (12.9%)
500 – 2000 ng/mL	29 (41.4%)	25 (44.6%)	28 (40.0%)
> 2000 ng/mL	18 (25.7%)	6 (10.7%)	18 (25.7%)
p-value compared with Group 3*	0.8048	0.0558	
Visit 8			
Number of available subjects	60	45	61
1 – 10 ng/mL	1 (1.7%)	0	0
10 – 30 ng/mL	0	0	1 (1.6%)

Table S21 Summary of Saliva Cotinine Concentration Levels (ng/mL) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
30 - 100 ng/mL	0	5 (11.1%)	2 (3.3%)
100 - 200 ng/mL	12 (20.0%)	12 (26.7%)	11 (18.0%)
200 - 500 ng/mL	9 (15.0%)	8 (17.8%)	10 (16.4%)
500 - 2000 ng/mL	27 (45.0%)	12 (26.7%)	28 (45.9%)
> 2000 ng/mL	11 (18.3%)	8 (17.8%)	9 (14.8%)
p-value compared with Group 3*	0.6191	0.1831	
Visit 9			
Number of available subjects	54	44	56
10 - 30 ng/mL	0	2 (4.5%)	1 (1.8%)
30 - 100 ng/mL	0	3 (6.8%)	0
100 - 200 ng/mL	17 (31.5%)	11 (25.0%)	15 (26.8%)
200 - 500 ng/mL	13 (24.1%)	9 (20.5%)	13 (23.2%)
500 - 2000 ng/mL	21 (38.9%)	12 (27.3%)	17 (30.4%)
> 2000 ng/mL	3 (5.6%)	7 (15.9%)	10 (17.9%)
p-value compared with Group 3*	0.4016	0.3713	
Visit 10			
Number of available subjects	50	39	52
10 - 30 ng/mL	0	2 (5.1%)	1 (1.9%)
30 - 100 ng/mL	1 (2.0%)	5 (12.8%)	4 (7.7%)
100 - 200 ng/mL	21 (42.0%)	9 (23.1%)	16 (30.8%)
200 - 500 ng/mL	14 (28.0%)	9 (23.1%)	9 (17.3%)
500 - 2000 ng/mL	10 (20.0%)	7 (17.9%)	18 (34.6%)
> 2000	4 (8.0%)	7 (17.9%)	4 (7.7%)

Table S21 Summary of Saliva Cotinine Concentration Levels (ng/mL) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
p-value compared with Group 3*	0.5909	0.8144	
Visit 11			
Number of available subjects	45	36	46
1 – 10 ng/mL	1 (2.2%)	0	0
10 – 30 ng/mL	0	1 (2.8%)	0
30 – 100 ng/mL	7 (15.6%)	2 (5.6%)	5 (10.9%)
100 – 200 ng/mL	20 (44.4%)	17 (47.2%)	23 (50.0%)
200 – 500 ng/mL	8 (17.8%)	6 (16.7%)	8 (17.4%)
500 – 2000 ng/mL	7 (15.6%)	7 (19.4%)	7 (15.2%)
> 2000 ng/mL	2 (4.4%)	3 (8.3%)	3 (6.5%)
p-value compared with Group 3*	0.5772	0.5518	
Visit 12			
Number of available subjects	34	23	32
1 – 10 ng/mL	1 (2.9%)	0	1 (3.1%)
10 – 30 ng/mL	0	2 (8.7%)	0
30 – 100 ng/mL	3 (8.8%)	2 (8.7%)	3 (9.4%)
100 – 200 ng/mL	18 (52.9%)	12 (52.2%)	19 (59.4%)
200 – 500 ng/mL	5 (14.7%)	3 (13.0%)	5 (15.6%)
500 – 2000 ng/mL	3 (8.8%)	0	3 (9.4%)
> 2000 ng/mL	4 (11.8%)	4 (17.4%)	1 (3.1%)

Table S21 Summary of Saliva Cotinine Concentration Levels (ng/mL) (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
p-value compared with Group 3*	0.4871	0.9473	

N = number of randomized subjects
% was based on the number of available subjects in the corresponding visit
No events were observed for saliva cotinine categories not specified at a specific visit.
* Two-sided Jonckheere-Terpstra test

Table S22.1 Summary of Minnesota Nicotine Withdrawal Questionnaire – Depressed Mood, Sad (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	115	86 (74.8%)	20 (17.4%)	6 (5.2%)	2 (1.7%)	1 (0.9%)	0.3064
	2	116	96 (82.8%)	14 (12.1%)	4 (3.4%)	2 (1.7%)	0	0.0135
	3	113	78 (69.0%)	22 (19.5%)	9 (8.0%)	4 (3.5%)	0	
2	1	116	84 (72.4%)	26 (22.4%)	4 (3.4%)	2 (1.7%)	0	0.9672
	2	114	94 (82.5%)	13 (11.4%)	5 (4.4%)	2 (1.8%)	0	0.1023
	3	113	83 (73.5%)	19 (16.8%)	8 (7.1%)	3 (2.7%)	0	
3	1	112	78 (69.6%)	22 (19.6%)	8 (7.1%)	4 (3.6%)	0	0.4702
	2	114	78 (68.4%)	27 (23.7%)	4 (3.5%)	5 (4.4%)	0	0.4151
	3	108	80 (74.1%)	19 (17.6%)	4 (3.7%)	4 (3.7%)	1 (0.9%)	
4	1	106	66 (62.3%)	23 (21.7%)	10 (9.4%)	6 (5.7%)	1 (0.9%)	0.2271
	2	108	70 (64.8%)	25 (23.1%)	7 (6.5%)	6 (5.6%)	0	0.4694
	3	107	76 (71.0%)	16 (15.0%)	8 (7.5%)	6 (5.6%)	1 (0.9%)	
5	1	99	52 (52.5%)	28 (28.3%)	11 (11.1%)	8 (8.1%)	0	0.0223
	2	93	58 (62.4%)	17 (18.3%)	12 (12.9%)	3 (3.2%)	3 (3.2%)	0.2536
	3	102	72 (70.6%)	14 (13.7%)	9 (8.8%)	7 (6.9%)	0	
6	1	82	45 (54.9%)	18 (22.0%)	12 (14.6%)	7 (8.5%)	0	0.3742

Table S22.1 Summary of Minnesota Nicotine Withdrawal Questionnaire – Depressed Mood, Sad (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
	2	71	44 (62.0%)	14 (19.7%)	8 (11.3%)	3 (4.2%)	2 (2.8%)	0.9968
	3	87	55 (63.2%)	13 (14.9%)	12 (13.8%)	7 (8.0%)	0	
7	1	69	35 (50.7%)	18 (26.1%)	10 (14.5%)	5 (7.2%)	1 (1.4%)	0.3197
	2	55	29 (52.7%)	15 (27.3%)	8 (14.5%)	2 (3.6%)	1 (1.8%)	0.5322
	3	68	42 (61.8%)	12 (17.6%)	6 (8.8%)	7 (10.3%)	1 (1.5%)	
8	1	58	32 (55.2%)	19 (32.8%)	3 (5.2%)	3 (5.2%)	1 (1.7%)	0.9832
	2	44	19 (43.2%)	16 (36.4%)	4 (9.1%)	5 (11.4%)	0	0.2159
	3	60	35 (58.3%)	13 (21.7%)	8 (13.3%)	3 (5.0%)	1 (1.7%)	
9	1	53	32 (60.4%)	13 (24.5%)	2 (3.8%)	4 (7.5%)	2 (3.8%)	0.6622
	2	41	21 (51.2%)	13 (31.7%)	5 (12.2%)	2 (4.9%)	0	0.2726
	3	55	35 (63.6%)	12 (21.8%)	6 (10.9%)	2 (3.6%)	0	
10	1	49	29 (59.2%)	16 (32.7%)	3 (6.1%)	1 (2.0%)	0	0.9875
	2	39	23 (59.0%)	12 (30.8%)	2 (5.1%)	1 (2.6%)	1 (2.6%)	0.9122
	3	52	31 (59.6%)	16 (30.8%)	4 (7.7%)	1 (1.9%)	0	
11	1	45	27 (60.0%)	10 (22.2%)	5 (11.1%)	3 (6.7%)	0	0.7965
	2	37	22 (59.5%)	10 (27.0%)	3 (8.1%)	2 (5.4%)	0	0.8959
	3	46	27 (58.7%)	15 (32.6%)	3 (6.5%)	1 (2.2%)	0	

Table S22.1 Summary of Minnesota Nicotine Withdrawal Questionnaire – Depressed Mood, Sad (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
12	1	32	16 (50.0%)	10 (31.3%)	3 (9.4%)	2 (6.3%)	1 (3.1%)	0.1035
	2	20	12 (60.0%)	5 (25.0%)	2 (10.0%)	1 (5.0%)	0	0.4674
	3	32	22 (68.8%)	7 (21.9%)	3 (9.4%)	0	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.2 Summary of Minnesota Nicotine Withdrawal Questionnaire – Insomnia, Sleep Problems, Awakening at Night (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	116	64 (55.2%)	23 (19.8%)	13 (11.2%)	9 (7.8%)	7 (6.0%)	0.7548
	2	116	60 (51.7%)	32 (27.6%)	14 (12.1%)	8 (6.9%)	2 (1.7%)	0.7559
	3	113	61 (54.0%)	31 (27.4%)	9 (8.0%)	9 (8.0%)	3 (2.7%)	
2	1	116	68 (58.6%)	20 (17.2%)	15 (12.9%)	9 (7.8%)	4 (3.4%)	0.4722
	2	116	67 (57.8%)	28 (24.1%)	11 (9.5%)	9 (7.8%)	1 (0.9%)	0.2800
	3	113	58 (51.3%)	28 (24.8%)	17 (15.0%)	6 (5.3%)	4 (3.5%)	
3	1	112	50 (44.6%)	36 (32.1%)	14 (12.5%)	6 (5.4%)	6 (5.4%)	0.0807
	2	114	59 (51.8%)	23 (20.2%)	18 (15.8%)	13 (11.4%)	1 (0.9%)	0.2537
	3	108	64 (59.3%)	22 (20.4%)	10 (9.3%)	7 (6.5%)	5 (4.6%)	
4	1	106	54 (50.9%)	23 (21.7%)	15 (14.2%)	11 (10.4%)	3 (2.8%)	0.7565
	2	109	49 (45.0%)	34 (31.2%)	11 (10.1%)	13 (11.9%)	2 (1.8%)	0.4492
	3	106	52 (49.1%)	32 (30.2%)	13 (12.3%)	7 (6.6%)	2 (1.9%)	
5	1	99	33 (33.3%)	26 (26.3%)	21 (21.2%)	15 (15.2%)	4 (4.0%)	0.0002
	2	94	47 (50.0%)	20 (21.3%)	16 (17.0%)	9 (9.6%)	2 (2.1%)	0.2312
	3	103	57 (55.3%)	28 (27.2%)	9 (8.7%)	8 (7.8%)	1 (1.0%)	

Table S22.2 Summary of Minnesota Nicotine Withdrawal Questionnaire – Insomnia, Sleep Problems, Awakening at Night (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
6	1	82	26 (31.7%)	27 (32.9%)	20 (24.4%)	7 (8.5%)	2 (2.4%)	0.7157
	2	71	36 (50.7%)	16 (22.5%)	11 (15.5%)	6 (8.5%)	2 (2.8%)	0.1443
	3	87	35 (40.2%)	23 (26.4%)	11 (12.6%)	13 (14.9%)	5 (5.7%)	
7	1	69	24 (34.8%)	18 (26.1%)	13 (18.8%)	13 (18.8%)	1 (1.4%)	0.2927
	2	55	26 (47.3%)	13 (23.6%)	9 (16.4%)	6 (10.9%)	1 (1.8%)	0.6692
	3	68	30 (44.1%)	19 (27.9%)	6 (8.8%)	8 (11.8%)	5 (7.4%)	
8	1	57	20 (35.1%)	22 (38.6%)	10 (17.5%)	3 (5.3%)	2 (3.5%)	0.5113
	2	44	16 (36.4%)	12 (27.3%)	10 (22.7%)	6 (13.6%)	0	0.9125
	3	60	19 (31.7%)	22 (36.7%)	11 (18.3%)	5 (8.3%)	3 (5.0%)	
9	1	53	19 (35.8%)	20 (37.7%)	8 (15.1%)	3 (5.7%)	3 (5.7%)	0.9533
	2	41	19 (46.3%)	14 (34.1%)	7 (17.1%)	1 (2.4%)	0	0.2325
	3	55	19 (34.5%)	23 (41.8%)	7 (12.7%)	3 (5.5%)	3 (5.5%)	
10	1	49	19 (38.8%)	15 (30.6%)	11 (22.4%)	4 (8.2%)	0	0.6118
	2	39	19 (48.7%)	13 (33.3%)	1 (2.6%)	5 (12.8%)	1 (2.6%)	0.5406
	3	52	21 (40.4%)	20 (38.5%)	6 (11.5%)	4 (7.7%)	1 (1.9%)	
11	1	45	22 (48.9%)	10 (22.2%)	12 (26.7%)	1 (2.2%)	0	0.8912

Table S22.2 Summary of Minnesota Nicotine Withdrawal Questionnaire – Insomnia, Sleep Problems, Awakening at Night (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
	2	37	21 (56.8%)	11 (29.7%)	3 (8.1%)	1 (2.7%)	1 (2.7%)	0.3110
	3	46	21 (45.7%)	16 (34.8%)	7 (15.2%)	0	2 (4.3%)	
12	1	32	17 (53.1%)	8 (25.0%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	0.6887
	2	20	8 (40.0%)	9 (45.0%)	3 (15.0%)	0	0	0.4654
	3	32	18 (56.3%)	8 (25.0%)	5 (15.6%)	0	1 (3.1%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.3 Summary of Minnesota Nicotine Withdrawal Questionnaire – Angry, Irritable, Frustrated (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	116	70 (60.3%)	34 (29.3%)	9 (7.8%)	2 (1.7%)	1 (0.9%)	0.7678
	2	116	81 (69.8%)	22 (19.0%)	3 (2.6%)	9 (7.8%)	1 (0.9%)	0.1647
	3	113	68 (60.2%)	29 (25.7%)	8 (7.1%)	8 (7.1%)	0	
2	1	115	66 (57.4%)	30 (26.1%)	14 (12.2%)	5 (4.3%)	0	0.8129
	2	116	80 (69.0%)	22 (19.0%)	10 (8.6%)	4 (3.4%)	0	0.1484
	3	113	69 (61.1%)	23 (20.4%)	12 (10.6%)	7 (6.2%)	2 (1.8%)	
3	1	111	55 (49.5%)	32 (28.8%)	11 (9.9%)	10 (9.0%)	3 (2.7%)	0.2358
	2	114	56 (49.1%)	36 (31.6%)	14 (12.3%)	5 (4.4%)	3 (2.6%)	0.3012
	3	108	58 (53.7%)	37 (34.3%)	7 (6.5%)	6 (5.6%)	0	
4	1	106	47 (44.3%)	34 (32.1%)	13 (12.3%)	10 (9.4%)	2 (1.9%)	0.2413
	2	109	48 (44.0%)	31 (28.4%)	13 (11.9%)	15 (13.8%)	2 (1.8%)	0.1262
	3	107	56 (52.3%)	30 (28.0%)	12 (11.2%)	8 (7.5%)	1 (0.9%)	
5	1	99	37 (37.4%)	31 (31.3%)	17 (17.2%)	9 (9.1%)	5 (5.1%)	0.0040
	2	94	46 (48.9%)	27 (28.7%)	13 (13.8%)	5 (5.3%)	3 (3.2%)	0.2608
	3	103	60 (58.3%)	23 (22.3%)	10 (9.7%)	9 (8.7%)	1 (1.0%)	
6	1	82	19 (23.2%)	27 (32.9%)	25 (30.5%)	10 (12.2%)	1 (1.2%)	0.1080

Table S22.3 Summary of Minnesota Nicotine Withdrawal Questionnaire – Angry, Irritable, Frustrated (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
	2	71	28 (39.4%)	19 (26.8%)	13 (18.3%)	9 (12.7%)	2 (2.8%)	0.8981
	3	87	32 (36.8%)	27 (31.0%)	14 (16.1%)	12 (13.8%)	2 (2.3%)	
7	1	69	19 (27.5%)	24 (34.8%)	16 (23.2%)	8 (11.6%)	2 (2.9%)	0.2942
	2	55	21 (38.2%)	17 (30.9%)	12 (21.8%)	4 (7.3%)	1 (1.8%)	0.8142
	3	68	25 (36.8%)	23 (33.8%)	9 (13.2%)	9 (13.2%)	2 (2.9%)	
8	1	58	21 (36.2%)	24 (41.4%)	7 (12.1%)	6 (10.3%)	0	0.3885
	2	44	19 (43.2%)	11 (25.0%)	8 (18.2%)	6 (13.6%)	0	0.4461
	3	59	29 (49.2%)	15 (25.4%)	10 (16.9%)	4 (6.8%)	1 (1.7%)	
9	1	53	27 (50.9%)	16 (30.2%)	5 (9.4%)	3 (5.7%)	2 (3.8%)	0.8100
	2	41	23 (56.1%)	8 (19.5%)	8 (19.5%)	2 (4.9%)	0	0.6253
	3	55	26 (47.3%)	19 (34.5%)	5 (9.1%)	4 (7.3%)	1 (1.8%)	
10	1	49	24 (49.0%)	18 (36.7%)	4 (8.2%)	1 (2.0%)	2 (4.1%)	0.8172
	2	39	17 (43.6%)	16 (41.0%)	5 (12.8%)	0	1 (2.6%)	0.5637
	3	52	28 (53.8%)	14 (26.9%)	8 (15.4%)	2 (3.8%)	0	
11	1	45	22 (48.9%)	16 (35.6%)	3 (6.7%)	4 (8.9%)	0	0.4369
	2	37	19 (51.4%)	13 (35.1%)	4 (10.8%)	1 (2.7%)	0	0.6792
	3	46	26 (56.5%)	14 (30.4%)	5 (10.9%)	1 (2.2%)	0	

Table S22.3 Summary of Minnesota Nicotine Withdrawal Questionnaire – Angry, Irritable, Frustrated (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
12	1	32	16 (50.0%)	15 (46.9%)	0	1 (3.1%)	0	0.3381
	2	20	9 (45.0%)	6 (30.0%)	2 (10.0%)	3 (15.0%)	0	0.0928
	3	32	20 (62.5%)	11 (34.4%)	0	1 (3.1%)	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.4 Summary of Minnesota Nicotine Withdrawal Questionnaire – Anxious, Nervous (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	115	49 (42.6%)	43 (37.4%)	17 (14.8%)	6 (5.2%)	0	0.1481
	2	116	73 (62.9%)	30 (25.9%)	3 (2.6%)	10 (8.6%)	0	0.1605
	3	113	61 (54.0%)	33 (29.2%)	10 (8.8%)	9 (8.0%)	0	
2	1	115	59 (51.3%)	31 (27.0%)	16 (13.9%)	8 (7.0%)	1 (0.9%)	0.4585
	2	116	59 (50.9%)	44 (37.9%)	8 (6.9%)	5 (4.3%)	0	0.9076
	3	113	61 (54.0%)	35 (31.0%)	10 (8.8%)	6 (5.3%)	1 (0.9%)	
3	1	112	47 (42.0%)	42 (37.5%)	14 (12.5%)	8 (7.1%)	1 (0.9%)	0.0854
	2	114	59 (51.8%)	40 (35.1%)	9 (7.9%)	5 (4.4%)	1 (0.9%)	0.9530
	3	108	57 (52.8%)	35 (32.4%)	12 (11.1%)	4 (3.7%)	0	
4	1	105	44 (41.9%)	32 (30.5%)	16 (15.2%)	11 (10.5%)	2 (1.9%)	0.1067
	2	109	53 (48.6%)	31 (28.4%)	13 (11.9%)	12 (11.0%)	0	0.5508
	3	107	56 (52.3%)	31 (29.0%)	8 (7.5%)	10 (9.3%)	2 (1.9%)	
5	1	99	25 (25.3%)	36 (36.4%)	24 (24.2%)	12 (12.1%)	2 (2.0%)	0.0050
	2	94	42 (44.7%)	29 (30.9%)	17 (18.1%)	5 (5.3%)	1 (1.1%)	0.8601
	3	103	45 (43.7%)	33 (32.0%)	15 (14.6%)	10 (9.7%)	0	
6	1	82	22 (26.8%)	28 (34.1%)	18 (22.0%)	14 (17.1%)	0	0.2407

Table S22.4 Summary of Minnesota Nicotine Withdrawal Questionnaire – Anxious, Nervous (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
	2	71	30 (42.3%)	19 (26.8%)	14 (19.7%)	5 (7.0%)	3 (4.2%)	0.5234
	3	87	31 (35.6%)	28 (32.2%)	15 (17.2%)	13 (14.9%)	0	
7	1	69	18 (26.1%)	30 (43.5%)	15 (21.7%)	6 (8.7%)	0	0.6707
	2	55	27 (49.1%)	14 (25.5%)	9 (16.4%)	3 (5.5%)	2 (3.6%)	0.1742
	3	67	24 (35.8%)	22 (32.8%)	11 (16.4%)	8 (11.9%)	2 (3.0%)	
8	1	58	20 (34.5%)	22 (37.9%)	13 (22.4%)	3 (5.2%)	0	0.4449
	2	44	22 (50.0%)	12 (27.3%)	3 (6.8%)	6 (13.6%)	1 (2.3%)	0.8623
	3	60	29 (48.3%)	13 (21.7%)	13 (21.7%)	5 (8.3%)	0	
9	1	53	18 (34.0%)	27 (50.9%)	6 (11.3%)	0	2 (3.8%)	0.3959
	2	41	22 (53.7%)	11 (26.8%)	5 (12.2%)	3 (7.3%)	0	0.7278
	3	55	28 (50.9%)	14 (25.5%)	9 (16.4%)	4 (7.3%)	0	
10	1	49	17 (34.7%)	25 (51.0%)	4 (8.2%)	3 (6.1%)	0	0.0576
	2	39	18 (46.2%)	14 (35.9%)	5 (12.8%)	2 (5.1%)	0	0.3132
	3	52	29 (55.8%)	17 (32.7%)	4 (7.7%)	2 (3.8%)	0	
11	1	45	18 (40.0%)	19 (42.2%)	4 (8.9%)	4 (8.9%)	0	0.1069
	2	36	21 (58.3%)	10 (27.8%)	4 (11.1%)	1 (2.8%)	0	0.9579
	3	46	26 (56.5%)	15 (32.6%)	3 (6.5%)	2 (4.3%)	0	

Table S22.4 Summary of Minnesota Nicotine Withdrawal Questionnaire – Anxious, Nervous (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
12	1	31	16 (51.6%)	15 (48.4%)	0	0	0	0.1005
	2	20	14 (70.0%)	4 (20.0%)	1 (5.0%)	1 (5.0%)	0	0.7210
	3	32	23 (71.9%)	9 (28.1%)	0	0	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.5 Summary of Minnesota Nicotine Withdrawal Questionnaire – Difficulty Concentrating (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	116	73 (62.9%)	28 (24.1%)	9 (7.8%)	4 (3.4%)	2 (1.7%)	0.0709
	2	116	83 (71.6%)	21 (18.1%)	6 (5.2%)	5 (4.3%)	1 (0.9%)	0.6049
	3	112	84 (75.0%)	15 (13.4%)	10 (8.9%)	3 (2.7%)	0	
2	1	116	72 (62.1%)	32 (27.6%)	7 (6.0%)	5 (4.3%)	0	0.5845
	2	116	84 (72.4%)	17 (14.7%)	8 (6.9%)	6 (5.2%)	1 (0.9%)	0.4586
	3	113	75 (66.4%)	25 (22.1%)	9 (8.0%)	4 (3.5%)	0	
3	1	112	65 (58.0%)	28 (25.0%)	12 (10.7%)	5 (4.5%)	2 (1.8%)	0.2473
	2	114	75 (65.8%)	22 (19.3%)	13 (11.4%)	4 (3.5%)	0	0.9851
	3	107	68 (63.6%)	29 (27.1%)	7 (6.5%)	2 (1.9%)	1 (0.9%)	
4	1	106	53 (50.0%)	25 (23.6%)	20 (18.9%)	6 (5.7%)	2 (1.9%)	0.0189
	2	109	59 (54.1%)	28 (25.7%)	11 (10.1%)	9 (8.3%)	2 (1.8%)	0.0932
	3	107	70 (65.4%)	20 (18.7%)	12 (11.2%)	4 (3.7%)	1 (0.9%)	
5	1	99	43 (43.4%)	31 (31.3%)	16 (16.2%)	7 (7.1%)	2 (2.0%)	0.0044
	2	94	53 (56.4%)	23 (24.5%)	10 (10.6%)	6 (6.4%)	2 (2.1%)	0.2444
	3	103	67 (65.0%)	18 (17.5%)	13 (12.6%)	5 (4.9%)	0	
6	1	81	27 (33.3%)	35 (43.2%)	13 (16.0%)	6 (7.4%)	0	0.0372

Table S22.5 Summary of Minnesota Nicotine Withdrawal Questionnaire – Difficulty Concentrating (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
	2	71	40 (56.3%)	17 (23.9%)	10 (14.1%)	3 (4.2%)	1 (1.4%)	0.7027
	3	87	45 (51.7%)	26 (29.9%)	11 (12.6%)	4 (4.6%)	1 (1.1%)	
7	1	69	29 (42.0%)	29 (42.0%)	9 (13.0%)	2 (2.9%)	0	0.0576
	2	55	28 (50.9%)	14 (25.5%)	9 (16.4%)	4 (7.3%)	0	0.1993
	3	68	42 (61.8%)	17 (25.0%)	3 (4.4%)	4 (5.9%)	2 (2.9%)	
8	1	58	26 (44.8%)	21 (36.2%)	8 (13.8%)	3 (5.2%)	0	0.1515
	2	44	25 (56.8%)	11 (25.0%)	6 (13.6%)	2 (4.5%)	0	0.7405
	3	60	36 (60.0%)	15 (25.0%)	5 (8.3%)	3 (5.0%)	1 (1.7%)	
9	1	53	27 (50.9%)	20 (37.7%)	4 (7.5%)	0	2 (3.8%)	0.1119
	2	41	21 (51.2%)	14 (34.1%)	5 (12.2%)	1 (2.4%)	0	0.1286
	3	55	37 (67.3%)	13 (23.6%)	2 (3.6%)	3 (5.5%)	0	
10	1	49	26 (53.1%)	15 (30.6%)	6 (12.2%)	2 (4.1%)	0	0.1004
	2	39	20 (51.3%)	15 (38.5%)	3 (7.7%)	1 (2.6%)	0	0.1248
	3	52	36 (69.2%)	11 (21.2%)	3 (5.8%)	2 (3.8%)	0	
11	1	45	22 (48.9%)	18 (40.0%)	5 (11.1%)	0	0	0.0505
	2	36	21 (58.3%)	12 (33.3%)	3 (8.3%)	0	0	0.3095
	3	46	32 (69.6%)	11 (23.9%)	3 (6.5%)	0	0	

Table S22.5 Summary of Minnesota Nicotine Withdrawal Questionnaire – Difficulty Concentrating (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
12	1	32	24 (75.0%)	7 (21.9%)	1 (3.1%)	0	0	0.3315
	2	20	13 (65.0%)	7 (35.0%)	0	0	0	0.1101
	3	32	27 (84.4%)	5 (15.6%)	0	0	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.6 Summary of Minnesota Nicotine Withdrawal Questionnaire – Restless, Impatient (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	115	53 (46.1%)	38 (33.0%)	14 (12.2%)	9 (7.8%)	1 (0.9%)	0.6981
	2	116	64 (55.2%)	34 (29.3%)	8 (6.9%)	9 (7.8%)	1 (0.9%)	0.3359
	3	113	56 (49.6%)	32 (28.3%)	18 (15.9%)	7 (6.2%)	0	
2	1	116	57 (49.1%)	41 (35.3%)	8 (6.9%)	10 (8.6%)	0	0.8561
	2	116	66 (56.9%)	33 (28.4%)	9 (7.8%)	8 (6.9%)	0	0.3986
	3	113	58 (51.3%)	36 (31.9%)	9 (8.0%)	10 (8.8%)	0	
3	1	112	42 (37.5%)	44 (39.3%)	16 (14.3%)	9 (8.0%)	1 (0.9%)	0.1657
	2	114	59 (51.8%)	27 (23.7%)	21 (18.4%)	7 (6.1%)	0	0.8421
	3	108	50 (46.3%)	38 (35.2%)	14 (13.0%)	6 (5.6%)	0	
4	1	106	38 (35.8%)	37 (34.9%)	18 (17.0%)	10 (9.4%)	3 (2.8%)	0.2096
	2	109	51 (46.8%)	28 (25.7%)	13 (11.9%)	14 (12.8%)	3 (2.8%)	0.8983
	3	107	47 (43.9%)	35 (32.7%)	14 (13.1%)	9 (8.4%)	2 (1.9%)	
5	1	98	23 (23.5%)	36 (36.7%)	24 (24.5%)	13 (13.3%)	2 (2.0%)	0.0005
	2	94	39 (41.5%)	33 (35.1%)	11 (11.7%)	7 (7.4%)	4 (4.3%)	0.5659
	3	103	45 (43.7%)	38 (36.9%)	10 (9.7%)	10 (9.7%)	0	
6	1	81	15 (18.5%)	30 (37.0%)	23 (28.4%)	12 (14.8%)	1 (1.2%)	0.1237

Table S22.6 Summary of Minnesota Nicotine Withdrawal Questionnaire – Restless, Impatient (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
	2	70	23 (32.9%)	16 (22.9%)	17 (24.3%)	11 (15.7%)	3 (4.3%)	0.5482
	3	86	26 (30.2%)	31 (36.0%)	15 (17.4%)	12 (14.0%)	2 (2.3%)	
7	1	68	15 (22.1%)	30 (44.1%)	17 (25.0%)	5 (7.4%)	1 (1.5%)	0.3353
	2	54	20 (37.0%)	17 (31.5%)	8 (14.8%)	8 (14.8%)	1 (1.9%)	0.9246
	3	68	24 (35.3%)	25 (36.8%)	6 (8.8%)	9 (13.2%)	4 (5.9%)	
8	1	58	16 (27.6%)	30 (51.7%)	7 (12.1%)	5 (8.6%)	0	0.2440
	2	43	17 (39.5%)	14 (32.6%)	4 (9.3%)	8 (18.6%)	0	0.4887
	3	59	25 (42.4%)	22 (37.3%)	6 (10.2%)	6 (10.2%)	0	
9	1	53	14 (26.4%)	28 (52.8%)	7 (13.2%)	2 (3.8%)	2 (3.8%)	0.2631
	2	41	20 (48.8%)	13 (31.7%)	3 (7.3%)	5 (12.2%)	0	0.5720
	3	55	22 (40.0%)	22 (40.0%)	7 (12.7%)	4 (7.3%)	0	
10	1	49	20 (40.8%)	19 (38.8%)	6 (12.2%)	4 (8.2%)	0	0.3139
	2	39	17 (43.6%)	18 (46.2%)	3 (7.7%)	1 (2.6%)	0	0.7987
	3	52	26 (50.0%)	18 (34.6%)	6 (11.5%)	2 (3.8%)	0	
11	1	45	17 (37.8%)	20 (44.4%)	7 (15.6%)	1 (2.2%)	0	0.3353
	2	37	19 (51.4%)	8 (21.6%)	8 (21.6%)	2 (5.4%)	0	0.7457
	3	46	23 (50.0%)	16 (34.8%)	4 (8.7%)	3 (6.5%)	0	

Table S22.6 Summary of Minnesota Nicotine Withdrawal Questionnaire – Restless, Impatient (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
12	1	32	15 (46.9%)	14 (43.8%)	2 (6.3%)	1 (3.1%)	0	0.2635
	2	20	9 (45.0%)	6 (30.0%)	3 (15.0%)	2 (10.0%)	0	0.1277
	3	32	20 (62.5%)	9 (28.1%)	3 (9.4%)	0	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.7 Summary of Minnesota Nicotine Withdrawal Questionnaire – Increased Appetite, Hungry, Weight Problem (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value*[a]
1	1	115	69 (60.0%)	25 (21.7%)	14 (12.2%)	5 (4.3%)	2 (1.7%)	0.5279
	2	115	72 (62.6%)	19 (16.5%)	9 (7.8%)	11 (9.6%)	4 (3.5%)	0.5283
	3	113	73 (64.6%)	20 (17.7%)	14 (12.4%)	6 (5.3%)	0	
2	1	115	85 (73.9%)	19 (16.5%)	9 (7.8%)	2 (1.7%)	0	0.3323
	2	116	79 (68.1%)	18 (15.5%)	8 (6.9%)	8 (6.9%)	3 (2.6%)	0.7582
	3	113	77 (68.1%)	24 (21.2%)	5 (4.4%)	6 (5.3%)	1 (0.9%)	
3	1	112	69 (61.6%)	23 (20.5%)	15 (13.4%)	5 (4.5%)	0	0.0700
	2	113	68 (60.2%)	27 (23.9%)	9 (8.0%)	8 (7.1%)	1 (0.9%)	0.0435
	3	108	80 (74.1%)	15 (13.9%)	5 (4.6%)	8 (7.4%)	0	
4	1	106	60 (56.6%)	29 (27.4%)	9 (8.5%)	7 (6.6%)	1 (0.9%)	0.6490
	2	109	58 (53.2%)	28 (25.7%)	9 (8.3%)	13 (11.9%)	1 (0.9%)	0.7616
	3	106	59 (55.7%)	24 (22.6%)	13 (12.3%)	7 (6.6%)	3 (2.8%)	
5	1	99	46 (46.5%)	26 (26.3%)	14 (14.1%)	10 (10.1%)	3 (3.0%)	0.1438
	2	94	39 (41.5%)	27 (28.7%)	13 (13.8%)	13 (13.8%)	2 (2.1%)	0.0332
	3	103	57 (55.3%)	26 (25.2%)	11 (10.7%)	8 (7.8%)	1 (1.0%)	

Table S22.7 Summary of Minnesota Nicotine Withdrawal Questionnaire – Increased Appetite, Hungry, Weight Problem (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
6	1	82	27 (32.9%)	20 (24.4%)	20 (24.4%)	9 (11.0%)	6 (7.3%)	0.4945
	2	70	21 (30.0%)	21 (30.0%)	14 (20.0%)	12 (17.1%)	2 (2.9%)	0.5074
	3	87	26 (29.9%)	20 (23.0%)	20 (23.0%)	15 (17.2%)	6 (6.9%)	
7	1	69	21 (30.4%)	19 (27.5%)	14 (20.3%)	11 (15.9%)	4 (5.8%)	0.9498
	2	55	13 (23.6%)	15 (27.3%)	16 (29.1%)	9 (16.4%)	2 (3.6%)	0.5144
	3	67	22 (32.8%)	19 (28.4%)	9 (13.4%)	10 (14.9%)	7 (10.4%)	
8	1	58	20 (34.5%)	15 (25.9%)	11 (19.0%)	7 (12.1%)	5 (8.6%)	0.7591
	2	44	9 (20.5%)	16 (36.4%)	10 (22.7%)	9 (20.5%)	0	0.6480
	3	60	18 (30.0%)	14 (23.3%)	20 (33.3%)	4 (6.7%)	4 (6.7%)	
9	1	53	17 (32.1%)	17 (32.1%)	13 (24.5%)	5 (9.4%)	1 (1.9%)	0.7492
	2	41	14 (34.1%)	13 (31.7%)	5 (12.2%)	8 (19.5%)	1 (2.4%)	0.8410
	3	55	18 (32.7%)	18 (32.7%)	6 (10.9%)	10 (18.2%)	3 (5.5%)	
10	1	49	18 (36.7%)	12 (24.5%)	10 (20.4%)	7 (14.3%)	2 (4.1%)	0.7698
	2	39	14 (35.9%)	13 (33.3%)	6 (15.4%)	5 (12.8%)	1 (2.6%)	0.5013
	3	52	16 (30.8%)	17 (32.7%)	9 (17.3%)	7 (13.5%)	3 (5.8%)	
11	1	45	16 (35.6%)	17 (37.8%)	4 (8.9%)	8 (17.8%)	0	0.6012

Table S22.7 Summary of Minnesota Nicotine Withdrawal Questionnaire – Increased Appetite, Hungry, Weight Problem (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
	2	37	11 (29.7%)	12 (32.4%)	10 (27.0%)	4 (10.8%)	0	0.8067
	3	46	13 (28.3%)	19 (41.3%)	9 (19.6%)	3 (6.5%)	2 (4.3%)	
12	1	32	11 (34.4%)	11 (34.4%)	7 (21.9%)	3 (9.4%)	0	0.8161
	2	20	8 (40.0%)	3 (15.0%)	5 (25.0%)	4 (20.0%)	0	0.6351
	3	32	14 (43.8%)	8 (25.0%)	4 (12.5%)	5 (15.6%)	1 (3.1%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S22.8 Summary of Minnesota Nicotine Withdrawal Questionnaire – Desire or Craving to Smoke (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	p-value[a]
1	1	115	7 (6.1%)	13 (11.3%)	26 (22.6%)	43 (37.4%)	26 (22.6%)	0.9101
	2	116	6 (5.2%)	11 (9.5%)	28 (24.1%)	49 (42.2%)	22 (19.0%)	0.9609
	3	113	8 (7.1%)	15 (13.3%)	21 (18.6%)	44 (38.9%)	25 (22.1%)	
2	1	116	10 (8.6%)	18 (15.5%)	29 (25.0%)	42 (36.2%)	17 (14.7%)	0.4365
	2	116	8 (6.9%)	16 (13.8%)	33 (28.4%)	49 (42.2%)	10 (8.6%)	0.5404
	3	113	14 (12.4%)	19 (16.8%)	23 (20.4%)	46 (40.7%)	11 (9.7%)	
3	1	112	7 (6.3%)	29 (25.9%)	22 (19.6%)	39 (34.8%)	15 (13.4%)	0.0428
	2	113	9 (8.0%)	17 (15.0%)	28 (24.8%)	51 (45.1%)	8 (7.1%)	0.0105
	3	108	20 (18.5%)	16 (14.8%)	33 (30.6%)	34 (31.5%)	5 (4.6%)	
4	1	106	5 (4.7%)	23 (21.7%)	30 (28.3%)	35 (33.0%)	13 (12.3%)	0.1589
	2	109	11 (10.1%)	21 (19.3%)	30 (27.5%)	39 (35.8%)	8 (7.3%)	0.5599
	3	107	14 (13.1%)	21 (19.6%)	30 (28.0%)	33 (30.8%)	9 (8.4%)	
5	1	99	8 (8.1%)	26 (26.3%)	31 (31.3%)	27 (27.3%)	7 (7.1%)	0.5145
	2	94	9 (9.6%)	27 (28.7%)	26 (27.7%)	29 (30.9%)	3 (3.2%)	0.9040
	3	103	13 (12.6%)	26 (25.2%)	30 (29.1%)	29 (28.2%)	5 (4.9%)	
6	1	82	9 (11.0%)	19 (23.2%)	21 (25.6%)	26 (31.7%)	7 (8.5%)	0.8123

Table S22.8 Summary of Minnesota Nicotine Withdrawal Questionnaire – Desire or Craving to Smoke (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
	2	71	4 (5.6%)	22 (31.0%)	15 (21.1%)	25 (35.2%)	5 (7.0%)	0.8947
	3	87	5 (5.7%)	22 (25.3%)	28 (32.2%)	23 (26.4%)	9 (10.3%)	
7	1	69	8 (11.6%)	26 (37.7%)	18 (26.1%)	13 (18.8%)	4 (5.8%)	0.7341
	2	55	6 (10.9%)	18 (32.7%)	17 (30.9%)	13 (23.6%)	1 (1.8%)	0.9810
	3	68	6 (8.8%)	29 (42.6%)	13 (19.1%)	13 (19.1%)	7 (10.3%)	
8	1	58	12 (20.7%)	20 (34.5%)	11 (19.0%)	9 (15.5%)	6 (10.3%)	0.7466
	2	44	6 (13.6%)	17 (38.6%)	8 (18.2%)	13 (29.5%)	0	0.9235
	3	60	9 (15.0%)	22 (36.7%)	14 (23.3%)	12 (20.0%)	3 (5.0%)	
9	1	53	12 (22.6%)	19 (35.8%)	10 (18.9%)	8 (15.1%)	4 (7.5%)	0.8057
	2	41	4 (9.8%)	19 (46.3%)	8 (19.5%)	9 (22.0%)	1 (2.4%)	0.6182
	3	55	10 (18.2%)	22 (40.0%)	10 (18.2%)	10 (18.2%)	3 (5.5%)	
10	1	49	15 (30.6%)	12 (24.5%)	14 (28.6%)	7 (14.3%)	1 (2.0%)	0.4627
	2	39	10 (25.6%)	16 (41.0%)	5 (12.8%)	7 (17.9%)	1 (2.6%)	0.3896
	3	52	10 (19.2%)	21 (40.4%)	8 (15.4%)	10 (19.2%)	3 (5.8%)	
11	1	45	14 (31.1%)	11 (24.4%)	12 (26.7%)	8 (17.8%)	0	0.7646
	2	37	9 (24.3%)	16 (43.2%)	5 (13.5%)	6 (16.2%)	1 (2.7%)	0.6749
	3	46	12 (26.1%)	15 (32.6%)	10 (21.7%)	5 (10.9%)	4 (8.7%)	

Table S22.8 Summary of Minnesota Nicotine Withdrawal Questionnaire – Desire or Craving to Smoke (ITT Population)

Visit	Treatment Group	N	None	Slight	Mild	Moderate	Severe	*p-value**
12	1	32	16 (50.0%)	9 (28.1%)	3 (9.4%)	2 (6.3%)	2 (6.3%)	0.0466
	2	20	7 (35.0%)	7 (35.0%)	3 (15.0%)	3 (15.0%)	0	0.3827
	3	32	7 (21.9%)	15 (46.9%)	2 (6.3%)	6 (18.8%)	2 (6.3%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S23.1 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Depressed Mood, Sad (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.1 (0.7)	0.2 (0.8)	0.0 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 3	-2, 4
p-value compared with Group 3*	0.3058	0.0402	
Visit 4			
Number of available subjects	106	108	107
Mean (SD)	0.3 (1.0)	0.3 (0.9)	0.1 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 3	-3, 3
p-value compared with Group 3*	0.3100	0.0609	
Visit 5			
Number of available subjects	99	93	102
Mean (SD)	0.4 (1.0)	0.4 (1.0)	0.1 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 4	-2, 3
p-value compared with Group 3*	0.0543	0.0601	
Visit 6			
Number of available subjects	82	71	87
Mean (SD)	0.4 (1.0)	0.4 (1.1)	0.4 (0.9)

Table S23.1 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Depressed Mood, Sad (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 4	-1, 3
p-value compared with Group 3*	0.7985	0.9686	
Visit 7			
Number of available subjects	69	55	68
Mean (SD)	0.5 (1.0)	0.4 (1.1)	0.4 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 4	-2, 4	-1, 4
p-value compared with Group 3*	0.6238	0.7161	
Visit 8			
Number of available subjects	58	44	60
Mean (SD)	0.3 (1.0)	0.5 (0.9)	0.4 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-1, 3	-1, 3
p-value compared with Group 3*	0.5941	0.3577	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.4 (1.2)	0.4 (0.9)	0.2 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-1, 3	-2, 3
p-value compared with Group 3*	0.7064	0.3179	

Table S23.1 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Depressed Mood, Sad (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 116)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	0.2 (0.8)	0.3 (1.1)	0.2 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 4	-2, 2
p-value compared with Group 3*	0.7542	0.8306	
Visit 11			
Number of available subjects	45	37	46
Mean (SD)	0.3 (1.0)	0.2 (0.9)	0.2 (0.7)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 3	-2, 2
p-value compared with Group 3*	0.7278	0.8248	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	0.5 (1.0)	0.3 (0.9)	0.1 (0.7)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 3	-1, 3	-1, 2
p-value compared with Group 3*	0.1314	0.5026	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.2 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Insomnia, Sleep Problems, Awakening at Night (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.2 (1.3)	0.2 (1.0)	-0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-2, 3	-4, 4
p-value compared with Group 3*	0.3439	0.2176	
Visit 4			
Number of available subjects	106	109	106
Mean (SD)	0.1 (1.2)	0.2 (1.0)	-0.0 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-2, 4	-4, 3
p-value compared with Group 3*	0.3474	0.1206	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	0.5 (1.4)	0.2 (1.1)	-0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-3, 4	-4, 3
p-value compared with Group 3*	0.0004	0.1265	
Visit 6			
Number of available subjects	82	71	87
Mean (SD)	0.4 (1.3)	0.2 (1.2)	0.4 (1.3)

Table S23.2 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Insomnia, Sleep Problems, Awakening at Night (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-3, 3	-4, 3
p-value compared with Group 3*	0.9646	0.1324	
Visit 7			
Number of available subjects	69	55	68
Mean (SD)	0.6 (1.5)	0.3 (1.2)	0.5 (1.3)
Median	1.0	0.0	0.0
Minimum, maximum	-4, 4	-2, 3	-4, 4
p-value compared with Group 3*	0.4013	0.4079	
Visit 8			
Number of available subjects	57	44	60
Mean (SD)	0.3 (1.4)	0.5 (1.1)	0.5 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-2, 3	-3, 4
p-value compared with Group 3*	0.4661	0.7548	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.5 (1.6)	0.3 (1.0)	0.4 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-3, 2	-3, 4
p-value compared with Group 3*	0.7565	0.6323	

Table S23.2 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Insomnia, Sleep Problems, Awakening at Night (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	0.3 (1.4)	0.3 (1.2)	0.2 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 3	-3, 4	-3, 3
p-value compared with Group 3*	0.4082	0.8613	
Visit 11			
Number of available subjects	45	37	46
Mean (SD)	0.1 (1.4)	0.1 (1.0)	0.1 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 3	-3, 3	-4, 2
p-value compared with Group 3*	0.7404	0.7697	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	0.1 (1.6)	-0.1 (1.2)	-0.1 (1.3)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 3	-3, 2	-4, 2
p-value compared with Group 3*	0.8001	0.9604	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.3 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Angry, Irritable, Frustrated (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 118)	Group 3 (N = 114)
Visit 3			
Number of available subjects	111	114	108
Mean (SD)	0.2 (1.2)	0.3 (1.0)	-0.0 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-3, 4	-4, 3
p-value compared with Group 3*	0.3431	0.0050	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.3 (1.2)	0.5 (1.2)	0.1 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-3, 4	-4, 3
p-value compared with Group 3*	0.5249	0.0214	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	0.5 (1.3)	0.4 (1.0)	0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-2, 4	-3, 3
p-value compared with Group 3*	0.0198	0.0421	
Visit 6			
Number of available subjects	82	71	87
Mean (SD)	0.8 (1.1)	0.7 (1.3)	0.5 (1.3)

