An Open-label, Randomized, Parallel Group, Controlled Study to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure and Biomarkers of Potential Harm in Adult Smokers Who Completely Switch to Using e-Vapor Products for 12 Weeks

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All data extracted from ALCS-RA-16-06-EV (Sept. 07, 2018) clinical study report

Primary Objective

Compare absolute changes in selected biomarkers from Baseline to End of Study between adult smokers who continue to smoke conventional cigarettes and adult smokers who have completely switched to the test e-vapor products for 12 weeks
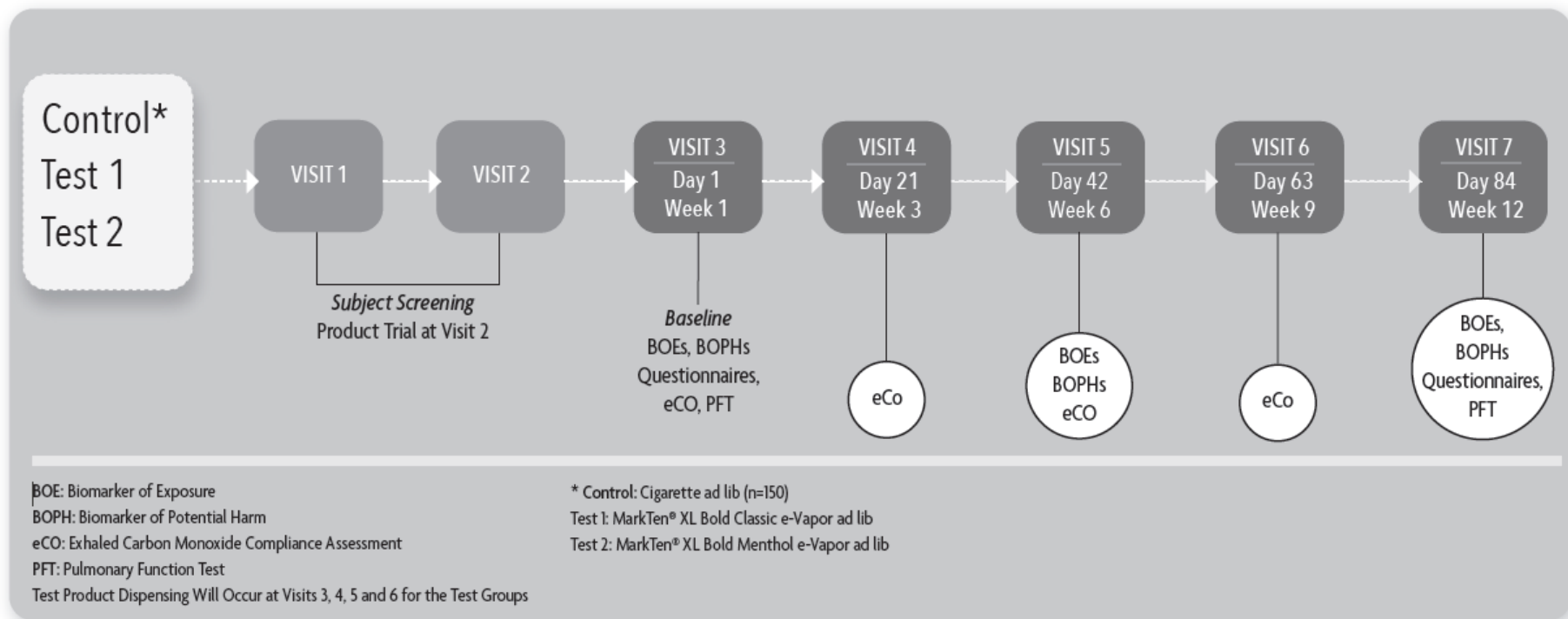
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Study Products

Battery Assembly **Cartridge**

Product	Nicotine (% by weight)	Nicotine[a] (mg/puff)
Classic Bold	4.0	0.20
Menthol Bold	4.0	0.23

[a] Based on 5s puff duration, 50mL puff volume and 30s inter-puff-interval

12 Week e-Vapor Switching Study

Control*
Test 1
Test 2

VISIT 1 → VISIT 2

Subject Screening
Product Trial at Visit 2

VISIT 3
Day 1
Week 1

Baseline
BOEs, BOPHs
Questionnaires,
eCO, PFT

VISIT 4
Day 21
Week 3

eCo

VISIT 5
Day 42
Week 6

BOEs
BOPHs
eCO

VISIT 6
Day 63
Week 9

eCo

VISIT 7
Day 84
Week 12

BOEs,
BOPHs
Questionnaires,
PFT

BOE: Biomarker of Exposure
BOPH: Biomarker of Potential Harm
eCO: Exhaled Carbon Monoxide Compliance Assessment
PFT: Pulmonary Function Test
Test Product Dispensing Will Occur at Visits 3, 4, 5 and 6 for the Test Groups

