

Supplementary Table 3. Analysis of Primary Endpoints, overall and by CEMA Quartiles^a – predominant THS Users vs. Cigarette Smokers.

Primary Endpoint	Time Point / Population	LS Means (95% CI) THS	LS Means (95% CI) Cigarettes	LS Means Ratio / Difference** (95% CI)	
sICAM-1 (ng/mL)	Baseline				
	Overall*	259 (247 ; 272)	264 (252 ; 277)	----	
	Month 3				
	Overall	258 (251 ; 266)	263 (256 ; 269)	98.4 (95.5 ; 101)	
	1. CEMA Quartile	246 (234 ; 260)	261 (255 ; 268)	94.4 (89.5 ; 99.6)	
	2. CEMA Quartile	249 (236 ; 263)	260 (254 ; 267)	95.9 (90.8 ; 101)	
	3. CEMA Quartile	259 (246 ; 273)	262 (255 ; 269)	98.8 (93.7 ; 104)	
	4. CEMA Quartile	276 (261 ; 291)	266 (259 ; 273)	104 (98.3 ; 109)	
	Month 6				
	Overall	257 (249 ; 265)	265 (258 ; 271)	97.1 (94.2 ; 100)	
	1. CEMA Quartile	241 (288 ; 253)	265 (259 ; 271)	90.8 (86.1 ; 95.7)	
	2. CEMA Quartile	252 (239 ; 265)	262 (256 ; 269)	96.0 (91.2 ; 101)	
	3. CEMA Quartile	260 (247 ; 273)	263 (257 ; 270)	98.6 (93.7 ; 104)	
	4. CEMA Quartile	270 (256 ; 285)	265 (259 ; 272)	102 (96.6 ; 107)	
	8-epi-PGF _{2α} (pg/mg creat.)	Baseline			
		Overall*	357 (355 ; 380)	363 (346 ; 380)	----
Month 3					
Overall		332 (315 ; 350)	354 (340 ; 368)	93.8 (88.1 ; 99.8)	
1. CEMA Quartile		287 (258 ; 318)	343 (329 ; 358)	83.5 (75.0 ; 93.1)	
2. CEMA Quartile		307 (277 ; 339)	344 (330 ; 358)	89.2 (80.3 ; 99.1)	
3. CEMA Quartile		340 (307 ; 376)	351 (337 ; 366)	96.9 (87.2 ; 108)	
4. CEMA Quartile		369 (332 ; 409)	353 (338 ; 368)	105 (93.2 ; 116)	
Month 6					
Overall		326 (309 ; 345)	350 (336 ; 365)	93.2 (87.2 ; 99.6)	
1. CEMA Quartile		252 (226 ; 280)	341 (326 ; 356)	73.8 (65.9 ; 82.7)	
2. CEMA Quartile		301 (270 ; 335)	341 (326 ; 356)	88.3 (78.8 ; 99.0)	
3. CEMA Quartile		344 (310 ; 382)	346 (332 ; 361)	99.4 (89.0 ; 111)	
4. CEMA Quartile		393 (350 ; 441)	349 (333 ; 365)	113 (99.8 ; 127)	
Total NNAL (pg/mg creat.)		Baseline			
		Overall*	296 (264 ; 332)	317 (290 ; 346)	----
	Month 3				
	Overall	174 (155 ; 194)	302 (276 ; 330)	57.5 (51.0 ; 64.8)	
	1. CEMA Quartile	39.7 (33.5 ; 47.1)	285 (266 ; 306)	13.9 (11.7 ; 16.6)	
2. CEMA Quartile	200 (171 ; 235)	275 (258 ; 294)	72.8 (61.7 ; 85.9)		