Table S23.3 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Angry, Irritable, Frustrated (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	1.0	0.0	0.0
Minimum, maximum	-1, 4	-2, 4	-3, 4
p-value compared with Group 3*	0.1673	0.5554	
Visit 7			
Number of available subjects	69	55	68
Mean (SD)	0.8 (1.2)	0.7 (1.0)	0.6 (1.2)
Median	1.0	1.0	0.5
Minimum, maximum	-1, 4	-2, 3	-2, 4
p-value compared with Group 3*	0.5950	0.4720	
Visit 8			
Number of available subjects	58	44	59
Mean (SD)	0.4 (1.1)	0.7 (1.2)	0.3 (1.1)
Median	0.0	0.5	0.0
Minimum, maximum	-1, 3	-2, 3	-2, 3
p-value compared with Group 3*	0.9727	0.1484	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.3 (1.1)	0.4 (1.0)	0.3 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 4	-2, 3	-2, 4
p-value compared with Group 3*	0.9107	0.4871	

Table S23.3 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Angry, Irritable, Frustrated (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	0.2 (1.1)	0.4 (1.1)	0.1 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-2, 4	-3, 3
p-value compared with Group 3*	0.8182	0.2030	
Visit 11			
Number of available subjects	45	37	46
Mean (SD)	0.2 (1.0)	0.3 (1.0)	0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 2	-2, 3	-3, 2
p-value compared with Group 3*	0.9399	0.5110	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	0.1 (0.7)	0.6 (1.2)	-0.1 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 1	-1, 3	-2, 1
p-value compared with Group 3*	0.4281	0.0692	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.4 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Anxious, Nervous (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.1 (1.1)	0.0 (0.9)	0.0 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-3, 3	-3, 3
p-value compared with Group 3*	0.4095	0.8341	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	0.2 (1.2)	0.2 (1.0)	0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 3	-2, 3
p-value compared with Group 3*	0.7550	0.7210	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	0.6 (1.2)	0.2 (1.0)	0.3 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-2, 3	-2, 3
p-value compared with Group 3*	0.0890	0.7186	
Visit 6			
Number of available subjects	82	71	87
Mean (SD)	0.6 (1.1)	0.4 (1.1)	0.5 (1.2)

Table S23.4 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Anxious, Nervous (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 4	-3, 3
p-value compared with Group 3*	0.6524	0.4614	
Visit 7			
Number of available subjects	69	55	67
Mean (SD)	0.4 (1.0)	0.2 (1.2)	0.6 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-3, 4	-1, 4
p-value compared with Group 3*	0.5536	0.0743	
Visit 8			
Number of available subjects	58	44	60
Mean (SD)	0.2 (1.0)	0.2 (1.3)	0.4 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 2	-3, 4	-2, 3
p-value compared with Group 3*	0.5861	0.3922	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.3 (1.2)	0.0 (1.1)	0.3 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-3, 3	-2, 3
p-value compared with Group 3*	0.7871	0.2022	

Table S23.4 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Anxious, Nervous (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	0.2 (1.1)	0.0 (1.2)	0.1 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-3, 3	-3, 3
p-value compared with Group 3*	0.3151	0.8807	
Visit 11			
Number of available subjects	45	36	46
Mean (SD)	0.2 (1.2)	-0.2 (1.1)	0.0 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-2, 3	-3, 3
p-value compared with Group 3*	0.3973	0.2682	
Visit 12			
Number of available subjects	31	20	32
Mean (SD)	-0.0 (0.9)	-0.4 (1.3)	-0.3 (0.9)
Median	0.0	-0.5	0.0
Minimum, maximum	-3, 1	-3, 3	-2, 1
p-value compared with Group 3*	0.1324	0.6031	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.5 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Difficulty Concentrating (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	107
Mean (SD)	0.1 (1.0)	0.1 (0.9)	0.0 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-3, 3	-2, 4
p-value compared with Group 3*	0.6534	0.8557	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.3 (1.1)	0.3 (1.1)	0.1 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-4, 4	-2, 3
p-value compared with Group 3*	0.1283	0.0866	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	0.4 (1.1)	0.3 (1.1)	0.1 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 4	-4, 4	-2, 3
p-value compared with Group 3*	0.1845	0.2821	
Visit 6			
Number of available subjects	81	71	87
Mean (SD)	0.5 (1.0)	0.3 (1.1)	0.3 (1.1)

Table S23.5 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Difficulty Concentrating (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 3	-3, 4	-2, 4
p-value compared with Group 3*	0.2200	0.9676	
Visit 7			
Number of available subjects	69	55	68
Mean (SD)	0.4 (0.8)	0.4 (1.2)	0.3 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 3	-4, 3	-2, 4
p-value compared with Group 3*	0.5099	0.4128	
Visit 8			
Number of available subjects	58	44	60
Mean (SD)	0.4 (1.0)	0.4 (1.1)	0.3 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 3	-4, 3	-2, 3
p-value compared with Group 3*	0.5169	0.5050	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.3 (1.0)	0.3 (1.0)	0.2 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 4	-4, 3	-2, 3
p-value compared with Group 3*	0.8255	0.3784	

Table S23.5 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Difficulty Concentrating (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	0.3 (0.9)	0.3 (1.0)	0.1 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 3	-4, 3	-2, 3
p-value compared with Group 3*	0.5146	0.2646	
Visit 11			
Number of available subjects	45	36	46
Mean (SD)	0.2 (0.8)	0.2 (1.0)	0.1 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 2	-4, 2	-2, 2
p-value compared with Group 3*	0.5163	0.3532	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	-0.1 (0.6)	0.1 (0.7)	-0.2 (0.7)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-2, 1
p-value compared with Group 3*	0.6321	0.2123	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.6 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Restless, Impatient (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.2 (1.1)	0.1 (0.9)	0.1 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-3, 3	-3, 3
p-value compared with Group 3*	0.2849	0.4877	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.3 (1.2)	0.3 (1.3)	0.2 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-3, 4	-3, 3
p-value compared with Group 3*	0.5349	0.8760	
Visit 5			
Number of available subjects	98	94	103
Mean (SD)	0.7 (1.2)	0.3 (1.2)	0.2 (1.1)
Median	1.0	0.0	0.0
Minimum, maximum	-2, 4	-3, 4	-3, 3
p-value compared with Group 3*	0.0045	0.3814	
Visit 6			
Number of available subjects	81	70	86
Mean (SD)	0.8 (1.2)	0.8 (1.3)	0.6 (1.4)

Table S23.6 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Restless, Impatient (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	1.0	0.5	0.5
Minimum, maximum	-2, 4	-1, 4	-3, 4
p-value compared with Group 3*	0.3865	0.6531	
Visit 7			
Number of available subjects	68	54	68
Mean (SD)	0.6 (1.1)	0.6 (1.2)	0.6 (1.4)
Median	1.0	0.0	0.0
Minimum, maximum	-2, 4	-3, 3	-3, 4
p-value compared with Group 3*	0.8450	0.9548	
Visit 8			
Number of available subjects	58	43	59
Mean (SD)	0.4 (1.0)	0.6 (1.2)	0.3 (1.2)
Median	0.0	1.0	0.0
Minimum, maximum	-2, 3	-3, 3	-3, 3
p-value compared with Group 3*	0.5194	0.2099	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.4 (1.1)	0.3 (1.2)	0.3 (1.3)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-3, 3	-3, 3
p-value compared with Group 3*	0.6844	0.7646	

Table S23.6 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Restless, Impatient (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	0.2 (1.1)	0.1 (1.1)	0.0 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-3, 2	-3, 3
p-value compared with Group 3*	0.5937	0.4135	
Visit 11			
Number of available subjects	45	37	46
Mean (SD)	0.1 (0.9)	0.2 (1.2)	0.0 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 2	-3, 2	-3, 3
p-value compared with Group 3*	0.4904	0.2454	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	0.0 (0.7)	0.3 (1.0)	-0.2 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 2	-2, 3	-3, 1
p-value compared with Group 3*	0.3682	0.0961	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.7 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Increased Appetite, Hungry, Weight Problem (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	108
Mean (SD)	0.2 (0.9)	0.0 (1.1)	-0.0 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-4, 3	-4, 3
p-value compared with Group 3*	0.0403	0.2934	
Visit 4			
Number of available subjects	106	109	106
Mean (SD)	0.3 (0.9)	0.2 (1.2)	0.3 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-4, 3	-3, 3
p-value compared with Group 3*	0.9615	0.5124	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	0.6 (1.1)	0.4 (1.4)	0.3 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 4	-4, 3	-4, 4
p-value compared with Group 3*	0.0472	0.4036	
Visit 6			
Number of available subjects	82	70	87
Mean (SD)	1.1 (1.4)	0.6 (1.4)	1.1 (1.3)

Table S23.7 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Increased Appetite, Hungry, Weight Problem (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	1.0	1.0	1.0
Minimum, maximum	-2, 4	-3, 4	-2, 4
p-value compared with Group 3*	0.9336	0.0740	
Visit 7			
Number of available subjects	69	55	67
Mean (SD)	1.1 (1.3)	0.8 (1.4)	1.1 (1.3)
Median	1.0	1.0	1.0
Minimum, maximum	-2, 4	-3, 4	0, 4
p-value compared with Group 3*	0.8022	0.2998	
Visit 8			
Number of available subjects	58	44	60
Mean (SD)	1.1 (1.4)	0.7 (1.5)	1.1 (1.3)
Median	1.0	1.0	1.0
Minimum, maximum	-2, 4	-3, 3	-2, 4
p-value compared with Group 3*	0.9956	0.1939	
0			
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	0.9 (1.0)	0.4 (1.4)	1.0 (1.4)
Median	1.0	0.0	1.0
Minimum, maximum	-2, 3	-3, 4	-3, 4
p-value compared with Group 3*	0.9310	0.0328	

Table S23.7 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Increased Appetite, Hungry, Weight Problem (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	1.0 (1.1)	0.3 (1.5)	1.0 (1.2)
Median	1.0	0.0	1.0
Minimum, maximum	-1, 3	-4, 4	-2, 4
p-value compared with Group 3*	0.9943	0.0176	
Visit 11			
Number of available subjects	45	37	46
Mean (SD)	0.8 (1.1)	0.3 (1.5)	0.8 (1.1)
Median	1.0	0.0	1.0
Minimum, maximum	-2, 3	-4, 3	-2, 4
p-value compared with Group 3*	0.9867	0.1246	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	0.8 (1.1)	0.4 (1.9)	0.7 (1.1)
Median	1.0	0.0	0.0
Minimum, maximum	-2, 3	-4, 3	-1, 3
p-value compared with Group 3*	0.3637	0.7762	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S23.8 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Desire or Craving to Smoke (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	108
Mean (SD)	-0.1 (1.2)	-0.0 (1.3)	-0.3 (1.3)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-3, 3	-4, 3
p-value compared with Group 3*	0.1310	0.1060	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.1 (1.3)	-0.2 (1.2)	-0.2 (1.3)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-3, 4	-4, 3
p-value compared with Group 3*	0.9008	0.5273	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-0.3 (1.4)	-0.5 (1.4)	-0.3 (1.4)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-4, 3	-4, 3
p-value compared with Group 3*	0.6655	0.4411	
Visit 6			
Number of available subjects	82	71	87
Mean (SD)	-0.3 (1.4)	-0.2 (1.5)	0.0 (1.7)

Table S23.8 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Desire or Craving to Smoke (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-3, 3	-4, 4
p-value compared with Group 3*	0.2270	0.3385	
Visit 7			
Number of available subjects	69	55	68
Mean (SD)	-0.6 (1.5)	-0.6 (1.5)	-0.2 (1.7)
Median	-1.0	-1.0	0.0
Minimum, maximum	-4, 4	-3, 3	-4, 3
p-value compared with Group 3*	0.2029	0.1349	
Visit 8			
Number of available subjects	58	44	60
Mean (SD)	-0.7 (1.6)	-0.7 (1.5)	-0.4 (1.8)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-4, 4	-3, 3	-4, 3
p-value compared with Group 3*	0.2634	0.3208	
Visit 9			
Number of available subjects	53	41	55
Mean (SD)	-0.8 (1.4)	-0.7 (1.4)	-0.5 (1.8)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-4, 3	-3, 3	-4, 4
p-value compared with Group 3*	0.3539	0.6743	

Table S23.8 Summary of Change From Baseline in Minnesota Nicotine Withdrawal Questionnaire – Desire or Craving to Smoke (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 110)	Group 3 (N = 114)
Visit 10			
Number of available subjects	49	39	52
Mean (SD)	-1.0 (1.2)	-1.0 (1.6)	-0.5 (1.6)
Median	-1.0	-1.0	0.0
Minimum, maximum	-4, 2	-4, 2	-3, 3
p-value compared with Group 3*	0.1154	0.1379	
Visit 11			
Number of available subjects	45	37	46
Mean (SD)	-1.0 (1.2)	-1.0 (1.6)	-0.6 (1.7)
Median	-1.0	-1.0	-0.5
Minimum, maximum	-4, 2	-4, 3	-4, 4
p-value compared with Group 3*	0.2011	0.3537	
Visit 12			
Number of available subjects	32	20	32
Mean (SD)	-1.3 (1.3)	-1.4 (1.6)	-0.5 (1.5)
Median	-1.0	-1.5	0.0
Minimum, maximum	-4, 1	-4, 2	-3, 3
p-value compared with Group 3*	0.0279	0.0625	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S24.1 Summary of Cigarette Evaluation Satisfaction Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	116	116	113
Mean (SD)	4.3 (1.4)	4.4 (1.4)	4.4 (1.1)
Median	4.5	4.5	4.0
Minimum, maximum	1, 7	1, 7	2, 7
p-value compared with Group 3*	0.7043	0.6965	
Visit 2			
Number of available subjects	116	116	114
Mean (SD)	4.2 (1.4)	4.4 (1.3)	4.2 (1.2)
Median	4.0	4.0	4.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.9473	0.2529	

Table S24.1 Summary of Cigarette Evaluation Satisfaction Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	3.4 (1.2)	3.5 (1.3)	3.5 (1.2)
Median	3.5	3.5	3.5
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.1375	0.5823	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	3.0 (1.3)	3.2 (1.1)	3.2 (1.2)
Median	3.0	3.0	3.0
Minimum, maximum	1, 6	1, 6	1, 6
p-value compared with Group 3*	0.0454	0.9150	
Visit 5			

Table S24.1 Summary of Cigarette Evaluation Satisfaction Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Number of available subjects	99	93	103
Mean (SD)	2.2 (1.1)	2.5 (1.2)	3.1 (1.3)
Median	2.0	2.0	3.0
Minimum, maximum	1, 6	1, 6	1, 7
p-value compared with Group 3*	<.0001	0.0006	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S24.2 Summary of Cigarette Evaluation Psychological Reward Scale (ITT Population)

	Group 1 (N = 110)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	116	116	113
Mean (SD)	3.1 (1.3)	2.8 (1.3)	3.0 (1.4)
Median	2.9	2.8	2.8
Minimum, maximum	1, 7	1, 7	1, 6
p-value compared with Group 3*	0.6466	0.3925	
Visit 2			
Number of available subjects	116	116	114
Mean (SD)	2.9 (1.3)	3.0 (1.3)	2.9 (1.2)
Median	2.8	3.0	2.7
Minimum, maximum	1, 7	1, 7	1, 6
p-value compared with Group 3*	0.7979	0.5049	

Table S24.2 Summary of Cigarette Evaluation Psychological Reward Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	2.4 (1.0)	2.5 (1.2)	2.4 (1.2)
Median	2.4	2.3	2.2
Minimum, maximum	1, 6	1, 7	1, 6
p-value compared with Group 3*	0.3957	0.4407	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	2.4 (1.0)	2.4 (1.1)	2.3 (1.0)
Median	2.2	2.2	2.2
Minimum, maximum	1, 6	1, 6	1, 6
p-value compared with Group 3*	0.3935	0.6497	
Visit 5			

Table S24.2 Summary of Cigarette Evaluation Psychological Reward Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Number of available subjects	99	93	103
Mean (SD)	1.9 (0.8)	2.0 (1.1)	2.2 (1.1)
Median	1.8	1.8	2.0
Minimum, maximum	1, 5	1, 7	1, 6
p-value compared with Group 3*	0.1926	0.2999	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S24.3 Summary of Cigarette Evaluation Nausea/Dizziness Scale (ITT Population)

	Group 1 (N = 118)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	116	116	113
Mean (SD)	1.2 (0.5)	1.3 (0.7)	1.3 (0.7)
Median	1.0	1.0	1.0
Minimum, maximum	1, 4	1, 7	1, 5
p-value compared with Group 3*	0.5670	0.8883	
Visit 2			
Number of available subjects	116	116	114
Mean (SD)	1.2 (0.5)	1.3 (0.7)	1.3 (0.6)
Median	1.0	1.0	1.0
Minimum, maximum	1, 5	1, 5	1, 4
p-value compared with Group 3*	0.3397	0.9298	

Table S24.3 Summary of Cigarette Evaluation Nausea/Dizziness Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	1.2 (0.5)	1.2 (0.6)	1.5 (0.9)
Median	1.0	1.0	1.0
Minimum, maximum	1, 4	1, 5	1, 7
p-value compared with Group 3*	0.0272	0.0048	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	1.3 (0.6)	1.2 (0.6)	1.4 (0.6)
Median	1.0	1.0	1.0
Minimum, maximum	1, 4	1, 4	1, 4
p-value compared with Group 3*	0.1338	0.0062	
Visit 5			

Table S24.3 Summary of Cigarette Evaluation Nausea/Dizziness Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Number of available subjects	99	93	103
Mean (SD)	1.3 (0.5)	1.2 (0.6)	1.3 (0.6)
Median	1.0	1.0	1.0
Minimum, maximum	1, 4	1, 4	1, 4
p-value compared with Group 3*	0.8197	0.1033	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S24.4 Summary of Cigarette Evaluation Enjoy Sensation Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 110)
Visit 1			
Number of available subjects	116	116	112
Mean (SD)	2.5 (1.6)	2.5 (1.7)	2.3 (1.4)
Median	2.0	2.0	2.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.7469	0.6783	
Visit 2			
Number of available subjects	116	116	113
Mean (SD)	2.6 (1.6)	2.8 (1.6)	2.7 (1.5)
Median	2.0	3.0	2.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.7550	0.6406	

Table S24.4 Summary of Cigarette Evaluation Enjoy Sensation Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	2.5 (1.3)	2.7 (1.5)	2.4 (1.4)
Median	2.0	3.0	2.0
Minimum, maximum	1, 6	1, 7	1, 6
p-value compared with Group 3*	0.3816	0.0845	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	2.5 (1.4)	2.5 (1.4)	2.6 (1.4)
Median	2.0	2.0	2.0
Minimum, maximum	1, 7	1, 7	1, 6
p-value compared with Group 3*	0.3478	0.5696	
Visit 5			

Table S24.4 Summary of Cigarette Evaluation Enjoy Sensation Scale (ITT Population)

	Group 1 (N = 118)	Group 2 (N = 116)	Group 3 (N = 114)
Number of available subjects	99	93	103
Mean (SD)	1.9 (1.0)	2.0 (1.3)	2.5 (1.3)
Median	2.0	2.0	2.0
Minimum, maximum	1, 6	1, 6	1, 7
p-value compared with Group 3*	0.0025	0.0078	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S24.5 Summary of Cigarette Evaluation Reduce Craving Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	111	113	108
Mean (SD)	4.3 (1.8)	4.6 (1.8)	4.2 (1.9)
Median	5.0	5.0	4.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.6917	0.0763	
Visit 2			
Number of available subjects	113	114	113
Mean (SD)	4.4 (1.5)	4.4 (1.6)	3.6 (1.7)
Median	4.0	4.0	4.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.0005	0.0012	

Table S24.5 Summary of Cigarette Evaluation Reduce Craving Scale (ITT Population)

	Group 1 (N = 118)	Group 2 (N = 118)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	3.5 (1.6)	3.5 (1.6)	3.5 (1.6)
Median	3.0	4.0	4.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.7349	0.9398	
Visit 4			
Number of available subjects	106	108	107
Mean (SD)	3.3 (1.5)	3.4 (1.6)	3.3 (1.6)
Median	3.0	3.0	3.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.8989	0.7320	
Visit 5			

Table S24.5 Summary of Cigarette Evaluation Reduce Craving Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Number of available subjects	99	93	103
Mean (SD)	2.8 (1.6)	2.9 (1.6)	3.3 (1.5)
Median	2.0	3.0	3.0
Minimum, maximum	1, 7	1, 7	1, 7
p-value compared with Group 3*	0.0096	0.0647	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S24.6 Summary of Cigarette Evaluation Scale – Was It Satisfying?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	3 (2.6%)	4 (3.4%)	14 (12.1%)	36 (31.0%)	31 (26.7%)	16 (13.8%)	12 (10.3%)	0.4118
	2	116	4 (3.4%)	4 (3.4%)	13 (11.2%)	35 (30.2%)	28 (24.1%)	17 (14.7%)	15 (12.9%)	0.6543
	3	112	1 (0.9%)	1 (0.9%)	11 (9.8%)	37 (33.0%)	33 (29.5%)	21 (18.8%)	8 (7.1%)	
2	1	116	2 (1.7%)	5 (4.3%)	16 (13.8%)	40 (34.5%)	29 (25.0%)	15 (12.9%)	9 (7.8%)	0.6984
	2	116	2 (1.7%)	3 (2.6%)	10 (8.6%)	44 (37.9%)	27 (23.3%)	18 (15.5%)	12 (10.3%)	0.1356
	3	113	3 (2.7%)	5 (4.4%)	16 (14.2%)	38 (33.6%)	32 (28.3%)	11 (9.7%)	8 (7.1%)	
3	1	112	2 (1.8%)	23 (20.5%)	29 (25.9%)	38 (33.9%)	11 (9.8%)	8 (7.1%)	1 (0.9%)	0.0618
	2	114	3 (2.6%)	19 (16.7%)	31 (27.2%)	40 (35.1%)	12 (10.5%)	4 (3.5%)	5 (4.4%)	0.1154
	3	108	8 (7.4%)	6 (5.6%)	24 (22.2%)	42 (38.9%)	22 (20.4%)	4 (3.7%)	2 (1.9%)	
4	1	106	10 (9.4%)	25 (23.6%)	34 (32.1%)	25 (23.6%)	6 (5.7%)	5 (4.7%)	1 (0.9%)	0.0209
	2	109	7 (6.4%)	16 (14.7%)	37 (33.9%)	35 (32.1%)	8 (7.3%)	5 (4.6%)	1 (0.9%)	0.5392
	3	107	9 (8.4%)	9 (8.4%)	38 (35.5%)	33 (30.8%)	15 (14.0%)	3 (2.8%)	0	
5	1	99	24 (24.2%)	33 (33.3%)	28 (28.3%)	10 (10.1%)	3 (3.0%)	1 (1.0%)	0	< .0001
	2	93	13 (14.0%)	37 (39.8%)	26 (28.0%)	7 (7.5%)	8 (8.6%)	2 (2.2%)	0	0.0003

**Table S24.6 Summary of Cigarette Evaluation Scale – Was It Satisfying?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	11 (10.7%)	18 (17.5%)	30 (29.1%)	27 (26.2%)	13 (12.6%)	3 (2.9%)	1 (1.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S24.7 Summary of Cigarette Evaluation Scale – Did It Taste Good?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	9 (7.8%)	14 (12.1%)	17 (14.7%)	28 (24.1%)	28 (24.1%)	10 (8.6%)	10 (8.6%)	0.9740
	2	116	8 (6.9%)	11 (9.5%)	13 (11.2%)	37 (31.9%)	24 (20.7%)	19 (16.4%)	4 (3.4%)	0.6226
	3	113	5 (4.4%)	11 (9.7%)	19 (16.8%)	39 (34.5%)	18 (15.9%)	14 (12.4%)	7 (6.2%)	
2	1	115	9 (7.8%)	15 (13.0%)	17 (14.8%)	35 (30.4%)	21 (18.3%)	9 (7.8%)	9 (7.8%)	0.8208
	2	116	7 (6.0%)	10 (8.6%)	19 (16.4%)	38 (32.8%)	22 (19.0%)	12 (10.3%)	8 (6.9%)	0.5411
	3	113	4 (3.5%)	10 (8.8%)	24 (21.2%)	39 (34.5%)	23 (20.4%)	7 (6.2%)	6 (5.3%)	
3	1	112	11 (9.8%)	29 (25.9%)	24 (21.4%)	34 (30.4%)	7 (6.3%)	6 (5.4%)	1 (0.9%)	0.4272
	2	114	12 (10.5%)	18 (15.8%)	32 (28.1%)	30 (26.3%)	12 (10.5%)	6 (5.3%)	4 (3.5%)	0.7310
	3	108	12 (11.1%)	19 (17.6%)	24 (22.2%)	39 (36.1%)	10 (9.3%)	2 (1.9%)	2 (1.9%)	
4	1	106	16 (15.1%)	34 (32.1%)	28 (26.4%)	13 (12.3%)	9 (8.5%)	6 (5.7%)	0	0.1722
	2	109	10 (9.2%)	25 (22.9%)	36 (33.0%)	24 (22.0%)	11 (10.1%)	3 (2.8%)	0	0.7643
	3	107	15 (14.0%)	24 (22.4%)	27 (25.2%)	28 (26.2%)	10 (9.3%)	3 (2.8%)	0	
5	1	99	36 (36.4%)	36 (36.4%)	15 (15.2%)	9 (9.1%)	2 (2.0%)	1 (1.0%)	0	< .0001
	2	93	27 (29.0%)	29 (31.2%)	21 (22.6%)	7 (7.5%)	7 (7.5%)	2 (2.2%)	0	0.0055

**Table S24.7 Summary of Cigarette Evaluation Scale – Did It Taste Good?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	18 (17.5%)	25 (24.3%)	26 (25.2%)	21 (20.4%)	8 (7.8%)	3 (2.9%)	2 (1.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S24.8 Summary of Cigarette Evaluation Scale – Did It Make You Dizzy?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[1]
1	1	116	99 (85.3%)	12 (10.3%)	4 (3.4%)	1 (0.9%)	0	0	0	0.6738
	2	116	103 (88.8%)	4 (3.4%)	4 (3.4%)	4 (3.4%)	0	0	1 (0.9%)	0.3263
	3	113	95 (84.1%)	8 (7.1%)	5 (4.4%)	3 (2.7%)	2 (1.8%)	0	0	
2	1	116	98 (84.5%)	12 (10.3%)	4 (3.4%)	2 (1.7%)	0	0	0	0.3189
	2	115	95 (82.6%)	10 (8.7%)	6 (5.2%)	3 (2.6%)	0	1 (0.9%)	0	0.6141
	3	114	91 (79.8%)	13 (11.4%)	5 (4.4%)	4 (3.5%)	0	1 (0.9%)	0	
3	1	112	97 (86.6%)	7 (6.3%)	8 (7.1%)	0	0	0	0	0.0146
	2	114	98 (86.0%)	6 (5.3%)	8 (7.0%)	2 (1.8%)	0	0	0	0.0255
	3	108	79 (73.1%)	17 (15.7%)	8 (7.4%)	3 (2.8%)	0	0	1 (0.9%)	
4	1	106	87 (82.1%)	11 (10.4%)	5 (4.7%)	3 (2.8%)	0	0	0	0.5959
	2	109	95 (87.2%)	7 (6.4%)	5 (4.6%)	2 (1.8%)	0	0	0	0.1284
	3	106	84 (79.2%)	12 (11.3%)	7 (6.6%)	3 (2.8%)	0	0	0	
5	1	99	86 (86.9%)	9 (9.1%)	2 (2.0%)	2 (2.0%)	0	0	0	0.1503
	2	92	81 (88.0%)	6 (6.5%)	5 (5.4%)	0	0	0	0	0.1092

**Table S24.8 Summary of Cigarette Evaluation Scale – Did It Make You Dizzy?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
3		101	80 (79.2%)	14 (13.9%)	5 (5.0%)	1 (1.0%)	0	1 (1.0%)	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S24.9 Summary of Cigarette Evaluation Scale – Did It Calm You Down?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	112	14 (12.5%)	14 (12.5%)	31 (27.7%)	24 (21.4%)	14 (12.5%)	7 (6.3%)	8 (7.1%)	0.2272
	2	115	18 (15.7%)	16 (13.9%)	27 (23.5%)	20 (17.4%)	17 (14.8%)	11 (9.6%)	6 (5.2%)	0.2025
	3	112	15 (13.4%)	12 (10.7%)	19 (17.0%)	26 (23.2%)	22 (19.6%)	14 (12.5%)	4 (3.6%)	
2	1	116	14 (12.1%)	23 (19.8%)	24 (20.7%)	32 (27.6%)	13 (11.2%)	7 (6.0%)	3 (2.6%)	0.5232
	2	116	11 (9.5%)	15 (12.9%)	25 (21.6%)	39 (33.6%)	15 (12.9%)	4 (3.4%)	7 (6.0%)	0.4529
	3	114	15 (13.2%)	13 (11.4%)	28 (24.6%)	35 (30.7%)	12 (10.5%)	6 (5.3%)	5 (4.4%)	
3	1	112	17 (15.2%)	22 (19.6%)	44 (39.3%)	19 (17.0%)	5 (4.5%)	5 (4.5%)	0	0.6716
	2	114	18 (15.8%)	16 (14.0%)	39 (34.2%)	28 (24.6%)	6 (5.3%)	3 (2.6%)	4 (3.5%)	0.5734
	3	108	22 (20.4%)	22 (20.4%)	23 (21.3%)	25 (23.1%)	8 (7.4%)	3 (2.8%)	5 (4.6%)	
4	1	106	14 (13.2%)	34 (32.1%)	35 (33.0%)	16 (15.1%)	4 (3.8%)	3 (2.8%)	0	0.9131
	2	108	15 (13.9%)	27 (25.0%)	41 (38.0%)	17 (15.7%)	4 (3.7%)	2 (1.9%)	2 (1.9%)	0.6598
	3	107	22 (20.6%)	23 (21.5%)	35 (32.7%)	18 (16.8%)	6 (5.6%)	2 (1.9%)	1 (0.9%)	
5	1	99	29 (29.3%)	33 (33.3%)	26 (26.3%)	7 (7.1%)	2 (2.0%)	0	2 (2.0%)	0.1747
	2	93	30 (32.3%)	29 (31.2%)	18 (19.4%)	9 (9.7%)	4 (4.3%)	1 (1.1%)	2 (2.2%)	0.2449

**Table S24.9 Summary of Cigarette Evaluation Scale – Did It Calm You Down?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	32 (31.1%)	21 (20.4%)	24 (23.3%)	17 (16.5%)	4 (3.9%)	5 (4.9%)	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S24.10 Summary of Cigarette Evaluation Scale – Did It Help You Concentrate?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
1	1	115	31 (27.0%)	18 (15.7%)	21 (18.3%)	27 (23.5%)	8 (7.0%)	5 (4.3%)	5 (4.3%)	0.2347
	2	116	46 (39.7%)	23 (19.8%)	16 (13.8%)	15 (12.9%)	6 (5.2%)	8 (6.9%)	2 (1.7%)	0.4019
	3	113	45 (39.8%)	13 (11.5%)	14 (12.4%)	20 (17.7%)	11 (9.7%)	7 (6.2%)	3 (2.7%)	
2	1	115	32 (27.8%)	22 (19.1%)	22 (19.1%)	27 (23.5%)	7 (6.1%)	3 (2.6%)	2 (1.7%)	0.9229
	2	116	35 (30.2%)	23 (19.8%)	25 (21.6%)	15 (12.9%)	12 (10.3%)	5 (4.3%)	1 (0.9%)	0.7881
	3	113	34 (30.1%)	22 (19.5%)	17 (15.0%)	26 (23.0%)	8 (7.1%)	3 (2.7%)	3 (2.7%)	
3	1	112	35 (31.3%)	22 (19.6%)	35 (31.3%)	13 (11.6%)	6 (5.4%)	1 (0.9%)	0	0.1813
	2	112	47 (42.0%)	21 (18.8%)	18 (16.1%)	17 (15.2%)	6 (5.4%)	0	3 (2.7%)	0.7870
	3	108	47 (43.5%)	18 (16.7%)	23 (21.3%)	11 (10.2%)	3 (2.8%)	3 (2.8%)	3 (2.8%)	
4	1	105	31 (29.5%)	30 (28.6%)	26 (24.8%)	14 (13.3%)	3 (2.9%)	1 (1.0%)	0	0.1476
	2	109	41 (37.6%)	23 (21.1%)	22 (20.2%)	17 (15.6%)	3 (2.8%)	3 (2.8%)	0	0.3647
	3	107	43 (40.2%)	28 (26.2%)	20 (18.7%)	10 (9.3%)	3 (2.8%)	3 (2.8%)	0	
5	1	99	43 (43.4%)	32 (32.3%)	18 (18.2%)	4 (4.0%)	1 (1.0%)	1 (1.0%)	0	0.6650
	2	92	44 (47.8%)	25 (27.2%)	13 (14.1%)	6 (6.5%)	3 (3.3%)	0	1 (1.1%)	0.5666

**Table S24.10 Summary of Cigarette Evaluation Scale – Did It Help You Concentrate?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	48 (46.6%)	23 (22.3%)	16 (15.5%)	11 (10.7%)	3 (2.9%)	2 (1.9%)	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S24.11 Summary of Cigarette Evaluation Scale – Did It Make You Feel More Awake? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	115	34 (29.6%)	17 (14.8%)	24 (20.9%)	22 (19.1%)	9 (7.8%)	5 (4.3%)	4 (3.5%)	0.3161
	2	116	46 (39.7%)	21 (18.1%)	14 (12.1%)	19 (16.4%)	10 (8.6%)	5 (4.3%)	1 (0.9%)	0.5155
	3	113	40 (35.4%)	20 (17.7%)	18 (15.9%)	17 (15.0%)	11 (9.7%)	5 (4.4%)	2 (1.8%)	
2	1	116	38 (32.8%)	21 (18.1%)	14 (12.1%)	23 (19.8%)	12 (10.3%)	6 (5.2%)	2 (1.7%)	0.8995
	2	116	30 (25.9%)	22 (19.0%)	21 (18.1%)	26 (22.4%)	10 (8.6%)	3 (2.6%)	4 (3.4%)	0.4894
	3	114	39 (34.2%)	14 (12.3%)	21 (18.4%)	22 (19.3%)	13 (11.4%)	4 (3.5%)	1 (0.9%)	
3	1	112	46 (41.1%)	25 (22.3%)	24 (21.4%)	9 (8.0%)	6 (5.4%)	2 (1.8%)	0	0.6167
	2	114	50 (43.9%)	18 (15.8%)	22 (19.3%)	18 (15.8%)	3 (2.6%)	0	3 (2.6%)	0.5531
	3	108	53 (49.1%)	18 (16.7%)	14 (13.0%)	13 (12.0%)	4 (3.7%)	3 (2.8%)	3 (2.8%)	
4	1	106	37 (34.9%)	37 (34.9%)	18 (17.0%)	9 (8.5%)	4 (3.8%)	1 (0.9%)	0	0.6875
	2	109	48 (44.0%)	21 (19.3%)	20 (18.3%)	12 (11.0%)	5 (4.6%)	2 (1.8%)	1 (0.9%)	0.8406
	3	107	48 (44.9%)	22 (20.6%)	16 (15.0%)	16 (15.0%)	4 (3.7%)	1 (0.9%)	0	
5	1	99	56 (56.6%)	23 (23.2%)	15 (15.2%)	3 (3.0%)	2 (2.0%)	0	0	0.1411
	2	93	51 (54.8%)	19 (20.4%)	13 (14.0%)	5 (5.4%)	3 (3.2%)	0	2 (2.2%)	0.4243

Table S24.11 Summary of Cigarette Evaluation Scale – Did It Make You Feel More Awake? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	51 (49.5%)	21 (20.4%)	18 (17.5%)	8 (7.8%)	4 (3.9%)	1 (1.0%)	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S24.12 Summary of Cigarette Evaluation Scale – Did It Reduce Your Hunger for Food? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	115	33 (28.7%)	12 (10.4%)	26 (22.6%)	22 (19.1%)	13 (11.3%)	4 (3.5%)	5 (4.3%)	0.6702
	2	116	44 (37.9%)	19 (16.4%)	14 (12.1%)	20 (17.2%)	12 (10.3%)	3 (2.6%)	4 (3.4%)	0.2845
	3	113	38 (33.6%)	13 (11.5%)	18 (15.9%)	23 (20.4%)	7 (6.2%)	10 (8.8%)	4 (3.5%)	
2	1	116	33 (28.4%)	15 (12.9%)	24 (20.7%)	27 (23.3%)	7 (6.0%)	6 (5.2%)	4 (3.4%)	0.7483
	2	116	29 (25.0%)	17 (14.7%)	25 (21.6%)	27 (23.3%)	9 (7.8%)	6 (5.2%)	3 (2.6%)	0.5059
	3	114	32 (28.1%)	15 (13.2%)	28 (24.6%)	24 (21.1%)	9 (7.9%)	4 (3.5%)	2 (1.8%)	
3	1	112	44 (39.3%)	24 (21.4%)	22 (19.6%)	15 (13.4%)	5 (4.5%)	1 (0.9%)	1 (0.9%)	0.4138
	2	113	43 (38.1%)	22 (19.5%)	25 (22.1%)	18 (15.9%)	3 (2.7%)	2 (1.8%)	0	0.2884
	3	108	50 (46.3%)	18 (16.7%)	20 (18.5%)	16 (14.8%)	3 (2.8%)	1 (0.9%)	0	
4	1	106	38 (35.8%)	28 (26.4%)	23 (21.7%)	11 (10.4%)	4 (3.8%)	1 (0.9%)	1 (0.9%)	0.8940
	2	109	42 (38.5%)	26 (23.9%)	19 (17.4%)	19 (17.4%)	2 (1.8%)	1 (0.9%)	0	0.9991
	3	107	43 (40.2%)	23 (21.5%)	20 (18.7%)	13 (12.1%)	6 (5.6%)	1 (0.9%)	1 (0.9%)	
5	1	99	53 (53.5%)	25 (25.3%)	14 (14.1%)	5 (5.1%)	2 (2.0%)	0	0	0.0487
	2	92	43 (46.7%)	24 (26.1%)	18 (19.6%)	6 (6.5%)	0	0	1 (1.1%)	0.2765

**Table S24.12 Summary of Cigarette Evaluation Scale – Did It Reduce Your Hunger for Food?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	47 (45.6%)	18 (17.5%)	18 (17.5%)	16 (15.5%)	3 (2.9%)	1 (1.0%)	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S24.13 Summary of Cigarette Evaluation Scale – Did It Make You Feel Nauseous?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	100 (86.2%)	10 (8.6%)	2 (1.7%)	3 (2.6%)	1 (0.9%)	0	0	0.4104
	2	116	102 (87.9%)	10 (8.6%)	0	0	1 (0.9%)	3 (2.6%)	0	0.6344
	3	113	102 (90.3%)	2 (1.8%)	5 (4.4%)	2 (1.8%)	2 (1.8%)	0	0	
2	1	116	107 (92.2%)	6 (5.2%)	1 (0.9%)	0	1 (0.9%)	0	1 (0.9%)	0.2579
	2	116	100 (86.2%)	9 (7.8%)	4 (3.4%)	2 (1.7%)	0	1 (0.9%)	0	0.7156
	3	114	100 (87.7%)	9 (7.9%)	2 (1.8%)	3 (2.6%)	0	0	0	
3	1	112	95 (84.8%)	9 (8.0%)	6 (5.4%)	2 (1.8%)	0	0	0	0.1190
	2	114	102 (89.5%)	5 (4.4%)	4 (3.5%)	2 (1.8%)	1 (0.9%)	0	0	0.0129
	3	108	83 (76.9%)	13 (12.0%)	5 (4.6%)	3 (2.8%)	2 (1.9%)	1 (0.9%)	1 (0.9%)	
4	1	106	89 (84.0%)	11 (10.4%)	3 (2.8%)	1 (0.9%)	0	2 (1.9%)	0	0.0973
	2	109	96 (88.1%)	5 (4.6%)	4 (3.7%)	4 (3.7%)	0	0	0	0.0176
	3	107	80 (74.8%)	16 (15.0%)	7 (6.5%)	2 (1.9%)	2 (1.9%)	0	0	
5	1	99	76 (76.8%)	10 (10.1%)	12 (12.1%)	1 (1.0%)	0	0	0	0.5387
	2	93	79 (84.9%)	6 (6.5%)	2 (2.2%)	4 (4.3%)	2 (2.2%)	0	0	0.4173

**Table S24.13 Summary of Cigarette Evaluation Scale – Did It Make You Feel Nauseous?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[*]
	3	103	82 (79.6%)	14 (13.6%)	4 (3.9%)	1 (1.0%)	2 (1.9%)	0	0	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S24.14 Summary of Cigarette Evaluation Scale – Did It Make You Feel Less Irritable? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p value*[a]
1	1	116	33 (28.4%)	15 (12.9%)	28 (24.1%)	22 (19.0%)	11 (9.5%)	2 (1.7%)	5 (4.3%)	0.9943
	2	114	37 (32.5%)	17 (14.9%)	21 (18.4%)	18 (15.8%)	6 (5.3%)	11 (9.6%)	4 (3.5%)	0.7916
	3	113	36 (31.9%)	14 (12.4%)	20 (17.7%)	23 (20.4%)	9 (8.0%)	7 (6.2%)	4 (3.5%)	
2	1	116	38 (32.8%)	16 (13.8%)	25 (21.6%)	18 (15.5%)	12 (10.3%)	5 (4.3%)	2 (1.7%)	0.3005
	2	116	38 (32.8%)	22 (19.0%)	19 (16.4%)	17 (14.7%)	9 (7.8%)	7 (6.0%)	4 (3.4%)	0.3930
	3	113	42 (37.2%)	16 (14.2%)	26 (23.0%)	16 (14.2%)	9 (8.0%)	2 (1.8%)	2 (1.8%)	
3	1	112	33 (29.5%)	31 (27.7%)	25 (22.3%)	17 (15.2%)	6 (5.4%)	0	0	0.4354
	2	113	48 (42.5%)	13 (11.5%)	19 (16.8%)	23 (20.4%)	7 (6.2%)	1 (0.9%)	2 (1.8%)	0.6444
	3	106	44 (41.5%)	17 (16.0%)	22 (20.8%)	14 (13.2%)	7 (6.6%)	1 (0.9%)	1 (0.9%)	
4	1	106	30 (28.3%)	28 (26.4%)	26 (24.5%)	18 (17.0%)	2 (1.9%)	1 (0.9%)	1 (0.9%)	0.1119
	2	108	35 (32.4%)	28 (25.9%)	26 (24.1%)	10 (9.3%)	4 (3.7%)	3 (2.8%)	2 (1.9%)	0.3331
	3	107	43 (40.2%)	19 (17.8%)	33 (30.8%)	8 (7.5%)	2 (1.9%)	2 (1.9%)	0	
5	1	99	39 (39.4%)	35 (35.4%)	18 (18.2%)	3 (3.0%)	3 (3.0%)	1 (1.0%)	0	0.8967
	2	93	41 (44.1%)	22 (23.7%)	19 (20.4%)	7 (7.5%)	2 (2.2%)	1 (1.1%)	1 (1.1%)	0.9904

**Table S24.14 Summary of Cigarette Evaluation Scale – Did It Make You Feel Less Irritable?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	47 (45.6%)	23 (22.3%)	17 (16.5%)	10 (9.7%)	2 (1.9%)	3 (2.9%)	1 (1.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S24.15 Summary of Cigarette Evaluation Scale – Did You Enjoy the Sensations in Your Throat? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	47 (40.5%)	21 (18.1%)	17 (14.7%)	17 (14.7%)	7 (6.0%)	4 (3.4%)	3 (2.6%)	0.7461
	2	116	47 (40.5%)	24 (20.7%)	9 (7.8%)	19 (16.4%)	9 (7.8%)	5 (4.3%)	3 (2.6%)	0.6775
	3	112	42 (37.5%)	28 (25.0%)	19 (17.0%)	13 (11.6%)	7 (6.3%)	2 (1.8%)	1 (0.9%)	
2	1	116	39 (33.6%)	23 (19.8%)	17 (14.7%)	25 (21.6%)	6 (5.2%)	4 (3.4%)	2 (1.7%)	0.7542
	2	116	34 (29.3%)	22 (19.0%)	20 (17.2%)	26 (22.4%)	5 (4.3%)	8 (6.9%)	1 (0.9%)	0.6399
	3	113	35 (31.0%)	22 (19.5%)	20 (17.7%)	24 (21.2%)	8 (7.1%)	3 (2.7%)	1 (0.9%)	
3	1	112	28 (25.0%)	36 (32.1%)	21 (18.8%)	20 (17.9%)	5 (4.5%)	2 (1.8%)	0	0.3811
	2	114	29 (25.4%)	25 (21.9%)	27 (23.7%)	22 (19.3%)	5 (4.4%)	4 (3.5%)	2 (1.8%)	0.0843
	3	108	40 (37.0%)	21 (19.4%)	22 (20.4%)	17 (15.7%)	6 (5.6%)	2 (1.9%)	0	
4	1	106	30 (28.3%)	35 (33.0%)	19 (17.9%)	11 (10.4%)	5 (4.7%)	5 (4.7%)	1 (0.9%)	0.3472
	2	109	30 (27.5%)	26 (23.9%)	34 (31.2%)	10 (9.2%)	4 (3.7%)	2 (1.8%)	3 (2.8%)	0.5689
	3	107	28 (26.2%)	29 (27.1%)	18 (16.8%)	24 (22.4%)	5 (4.7%)	3 (2.8%)	0	
5	1	99	38 (38.4%)	42 (42.4%)	10 (10.1%)	6 (6.1%)	2 (2.0%)	1 (1.0%)	0	0.0025
	2	93	43 (46.2%)	22 (23.7%)	18 (19.4%)	4 (4.3%)	4 (4.3%)	2 (2.2%)	0	0.0078