* Control: Cigarette ad lib (n=150)
Test 1: MarkTen® XL Bold Classic e-Vapor ad lib
Test 2: MarkTen® XL Bold Menthol e-Vapor ad lib

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Key Measurements

Biomarkers of Exposure		
Biomarker	**Constituent**	**FDA Classification**
Total NNAL	NNK	Carcinogen
Carboxyhemoglobin (COHb)	Carbon Monoxide	Reproductive or Developmental Toxicant
Nicotine Equivalents (nicotine and 5 metabolites)	Nicotine	Reproductive or Developmental Toxicant, Addictive

Biomarkers of Potential Harm	
Biomarker	**Indication**
White Blood Cells (WBC)	Inflammation
High-density lipoprotein cholesterol (HDL-C)	Cardiovascular Risk
8-Epi-prostaglandin F2α (8-epi-PG F2α)	Oxidative Stress
11-Dehydrothromboxane B2 (11-DTX B2)	Platelet Activation
Soluble intercellular adhesion molecule-1 (sICAM-1)	Endothelial Function

Demographics

Trait	Category/Statistics	Classic Bold (n=151)	Menthol Bold (n=150)	Control (n=149)	Overall (n=450)
Gender	**Female**	**74** (49%)	**75** (50%)	**73** (49%)	**222** (49%)
	Male	**77** (51%)	**75** (50%)	**76** (51%)	**228** (51%)
Race	**White/Caucasian**	**103** (68%)	**111** (74%)	**106** (71%)	**320** (71%)
	Black or African American	**44** (29%)	**37** (25%)	**38** (26%)	**119** (26%)
	Other	**4** (3%)	**2** (1%)	**5** (3%)	**11** (2%)
Age (yrs)	**Mean**	**43.9** (SD±8.5)	**44.1** (SD±9.3)	**44.4** (SD±10.0)	**44.1** (SD±9.2)
BMI (kg/m²)	**Mean**	**27.8** (SD±5.1)	**27.9** (SD±5.2)	**27.7** (SD±5.0)	**27.8** (SD±5.1)

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Tobacco History

		Classic Bold	Menthol Bold	Control	Overall
	n	151	150	149	450
Cigarettes per Day	**mean**	**18.2** (SD±5.7)	**17** (SD±5.2)	**17.4** (SD±5.8)	**17.5** (SD±5.6)
Years Smoked	**mean**	**24.1** (SD±8.3)	**25** (SD±9.5)	**24.5** (SD±9.8)	**24.5** (SD±9.2)

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Study Product Use

Cigarettes per Day

Average Cartridges per Day		
Group		**Week 12**
Classic Bold	N	120
	Mean	1.44
	SD	0.979
Menthol Bold	N	122
	Mean	1.31
	SD	0.831

Arithmetic Means ±SD

Compliance With Test Product Use

Group	Week	N	eCO Category n (%) ≤5	eCO Category n (%) >5 - ≤8	eCO Category n (%) >8
Classic Bold	Baseline	146	10%	4%	86%
	3	136	63%	13%	24%
	6	124	75%	10%	15%
	9	116	68%	15%	17%
	12	112	68%	12%	21%
Menthol Bold	Baseline	147	4%	12%	84%
	3	134	60%	14%	25%
	6	126	71%	13%	16%
	9	123	67%	10%	24%
	12	121	64%	17%	19%
Control	Baseline	147	8%	10%	82%
	12	129	4%	9%	87%