Primary Endpoint	Time Point / Population	LS Means (95% CI) THS	LS Means (95% CI) Cigarettes	LS Means Ratio / Difference** (95% CI)	
11-DTX-B ₂ (pg/mg creat.)	3. CEMA Quartile	252 (217 ; 292)	292 (274 ; 310)	86.4 (73.8 ; 101)	
	4. CEMA Quartile	370 (316 ; 432)	304 (285 ; 324)	122 (103 ; 143)	
	Month 6				
	Overall	159 (140 ; 181)	281 (254 ; 311)	56.5 (48.8 ; 65.3)	
	1. CEMA Quartile	28.6 (22.9 ; 35.8)	259 (238 ; 283)	11.0 (8.74 ; 13.9)	
	2. CEMA Quartile	178 (146 ; 219)	264 (244 ; 286)	67.6 (54.6 ; 83.8)	
	3. CEMA Quartile	256 (210 ; 313)	267 (246 ; 288)	96.2 (78.0 ; 119)	
	4. CEMA Quartile	350 (286 ; 428)	285 (263 ; 308)	123 (99.4 ; 152)	
	Baseline				
	Overall*	588 (535 ; 647)	577 (535 ; 622)	----	
	Month 3				
	Overall	508 (467 ; 552)	531 (498 ; 566)	95.6 (86.5 ; 106)	
	1. CEMA Quartile	562 (474 ; 665)	526 (492 ; 563)	107 (89.5 ; 127)	
	2. CEMA Quartile	455 (383 ; 540)	519 (484 ; 556)	87.6 (73.2 ; 105)	
	3. CEMA Quartile	457 (386 ; 541)	528 (493 ; 566)	86.6 (72.4 ; 103)	
	4. CEMA Quartile	536 (449 ; 638)	527 (490 ; 566)	102 (84.7 ; 122)	
Month 6					
Overall	502 (458 ; 550)	527 (491 ; 564)	95.3 (85.3; 106)		
1. CEMA Quartile	467 (386 ; 564)	527 (489 ; 567)	88.7 (72.8 ; 108)		
2. CEMA Quartile	444 (366 ; 538)	512 (470 ; 557)	86.8 (71.1 ; 106)		
3. CEMA Quartile	535 (444 ; 644)	523 (485 ; 564)	102 (84.0 ; 124)		
4. CEMA Quartile	537 (442 ; 653)	523 (484 ; 565)	103 (83.7 ; 126)		
COHb (%)	Baseline				
	Overall*	4.30 (4.03 ; 4.58)	4.55 (4.34 ; 4.76)	----	
	Month 3				
	Overall	2.91 (2.67 ; 3.18)	4.24 (3.94 ; 4.57)	68.7 (62.8 ; 75.1)	
	1. CEMA Quartile	1.54 (1.33 ; 1.77)	4.18 (3.87 ; 4.51)	36.7 (32.0 ; 42.3)	
	2. CEMA Quartile	2.78 (2.43 ; 3.17)	4.17 (3.87 ; 4.48)	66.6 (58.6 ; 75.8)	
	3. CEMA Quartile	3.35 (2.93 ; 3.84)	4.14 (3.86 ; 4.44)	81.0 (70.7 ; 92.7)	
	4. CEMA Quartile	4.69 (4.11 ; 5.34)	4.27 (3.97 ; 5.34)	110 (96.7 ; 125)	
	Month 6				
	Overall	2.95 (2.69 ; 3.24)	4.35 (4.03 ; 4.70)	67.8 (61.6 ; 74.7)	
	1. CEMA Quartile	1.27 (1.09 ; 1.48)	4.27 (3.96 ; 4.61)	29.8 (25.6 ; 34.6)	
	2. CEMA Quartile	2.73 (2.38 ; 3.13)	4.28 (3.96 ; 4.61)	63.8 (55.7 ; 73.0)	
	3. CEMA Quartile	3.79 (3.32 ; 4.33)	4.28 (3.99 ; 4.60)	88.6 (78.0 ; 100)	
	4. CEMA Quartile	5.18 (4.53 ; 5.94)	4.34 (4.03 ; 4.67)	120 (105 ; 136)	
	FEV ₁ %pred (post BDR)	Baseline			