Table S24.15 Summary of Cigarette Evaluation Scale – Did You Enjoy the Sensations in Your Throat?
(ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	31 (30.1%)	24 (23.3%)	25 (24.3%)	16 (15.5%)	5 (4.9%)	1 (1.0%)	1 (1.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S24.16 Summary of Cigarette Evaluation Scale – Did It Immediately Reduce Your Craving for Cigarette? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	111	13 (11.7%)	6 (5.4%)	14 (12.6%)	20 (18.0%)	30 (27.0%)	15 (13.5%)	13 (11.7%)	0.6909
	2	113	12 (10.6%)	1 (0.9%)	12 (10.6%)	20 (17.7%)	32 (28.3%)	18 (15.9%)	18 (15.9%)	0.0762
	3	108	17 (15.7%)	7 (6.5%)	8 (7.4%)	23 (21.3%)	23 (21.3%)	22 (20.4%)	8 (7.4%)	
2	1	113	7 (6.2%)	2 (1.8%)	18 (15.9%)	32 (28.3%)	30 (26.5%)	11 (9.7%)	13 (11.5%)	0.0005
	2	114	8 (7.0%)	5 (4.4%)	18 (15.8%)	30 (26.3%)	24 (21.1%)	14 (12.3%)	15 (13.2%)	0.0012
	3	113	19 (16.8%)	10 (8.8%)	23 (20.4%)	24 (21.2%)	20 (17.7%)	14 (12.4%)	3 (2.7%)	
3	1	112	11 (9.8%)	22 (19.6%)	26 (23.2%)	26 (23.2%)	13 (11.6%)	9 (8.0%)	5 (4.5%)	0.7341
	2	114	17 (14.9%)	14 (12.3%)	22 (19.3%)	31 (27.2%)	16 (14.0%)	10 (8.8%)	4 (3.5%)	0.9389
	3	108	15 (13.9%)	13 (12.0%)	25 (23.1%)	27 (25.0%)	16 (14.8%)	5 (4.6%)	7 (6.5%)	
4	1	106	14 (13.2%)	18 (17.0%)	29 (27.4%)	26 (24.5%)	9 (8.5%)	7 (6.6%)	3 (2.8%)	0.8980
	2	108	14 (13.0%)	19 (17.6%)	28 (25.9%)	20 (18.5%)	15 (13.9%)	8 (7.4%)	4 (3.7%)	0.7312
	3	107	19 (17.8%)	17 (15.9%)	19 (17.8%)	30 (28.0%)	13 (12.1%)	6 (5.6%)	3 (2.8%)	
5	1	99	22 (22.2%)	32 (32.3%)	17 (17.2%)	14 (14.1%)	6 (6.1%)	6 (6.1%)	2 (2.0%)	0.0095
	2	93	18 (19.4%)	23 (24.7%)	26 (28.0%)	12 (12.9%)	7 (7.5%)	3 (3.2%)	4 (4.3%)	0.0645

Table S24.16 Summary of Cigarette Evaluation Scale – Did It Immediately Reduce Your Craving for Cigarette? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	14 (13.6%)	21 (20.4%)	23 (22.3%)	25 (24.3%)	13 (12.6%)	4 (3.9%)	3 (2.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S25.1 Summary of Change From Baseline in Cigarette Evaluation Satisfaction Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.8 (1.5)	-0.9 (1.6)	-0.7 (1.4)
Median	-1.0	-0.5	-0.5
Minimum, maximum	-5, 5	-6, 3	-5, 3
p-value compared with Group 3*	0.4917	0.4456	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-1.2 (1.7)	-1.1 (1.5)	-1.0 (1.4)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 4	-6, 2	-5, 2
p-value compared with Group 3*	0.1204	0.6843	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-1.9 (1.6)	-1.8 (1.5)	-1.1 (1.6)
Median	-1.5	-1.5	-1.0
Minimum, maximum	-6, 3	-5, 1	-6, 4
p-value compared with Group 3*	0.0004	0.0018	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S25.2 Summary of Change From Baseline in Cigarette Evaluation Psychological Reward Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.5 (1.1)	-0.5 (1.1)	-0.5 (1.1)
Median	-0.4	-0.2	-0.4
Minimum, maximum	-5, 2	-3, 2	-4, 3
p-value compared with Group 3*	0.8221	0.9100	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.6 (1.2)	-0.6 (1.1)	-0.6 (1.1)
Median	-0.4	-0.4	-0.4
Minimum, maximum	-4, 3	-4, 3	-4, 2
p-value compared with Group 3*	0.8465	0.7339	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-1.0 (1.3)	-0.9 (1.2)	-0.7 (1.3)
Median	-1.0	-0.8	-0.4
Minimum, maximum	-5, 2	-5, 2	-5, 3
p-value compared with Group 3*	0.0532	0.0915	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S25.3 Summary of Change From Baseline in Cigarette Evaluation Nausea/Dizziness Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.0 (0.7)	-0.0 (0.9)	0.2 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 2	-4, 4	-3, 6
p-value compared with Group 3*	0.5883	0.0332	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.1 (0.7)	-0.1 (0.8)	0.1 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 3	-4, 3	-3, 3
p-value compared with Group 3*	0.8492	0.0526	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	0.1 (0.7)	-0.0 (0.8)	0.0 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 3	-4, 3	-3, 3
p-value compared with Group 3*	0.2199	0.3770	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S25.4 Summary of Change From Baseline in Cigarette Evaluation Enjoy Sensation Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.1 (1.3)	-0.0 (1.4)	-0.3 (1.6)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-4, 3	-6, 4
p-value compared with Group 3*	0.3456	0.2606	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.1 (1.4)	-0.2 (1.7)	-0.1 (1.4)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-5, 4	-4, 4
p-value compared with Group 3*	0.8072	0.6596	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-0.6 (1.6)	-0.7 (1.6)	-0.2 (1.5)
Median	0.0	-1.0	0.0
Minimum, maximum	-6, 3	-5, 4	-4, 3
p-value compared with Group 3*	0.1824	0.0340	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S25.5 Summary of Change From Baseline in Cigarette Evaluation Reduce Craving Scale (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	110	114	108
Mean (SD)	-0.9 (1.9)	-0.9 (1.9)	-0.1 (1.6)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 4	-6, 6	-6, 3
p-value compared with Group 3*	0.0016	0.0006	
Visit 4			
Number of available subjects	104	108	107
Mean (SD)	-1.1 (2.0)	-1.1 (2.1)	-0.3 (1.7)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 4	-6, 6	-6, 3
p-value compared with Group 3*	0.0016	0.0010	
Visit 5			
Number of available subjects	98	93	103
Mean (SD)	-1.7 (2.1)	-1.6 (2.1)	-0.4 (2.0)
Median	-2.0	-1.0	0.0
Minimum, maximum	-6, 3	-6, 6	-5, 6
p-value compared with Group 3*	<.0001	<.0001	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.6 Summary of Change From Baseline in Cigarette Evaluation Scale – Was It Satisfying?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 118)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.9 (1.6)	-1.0 (1.7)	-0.6 (1.6)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 5	-6, 3	-6, 3
p-value compared with Group 3*	0.2015	0.0945	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-1.4 (1.7)	-1.3 (1.5)	-1.0 (1.6)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-6, 4	-5, 2	-6, 3
p-value compared with Group 3*	0.0340	0.2291	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-2.1 (1.7)	-2.0 (1.4)	-1.1 (1.7)
Median	-2.0	-2.0	-1.0
Minimum, maximum	-6, 3	-5, 1	-6, 4
p-value compared with Group 3*	<.0001	0.0003	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.7 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Taste Good?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.8 (1.6)	-0.7 (1.8)	-0.8 (1.5)
Median	-1.0	-0.5	-1.0
Minimum, maximum	-5, 5	-6, 4	-4, 3
p-value compared with Group 3*	0.8332	0.7944	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-1.1 (1.8)	-1.0 (1.7)	-1.0 (1.5)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 5	-6, 3	-5, 4
p-value compared with Group 3*	0.4359	0.6881	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-1.8 (1.8)	-1.7 (1.7)	-1.1 (1.7)
Median	-2.0	-1.0	-1.0
Minimum, maximum	-6, 3	-6, 2	-6, 5
p-value compared with Group 3*	0.0058	0.0268	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.8 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Make You Dizzy?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 118)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.0 (0.7)	-0.1 (0.9)	0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 2	-4, 3	-3, 6
p-value compared with Group 3*	0.6493	0.2496	
Visit 4			
Number of available subjects	106	109	106
Mean (SD)	0.1 (0.9)	-0.1 (1.0)	-0.0 (0.9)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 3	-5, 3	-3, 3
p-value compared with Group 3*	0.3181	0.7733	
Visit 5			
Number of available subjects	99	92	101
Mean (SD)	-0.0 (0.6)	-0.1 (0.7)	-0.1 (1.1)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 3	-3, 2	-5, 5
p-value compared with Group 3*	0.5326	0.8467	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.9 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Calm You Down?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.5 (1.5)	-0.5 (1.4)	-0.5 (1.6)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 3	-4, 2	-6, 4
p-value compared with Group 3*	0.8137	0.9526	
Visit 4			
Number of available subjects	106	108	107
Mean (SD)	-0.6 (1.7)	-0.8 (1.4)	-0.7 (1.5)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 4	-4, 3	-5, 3
p-value compared with Group 3*	0.7815	0.3567	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-1.0 (1.8)	-1.3 (1.6)	-0.9 (1.8)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 4	-6, 3	-6, 3
p-value compared with Group 3*	0.2652	0.0810	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.10 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Help You Concentrate?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	112	108
Mean (SD)	-0.3 (1.4)	-0.4 (1.5)	-0.5 (1.8)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 3	-5, 4	-6, 6
p-value compared with Group 3*	0.2632	0.5843	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-0.5 (1.4)	-0.4 (1.4)	-0.6 (1.5)
Median	0.0	0.0	0.0
Minimum, maximum	-5, 3	-4, 3	-6, 3
p-value compared with Group 3*	0.6610	0.2725	
Visit 5			
Number of available subjects	99	92	103
Mean (SD)	-0.8 (1.5)	-0.7 (1.5)	-0.7 (1.6)
Median	-1.0	0.0	0.0
Minimum, maximum	-5, 3	-5, 3	-6, 3
p-value compared with Group 3*	0.2195	0.7403	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.11 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Make You Feel More Awake?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.6 (1.4)	-0.6 (1.6)	-0.5 (1.6)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 3	-6, 4	-5, 5
p-value compared with Group 3*	0.8828	0.5448	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.6 (1.5)	-0.7 (1.5)	-0.6 (1.5)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 2	-6, 4	-5, 3
p-value compared with Group 3*	0.7883	0.6530	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-1.0 (1.7)	-1.0 (1.6)	-0.8 (1.5)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 2	-5, 4	-5, 3
p-value compared with Group 3*	0.2859	0.2202	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.12 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Reduce Your Hunger for Food?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	108
Mean (SD)	-0.7 (1.5)	-0.7 (1.4)	-0.7 (1.5)
Median	0.0	0.0	-1.0
Minimum, maximum	-6, 4	-4, 3	-5, 3
p-value compared with Group 3*	0.8533	0.7050	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.8 (1.7)	-0.8 (1.6)	-0.6 (1.6)
Median	0.0	-1.0	0.0
Minimum, maximum	-6, 3	-5, 3	-5, 4
p-value compared with Group 3*	0.5348	0.4717	
Visit 5			
Number of available subjects	99	92	103
Mean (SD)	-1.2 (1.5)	-1.0 (1.7)	-0.7 (1.7)
Median	-1.0	-1.0	0.0
Minimum, maximum	-5, 2	-6, 6	-6, 3
p-value compared with Group 3*	0.0300	0.1835	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.13 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Make You Feel Nauseous?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.1 (1.0)	-0.0 (1.0)	0.3 (1.3)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 3	-5, 4	-3, 6
p-value compared with Group 3*	0.5518	0.0262	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.1 (0.8)	-0.0 (0.9)	0.2 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 5	-5, 3	-3, 4
p-value compared with Group 3*	0.3160	0.0220	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	0.2 (1.1)	0.1 (1.1)	0.1 (0.8)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 3	-5, 4	-3, 4
p-value compared with Group 3*	0.2277	0.3533	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

**Table S25.14 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Make You Feel Less Irritable?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	106
Mean (SD)	-0.4 (1.6)	-0.3 (1.8)	-0.2 (1.5)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 4	-6, 3	-4, 4
p-value compared with Group 3*	0.4404	0.8938	
Visit 4			
Number of available subjects	106	108	107
Mean (SD)	-0.4 (1.7)	-0.4 (1.8)	-0.3 (1.5)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 3	-6, 3	-4, 4
p-value compared with Group 3*	0.9754	0.7504	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-0.8 (1.8)	-0.7 (1.6)	-0.4 (1.9)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 4	-6, 3	-6, 6
p-value compared with Group 3*	0.1861	0.2036	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S25.15 Summary of Change From Baseline in Cigarette Evaluation Scale – Did You Enjoy the Sensations in Your Throat? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.1 (1.3)	-0.0 (1.4)	-0.3 (1.6)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 4	-4, 3	-6, 4
p-value compared with Group 3*	0.3456	0.2606	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.1 (1.4)	-0.2 (1.7)	-0.1 (1.4)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 4	-5, 4	-4, 4
p-value compared with Group 3*	0.8072	0.6596	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-0.6 (1.6)	-0.7 (1.6)	-0.2 (1.5)
Median	0.0	-1.0	0.0
Minimum, maximum	-6, 3	-5, 4	-4, 3
p-value compared with Group 3*	0.1824	0.0340	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S25.16 Summary of Change From Baseline in Cigarette Evaluation Scale – Did It Immediately Reduce Your Craving for Cigarette? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	110	114	108
Mean (SD)	-0.9 (1.9)	-0.9 (1.9)	-0.1 (1.6)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 4	-6, 6	-6, 3
p-value compared with Group 3*	0.0016	0.0006	
Visit 4			
Number of available subjects	104	108	107
Mean (SD)	-1.1 (2.0)	-1.1 (2.1)	-0.3 (1.7)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 4	-6, 6	-6, 3
p-value compared with Group 3*	0.0016	0.0010	
Visit 5			
Number of available subjects	98	93	103
Mean (SD)	-1.7 (2.1)	-1.6 (2.1)	-0.4 (2.0)
Median	-2.0	-1.0	0.0
Minimum, maximum	-6, 3	-6, 6	-5, 6
p-value compared with Group 3*	<.0001	<.0001	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S26.1 Summary of Sensory Questionnaire – How Much Did You Like the Puffs of Your Last Cigarette? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	3 (2.6%)	8 (6.9%)	18 (15.5%)	35 (30.2%)	30 (25.9%)	13 (11.2%)	9 (7.8%)	0.2653
	2	116	3 (2.6%)	6 (5.2%)	12 (10.3%)	38 (32.8%)	31 (26.7%)	14 (12.1%)	12 (10.3%)	0.9785
	3	112	2 (1.8%)	2 (1.8%)	17 (15.2%)	32 (28.6%)	38 (33.9%)	14 (12.5%)	7 (6.3%)	
2	1	116	1 (0.9%)	10 (8.6%)	24 (20.7%)	37 (31.9%)	23 (19.8%)	16 (13.8%)	5 (4.3%)	0.9583
	2	116	2 (1.7%)	8 (6.9%)	14 (12.1%)	45 (38.8%)	25 (21.6%)	14 (12.1%)	8 (6.9%)	0.2998
	3	113	4 (3.5%)	5 (4.4%)	25 (22.1%)	35 (31.0%)	28 (24.8%)	10 (8.8%)	6 (5.3%)	
3	1	112	3 (2.7%)	22 (19.6%)	27 (24.1%)	42 (37.5%)	12 (10.7%)	4 (3.6%)	2 (1.8%)	0.6439
	2	114	5 (4.4%)	15 (13.2%)	28 (24.6%)	40 (35.1%)	15 (13.2%)	7 (6.1%)	4 (3.5%)	0.1423
	3	108	8 (7.4%)	20 (18.5%)	26 (24.1%)	35 (32.4%)	9 (8.3%)	7 (6.5%)	3 (2.8%)	
4	1	105	5 (4.8%)	24 (22.9%)	42 (40.0%)	23 (21.9%)	8 (7.6%)	3 (2.9%)	0	0.1010
	2	109	8 (7.3%)	27 (24.8%)	32 (29.4%)	28 (25.7%)	6 (5.5%)	6 (5.5%)	2 (1.8%)	0.1909
	3	107	7 (6.5%)	18 (16.8%)	34 (31.8%)	28 (26.2%)	15 (14.0%)	3 (2.8%)	2 (1.9%)	
5	1	99	22 (22.2%)	39 (39.4%)	21 (21.2%)	12 (12.1%)	2 (2.0%)	3 (3.0%)	0	< .0001
	2	94	25 (26.6%)	22 (23.4%)	24 (25.5%)	14 (14.9%)	6 (6.4%)	1 (1.1%)	2 (2.1%)	0.0011

Table S26.1 Summary of Sensory Questionnaire – How Much Did You Like the Puffs of Your Last Cigarette? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	9 (8.7%)	25 (24.3%)	24 (23.3%)	29 (28.2%)	12 (11.7%)	2 (1.9%)	2 (1.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S26.2 Summary of Sensory Questionnaire – How Satisfying Were the Puffs of Your Last Cigarette? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	1 (0.9%)	7 (6.0%)	18 (15.5%)	37 (31.9%)	30 (25.9%)	15 (12.9%)	8 (6.9%)	0.3566
	2	116	2 (1.7%)	8 (6.9%)	14 (12.1%)	36 (31.0%)	28 (24.1%)	15 (12.9%)	13 (11.2%)	0.8069
	3	112	1 (0.9%)	4 (3.6%)	13 (11.6%)	34 (30.4%)	40 (35.7%)	15 (13.4%)	5 (4.5%)	
2	1	116	2 (1.7%)	5 (4.3%)	22 (19.0%)	39 (33.6%)	29 (25.0%)	13 (11.2%)	6 (5.2%)	0.6750
	2	116	2 (1.7%)	8 (6.9%)	11 (9.5%)	46 (39.7%)	28 (24.1%)	13 (11.2%)	8 (6.9%)	0.3048
	3	113	3 (2.7%)	7 (6.2%)	17 (15.0%)	42 (37.2%)	29 (25.7%)	12 (10.6%)	3 (2.7%)	
3	1	112	4 (3.6%)	27 (24.1%)	23 (20.5%)	40 (35.7%)	11 (9.8%)	4 (3.6%)	3 (2.7%)	0.4283
	2	114	4 (3.5%)	17 (14.9%)	27 (23.7%)	42 (36.8%)	12 (10.5%)	9 (7.9%)	3 (2.6%)	0.5473
	3	108	8 (7.4%)	10 (9.3%)	32 (29.6%)	39 (36.1%)	10 (9.3%)	5 (4.6%)	4 (3.7%)	
4	1	105	6 (5.7%)	29 (27.6%)	34 (32.4%)	24 (22.9%)	6 (5.7%)	5 (4.8%)	1 (1.0%)	0.0509
	2	109	4 (3.7%)	28 (25.7%)	38 (34.9%)	24 (22.0%)	7 (6.4%)	5 (4.6%)	3 (2.8%)	0.1701
	3	107	6 (5.6%)	19 (17.8%)	32 (29.9%)	30 (28.0%)	13 (12.1%)	6 (5.6%)	1 (0.9%)	
5	1	99	25 (25.3%)	33 (33.3%)	26 (26.3%)	10 (10.1%)	2 (2.0%)	3 (3.0%)	0	< .0001
	2	94	19 (20.2%)	26 (27.7%)	27 (28.7%)	14 (14.9%)	5 (5.3%)	2 (2.1%)	1 (1.1%)	0.0084

Table S26.2 Summary of Sensory Questionnaire – How Satisfying Were the Puffs of Your Last Cigarette? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	9 (8.7%)	27 (26.2%)	26 (25.2%)	26 (25.2%)	11 (10.7%)	3 (2.9%)	1 (1.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S26.3 Summary of Sensory Questionnaire – How High in Nicotine Do You Think the Puffs Were? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
1	1	116	1 (0.9%)	2 (1.7%)	13 (11.2%)	48 (41.4%)	30 (25.9%)	15 (12.9%)	7 (6.0%)	0.6430
	2	116	2 (1.7%)	1 (0.9%)	9 (7.8%)	55 (47.4%)	28 (24.1%)	12 (10.3%)	9 (7.8%)	0.5994
	3	111	1 (0.9%)	1 (0.9%)	12 (10.8%)	40 (36.0%)	41 (36.9%)	9 (8.1%)	7 (6.3%)	
2	1	115	0	2 (1.7%)	9 (7.8%)	54 (47.0%)	30 (26.1%)	13 (11.3%)	7 (6.1%)	0.8920
	2	116	0	2 (1.7%)	13 (11.2%)	46 (39.7%)	31 (26.7%)	16 (13.8%)	8 (6.9%)	0.6347
	3	112	1 (0.9%)	2 (1.8%)	9 (8.0%)	51 (45.5%)	30 (26.8%)	14 (12.5%)	5 (4.5%)	
3	1	112	3 (2.7%)	35 (31.3%)	29 (25.9%)	33 (29.5%)	7 (6.3%)	2 (1.8%)	3 (2.7%)	0.0106
	2	114	3 (2.6%)	34 (29.8%)	35 (30.7%)	36 (31.6%)	3 (2.6%)	2 (1.8%)	1 (0.9%)	0.0015
	3	108	3 (2.8%)	19 (17.6%)	26 (24.1%)	40 (37.0%)	11 (10.2%)	8 (7.4%)	1 (0.9%)	
4	1	105	11 (10.5%)	56 (53.3%)	16 (15.2%)	17 (16.2%)	4 (3.8%)	1 (1.0%)	0	< .0001
	2	109	5 (4.6%)	55 (50.5%)	26 (23.9%)	19 (17.4%)	3 (2.8%)	1 (0.9%)	0	< .0001
	3	107	4 (3.7%)	24 (22.4%)	28 (26.2%)	39 (36.4%)	6 (5.6%)	4 (3.7%)	2 (1.9%)	
5	1	99	37 (37.4%)	42 (42.4%)	9 (9.1%)	5 (5.1%)	3 (3.0%)	3 (3.0%)	0	< .0001
	2	94	34 (36.2%)	36 (38.3%)	8 (8.5%)	11 (11.7%)	3 (3.2%)	0	2 (2.1%)	< .0001

Table S26.3 Summary of Sensory Questionnaire – How High in Nicotine Do You Think the Puffs Were? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	10 (9.7%)	31 (30.1%)	24 (23.3%)	25 (24.3%)	9 (8.7%)	3 (2.9%)	1 (1.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S26.4 Summary of Sensory Questionnaire – How Similar to Your Own Brand Were These Puffs? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	6	3 (50.0%)	0	0	0	1 (16.7%)	0	2 (33.3%)	0.5066
	2	4	0	0	0	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	0.7645
	3	4	0	0	0	1 (25.0%)	2 (50.0%)	0	1 (25.0%)	
2	1	5	1 (20.0%)	0	0	0	0	1 (20.0%)	3 (60.0%)	0.6001
	2	4	0	0	0	0	2 (50.0%)	0	2 (50.0%)	0.4184
	3	7	0	0	0	3 (42.9%)	1 (14.3%)	0	3 (42.9%)	
3	1	112	32 (28.6%)	20 (17.9%)	26 (23.2%)	11 (9.8%)	12 (10.7%)	9 (8.0%)	2 (1.8%)	0.0889
	2	114	23 (20.2%)	35 (30.7%)	28 (24.6%)	7 (6.1%)	14 (12.3%)	5 (4.4%)	2 (1.8%)	0.0343
	3	108	18 (16.7%)	19 (17.6%)	30 (27.8%)	17 (15.7%)	15 (13.9%)	8 (7.4%)	1 (0.9%)	
4	1	105	41 (39.0%)	29 (27.6%)	20 (19.0%)	6 (5.7%)	6 (5.7%)	2 (1.9%)	1 (1.0%)	0.0022
	2	108	39 (36.1%)	28 (25.9%)	22 (20.4%)	12 (11.1%)	5 (4.6%)	1 (0.9%)	1 (0.9%)	0.0119
	3	107	25 (23.4%)	25 (23.4%)	27 (25.2%)	17 (15.9%)	9 (8.4%)	3 (2.8%)	1 (0.9%)	
5	1	98	65 (66.3%)	12 (12.2%)	12 (12.2%)	5 (5.1%)	2 (2.0%)	2 (2.0%)	0	< .0001
	2	94	53 (56.4%)	20 (21.3%)	8 (8.5%)	4 (4.3%)	5 (5.3%)	0	4 (4.3%)	0.0004

Table S26.4 Summary of Sensory Questionnaire – How Similar to Your Own Brand Were These Puffs? (ITT Population)

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	33 (32.0%)	20 (19.4%)	26 (25.2%)	13 (12.6%)	7 (6.8%)	2 (1.9%)	2 (1.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S26.5 Summary of Sensory Questionnaire – Strength of Puffs on Tongue?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	11 (9.5%)	12 (10.3%)	27 (23.3%)	39 (33.6%)	21 (18.1%)	3 (2.6%)	3 (2.6%)	0.8449
	2	116	11 (9.5%)	16 (13.8%)	18 (15.5%)	47 (40.5%)	15 (12.9%)	7 (6.0%)	2 (1.7%)	0.8230
	3	113	7 (6.2%)	21 (18.6%)	19 (16.8%)	43 (38.1%)	16 (14.2%)	4 (3.5%)	3 (2.7%)	
2	1	115	11 (9.6%)	14 (12.2%)	29 (25.2%)	35 (30.4%)	20 (17.4%)	5 (4.3%)	1 (0.9%)	0.8637
	2	116	6 (5.2%)	16 (13.8%)	23 (19.8%)	46 (39.7%)	16 (13.8%)	8 (6.9%)	1 (0.9%)	0.4310
	3	114	7 (6.1%)	13 (11.4%)	34 (29.8%)	38 (33.3%)	12 (10.5%)	9 (7.9%)	1 (0.9%)	
3	1	112	8 (7.1%)	42 (37.5%)	33 (29.5%)	22 (19.6%)	3 (2.7%)	3 (2.7%)	1 (0.9%)	0.0163
	2	114	11 (9.6%)	30 (26.3%)	36 (31.6%)	25 (21.9%)	8 (7.0%)	2 (1.8%)	2 (1.8%)	0.1976
	3	108	10 (9.3%)	24 (22.2%)	29 (26.9%)	27 (25.0%)	11 (10.2%)	4 (3.7%)	3 (2.8%)	
4	1	105	12 (11.4%)	41 (39.0%)	33 (31.4%)	15 (14.3%)	3 (2.9%)	0	1 (1.0%)	0.0009
	2	109	7 (6.4%)	37 (33.9%)	30 (27.5%)	23 (21.1%)	7 (6.4%)	4 (3.7%)	1 (0.9%)	0.3234
	3	107	6 (5.6%)	30 (28.0%)	30 (28.0%)	28 (26.2%)	11 (10.3%)	1 (0.9%)	1 (0.9%)	
5	1	99	17 (17.2%)	46 (46.5%)	19 (19.2%)	11 (11.1%)	3 (3.0%)	2 (2.0%)	1 (1.0%)	0.0041
	2	94	19 (20.2%)	29 (30.9%)	26 (27.7%)	11 (11.7%)	8 (8.5%)	1 (1.1%)	0	0.0741

**Table S26.5 Summary of Sensory Questionnaire – Strength of Puffs on Tongue?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	14 (13.6%)	29 (28.2%)	24 (23.3%)	26 (25.2%)	8 (7.8%)	0	2 (1.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S26.6 Summary of Sensory Questionnaire – Strength of Puffs in Nose?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	21 (18.1%)	28 (24.1%)	27 (23.3%)	30 (25.9%)	6 (5.2%)	2 (1.7%)	2 (1.7%)	0.9527
	2	116	25 (21.6%)	25 (21.6%)	20 (17.2%)	33 (28.4%)	10 (8.6%)	3 (2.6%)	0	0.8094
	3	113	22 (19.5%)	26 (23.0%)	26 (23.0%)	28 (24.8%)	9 (8.0%)	0	2 (1.8%)	
2	1	115	19 (16.5%)	34 (29.6%)	25 (21.7%)	21 (18.3%)	14 (12.2%)	2 (1.7%)	0	0.8436
	2	116	14 (12.1%)	25 (21.6%)	28 (24.1%)	34 (29.3%)	10 (8.6%)	5 (4.3%)	0	0.0563
	3	114	22 (19.3%)	28 (24.6%)	27 (23.7%)	28 (24.6%)	4 (3.5%)	4 (3.5%)	1 (0.9%)	
3	1	112	22 (19.6%)	50 (44.6%)	25 (22.3%)	12 (10.7%)	1 (0.9%)	2 (1.8%)	0	0.6266
	2	113	21 (18.6%)	44 (38.9%)	26 (23.0%)	17 (15.0%)	4 (3.5%)	0	1 (0.9%)	0.6729
	3	108	31 (28.7%)	27 (25.0%)	29 (26.9%)	15 (13.9%)	3 (2.8%)	1 (0.9%)	2 (1.9%)	
4	1	105	22 (21.0%)	47 (44.8%)	23 (21.9%)	10 (9.5%)	3 (2.9%)	0	0	0.1168
	2	108	19 (17.6%)	41 (38.0%)	28 (25.9%)	15 (13.9%)	3 (2.8%)	2 (1.9%)	0	0.8318
	3	107	23 (21.5%)	34 (31.8%)	24 (22.4%)	21 (19.6%)	3 (2.8%)	1 (0.9%)	1 (0.9%)	
5	1	99	31 (31.3%)	42 (42.4%)	14 (14.1%)	7 (7.1%)	2 (2.0%)	2 (2.0%)	1 (1.0%)	0.0279
	2	94	22 (23.4%)	40 (42.6%)	16 (17.0%)	11 (11.7%)	4 (4.3%)	1 (1.1%)	0	0.3474

**Table S26.6 Summary of Sensory Questionnaire – Strength of Puffs in Nose?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	30 (29.1%)	22 (21.4%)	26 (25.2%)	20 (19.4%)	3 (2.9%)	1 (1.0%)	1 (1.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S26.7 Summary of Sensory Questionnaire – Strength of Puffs in Back of Mouth and Throat?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
1	1	116	7 (6.0%)	9 (7.8%)	23 (19.8%)	44 (37.9%)	22 (19.0%)	8 (6.9%)	3 (2.6%)	0.8462
	2	116	9 (7.8%)	8 (6.9%)	19 (16.4%)	39 (33.6%)	28 (24.1%)	11 (9.5%)	2 (1.7%)	0.6201
	3	113	8 (7.1%)	11 (9.7%)	18 (15.9%)	41 (36.3%)	23 (20.4%)	7 (6.2%)	5 (4.4%)	
2	1	115	7 (6.1%)	11 (9.6%)	25 (21.7%)	44 (38.3%)	20 (17.4%)	7 (6.1%)	1 (0.9%)	0.9967
	2	116	4 (3.4%)	9 (7.8%)	19 (16.4%)	46 (39.7%)	20 (17.2%)	16 (13.8%)	2 (1.7%)	0.0524
	3	114	4 (3.5%)	15 (13.2%)	23 (20.2%)	47 (41.2%)	13 (11.4%)	10 (8.8%)	2 (1.8%)	
3	1	112	5 (4.5%)	36 (32.1%)	36 (32.1%)	27 (24.1%)	5 (4.5%)	2 (1.8%)	1 (0.9%)	0.0023
	2	114	11 (9.6%)	25 (21.9%)	28 (24.6%)	35 (30.7%)	12 (10.5%)	0	3 (2.6%)	0.0595
	3	107	11 (10.3%)	17 (15.9%)	23 (21.5%)	25 (23.4%)	20 (18.7%)	7 (6.5%)	4 (3.7%)	
4	1	105	5 (4.8%)	41 (39.0%)	34 (32.4%)	17 (16.2%)	4 (3.8%)	3 (2.9%)	1 (1.0%)	0.0004
	2	109	4 (3.7%)	33 (30.3%)	28 (25.7%)	24 (22.0%)	14 (12.8%)	4 (3.7%)	2 (1.8%)	0.2862
	3	107	7 (6.5%)	18 (16.8%)	31 (29.0%)	33 (30.8%)	10 (9.3%)	7 (6.5%)	1 (0.9%)	
5	1	99	18 (18.2%)	35 (35.4%)	22 (22.2%)	12 (12.1%)	8 (8.1%)	3 (3.0%)	1 (1.0%)	0.0482
	2	94	18 (19.1%)	27 (28.7%)	26 (27.7%)	11 (11.7%)	7 (7.4%)	5 (5.3%)	0	0.1057

**Table S26.7 Summary of Sensory Questionnaire – Strength of Puffs in Back of Mouth and Throat?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	18 (17.5%)	19 (18.4%)	28 (27.2%)	22 (21.4%)	11 (10.7%)	2 (1.9%)	3 (2.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S26.8 Summary of Sensory Questionnaire – Strength of Puffs in Windpipe?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	8 (6.9%)	7 (6.0%)	24 (20.7%)	38 (32.8%)	25 (21.6%)	8 (6.9%)	6 (5.2%)	0.3075
	2	116	10 (8.6%)	6 (5.2%)	15 (12.9%)	47 (40.5%)	27 (23.3%)	9 (7.8%)	2 (1.7%)	0.1903
	3	113	9 (8.0%)	12 (10.6%)	17 (15.0%)	48 (42.5%)	15 (13.3%)	8 (7.1%)	4 (3.5%)	
2	1	115	4 (3.5%)	13 (11.3%)	21 (18.3%)	41 (35.7%)	27 (23.5%)	8 (7.0%)	1 (0.9%)	0.0525
	2	116	2 (1.7%)	7 (6.0%)	22 (19.0%)	52 (44.8%)	18 (15.5%)	14 (12.1%)	1 (0.9%)	0.0050
	3	114	6 (5.3%)	19 (16.7%)	24 (21.1%)	43 (37.7%)	12 (10.5%)	6 (5.3%)	4 (3.5%)	
3	1	112	7 (6.3%)	37 (33.0%)	24 (21.4%)	33 (29.5%)	7 (6.3%)	3 (2.7%)	1 (0.9%)	0.0551
	2	113	10 (8.8%)	23 (20.4%)	37 (32.7%)	29 (25.7%)	12 (10.6%)	0	2 (1.8%)	0.1420
	3	108	12 (11.1%)	18 (16.7%)	25 (23.1%)	28 (25.9%)	16 (14.8%)	6 (5.6%)	3 (2.8%)	
4	1	105	7 (6.7%)	40 (38.1%)	28 (26.7%)	19 (18.1%)	7 (6.7%)	3 (2.9%)	1 (1.0%)	0.0033
	2	109	5 (4.6%)	36 (33.0%)	27 (24.8%)	24 (22.0%)	12 (11.0%)	3 (2.8%)	2 (1.8%)	0.1479
	3	107	8 (7.5%)	15 (14.0%)	39 (36.4%)	27 (25.2%)	10 (9.3%)	7 (6.5%)	1 (0.9%)	
5	1	99	19 (19.2%)	34 (34.3%)	20 (20.2%)	9 (9.1%)	11 (11.1%)	5 (5.1%)	1 (1.0%)	0.1676
	2	94	19 (20.2%)	26 (27.7%)	26 (27.7%)	13 (13.8%)	7 (7.4%)	2 (2.1%)	1 (1.1%)	0.1170

**Table S26.8 Summary of Sensory Questionnaire – Strength of Puffs in Windpipe?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	102	20 (19.6%)	20 (19.6%)	22 (21.6%)	22 (21.6%)	15 (14.7%)	1 (1.0%)	2 (2.0%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

**Table S26.9 Summary of Sensory Questionnaire – Strength of Puffs in Chest?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value*[a]
1	1	116	9 (7.8%)	9 (7.8%)	23 (19.8%)	38 (32.8%)	23 (19.8%)	9 (7.8%)	5 (4.3%)	0.7869
	2	116	9 (7.8%)	7 (6.0%)	14 (12.1%)	51 (44.0%)	21 (18.1%)	12 (10.3%)	2 (1.7%)	0.7382
	3	113	9 (8.0%)	8 (7.1%)	13 (11.5%)	52 (46.0%)	19 (16.8%)	7 (6.2%)	5 (4.4%)	
2	1	115	5 (4.3%)	13 (11.3%)	17 (14.8%)	41 (35.7%)	28 (24.3%)	8 (7.0%)	3 (2.6%)	0.2332
	2	116	3 (2.6%)	6 (5.2%)	19 (16.4%)	51 (44.0%)	23 (19.8%)	13 (11.2%)	1 (0.9%)	0.0506
	3	114	7 (6.1%)	13 (11.4%)	18 (15.8%)	51 (44.7%)	12 (10.5%)	9 (7.9%)	4 (3.5%)	
3	1	112	9 (8.0%)	38 (33.9%)	26 (23.2%)	25 (22.3%)	10 (8.9%)	2 (1.8%)	2 (1.8%)	0.0267
	2	114	10 (8.8%)	25 (21.9%)	33 (28.9%)	35 (30.7%)	9 (7.9%)	1 (0.9%)	1 (0.9%)	0.1446
	3	108	9 (8.3%)	22 (20.4%)	24 (22.2%)	31 (28.7%)	14 (13.0%)	5 (4.6%)	3 (2.8%)	
4	1	105	6 (5.7%)	41 (39.0%)	33 (31.4%)	13 (12.4%)	8 (7.6%)	3 (2.9%)	1 (1.0%)	0.0103
	2	109	6 (5.5%)	36 (33.0%)	28 (25.7%)	25 (22.9%)	9 (8.3%)	4 (3.7%)	1 (0.9%)	0.2182
	3	107	8 (7.5%)	23 (21.5%)	31 (29.0%)	27 (25.2%)	11 (10.3%)	5 (4.7%)	2 (1.9%)	
5	1	99	21 (21.2%)	37 (37.4%)	17 (17.2%)	13 (13.1%)	5 (5.1%)	4 (4.0%)	2 (2.0%)	0.0148
	2	94	22 (23.4%)	25 (26.6%)	23 (24.5%)	11 (11.7%)	11 (11.7%)	2 (2.1%)	0	0.0587

**Table S26.9 Summary of Sensory Questionnaire – Strength of Puffs in Chest?
(ITT Population)**

Visit	Treatment Group	N	Not at All	Very Little	A Little	Moderately	A Lot	Quite A Lot	Extremely	*p-value**
	3	103	15 (14.6%)	26 (25.2%)	21 (20.4%)	26 (25.2%)	11 (10.7%)	1 (1.0%)	3 (2.9%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S27.1 Summary of Change From Baseline in Sensory Questionnaire – How Much Did You Like the Puffs of Your Last Cigarette? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 118)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.6 (1.3)	-0.6 (1.5)	-0.8 (1.5)
Median	-1.0	-0.5	0.0
Minimum, maximum	-5, 2	-4, 4	-6, 4
p-value compared with Group 3*	0.6329	0.7390	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-1.0 (1.3)	-1.1 (1.4)	-0.8 (1.4)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-4, 2	-5, 3	-6, 2
p-value compared with Group 3*	0.1005	0.0861	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-1.7 (1.6)	-1.7 (1.5)	-1.0 (1.7)
Median	-2.0	-1.0	-1.0
Minimum, maximum	-6, 2	-6, 1	-6, 2
p-value compared with Group 3*	0.0007	0.0006	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S27.2 Summary of Change From Baseline in Sensory Questionnaire – How Satisfying Were the Puffs of Your Last Cigarette? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.8 (1.4)	-0.7 (1.5)	-0.6 (1.4)
Median	-1.0	-1.0	0.0
Minimum, maximum	-5, 4	-5, 3	-4, 3
p-value compared with Group 3*	0.2994	0.6313	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-1.2 (1.4)	-1.1 (1.5)	-0.8 (1.5)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 2	-5, 3	-5, 3
p-value compared with Group 3*	0.0419	0.1302	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-1.9 (1.5)	-1.7 (1.3)	-1.1 (1.6)
Median	-2.0	-1.5	-1.0
Minimum, maximum	-6, 2	-5, 1	-5, 2
p-value compared with Group 3*	0.0003	0.0050	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S27.3 Summary of Change From Baseline in Sensory Questionnaire – How High in Nicotine Do You Think the Puffs Were? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-1.3 (1.4)	-1.5 (1.5)	-0.9 (1.5)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 2	-5, 1	-6, 3
p-value compared with Group 3*	0.0449	0.0085	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-2.0 (1.4)	-2.0 (1.5)	-1.1 (1.6)
Median	-2.0	-2.0	-1.0
Minimum, maximum	-5, 2	-6, 1	-5, 3
p-value compared with Group 3*	<.0001	<.0001	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-2.5 (1.4)	-2.5 (1.7)	-1.5 (1.7)
Median	-3.0	-3.0	-2.0
Minimum, maximum	-6, 1	-6, 3	-5, 5
p-value compared with Group 3*	<.0001	<.0001	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S27.4 Summary of Change From Baseline in Sensory Questionnaire – How Similar to Your Own Brand Were These Puffs? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	6	4	9
Mean (SD)	-1.7 (2.7)	-2.3 (1.0)	-1.6 (0.9)
Median	-2.0	-2.5	-2.0
Minimum, maximum	-4, 2	-3, -1	-3, 0
p-value compared with Group 3*	0.9521	0.2566	
Visit 4			
Number of available subjects	6	3	9
Mean (SD)	-2.0 (3.0)	-3.0 (2.6)	-2.6 (1.5)
Median	-2.0	-4.0	-2.0
Minimum, maximum	-5, 2	-5, 0	-5, -1
p-value compared with Group 3*	0.7654	0.7777	
Visit 5			
Number of available subjects	5	2	7
Mean (SD)	-2.4 (2.3)	-3.0 (1.4)	-2.9 (2.2)
Median	-3.0	-3.0	-2.0
Minimum, maximum	-5, 0	-4, -2	-6, 0
p-value compared with Group 3*	0.7423	1.0000	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

**Table S27.5 Summary of Change From Baseline in Sensory Questionnaire – Strength of Puffs on Tongue?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.6 (1.3)	-0.6 (1.6)	-0.3 (1.4)
Median	-1.0	-1.0	0.0
Minimum, maximum	-4, 5	-5, 5	-4, 3
p-value compared with Group 3*	0.0511	0.0995	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-0.9 (1.4)	-0.7 (1.6)	-0.5 (1.3)
Median	-1.0	-1.0	0.0
Minimum, maximum	-5, 3	-5, 5	-4, 2
p-value compared with Group 3*	0.0069	0.2203	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-1.0 (1.5)	-1.2 (1.6)	-0.7 (1.5)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-5, 4	-5, 4	-4, 3
p-value compared with Group 3*	0.0433	0.0385	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S27.6 Summary of Change From Baseline in Sensory Questionnaire – Strength of Puffs in Nose?
(ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	108
Mean (SD)	-0.5 (1.2)	-0.6 (1.4)	-0.4 (1.3)
Median	0.0	-1.0	0.0
Minimum, maximum	-4, 4	-5, 3	-5, 3
p-value compared with Group 3*	0.2039	0.1101	
Visit 4			
Number of available subjects	105	108	107
Mean (SD)	-0.6 (1.3)	-0.6 (1.5)	-0.3 (1.3)
Median	-1.0	-1.0	0.0
Minimum, maximum	-4, 3	-4, 4	-4, 3
p-value compared with Group 3*	0.0324	0.0318	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-0.6 (1.4)	-0.9 (1.5)	-0.3 (1.4)
Median	-1.0	-1.0	0.0
Minimum, maximum	-5, 3	-4, 3	-4, 5
p-value compared with Group 3*	0.0731	0.0016	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

**Table S27.7 Summary of Change From Baseline in Sensory Questionnaire – Strength of Puffs in Back of Mouth and Throat?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	107
Mean (SD)	-0.7 (1.4)	-0.9 (1.7)	-0.2 (1.4)
Median	0.0	-1.0	0.0
Minimum, maximum	-5, 3	-5, 5	-4, 4
p-value compared with Group 3*	0.0253	0.0018	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-0.8 (1.5)	-0.8 (1.7)	-0.4 (1.3)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 3	-5, 4	-4, 3
p-value compared with Group 3*	0.0300	0.0445	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-1.0 (1.6)	-1.3 (1.8)	-0.7 (1.5)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-6, 3	-6, 4	-5, 3
p-value compared with Group 3*	0.2305	0.0159	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

**Table S27.8 Summary of Change From Baseline in Sensory Questionnaire – Strength of Puffs in Windpipe?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	108
Mean (SD)	-0.8 (1.5)	-0.9 (1.5)	-0.2 (1.4)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 3	-5, 3	-4, 4
p-value compared with Group 3*	0.0097	0.0020	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-1.0 (1.5)	-0.9 (1.6)	-0.3 (1.3)
Median	-1.0	-1.0	0.0
Minimum, maximum	-5, 3	-5, 3	-4, 3
p-value compared with Group 3*	0.0007	0.0024	
Visit 5			
Number of available subjects	99	94	102
Mean (SD)	-1.1 (1.8)	-1.4 (1.7)	-0.6 (1.6)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-6, 4	-5, 2	-5, 3
p-value compared with Group 3*	0.0301	0.0022	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

**Table S27.9 Summary of Change From Baseline in Sensory Questionnaire – Strength of Puffs in Chest?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	-0.9 (1.6)	-1.0 (1.3)	-0.4 (1.4)
Median	-1.0	-1.0	0.0
Minimum, maximum	-6, 3	-5, 2	-4, 3
p-value compared with Group 3*	0.0060	0.0020	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	-1.1 (1.6)	-1.0 (1.4)	-0.5 (1.3)
Median	-1.0	-1.0	0.0
Minimum, maximum	-5, 3	-5, 2	-4, 2
p-value compared with Group 3*	0.0067	0.0146	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	-1.3 (1.7)	-1.5 (1.6)	-0.7 (1.6)
Median	-1.0	-1.0	-1.0
Minimum, maximum	-6, 4	-5, 2	-5, 5
p-value compared with Group 3*	0.0107	0.0014	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S28 Summary of Fagerström Test for Nicotine Dependence Score (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Number of available subjects	114	115	112
Mean (SD)	6.1 (2.2)	5.9 (1.9)	6.1 (2.1)
Median	6.0	6.0	6.0
Minimum, maximum	1, 10	2, 10	1, 10
p-value compared with Group 3*	0.8012	0.5722	
Visit 2			
Number of available subjects	114	116	114
Mean (SD)	6.2 (2.2)	6.1 (2.0)	6.2 (2.1)
Median	6.0	6.0	6.0
Minimum, maximum	1, 10	2, 10	1, 10
p-value compared with Group 3*	0.7202	0.6901	
Visit 3			
Number of available subjects	110	109	108
Mean (SD)	6.3 (2.1)	6.2 (2.1)	6.2 (2.2)
Median	6.0	6.0	6.0
Minimum, maximum	1, 10	1, 10	1, 10
p-value compared with Group 3*	0.8707	0.9704	
Visit 4			
Number of available subjects	106	107	106
Mean (SD)	6.3 (2.2)	6.2 (2.1)	6.2 (2.2)