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Biomarkers of Exposure

NNAL
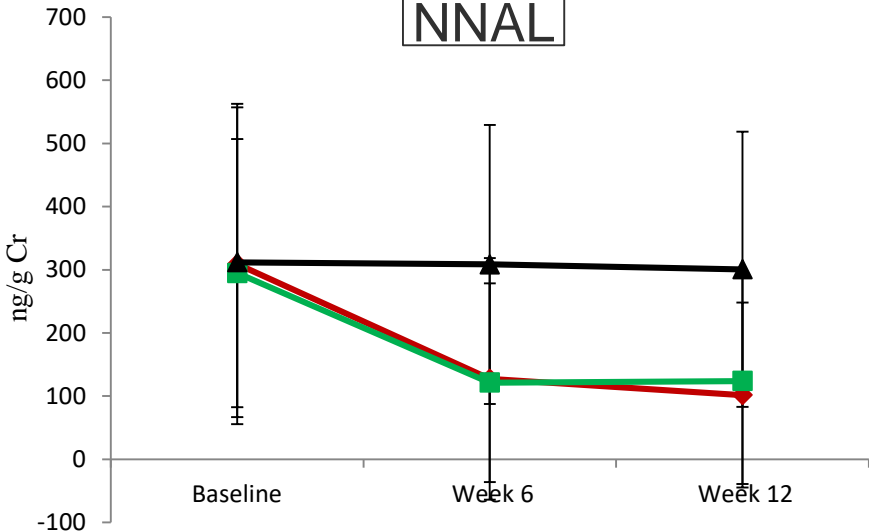
COHb
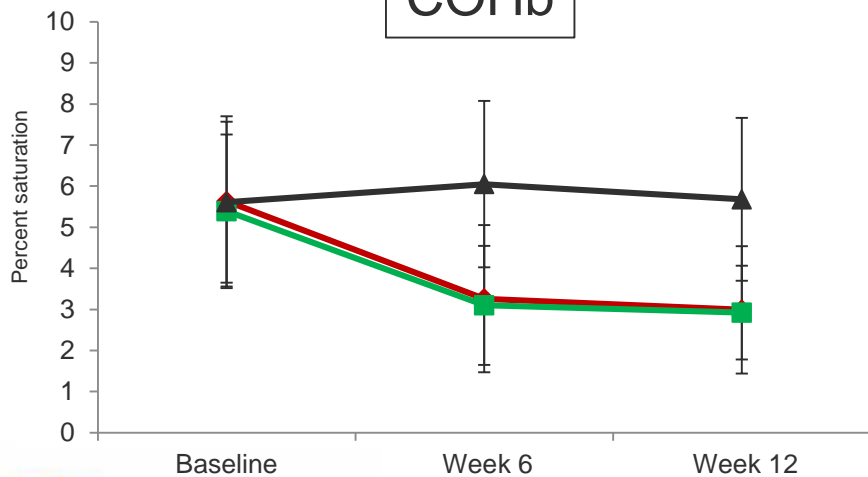
Nicotine Equivalents

Classic Bold
Menthol Bold
Control

Arithmetic Means ±SD

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Biomarkers of Exposure

Biomarker	Group	Absolute Change from Baseline to 12 Weeks			
		LS Means			
		Test (n)	Control (n)	LS Mean Difference (Test - Control)	p-value^
Urine Total NNAL (ng/g Cr)	Classic Bold	-184.391 (112)	-7.764 (128)	-176.627	<.0001
	Menthol Bold	-161.576 (120)	-7.764 (128)	-153.812	<.0001
Whole Blood COHb (% Saturation)	Classic Bold	-2.415 (111)	0.099 (128)	-2.514	<.0001
	Menthol Bold	-2.486 (120)	0.099 (128)	-2.586	<.0001
Nicotine Equivalents (mg/g Cr)	Classic Bold	0.277 (112)	-0.699 (127)	0.977	0.3280
	Menthol Bold	0.525 (119)	-0.699 (127)	1.225	0.1367

Biomarkers of Potential Harm
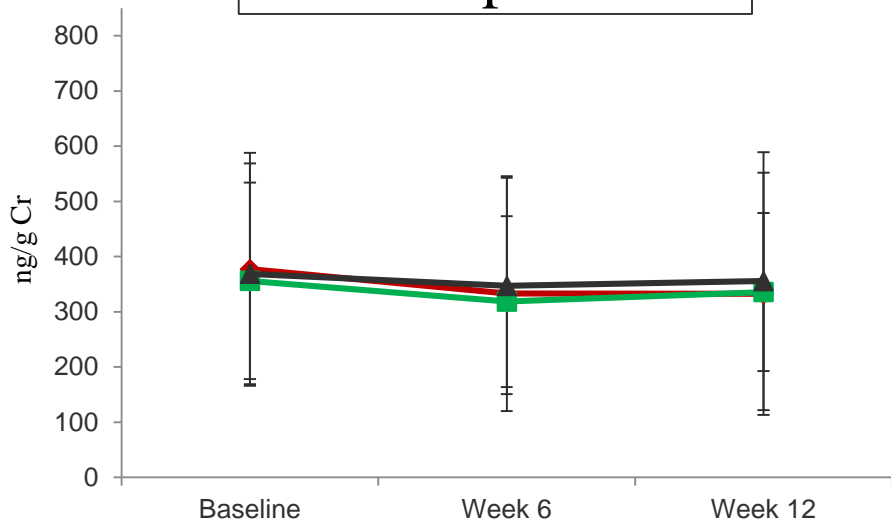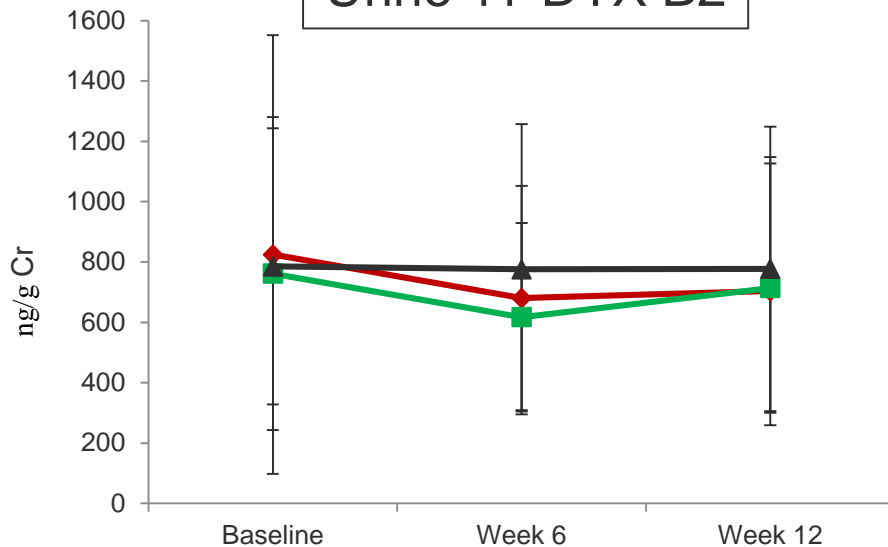