Primary Endpoint	Time Point / Population	LS Means (95% CI) THS	LS Means (95% CI) Cigarettes	LS Means Ratio / Difference** (95% CI)
HDL-C (mg/dL)	Overall*	96.4 (94.8 ; 98.1)	95.9 (94.6 ; 97.1)	----
	Month 3			
	Overall	95.3 (94.5 ; 96.1)	94.5 (93.9 ; 95.2)	0.792 (-0.00581 ; 1.59)
	1. CEMA Quartile	97.3 (95.9 ; 98.7)	94.6 (93.8 ; 95.3)	2.73 (1.36 ; 4.11)
	2. CEMA Quartile	95.8 (94.4 ; 97.3)	95.0 (94.2 ; 95.8)	0.819 (-0.516 ; 2.15)
	3. CEMA Quartile	93.7 (92.3 ; 95.1)	94.4 (93.7 ; 95.2)	-0.771 (-2.17 ; 0.630)
	4. CEMA Quartile	94.6 (93.2 ; 96.0)	94.1 (93.3 ; 94.9)	0.511 (-0.841 ; 1.86)
	Month 6			
	Overall	94.4 (93.4 ; 95.3)	93.1 (92.3 ; 93.9)	1.28 (0.248 ; 2.32)
	1. CEMA Quartile	95.7 (93.9 ; 97.6)	93.4 (92.6 ; 94.3)	2.30 (0.401 ; 4.20)
	2. CEMA Quartile	95.2 (93.4 ; 97.0)	93.2 (92.4 ; 94.1)	1.97 (0.120 ; 3.81)
	3. CEMA Quartile	94.0 (92.1 ; 95.9)	93.1 (92.2 ; 94.0)	0.900 (-0.986 ; 2.79)
	4. CEMA Quartile	93.1 (91.4 ; 94.9)	92.7 (91.8 ; 93.5)	0.457 (-1.36 ; 2.28)
	Baseline			
	Overall*	53.5 (51.6 ; 55.5)	53.7 (52.1 ; 55.3)	----
	Month 3			
	Overall	54.5 (53.2 ; 55.9)	52.9 (51.9 ; 54.0)	1.62 (-0.0105 ; 3.25)
	1. CEMA Quartile	57.0 (54.5 ; 59.5)	52.6 (51.6 ; 53.6)	4.37 (1.79 ; 6.94)
	2. CEMA Quartile	52.3 (49.9 ; 54.7)	52.9 (51.9 ; 53.9)	-0.596 (-3.13 ; 1.93)
	3. CEMA Quartile	52.9 (50.6 ; 55.2)	52.7 (51.8 ; 53.7)	0.188 (-2.25 ; 2.62)
4. CEMA Quartile	55.7 (52.9 ; 58.4)	53.0 (51.8 ; 54.1)	2.72 (-0.152 ; 5.60)	
Month 6				
Overall	54.6 (53.1 ; 56.2)	51.6 (50.4 ; 52.7)	3.09 (1.28 ; 4.91)	
1. CEMA Quartile	54.1 (51.5 ; 56.8)	51.3 (50.2 ; 52.3)	2.84 (0.0764 ; 5.61)	
2. CEMA Quartile	53.0 (50.5 ; 55.6)	51.5 (50.5 ; 52.5)	1.58 (-1.09 ; 4.26)	
3. CEMA Quartile	54.9 (52.4 ; 57.5)	51.5 (50.4 ; 52.5)	3.45 (0.752 ; 6.15)	
4. CEMA Quartile	56.4 (53.3 ; 59.5)	51.4 (50.2 ; 52.6)	4.98 (1.75 ; 8.20)	
Leukocytes (GI/L)	Baseline			
	Overall*	7.33 (7.09 ; 7.58)	7.47 (7.28 ; 7.67)	----
	Month 3			
	Overall	7.05 (6.81 ; 7.28)	7.52 (7.33 ; 7.72)	-0.475 (-0.728 ; -0.222)
	1. CEMA Quartile	6.95 (6.52 ; 7.37)	7.54 (7.37 ; 7.71)	-0.597 (-1.04 ; -0.153)
	2. CEMA Quartile	6.83 (6.38 ; 7.28)	7.54 (7.32 ; 7.77)	-0.711 (-1.16 ; -0.261)
	3. CEMA Quartile	7.12 (6.68 ; 7.55)	7.56 (7.34 ; 7.77)	-0.439 (-0.882 ; 0.00345)
	4. CEMA Quartile	7.38 (6.94 ; 7.82)	7.57 (7.36 ; 7.78)	-0.190 (-0.635 ; 0.254)
	Month 6			
	Overall	7.06 (6.81 ; 7.31)	7.48 (7.28 ; 7.68)	-0.420 (-0.690 ; -0.150)

Primary Endpoint	Time Point / Population	LS Means (95% CI) THS	LS Means (95% CI) Cigarettes	LS Means Ratio / Difference** (95% CI)
	1. CEMA Quartile	6.56 (6.12 ; 7.00)	7.49 (7.28 ; 7.70)	-0.934 (-1.38 ; -0.491)
	2. CEMA Quartile	6.97 (6.53 ; 7.42)	7.55 (7.33 ; 7.77)	-0.576 (-1.03 ; -0.127)
	3. CEMA Quartile	7.15 (6.74 ; 7.56)	7.49 (7.33 ; 7.66)	-0.345 (-0.775 ; 0.0856)
	4. CEMA Quartile	7.53 (7.07 ; 7.99)	7.52 (7.30 ; 7.74)	0.00803 (-0.475 ; 0.473)

* Geometric means for baseline of sICAM-1, 8-epi-PGF_{2α}, Total NNAL, 11-DTX-B2, and COHb; arithmetic means for FEV₁%pred, HDL-C, and Leukocytes

** LS Mean Ratios for sICAM-1, 8-epi-PGF_{2α}, Total NNAL, 11-DTX-B2, and COHb.

LS Mean Differences for FEV₁%pred, HDL-C, and Leukocytes.

^a Boundaries of CEMA Quartiles at Month 3 (n): 0.73-39.9 (60), 41.2-112 (60), 113-190 (61), 191-1850 (60).

Boundaries of CEMA Quartiles at Month 6 (n): 1.16-32.3 (56), 32.4-128 (56), 130-227 (57), 228-784 (56).

sICAM-1 = soluble intercellular adhesion molecule-1; 8-epi-PGF_{2α} = 8-epi-prostaglandin F2 alpha; Total NNAL = total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; 11-DTX-B2 = 11-dehydrothromboxane B2;

COHb = carboxyhemoglobin; FEV₁ = forced expiratory volume in one second; HDL-C = high-density lipoprotein cholesterol; Leukocytes = white blood cell total count.

THS refers to predominant THS use of 70% or more; Cigarettes refers to THS use of less than 1%.

Visit 7 and Visit 10 data represent Months 3 and 6, respectively.

BDR = post bronchodilator