Table S28 Summary of Fagerström Test for Nicotine Dependence Score (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	7.0	6.0	6.0
Minimum, maximum	0, 10	2, 10	1, 10
p-value compared with Group 3*	0.4578	0.8947	
Visit 5			
Number of available subjects	98	92	100
Mean (SD)	5.6 (2.5)	5.4 (2.3)	5.9 (2.3)
Median	6.0	6.0	6.0
Minimum, maximum	0, 10	0, 10	1, 10
p-value compared with Group 3*	0.5583	0.2039	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S29 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence Score (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	109	109	108
Mean (SD)	0.0 (1.3)	0.2 (1.1)	0.1 (1.0)
Median	0.0	0.0	0.0
Minimum, maximum	-4, 5	-5, 3	-2, 3
p-value compared with Group 3*	0.8953	0.4242	
Visit 4			
Number of available subjects	105	107	106
Mean (SD)	0.2 (1.6)	0.2 (1.4)	0.0 (1.2)
Median	0.0	0.0	0.0
Minimum, maximum	-5, 5	-5, 5	-3, 3
p-value compared with Group 3*	0.2488	0.2615	
Visit 5			
Number of available subjects	97	92	100
Mean (SD)	-0.6 (2.0)	-0.5 (1.8)	-0.3 (1.4)
Median	0.0	0.0	0.0
Minimum, maximum	-6, 6	-6, 4	-5, 4
p-value compared with Group 3*	0.3031	0.4201	

N = number of randomized subjects
* Two-sided Wilcoxon rank-sum test

Table S30.2 Summary of Fagerström Test for Nicotine Dependence – Do You Find it Difficult to Refrain from Smoking in Places Where it is Forbidden, e.g. in Church, at the Library, in Cinema, etc.? (ITT Population)

Visit	Treatment Group	N	Yes	No	*p value**
1	1	116	51 (44.0%)	65 (56.0%)	0.9739
	2	115	44 (38.3%)	71 (61.7%)	0.4015
	3	112	49 (43.8%)	63 (56.3%)	
2	1	116	41 (35.3%)	75 (64.7%)	0.4348
	2	116	35 (30.2%)	81 (69.8%)	0.1069
	3	114	46 (40.4%)	68 (59.6%)	
3	1	112	29 (25.9%)	83 (74.1%)	0.4432
	2	114	30 (26.3%)	84 (73.7%)	0.4847
	3	108	33 (30.6%)	75 (69.4%)	
4	1	106	26 (24.5%)	80 (75.5%)	0.5617
	2	109	29 (26.6%)	80 (73.4%)	0.8138
	3	107	30 (28.0%)	77 (72.0%)	
5	1	99	22 (22.2%)	77 (77.8%)	0.7310
	2	94	18 (19.1%)	76 (80.9%)	0.3858
	3	103	25 (24.3%)	78 (75.7%)	

N = number of available subjects
%
was based on the number of available subjects in the corresponding vis
it
* Two-sided Jonckheere-Terpstra test

Table S30.3 Summary of Fagerström Test for Nicotine Dependence – Which Cigarette Would You Hate Most to Give Up? (ITT Population)

Visit	Treatment Group	N	The first one in the morning	All others	*p-value**
1	1	116	59 (50.9%)	57 (49.1%)	0.3426
	2	115	61 (53.0%)	54 (47.0%)	0.5356
	3	112	64 (57.1%)	48 (42.9%)	
2	1	116	64 (55.2%)	52 (44.8%)	0.5823
	2	116	69 (59.5%)	47 (40.5%)	0.9129
	3	114	67 (58.8%)	47 (41.2%)	
3	1	111	66 (59.5%)	45 (40.5%)	0.8658
	2	112	60 (53.6%)	52 (46.4%)	0.4780
	3	108	63 (58.3%)	45 (41.7%)	
4	1	106	59 (55.7%)	47 (44.3%)	0.7822
	2	107	58 (54.2%)	49 (45.8%)	0.6242
	3	106	61 (57.5%)	45 (42.5%)	
5	1	98	65 (66.3%)	33 (33.7%)	0.6340
	2	92	48 (52.2%)	44 (47.8%)	0.1236
	3	103	65 (63.1%)	38 (36.9%)	

N = number of available subjects
%
was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S30.4 Summary of Fagerström Test for Nicotine Dependence – How Many Cigarettes/Day Do You Smoke? (ITT Population)

Visit	Treatment Group	N	10 or less	11-20	21-30	31 or more	p-value*
1	1	116	0	41 (35.3%)	44 (37.9%)	31 (26.7%)	0.1565
	2	115	0	58 (50.4%)	38 (33.0%)	19 (16.5%)	0.2847
	3	112	0	49 (43.8%)	40 (35.7%)	23 (20.5%)	
2	1	115	1 (0.9%)	38 (33.0%)	46 (40.0%)	30 (26.1%)	0.8201
	2	116	0	50 (43.1%)	36 (31.0%)	30 (25.9%)	0.4802
	3	114	0	41 (36.0%)	44 (38.6%)	29 (25.4%)	
3	1	111	0	22 (19.8%)	52 (46.8%)	37 (33.3%)	0.4242
	2	112	1 (0.9%)	25 (22.3%)	51 (45.5%)	35 (31.3%)	0.7884
	3	108	1 (0.9%)	32 (29.6%)	37 (34.3%)	38 (35.2%)	
4	1	106	2 (1.9%)	18 (17.0%)	41 (38.7%)	45 (42.5%)	0.4100
	2	109	2 (1.8%)	21 (19.3%)	42 (38.5%)	44 (40.4%)	0.6480
	3	107	0	32 (29.9%)	30 (28.0%)	45 (42.1%)	
5	1	99	15 (15.2%)	27 (27.3%)	31 (31.3%)	26 (26.3%)	0.1381
	2	94	9 (9.6%)	31 (33.0%)	28 (29.8%)	26 (27.7%)	0.2671
	3	102	6 (5.9%)	31 (30.4%)	31 (30.4%)	34 (33.3%)	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Jonckheere-Terpstra test

Table S30.5 Summary of Fagerström Test of Nicotine Dependence – Do You Smoke More Frequently During the First Hours After Awakening Than During the Rest of the Day? (ITT Population)

Visit	Treatment Group	N	Yes	No	*p-value**
1	1	116	66 (56.9%)	50 (43.1%)	0.8622
	2	115	59 (51.3%)	56 (48.7%)	0.3095
	3	112	65 (58.0%)	47 (42.0%)	
2	1	116	67 (57.8%)	49 (42.2%)	0.6071
	2	116	59 (50.9%)	57 (49.1%)	0.5934
	3	114	62 (54.4%)	52 (45.6%)	
3	1	112	63 (56.3%)	49 (43.8%)	0.4652
	2	113	57 (50.4%)	56 (49.6%)	0.1113
	3	108	66 (61.1%)	42 (38.9%)	
4	1	106	66 (62.3%)	40 (37.7%)	0.2922
	2	109	57 (52.3%)	52 (47.7%)	0.6756
	3	107	59 (55.1%)	48 (44.9%)	
5	1	99	61 (61.6%)	38 (38.4%)	0.9476
	2	93	48 (51.6%)	45 (48.4%)	0.1789
	3	103	63 (61.2%)	40 (38.8%)	

N = number of available subjects
%
was based on the number of available subjects in the corresponding vis
it
* Two-sided Jonckheere-Terpstra test

Table S30.6
Summary of Fagerström Test for Nicotine Dependence – Do You Smoke if You Are So Ill That You Are in Bed Most of the Day?
(ITT Population)

Visit	Treatment Group	N	Yes	No	*p-value**
1	1	114	59 (51.8%)	55 (48.2%)	0.3438
	2	115	63 (54.8%)	52 (45.2%)	0.6220
	3	112	65 (58.0%)	47 (42.0%)	
2	1	115	68 (59.1%)	47 (40.9%)	0.8498
	2	116	67 (57.8%)	49 (42.2%)	0.9834
	3	114	66 (57.9%)	48 (42.1%)	
3	1	112	61 (54.5%)	51 (45.5%)	0.5638
	2	114	64 (56.1%)	50 (43.9%)	0.7419
	3	108	63 (58.3%)	45 (41.7%)	
4	1	106	56 (52.8%)	50 (47.2%)	0.3752
	2	109	60 (55.0%)	49 (45.0%)	0.5704
	3	107	63 (58.9%)	44 (41.1%)	
5	1	99	51 (51.5%)	48 (48.5%)	0.9497
	2	93	42 (45.2%)	51 (54.8%)	0.3440
	3	102	53 (52.0%)	49 (48.0%)	

N = number of available subjects
%
was based on the number of available subjects in the corresponding vis
it
* Two-sided Jonckheere-Terpstra test

Table S31.1 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence – How Soon After You Wake Do You Smoke Your First Cigarette? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.1 (0.6)	-0.1 (0.5)	0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 2	-2, 1	-1, 1
p-value compared with Group 3*	0.7450	0.1685	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.0 (0.8)	0.1 (0.5)	0.1 (0.5)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 3	-1, 1	-1, 2
p-value compared with Group 3*	0.6276	0.9875	
Visit 5			
Number of available subjects	99	93	102
Mean (SD)	0.3 (0.9)	0.2 (0.7)	0.2 (0.5)
Median	0.0	0.0	0.0
Minimum, maximum	-2, 2	-2, 2	-1, 3
p-value compared with Group 3*	0.2989	0.3777	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S31.2 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence – Do You Find it Difficult to Refrain from Smoking in Places Where it is Forbidden, e.g. in Church, at the Library, in Cinema, etc.? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	114	108
Mean (SD)	0.1 (0.4)	0.0 (0.3)	0.1 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.8086	0.1103	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.1 (0.4)	0.0 (0.3)	0.1 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.4666	0.0508	
Visit 5			
Number of available subjects	99	94	103
Mean (SD)	0.1 (0.4)	0.1 (0.4)	0.2 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1

Table S31.2 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence – Do You Find it Difficult to Refrain from Smoking in Places Where it is Forbidden, e.g. in Church, at the Library, in Cinema, etc.? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
p-value compared with Group 3*	0.6007	0.5300	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S31.3 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence – Which Cigarette Would You Hate Most to Give Up? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	111	112	108
Mean (SD)	-0.0 (0.4)	0.1 (0.4)	0.0 (0.3)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.2767	0.3876	
Visit 4			
Number of available subjects	106	107	106
Mean (SD)	0.0 (0.4)	0.0 (0.4)	0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	1.0000	0.5070	
Visit 5			
Number of available subjects	98	92	103
Mean (SD)	-0.1 (0.4)	0.0 (0.4)	-0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.3061	0.2470	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S31.4 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence – How Many Cigarettes/Day Do You Smoke? (ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	111	112	108
Mean (SD)	0.2 (0.6)	0.3 (0.7)	0.1 (0.6)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 2	-2, 2	-1, 2
p-value compared with Group 3*	0.4006	0.2580	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	0.3 (0.7)	0.4 (0.8)	0.2 (0.7)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 2	-3, 2	-2, 2
p-value compared with Group 3*	0.1887	0.1444	
Visit 5			
Number of available subjects	99	94	102
Mean (SD)	-0.2 (1.0)	-0.0 (1.0)	0.0 (0.7)
Median	0.0	0.0	0.0
Minimum, maximum	-3, 2	-3, 2	-2, 2
p-value compared with Group 3*	0.1937	0.9273	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S31.5 Summary of Change From Baseline in Fagerström Test of Nicotine Dependence – Do You Smoke More Frequently During the First Hours After Awakening Than During the Rest of the Day?
(ITT Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	112	113	108
Mean (SD)	0.0 (0.4)	0.0 (0.5)	-0.1 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.1375	0.2723	
Visit 4			
Number of available subjects	106	109	107
Mean (SD)	-0.0 (0.4)	-0.0 (0.4)	-0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.6224	0.8772	
Visit 5			
Number of available subjects	99	93	103
Mean (SD)	-0.0 (0.5)	-0.1 (0.5)	-0.1 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1

**Table S31.5 Summary of Change From Baseline in Fagerström Test of Nicotine Dependence – Do You Smoke More Frequently During the First Hours After Awakening Than During the Rest of the Day?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
p-value compared with Group 3*	0.5755	0.9494	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

**Table S31.6 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence –
Do You Smoke if You Are So Ill That You Are in Bed Most of the Day?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 3			
Number of available subjects	111	114	108
Mean (SD)	0.0 (0.3)	0.0 (0.3)	0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.3658	0.7182	
Visit 4			
Number of available subjects	105	109	107
Mean (SD)	0.1 (0.3)	0.0 (0.4)	0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1
p-value compared with Group 3*	0.2115	0.4904	
Visit 5			
Number of available subjects	98	93	102
Mean (SD)	0.1 (0.4)	0.1 (0.4)	0.0 (0.4)
Median	0.0	0.0	0.0
Minimum, maximum	-1, 1	-1, 1	-1, 1

**Table S31.6 Summary of Change From Baseline in Fagerström Test for Nicotine Dependence –
Do You Smoke if You Are So Ill That You Are in Bed Most of the Day?
(ITT Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
p-value compared with Group 3*	0.5930	0.3356	

N = number of available subjects
% was based on the number of available subjects in the corresponding visit
* Two-sided Wilcoxon rank-sum test

Table S32 Summary of Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

NO ADVERSE EVENTS QUALIFY FOR THIS REPORT

N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Subjects with Any Adverse Events	71 (61%)	61 (53%)	69 (61%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (<1%)	0	0
LYMPHADENOPATHY	1 (<1%)	0	0
CARDIAC DISORDERS	1 (<1%)	1 (<1%)	3 (3%)
CORONARY ARTERY DISEASE	0	0	1 (<1%)
PALPITATIONS	1 (<1%)	0	1 (<1%)
TACHYCARDIA	0	0	1 (<1%)
SUPRAVENTRICULAR EXTRASYSTOLES	0	1 (<1%)	0
EAR AND LABYRINTH DISORDERS	0	0	1 (<1%)
VERTIGO	0	0	1 (<1%)
ENDOCRINE DISORDERS	1 (<1%)	0	0
HYPOTHYROIDISM	1 (<1%)	0	0
EYE DISORDERS	2 (2%)	0	3 (3%)
BLEPHAROSPASM	0	0	1 (<1%)
CONJUNCTIVITIS	1 (<1%)	0	1 (<1%)
EYE PRURITUS	0	0	1 (<1%)
EYELID OEDEMA	1 (<1%)	0	0

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
GASTROINTESTINAL DISORDERS	15 (13%)	11 (9%)	14 (12%)
NAUSEA	8 (7%)	7 (6%)	5 (4%)
DIARRHOEA	2 (2%)	3 (3%)	2 (2%)
DYSPEPSIA	3 (3%)	1 (<1%)	2 (2%)
STOMACH DISCOMFORT	1 (<1%)	0	2 (2%)
ABDOMINAL ADHESIONS	0	0	1 (<1%)
ABDOMINAL DISCOMFORT	0	0	1 (<1%)
ABDOMINAL DISTENSION	0	0	1 (<1%)
ABDOMINAL PAIN	2 (2%)	1 (<1%)	1 (<1%)
ABDOMINAL PAIN UPPER	0	0	1 (<1%)
APHTHOUS STOMATITIS	0	0	1 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	0	1 (<1%)	1 (<1%)
CONSTIPATION	0	1 (<1%)	0
DRY MOUTH	1 (<1%)	0	0
FLATULENCE	1 (<1%)	0	0
STOMATITIS	1 (<1%)	0	0
TOOTH IMPACTED	1 (<1%)	0	0
TOOTHACHE	1 (<1%)	1 (<1%)	0
VOMITING	2 (2%)	3 (3%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (14%)	13 (11%)	16 (14%)
APPLICATION SITE PRURITUS	8 (7%)	1 (<1%)	5 (4%)
FATIGUE	3 (3%)	3 (3%)	3 (3%)

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 110)	Group 3 (N = 114)
APPLICATION SITE DERMATITIS	1 (<1%)	1 (<1%)	2 (2%)
APPLICATION SITE DISCOMFORT	0	0	2 (2%)
APPLICATION SITE IRRITATION	0	2 (2%)	2 (2%)
CHEST DISCOMFORT	1 (<1%)	0	2 (2%)
MALAISE	0	0	1 (<1%)
OEDEMA PERIPHERAL	2 (2%)	1 (<1%)	1 (<1%)
APPLICATION SITE DISCOLOURATION	2 (2%)	0	0
APPLICATION SITE ERYTHEMA	4 (3%)	2 (2%)	0
ASTHENIA	0	1 (<1%)	0
CHEST PAIN	0	1 (<1%)	0
FEELING JITTERY	1 (<1%)	0	0
NON-CARDIAC CHEST PAIN	0	1 (<1%)	0
PAIN	1 (<1%)	0	0
IMMUNE SYSTEM DISORDERS	0	0	4 (4%)
HYPERSENSITIVITY	0	0	2 (2%)
SEASONAL ALLERGY	0	0	2 (2%)
INFECTIONS AND INFESTATIONS	13 (11%)	15 (13%)	23 (20%)
NASOPHARYNGITIS	3 (3%)	2 (2%)	8 (7%)
UPPER RESPIRATORY TRACT INFECTION	2 (2%)	2 (2%)	6 (5%)

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
TOOTH ABSCESS	0	0	2 (2%)
CELLULITIS	0	0	1 (<1%)
EAR INFECTION	0	2 (2%)	1 (<1%)
GASTROENTERITIS VIRAL	0	1 (<1%)	1 (<1%)
INFLUENZA	1 (<1%)	0	1 (<1%)
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	1 (<1%)
PNEUMONIA	0	1 (<1%)	1 (<1%)
RHINITIS	0	0	1 (<1%)
URINARY TRACT INFECTION	0	0	1 (<1%)
WOUND INFECTION	0	0	1 (<1%)
BRONCHITIS	0	4 (3%)	0
BRONCHITIS ACUTE	0	1 (<1%)	0
CHRONIC SINUSITIS	0	1 (<1%)	0
CYSTITIS	0	1 (<1%)	0
EYE INFECTION	0	1 (<1%)	0
FURUNCLE	1 (<1%)	0	0
HERPES ZOSTER	1 (<1%)	0	0
INFECTED CYST	0	1 (<1%)	0
OTITIS EXTERNA	1 (<1%)	0	0
OTITIS MEDIA	1 (<1%)	0	0
SINUSITIS	2 (2%)	1 (<1%)	0
SUBCUTANEOUS ABSCESS	0	1 (<1%)	0
TOOTH INFECTION	0	1 (<1%)	0
VAGINAL MYCOSIS	0	1 (<1%)	0

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8 (7%)	6 (5%)	5 (4%)
FIBULA FRACTURE	0	0	1 (<1%)
JOINT INJURY	0	0	1 (<1%)
LACERATION	0	0	1 (<1%)
LIGAMENT SPRAIN	0	0	1 (<1%)
POST PROCEDURAL PAIN	2 (2%)	1 (<1%)	1 (<1%)
TIBIA FRACTURE	0	0	1 (<1%)
ANKLE FRACTURE	1 (<1%)	0	0
ARTHROPOD BITE	0	2 (2%)	0
ARTHROPOD STING	1 (<1%)	1 (<1%)	0
BACK INJURY	1 (<1%)	0	0
CONTUSION	0	2 (2%)	0
EXCORIATION	1 (<1%)	0	0
FOOT FRACTURE	0	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0	0
SKIN LACERATION	1 (<1%)	0	0
INVESTIGATIONS	4 (3%)	3 (3%)	2 (2%)
WEIGHT DECREASED	0	0	1 (<1%)
WEIGHT INCREASED	1 (<1%)	1 (<1%)	1 (<1%)
BLOOD CHOLESTEROL INCREASED	2 (2%)	0	0
BLOOD PRESSURE INCREASED	1 (<1%)	0	0
BLOOD TRIGLYCERIDES INCREASED	1 (<1%)	0	0

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ELECTROCARDIOGRAM ABNORMAL	0	1 (<1%)	0
HEPATIC ENZYME INCREASED	0	1 (<1%)	0
METABOLISM AND NUTRITION DISORDERS	1 (<1%)	0	5 (4%)
INCREASED APPETITE	0	0	3 (3%)
ANOREXIA	0	0	1 (<1%)
DIABETES MELLITUS	0	0	1 (<1%)
GOUT	1 (<1%)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	9 (8%)	15 (13%)	7 (6%)
CHEST WALL PAIN	0	1 (<1%)	2 (2%)
MUSCLE SPASMS	0	1 (<1%)	2 (2%)
PAIN IN EXTREMITY	1 (<1%)	0	2 (2%)
SHOULDER PAIN	0	1 (<1%)	2 (2%)
MYALGIA	1 (<1%)	2 (2%)	1 (<1%)
ARTHRALGIA	0	1 (<1%)	0
ARTHRITIS	1 (<1%)	0	0
BACK PAIN	4 (3%)	6 (5%)	0
FLANK PAIN	0	1 (<1%)	0
MUSCULOSKELETAL PAIN	1 (<1%)	0	0
NECK PAIN	1 (<1%)	3 (3%)	0
PAIN IN JAW	2 (2%)	0	0

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (<1%)	0	0
BLADDER NEOPLASM	1 (<1%)	0	0
NERVOUS SYSTEM DISORDERS	16 (14%)	16 (14%)	14 (12%)
HEADACHE	7 (6%)	12 (10%)	4 (4%)
DIZZINESS	4 (3%)	2 (2%)	2 (2%)
PARAESTHESIA	1 (<1%)	0	2 (2%)
DISTURBANCE IN ATTENTION	2 (2%)	1 (<1%)	1 (<1%)
DYSGEUSIA	1 (<1%)	0	1 (<1%)
HYPOAESTHESIA	0	0	1 (<1%)
MENTAL IMPAIRMENT	0	0	1 (<1%)
MIGRAINE	1 (<1%)	1 (<1%)	1 (<1%)
SINUS HEADACHE	0	0	1 (<1%)
TENSION HEADACHE	0	0	1 (<1%)
LETHARGY	1 (<1%)	0	0
PSYCHIATRIC DISORDERS	34 (29%)	16 (14%)	14 (12%)
INSOMNIA	15 (13%)	6 (5%)	7 (6%)
ABNORMAL DREAMS	4 (3%)	1 (<1%)	4 (4%)
ANXIETY	8 (7%)	2 (2%)	3 (3%)
DEPRESSION	1 (<1%)	3 (3%)	3 (3%)
IRRITABILITY	7 (6%)	2 (2%)	2 (2%)
SLEEP DISORDER	1 (<1%)	0	1 (<1%)

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DEPRESSED MOOD	0	1 (<1%)	0
EMOTIONAL DISORDER	1 (<1%)	0	0
INITIAL INSOMNIA	0	2 (2%)	0
MOOD SWINGS	1 (<1%)	0	0
NERVOUSNESS	4 (3%)	0	0
NIGHTMARE	2 (2%)	1 (<1%)	0
RESTLESSNESS	1 (<1%)	0	0
RENAL AND URINARY DISORDERS	1 (<1%)	0	1 (<1%)
POLLAKIURIA	0	0	1 (<1%)
HAEMATURIA	1 (<1%)	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (<1%)
MENSTRUATION IRREGULAR	0	0	1 (<1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13 (11%)	13 (11%)	15 (13%)
COUGH	4 (3%)	2 (2%)	7 (6%)
PHARYNGOLARYNGEAL PAIN	5 (4%)	2 (2%)	3 (3%)
DYSPNOEA	3 (3%)	2 (2%)	2 (2%)
SINUS CONGESTION	0	0	2 (2%)
EPISTAXIS	0	1 (<1%)	1 (<1%)
NASAL CONGESTION	0	0	1 (<1%)
PRODUCTIVE COUGH	2 (2%)	2 (2%)	1 (<1%)

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
RHINORRHOEA	0	0	1 (<1%)
RHONCHI	0	0	1 (<1%)
THROAT IRRITATION	0	0	1 (<1%)
ALLERGIC SINUSITIS	0	1 (<1%)	0
ASTHMA	1 (<1%)	0	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (<1%)	0
NASAL DISCOMFORT	1 (<1%)	0	0
POSTNASAL DRIP	1 (<1%)	0	0
RESPIRATORY TRACT CONGESTION	0	2 (2%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (7%)	3 (3%)	7 (6%)
DERMATITIS CONTACT	1 (<1%)	1 (<1%)	2 (2%)
RASH	0	0	2 (2%)
ECZEMA	1 (<1%)	0	1 (<1%)
PRURITUS	1 (<1%)	1 (<1%)	1 (<1%)
URTICARIA	2 (2%)	1 (<1%)	1 (<1%)
ACTINIC KERATOSIS	1 (<1%)	0	0
DRY SKIN	1 (<1%)	0	0
SKIN IRRITATION	1 (<1%)	0	0
SURGICAL AND MEDICAL PROCEDURES	1 (<1%)	2 (2%)	1 (<1%)
SKIN NEOPLASM EXCISION	0	0	1 (<1%)
ENDODONTIC PROCEDURE	0	1 (<1%)	0
TOOTH EXTRACTION	0	1 (<1%)	0

Table S33 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
TOOTH REPAIR	1 (<1%)	0	0
VASCULAR DISORDERS	3 (3%)	0	3 (3%)
HOT FLUSH	0	0	2 (2%)
HYPERTENSION	2 (2%)	0	1 (<1%)
AORTIC ANEURYSM	1 (<1%)	0	0

N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S34 Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Subjects with Any Treatment-related Adverse Events	51 (44%)	32 (28%)	42 (37%)
CARDIAC DISORDERS	1 (<1%)	0	1 (<1%)
PALPITATIONS	1 (<1%)	0	1 (<1%)
EYE DISORDERS	0	0	2 (2%)
BLEPHAROSPASM	0	0	1 (<1%)
EYE PRURITUS	0	0	1 (<1%)
GASTROINTESTINAL DISORDERS	5 (4%)	5 (4%)	5 (4%)
NAUSEA	5 (4%)	4 (3%)	4 (4%)
DYSPEPSIA	0	1 (<1%)	1 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	0	1 (<1%)	1 (<1%)
DRY MOUTH	1 (<1%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (10%)	9 (8%)	12 (11%)
APPLICATION SITE PRURITUS	8 (7%)	1 (<1%)	5 (4%)
APPLICATION SITE DERMATITIS	1 (<1%)	1 (<1%)	2 (2%)
APPLICATION SITE DISCOMFORT	0	0	2 (2%)
APPLICATION SITE IRRITATION	0	2 (2%)	2 (2%)

Table S34 Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N=116)	Group 2 (N=116)	Group 3 (N=114)
FATIGUE	1 (<1%)	1 (<1%)	2 (2%)
CHEST DISCOMFORT	0	0	1 (<1%)
APPLICATION SITE DISCOLOURATION	1 (<1%)	0	0
APPLICATION SITE ERYTHEMA	4 (3%)	2 (2%)	0
ASTHENIA	0	1 (<1%)	0
CHEST PAIN	0	1 (<1%)	0
FEELING JITTERY	1 (<1%)	0	0
OEDEMA PERIPHERAL	1 (<1%)	0	0
INFECTIONS AND INFESTATIONS	2 (2%)	1 (<1%)	0
NASOPHARYNGITIS	1 (<1%)	0	0
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)	0
INVESTIGATIONS	1 (<1%)	2 (2%)	1 (<1%)
WEIGHT DECREASED	0	0	1 (<1%)
ELECTROCARDIOGRAM ABNORMAL	0	1 (<1%)	0
WEIGHT INCREASED	1 (<1%)	1 (<1%)	0
METABOLISM AND NUTRITION DISORDERS	0	0	4 (4%)
INCREASED APPETITE	0	0	2 (2%)
ANOREXIA	0	0	1 (<1%)
DIABETES MELLITUS	0	0	1 (<1%)

Table S34 Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (<1%)	0
MYALGIA	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	13 (11%)	13 (11%)	9 (8%)
DIZZINESS	3 (3%)	2 (2%)	2 (2%)
HEADACHE	6 (5%)	9 (8%)	2 (2%)
DISTURBANCE IN ATTENTION	2 (2%)	1 (<1%)	1 (<1%)
DYSGEUSIA	1 (<1%)	0	1 (<1%)
MENTAL IMPAIRMENT	0	0	1 (<1%)
MIGRAINE	1 (<1%)	1 (<1%)	1 (<1%)
PARAESTHESIA	0	0	1 (<1%)
TENSION HEADACHE	0	0	1 (<1%)
PSYCHIATRIC DISORDERS	28 (24%)	13 (11%)	12 (11%)
INSOMNIA	12 (10%)	6 (5%)	6 (5%)
ABNORMAL DREAMS	4 (3%)	1 (<1%)	4 (4%)
DEPRESSION	0	1 (<1%)	3 (3%)
ANXIETY	4 (3%)	2 (2%)	2 (2%)
IRRITABILITY	7 (6%)	2 (2%)	2 (2%)
SLEEP DISORDER	1 (<1%)	0	1 (<1%)
EMOTIONAL DISORDER	1 (<1%)	0	0
INITIAL INSOMNIA	0	2 (2%)	0
MOOD SWINGS	1 (<1%)	0	0
NERVOUSNESS	3 (3%)	0	0

Table S34 Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
NIGHTMARE	2 (2%)	1 (<1%)	0
RESTLESSNESS	1 (<1%)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (5%)	4 (3%)	9 (8%)
COUGH	3 (3%)	1 (<1%)	5 (4%)
PHARYNGOLARYNGEAL PAIN	3 (3%)	1 (<1%)	2 (2%)
DYSPNOEA	1 (<1%)	2 (2%)	1 (<1%)
EPISTAXIS	0	0	1 (<1%)
RHINORRHOEA	0	0	1 (<1%)
THROAT IRRITATION	0	0	1 (<1%)
ASTHMA	1 (<1%)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (3%)	2 (2%)	3 (3%)
DERMATITIS CONTACT	0	0	1 (<1%)
ECZEMA	0	0	1 (<1%)
PRURITUS	0	1 (<1%)	1 (<1%)
ACTINIC KERATOSIS	1 (<1%)	0	0
SKIN IRRITATION	1 (<1%)	0	0
URTICARIA	1 (<1%)	1 (<1%)	0
VASCULAR DISORDERS	2 (2%)	0	1 (<1%)
HOT FLUSH	0	0	1 (<1%)

Table S34 Summary of Treatment-Related Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
HYPERTENSION	2 (2%)	0	0

N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Subjects with Any Adverse Events	71 (61%)	61 (53%)	69 (61%)
Mild	36 (31%)	31 (27%)	40 (35%)
Moderate	28 (24%)	27 (23%)	26 (23%)
Severe	7 (6%)	3 (3%)	3 (3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (<1%)	0	0
LYMPHADENOPATHY	1 (<1%)	0	0
Mild	1 (<1%)	0	0
CARDIAC DISORDERS	1 (<1%)	1 (<1%)	3 (3%)
CORONARY ARTERY DISEASE	0	0	1 (<1%)
Mild	0	0	1 (<1%)
PALPITATIONS	1 (<1%)	0	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
SUPRAVENTRICULAR EXTRASYSTOLES	0	1 (<1%)	0
Mild	0	1 (<1%)	0
TACHYCARDIA	0	0	1 (<1%)
Mild	0	0	1 (<1%)
EAR AND LABYRINTH DISORDERS	0	0	1 (<1%)
VERTIGO	0	0	1 (<1%)
Mild	0	0	1 (<1%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ENDOCRINE DISORDERS	1 (<1%)	0	0
HYPOTHYROIDISM	1 (<1%)	0	0
Mild	1 (<1%)	0	0
EYE DISORDERS	2 (2%)	0	3 (3%)
BLEPHAROSPASM	0	0	1 (<1%)
Mild	0	0	1 (<1%)
CONJUNCTIVITIS	1 (<1%)	0	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
EYE PRURITUS	0	0	1 (<1%)
Mild	0	0	1 (<1%)
EYELID OEDEMA	1 (<1%)	0	0
Mild	1 (<1%)	0	0
GASTROINTESTINAL DISORDERS	15 (13%)	11 (9%)	14 (12%)
ABDOMINAL ADHESIONS	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
ABDOMINAL DISCOMFORT	0	0	1 (<1%)
Mild	0	0	1 (<1%)
ABDOMINAL DISTENSION	0	0	1 (<1%)
Mild	0	0	1 (<1%)
ABDOMINAL PAIN	2 (2%)	1 (<1%)	1 (<1%)
Mild	2 (2%)	0	1 (<1%)
Moderate	0	1 (<1%)	0
ABDOMINAL PAIN UPPER	0	0	1 (<1%)
Mild	0	0	1 (<1%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Moderate	0	0	1 (<1%)
APHTHOUS STOMATITIS	0	0	1 (<1%)
Mild	0	0	1 (<1%)
CONSTIPATION	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
DIARRHOEA	2 (2%)	3 (3%)	2 (2%)
Mild	2 (2%)	2 (2%)	2 (2%)
Moderate	0	1 (<1%)	0
DRY MOUTH	1 (<1%)	0	0
Mild	1 (<1%)	0	0
DYSPEPSIA	3 (3%)	1 (<1%)	2 (2%)
Mild	1 (<1%)	1 (<1%)	2 (2%)
Moderate	2 (2%)	0	0
FLATULENCE	1 (<1%)	0	0
Mild	1 (<1%)	0	0
GASTROOESOPHAGEAL REFLUX DISEASE	0	1 (<1%)	1 (<1%)
Mild	0	1 (<1%)	0
Moderate	0	0	1 (<1%)
NAUSEA	8 (7%)	7 (6%)	5 (4%)
Mild	5 (4%)	6 (5%)	4 (4%)
Moderate	2 (2%)	1 (<1%)	1 (<1%)
Severe	1 (<1%)	0	0
STOMACH DISCOMFORT	1 (<1%)	0	2 (2%)
Mild	1 (<1%)	0	0
Moderate	0	0	2 (2%)
STOMATITIS	1 (<1%)	0	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Mild	1 (<1%)	0	0
TOOTH IMPACTED	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
TOOTHACHE	1 (<1%)	1 (<1%)	0
Mild	1 (<1%)	1 (<1%)	0
VOMITING	2 (2%)	3 (3%)	0
Mild	0	2 (2%)	0
Moderate	1 (<1%)	1 (<1%)	0
Severe	1 (<1%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (14%)	13 (11%)	16 (14%)
APPLICATION SITE DERMATITIS	1 (<1%)	1 (<1%)	2 (2%)
Mild	0	1 (<1%)	2 (2%)
Severe	1 (<1%)	0	0
APPLICATION SITE DISCOLOURATION	2 (2%)	0	0
Mild	2 (2%)	0	0
APPLICATION SITE DISCOMFORT	0	0	2 (2%)
Mild	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
APPLICATION SITE ERYTHEMA	4 (3%)	2 (2%)	0
Mild	3 (3%)	2 (2%)	0
Moderate	1 (<1%)	0	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
APPLICATION SITE IRRITATION	0	2 (2%)	2 (2%)
Mild	0	2 (2%)	2 (2%)
APPLICATION SITE PRURITUS	8 (7%)	1 (<1%)	5 (4%)
Mild	6 (5%)	1 (<1%)	5 (4%)
Moderate	1 (<1%)	0	0
Severe	1 (<1%)	0	0
ASTHENIA	0	1 (<1%)	0
Mild	0	1 (<1%)	0
CHEST DISCOMFORT	1 (<1%)	0	2 (2%)
Mild	0	0	2 (2%)
Severe	1 (<1%)	0	0
CHEST PAIN	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
FATIGUE	3 (3%)	3 (3%)	3 (3%)
Mild	2 (2%)	3 (3%)	3 (3%)
Moderate	1 (<1%)	0	0
FEELING JITTERY	1 (<1%)	0	0
Mild	1 (<1%)	0	0
MALAISE	0	0	1 (<1%)
Mild	0	0	1 (<1%)
NON-CARDIAC CHEST PAIN	0	1 (<1%)	0
Mild	0	1 (<1%)	0
OEDEMA PERIPHERAL	2 (2%)	1 (<1%)	1 (<1%)
Mild	2 (2%)	0	0
Moderate	0	1 (<1%)	1 (<1%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PAIN	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
IMMUNE SYSTEM DISORDERS	0	0	4 (4%)
HYPERSENSITIVITY	0	0	2 (2%)
Moderate	0	0	2 (2%)
SEASONAL ALLERGY	0	0	2 (2%)
Mild	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
INFECTIONS AND INFESTATIONS	13 (11%)	15 (13%)	23 (20%)
BRONCHITIS	0	4 (3%)	0
Mild	0	2 (2%)	0
Moderate	0	2 (2%)	0
BRONCHITIS ACUTE	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
CELLULITIS	0	0	1 (<1%)
Mild	0	0	1 (<1%)
CHRONIC SINUSITIS	0	1 (<1%)	0
Mild	0	1 (<1%)	0
CYSTITIS	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
EAR INFECTION	0	2 (2%)	1 (<1%)
Mild	0	1 (<1%)	0
Moderate	0	1 (<1%)	1 (<1%)
EYE INFECTION	0	1 (<1%)	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Mild	0	1 (<1%)	0
FURUNCLE	1 (<1%)	0	0
Mild	1 (<1%)	0	0
GASTROENTERITIS VIRAL	0	1 (<1%)	1 (<1%)
Mild	0	1 (<1%)	0
Moderate	0	0	1 (<1%)
HERPES ZOSTER	1 (<1%)	0	0
Mild	1 (<1%)	0	0
INFECTED CYST	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
INFLUENZA	1 (<1%)	0	1 (<1%)
Mild	0	0	1 (<1%)
Severe	1 (<1%)	0	0
NASOPHARYNGITIS	3 (3%)	2 (2%)	8 (7%)
Mild	3 (3%)	1 (<1%)	6 (5%)
Moderate	0	1 (<1%)	2 (2%)
OTITIS EXTERNA	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
OTITIS MEDIA	1 (<1%)	0	0
Mild	1 (<1%)	0	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	1 (<1%)
Moderate	1 (<1%)	0	1 (<1%)
PNEUMONIA	0	1 (<1%)	1 (<1%)
Mild	0	0	1 (<1%)
Moderate	0	1 (<1%)	0
RHINITIS	0	0	1 (<1%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Mild	0	0	1 (<1%)
SINUSITIS	2 (2%)	1 (<1%)	0
Mild	1 (<1%)	0	0
Moderate	1 (<1%)	1 (<1%)	0
SUBCUTANEOUS ABSCESS	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
TOOTH ABSCESS	0	0	2 (2%)
Mild	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
TOOTH INFECTION	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
UPPER RESPIRATORY TRACT INFECTION	2 (2%)	2 (2%)	6 (5%)
Mild	1 (<1%)	2 (2%)	2 (2%)
Moderate	1 (<1%)	0	2 (2%)
Severe	0	0	2 (2%)
URINARY TRACT INFECTION	0	0	1 (<1%)
Mild	0	0	1 (<1%)
VAGINAL MYCOSIS	0	1 (<1%)	0
Mild	0	1 (<1%)	0
WOUND INFECTION	0	0	1 (<1%)
Mild	0	0	1 (<1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8 (7%)	6 (5%)	5 (4%)
ANKLE FRACTURE	1 (<1%)	0	0
Moderate	1 (<1%)	0	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 110)	Group 2 (N = 116)	Group 3 (N = 114)
ARTHROPOD BITE	0	2 (2%)	0
Mild	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
ARTHROPOD STING	1 (<1%)	1 (<1%)	0
Mild	1 (<1%)	1 (<1%)	0
BACK INJURY	1 (<1%)	0	0
Severe	1 (<1%)	0	0
CONTUSION	0	2 (2%)	0
Mild	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
EXCORIATION	1 (<1%)	0	0
Mild	1 (<1%)	0	0
FIBULA FRACTURE	0	0	1 (<1%)
Severe	0	0	1 (<1%)
FOOT FRACTURE	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
JOINT INJURY	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
LACERATION	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
LIGAMENT SPRAIN	0	0	1 (<1%)
Mild	0	0	1 (<1%)
POST PROCEDURAL PAIN	2 (2%)	1 (<1%)	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
Moderate	1 (<1%)	1 (<1%)	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
SKIN LACERATION	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
TIBIA FRACTURE	0	0	1 (<1%)
Severe	0	0	1 (<1%)
INVESTIGATIONS	4 (3%)	3 (3%)	2 (2%)
BLOOD CHOLESTEROL INCREASED	2 (2%)	0	0
Mild	2 (2%)	0	0
BLOOD PRESSURE INCREASED	1 (<1%)	0	0
Severe	1 (<1%)	0	0
BLOOD TRIGLYCERIDES INCREASED	1 (<1%)	0	0
Mild	1 (<1%)	0	0
ELECTROCARDIOGRAM ABNORMAL	0	1 (<1%)	0
Mild	0	1 (<1%)	0
HEPATIC ENZYME INCREASED	0	1 (<1%)	0
Mild	0	1 (<1%)	0
WEIGHT DECREASED	0	0	1 (<1%)
Mild	0	0	1 (<1%)
WEIGHT INCREASED	1 (<1%)	1 (<1%)	1 (<1%)
Mild	1 (<1%)	0	0
Moderate	0	1 (<1%)	1 (<1%)
METABOLISM AND NUTRITION DISORDERS	1 (<1%)	0	5 (4%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ANOREXIA	0	0	1 (<1%)
Mild	0	0	1 (<1%)
DIABETES MELLITUS	0	0	1 (<1%)
Mild	0	0	1 (<1%)
GOUT	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
INCREASED APPETITE	0	0	3 (3%)
Mild	0	0	3 (3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	9 (8%)	15 (13%)	7 (6%)
ARTHRALGIA	0	1 (<1%)	0
Mild	0	1 (<1%)	0
ARTHRITIS	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
BACK PAIN	4 (3%)	6 (5%)	0
Mild	3 (3%)	0	0
Moderate	1 (<1%)	6 (5%)	0
CHEST WALL PAIN	0	1 (<1%)	2 (2%)
Mild	0	0	2 (2%)
Moderate	0	1 (<1%)	0
FLANK PAIN	0	1 (<1%)	0
Mild	0	1 (<1%)	0
MUSCLE SPASMS	0	1 (<1%)	2 (2%)
Mild	0	0	1 (<1%)
Moderate	0	0	1 (<1%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Severe	0	1 (<1%)	0
MUSCULOSKELETAL PAIN	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
MYALGIA	1 (<1%)	2 (2%)	1 (<1%)
Mild	0	1 (<1%)	0
Moderate	1 (<1%)	1 (<1%)	1 (<1%)
NECK PAIN	1 (<1%)	3 (3%)	0
Mild	0	1 (<1%)	0
Moderate	1 (<1%)	2 (2%)	0
PAIN IN EXTREMITY	1 (<1%)	0	2 (2%)
Mild	0	0	2 (2%)
Moderate	1 (<1%)	0	0
PAIN IN JAW	2 (2%)	0	0
Mild	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
SHOULDER PAIN	0	1 (<1%)	2 (2%)
Mild	0	0	1 (<1%)
Moderate	0	1 (<1%)	1 (<1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (<1%)	0	0
BLADDER NEOPLASM	1 (<1%)	0	0
Severe	1 (<1%)	0	0
NERVOUS SYSTEM DISORDERS	16 (14%)	16 (14%)	14 (12%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DISTURBANCE IN ATTENTION	2 (2%)	1 (<1%)	1 (<1%)
Mild	1 (<1%)	1 (<1%)	1 (<1%)
Moderate	1 (<1%)	0	0
DIZZINESS	4 (3%)	2 (2%)	2 (2%)
Mild	4 (3%)	2 (2%)	2 (2%)
DYSGEUSIA	1 (<1%)	0	1 (<1%)
Mild	0	0	1 (<1%)
Moderate	1 (<1%)	0	0
HEADACHE	7 (6%)	12 (10%)	4 (4%)
Mild	5 (4%)	8 (7%)	2 (2%)
Moderate	2 (2%)	4 (3%)	2 (2%)
HYPOAESTHESIA	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
LETHARGY	1 (<1%)	0	0
Mild	1 (<1%)	0	0
MENTAL IMPAIRMENT	0	0	1 (<1%)
Mild	0	0	1 (<1%)
MIGRAINE	1 (<1%)	1 (<1%)	1 (<1%)
Moderate	1 (<1%)	0	1 (<1%)
Severe	1 (<1%)	1 (<1%)	0
PARAESTHESIA	1 (<1%)	0	2 (2%)
Mild	0	0	1 (<1%)
Moderate	1 (<1%)	0	1 (<1%)
SINUS HEADACHE	0	0	1 (<1%)
Mild	0	0	1 (<1%)
TENSION HEADACHE	0	0	1 (<1%)

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Moderate	0	0	1 (<1%)
PSYCHIATRIC DISORDERS	34 (29%)	16 (14%)	14 (12%)
ABNORMAL DREAMS	4 (3%)	1 (<1%)	4 (4%)
Mild	3 (3%)	1 (<1%)	4 (4%)
Moderate	1 (<1%)	0	0
ANXIETY	8 (7%)	2 (2%)	3 (3%)
Mild	7 (6%)	2 (2%)	2 (2%)
Moderate	1 (<1%)	0	1 (<1%)
DEPRESSED MOOD	0	1 (<1%)	0
Mild	0	1 (<1%)	0
DEPRESSION	1 (<1%)	3 (3%)	3 (3%)
Mild	1 (<1%)	2 (2%)	1 (<1%)
Moderate	0	1 (<1%)	2 (2%)
EMOTIONAL DISORDER	1 (<1%)	0	0
Mild	1 (<1%)	0	0
INITIAL INSOMNIA	0	2 (2%)	0
Mild	0	2 (2%)	0
INSOMNIA	15 (13%)	6 (5%)	7 (6%)
Mild	9 (8%)	3 (3%)	5 (4%)
Moderate	6 (5%)	3 (3%)	2 (2%)
IRRITABILITY	7 (6%)	2 (2%)	2 (2%)
Mild	5 (4%)	2 (2%)	2 (2%)
Moderate	2 (2%)	0	1 (<1%)
MOOD SWINGS	1 (<1%)	0	0
Mild	1 (<1%)	0	0
NERVOUSNESS	4 (3%)	0	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Mild	4 (3%)	0	0
NIGHTMARE	2 (2%)	1 (<1%)	0
Mild	2 (2%)	1 (<1%)	0
RESTLESSNESS	1 (<1%)	0	0
Mild	1 (<1%)	0	0
SLEEP DISORDER	1 (<1%)	0	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
Moderate	1 (<1%)	0	0
RENAL AND URINARY DISORDERS	1 (<1%)	0	1 (<1%)
HAEMATURIA	1 (<1%)	0	0
Mild	1 (<1%)	0	0
POLLAKIURIA	0	0	1 (<1%)
Mild	0	0	1 (<1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (<1%)
MENSTRUATION IRREGULAR	0	0	1 (<1%)
Mild	0	0	1 (<1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13 (11%)	13 (11%)	15 (13%)
ALLERGIC SINUSITIS	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
ASTHMA	1 (<1%)	0	0
Moderate	1 (<1%)	0	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (<1%)	0
Severe	0	1 (<1%)	0
COUGH	4 (3%)	2 (2%)	7 (6%)
Mild	3 (3%)	1 (<1%)	3 (3%)
Moderate	0	1 (<1%)	4 (4%)
Severe	1 (<1%)	0	0
DYSPNOEA	3 (3%)	2 (2%)	2 (2%)
Mild	2 (2%)	0	2 (2%)
Moderate	1 (<1%)	2 (2%)	0
EPISTAXIS	0	1 (<1%)	1 (<1%)
Mild	0	1 (<1%)	1 (<1%)
NASAL CONGESTION	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
NASAL DISCOMFORT	1 (<1%)	0	0
Mild	1 (<1%)	0	0
PHARYNGOLARYNGEAL PAIN	5 (4%)	2 (2%)	3 (3%)
Mild	4 (3%)	2 (2%)	2 (2%)
Moderate	1 (<1%)	0	1 (<1%)
POSTNASAL DRIP	1 (<1%)	0	0
Mild	1 (<1%)	0	0
PRODUCTIVE COUGH	2 (2%)	2 (2%)	1 (<1%)
Mild	2 (2%)	2 (2%)	0
Moderate	0	0	1 (<1%)
RESPIRATORY TRACT CONGESTION	0	2 (2%)	0
Mild	0	2 (2%)	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
RHINORRHOEA	0	0	1 (<1%)
Mild	0	0	1 (<1%)
RHONCHI	0	0	1 (<1%)
Mild	0	0	1 (<1%)
SINUS CONGESTION	0	0	2 (2%)
Mild	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
THROAT IRRITATION	0	0	1 (<1%)
Mild	0	0	1 (<1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (7%)	3 (3%)	7 (6%)
ACTINIC KERATOSIS	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
DERMATITIS CONTACT	1 (<1%)	1 (<1%)	2 (2%)
Mild	1 (<1%)	1 (<1%)	1 (<1%)
Moderate	0	0	1 (<1%)
DRY SKIN	1 (<1%)	0	0
Mild	1 (<1%)	0	0
ECZEMA	1 (<1%)	0	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
PRURITUS	1 (<1%)	1 (<1%)	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
Moderate	0	1 (<1%)	0
RASH	0	0	2 (2%)
Moderate	0	0	2 (2%)
SKIN IRRITATION	1 (<1%)	0	0

Table S35 Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Mild	1 (<1%)	0	0
URTICARIA	2 (2%)	1 (<1%)	1 (<1%)
Mild	1 (<1%)	1 (<1%)	1 (<1%)
Moderate	1 (<1%)	0	0
SURGICAL AND MEDICAL PROCEDURES	1 (<1%)	2 (2%)	1 (<1%)
ENDODONTIC PROCEDURE	0	1 (<1%)	0
Moderate	0	1 (<1%)	0
SKIN NEOPLASM EXCISION	0	0	1 (<1%)
Moderate	0	0	1 (<1%)
TOOTH EXTRACTION	0	1 (<1%)	0
Mild	0	1 (<1%)	0
TOOTH REPAIR	1 (<1%)	0	0
Mild	1 (<1%)	0	0
VASCULAR DISORDERS	3 (3%)	0	3 (3%)
AORTIC ANEURYSM	1 (<1%)	0	0
Moderate	1 (<1%)	0	0
HOT FLUSH	0	0	2 (2%)
Moderate	0	0	2 (2%)
HYPERTENSION	2 (2%)	0	1 (<1%)
Mild	1 (<1%)	0	1 (<1%)
Moderate	1 (<1%)	0	0

N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
Subjects with Any Adverse Events After Visit 4	56 (51%)	40 (36%)	53 (50%)
CARDIAC DISORDERS	1 (<1%)	0	3 (3%)
CORONARY ARTERY DISEASE	0	0	1 (<1%)
PALPITATIONS	1 (<1%)	0	1 (<1%)
TACHYCARDIA	0	0	1 (<1%)
EAR AND LABYRINTH DISORDERS	0	0	1 (<1%)
VERTIGO	0	0	1 (<1%)
ENDOCRINE DISORDERS	1 (<1%)	0	0
HYPOTHYROIDISM	1 (<1%)	0	0
EYE DISORDERS	1 (<1%)	0	3 (3%)
BLEPHAROSPASM	0	0	1 (<1%)
CONJUNCTIVITIS	1 (<1%)	0	1 (<1%)
EYE PRURITUS	0	0	1 (<1%)
GASTROINTESTINAL DISORDERS	10 (9%)	3 (3%)	8 (7%)
ABDOMINAL ADHESIONS	0	0	1 (<1%)
ABDOMINAL DISCOMFORT	0	0	1 (<1%)
ABDOMINAL DISTENSION	0	0	1 (<1%)
ABDOMINAL PAIN	1 (<1%)	0	1 (<1%)

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
ABDOMINAL PAIN UPPER	0	0	1 (<1%)
APHTHOUS STOMATITIS	0	0	1 (<1%)
DIARRHOEA	2 (2%)	1 (<1%)	1 (<1%)
DYSPEPSIA	2 (2%)	0	1 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	0	0	1 (<1%)
NAUSEA	4 (4%)	2 (2%)	1 (<1%)
FLATULENCE	1 (<1%)	0	0
STOMACH DISCOMFORT	1 (<1%)	0	0
STOMATITIS	1 (<1%)	0	0
VOMITING	1 (<1%)	1 (<1%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	11 (10%)	7 (6%)	12 (11%)
APPLICATION SITE PRURITUS	6 (6%)	1 (<1%)	4 (4%)
APPLICATION SITE DERMATITIS	1 (<1%)	0	2 (2%)
APPLICATION SITE DISCOMFORT	0	0	2 (2%)
APPLICATION SITE IRRITATION	0	1 (<1%)	2 (2%)
FATIGUE	0	1 (<1%)	2 (2%)
CHEST DISCOMFORT	0	0	1 (<1%)
APPLICATION SITE DISCOLOURATION	2 (2%)	0	0
APPLICATION SITE ERYTHEMA	2 (2%)	2 (2%)	0

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
CHEST PAIN	0	1 (<1%)	0
FEELING JITTERY	1 (<1%)	0	0
OEDEMA PERIPHERAL	1 (<1%)	1 (<1%)	0
PAIN	1 (<1%)	0	0
IMMUNE SYSTEM DISORDERS	0	0	2 (2%)
HYPERSENSITIVITY	0	0	1 (<1%)
SEASONAL ALLERGY	0	0	1 (<1%)
INFECTIONS AND INFESTATIONS	9 (8%)	8 (7%)	18 (17%)
NASOPHARYNGITIS	2 (2%)	1 (<1%)	7 (7%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)	5 (5%)
TOOTH ABSCESS	0	0	2 (2%)
CELLULITIS	0	0	1 (<1%)
EAR INFECTION	0	2 (2%)	1 (<1%)
INFLUENZA	1 (<1%)	0	1 (<1%)
RHINITIS	0	0	1 (<1%)
WOUND INFECTION	0	0	1 (<1%)
BRONCHITIS	0	3 (3%)	0
BRONCHITIS ACUTE	0	1 (<1%)	0
CHRONIC SINUSITIS	0	1 (<1%)	0
CYSTITIS	0	1 (<1%)	0
GASTROENTERITIS VIRAL	0	1 (<1%)	0
HERPES ZOSTER	1 (<1%)	0	0
OTITIS EXTERNA	1 (<1%)	0	0

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
OTITIS MEDIA	1 (<1%)	0	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	0
SINUSITIS	1 (<1%)	1 (<1%)	0
VAGINAL MYCOSIS	0	1 (<1%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (6%)	5 (5%)	3 (3%)
FIBULA FRACTURE	0	0	1 (<1%)
JOINT INJURY	0	0	1 (<1%)
POST PROCEDURAL PAIN	1 (<1%)	1 (<1%)	1 (<1%)
TIBIA FRACTURE	0	0	1 (<1%)
ARTHROPOD BITE	0	1 (<1%)	0
ARTHROPOD STING	1 (<1%)	1 (<1%)	0
BACK INJURY	1 (<1%)	0	0
CONTUSION	0	2 (2%)	0
EXCORIATION	1 (<1%)	0	0
FOOT FRACTURE	0	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0	0
SKIN LACERATION	1 (<1%)	0	0
INVESTIGATIONS	1 (<1%)	1 (<1%)	0
BLOOD CHOLESTEROL INCREASED	1 (<1%)	0	0
HEPATIC ENZYME INCREASED	0	1 (<1%)	0

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
METABOLISM AND NUTRITION DISORDERS	1 (<1%)	0	4 (4%)
INCREASED APPETITE	0	0	3 (3%)
DIABETES MELLITUS	0	0	1 (<1%)
GOUT	1 (<1%)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (7%)	11 (10%)	6 (6%)
PAIN IN EXTREMITY	0	0	2 (2%)
SHOULDER PAIN	0	0	2 (2%)
CHEST WALL PAIN	0	1 (<1%)	1 (<1%)
MUSCLE SPASMS	0	1 (<1%)	1 (<1%)
MYALGIA	1 (<1%)	2 (2%)	1 (<1%)
ARTHRITIS	1 (<1%)	0	0
BACK PAIN	4 (4%)	4 (4%)	0
FLANK PAIN	0	1 (<1%)	0
MUSCULOSKELETAL PAIN	1 (<1%)	0	0
NECK PAIN	0	2 (2%)	0
PAIN IN JAW	2 (2%)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (<1%)	0	0
BLADDER NEOPLASM	1 (<1%)	0	0
NERVOUS SYSTEM DISORDERS	6 (6%)	7 (6%)	6 (6%)

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
HEADACHE	1 (<1%)	4 (4%)	2 (2%)
PARAESTHESIA	0	0	2 (2%)
DISTURBANCE IN ATTENTION	1 (<1%)	1 (<1%)	1 (<1%)
DYSGEUSIA	0	0	1 (<1%)
TENSION HEADACHE	0	0	1 (<1%)
DIZZINESS	3 (3%)	1 (<1%)	0
LETHARGY	1 (<1%)	0	0
MIGRAINE	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	21 (19%)	11 (10%)	12 (11%)
ABNORMAL DREAMS	2 (2%)	1 (<1%)	4 (4%)
ANXIETY	3 (3%)	1 (<1%)	3 (3%)
INSOMNIA	11 (10%)	2 (2%)	3 (3%)
DEPRESSION	1 (<1%)	3 (3%)	2 (2%)
IRRITABILITY	2 (2%)	2 (2%)	2 (2%)
SLEEP DISORDER	1 (<1%)	0	1 (<1%)
DEPRESSED MOOD	0	1 (<1%)	0
INITIAL INSOMNIA	0	2 (2%)	0
MOOD SWINGS	1 (<1%)	0	0
NERVOUSNESS	2 (2%)	0	0
NIGHTMARE	2 (2%)	1 (<1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (6%)	8 (7%)	8 (7%)
DYSPNOEA	2 (2%)	2 (2%)	2 (2%)
COUGH	1 (<1%)	0	1 (<1%)

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
EPISTAXIS	0	1 (<1%)	1 (<1%)
PHARYNGOLARYNGEAL PAIN	2 (2%)	1 (<1%)	1 (<1%)
PRODUCTIVE COUGH	1 (<1%)	1 (<1%)	1 (<1%)
RHONCHI	0	0	1 (<1%)
SINUS CONGESTION	0	0	1 (<1%)
ALLERGIC SINUSITIS	0	1 (<1%)	0
ASTHMA	1 (<1%)	0	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (<1%)	0
NASAL DISCOMFORT	1 (<1%)	0	0
POSTNASAL DRIP	1 (<1%)	0	0
RESPIRATORY TRACT CONGESTION	0	1 (<1%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (5%)	3 (3%)	7 (7%)
DERMATITIS CONTACT	0	1 (<1%)	2 (2%)
RASH	0	0	2 (2%)
ECZEMA	1 (<1%)	0	1 (<1%)
PRURITUS	0	1 (<1%)	1 (<1%)
URTICARIA	1 (<1%)	1 (<1%)	1 (<1%)
ACTINIC KERATOSIS	1 (<1%)	0	0
DRY SKIN	1 (<1%)	0	0
SKIN IRRITATION	1 (<1%)	0	0
SURGICAL AND MEDICAL PROCEDURES	1 (<1%)	2 (2%)	1 (<1%)

Table S36 Summary of Adverse Events After Visit 4 by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 109)	Group 2 (N = 110)	Group 3 (N = 107)
SKIN NEOPLASM EXCISION	0	0	1 (<1%)
ENDODONTIC PROCEDURE	0	1 (<1%)	0
TOOTH EXTRACTION	0	1 (<1%)	0
TOOTH REPAIR	1 (<1%)	0	0
VASCULAR DISORDERS	3 (3%)	0	1 (<1%)
HOT FLUSH	0	0	1 (<1%)
AORTIC ANEURYSM	1 (<1%)	0	0
HYPERTENSION	2 (2%)	0	0

N = number of randomized subjects who received study treatment and discontined study at or after Visit 4
% = n/N x 100%

Table S37 Summary of Severe or Life Threatening Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Subjects with Any Severe or Life Threatening Adverse Events	7 (6%)	3 (3%)	3 (3%)
GASTROINTESTINAL DISORDERS	1 (<1%)	0	0
NAUSEA	1 (<1%)	0	0
VOMITING	1 (<1%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2%)	0	0
APPLICATION SITE DERMATITIS	1 (<1%)	0	0
APPLICATION SITE PRURITUS	1 (<1%)	0	0
CHEST DISCOMFORT	1 (<1%)	0	0
INFECTIONS AND INFESTATIONS	1 (<1%)	0	2 (2%)
UPPER RESPIRATORY TRACT INFECTION	0	0	2 (2%)
INFLUENZA	1 (<1%)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (<1%)	0	1 (<1%)
FIBULA FRACTURE	0	0	1 (<1%)
TIBIA FRACTURE	0	0	1 (<1%)
BACK INJURY	1 (<1%)	0	0

Table S37 Summary of Severe or Life Threatening Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
INVESTIGATIONS	1 (<1%)	0	0
BLOOD PRESSURE INCREASED	1 (<1%)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (<1%)	0
MUSCLE SPASMS	0	1 (<1%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (<1%)	0	0
BLADDER NEOPLASM	1 (<1%)	0	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)	0
MIGRAINE	1 (<1%)	1 (<1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (<1%)	1 (<1%)	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (<1%)	0
COUGH	1 (<1%)	0	0

N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Visit 1			
Heart rate (bpm)			
Number of available subjects	116	116	114
Mean (SD)	75.1 (10.7)	77.2 (11.1)	76.4 (9.8)
Median	73.5	76.0	76.0
Minimum, maximum	48, 119	52, 114	59, 104
Systolic Blood Pressure (mmHg)			
Number of available subjects	116	116	114
Mean (SD)	122.1 (11.2)	119.1 (12.4)	120.2 (12.0)
Median	122.5	120.0	120.0
Minimum, maximum	95, 140	88, 140	90, 140
Diastolic Blood Pressure (mmHg)			
Number of available subjects	116	116	114
Mean (SD)	76.5 (7.5)	75.0 (8.8)	76.1 (8.1)
Median	78.0	76.0	78.0
Minimum, maximum	58, 90	52, 90	54, 90
Visit 2			
Heart rate (bpm)			
Number of available subjects	116	116	114
Mean (SD)	75.8 (11.0)	77.7 (11.9)	76.6 (9.9)
Median	74.0	75.0	76.0
Minimum, maximum	54, 104	52, 106	58, 102

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Systolic Blood Pressure (mmHg)			
Number of available subjects	116	116	114
Mean (SD)	124.1 (10.7)	119.4 (12.2)	121.7 (11.6)
Median	124.0	120.5	122.5
Minimum, maximum	92, 154	90, 144	91, 140
Diastolic Blood Pressure (mmHg)			
Number of available subjects	115	116	114
Mean (SD)	76.4 (8.3)	74.9 (8.9)	75.8 (8.6)
Median	78.0	76.0	77.0
Minimum, maximum	50, 90	50, 90	50, 90
Visit 3			
Heart rate (bpm)			
Number of available subjects	113	114	109
Mean (SD)	77.1 (11.5)	77.1 (11.9)	76.5 (11.3)
Median	76.0	76.0	76.0
Minimum, maximum	53, 112	57, 112	52, 108
Systolic Blood Pressure (mmHg)			
Number of available subjects	113	114	109
Mean (SD)	123.2 (11.8)	117.9 (12.9)	119.7 (14.4)
Median	124.0	120.0	122.0
Minimum, maximum	92, 158	84, 140	88, 152

**Table S38 Summary of Vital Signs
(Safety Population)**

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Diastolic Blood Pressure (mmHg)			
Number of available subjects	113	114	109
Mean (SD)	77.0 (8.1)	74.2 (8.8)	75.0 (9.2)
Median	78.0	74.0	75.0
Minimum, maximum	52, 98	47, 92	50, 100
Visit 4			
Heart rate (bpm)			
Number of available subjects	108	110	107
Mean (SD)	77.6 (11.8)	76.5 (10.8)	76.3 (9.4)
Median	76.0	74.0	76.0
Minimum, maximum	58, 113	60, 104	50, 98
Systolic Blood Pressure (mmHg)			
Number of available subjects	108	110	107
Mean (SD)	121.4 (11.1)	120.0 (13.9)	121.0 (12.9)
Median	122.0	120.0	120.0
Minimum, maximum	94, 144	80, 160	92, 154
Diastolic Blood Pressure (mmHg)			
Number of available subjects	108	110	107
Mean (SD)	76.3 (8.7)	74.2 (9.3)	75.4 (8.0)
Median	77.5	74.0	74.0
Minimum, maximum	52, 96	50, 90	54, 90
Visit 5			

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Heart rate (bpm)			
Number of available subjects	101	98	104
Mean (SD)	77.2 (11.6)	75.9 (11.7)	76.4 (10.6)
Median	76.0	72.0	77.5
Minimum, maximum	60, 112	52, 113	50, 112
Systolic Blood Pressure (mmHg)			
Number of available subjects	101	98	104
Mean (SD)	120.1 (11.9)	118.4 (12.0)	120.6 (12.4)
Median	120.0	118.0	120.5
Minimum, maximum	88, 150	92, 139	90, 149
Diastolic Blood Pressure (mmHg)			
Number of available subjects	101	98	104
Mean (SD)	75.2 (8.3)	73.7 (9.5)	74.9 (8.8)
Median	76.0	72.0	76.0
Minimum, maximum	58, 108	50, 96	50, 92
Visit 6			
Heart rate (bpm)			
Number of available subjects	87	79	95
Mean (SD)	73.5 (10.4)	73.9 (10.4)	74.1 (10.3)
Median	72.0	73.0	72.0
Minimum, maximum	60, 112	49, 100	48, 104
Systolic Blood Pressure (mmHg)			
Number of available subjects	87	79	95

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Mean (SD)	120.1 (11.1)	119.3 (12.0)	120.7 (13.6)
Median	120.0	120.0	120.0
Minimum, maximum	90, 140	92, 152	92, 172
Diastolic Blood Pressure (mmHg)			
Number of available subjects	87	79	95
Mean (SD)	74.4 (8.3)	74.1 (9.2)	75.3 (8.5)
Median	74.0	74.0	76.0
Minimum, maximum	56, 100	52, 90	50, 90
Visit 7			
Heart rate (bpm)			
Number of available subjects	70	56	70
Mean (SD)	73.1 (9.7)	74.3 (10.7)	74.6 (11.6)
Median	71.5	72.0	74.0
Minimum, maximum	58, 108	56, 100	51, 114
Systolic Blood Pressure (mmHg)			
Number of available subjects	70	56	70
Mean (SD)	120.4 (9.9)	119.4 (10.6)	120.1 (12.7)
Median	120.0	120.0	120.0
Minimum, maximum	100, 148	92, 140	94, 164
Diastolic Blood Pressure (mmHg)			
Number of available subjects	70	56	70
Mean (SD)	75.0 (8.3)	74.7 (7.3)	74.1 (8.9)

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Median	74.0	74.0	74.5
Minimum, maximum	56, 98	58, 88	56, 96
Visit 8			
Heart rate (bpm)			
Number of available subjects	60	45	60
Mean (SD)	76.2 (12.6)	73.3 (8.1)	73.1 (10.1)
Median	74.0	72.0	72.0
Minimum, maximum	58, 120	60, 97	60, 96
Systolic Blood Pressure (mmHg)			
Number of available subjects	60	45	60
Mean (SD)	118.8 (9.9)	118.2 (10.8)	120.3 (14.1)
Median	120.0	120.0	120.5
Minimum, maximum	100, 136	98, 139	88, 176
Diastolic Blood Pressure (mmHg)			
Number of available subjects	60	45	60
Mean (SD)	74.8 (8.4)	73.7 (8.2)	75.7 (9.5)
Median	74.5	74.0	76.0
Minimum, maximum	58, 89	58, 89	50, 95
Visit 9 Heart rate (bpm)			
Number of available subjects	54	43	56
Mean (SD)	74.5 (11.3)	74.0 (9.4)	74.3 (10.3)
Median	70.0	76.0	75.5

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Minimum, maximum	52, 100	60, 92	58, 99
Systolic Blood Pressure (mmHg)			
Number of available subjects	54	43	56
Mean (SD)	119.6 (10.4)	118.1 (12.4)	117.7 (13.8)
Median	119.5	120.0	118.0
Minimum, maximum	94, 140	86, 140	88, 166
Diastolic Blood Pressure (mmHg)			
Number of available subjects	54	43	56
Mean (SD)	75.1 (7.2)	74.5 (8.5)	73.7 (8.6)
Median	76.0	76.0	76.0
Minimum, maximum	58, 90	50, 90	50, 88
Visit 10			
Heart rate (bpm)			
Number of available subjects	49	39	52
Mean (SD)	72.3 (9.6)	73.0 (7.2)	73.3 (8.9)
Median	72.0	72.0	74.0
Minimum, maximum	58, 103	60, 88	52, 92
Systolic Blood Pressure (mmHg)			
Number of available subjects	49	39	52
Mean (SD)	120.2 (8.1)	119.5 (10.1)	118.4 (11.0)
Median	120.0	122.0	118.0
Minimum, maximum	98, 137	98, 138	94, 157

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Diastolic Blood Pressure (mmHg)			
Number of available subjects	49	39	52
Mean (SD)	75.0 (6.3)	75.4 (7.8)	74.0 (7.1)
Median	74.0	76.0	74.0
Minimum, maximum	64, 88	58, 90	58, 89
Visit 11			
Heart rate (bpm)			
Number of available subjects	45	37	45
Mean (SD)	72.5 (11.2)	74.8 (9.9)	73.8 (10.2)
Median	70.0	72.0	72.0
Minimum, maximum	58, 104	60, 107	50, 107
Systolic Blood Pressure (mmHg)			
Number of available subjects	45	37	45
Mean (SD)	118.7 (8.8)	118.6 (10.6)	121.9 (13.5)
Median	120.0	118.0	120.0
Minimum, maximum	100, 135	90, 142	100, 183
Diastolic Blood Pressure (mmHg)			
Number of available subjects	45	37	45
Mean (SD)	74.1 (7.2)	73.2 (8.0)	74.4 (7.2)
Median	74.0	72.0	74.0
Minimum, maximum	58, 90	58, 100	58, 92
Visit 12			

Table S38 Summary of Vital Signs
(Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
Heart rate (bpm)			
Number of available subjects	32	20	32
Mean (SD)	77.6 (13.5)	72.5 (8.5)	74.9 (10.5)
Median	73.0	71.0	72.5
Minimum, maximum	54, 113	63, 90	60, 106
Systolic Blood Pressure (mmHg)			
Number of available subjects	32	20	32
Mean (SD)	124.0 (10.8)	120.2 (8.0)	121.1 (11.7)
Median	123.0	121.0	122.0
Minimum, maximum	102, 140	102, 135	100, 145
Diastolic Blood Pressure (mmHg)			
Number of available subjects	32	20	32
Mean (SD)	76.5 (8.1)	75.2 (5.9)	75.0 (8.3)
Median	76.0	74.0	75.0
Minimum, maximum	62, 98	65, 89	58, 88

N = number of randomized subjects who received study treatment

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS	1 (<1%)	0	1 (<1%)
LOTREL	1 (<1%)	0	1 (<1%)
ACE INHIBITORS AND DIURETICS	0	1 (<1%)	0
PRINZIDE	0	1 (<1%)	0
ACE INHIBITORS, PLAIN	8 (7%)	5 (4%)	8 (7%)
LISINOPRIL	2 (2%)	4 (3%)	4 (4%)
RAMIPRIL	4 (3%)	0	2 (2%)
FOSINOPRIL SODIUM	0	0	1 (<1%)
QUINAPRIL HYDROCHLORIDE	2 (2%)	0	1 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	1 (<1%)	0
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	2 (2%)	1 (<1%)	0
ARTHROTEC	0	1 (<1%)	0
DICLOFENAC	1 (<1%)	0	0
INDOMETACIN	1 (<1%)	0	0
ACIDIFIERS	0	1 (<1%)	0
AQUA-BAN	0	1 (<1%)	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ADRENERGICS AND OTH.DRUGS FOR OBSTRUCT.AIRWAY DIS.	2 (2%)	2 (2%)	4 (4%)
SERETIDE MITE	2 (2%)	2 (2%)	3 (3%)
COMBIVENT /GFR/	0	0	1 (<1%)
ALL OTHER THERAPEUTIC PRODUCTS	4 (3%)	2 (2%)	1 (<1%)
ALL OTHER THERAPEUTIC PRODUCTS	4 (3%)	2 (2%)	1 (<1%)
ALPHA AND BETA BLOCKING AGENTS	0	1 (<1%)	1 (<1%)
LABETALOL	0	0	1 (<1%)
CARVEDILOL	0	1 (<1%)	0
ALPHA-ADRENORECEPTOR ANTAGONISTS	0	1 (<1%)	2 (2%)
DOXAZOSIN MESILATE	0	0	1 (<1%)
PRAZOSIN	0	0	1 (<1%)
TAMSULOSIN HYDROCHLORIDE	0	1 (<1%)	0
AMINO ACIDS AND DERIVATIVES	0	1 (<1%)	0
CARNITINE	0	1 (<1%)	0
AMINOALKYL ETHERS	2 (2%)	2 (2%)	5 (4%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (<1%)	1 (<1%)	5 (4%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DIPHENHYDRAMINE	1 (<1%)	1 (<1%)	0
AMINOQUINOLINES	1 (<1%)	0	0
HYDROXYCHLOROQUINE SULFATE	1 (<1%)	0	0
AMINOSALICYLIC ACID AND SIMILAR AGENTS	0	1 (<1%)	0
MESALAZINE	0	1 (<1%)	0
ANESTHETICS FOR TOPICAL USE	1 (<1%)	0	0
BENZOCAINE	1 (<1%)	0	0
LANACANE	1 (<1%)	0	0
ANGIOTENSIN II ANTAGONISTS AND DIURETICS	1 (<1%)	2 (2%)	2 (2%)
BENICAR HCT	0	1 (<1%)	1 (<1%)
KARVEA HCT	0	0	1 (<1%)
CO-DIOVAN	1 (<1%)	1 (<1%)	0
ANGIOTENSIN II ANTAGONISTS, PLAIN	4 (3%)	3 (3%)	1 (<1%)
OLMESARTAN MEDOXOMIL	0	1 (<1%)	1 (<1%)
CANDESARTAN CILEXETIL	0	1 (<1%)	0
LOSARTAN POTASSIUM	0	1 (<1%)	0
VALSARTAN	4 (3%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ANILIDES	12 (10%)	18 (16%)	13 (11%)
PARACETAMOL	9 (8%)	11 (9%)	9 (8%)
CO-TYLENOL	1 (<1%)	0	2 (2%)
PARA-SELTZER	1 (<1%)	2 (2%)	1 (<1%)
SINUTAB "ACHE"	0	0	1 (<1%)
ALKA-SELTZER PLUS COLD & COUGH	0	1 (<1%)	0
BENYLIN 4 FLU	1 (<1%)	0	0
COMTREX	0	1 (<1%)	0
MEDINITE	1 (<1%)	1 (<1%)	0
PAMPRIN	0	1 (<1%)	0
THOMAPYRIN N	0	2 (2%)	0
ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	1 (<1%)	0	0
ANTIALLERGIC AGENTS, EXCL CORTICOSTEROIDS	1 (<1%)	0	0
ANTIARRHYTHMICS, CLASS III	0	1 (<1%)	0
AMIODARONE	0	1 (<1%)	0
ANTICHOLINERGICS	0	1 (<1%)	2 (2%)
TIOTROPIUM BROMIDE	0	0	2 (2%)
IPRATROPIUM BROMIDE	0	1 (<1%)	0
ANTIINFECT. AND ANTISEPT. FOR LOCAL ORAL TREATMENT	0	0	1 (<1%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DOXYCYCLINE HYCLATE	0	0	1 (<1%)
ANTIINFECTIVES	1 (<1%)	0	0
FLOXIN OTIC	1 (<1%)	0	0
ANTIINFLAMMATORY/ANTIRHEUMATIC PROD.,NON-STEROIDS	1 (<1%)	0	0
GLUCOSAMINE W/CHONDROITIN	1 (<1%)	0	0
ASCORBIC ACID (VITAMIN C), PLAIN	6 (5%)	4 (3%)	4 (4%)
ASCORBIC ACID	6 (5%)	4 (3%)	4 (4%)
AZASPIRODECANEDIONE DERIVATIVES	0	0	1 (<1%)
BUSPIRONE HYDROCHLORIDE	0	0	1 (<1%)
BELLADONNA ALKALOIDS, TERTIARY AMINES	1 (<1%)	0	0
HYOSCYAMINE SULFATE	1 (<1%)	0	0
BELLADONNA AND DERIVATIVES IN COMB.WITH PSYCHOLEP.	1 (<1%)	0	0
DONNATAL	1 (<1%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
BENZODIAZEPINE RELATED DRUGS	0	0	1 (<1%)
ZOLPIDEM TARTRATE	0	0	1 (<1%)
BENZOTHIAZEPINE DERIVATIVES	0	0	1 (<1%)
DILTIAZEM	0	0	1 (<1%)
BETA BLOCKING AGENTS	0	0	1 (<1%)
TIMOLOL	0	0	1 (<1%)
BETA BLOCKING AGENTS, NON-SELECTIVE	0	1 (<1%)	1 (<1%)
NADOLOL	0	0	1 (<1%)
PROPRANOLOL	0	1 (<1%)	0
BETA BLOCKING AGENTS, SELECTIVE	8 (7%)	6 (5%)	3 (3%)
ATENOLOL	3 (3%)	3 (3%)	3 (3%)
METOPROLOL	3 (3%)	0	0
METOPROLOL SUCCINATE	1 (<1%)	3 (3%)	0
METOPROLOL TARTRATE	1 (<1%)	0	0
BIGUANIDES	1 (<1%)	3 (3%)	2 (2%)
METFORMIN	1 (<1%)	3 (3%)	2 (2%)
BISPHOSPHONATES	2 (2%)	1 (<1%)	2 (2%)
ALENDRONATE SODIUM	1 (<1%)	1 (<1%)	1 (<1%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
RISEDRONATE SODIUM	1 (<1%)	0	1 (<1%)
BULK PRODUCERS	0	0	1 (<1%)
POLYCARBOPHIL CALCIUM	0	0	1 (<1%)
CALCITONIN PREPARATIONS	0	1 (<1%)	0
CALCITONIN, SALMON	0	1 (<1%)	0
CALCIUM	3 (3%)	1 (<1%)	8 (7%)
CALCIUM	2 (2%)	0	8 (7%)
CALCIUM WITH VITAMIN D	1 (<1%)	1 (<1%)	0
CALCIUM COMPOUNDS	4 (3%)	2 (2%)	5 (4%)
CALCIUM CARBONATE	4 (3%)	2 (2%)	5 (4%)
CALCIUM, COMBINATIONS WITH OTHER DRUGS	0	1 (<1%)	0
OS-CAL	0	1 (<1%)	0
CARBAMIC ACID ESTERS	0	0	1 (<1%)
METHOCARBAMOL	0	0	1 (<1%)
CEPHALOSPORINS AND RELATED SUBSTANCES	0	1 (<1%)	0
CEFALEXIN	0	1 (<1%)	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
COMB AND COMPL. OF ALUMIN., CALC. AND MAGNES. COMP	1 (<1%)	0	0
MAALOX /USA/	1 (<1%)	0	0
COMB OF PENICILLINS, INCL. BETA-LACTAMASE INHIB.	1 (<1%)	0	0
AMOXICILLIN W/CLAVULANATE POTASSIUM	1 (<1%)	0	0
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	2 (2%)	1 (<1%)	1 (<1%)
GLIBOMET	2 (2%)	1 (<1%)	1 (<1%)
CONTACT LAXATIVES	0	1 (<1%)	0
BISACODYL	0	1 (<1%)	0
CORTICOSTEROIDS	1 (<1%)	0	0
TRIAMCINOLONE ACETONIDE	1 (<1%)	0	0
CORTICOSTEROIDS, POTENT (GROUP III)	1 (<1%)	0	0
FLUOCINOLONE ACETONIDE	1 (<1%)	0	0
COXIBS	2 (2%)	0	0
CELECOXIB	2 (2%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DIGITALIS GLYCOSIDES	0	1 (<1%)	0
DIGOXIN	0	1 (<1%)	0
DIHYDROPYRIDINE DERIVATIVES	4 (3%)	1 (<1%)	5 (4%)
AMLODIPINE	4 (3%)	1 (<1%)	4 (4%)
NIFEDIPINE	0	0	1 (<1%)
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	2 (2%)	0	0
METHYLSULFONYLMETHANE	2 (2%)	0	0
DRUGS USED IN ERECTILE DYSFUNCTION	2 (2%)	2 (2%)	2 (2%)
SILDENAFIL CITRATE	2 (2%)	2 (2%)	2 (2%)
TADALAFIL	0	0	1 (<1%)
DRUGS USED IN NICOTINE DEPENDENCE	0	0	1 (<1%)
BUPROPION HYDROCHLORIDE	0	0	1 (<1%)
ESTROGENS	1 (<1%)	0	0
ESTROGEN NOS	1 (<1%)	0	0
FIBRATES	1 (<1%)	2 (2%)	1 (<1%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
GEMFIBROZIL	0	0	1 (<1%)
FENOFIBRATE	1 (<1%)	2 (2%)	0
FLUOROQUINOLONES	0	1 (<1%)	1 (<1%)
MOXIFLOXACIN HYDROCHLORIDE	0	0	1 (<1%)
LEVOFLOXACIN	0	1 (<1%)	0
FOLIC ACID AND DERIVATIVES	0	0	1 (<1%)
FOLIC ACID	0	0	1 (<1%)
GLUCOCORTICOIDS	1 (<1%)	1 (<1%)	1 (<1%)
METHYLPREDNISOLONE	0	0	1 (<1%)
BUDESONIDE	0	1 (<1%)	0
PREDNISONE	1 (<1%)	0	0
H2-RECEPTOR ANTAGONISTS	5 (4%)	3 (3%)	2 (2%)
FAMOTIDINE	4 (3%)	1 (<1%)	1 (<1%)
RANITIDINE	0	0	1 (<1%)
CIMETIDINE	0	2 (2%)	0
RANITIDINE HYDROCHLORIDE	1 (<1%)	0	0
HMG COA REDUCTASE INHIBITORS	15 (13%)	10 (9%)	15 (13%)
ATORVASTATIN	6 (5%)	5 (4%)	6 (5%)
SIMVASTATIN	6 (5%)	1 (<1%)	4 (4%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
INEGY	0	0	2 (2%)
ADVICOR - SLOW RELEASE	0	0	1 (<1%)
CADUET	0	0	1 (<1%)
PRAVASTATIN SODIUM	1 (<1%)	0	1 (<1%)
FLUVASTATIN	1 (<1%)	0	0
LOVASTATIN	0	1 (<1%)	0
ROSUVASTATIN CALCIUM	1 (<1%)	3 (3%)	0
INSULINS AND ANAL.,INTERM.-ACTING,COMB.W/FAST ACT.	0	1 (<1%)	0
HUMAN MIXTARD	0	1 (<1%)	0
INSULINS AND ANALOGUES, FAST-ACTING	1 (<1%)	1 (<1%)	1 (<1%)
INSULIN HUMAN	0	0	1 (<1%)
INSULIN	0	1 (<1%)	0
INSULIN ASPART	1 (<1%)	0	0
INSULINS AND ANALOGUES, INTERMEDIATE-ACTING	0	0	1 (<1%)
INSULIN HUMAN INJECTION, ISOPHANE	0	0	1 (<1%)
INSULINS AND ANALOGUES, LONG-ACTING	1 (<1%)	1 (<1%)	0
INSULIN GLARGINE	1 (<1%)	1 (<1%)	0
INTERFERONS	1 (<1%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PEGINTERFERON ALFA-2A	1 (<1%)	0	0
LAXATIVES	0	1 (<1%)	0
LAXATIVES	0	1 (<1%)	0
LEUKOTRIENE RECEPTOR ANTAGONISTS	2 (2%)	2 (2%)	1 (<1%)
MONTELUKAST	2 (2%)	2 (2%)	1 (<1%)
LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (<1%)	0
DYAZIDE	0	1 (<1%)	0
MACROLIDES	2 (2%)	0	1 (<1%)
AZITHROMYCIN	0	0	1 (<1%)
CLARITHROMYCIN	1 (<1%)	0	0
ERYTHROMYCIN	1 (<1%)	0	0
MAGNESIUM COMPOUNDS	0	1 (<1%)	0
MAGNESIUM OXIDE	0	1 (<1%)	0
MULTIVITAMINS WITH MINERALS	2 (2%)	3 (3%)	4 (4%)
CENTRUM	2 (2%)	1 (<1%)	3 (3%)
ONE-A-DAY MEN'S	0	0	1 (<1%)
CENTRUM SILVER	0	1 (<1%)	0
MULTIVITAMINS AND IRON	0	1 (<1%)	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
MULTIVITAMINS, OTHER COMBINATIONS	17 (15%)	20 (17%)	21 (18%)
MULTIVITAMINS	17 (15%)	20 (17%)	21 (18%)
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (2%)	2 (2%)
ESTROGENS CONJUGATED	0	1 (<1%)	2 (2%)
ESTRADIOL	0	1 (<1%)	0
NATURAL OPIUM ALKALOIDS	0	1 (<1%)	0
VICODIN	0	1 (<1%)	0
NICOTINIC ACID AND DERIVATIVES	0	0	1 (<1%)
NICOTINIC ACID	0	0	1 (<1%)
NUCLEOSIDES AND NUCLEOTIDES EXCL REV.TRANSCR.INHIB	0	1 (<1%)	1 (<1%)
ACICLOVIR	0	0	1 (<1%)
ACICLOVIR SODIUM	0	1 (<1%)	0
OPIUM ALKALOIDS AND DERIVATIVES	1 (<1%)	0	0
BENADRYL COLD AND FLU TABLETS	1 (<1%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
OPIUM DERIVATIVES AND EXPECTORANTS	0	0	1 (<1%)
NOVAHISTINE DMX	0	0	1 (<1%)
ORGANIC NITRATES	2 (2%)	0	1 (<1%)
ISOSORBIDE MONONITRATE	0	0	1 (<1%)
GLYCERYL TRINITRATE	2 (2%)	0	0
OTHER ANALGESICS AND ANTIPYRETICS	0	3 (3%)	3 (3%)
TYLENOL PM	0	1 (<1%)	2 (2%)
GABAPENTIN	0	2 (2%)	1 (<1%)
OTHER ANTI-DEMENTIA DRUGS	2 (2%)	0	1 (<1%)
GINKGO BILOBA	2 (2%)	0	1 (<1%)
OTHER ANTIDEPRESSANTS	2 (2%)	1 (<1%)	0
MIRTAZAPINE	1 (<1%)	0	0
TRAZODONE	1 (<1%)	1 (<1%)	0
OTHER ANTIEPILEPTICS	0	1 (<1%)	0
TOPIRAMATE	0	1 (<1%)	0
OTHER ANTIFUNGALS FOR TOPICAL USE	0	0	2 (2%)
TERBINAFINE	0	0	2 (2%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	4 (3%)	4 (3%)	5 (4%)
ALLEGRA-D - SLOW RELEASE	1 (<1%)	1 (<1%)	3 (3%)
FEXOFENADINE HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
LORATADINE	3 (3%)	2 (2%)	1 (<1%)
OTHER ANTIINFL./ANTIRHEUMATIC AGENTS, NON-STEROIDS	4 (3%)	1 (<1%)	1 (<1%)
AFLEXA	0	0	1 (<1%)
CHONDROITIN SULFATE	1 (<1%)	0	0
GLUCOSAMINE	4 (3%)	0	0
NABUMETONE	0	1 (<1%)	0
OTHER ANTIPSORIATICS FOR TOPICAL USE	0	0	1 (<1%)
CALCIPOTRIOL	0	0	1 (<1%)
OTHER CARDIAC PREPARATIONS	2 (2%)	0	2 (2%)
UBIDECARENONE	2 (2%)	0	2 (2%)
OTHER CENTRALLY ACTING AGENTS	0	0	1 (<1%)
CYCLOBENZAPRINE	0	0	1 (<1%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
OTHER CHEMOTHERAPEUTICS	0	1 (<1%)	0
METRONIDAZOLE	0	1 (<1%)	0
OTHER CHOLESTEROL AND TRIGLYCERIDE REDUCERS	3 (3%)	3 (3%)	3 (3%)
EZETIMIBE	1 (<1%)	2 (2%)	2 (2%)
FISH OIL	2 (2%)	1 (<1%)	1 (<1%)
OTHER DERMATOLOGICALS	1 (<1%)	0	0
MINOXIDIL	1 (<1%)	0	0
OTHER DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	0	0	1 (<1%)
SERENOA REPENS	0	0	1 (<1%)
OTHER EMOLLIENTS AND PROTECTIVES	2 (2%)	0	0
AMMONIUM LACTATE	1 (<1%)	0	0
OTHER EMOLLIENTS AND PROTECTIVES	1 (<1%)	0	0
OTHER PLAIN VITAMIN PREPARATIONS	4 (3%)	5 (4%)	3 (3%)
TOCOPHEROL	4 (3%)	5 (4%)	3 (3%)
VITAMIN B	1 (<1%)	0	0
OTHER QUINOLONES	1 (<1%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PIROMIDIC ACID	1 (<1%)	0	0
OTHER THERAPEUTIC PRODUCTS	4 (3%)	2 (2%)	0
GINSENG	1 (<1%)	0	0
LINUM USITATISSIMUM SEED OIL	1 (<1%)	1 (<1%)	0
MEDICAGO SATIVA	1 (<1%)	0	0
VITIS VINIFERA EXTRACT	1 (<1%)	0	0
VITIS VINIFERA SEED	0	1 (<1%)	0
OXICAMS	0	0	1 (<1%)
MELOXICAM	0	0	1 (<1%)
PHENYLPIPERIDINE DERIVATIVES	0	1 (<1%)	0
MEPERGAN	0	1 (<1%)	0
PIPERAZINE DERIVATIVES	0	1 (<1%)	2 (2%)
CETIRIZINE HYDROCHLORIDE	0	1 (<1%)	2 (2%)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	16 (14%)	11 (9%)	17 (15%)
ACETYLSALICYLIC ACID	15 (13%)	11 (9%)	17 (15%)
CLOPIDOGREL	1 (<1%)	0	0
CLOPIDOGREL SULFATE	0	1 (<1%)	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
POTASSIUM	0	0	1 (<1%)
POTASSIUM	0	0	1 (<1%)
PREPARATIONS INHIBITING URIC ACID PRODUCTION	0	1 (<1%)	0
ALLOPURINOL	0	1 (<1%)	0
PREPARATIONS WITH SALICYLIC ACID DERIVATIVES	6 (5%)	4 (3%)	5 (4%)
ACETYLSALICYLIC ACID	6 (5%)	4 (3%)	5 (4%)
PROGESTOGENS	2 (2%)	0	2 (2%)
MEDROXYPROGESTERONE ACETATE	2 (2%)	0	2 (2%)
PROGESTOGENS AND ESTROGENS IN COMBINATION	1 (<1%)	0	0
PROVELLA-14	1 (<1%)	0	0
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	1 (<1%)	6 (5%)	4 (4%)
CILEST	1 (<1%)	0	1 (<1%)
EUGYNON	0	1 (<1%)	1 (<1%)
MARVELON	0	1 (<1%)	1 (<1%)
NUVARING	0	0	1 (<1%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ANOVLAR	0	1 (<1%)	0
ETHINYL ESTRADIOL W/NORGESTREL	0	1 (<1%)	0
EVRA	0	1 (<1%)	0
PETIBELLE FILMTABLETTEN	0	1 (<1%)	0
PROPIONIC ACID DERIVATIVES	20 (17%)	20 (17%)	22 (19%)
IBUPROFEN	15 (13%)	16 (14%)	14 (12%)
CO-ADVIL	0	0	3 (3%)
NAPROXEN SODIUM	5 (4%)	2 (2%)	3 (3%)
NAPROXEN	0	2 (2%)	2 (2%)
PROSTAGLANDIN ANALOGUES	1 (<1%)	0	0
TRAVOPROST	1 (<1%)	0	0
PROTON PUMP INHIBITORS	7 (6%)	7 (6%)	4 (4%)
ESOMEPRAZOLE MAGNESIUM	0	2 (2%)	3 (3%)
LANSOPRAZOLE	2 (2%)	2 (2%)	1 (<1%)
OMEPRAZOLE	2 (2%)	1 (<1%)	0
PANTOPRAZOLE SODIUM	3 (3%)	1 (<1%)	0
RABEPRAZOLE SODIUM	0	1 (<1%)	0
PURINE DERIVATIVES	1 (<1%)	0	0
PENTOXIFYLLINE	1 (<1%)	0	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PYRAZOLONES	0	2 (2%)	3 (3%)
TYLENOL SINUS MEDICATION	0	2 (2%)	3 (3%)
SALICYLIC ACID AND DERIVATIVES	1 (<1%)	0	1 (<1%)
DOANS PILLS	0	0	1 (<1%)
VINCENTS TABLETS	1 (<1%)	0	1 (<1%)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	5 (4%)	5 (4%)	4 (4%)
SALBUTAMOL	5 (4%)	5 (4%)	4 (4%)
SELECTIVE ESTROGEN RECEPTOR MODULATORS	0	0	2 (2%)
RALOXIFENE HYDROCHLORIDE	0	0	2 (2%)
SELECTIVE IMMUNOSUPPRESSIVE AGENTS	0	0	1 (<1%)
ETANERCEPT	0	0	1 (<1%)
SELECTIVE SEROTONIN (5HT1) AGONISTS	1 (<1%)	2 (2%)	0
ELETRIPTAN HYDROBROMIDE	0	1 (<1%)	0
RIZATRIPTAN BENZOATE	1 (<1%)	1 (<1%)	0

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
SUMATRIPTAN SUCCINATE	0	1 (<1%)	0
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	1 (<1%)	0	0
FLUVOXAMINE MALEATE	1 (<1%)	0	0
SERUM LIPID REDUCING AGENTS	0	0	1 (<1%)
SERUMLIPIDREDUCING AGENTS	0	0	1 (<1%)
SUBSTITUTED ALKYLAMINES	1 (<1%)	1 (<1%)	0
CHLORPHENAMINE	1 (<1%)	0	0
CHLORPHENAMINE MALEATE	0	1 (<1%)	0
SULFONAMIDES, PLAIN	0	1 (<1%)	0
CHLORTALIDONE	0	1 (<1%)	0
SULFONAMIDES, UREA DERIVATIVES	2 (2%)	2 (2%)	3 (3%)
GLIPIZIDE	1 (<1%)	2 (2%)	2 (2%)
GLIBENCLAMIDE	0	0	1 (<1%)
GLIMEPIRIDE	1 (<1%)	0	0
SYMPATHOMIMETICS	4 (3%)	2 (2%)	3 (3%)
PSEUDOEPHEDRINE HYDROCHLORIDE	3 (3%)	1 (<1%)	2 (2%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ACTIFED	1 (<1%)	0	1 (<1%)
NAPROXEN SODIUM W/PSEUDOEPHEDRINE HCL	0	1 (<1%)	0
SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (<1%)	0	0
BRIMONIDINE TARTRATE	1 (<1%)	0	0
SYMPATHOMIMETICS, PLAIN	1 (<1%)	0	2 (2%)
OXYMETAZOLINE HYDROCHLORIDE	1 (<1%)	0	2 (2%)
SYNTHETIC ESTROGENS, PLAIN	0	1 (<1%)	0
ESTROPIPATE	0	1 (<1%)	0
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX	0	1 (<1%)	0
MELATONIN	0	1 (<1%)	0
TETRACYCLINES	0	0	1 (<1%)
DOXYCYCLINE	0	0	1 (<1%)
THIAZIDES, PLAIN	3 (3%)	0	1 (<1%)
HYDROCHLOROTHIAZIDE	3 (3%)	0	1 (<1%)
THIAZOLIDINEDIONES	2 (2%)	2 (2%)	2 (2%)
PIOGLITAZONE	1 (<1%)	2 (2%)	2 (2%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ROSIGLITAZONE MALEATE	1 (<1%)	0	0
THYROID HORMONES	6 (5%)	4 (3%)	1 (<1%)
LEVOTHYROXINE SODIUM	3 (3%)	4 (3%)	1 (<1%)
LEVOTHYROXINE	3 (3%)	0	0
TRIAZOLE DERIVATIVES	1 (<1%)	1 (<1%)	0
FLUCONAZOLE	1 (<1%)	1 (<1%)	0
URINARY ANTISPASMODICS	2 (2%)	1 (<1%)	0
OXYBUTYNIN HYDROCHLORIDE	0	1 (<1%)	0
TOLTERODINE L-TARTRATE	2 (2%)	0	0
VITAMIN A, PLAIN	1 (<1%)	0	1 (<1%)
RETINOL	1 (<1%)	0	1 (<1%)
VITAMIN B-COMPLEX WITH VITAMIN C	0	1 (<1%)	0
MULTIPLE VITAMINS	0	1 (<1%)	0
VITAMIN B-COMPLEX, PLAIN	0	0	1 (<1%)
NICOTINAM. W/PYRIDOXI. HCL/RIBOFL./THIAM. HCL	0	0	1 (<1%)
VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	1 (<1%)	0	1 (<1%)

Table S39 Summary of Baseline Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
CYANOCOBALAMIN	1 (<1%)	0	1 (<1%)
VITAMIN D AND ANALOGUES	1 (<1%)	0	1 (<1%)
ERGOCALCIFEROL	1 (<1%)	0	1 (<1%)
VITAMINS	1 (<1%)	0	0
VITAMINS	1 (<1%)	0	0
VITAMINS, OTHER COMBINATIONS	1 (<1%)	0	0
VITAMINS, OTHER COMBINATIONS	1 (<1%)	0	0
XANTHINES	1 (<1%)	0	0
THEOPHYLLINE	1 (<1%)	0	0
ZINC	2 (2%)	0	0
ZINC	1 (<1%)	0	0
ZINC SULFATE	1 (<1%)	0	0

Baseline concomitant medications were medications that were used on or before the first dose date
N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS	1 (<1%)	0	1 (<1%)
LOTREL	1 (<1%)	0	1 (<1%)
ACE INHIBITORS AND DIURETICS	0	1 (<1%)	0
PRINZIDE	0	1 (<1%)	0
ACE INHIBITORS, PLAIN	8 (7%)	5 (4%)	8 (7%)
LISINOPRIL	2 (2%)	4 (3%)	4 (4%)
RAMIPRIL	4 (3%)	0	2 (2%)
FOSINOPRIL SODIUM	0	0	1 (<1%)
QUINAPRIL HYDROCHLORIDE	2 (2%)	0	1 (<1%)
BENAZEPRIL HYDROCHLORIDE	0	1 (<1%)	0
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	2 (2%)	3 (3%)	0
ARTHROTEC	0	1 (<1%)	0
DICLOFENAC	1 (<1%)	0	0
INDOMETACIN	1 (<1%)	0	0
KETOROLAC TROMETHAMINE	0	2 (2%)	0
ACIDIFIERS	0	1 (<1%)	0
AQUA-BAN	0	1 (<1%)	0
ADRENERGICS AND OTH.DRUGS FOR OBSTRUCT.AIRWAY DIS.	3 (3%)	3 (3%)	4 (4%)
SERETIDE MITE	2 (2%)	3 (3%)	3 (3%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
COMBIVENT /GFR/	1 (<1%)	0	1 (<1%)
ALL OTHER THERAPEUTIC PRODUCTS	5 (4%)	2 (2%)	2 (2%)
ALL OTHER THERAPEUTIC PRODUCTS	5 (4%)	2 (2%)	2 (2%)
ALPHA AND BETA BLOCKING AGENTS	0	1 (<1%)	1 (<1%)
LABETALOL	0	0	1 (<1%)
CARVEDILOL	0	1 (<1%)	0
ALPHA-ADRENORECEPTOR ANTAGONISTS	0	0	2 (2%)
DOXAZOSIN MESILATE	0	0	1 (<1%)
PRAZOSIN	0	0	1 (<1%)
ALUMINIUM COMPOUNDS	1 (<1%)	0	0
DIHYDROXYALUMINUM SODIUM CARBONATE	1 (<1%)	0	0
AMINO ACIDS AND DERIVATIVES	0	1 (<1%)	0
CARNITINE	0	1 (<1%)	0
AMINOALKYL ETHERS	5 (4%)	5 (4%)	8 (7%)
DIPHENHYDRAMINE HYDROCHLORIDE	3 (3%)	4 (3%)	7 (6%)
CLEMASTINE FUMARATE	0	0	1 (<1%)
DIPHENHYDRAMINE	2 (2%)	1 (<1%)	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
AMINOQUINOLINES	1 (<1%)	0	0
HYDROXYCHLOROQUINE SULFATE	1 (<1%)	0	0
AMINOSALICYLIC ACID AND SIMILAR AGENTS	0	1 (<1%)	0
MESALAZINE	0	1 (<1%)	0
ANESTHETICS FOR TOPICAL USE	1 (<1%)	0	0
LANACANE	1 (<1%)	0	0
ANESTHETICS, GENERAL	1 (<1%)	0	0
ANAESTHETICS, GENERAL	1 (<1%)	0	0
ANGIOTENSIN II ANTAGONISTS AND DIURETICS	1 (<1%)	2 (2%)	2 (2%)
BENICAR HCT	0	1 (<1%)	1 (<1%)
KARVEA HCT	0	0	1 (<1%)
CO-DIOVAN	1 (<1%)	1 (<1%)	0
ANGIOTENSIN II ANTAGONISTS, PLAIN	5 (4%)	3 (3%)	1 (<1%)
OLMESARTAN MEDOXOMIL	0	1 (<1%)	1 (<1%)
CANDESARTAN CILEXETIL	0	1 (<1%)	0
LOSARTAN POTASSIUM	0	1 (<1%)	0
VALSARTAN	5 (4%)	0	0
ANILIDES	13 (11%)	23 (20%)	17 (15%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PARACETAMOL	9 (8%)	16 (14%)	11 (10%)
CO-TYLENOL	1 (<1%)	0	2 (2%)
COTYLENOL	1 (<1%)	1 (<1%)	2 (2%)
MEDINITE	0	3 (3%)	2 (2%)
PARA-SELTZER	1 (<1%)	2 (2%)	2 (2%)
ALKA-SELTZER PLUS COLD & COUGH	0	1 (<1%)	0
PANLOR DC	1 (<1%)	0	0
PERCOGESIC	0	1 (<1%)	0
THOMAPYRIN N	1 (<1%)	2 (2%)	0
ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	1 (<1%)	0	0
ANTIALLERGIC AGENTS, EXCL CORTICOSTEROIDS	1 (<1%)	0	0
ANTIARRHYTHMICS, CLASS III	0	1 (<1%)	0
AMIODARONE	0	1 (<1%)	0
ANTIBIOTICS	0	0	2 (2%)
NEOMYCIN	0	0	1 (<1%)
TOBRAMYCIN	0	0	1 (<1%)
ANTICHOLINERGICS	0	2 (2%)	2 (2%)
TIOTROPIUM BROMIDE	0	1 (<1%)	2 (2%)
IPRATROPIUM BROMIDE	0	1 (<1%)	0
ANTIHISTAMINES FOR TOPICAL USE	0	1 (<1%)	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DIPHENHYDRAMINE HYDROCHLORIDE	0	1 (<1%)	0
ANTIINFECT. AND ANTISEPT. FOR LOCAL ORAL TREATMENT	0	0	1 (<1%)
DOXYCYCLINE HYCLATE	0	0	1 (<1%)
ANTIINFECTIVES	1 (<1%)	0	0
FLOXIN OTIC	1 (<1%)	0	0
ANTIINFLAMMATORY/ANTIRHEUMATIC PROD.,NON-STEROIDS	1 (<1%)	0	0
GLUCOSAMINE W/CHONDROITIN	1 (<1%)	0	0
ANTIPROPULSIVES	0	0	2 (2%)
LOPERAMIDE HYDROCHLORIDE	0	0	2 (2%)
ASCORBIC ACID (VITAMIN C), PLAIN	6 (5%)	4 (3%)	4 (4%)
ASCORBIC ACID	6 (5%)	4 (3%)	4 (4%)
AZASPIRODECANEDIONE DERIVATIVES	0	0	1 (<1%)
BUSPIRONE HYDROCHLORIDE	0	0	1 (<1%)
BELLADONNA ALKALOIDS, TERTIARY AMINES	1 (<1%)	0	0
HYOSCYAMINE SULFATE	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
BELLADONNA AND DERIVATIVES IN COMB.WITH PSYCHOLEP.	1 (<1%)	0	0
DONNATAL	1 (<1%)	0	0
BENZODIAZEPINE DERIVATIVES	2 (2%)	0	1 (<1%)
CHLORDIAZEPOXIDE HYDROCHLORIDE	0	0	1 (<1%)
ALPRAZOLAM	2 (2%)	0	0
BENZODIAZEPINE RELATED DRUGS	1 (<1%)	0	1 (<1%)
ZOLPIDEM TARTRATE	1 (<1%)	0	1 (<1%)
BENZOTHIAZEPINE DERIVATIVES	0	0	2 (2%)
DILTIAZEM	0	0	1 (<1%)
DILTIAZEM HYDROCHLORIDE	0	0	1 (<1%)
BETA BLOCKING AGENTS	0	0	1 (<1%)
TIMOLOL	0	0	1 (<1%)
BETA BLOCKING AGENTS, NON-SELECTIVE	0	1 (<1%)	1 (<1%)
NADOLOL	0	0	1 (<1%)
PROPRANOLOL	0	1 (<1%)	0
BETA BLOCKING AGENTS, SELECTIVE	8 (7%)	6 (5%)	4 (4%)
ATENOLOL	3 (3%)	3 (3%)	3 (3%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
METOPROLOL SUCCINATE	1 (<1%)	3 (3%)	1 (<1%)
METOPROLOL	3 (3%)	0	0
METOPROLOL TARTRATE	1 (<1%)	0	0
BETA-LACTAMASE SENSITIVE PENICILLINS	0	1 (<1%)	2 (2%)
PHENOXYMETHYLPENICILLIN POTASSIUM	0	1 (<1%)	2 (2%)
BIGUANIDES	1 (<1%)	3 (3%)	2 (2%)
METFORMIN	1 (<1%)	3 (3%)	2 (2%)
BISMUTH PREPARATIONS	0	1 (<1%)	0
BISMUTH SUBSALICYLATE	0	1 (<1%)	0
BISPHOSPHONATES	2 (2%)	2 (2%)	2 (2%)
ALENDRONATE SODIUM	1 (<1%)	2 (2%)	1 (<1%)
RISEDRONATE SODIUM	1 (<1%)	0	1 (<1%)
BULK PRODUCERS	0	0	1 (<1%)
POLYCARBOPHIL CALCIUM	0	0	1 (<1%)
CALCITONIN PREPARATIONS	0	1 (<1%)	0
CALCITONIN, SALMON	0	1 (<1%)	0
CALCIUM	3 (3%)	1 (<1%)	9 (8%)
CALCIUM	2 (2%)	0	8 (7%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
CALCIUM CITRATE	0	0	1 (<1%)
CALCIUM WITH VITAMIN D	1 (<1%)	1 (<1%)	0
CALCIUM COMPOUNDS	4 (3%)	4 (3%)	5 (4%)
CALCIUM CARBONATE	4 (3%)	4 (3%)	5 (4%)
CALCIUM, COMBINATIONS WITH OTHER DRUGS	0	1 (<1%)	0
OS-CAL	0	1 (<1%)	0
CARBAMIC ACID ESTERS	0	0	1 (<1%)
METHOCARBAMOL	0	0	1 (<1%)
CEPHALOSPORINS AND RELATED SUBSTANCES	2 (2%)	3 (3%)	3 (3%)
CEFDINIR	0	0	2 (2%)
CEFALEXIN	1 (<1%)	1 (<1%)	1 (<1%)
CEFAZOLIN SODIUM	1 (<1%)	0	0
CEFPROZIL	0	2 (2%)	0
COMB AND COMPL. OF ALUMIN., CALC. AND MAGNES. COMP	0	1 (<1%)	0
MAALOX /USA/	0	1 (<1%)	0
COMB OF PENICILLINS, INCL. BETA-LACTAMASE INHIB.	1 (<1%)	0	0
AMOXICILLIN W/CLAVULANATE POTASSIUM	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
COMB.SULFONAMIDES & TRIMETHOPRIM INCL. DERIVATIVES	0	1 (<1%)	1 (<1%)
KELFIPRIM	0	0	1 (<1%)
BACTRIM	0	1 (<1%)	0
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	2 (2%)	1 (<1%)	1 (<1%)
GLIBOMET	2 (2%)	1 (<1%)	1 (<1%)
CONTACT LAXATIVES	0	1 (<1%)	0
BISACODYL	0	1 (<1%)	0
CORTICOSTEROIDS	1 (<1%)	1 (<1%)	3 (3%)
FLUTICASONE PROPIONATE	0	1 (<1%)	2 (2%)
MOMETASONE FUROATE	0	0	1 (<1%)
TRIAMCINOLONE ACETONIDE	1 (<1%)	0	0
CORTICOSTEROIDS, POTENT (GROUP III)	1 (<1%)	0	0
FLUOCINOLONE ACETONIDE	1 (<1%)	0	0
CORTICOSTEROIDS, WEAK (GROUP I)	1 (<1%)	2 (2%)	0
CORTISONE	0	1 (<1%)	0
HYDROCORTISONE	1 (<1%)	1 (<1%)	0
COXIBS	2 (2%)	0	1 (<1%)
CELECOXIB	2 (2%)	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DIGITALIS GLYCOSIDES	0	1 (<1%)	0
DIGOXIN	0	1 (<1%)	0
DIHYDROPYRIDINE DERIVATIVES	4 (3%)	1 (<1%)	5 (4%)
AMLODIPINE	4 (3%)	1 (<1%)	4 (4%)
ISRADIPINE	0	0	1 (<1%)
NIFEDIPINE	0	0	1 (<1%)
DIPHENYLPROPYLAMINE DERIVATIVES	2 (2%)	1 (<1%)	0
PROPACET	2 (2%)	1 (<1%)	0
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	2 (2%)	0	0
METHYLSULFONYLMETHANE	2 (2%)	0	0
DRUGS USED IN ERECTILE DYSFUNCTION	2 (2%)	2 (2%)	2 (2%)
SILDENAFIL CITRATE	2 (2%)	2 (2%)	2 (2%)
TADALAFIL	0	0	1 (<1%)
DRUGS USED IN NICOTINE DEPENDENCE	0	0	3 (3%)
NICOTINE	0	0	2 (2%)
BUPROPION HYDROCHLORIDE	0	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ESTROGENS	1 (<1%)	0	0
ESTROGEN NOS	1 (<1%)	0	0
EXPECTORANTS	0	0	1 (<1%)
GUAIFENESIN	0	0	1 (<1%)
FIBRATES	1 (<1%)	2 (2%)	1 (<1%)
GEMFIBROZIL	0	0	1 (<1%)
FENOFIBRATE	1 (<1%)	2 (2%)	0
FLUOROQUINOLONES	3 (3%)	2 (2%)	1 (<1%)
CIPROFLOXACIN	2 (2%)	1 (<1%)	1 (<1%)
LEVOFLOXACIN	1 (<1%)	1 (<1%)	1 (<1%)
MOXIFLOXACIN HYDROCHLORIDE	0	1 (<1%)	1 (<1%)
FOLIC ACID AND DERIVATIVES	0	0	1 (<1%)
FOLIC ACID	0	0	1 (<1%)
GLUCOCORTICOIDS	3 (3%)	3 (3%)	5 (4%)
CORTISONE	0	1 (<1%)	2 (2%)
METHYLPREDNISOLONE	1 (<1%)	0	2 (2%)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (<1%)	0	1 (<1%)
PREDNISONE	2 (2%)	1 (<1%)	1 (<1%)
BUDESONIDE	0	1 (<1%)	0
H2-RECEPTOR ANTAGONISTS	4 (3%)	4 (3%)	3 (3%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
RANITIDINE	0	0	2 (2%)
FAMOTIDINE	3 (3%)	1 (<1%)	1 (<1%)
CIMETIDINE	0	2 (2%)	0
RANITIDINE HYDROCHLORIDE	1 (<1%)	1 (<1%)	0
HMG COA REDUCTASE INHIBITORS	16 (14%)	10 (9%)	16 (14%)
ATORVASTATIN	7 (6%)	5 (4%)	6 (5%)
SIMVASTATIN	6 (5%)	1 (<1%)	4 (4%)
INEGY	0	0	3 (3%)
ADVICOR - SLOW RELEASE	0	0	1 (<1%)
CADUET	0	0	1 (<1%)
PRAVASTATIN SODIUM	1 (<1%)	0	1 (<1%)
FLUVASTATIN	1 (<1%)	0	0
LOVASTATIN	0	1 (<1%)	0
ROSUVASTATIN CALCIUM	2 (2%)	3 (3%)	0
HYPNOTICS & SEDATIVES COMB., EXCL BARBITURATES	0	1 (<1%)	0
SOMINEX /USA/	0	1 (<1%)	0
IMIDAZOLE DERIVATIVES	0	1 (<1%)	1 (<1%)
METRONIDAZOLE	0	1 (<1%)	1 (<1%)
INSULINS AND ANAL.,INTERM.-ACTING,COMB.W/FAST ACT.	0	1 (<1%)	0
HUMAN MIXTARD	0	1 (<1%)	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N=116)	Group 2 (N = 116)	Group 3 (N = 114)
INSULINS AND ANALOGUES, FAST-ACTING	1 (<1%)	1 (<1%)	1 (<1%)
INSULIN HUMAN	0	0	1 (<1%)
INSULIN	0	1 (<1%)	0
INSULIN ASPART	1 (<1%)	0	0
INSULINS AND ANALOGUES, INTERMEDIATE-ACTING	0	0	1 (<1%)
INSULIN HUMAN INJECTION, ISOPHANE	0	0	1 (<1%)
INSULINS AND ANALOGUES, LONG-ACTING	1 (<1%)	1 (<1%)	0
INSULIN GLARGINE	1 (<1%)	1 (<1%)	0
INTERFERONS	1 (<1%)	0	0
PEGINTERFERON ALFA-2A	1 (<1%)	0	0
LAXATIVES	0	1 (<1%)	0
LAXATIVES	0	1 (<1%)	0
LEUKOTRIENE RECEPTOR ANTAGONISTS	2 (2%)	2 (2%)	1 (<1%)
MONTELUKAST	2 (2%)	2 (2%)	1 (<1%)
LINCOSAMIDES	0	0	1 (<1%)
CLINDAMYCIN	0	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	0	1 (<1%)	0
DYAZIDE	0	1 (<1%)	0
MACROLIDES	3 (3%)	3 (3%)	4 (4%)
AZITHROMYCIN	1 (<1%)	1 (<1%)	3 (3%)
CLARITHROMYCIN	1 (<1%)	0	1 (<1%)
ERYTHROMYCIN	1 (<1%)	1 (<1%)	0
TELITHROMYCIN	0	1 (<1%)	0
MAGNESIUM COMPOUNDS	0	1 (<1%)	0
MAGNESIUM OXIDE	0	1 (<1%)	0
MULTIVITAMINS WITH MINERALS	2 (2%)	3 (3%)	4 (4%)
CENTRUM	2 (2%)	1 (<1%)	3 (3%)
ONE-A-DAY MEN'S	0	0	1 (<1%)
CENTRUM SILVER	0	1 (<1%)	0
MULTIVITAMINS AND IRON	0	1 (<1%)	0
MULTIVITAMINS, OTHER COMBINATIONS	17 (15%)	21 (18%)	21 (18%)
MULTIVITAMINS	17 (15%)	21 (18%)	21 (18%)
NASAL DECONGESTANTS FOR SYSTEMIC USE	1 (<1%)	0	1 (<1%)
NARINE REPETABS	1 (<1%)	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (2%)	3 (3%)
ESTROGENS CONJUGATED	0	1 (<1%)	3 (3%)
ESTRADIOL	0	1 (<1%)	0
NATURAL OPIUM ALKALOIDS	4 (3%)	7 (6%)	5 (4%)
VICODIN	1 (<1%)	5 (4%)	5 (4%)
HYDROMORPHONE HYDROCHLORIDE	0	0	1 (<1%)
HYDROMORPHONE	1 (<1%)	0	0
OXYCOCET	2 (2%)	1 (<1%)	0
PANADEINE CO	1 (<1%)	1 (<1%)	0
NICOTINIC ACID AND DERIVATIVES	0	0	2 (2%)
NICOTINIC ACID	0	0	2 (2%)
NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	0	1 (<1%)	0
AMITRIPTYLINE HYDROCHLORIDE	0	1 (<1%)	0
NUCLEOSIDES AND NUCLEOTIDES EXCL REV.TRANSCR.INHIB	1 (<1%)	1 (<1%)	1 (<1%)
ACICLOVIR	0	0	1 (<1%)
ACICLOVIR SODIUM	0	1 (<1%)	0
VALACICLOVIR HYDROCHLORIDE	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
OPIUM ALKALOIDS AND DERIVATIVES	2 (2%)	0	1 (<1%)
PROCET /USA/	0	0	1 (<1%)
FORMULA 44	1 (<1%)	0	0
ROBITUSSIN NIGTH-TIME	1 (<1%)	0	0
OPIUM DERIVATIVES AND EXPECTORANTS	0	1 (<1%)	1 (<1%)
NOVAHISTINE DMX	0	0	1 (<1%)
PHENERGAN WITH CODEINE	0	1 (<1%)	0
ORGANIC NITRATES	2 (2%)	0	2 (2%)
ISOSORBIDE MONONITRATE	0	0	2 (2%)
GLYCERYL TRINITRATE	2 (2%)	0	1 (<1%)
OTHER ANALGESICS AND ANTIPYRETICS	1 (<1%)	3 (3%)	3 (3%)
TYLENOL PM	1 (<1%)	1 (<1%)	2 (2%)
GABAPENTIN	0	2 (2%)	1 (<1%)
OTHER ANTI-DEMENTIA DRUGS	2 (2%)	0	1 (<1%)
GINKGO BILOBA	2 (2%)	0	1 (<1%)
OTHER ANTIBIOTICS FOR TOPICAL USE	0	1 (<1%)	3 (3%)
NEOTRACIN	0	0	2 (2%)
MUPIROCIN	0	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
OTHER ANTIBIOTICS FOR TOPICAL USE	0	1 (<1%)	0
OTHER ANTIDEPRESSANTS	2 (2%)	1 (<1%)	0
TRAZODONE	2 (2%)	1 (<1%)	0
OTHER ANTIEPILEPTICS	0	1 (<1%)	0
TOPIRAMATE	0	1 (<1%)	0
OTHER ANTIFUNGALS FOR TOPICAL USE	0	0	2 (2%)
TERBINAFINE	0	0	2 (2%)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	6 (5%)	3 (3%)	11 (10%)
LORATADINE	5 (4%)	2 (2%)	5 (4%)
ALLEGRA-D - SLOW RELEASE	1 (<1%)	0	3 (3%)
FEXOFENADINE HYDROCHLORIDE	0	1 (<1%)	2 (2%)
DESLORATADINE	0	0	1 (<1%)
OTHER ANTIINFL./ANTIRHEUMATIC AGENTS, NON-STEROIDS	4 (3%)	1 (<1%)	1 (<1%)
AFLEXA	0	0	1 (<1%)
CHONDROITIN SULFATE	1 (<1%)	0	0
GLUCOSAMINE	4 (3%)	0	0
NABUMETONE	0	1 (<1%)	0
OTHER ANTIPRURITICS	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
MENTHOL W/METHYL SALICYLATE	1 (<1%)	0	0
OTHER ANTIPSORIATICS FOR TOPICAL USE	0	0	1 (<1%)
CALCIPOTRIOL	0	0	1 (<1%)
OTHER CARDIAC PREPARATIONS	2 (2%)	0	2 (2%)
UBIDECARENONE	2 (2%)	0	2 (2%)
OTHER CENTRALLY ACTING AGENTS	1 (<1%)	3 (3%)	2 (2%)
CYCLOBENZAPRINE	0	0	1 (<1%)
CYCLOBENZAPRINE HYDROCHLORIDE	1 (<1%)	3 (3%)	1 (<1%)
OTHER CHEMOTHERAPEUTICS	0	1 (<1%)	0
METRONIDAZOLE	0	1 (<1%)	0
OTHER CHOLESTEROL AND TRIGLYCERIDE REDUCERS	4 (3%)	3 (3%)	3 (3%)
EZETIMIBE	2 (2%)	2 (2%)	2 (2%)
FISH OIL	2 (2%)	1 (<1%)	1 (<1%)
OTHER COUGH SUPPRESSANTS	0	0	2 (2%)
BENZONATATE	0	0	2 (2%)
OTHER DERMATOLOGICALS	1 (<1%)	0	0
MINOXIDIL	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
OTHER DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	0	0	1 (<1%)
SERENOA REPENS	0	0	1 (<1%)
OTHER EMOLLIENTS AND PROTECTIVES	2 (2%)	0	0
AMMONIUM LACTATE	1 (<1%)	0	0
OTHER EMOLLIENTS AND PROTECTIVES	1 (<1%)	0	0
OTHER PLAIN VITAMIN PREPARATIONS	4 (3%)	5 (4%)	3 (3%)
TOCOPHEROL	4 (3%)	5 (4%)	3 (3%)
VITAMIN B	1 (<1%)	0	0
OTHER THERAPEUTIC PRODUCTS	4 (3%)	2 (2%)	0
GINSENG	1 (<1%)	0	0
LINUM USITATISSIMUM SEED OIL	1 (<1%)	1 (<1%)	0
MEDICAGO SATIVA	1 (<1%)	0	0
VITIS VINIFERA EXTRACT	1 (<1%)	0	0
VITIS VINIFERA SEED	0	1 (<1%)	0
OXAZOL, THIAZINE, AND TRIAZINE DERIVATIVES	2 (2%)	1 (<1%)	0
CHLORZOXAZONE	0	1 (<1%)	0
METAXALONE	2 (2%)	0	0
OXICAMS	1 (<1%)	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
MELOXICAM	1 (<1%)	0	1 (<1%)
PENICILLINS WITH EXTENDED SPECTRUM	3 (3%)	4 (3%)	3 (3%)
AMOXICILLIN	3 (3%)	4 (3%)	3 (3%)
PHENOTHIAZINE DERIVATIVES	2 (2%)	1 (<1%)	0
PROMETHAZINE HYDROCHLORIDE	2 (2%)	1 (<1%)	0
PHENYLALKYLAMINE DERIVATIVES	1 (<1%)	0	0
VERAPAMIL	1 (<1%)	0	0
PHENYLPIPERIDINE DERIVATIVES	2 (2%)	0	0
PETHIDINE HYDROCHLORIDE	2 (2%)	0	0
PIPERAZINE DERIVATIVES	1 (<1%)	1 (<1%)	3 (3%)
CETIRIZINE HYDROCHLORIDE	0	1 (<1%)	3 (3%)
MECLOZINE HYDROCHLORIDE	1 (<1%)	0	0
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	16 (14%)	11 (9%)	18 (16%)
ACETYLSALICYLIC ACID	15 (13%)	11 (9%)	18 (16%)
CLOPIDOGREL	1 (<1%)	0	0
CLOPIDOGREL SULFATE	1 (<1%)	1 (<1%)	0
POTASSIUM	0	0	1 (<1%)
POTASSIUM	0	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PREPARATIONS INHIBITING URIC ACID PRODUCTION	0	1 (<1%)	0
ALLOPURINOL	0	1 (<1%)	0
PREPARATIONS WITH SALICYLIC ACID DERIVATIVES	5 (4%)	4 (3%)	4 (4%)
ACETYLSALICYLIC ACID	5 (4%)	4 (3%)	4 (4%)
PROGESTOGENS	2 (2%)	0	2 (2%)
MEDROXYPROGESTERONE ACETATE	2 (2%)	0	2 (2%)
PROGESTOGENS AND ESTROGENS IN COMBINATION	1 (<1%)	0	1 (<1%)
PROVELLA-14	1 (<1%)	0	1 (<1%)
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	1 (<1%)	6 (5%)	4 (4%)
CILEST	1 (<1%)	0	1 (<1%)
EUGYNON	0	1 (<1%)	1 (<1%)
MARVELON	0	1 (<1%)	1 (<1%)
NUVARING	0	0	1 (<1%)
ANOVLAR	0	1 (<1%)	0
ETHINYL ESTRADIOL W/NORGESTREL	0	1 (<1%)	0
EVRA	0	1 (<1%)	0
PETIBELLE FILMTABLETTEN	0	1 (<1%)	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PROPIONIC ACID DERIVATIVES	26 (22%)	28 (24%)	28 (25%)
IBUPROFEN	21 (18%)	25 (22%)	20 (18%)
CO-ADVIL	0	0	5 (4%)
NAPROXEN SODIUM	6 (5%)	4 (3%)	4 (4%)
NAPROXEN	0	3 (3%)	2 (2%)
PROSTAGLANDIN ANALOGUES	1 (<1%)	0	0
TRAVOPROST	1 (<1%)	0	0
PROTON PUMP INHIBITORS	8 (7%)	8 (7%)	6 (5%)
ESOMEPRAZOLE MAGNESIUM	0	2 (2%)	4 (4%)
LANSOPRAZOLE	2 (2%)	2 (2%)	1 (<1%)
PANTOPRAZOLE SODIUM	5 (4%)	1 (<1%)	1 (<1%)
RABEPRAZOLE SODIUM	1 (<1%)	1 (<1%)	1 (<1%)
OMEPRAZOLE	2 (2%)	2 (2%)	0
PURINE DERIVATIVES	1 (<1%)	0	0
PENTOXIFYLLINE	1 (<1%)	0	0
PYRAZOLONES	1 (<1%)	2 (2%)	4 (4%)
TYLENOL SINUS MEDICATION	1 (<1%)	2 (2%)	4 (4%)
PYRIMIDINE ANALOGUES	1 (<1%)	0	0
FLUOROURACIL	1 (<1%)	0	0
SALICYLIC ACID AND DERIVATIVES	1 (<1%)	0	2 (2%)
ALKA-SELTZER PLUS	0	0	1 (<1%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
DOANS PILLS	0	0	1 (<1%)
VINCENTS TABLETS	1 (<1%)	0	1 (<1%)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	5 (4%)	7 (6%)	5 (4%)
SALBUTAMOL	5 (4%)	5 (4%)	4 (4%)
SALBUTAMOL SULFATE	0	1 (<1%)	1 (<1%)
FORMOTEROL	0	1 (<1%)	0
SELECTIVE ESTROGEN RECEPTOR MODULATORS	0	0	2 (2%)
RALOXIFENE HYDROCHLORIDE	0	0	2 (2%)
SELECTIVE IMMUNOSUPPRESSIVE AGENTS	0	0	1 (<1%)
ETANERCEPT	0	0	1 (<1%)
SELECTIVE SEROTONIN (5HT1) AGONISTS	1 (<1%)	2 (2%)	0
ELETRIPTAN HYDROBROMIDE	0	1 (<1%)	0
RIZATRIPTAN BENZOATE	1 (<1%)	1 (<1%)	0
SUMATRIPTAN SUCCINATE	0	1 (<1%)	0
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	3 (3%)	1 (<1%)	1 (<1%)
FLUOXETINE	0	0	1 (<1%)
ESCITALOPRAM OXALATE	1 (<1%)	1 (<1%)	0
FLUVOXAMINE MALEATE	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
PAROXETINE HYDROCHLORIDE	1 (<1%)	0	0
SERUM LIPID REDUCING AGENTS	0	0	1 (<1%)
SERUMLIPIDREDUCING AGENTS	0	0	1 (<1%)
SUBSTITUTED ALKYLAMINES	1 (<1%)	1 (<1%)	0
CHLORPHENAMINE	1 (<1%)	0	0
CHLORPHENAMINE MALEATE	0	1 (<1%)	0
SULFONAMIDES, PLAIN	0	2 (2%)	0
CHLORTALIDONE	0	1 (<1%)	0
FUROSEMIDE	0	1 (<1%)	0
SULFONAMIDES, UREA DERIVATIVES	2 (2%)	2 (2%)	3 (3%)
GLIPIZIDE	1 (<1%)	2 (2%)	2 (2%)
GLIBENCLAMIDE	0	0	1 (<1%)
GLIMEPIRIDE	1 (<1%)	0	0
SYMPATHOMIMETICS	7 (6%)	4 (3%)	6 (5%)
PSEUDOEPHEDRINE HYDROCHLORIDE	4 (3%)	2 (2%)	4 (4%)
ACTIFED	1 (<1%)	1 (<1%)	1 (<1%)
CONTAC 700	0	0	1 (<1%)
DRIXORAL COLD & FLU	1 (<1%)	0	0
NAPROXEN SODIUM W/PSEUDOEPHEDRINE HCL	0	1 (<1%)	0
PSEUDOEPHEDRINE	1 (<1%)	0	0

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
SYMPATHOMIMETICS IN GLAUCOMA THERAPY	1 (<1%)	0	0
BRIMONIDINE TARTRATE	1 (<1%)	0	0
SYMPATHOMIMETICS, PLAIN	1 (<1%)	1 (<1%)	2 (2%)
OXYMETAZOLINE HYDROCHLORIDE	1 (<1%)	0	2 (2%)
PHENYLEPHRINE HYDROCHLORIDE	0	1 (<1%)	0
SYNTHETIC ESTROGENS, PLAIN	0	1 (<1%)	0
ESTROPIPATE	0	1 (<1%)	0
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX	0	1 (<1%)	0
MELATONIN	0	1 (<1%)	0
TETANUS VACCINES	1 (<1%)	0	0
TETANUS TOXOID	1 (<1%)	0	0
TETRACYCLINES	0	0	1 (<1%)
DOXYCYCLINE	0	0	1 (<1%)
THIAZIDES, PLAIN	3 (3%)	0	1 (<1%)
HYDROCHLOROTHIAZIDE	3 (3%)	0	1 (<1%)
THIAZOLIDINEDIONES	2 (2%)	2 (2%)	3 (3%)
PIOGLITAZONE	1 (<1%)	2 (2%)	2 (2%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
ROSIGLITAZONE MALEATE	1 (<1%)	0	1 (<1%)
THYROID HORMONES	7 (6%)	4 (3%)	1 (<1%)
LEVOTHYROXINE SODIUM	4 (3%)	4 (3%)	1 (<1%)
LEVOTHYROXINE	3 (3%)	0	0
TRIAZOLE DERIVATIVES	1 (<1%)	1 (<1%)	0
FLUCONAZOLE	1 (<1%)	1 (<1%)	0
URINARY ANTISPASMODICS	2 (2%)	1 (<1%)	0
OXYBUTYNIN HYDROCHLORIDE	0	1 (<1%)	0
TOLTERODINE L-TARTRATE	2 (2%)	0	0
VITAMIN A, PLAIN	1 (<1%)	0	1 (<1%)
RETINOL	1 (<1%)	0	1 (<1%)
VITAMIN B-COMPLEX WITH VITAMIN C	0	1 (<1%)	0
MULTIPLE VITAMINS	0	1 (<1%)	0
VITAMIN B-COMPLEX, PLAIN	0	0	1 (<1%)
NICOTINAM. W/PYRIDOXI. HCL/RIBOFL./THIAM. HCL	0	0	1 (<1%)
VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	1 (<1%)	0	2 (2%)
CYANOCOBALAMIN	1 (<1%)	0	2 (2%)

Table S40 Summary of On-Study Concomitant Medications by ACT Term and Drug Class (Safety Population)

	Group 1 (N = 116)	Group 2 (N = 116)	Group 3 (N = 114)
VITAMIN D AND ANALOGUES	1 (<1%)	0	1 (<1%)
ERGOCALCIFEROL	1 (<1%)	0	1 (<1%)
VITAMIN K ANTAGONISTS	0	0	1 (<1%)
WARFARIN SODIUM	0	0	1 (<1%)
VITAMINS	1 (<1%)	0	0
VITAMINS	1 (<1%)	0	0
VITAMINS, OTHER COMBINATIONS	1 (<1%)	0	0
VITAMINS, OTHER COMBINATIONS	1 (<1%)	0	0
XANTHINES	1 (<1%)	0	0
THEOPHYLLINE	1 (<1%)	0	0
ZINC	2 (2%)	0	0
ZINC	1 (<1%)	0	0
ZINC SULFATE	1 (<1%)	0	0

On-study concomitant medications were medications that were used on or after the first dose date
N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S41 Summary of Medical History by Body Category (ITT Population)

	Group 1 (N = 116) n (%)	Group 2 (N = 116) n (%)	Group 3 (N = 114) n (%)
Allergic/Immunologic			
Abnormal	47 (40.5%)	63 (54.3%)	47 (41.2%)
Cardiovascular			
Abnormal	31 (26.7%)	40 (34.5%)	30 (26.3%)
Dermatological			
Abnormal	39 (33.6%)	28 (24.1%)	31 (27.2%)
Ears, Nose, Throat			
Abnormal	47 (40.5%)	33 (28.4%)	42 (36.8%)
Endocrine			
Abnormal	27 (23.3%)	29 (25.0%)	25 (21.9%)
Gastrointestinal			
Abnormal	59 (50.9%)	58 (50.0%)	56 (49.1%)
Genitourinary			
Abnormal	51 (44.0%)	66 (56.9%)	50 (43.9%)
Hematological			
Abnormal	12 (10.3%)	9 (7.8%)	9 (7.9%)
Musculoskeletal			
Abnormal	57 (49.1%)	58 (50.0%)	59 (51.8%)
Neurological			
Abnormal	37 (31.9%)	40 (34.5%)	33 (28.9%)
Ocular			
Abnormal	24 (20.7%)	20 (17.2%)	21 (18.4%)
Psychiatric			
Abnormal	15 (12.9%)	21 (18.1%)	20 (17.5%)
Respiratory			
Abnormal	32 (27.6%)	34 (29.3%)	24 (21.1%)

Table S41 Summary of Medical History by Body Category (ITT Population)

	Group 1 (N = 116) n (%)	Group 2 (N = 116) n (%)	Group 3 (N = 114) n (%)
Substance Abuse			
Abnormal	5 (4.3%)	2 (1.7%)	0

N = number of randomized subjects who received study treatment
% = n/N x 100%

Table S42.1 Summary of Physical Examination by Body Category at Baseline (ITT Population)

	Group 1 (N = 116) n (%)	Group 2 (N = 116) n (%)	Group 3 (N = 114) n (%)
Abdominal			
Abnormal	11 (9.5%)	16 (13.8%)	12 (10.5%)
Chest:Heart			
Abnormal	4 (3.4%)	3 (2.6%)	0
Chest:Thorax			
Abnormal	7 (6.0%)	2 (1.7%)	5 (4.4%)
EENT			
Abnormal	20 (17.2%)	18 (15.5%)	24 (21.1%)
Extremities			
Abnormal	7 (6.0%)	10 (8.6%)	8 (7.0%)
General Appearance			
Abnormal	13 (11.2%)	16 (13.8%)	13 (11.4%)
Musculoskeletal			
Abnormal	7 (6.0%)	4 (3.4%)	6 (5.3%)
Neurological			
Abnormal	3 (2.6%)	1 (0.9%)	1 (0.9%)
Skin			
Abnormal	28 (24.1%)	37 (31.9%)	31 (27.2%)

N = Number of randomized subjects with available data
% = n/N x 100%

Table S42.2 Summary of Physical Examination by Body Category at Visit 10 (ITT Population)

	Group 1 (N = 51) n (%)	Group 2 (N = 40) n (%)	Group 3 (N = 56) n (%)
Abdominal			
Abnormal	4 (7.8%)	6 (15.0%)	7 (12.5%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
Chest:Heart			
Abnormal	3 (5.9%)	1 (2.5%)	0
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
Chest:Thorax			
Abnormal	0	1 (2.5%)	3 (5.4%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
EENT			
Abnormal	6 (11.8%)	4 (10.0%)	11 (19.6%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
Extremities			
Abnormal	3 (5.9%)	5 (12.5%)	5 (8.9%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
General Appearance			
Abnormal	6 (11.8%)	6 (15.0%)	5 (8.9%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
Musculoskeletal			
Abnormal	4 (7.8%)	1 (2.5%)	2 (3.6%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
Neurological			
Abnormal	0	1 (2.5%)	0
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)
Skin			
Abnormal	13 (25.5%)	13 (32.5%)	16 (28.6%)

Table S42.2 Summary of Physical Examination by Body Category at Visit 10 (ITT Population)

	Group 1 (N = 51) n (%)	Group 2 (N = 40) n (%)	Group 3 (N = 56) n (%)
Unknown	1 (2.0%)	1 (2.5%)	3 (5.4%)

N = Number of randomized subjects with available data
% = n/N x 100%

**Table S43.3 Summary of Physical Examination by Body Category at End of Study
(ITT Population)**

	Group 1 (N = 97) n (%)	Group 2 (N = 104) n (%)	Group 3 (N = 95) n (%)
Abdominal			
Abnormal	5 (5.2%)	6 (5.8%)	1 (1.1%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
Chest:Heart			
Abnormal	2 (2.1%)	0	1 (1.1%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
Chest:Thorax			
Abnormal	2 (2.1%)	1 (1.0%)	4 (4.2%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
EENT			
Abnormal	7 (7.2%)	9 (8.7%)	9 (9.5%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
Extremities			
Abnormal	1 (1.0%)	4 (3.8%)	4 (4.2%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
General Appearance			
Abnormal	5 (5.2%)	6 (5.8%)	9 (9.5%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
Musculoskeletal			
Abnormal	4 (4.1%)	3 (2.9%)	2 (2.1%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
Neurological			
Abnormal	1 (1.0%)	0	1 (1.1%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)
Skin			

**Table S43.3 Summary of Physical Examination by Body Category at End of Study
(ITT Population)**

	Group 1 (N = 97) n (%)	Group 2 (N = 104) n (%)	Group 3 (N = 95) n (%)
Abnormal	8 (8.2%)	12 (11.5%)	12 (12.6%)
Unknown	48 (49.5%)	56 (53.8%)	47 (49.5%)

N = Number of randomized subjects with available data
% = n/N x 100%

APPENDIX B – ADVERSE EVENT SUMMARIES

Serious Adverse Events

Subject 03064 is a 60 year old female with past medical history significant for previous myocardial infarction in 1997, hypertension regulated by medication, and previous angioplasty in 2003. This subject was enrolled on April 26, 2005, and randomized on May 4, 2005, to Group 1. She experienced chest pressure on (b) (6) , and a blood pressure of 190/94 by home monitor. She woke up the following morning feeling chest pressure and was admitted to the hospital. The subject underwent cardiac catheterization showing 92% and 97% stenosis in two coronary arteries. The subject subsequently underwent angioplasty and stent placement and was discharged home on May 24, 2005. The event was classified as not related to the study drug by both the investigator and the medical monitor.

Disposition: The subject was discontinued from the study due to the adverse event.

Subject 01084 is 59 year old male with history of a ventral hernia in 2005 and onychomycosis of the toenails in 2003. This subject was enrolled on April 27, 2005, and randomized on May 3, 2005, to Group 1. The subject reported hospitalization on (b) (6) (b) (6), for the removal of a bladder tumor as noted on routine physical exam on (b) (6) (b) (6) Surgical pathology report revealed papillary urothelial carcinoma with areas of high grade tumor (grade 3 of 4); no evidence of invasive carcinoma and no flat carcinoma *in situ* evident. The subject experienced no further complications due to the procedure. The Investigator and medical monitor assessed the event as not related to the investigational product.

Disposition: The subject remained in the study.

Subject 05121 is 64 year old female with history of anxiety, depression, hypercholesterolemia, dermatitis, lichen sclerosis, chronic cough, insomnia, low back

pain, hemorrhoids, and liver damage. This subject was enrolled on April 26, 2005, and randomized on May 5, 2005, to Group 3. The subject was hospitalized on (b) (6) (b) (6) for open reduction internal fixation of displaced left tibial-fibial shaft fracture. She was anticoagulated with coumadin and enoxaparin. She was discharged on October 12, and reported the event to the site on November 14, 2005. The Investigator and medical monitor assessed the event as not related to the investigational product.

Disposition: The subject recovered/resolved with cast removal on January 6, 2006; the subject remained in trial.

Adverse Events Resulting in Study Discontinuation[1]

Subject 01295 was a 20 year old man with a history of acne, partial hearing loss of the left ear, appendectomy, mild anxiety, and mild depression. The sponsor was notified about the age after randomization. The subject was enrolled in the study on May 19, 2005, and randomized on May 26, 2005, to Group 1. He experienced nausea from May 26, 2005, until May 28, 2005. This was a continuous problem of moderate severity which resolved without sequelae. It was judged to be probably study treatment related and not a Serious Adverse Event. He experienced impacted wisdom teeth on June 8, 2005. This was a continuous problem of moderate severity which resolved without sequelae. This was judged to be not study product related and not a Serious Adverse Event. He fractured his right ankle on June 3, 2005. This was a continuous problem of moderate severity, which was ongoing at the time of the report. This was judged to be not study product related and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on June 13, 2005, because of the Adverse Event: nausea.

Subject 01311 was a 52 year old woman with a history of penicillin allergy, erythromycin allergy, tetracycline allergy, tonsilectomy, cholecystectomy, bunionectomy of the right foot, bladder reconstruction, hysterectomy, seasonal allergies, hemorrhoids, osteoarthritis, tendonitis of left elbow, cervical lumbar disc disease, osteopenia, and back pain. She was enrolled on May 25, 2005, and randomized on June 2, 2005, to Group 3. She experienced a headache from June 2, 2005 until June 3, 2005. This was a continuous problem of moderate severity which resolved without sequelae. It was judged to be possibly study product related and not a Serious Adverse Event. She experienced a cough from June 2, 2005, until June 3, 2005. This was a continuous problem of moderate severity which resolved without sequelae. This was judged to be possibly study product related and not a Serious Adverse Event.

[1] Subjects 3051, 04015, and 05242 experienced AEs that lead to stopping the study product, but where the primary reason for discontinuation was not due to an AE.

Disposition: The subject was discontinued from the study on June 6, 2005, because of the Adverse Event: headache and cough.

Subject 02043 was a 23 year old woman with a history of sulfa drug allergy, sinusitis, scoliosis, cervical dilation and curettage, and allergy to dust and mold. She was enrolled on May 4, 2005, and randomized on June 2, 2005, to Group 3. The subject experienced contact dermatitis from June 24, 2005, until July 8, 2005. This was a continuous problem of mild severity which resolved without sequelae. This was judged to be definitely study product related and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on July 8, 2006, because of the Adverse Event: contact dermatitis.

Subject 03051 is a 62 year old male with a history of a benign left shoulder cyst, seasonal allergies, colon polyps, hypercholesterolemia, back injury, prostatitis, intermittent chronic sinusitis, myopia, hyperopia, gum disease, appendectomy, tonsillectomy, inguinal hernia, idiopathic thrombocytopenia purpura, and splenectomy. He was enrolled on April 26, 2005 and randomized to group 1 on May 2, 2005. He experienced a common cold from May 4, 2005 until May 28, 2005. This was a continuous problem of mild severity which resolved without sequealae. It was judged to be not related to the study product and not a Serious Adverse Event. He experienced redness at patch sites from June 14, 2005 until July 1, 2005. This was a continuous problem of mild severity which resolved without sequealae. It was judged to be definitely related to the study product and not a Serious Adverse Event. He experienced nausea from June 28, 2005 until July 1, 2005. This was an intermittent problem of mild severity which resolved without sequealae. It was judged to be possibly study product related and not a Serious Adverse Event. He experienced vivid dreams from June 28, 2006 until July 1, 2006. This was an intermittent problem of mild severity which resolved without sequealae. It was judged to be possible study product related and not a Serious Adverse Event. The study product was stopped due to naseau and vivid dreams.

Disposition: The subject was discontinued from the study on July 11, 2005 because of a request/withdrawal of consent.

Subject 03060 was a 23 year old man with a history of wisdom tooth extraction and scoliosis. He was enrolled on April 26, 2005, and randomized on May 3, 2005, to Group 2. He experienced itching of the chest on June 3, 2005. This was an intermittent problem of moderate severity which was ongoing at the time of the report. It was judged to be definitely study related and not a Serious Adverse Event. The subject experienced itching of the legs on June 3, 2005. This was an intermittent problem of moderate severity which was ongoing at the time of the report. It was judged to be definitely related to the study product and not a Serious Adverse Event. The subject experienced redness under patch site on June 1, 2005. This was an intermittent problem of mild severity which resolved without sequelae. This was judged to be definitely related to the study product and not a Serious Adverse Event. The subject experienced back pain on June 14, 2005. This was an intermittent problem of moderate severity which was ongoing at the time of the report. It was judged to be not related to the study product and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on June 14, 2005, because of the Adverse Events: itching of the chest and legs and redness under the patch site.

Subject 03064 was a 60 year old woman with a history of penicillin allergy, sulfa drug allergy, jaundice, hyperopia, stomach ulcer, hypercholesterolemia, osteoarthritis of the left hand, depression, stress urinary incontinence, fibrocystic disease of the breast, pancreatitis, gall stones, gastroesophageal reflux, seasonal allergies, hysterectomy, tubal ligation, hyperthyroidism, partial thyroidectomy, angina, hypertension, peripheral vascular disease, cardiac catheterization, angioplasty, and myocardial infarction. This subject was enrolled on April 26, 2005, and randomized on May 4, 2005, to Group 1. She experienced chest pressure, and a blood pressure of 190/94 by home monitor on (b) (6) (b) (6) She woke up the following morning feeling chest pressure and was admitted to the hospital. The subject underwent cardiac catheterization showing 92% and 97%

stenosis in two coronary arteries. The subject subsequently underwent angioplasty and stent placement and was discharged home on May 24, 2005. These were both single episodes of severe severity which resolved as above. They were judged by both the investigator and the medical monitor as not related to the study product and were both Serious Adverse Events. The subject experienced neck pain from May 22, 2005, until May 23, 2005. This was a single episode of moderate severity which resolved without sequelae. It was judged to be not related to study product and not a Serious Adverse Event. This subject experienced left arm pain form May 22, 2005 until May 23, 2005. This was a single episode of moderate severity which resolved without sequelae. It was judged to be not related to the study product and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on June 13, 2005 because of the Adverse Event: chest pressure.

Subject 03067 was a 52 year old woman with a history of codeine allergy, shingles, tonsillectomy, hypothyroidism, myopia, esophagitis, rheumatoid arthritis, bilateral carpal tunnel syndrome, allergy to poison ivy, gastroesophageal reflux disease, gastritis, polyarthropy, duodenal ulcer, hyperopia, astigmatism, tubal ligation, squamous cell carcinoma with excision, and appendectomy. She was enrolled on May 2, 2005, and randomized on May 9, 2005, to Group 1. The subject experienced a swollen neck gland on May 30, 2005. This was a continuous problem of mild severity which was ongoing at the time of the report. It was judged to be not related to the study product and not a Serious Adverse Event. The subject experienced a rash at the patch site on June 7, 2005. This was a continuous problem of severe severity which resolved without sequelae. It was judged to be definitely related to the study product and not a Serious Adverse Event. The subject experienced itching at the patch site on June 7, 2005. This was a continuous problem of severe severity which resolved without sequelae. It was judged to be definitely related to the study product and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on June 7, 2005 because of the Adverse Events: rash and itching at the patch site.

Subject 04003 was a 44 year old man with a history of seasonal allergies, sinus headaches, and substance abuse. He was enrolled on April 21, 2005, and randomized on April 27, 2005, to Group 2. He experienced shortness of breath from May 26, 2005, until May 30, 2005. This was a continuous problem of moderate severity which resolved without sequelae. This was judged to be probably related to the study product and not a Serious Adverse Event. The subject experienced chest pain from May 26, 2005, until May 30, 2005. This was a continuous problem of moderate severity which resolved without sequelae. It was judged to be probably related to the study product and not a Serious Adverse Event. The subject experienced insomnia from May 26, 2005, until May 30, 2005. This was a continuous problem of moderate severity which resolved without sequelae. It was judged to be probably related to the study product and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on June 8, 2005, because of the Adverse Events: shortness of breath, chest pain and insomnia.

Subject 04015 is a 45 year old male with a history of esophageal reflux, back pain, insomnia, vasectomy, dyspepsia, heartburn and headache. He was enrolled on April 21, 2005 and randomized to group 1 on April 28, 2005. He experienced an exacerbation of insomnia from May 8, 2005 until June 20, 2005. This was an intermittent problem of mild severity which resolved without sequealae. It was judged to be possible related to the study product and not a Serious Adverse Event. He experienced urticaria of the chest from May 27, 2005 until May 29, 2005. This was a single episode of mild severity which resolved without sequealae. It was judged to be definitely related to the study product and not a Serious Adverse Event. The study product was stopped due to this event.
Disposition: The subject was discontinued from the study on June 30, 2005 because of a failure to quit smoking.

Subject 05110 was a 40 year old woman with a history of sulfa drug allergy, hypoglycemia, anemia during pregnancy, stiff neck, headaches, environmental allergies, allergy related shortness of breath, insomnia and heavy irregular periods. She was

enrolled on April 26, 2005, and randomized on May 3, 2005, to Group 3. The subject experienced nausea from May 16, 2005 until May 17, 2005. This was a continuous problem of mild severity which resolved without sequelae. It was judged to be not related to the study product and not a Serious Adverse Event. The subject experienced diarrhea from May 17, 2005 until May 18, 2005. This was an intermittent problem of mild severity which resolved without sequelae. It was judged to be not related to the study product and not a Serious Adverse Event. The subject experienced chest tightness, non cardiac, from June 15, 2005 until June 16, 2005. This was an intermittent problem of mild severity which resolved without sequelae. It was judged to be probably related to the study product and not a Serious Adverse Event. She experienced localized muscle aches at the patch site from July 3, 2005 until July 6, 2005. This was a continuous problem of mild severity which resolved without sequelae. This was judged to be possibly related to the study product and not a Serious Adverse Event.
Disposition: The subject was discontinued from the study on July 13, 2005 because off the Adverse Event: muscle aches.

Subject 05245 is a 60 year old male with a history of penicillin allergy, endentulousness, high iron levels, perforated peptic ulcer, seasonal headaches, hymenoptera allergy, heartburn, and appendectomy. He was enrolled on May 10, 2005 and randomized to group 3 on May 17, 2005. He experienced nausea from June 10, 2005 until June 25, 2005. This was a continuous problem of mild severity which resolved without sequealae. It was judged to be possible study product related and not a Serious Adverse Event. He experienced lack of appetite from June 10, 2005 until June 25, 2005. This was a continuous problem of mild severity which resolved without sequealae. It was judged to be possibly study product related and not a Serious Adverse Event. He experienced weight loss from June 2, 2005 until June 28, 2005. This was a continuous problem of mild severity which resolved without sequealae. It was judged to be possibly study product related and not a Serious Adverse Event. He experienced a rash at the patch site from July 3, 2005 until July 4, 2005. This was an intermittent problem of mild severity which resolved without sequealae. It was judged to probably be study product related

and not a Serious Adverse Event. The study product was stopped due the rash at the patch site.

Disposition: The subject was discontinued on July 13, 2005 because of failure to quit smoking.

APPENDIX C – REVISION HISTORY

Revision History

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
Executive Summary (p. 22)	**Treatment failure imputation was used to impute missing values for subjects who dropped out due to lack of efficacy and/or for whom abstinence status could not be determined. Abstinence status for all other subjects (i.e., subjects who withdrew consent) was imputed following the multiple imputation method of Rubin (1987). All analyses were performed with a one-sided significance level including a conservative adjustment for multiple comparisons. Four-week abstinence proportions by method of imputation are summarized in the table below and in the figure on the following page.**	**Analysis of the primary endpoint, 4 weeks of continuous abstinence, included a series of sensitivity tests, employing a range of imputation methods for missing data, to determine whether the 4-week abstinence rate was statistically different between Groups 1 and 3, and Groups 2 and 3. Analysis of the primary endpoint was an ITT analysis using treatment failure imputation. Subsequently, the sensitivity of this analysis was examined using statistical methodology to impute missing values. The additional sensitivity analyses on the ITT population were based on multiple imputation (Rubin 1987), all available data, and treatment failure for subjects who discontinued due to lack of efficacy; and, finally, a treatment failure analysis on the per-protocol analysis was conducted. The results of these analyses are summarized in the table below and in the figure on the following page.**
Executive Summary, Table (p. 22)	Group 1 proportion (p-value*) using treatment failure (ITT population) = 32.8% (**0.0499**).	Group 1 proportion (p-value*) using treatment failure (ITT population) = 32.8% (**0.0449**).
	Group 1 proportion (p-value*)	Group 1 proportion (p-value*)

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
	using treatment failure (per-protocol population) = 44.8% (**0.0253**).	using treatment failure (per-protocol population) = 45.5% (**0.0213**).
	* One-sided Fisher's exact test for four-week abstinence proportions compared with Group 3, at the 0.05 and **0.25** levels using Bonferroni adjustment.	* One-sided Fisher's exact test for four-week abstinence proportions compared with Group 3, at the 0.05 and **0.025** levels using Bonferroni adjustment.
Executive Summary, Table (p. 22)	Note: Documents a change in order, not a change in content.	Note: Documents a change in order, not a change in content.
	Using Treatment Failure (ITT Population)	**Primary Analysis**
	Using Treatment Failure for Subjects Who Discontinued Due to Lack of Efficacy (ITT Population Excluding Subjects Whose Abstinence Status Could Not be Determined)	**Using Treatment Failure (ITT) Population**
	Using Multiple Imputation (ITT Population)	**Additional Sensitivity Analyses**
	Using Treatment Failure (Per-Protocol Population)	**Using Multiple Imputation (ITT Population)**
		Based on Available Data (ITT Population)
		Using Treatment Failure for Subjects Who Discontinued Due to Lack of Efficacy (ITT Population Excluding Subjects Whose Abstinence Status Could Not be Determined)
		Using Treatment Failure (Per-Protocol Population)
Executive Summary, Bar Graph (p. 23)	Group 1, per-protocol treatment failure imputation proportion with 4-week abstinence statistically significant at p = **0.05** level (Group 1 compared with Group 3).	Group 1, per-protocol treatment failure imputation proportion with 4-week abstinence statistically significant at p = **0.025** level (Group 1 compared with Group 3).

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
Executive Summary, Bar Graph (p. 23)	Changed the order of the bars from: **ITT – Available Data** **ITT – Multiple Imputation** **ITT – Treatment Failure Imputation** **PP – Treatment Failure Imputation** **ITT – Failure = Discontinuation Due to Lack of Efficacy**	Changed the order of the bars to be: **ITT - Treatment Failure Imputation (primary analysis)** **ITT – Multiple Imputation (sensitivity analysis)** **ITT – Available Data (sensitivity analysis)** **ITT – Failure = Discontinuation Due to Lack of Efficiacy (sensitivity analysis)** **PP – Treatment Failure Imputation (sensitivity analysis)**
Executive Summary (p. 24)	The treatment effects that could be statistically tested (ITT with treatment failure imputation, ITT with multiple imputation, ITT with discontinuation due to lack of efficacy, and per-protocol analysis with treatment failure imputation) were significant at the 0.05 significance level ~~**and close to significant with a multiplicity adjustment**~~.	The treatment effects that could be statistically tested (ITT with treatment failure imputation, ITT with multiple imputation, ITT with discontinuation due to lack of efficacy, and per-protocol analysis with treatment failure imputation) were significant at the 0.05 significance level.
Executive Summary (p. 24)	Statistical significance was maintained upon adjustment in the ITT treatment failure analysis for subjects who discontinued due to lack of efficacy.	Statistical significance was maintained upon adjustment in the ITT treatment failure analysis for subjects who discontinued due to lack of efficacy **and in the per-protocol analysis with treatment failure imputation.**
Section 5.0 (p. 39)	Three hundred forty-six (346) smokers who provided informed consent for participation in this trial, ~~**who**~~ were capable of comprehending the nature of the study, and ~~**who**~~ were likely to comply with the visit schedule were entered into the study,	Three hundred forty-six (346) smokers who **1)** provided informed consent for participation in this trial; **2)** were capable of comprehending the nature of the study; and **3)** were likely to comply with the visit schedule were entered into the study,

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
	provided they also conformed to the following criteria.	provided they also conformed to the following criteria.
Section 5.0 (p. 39)	Subjects were required to read, understand, complete, and sign the Informed Consent form.	Subjects were required to read, understand, complete, and sign the **i**nformed **c**onsent form.
Section 6.1 (p. 43)	All participating subjects smoked for 6 weeks (either Quest 1, Quest 2, Quest 3, or conventional "faded" cigarettes) and received 12 weeks of application of the nicotine and/or placebo patch.	All participating subjects smoked for 6 weeks (either Quest 1, Quest 2, Quest 3, or conventional "faded" cigarettes) and received 12 weeks of application of the nicotine and/or placebo patch **with no subjects receiving more than 10 weeks of active NRT.**
Section 11, Table 2 (p. 74)	Added footnote to table for the row labeled, "Completed Study."	**Subject disposition data from CRF Study Completion/Early Withdrawal from the question, "Did the patient complete study?"**
Section 11, Table 3 (p. 75)	Arrangement of analyses: Primary Analysis Imputed as failure Imputed by multiple imputation **Not imputed (Available)** Treatment Failure Imputed as failure **Not imputed (Available)** Treatment Failure due to Lack of Efficacy Imputed as failure **Not imputed (Available)** Excluded Per-Protocol Imputed as failure **Not imputed (Available)**	Arrangement of analyses: Primary Analysis **Treatment Failure** **Imputed as failure** **Not imputed (Success)** **Not imputed (Failure)** **Additional Sensitivity Analyses** **Imputed by multiple imputation** **Imputed as failure** **Not imputed (Success)** **Not imputed (Failure)** **Based on Available Data** **Not imputed (Success)** **Not imputed (Failure)** **Excluded** Treatment Failure due to Lack

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
	Excluded	of Efficacy Imputed as Failure **Not imputed (Success)** **Not imputed (Failure)** Excluded Per-protocol Imputed as failure **Not imputed (Success)** **Not imputed (Failure)** Excluded
	Primary Analysis: **Not imputed (Available): Group 1 = 88 (75.9%), Group 2 = 79 (68.1%), Group 3 = 95 (83.3%)**	Primary Analysis: **Not imputed (Success): Group 1 = 38 (32.8%), Group 2 = 19 (16.4%), Group 3 = 25 (21.9%)** **Not imputed (Failure): Group 1 = 50 (43.1%), Group 2 = 60 (51.7%), Group 3 = 70 (61.4%)**
	Treatment Failure: **Not imputed (Available): Group 1 = 88 (75.9%), Group 2 = 79 (68.1%), Group 3 = 95 (83.3%)**	Treatment Failure: **Not imputed (Success): Group 1 = 38 (32.8%), Group 2 = 19 (16.4%), Group 3 = 25 (21.9%)** **Not imputed (Failure): Group 1 = 50 (43.1%), Group 2 = 60 (51.7%), Group 3 = 70 (61.4%)**
	Treatment Failure due to Lack of Efficacy: **Not imputed (Available): Group 1 = 88 (75.9%), Group 2 = 79 (68.1%), Group 3 = 95 (83.3%)**	Treatment Failure due to Lack of Efficacy: **Not imputed (Success): Group 1 = 38 (32.8%), Group 2 = 19 (16.4%), Group 3 = 25 (21.9%)** **Not imputed (Failure): Group 1 = 50 (43.1%), Group 2 = 60 (51.7%), Group 3 = 70 (61.4%)**

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
Section 11, Table 3 (p. 75)	Per-Protocol: **Not imputed (Available): Group 1 = 66 (56.9%), Group 2 = 65 (56.0%), Group 3 = 79 (69.3%)**	Per-Protocol: **Not imputed (Success): Group 1 = 30 (25.9%), Group 2 = 13 (11.2%), Group 3 = 22 (19.3%)** **Not imputed (Failure): Group 1 = 36 (31.0%), Group 2 = 52 (44.8%), Group 3 = 57 (50.0%)**
Section 11, Figure F (p. 77)	Added footnote.	***36 subjects exceeded the 32 week cutoff in order complete Visit 12 at a later week**
Section 11, Table 4.1 (p. 78)	Footnote: Available = number of subjects with available data	Footnote: Available = number of subjects with **any** available data
Section 11, Table 4.2 (p. 79)	Footnote: Available = number of subjects with available data	Footnote: Available = number of subjects with **any** available data
Section 14 (entire section) (p. 94-111)	Note: Documents a change in order, not a change in content. 14.0 Primary Efficacy Endpoint – **Continuous 4 Weeks** of Continuous Abstinence **14.1 Primary Endpoint – Available Data, ITT Population** **14.2 Primary Endpoint – Treatment Failure, ITT Population** **14.3 Primary Endpoint – Multiple Imputation, ITT Population** **14.4 Primary Endpoint – Per-Protocol Population** Note: Section 14.4 included summary Figure G.	Note: Documents a change in order, not a change in content. Corresponding table and figure numbers have been updated accordingly. 14.0 Primary Efficacy Endpoint – **Four Weeks of** Continuous Abstinence **14.1 Primary Analysis: Four Weeks of Continuous Abstinence – Treatment Failure, ITT Population** **14.2 Additional Analyses** **14.2.1 Four Weeks of Continuous Abstinence – Multiple Imputation, ITT Population** **14.2.2 Four Weeks of Continuous Abstinence – Available Data, ITT Population** **14.2.3 Four Weeks of**

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
		Continuous Abstinence – Treatment Failure for Subjects Who Discontinued Due to Lack of Efficacy, ITT Population Excluding Subjects Whose Abstinence Status Could Not be Determined **14.2.4 Four Weeks of Continuous Abstinence – Per-Protocol Population** **14.3 Summary**
Section 14.0 (p. 94)	**The first involved** an ITT analysis using **all available data.**	**Analysis of the primary endpoint was** an ITT analysis using **treatment failure imputation.**
	Subsequently, **the ITT population was analyzed** using statistical methodology to impute missing values: **treatment failure, treatment failure for subjects who discontinued due to lack of efficacy, and multiple imputation.** A per-protocol analysis was **also performed.**	Subsequently, **the sensitivity of this analysis was examined** using statistical methodology to impute missing values. **The additional sensitivity analyses on the ITT population were based on multiple imputation, all available data, and treatment failure for subjects who discontinued due to lack of efficacy; and, finally, a treatment failure analysis on the per-protocol analysis was conducted.**
Section 14.0, Table 12 (p. 94)	Note: Documents a change in the order of the rows of the table, not a change in content of the table. **Based on Available Data (ITT Population)**** **Using Treatment Failure (ITT Population)** **Using Treatment Failure for Subjects Who Discontinued Due to Lack of Efficacy (Excluding Subjects Whose Abstinence Status Could Not be Determined)**	**Primary Analysis** **Using Treatment Failure (ITT) Population** **Additional Sensitivity Analyses** **Using Multiple Imputation (ITT Population)** **Based on Available Data (ITT Population)**** **Using Treatment Failure for Subjects Who Discontinued** **Due to Lack of Efficacy (ITT Population Excluding Subjects Whose**

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
	Using Multiple Imputation (ITT Population) **Using Treatment Failure (Per-Protocol Population)**	**Abstinence Status Could Not be Determined)** **Using Treatment Failure (Per-Protocol Population)**
Section 14.0, Table 12 (p. 94)	Group 1 proportion (p-value*) using treatment failure (ITT population) = 32.8% (**0.0499**).	Group 1 proportion (p-value*) using treatment failure (ITT population) = 32.8% (**0.0449**).
Section 14.0, Table 12 (p. 94)	Group 1 proportion (p-value*) using treatment failure (per-protocol population) = **44.8%** (**0.0253**).	Group 1 proportion (p-value*) using treatment failure (per-protocol population) = **45.5%** (**0.0213**).
Section 14.0, Table 12 (p. 94)	* One-sided Fisher's exact test for four-week abstinence proportions compared with Group 3, at the 0.05 and **0.25** levels using Bonferonni adjustment.	* One-sided Fisher's exact test for four-week abstinence proportions compared with Group 3, at the 0.05 and **0.025** levels using Bonferonni adjustment.
Section 14.0, Table 12 (p. 94)	Using Treatment Failure for Subjects Who Discontinued Due to Lack of Efficacy (Excluding Subjects Whose Abstinence Status Could Not be Determined)	Using Treatment Failure for Subjects Who Discontinued Due to Lack of Efficacy (**ITT Population** Excluding Subjects Whose Abstinence Status Could Not be Determined)
	Subjects whose **criterion** cannot be determined were treated as not meeting **the** criterion.	Subjects whose **corrected CO < 10ppm, number of cigarettes smoked since last visit, or four-week abstinence** cannot be determined were treated as not meeting **that** criterion.
	* One-sided Fisher's exact test for four-week abstinence proportions compared with Group 3, at the 0.05 and **0.25** levels using Bonferonni adjustment.	* One-sided Fisher's exact test for four-week abstinence proportions compared with Group 3, at the 0.05 and **0.025** levels using Bonferonni adjustment.
Section 14.0, Table 12 (p. 94)	Covariates selected by a backward elimination procedure at a significance level of 0.1. Treatment group was always included in the model.	Covariates selected by a backward elimination procedure at a **two-sided** significance level of 0.1. Treatment group was always included in the model.

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
Section 14.2 (p.96)	Note: Added definition of the primary endpoint for clarification.	**The primary endpoint of this study was 4 weeks of continuous abstinence.**
Section 14.2, Table 14 (p.97)	Four-Week (Visits 6 and 7) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined)	Four-Week (Visits 6 and 7) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (**ITT Population** Excluding Subjects Whose Abstinence Status Could Not Be Determined)
Section 14.2, Table 14 (p. 97)	Table 18 Four-Week (Visits 6 and 7) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (Excluding Subjects Whose Abstinence Status Could Not Be Determined), Stratified by Study Site	Table 18 Four-Week (Visits 6 and 7) Abstinence Proportions Using Treatment Failure Imputation for Subjects Who Discontinued Due to Lack of Efficacy Only (**ITT Population** Excluding Subjects Whose Abstinence Status Could Not Be Determined), Stratified by Study Site
Section 14.2, Table 16 (p. 100)	The calculated proportion of subjects abstinent at 4 weeks was 44.0% for Group 1, 29.3% for Group 2, and 28.6% for Group.	The calculated proportion of subjects abstinent at 4 weeks was 44.0% for Group 1, 29.3% for Group 2, and 28.6% for Group **3**.
Section 14.2, Table 17 (p. 101)	Four-week abstinence proportions were 44.8% for Group 1, 20.0% for Group 2, and 27.8% for Group 3. Group 1 had a higher proportion of subjects who abstained than Group 3 (p = 0.0253), while Group 2 had a lower proportion of subjects who abstained compared to Group 3 (p = 0.9017).	Four-week abstinence proportions were **45.5%** for Group 1, 20.0% for Group 2, and 27.8% for Group 3. Group 1 had a higher proportion of subjects who abstained than Group 3 (p = **0.0213**), while Group 2 had a lower proportion of subjects who abstained compared to Group 3 (p = 0.9017).
Section 14.2, Table 18 (p. 102-103)	Group 1 (N = 67) Corrected exhaled CO < 10ppm – n (%) = 35 (**52.2**%).	Group 1 (N = 67) Corrected exhaled CO < 10ppm – n (%) = 35/**66** (**53.0**%).

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
Section 14.3 (p. 104)	Group 2 (N = 65) Corrected exhaled CO < 10ppm – n% = 23 (**35.4**%)	Group 2 (N = 65) Corrected exhaled CO < 10ppm – n% = 23/**62** (**37.1**%)
Section 14.4 (p. 106)	Group 3 (N = 79) Corrected exhaled CO < 10ppm – n% = 34 (**43.0**%)	Group 3 (N = 79) Corrected exhaled CO < 10ppm – n% = 34/**78** (**43.6**%)
Section 14.4, Table 21 (p. 107)	Group 1 (N = 67) No cigarettes smoked since last visit – n% = 41 (**61.2**%)	Group 1 (N = 67) No cigarettes smoked since last visit – n% = 41/**65** (**63.1**%)
	Group 2 (N = 65) No cigarettes smoked since last visit – n% = 20 (30.8%)	Group 2 (N = 65) No cigarettes smoked since last visit – n% = 20/**65** (30.8%)
	Group 3 (N = 79) No cigarettes smoked since last visit – n% = 29 (**36.7**%)	Group 3 (N = 79) No cigarettes smoked since last visit – n% = 29/**78** (**37.2**%)
	Group 1 (N = 67) Four week abstinence – n% = 30 (**44.8**%)	Group 1 (N = 67) Four week abstinence – n% = 30/**66** (**45.5**%)
	Group 2 (N =65) Four week abstinence – n% = 13 (20.0%)	Group 1 (N = 67) Four week abstinence – n% = 13/**65** (20.0%)
	Group 3 (N = 79) Four week abstinence – n% = 22 (27.8%)	Group 3 (N= 79) Four week abstinence – n% = 22/**79** (27.8%)
	Group 1 (N = 67) 95% CI for 4-week abstinence rate = (**32.6%, 57.4%**)	Group 1 (N = 67) 95% CI for 4-week abstinence rate = (**33.1%, 58.2%**)
	Group 1 (N = 67) *p-value* compared with Group 3 = **0.0253**	Group 1 (N = 67) *p-value* compared with Group 3 = **0.0213**
	Note: Added additional footnote to table for clarification of sample sizes.	*There are 1, 3 and 2 subjects in Groups 1, 2 and 3, respectively, having 1 missing component of the 4-week abstinence and a negative response of the other component. This results in a negative response for the 4-week abstinence and different numbers of subjects in the summary.
	Note: Added additional footnote to table for clarification of sample sizes.	*There are 1, 3 and 2 subjects in Groups 1, 2 and 3, respectively, having 1 missing component of the 4-week abstinence and a negative response of the other component. This results in a negative response

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
		for the 4-week abstinence and different numbers of subjects in the summary.
	The 4-week abstinence proportions observed in Group 1 (Quest 1, 2, and 3 with NRT) were significantly higher than the 4-week abstinence proportions observed in Group 3 (Active Control cigarettes with NRT) for multiple imputation in the ITT population ($p < 0.05$), for treatment failure imputation in the ITT and per-protocol populations ($p < \mathbf{0.05}$), and for treatment failure imputation for subjects who discontinued due to lack of efficacy in the ITT population ($p < 0.025$).	The 4-week abstinence proportions observed in Group 1 (Quest 1, 2, and 3 with NRT) were significantly higher than the 4-week abstinence proportions observed in Group 3 (Active Control cigarettes with NRT) for multiple imputation in the ITT population ($p < 0.05$), for treatment failure imputation in the ITT **population ($p < 0.05$), for treatment failure imputation in the ~~and~~** per-protocol populations ($p < \mathbf{0.025}$), and for treatment failure imputation for subjects who discontinued due to lack of efficacy in the ITT population ($p < 0.025$).
Section 14.4, Table 21 (p. 107)	Group 1, per-protocol treatment failure imputation proportion with 4-week abstinence is statistically significant at $p = \mathbf{0.05}$ level (Group 1 compared with Group 3).	Group 1, per-protocol treatment failure imputation proportion with 4-week abstinence is statistically significant at $p = \mathbf{0.025}$ level (Group 1 compared with Group 3).
Section 14.4, Table 22 (p. 108 -109)	Using the Bonferroni adjusted value (i.e., 0.025), statistical significance was maintained in the ITT treatment failure analysis for subjects who discontinued due to lack of efficacy.	Using the Bonferroni adjusted value (i.e., 0.025), statistical significance was maintained in the ITT treatment failure analysis for subjects who discontinued due to lack of efficacy **and in the per-protocol analysis with treatment failure imputation.**
Section 14.4 (p. 109 - 110)	Note: Changed the order of the analyses in the following sentence to reflect the order changes made to section 14. The 4-week abstinence proportions	The 4-week abstinence proportions observed in Group 1 (Quest 1, 2, and 3 with NRT) were significantly higher than the 4-week abstinence proportions observed in Group 3 (Active

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	observed in Group 1 (Quest 1, 2, and 3 with NRT) were significantly higher than the 4-week abstinence proportions observed in Group 3 (Active Control cigarettes with NRT) **for multiple imputation in the ITT population ($p < 0.05$), for treatment failure imputation in the ITT population ($p < 0.05$), for treatment failure imputation in the per-protocol population ($p < 0.025$), and for treatment failure imputation for subjects who discontinued due to lack of efficacy in the ITT population ($p < 0.025$).**	Control cigarettes with NRT) **for the primary analysis, treatment failure imputation in the ITT population ($p < 0.05$), as well as for the additional sensitivity analyses: for multiple imputation in the ITT population ($p < 0.05$), for treatment failure imputation for subjects who discontinued due to lack of efficacy in the ITT population ($p < 0.025$), and for treatment failure imputation in the per-protocol population ($p < 0.025$).**
Section 14.4, Figure G (p. 110)	The treatment effects were statistically significant at the 0.05 significance level ($p = 0.0449$) ~~**and are close to significance with a multiplicity adjustment**~~.	The treatment effects were statistically significant at the 0.05 significance level ($p = 0.0449$).
Section 14.4, Figure G (p. 110)	Changed the order of the bars from: **ITT – Available Data** **ITT – Multiple Imputation** **ITT – Treatment Failure Imputation** **PP – Treatment Failure Imputation** **ITT – Failure = Discontinuation Due to Lack of Efficacy**	Changed the order of the bars to be: **ITT - Treatment Failure Imputation (primary analysis)** **ITT – Multiple Imputation (sensitivity analysis)** **ITT – Available Data (sensitivity analysis)** **ITT – Failure = Discontinuation Due to Lack of Efficiacy (sensitivity analysis)** **PP – Treatment Failure Imputation (sensitivity analysis)**
Section 14.4 (p. 110 – 111)	Finally, 4-week abstinence proportions using the treatment failure imputation for the per-protocol population were **44.8%** for Group 1, 20.0% for Group 2,	Finally, 4-week abstinence proportions using the treatment failure imputation for the per-protocol population were **45.5%** for Group 1, 20.0% for Group 2,

Section (page #)	Original (6/08/2006)	Revised (v1.0) (10/13/2006)
	and 27.8% for Group 3.	and 27.8% for Group 3.
Section 14.4 (p. 109 – 110)	Using the one-sided Fisher's exact test, the *p-value* was **either** significant **or showed a trend toward significance** (p = **0.0253**) upon adjustment (p = **0.025**) when comparing Group 1 with Group 3.	Using the one-sided Fisher's exact test, the *p-value* was **either** significant ~~**or showed a trend toward significance**~~ (p = **0.0213**) **both at the 0.05 significance level and** upon **using the multiplicity** adjustment ~~**(p = 0.025)**~~ when comparing Group 1 with Group 3.
Section 16.2, Table 27 (p. 127)	Text formatted in all caps.	Removed all caps formatting to be standard text format. No changes made to the content of the text.
Section 16.2, Table 28 (p. 128)	Text formatted in all caps.	Removed all caps formatting to be standard text format. No changes made to the content of the text.
Section 17.0 (p. 133)	The safety population, which consisted of all randomized subjects who received **study treatment** (n = 346).	The safety population, which consisted of all randomized subjects who received **at least one study cigarette** (n = 346).

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Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation

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ABSTRACT

Aims To examine the effects of reduced nicotine cigarettes on smoking behavior, toxicant exposure, dependence and abstinence. **Design** Randomized, parallel arm, semi-blinded study. **Setting** University of Minnesota Tobacco Use Research Center. **Interventions** Six weeks of: (i) 0.05 mg nicotine yield cigarettes; (ii) 0.3 mg nicotine yield cigarettes; or (iii) 4 mg nicotine lozenge; 6 weeks of follow-up. **Measurements** Compensatory smoking behavior, biomarkers of exposure, tobacco dependence, tobacco withdrawal and abstinence rate. **Findings** Unlike the 0.3 mg cigarettes, 0.05 mg cigarettes were not associated with compensatory smoking behaviors. Furthermore, the 0.05 mg cigarettes and nicotine lozenge were associated with reduced carcinogen exposure, nicotine dependence and product withdrawal scores. The 0.05 mg cigarette was associated with greater relief of withdrawal from usual brand cigarettes than the nicotine lozenge. The 0.05 mg cigarette led to a significantly higher rate of cessation than the 0.3 mg cigarette and a similar rate as nicotine lozenge. **Conclusion** The 0.05 mg nicotine yield cigarettes may be a tobacco product that can facilitate cessation; however, future research is clearly needed to support these preliminary findings.

Keywords Biomarkers of exposure, compensatory smoking, nicotine dependence, reduced nicotine cigarettes, tobacco cessation, tobacco withdrawal.

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INTRODUCTION

In recent years, tobacco companies have renewed their efforts to manufacture and market potential reduced exposure tobacco products (called PREPs) to cigarette smokers. These products include cigarettes modified to reduce toxicants but maintain levels of nicotine [1,2]. However, to date these modified cigarettes have not shown great promise for reducing exposure to toxicants significantly [3,4]. Alternatively, cigarettes with significantly reduced nicotine (the major known addictive constituent in cigarettes) may have promise in dramatically reducing cigarette use [5]. Unlike 'light' or 'mild' cigarettes that reduce nicotine yields through filter ventilation but which lead to similar levels of cotinine and toxicants as regular cigarettes due to compensatory smoking behavior [6–8], reduced nicotine in cigarette tobacco makes compensatory smoking more difficult. Limited data from previous studies of such products suggest that compensatory smoking does not occur, toxicant exposure does not increase and abstinence may be facilitated [9,10]. Theoretically, reducing levels of nicotine to the point of non-reinforcement would lead to extinction or cessation of smoking as well as unlearning cues associated with reinforcement.

No clinical trial has examined the effects of smoking reduced nicotine cigarettes on smoking behavior, on resulting toxicant exposure, on withdrawal symptoms and craving, on dependence scores or on abstinence rates compared with medicinal nicotine products.

To address these questions, we conducted a study in which smokers were randomized to 6 weeks of 0.3 mg

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nicotine yield cigarettes, 0.05 mg nicotine yield cigarettes or to 4 mg medicinal nicotine lozenges. Medicinal nicotine has been recommended as the comparator to which PREPs should be tested for toxicant exposure [11] and also serves as a usual care condition to compare abstinence rates across products. As primary outcomes, we hypothesized that smoking behavior, toxicant exposure, withdrawal and craving upon product discontinuation and product dependence would be relatively less for the 0.05 mg nicotine yield cigarette compared to the 0.3 mg nicotine yield cigarette, because the 0.05 mg cigarette would lead to less reinforcement from smoking than the 0.3 mg cigarette. As a secondary outcome, we hypothesized that pre-treatment with 0.05 mg cigarettes will produce favorable quit rates that are similar to nicotine lozenges and better than 0.3 mg cigarettes.

Our goal was to examine the feasibility of using these cigarettes as a method to reduce smoking behavior significantly and as a potential cessation tool, which would lead subsequently to reduction in harm. The results also provide information on the role that different aspects of tobacco use (nicotine versus sensory aspects of smoking) contributes to tobacco addiction.

METHODS

Subjects

Smokers of 'light' cigarettes (0.7–1.0 mg nicotine/cigarette) between the ages of 18 and 70 years who were interested in quitting smoking were recruited via advertisement. To be eligible smokers had to (i) have smoked 10–40 cigarettes daily for the past year (the range was instituted to reduce heterogeneity); (ii) be in good physical health; (iii) be in good psychiatric health; and (iv) have no contraindications for medicinal nicotine use. Subjects using other tobacco or nicotine products were excluded, as were subjects who were pregnant or nursing.

Study design

After a telephone screening to determine preliminary eligibility, an orientation session was held at which the study was explained further, written informed consent was obtained and a more thorough screening for eligibility was performed.

After a 2-week period during which baseline measurements were collected while subjects smoked *ad libitum*, subjects were assigned to one of three conditions: (i) 0.3 mg nicotine yield cigarettes, (ii) 0.05 mg nicotine yield cigarettes or (iii) nicotine lozenges (4 mg). Quest cigarettes (manufactured by Vector; Vector Tobacco Inc., Durham, NC, USA) were chosen because they are commercially available reduced nicotine cigarettes (nicotine yield as measured in mainstream smoke by the Federal Trade Commission method) with reduced levels of tobacco-specific carcinogens compared to conventional cigarettes [12]. Subjects assigned to the cigarette conditions were blinded as to which cigarette they received (i.e. 0.05 mg versus 0.3 mg). Subjects were instructed to use their assigned treatment for 6 weeks (after which time they were to discontinue product use) and to not use other nicotine or tobacco products during the treatment or any products during the follow-up period. Subjects were seen weekly during the 6-week treatment period and at 1, 2, 4 and 6 weeks after cessation. Subjects who completed the study were paid up to $345.

To allow for compensatory smoking, at each visit subjects assigned to either cigarette condition were provided a supply equivalent to 150% of their baseline smoking rate and were told to smoke *ad libitum*. Subjects assigned to receive the 4 mg nicotine lozenge were asked to quit smoking and to use at least six to eight pieces per day, the mean number of lozenges used among smokers enrolled in a clinical trial [13]. If side effects suggested that the dose was too high, the 2 mg nicotine lozenge was substituted at that time. Subjects maintained a daily smoking diary in which they recorded any cigarettes smoked (either those assigned to them or their own). If they smoked cigarettes other than those assigned, they were to note when that cigarette was smoked. They were not penalized for smoking that cigarette, but told that although we do not encourage them to smoke cigarettes other than those assigned, it is crucial to the study that they indicate to us whenever they smoked any other cigarettes.

Brief (approximately 10 minutes) standardized counseling was provided at each of the visits during the treatment phase of the study. Subjects assigned to the cigarette conditions were counseled to consider the use of these products as a step towards quitting. They discussed any difficulties they experienced with switching cigarettes and behavioral strategies to resist smoking other (non-Quest) cigarettes. Subjects assigned to the nicotine lozenge condition were provided with treatment tools recommended by the US Clinical Practice Guideline [14]. During the abstinence phase, all subjects received counseling similar to that received by the subjects assigned to the nicotine lozenge condition. Therefore, all three treatment groups received similar amounts of behavioral support.

Outcome measures

Biomarkers of tobacco toxicant exposure measures included: (i) urinary cotinine plus cotinine–glucuronide (total cotinine), a direct measure of nicotine exposure (product nicotine delivery and amount consumed) [15,16]; (ii) alveolar carbon monoxide (CO) measured using the Bedfont Micro Smokerlyzer® (Bedfont Scientific Limited, Kent, UK); (iii) urinary 4-(methylnitrosamino)-1-

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(3-pyridyl)-1-butanol and its glucuronides (total NNAL), metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone ((NNK; [17]); (iv) urinary *N′*-nitrosonornicotine and its glucuronide (total NNN), metabolites of the tobacco-specific carcinogen *N′*-nitrosonornicotine [18]; (v) urinary 1-hydroxypyrene and its glucuronide and sulfate (total 1-HOP), a metabolite of pyrene which is an accepted biomarker for uptake of carcinogenic polycyclic aromatic hydrocarbons (PAH; [19]); (vi) urinary 3-hydroxypropylmercapturic acid (3-HPMA), a metabolite of the toxicant, acrolein [20]; and (vii) *S*-phenylmercapturic acid (S-PMA), a metabolite of the human leukemogen, benzene [21]. These biomarkers reflect exposure to particulate or smoke constituents in cigarettes. All measures were assessed at baseline. Additionally, carbon monoxide was assessed at each treatment clinic visit, cotinine at weeks 2 and 6 of treatment and at follow-up visits (except at 1 week post-treatment) and biomarkers for other exposure measures at weeks 2 and 6 of treatment. CO, 1-HOP, 3-HPMA, S-PMA are influenced by factors other than tobacco while total cotinine, total NNAL and total NNN are tobacco-specific.

Subjective measures included: (i) a tobacco use questionnaire that asked about current tobacco use status (cigarettes and other tobacco products), number of ≥24-hour quit attempts and duration of abstinence during these quit attempts; (ii) a daily diary detailing the number of cigarettes smoked; (iii) the Minnesota Nicotine Withdrawal Scale, a widely used scale that assesses withdrawal from cigarettes [22–24], nicotine gum [25,26] and smokeless tobacco [25,27]; (iv) the Fagerstrom Test for Nicotine Dependence (FTND, [28]), the most widely used and psychometrically tested scale for nicotine dependence; and (v) perceived health risk, a ladder involving rating risk for addiction of a product on a scale ranging from 1 to 10. All these measures were assessed at baseline. Cigarette or product use was assessed daily, the tobacco use questionnaire and Minnesota Nicotine Withdrawal Scale at each clinic visit, and the FTND and perceived health risk at weeks 2 and 6.

This study was approved by the University of Minnesota Research Subjects Protection Programs Institutional Review Board.

Statistical analysis

Subjects' baseline characteristics including demographics and smoking history were compared among three treatment groups. Discrete variables were analyzed using Pearson's χ^2 test or Fisher's exact test. Continuous variables were analyzed using either one-way analysis of variance (ANOVA) or Kruskall–Wallis test.

For outcome variables measured at each baseline visit, the average was used as the baseline measurement. Repeated-measures ANOVA was used for outcomes that had been measured repeatedly from baseline to the end of the treatment phase. Each repeated-measures ANOVA model contained five terms: treatment effect, visit effect, interaction effect between treatment and visit, random subject effect (between-subject error) and random error (within-subject error). The variance–covariance structure was specified as the first-order autoregression, and variance parameters were estimated using restricted maximum likelihood method with Satterthwaite approximation. The *P*-values reported for multiple comparisons were unadjusted. Biomarkers including cotinine, NNN, NNAL, 1-HOP, 3-HPMA and S-PMA were analyzed in a natural log scale for repeated-measures ANOVA such that the model assumptions of normality and equal variances can hold, and geometric means in original units were also calculated. The differences in the point prevalence (no smoking in past 7 days) and continuous abstinence (no smoking in past 4 weeks) rates during the follow-up period between treatment groups were evaluated using χ^2 tests, as were dropout rates. SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) was used. A *P*-value <0.05 indicated statistical significance.

RESULTS

Subjects

Of 883 subjects screened over the telephone, 462 were considered eligible for participation. Primary reasons for ineligibility were smoking outside the range of eligible cigarettes per day, smoking ineligible cigarettes or unstable illness. Two hundred and twenty-eight attended the orientation meeting, 225 signed the informed consent form and 165 were assigned randomly to treatment (53 to 0.05 mg cigarettes; 52 to 0.3 mg cigarettes and 60 to nicotine lozenges). Dropout rates throughout the study were highest in those assigned to nicotine lozenges and lowest in those assigned to 0.3 mg nicotine yield cigarettes, with significant differences observed between groups at the end of the 6-week treatment period (48.3% dropout rate for nicotine lozenge versus 39.6% for 0.05 mg nicotine cigarettes versus 25.0% for 0.3 mg nicotine cigarettes; $\chi^2 = 6.49$, $P = 0.0389$). Figure 1 illustrates the number of dropouts in each group at various stages throughout the study with reasons for dropouts indicated. The demographics and smoking history of smokers are shown in Table 1, with no significant differences among the experimental groups except age of becoming a regular smoker ($P = 0.0195$). There were no significant differences in demographics between subjects who dropped out of the study after randomization and those who completed the entire study.

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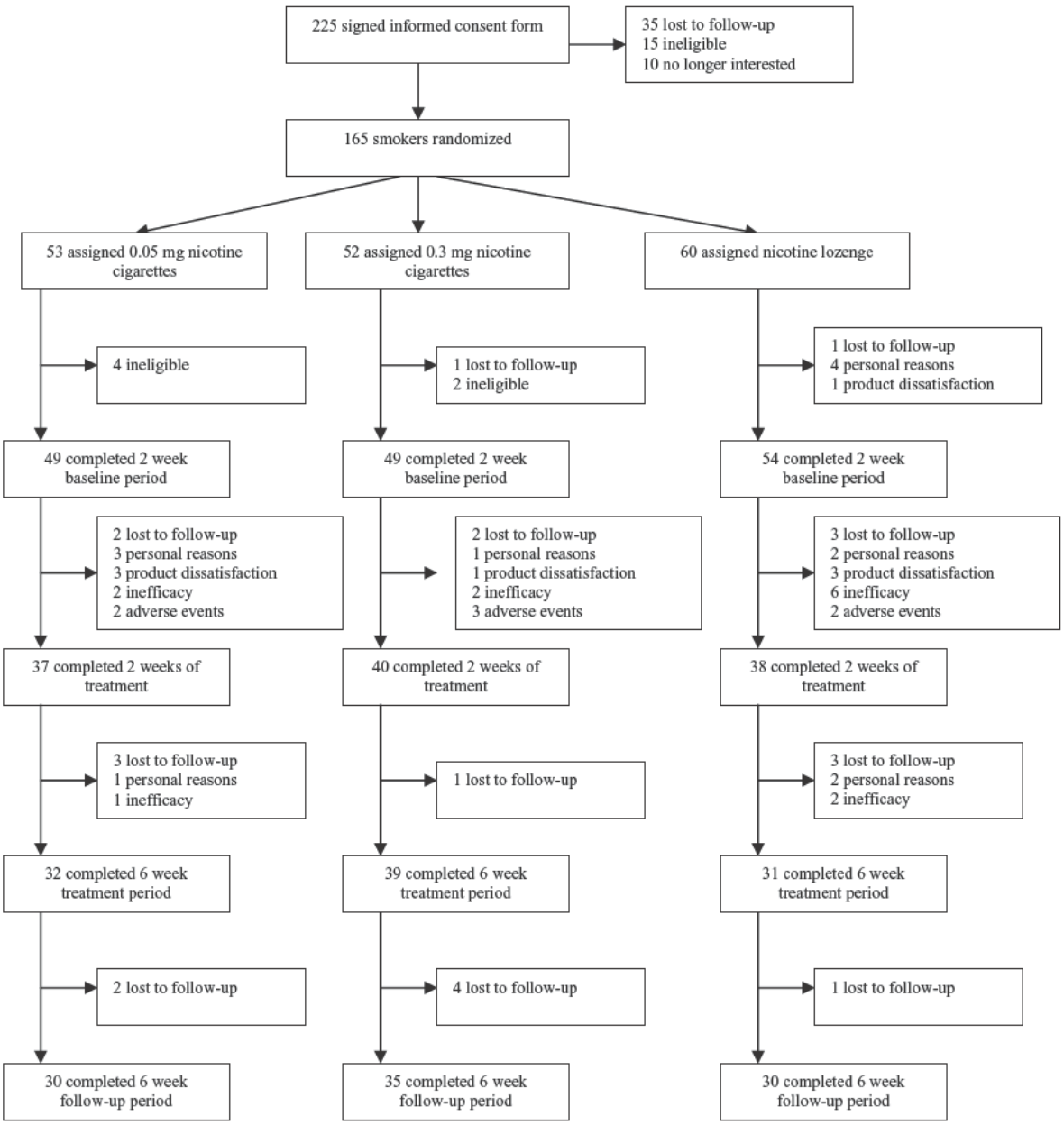


Figure 1 Flow of subjects through study

Product use during treatment

The number of assigned cigarettes smoked per day during the treatment period is illustrated in Fig. 2a. Significant treatment ($F_{(2, 180)} = 102.48$, $P < 0.0001$), time ($F_{(6, 648)} = 37.77$, $P < 0.0001$) and treatment × time ($F_{(12, 648)} = 62.38$, $P < 0.0001$) effects were observed. In those smoking 0.3 mg cigarettes, the number of cigarettes smoked per day increased significantly ($P = 0.0127$ to $P < 0.0001$) at each of the first 5 weeks of treatment compared to the number of usual brand cigarettes they were smoking at baseline (Fig. 2a). This is in contrast to the significantly decreased ($P = 0.0043$ to $P < 0.0001$) number of cigarettes smoked per day (relative to baseline) observed after week 2 in those assigned 0.05 mg cigarettes. At week 6, the mean number of 0.3 mg cigarettes smoked per day was significantly greater than that of 0.05 mg cigarettes smoked ($t = 4.73$, $P < 0.0001$). Nicotine lozenge use (among those assigned to this condition) remained relatively stable throughout the 6-week treatment period and ranged from a mean of 5.9 [standard deviation (SD = 2.4] lozenges per day at week 6 to a mean of 6.9 (SD = 3.5) lozenges per day at week 3.

Of those subjects who had not dropped out at the visit in question, subjects were most likely to use a nicotine or tobacco product other than what was assigned to them

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Table 1 Baseline demographics and smoking history of subjects in each of the three treatment groups. In instances where data are missing, the total number of subjects used in calculating values is fewer than the 165 randomized to treatment.

Demographics	*0.3 mg nicotine cigarettes (n = 52)*		*0.05 mg nicotine cigarettes (n = 53)*		*Nicotine lozenges (n = 60)*		*P-value*
Age (years)	51	39.4 ± 14.0	53	40.7 ± 13.3	59	43.1 ± 12.4	0.3312
Female	26	50.0%	23	43.4%	29	48.3%	0.6967
Non-Hispanic whites	47	90.4%	44	83.0%	49	81.7%	0.7653
Education							0.8782
Less than high school graduate	2	3.9%	2	3.8%	3	5.0%	
High school graduate	12	23.1%	11	20.8%	17	28.3%	
Greater than high school graduate	37	71.2%	40	75.5%	39	65.0%	
Marital status							0.1052
Never married	22	42.3%	25	47.2%	22	36.7%	
Currently married	22	42.3%	17	32.1%	16	26.7%	
Currently not married	8	15.4%	11	20.8%	21	35.0%	
Cigarettes per day	52	19.8 ± 7.8	53	21.1 ± 8.1	60	21.3 ± 9.6	0.6066
Duration of having smoked at this rate (years)	52	15.4 ± 13.0	53	14.1 ± 12.6	59	15.7 ± 14.1	0.7960
Age smoking first cigarette (years)	52	14.4 ± 2.9	53	15.5 ± 4.8	60	14.5 ± 2.9	0.2518
Age becoming a regular smoker (years)	52	16.5 ± 3.0	52	19.4 ± 7.3	58	17.7 ± 4.1	0.0195
Motivation to quit (0–10 scale)	52	9.0 ± 1.1	53	9.2 ± 1.0	59	9.2 ± 1.3	0.6928
Number of quit attempts							0.4482
1–2	13	25.0%	17	32.1%	13	21.7%	
3–5	14	26.9%	14	26.4%	24	40.0%	
6–10	12	23.1%	10	18.9%	13	21.7%	
11+	10	19.2%	4	7.6%	9	15.0%	
Spouse or significant other smokes	20	38.5%	20	37.7%	21	35.0%	0.9515

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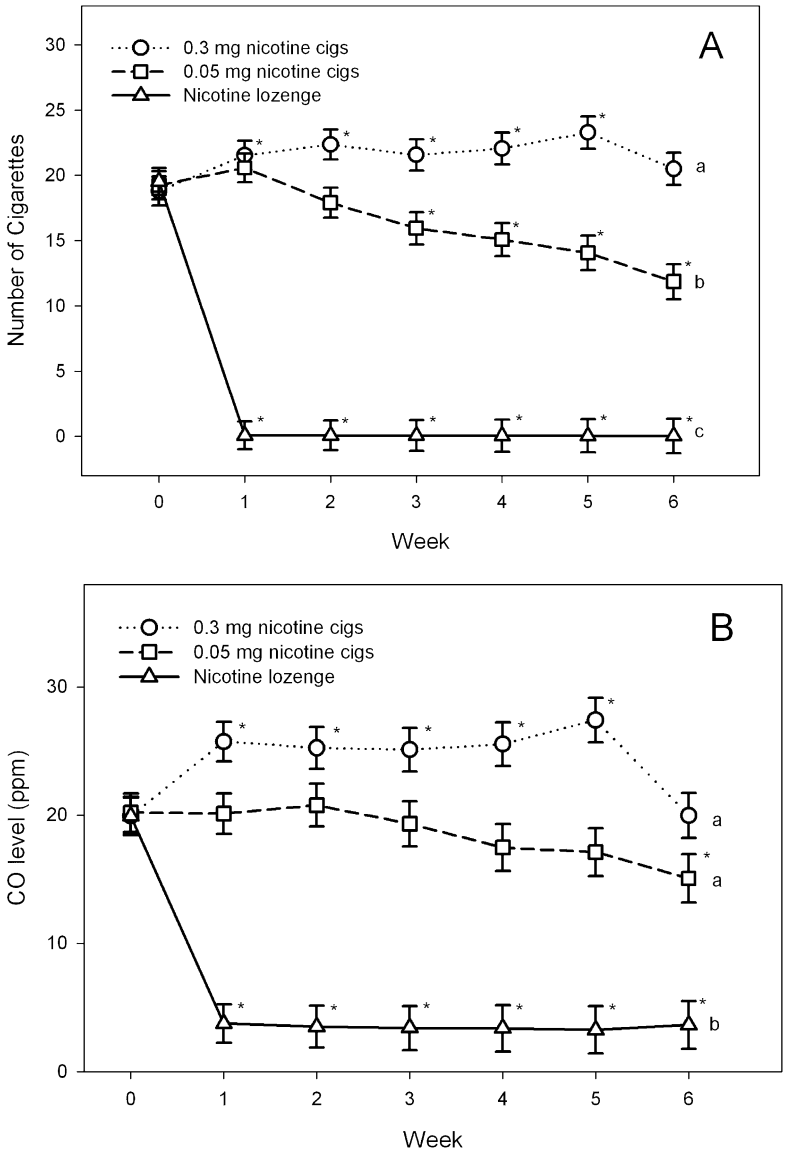


Figure 2 Least squares (LS) mean (±standard error) of number of cigarettes smoked per day and exhaled carbon monoxide (CO). *$P < 0.05$ at that visit compared to baseline (within-group comparison). Groups with different letters were significantly different ($P < 0.05$) at the week 6 treatment visit (between-group comparison). For example, cigarettes per day are significantly different between each of the groups, but CO concentrations are significantly different between the nicotine lozenge group and each of the two cigarette groups, but the two cigarette groups are not different from each other

during the first week of treatment with 30.4% of those assigned to 0.05 cigarettes, 22.9% of those assigned to 0.3 mg and 40.8% assigned to nicotine lozenges reporting such use. After week 1, the percentage who reported using a non-study-assigned nicotine or tobacco product ranged from 0 to 12.5% (during weeks 2–6) in the 0.05 mg cigarette group, 5.0 to 10.5% in the 0.3 mg cigarette group and 8.3 to 21.9% in the nicotine lozenge group. No significant difference between groups was observed in the percentage of subjects using tobacco or nicotine products other than those assigned at any weekly visit except for week 6. At the week 6 visit, 5.3% in the 0.05 mg cigarette group, 0% in the 0.3 mg cigarette group and 21.9% in the nicotine lozenge group ($P = 0.0056$) reported using such products. Among those reporting smoking usual brand cigarettes during the treatment period, the mean number of cigarettes smoked ranged from 0.3 to at most 6.4 per week. Distribution of cotinine concentrations at week 6 demonstrates that, in the 0.05 mg nicotine cigarette group, very few individuals had substantial cotinine concentrations, suggesting that most did not use non-study nicotine-containing products during the study. The distribution shows that 22 subjects had cotinine concentrations between 0 and 250 ng/ml, four between 251 and 500 ng/ml, three between 501 and 1000 ng/ml and three had >5000 ng/ml.

Effects of products on biomarkers of exposure during treatment

Biomarker concentrations during the treatment period for exhaled CO are illustrated in Fig. 2b. Urinary total cotinine, total NNAL, total NNN, total 1-HOP, 3-HPMA and S-PMA are presented in Table 2.

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Table 2 Geometric means of biomarkers at baseline and weeks 2 and 6 of treatment period by treatment groups. Values are for all subjects from whom data were collected at the visit in question.

	Geometric mean (95% confidence interval)		
Biomarkers	*Baseline*	*Week 2*	*Week 6*
Total cotinine[1]			
0.3 mg cigarettes	4057 (3323, 4952)	2150 (1696, 2725)*	2093 (1611, 2719)*[a]
0.05 mg cigarettes	4216 (3492, 5090)	278 (174, 442)*	188 (111, 319)*[b]
Nicotine lozenge	3917 (3399, 4514)	2291 (1708, 3073)*	2154 (1312, 3536)*[a]
Total NNAL[2]			
0.3 mg cigarettes	0.96 (0.73, 1.26)	0.54 (0.41, 0.69)*	0.47 (0.30, 0.73)*[a]
0.05 mg cigarettes	0.92 (0.70, 1.21)	0.34 (0.20, 0.57)*	0.20 (0.11, 0.34)*[b]
Nicotine lozenge	1.06 (0.84, 1.35)	0.24 (0.18, 0.32)*	0.14 (0.07, 0.26)*[b]
Total NNN[2]			
0.3 mg cigarettes	0.10 (0.06, 0.16)	0.09 (0.06, 0.14)	0.06 (0.04, 0.10)[a]
0.05 mg cigarettes	0.09 (0.05, 0.15)	0.06 (0.04, 0.11)	0.03 (0.02, 0.07)*[ab]
Nicotine lozenge	0.08 (0.05, 0.12)	0.02 (0.01, 0.04)*	0.02 (0.01, 0.04)*[b]
Total 1-HOP[2]			
0.3 mg cigarettes	0.84 (0.70, 1.02)	0.95 (0.58, 1.53)	0.73 (0.59, 0.90)[a]
0.05 mg cigarettes	0.89 (0.71, 1.12)	0.75 (0.56, 1.01)	0.57 (0.42, 0.78)*[a]
Nicotine lozenge	0.94 (0.71, 1.24)	0.40 (0.29, 0.56)*	0.34 (0.21, 0.57)*[b]
3-HPMA[2]			
0.3 mg cigarettes	3662 (2868, 4674)	2838 (2226, 3619)	2732 (2110, 3537)[a]
0.05 mg cigarettes	3320 (2667, 4134)	1639 (1215, 2211)*	1453 (1039, 2032)*[b]
Nicotine lozenge	3445 (2539, 4673)	911 (670, 1239)*	1062 (749, 1508)*[b]
S-PMA[2]			
0.3 mg cigarettes	2.21 (1.54, 3.18)	1.30 (0.88, 1.92)*	1.35 (0.94, 1.93)*[a]
0.05 mg cigarettes	2.46 (1.68, 3.62)	1.54 (1.03, 2.31)*	0.76 (0.48, 1.20)*[b]
Nicotine lozenge	2.69 (1.95, 3.72)	0.33 (0.22, 0.49)*	0.48 (0.30, 0.78)*[b]

[1]ng/ml. [2]pmol/mg creatinine. *$P < 0.05$ at that visit compared to baseline (within-group comparison). Groups with different letters were significantly different ($P < 0.05$) at the week 6 treatment visit (between-group comparison). For example, total cotinine is significantly different between the 0.05 mg cigarette group with 0.3 mg cigarette group and with nicotine lozenge group, but the 0.3 mg cigarette group is not significantly different from the nicotine lozenge group. Total NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides; total NNN: *N*′-nitrosonornicotine and its glucuronide; total 1-HOP: 1-hydroxypyrene and its glucuronide and sulfate; 3-HPMA: 3-hydroxypropylmercapturic acid; S-PMA: *S*-phenylmercapturic acid.

For all seven biomarkers of exposure, significant treatment effects (*P*-values 0.0131–<0.0001), time effects (*P*-values 0.0001–<0.0001) and treatment × time interaction effects (*P*-values 0.0045–<0.0001) were found.

As illustrated in Fig. 2b, exhaled CO concentrations followed a similar pattern as seen for number of cigarettes smoked per day. Exhaled CO concentrations increased during the first 5 weeks of treatment in those using 0.3 mg cigarettes, whereas in those receiving 0.05 mg cigarettes exhaled CO decreased gradually, with a statistically significant decrease observed at week 6 of treatment when compared with baseline ($P = 0.0247$). At week 6, exhaled CO concentrations were nearly significantly different ($P = 0.0569$) between the two cigarette groups. Urinary cotinine concentrations decreased significantly in all treatment groups, with the greatest decrease observed in the 0.05 mg cigarette group and moderate decreases occurring in the 0.3 mg cigarette and nicotine lozenge groups (Table 2). For the other biomarkers assessed, greatest decreases from baseline were found in the group receiving nicotine lozenge with the smallest changes in biomarker concentrations observed mainly in the group receiving 0.3 mg cigarettes (Table 2).

Effects of products on subjective responses during treatment

Dependence

FTND score and perceived risk for addiction score during treatment are illustrated in Fig. 3a,b. Both these measures showed significant treatment ($P = 0.0124$ and <0.0001, respectively), time (*P*-values <0.0001) and treatment × time interaction (*P*-values <0.0001) effects. Significant decreases in FTND and perceived risk of addiction scores were observed for the 0.05 mg cigarette and nicotine lozenge groups (all *P*-values ≤ 0.001) at week 6 compared to baseline. For the 0.3 mg cigarette group, perceived risk of addiction decreased significantly

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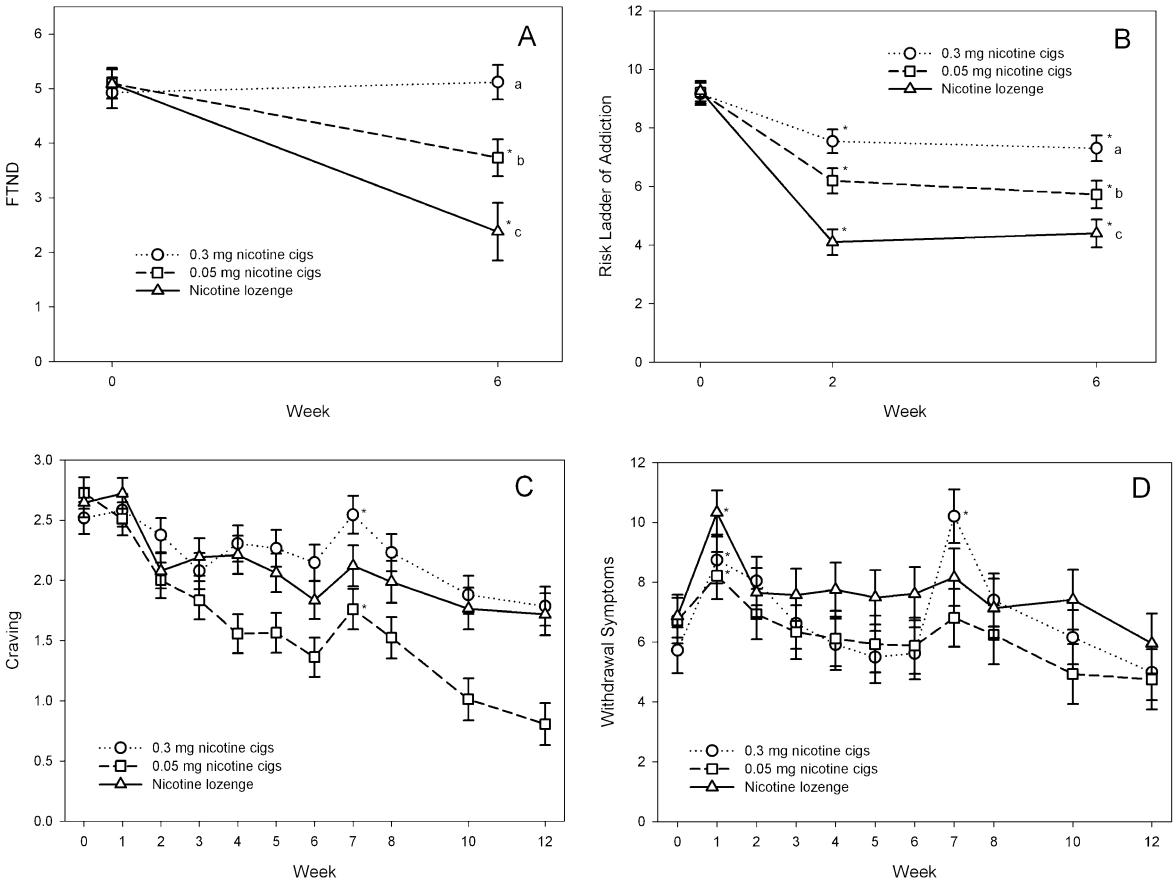


Figure 3 Least squares (LS) mean [±standard error (SE)] of Fagerstrom Test for Nicotine Dependence (FTND) score and perceived risk for addiction score (Panels A and B). *$P < 0.05$ at that visit compared to baseline (within-group comparison). Groups with different letters were significantly different ($P < 0.05$) at the week 6 treatment visit (between-group comparison). Least squares (LS) mean (±SE) of craving and withdrawal symptoms craving and withdrawal symptoms (Panels C and D). *$P < 0.05$ at that visit compared to the previous visit (i.e. week 1 versus week 0 and week 7 versus week 6)

between baseline and week 6 ($P < 0.0001$); however, FTND score did not ($P = 0.4810$). At week 6, significant differences between groups were found in FTND (P-values 0.0315–<0.0001) and perceived risk of addiction (P-values 0.0456–<0.0001), with the highest levels observed in those assigned to 0.3 mg cigarettes and the lowest in those assigned to nicotine lozenge.

Nicotine craving and withdrawal symptoms during treatment and follow-up are illustrated in Fig. 3c,d. Nicotine craving and withdrawal symptoms at the time of switching to products (week 1) and cessation from products (week 7) were examined. Upon cessation of usual brand cigarettes and switching to the products, there was a significant increase in withdrawal symptoms (P-values 0.0188–<0.0001) and no significant change in craving in all three treatment groups. Increase in nicotine withdrawal scores upon cessation of usual brand cigarettes (week 1 compared to baseline) was significantly smaller for the group assigned to 0.05 mg cigarettes compared to the group assigned nicotine lozenges ($P = 0.0253$) and nearly significantly smaller ($P = 0.0917$) than for those assigned to 0.3 mg cigarettes. Upon cessation of the product (week 7 compared to week 6), significant increase in craving ($P = 0.0079$) and withdrawal symptoms ($P < 0.0001$) were observed for the 0.3 mg cigarette group. In those discontinuing 0.05 mg cigarettes, craving increased significantly ($P = 0.0138$), but withdrawal symptoms did not ($P = 0.2297$). In those discontinuing nicotine lozenge, neither changes in craving ($P = 0.0814$) nor withdrawal symptoms ($P = 0.4856$) were increased significantly. Change in withdrawal symptoms was significantly lower in those discontinuing 0.05 mg cigarettes ($P = 0.0006$) or nicotine lozenges ($P = 0.0002$) compared to those discontinuing 0.3 mg cigarettes, with no significant differences in craving observed between groups.

Abstinence

Abstinence rates were calculated using the intent-to-treat sample (at the point of random assignment to the

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Table 3 Continuous (past 4 weeks) and point-prevalence (past 1 week) post-treatment abstinence rates. Products with different superscript letters were significantly different ($P < 0.05$).

	Treatments						
	0.3 mg nicotine cigarettes (n = 52)		*Nicotine lozenges (n = 60)*		*0.05 mg nicotine cigarettes (n = 53)*		
	# abstinent	*%*	*# abstinent*	*%*	*# abstinent*	*%*	*P-value*
Continuous abstinence							
[1]CO verified	11	21.2	21	35.0	23	43.4	0.0508
[2]CO and cotinine verified	7	13.5	11	18.3	16	30.2	0.0913
CO verified point prevalence abstinence							
Follow-up week							
1	18	34.6	25	41.7	22	41.5	0.6954
2	17	32.7	25	41.7	29	54.7	0.0719
4	12	23.1	22	36.7	23	43.4	0.0829
6	12	23.1[a]	22	36.7[a,b]	25	47.2[b]	0.0357
CO and cotinine verified point prevalence abstinence							
Follow-up week							
2	12	23.1[a]	16	26.7[a]	24	45.3[b]	0.0298
4	8	15.4[a]	13	21.7[a]	21	39.6[b]	0.0120
6	7	13.5[a]	12	20.0[a,b]	19	35.9[b]	0.0192

[1]Carbon monoxide (CO) verified abstinence represents abstinence from cigarettes but usage of nicotine lozenge is allowed. [2]CO and cotinine verified represents abstinence from all nicotine-containing products, including nicotine lozenge.

product and before baseline measures). Dropouts were considered treatment failures. Biochemically verified [CO < 8 parts per million (p.p.m.)] point prevalence rates of abstinence from cigarettes at each of the follow-up visits and 4-week continuous abstinence rates are shown in Table 3. In this analysis, subjects were allowed to use lozenges. Similarly, biochemically verified (CO < 8 p.p.m. and total cotinine <35 ng/ml) abstinence from all nicotine-containing products (including lozenges) is also listed in Table 3. For abstinence from cigarettes, 4-week continuous abstinence rates were highest in those receiving 0.05 mg nicotine cigarettes and lowest in those receiving 0.3 mg nicotine cigarettes, with the difference across the three groups nearly significant (Table 3). Point prevalence abstinence rates followed a similar pattern, with significant differences between groups observed in abstinence rates verified by both CO and urinary cotinine concentrations. CO verified point prevalence abstinence rates were statistically significant only at the week 6 post-treatment visit and nearly significant at the weeks 2 and 4 post-treatment visits.

Unlike the cigarette conditions, the nicotine lozenge condition involved complete cessation from cigarettes from the onset of treatment, providing a potentially unfair advantage to the cigarette conditions. Therefore, to determine if duration of cigarette abstinence had an impact on abstinence rates in the nicotine lozenge condition, the continuous CO verified abstinence rates from the last 4 weeks of product use without smoking was compared with the 4-week continuous CO verified abstinence rates at the end of the follow-up period. The results were identical (35%). In addition, the point prevalence rate at the end of 6 weeks of product use was compared with the rate at the end of the follow-up period and the rates were similar (40.0% versus 36.7%).

DISCUSSION

This study showed that, unlike the 0.3 mg nicotine yield cigarettes, 0.05 mg nicotine yield cigarettes were not associated with compensatory smoking behavior. Thus, although increased smoking and exhaled CO were observed with the 0.3 mg cigarettes, decreases in cigarette intake and eventually in exhaled CO were observed for the 0.05 mg cigarettes, a finding similar to another study [29]. The 0.05 mg cigarettes were also associated with reduced exposure biomarker levels (e.g. total NNAL, total NNN, 3-HPMA, S-PMA), reduced nicotine dependence and withdrawal scores. Conversely, the 0.3 mg cigarettes did not result in significant decreases in most exposure biomarkers, led to persistent self-reported dependence and higher levels of withdrawal from this product compared to the other products. As expected, nicotine lozenge was associated with the most consistent reductions in toxicant exposure, dependence on cigarettes and perceived risk for addiction. It is important to

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note that levels of total 1-HOP, 3-HPMA, and SPMA did not attain zero values for the nicotine lozenge group because there are environmental and endogenous sources of pyrene, acrolein and benzene other than tobacco smoke exposure. [30] Furthermore, total NNAL has a long half-life [31] and there is evidence for endogenous formation of NNN is some users of nicotine replacement therapy [32] In addition, the results showed that a few subjects in the nicotine lozenge group had reported using cigarettes or other non-assigned tobacco products during the first 6 weeks (8.3–21.9%). Interestingly, the 0.05 mg cigarette led to the highest abstinence rates of the three products tested, although difference in continuous abstinence rates did not reach statistical significance.

The slope of the decline in cigarette smoking rate was slightly faster than the decline in exhaled CO concentrations for the 0.05 mg condition. This result may reflect the use of usual cigarettes among some subjects during the first few weeks of treatment, or may reflect subjects' engagement in some compensatory smoking behavior during the initial period of adjustment to the product. None the less, CO decreased over time, as the number of cigarettes smoked decreased and the minimal compensatory smoking observed when subjects were converted to the 0.05 mg cigarettes is consistent with the results of several small studies in which limited or no compensatory smoking was found when subjects smoked either a single reduced nicotine cigarette in a laboratory setting or smoked one of five progressively lower nicotine content cigarettes for a week [9,10]. Conversely, studies examining use of highly ventilated low-yield cigarettes have found that substantial compensation occurs [33].

The reduction in levels of urinary total NNAL and NNN is consistent with reduced tobacco specific nitrosamine levels found in these products [12]. For example, Marlboro and Camel 'light' cigarettes have NNK levels of 0.68 and 0.55 μg/g wet weight and NNN levels of 2.8 and 2.7 μg/g wet weight, respectively, while the corresponding values for the 0.3 mg and 0.05 mg Quest products were 0.19 and 0.054 μg/g wet weight NNK and 0.82 and 0.83 μg/g wet weight NNN. For the 0.05 mg cigarettes, additional reduction in carcinogen and toxicant exposures (to acrolein and benzene) is probably attributable to the observed reduction in cigarette intake such that, by the end of treatment, most biomarker levels in this group were not significantly different from those in the nicotine lozenge group. Therefore, the observed reduction in biomarker levels is due probably to differences in the amount of the constituents related to the biomarkers in the product itself and in the case of the cigarettes, the amount of product use. On the other hand, no reductions were observed for 1-HOP, which may indicate that exposure to polycyclic aromatic hydrocarbons may be significant when using both the 0.3 mg and 0.05 mg cigarettes and not affected by the degree of reduction in smoking behavior observed in this study.

Although blind to the nicotine content of their assigned cigarettes, only smokers in the 0.05 mg group appeared to experience a reduction on a scale measuring nicotine dependence. However, the perceived risk for addiction decreased for both cigarette products. The reduced nicotine dependence associated with the 0.05 mg cigarettes is consistent with other studies which show reduced FTND scores [9] or decreased motivation to smoke [29] after smoking low nicotine content or denicotinized cigarettes. Another indicator of reduced dependence is the reduction in withdrawal symptoms experienced after cessation from the 0.05 mg cigarettes and the nicotine lozenge compared to withdrawal from 0.3 mg cigarettes. It is notable that, although the 0.3 mg cigarettes and nicotine lozenges were associated with similar cotinine levels, less withdrawal was observed after nicotine lozenge discontinuation. This suggests that withdrawal may be affected by the nicotine pharmacokinetics of the discontinued product. On the other hand, craving increased for both 0.3 mg and 0.05 mg cigarette conditions after cessation of these products, but not for nicotine lozenge. This finding would indicate that craving for cigarettes has a different abstinence pattern than total withdrawal [34] and may be affected by different aspects of smoking (e.g. missing the sensory aspects of smoking as opposed to primarily nicotine).

Our finding that use of 0.05 mg cigarettes led to greater withdrawal symptom relief than use of nicotine lozenge and no difference than the relief with use of 0.3 mg cigarettes suggests further that non-nicotine components of cigarette dependence (e.g. other tobacco constituents, sensory aspects of smoking) contribute to the relief of withdrawal symptoms. On the other hand, all products appeared to relieve craving equally. These findings are consistent with other studies demonstrating that use of denicotinized cigarettes reduce craving, negative affect and in some studies, withdrawal symptoms or a subset of symptoms during periods of short-term abstinence [9,35–46]. The use of 0.05 mg nicotine cigarettes, by reducing dependence and withdrawal symptoms, may therefore be a promising tool for achieving smoking cessation. Indeed, our study demonstrated that smoking cessation rates in those receiving 0.05 mg cigarettes were equivalent to (if not slightly higher than) cessation rates in those receiving nicotine lozenges. A study by Benowitz *et al.* found that 4 weeks following the end of a progressive reduction in nicotine content of cigarettes 20% of subjects attained abstinence [9]. This rate is surprisingly high, given that these subjects were not enrolling in a cessation study.

Our study suggests that significantly reducing nicotine content of cigarettes may facilitate abstinence by

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making smoking cessation easier to achieve. For the subpopulation of smokers who rely on nicotine for self-medication the use of medicinal products, either in its current form or in a form that results in faster delivery, greater amounts or in other ways that are more satisfying could be considered [47]. This approach is supported by several prior studies suggesting that the use of denicotinized cigarettes in combination with nicotine patch for smoking cessation show promise [48–50].

A major limitation of the current study was the large number of dropouts. About a third to almost half the population dropped out before the end of follow-up and about one-fifth to more than a third dropped out during treatment, with dropout rates lowest in the 0.3 mg cigarette group and highest in the nicotine lozenge group. Another limitation was the inability to determine if smokers were compliant with the study procedures (i.e. that they used the assigned products solely), although the observed cotinine levels are generally consistent with what would be expected with each product (i.e. larger decreases in the 0.05 mg nicotine cigarette group than the other two groups). Despite the fact that the data may be contaminated by smokers who smoked usual brand cigarettes during intervention, the results show that the 0.05 mg cigarette does not lead to greater toxicant exposure and it seems to reduce dependence and to support to abstinence. A third limitation was that the study was underpowered to examine abstinence difference among treatment conditions and the duration of follow-up was short. However, these preliminary results indicate that a future larger trial with longer follow-up is warranted. Finally, this study is generalizable to only one type of near nicotine-free cigarettes.

In summary, reduced nicotine content cigarettes of at least 0.05 mg nicotine yield can lead to reductions in toxicant exposure by way of changing smoking behavior and in dependence and can possibly facilitate abstinence among smokers interested in quitting. These cigarettes can be used potentially as a cessation tool. More research should be conducted on the threshold dose for nicotine addiction during the extinction phase and factors that moderate the threshold dose, the effects of reduced nicotine content cigarettes on vulnerable populations and adjunctive methods that might facilitate cessation.

Clinical trial registration number

NCT 00777569.

Declarations of interest

Peter Shields has served as an expert witness on behalf of plaintiffs in litigation cases against tobacco companies and Stephen Hecht is an expert witness for the plaintiff in 'Kelly Hill *et al.* v. U.S. Smokeless Tobacco Company'. Dorothy Hatsukami has consulted for Pfizer, Abbott Laboratories and Novartis (travel expenses only) and has received a research grant from Nabi Biopharmaceuticals.

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References

1. Stratton K., Shetty P., Wallace R., Bondurant S. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: Institute of Medicine, National Academy Press; 2001.
2. Royal College of Physicians. Harm reduction in nicotine addiction. Helping people who can't quit. In: *A Report by the Tobacco Advisory Group of the Royal College of Physicians*. London: Royal College of Physicians; 2007, p. 176.
3. Hatsukami D., Hecht S. S. Hope or hazard: what research tells us about 'potentially reduced-exposure' tobacco products. Minneapolis, University of Minnesota Transdisciplinary Tobacco Use Research Center. 2005. Available from http://www.rwjf.org/files/research/Hope%20or%20Hazard.pdf (accessed 9 December 2009).
4. Hatsukami D., Joseph A. M., LeSage M., Jensen, J., Murphy, S. E., Pentel, P. R. *et al.* Developing the science base for reducing tobacco harm. *Nicotine Tob Res* 2007; **9**: S537–53.
5. US Department of Health and Human Services (USDHHS). *The Health Consequences of Smoking: Nicotine and Addiction. A Report of the Surgeon General*. Rockville, MD: USDHHS; 1988.
6. National Cancer Institute. *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*. Smoking and Tobacco Control Monograph no. 13. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2001.
7. Hecht S. S., Murphy S. E., Carmella S. G., Li, S., Jensen, J., Le, C. *et al.* Similar uptake of lung carcinogens by smokers of regular, light, and ultralight cigarettes. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 693–8.
8. Bernert J. T., Jain R. B., Pirkle J. L., Wang, L., Miller, B. B., Sampson, E. J. Urinary tobacco-specific nitrosamines and 4-aminobiphenyl hemoglobin adducts measured in smokers of either regular or light cigarettes. *Nicotine Tob Res* 2005; **7**: 729–38.
9. Benowitz N. L., Hall S. M., Stewart S., Wilson, M., Dempsey, D., Jacob, P., 3RD. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2479–85.
10. Benowitz N. L., Jacob P. III, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther* 2006; **80**: 703–14.
11. Hatsukami D. K., Lemmonds C., Zhang Y., Murphy, S. E., Le, C., Carmella, S. G. *et al.* Evaluation of carcinogen exposure in people who used 'reduced exposure' tobacco products. *J Natl Cancer Inst* 2004; **96**: 844–52.
12. Stepanov I., Jensen J., Hatsukami D., Hecht S. S. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res* 2006; **8**: 309–13.

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13. Shiffman S., Dresler C. M., Hajek P., Gilburt, S. J., Targett, D. A., Strahs, K. R. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 2002; **162**: 1267–76.
14. Fiore M. C., Bailey W., Cohen S., Dorfman, S., Goldstein, M., Gritz, E. *et al. Treating Tobacco Use and Dependence. Clinical Practice Guideline*. Rockville, MD: US Department of Health and Human Services Public Health Service; 2000.
15. Jacob P. III, Byrd G. D. Use of chromatographic and mass spectrometric techniques for the determination of nicotine and its metabolites. In: Gorrod J. W., Jacob III, P., editors. *Analytical Determination of Nicotine and Related Compounds and Their Metabolites*. Amsterdam: Elsevier; 1999, p. 191–224.
16. Hecht S. S., Carmella S. G., Murphy S. E. Effects of watercress consumption on urinary metabolites of nicotine in smokers. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 907–13.
17. Carmella S. G., Han S., Fristad A., Yang Y., Hecht S. S. Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 1257–61.
18. Stepanov I., Hecht S. S. Tobacco-specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 885–91.
19. Carmella S. G., Le K. A., Hecht S. S. Improved method for determination of 1-hydroxypyrene in human urine. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1261–4.
20. Carmella S. G., Chen M., Zhang Y., Zhang S., Hatsukami D. K., Hecht S. S. Quantitation of acrolein-derived (3-hydroxypropyl)mercapturic acid in human urine by liquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry: effects of cigarette smoking. *Chem Res Toxicol* 2007; **20**: 986–90.
21. Scherer G., Engl J., Urban M., Gilch G., Janket D., Riedel K. Relationship between machine-derived smoke yields and biomarkers in cigarette smokers in Germany. *Regul Toxicol Pharmacol* 2007; **47**: 171–83.
22. Hatsukami D., McBride C., Pirie P., Hellerstedt W., Lando H. Effects of nicotine gum on prevalence and severity of withdrawal in female cigarette smokers. *J Subst Abuse* 1991; **3**: 427–40.
23. Hughes J. R., Gust S. W., Skoog K., Keenan R. M., Fenwick J. W. Symptoms of tobacco withdrawal: a replication and extension. *Arch Gen Psychiatry* 1991; **48**: 52–9.
24. Hughes J. R., Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986; **43**: 289–94.
25. Hatsukami D., Anton D., Keenan R., Callies A. Smokeless tobacco abstinence effects and nicotine gum dose. *Psychopharmacology* 1992; **106**: 60–6.
26. Hatsukami D., Huber M., Callies A. Physical dependence on nicotine gum: effect of duration on use. *Psychopharmacology* 1993; **111**: 449–56.
27. Hatsukami D., Gust S. W., Keenan R. Physiologic and subjective changes from smokeless tobacco withdrawal. *Clin Pharmacol Ther* 1987; **41**: 103–7.
28. Heatherton T. F., Koslowski L. T., Frecker R. C., Fagerström K.-O. The Fagerström Test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict* 1991; **86**: 1119–27.
29. Donny E. C., Houtsmuller E., Stitzer M. L. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days [see Comment]. *Addiction* 2007; **102**: 324–34.
30. Carmella S. G., Chen M., Han S., Briggs A., Jensen J., Hatsukami D. K. *et al.* Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. *Chem Res Toxicol* 2009; **22**: 734–41.
31. Hecht S. S., Carmella S. G., Chen M., Dor Koch J. F., Miller A. T., Murphy S. E. *et al.* Quantitation of urinary metabolites of a tobacco-specific lung carcinogen after smoking cessation. *Cancer Res* 1999; **59**: 590–6.
32. Stepanov I., Carmella S. G., Han S., Pinto A., Strasser A. A., Lerman C. *et al.* Evidence for endogenous formation of N′-nitrosonornicotine in some long-term nicotine patch users. *Nicotine Tob Res* 2009; **11**: 99–105.
33. Rose J., Behm F. Effects of low nicotine content cigarettes on smoke intake. *Nicotine Tob Res* 2004; **6**: 309–19.
34. Hughes J. R., Hatsukami D. K. The nicotine withdrawal syndrome: a brief review and update. *International Journal of Smoking Cessation* 1992; **1**: 21–6.
35. Baldinger B., Hasenfratz M., Battig K. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field conditions. *Hum Psychopharmacol* 1995; **10**: 127–36.
36. Breland A. B., Buchhalter A. R., Evans S. E., Eissenberg T. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine Tob Res* 2002; **4**: S131–40.
37. Buchhalter A. R., Schrinel L., Eissenberg T. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine Tob Res* 2001; **3**: 111–8.
38. Butschky M. F., Bailey D., Henningfield J. E., Pickworth W. B. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacol Biochem Behav* 1995; **50**: 91–6.
39. Dallery J., Houtsmuller E. J., Pickworth W. B., Stitzer M. L. Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking. *Psychopharmacology (Berl)* 2003; **165**: 172–80.
40. Eid N. C., Fant R. V., Moolchan E. T., Pickworth W. B. Placebo cigarettes in a spaced smoking paradigm. *Pharmacol Biochem Behav* 2005; **81**: 158–64.
41. Gross J., Lee J., Stitzer M. L. Nicotine-containing versus de-nicotinized cigarettes: effects on craving and withdrawal. *Pharmacol Biochem Behav* 1997; **57**: 159–65.
42. Pickworth W. B., Fant R. V., Nelson R. A., Rohrer M. S., Henningfield J. E. Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine Tob Res* 1999; **1**: 357–64.
43. Rose J., Behm F. M., Westman E. C., Johnson M. Dissociating nicotine and non-nicotine components of cigarette smoking. *Pharmacol Biochem Behav* 2000; **67**: 71–81.
44. Brauer L., Behm F., Lane J., Westman E., Perkins C., Rose J. Individual differences in smoking reward from de-nicotinized cigarettes. *Nicotine Tob Res* 2001; **3**: 101–9.
45. Rose J., Behm F. M., Westman E. C., Bates J. E., Salley A. Pharmacologic and sensorimotor components of satiation in cigarette smoking. *Pharmacol Biochem Behav* 2003; **76**: 243–50.
46. Buchhalter A. R., Acosta M. C., Evans S. E., Breland A. B., Eissenberg T. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction* 2005; **100**: 550–9.
47. Henningfield J., Benowitz N. L., Slade J., Houston T. P., Davis

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R. M., Deitchman S. D. Reducing the addictiveness of cigarettes. Council on Scientific Affairs, American Medical Association. *Tob Control* 1998; **7**: 281–93.

48. Becker K. M., Rose J. E., Albino A. P. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. *Nicotine Tob Res* 2008; **10**: 1139–48.
49. Rose J., Behm F. M., Westman E. C., Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine Tob Res* 2006; **8**: 89–101.
50. Rose J., Behm F., Westman E. C., Bates J. E., Salley A. Pharmacologic and sensorimotor components for satiation in cigarette smoking. *Pharmacol Biochem Behav* 2003; **76**: 243–50.

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