WBC

HDL-C

sICAM-1
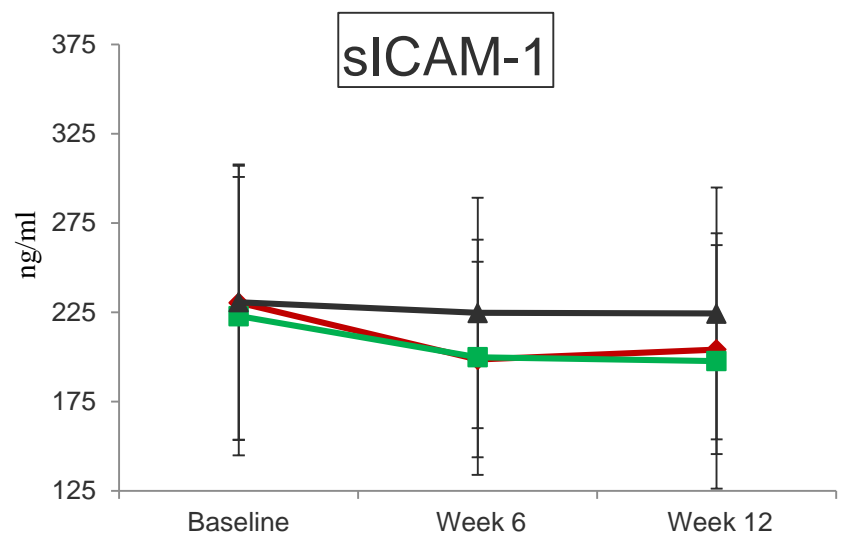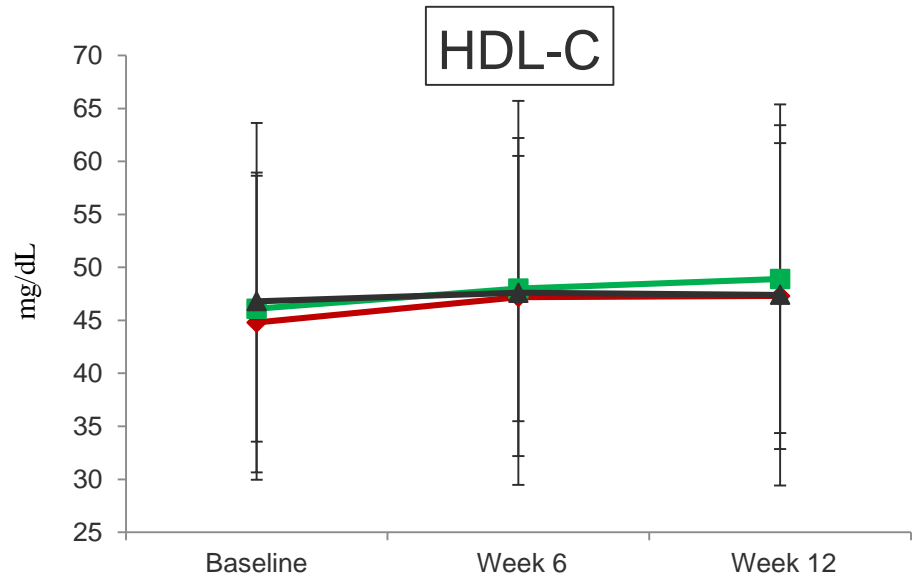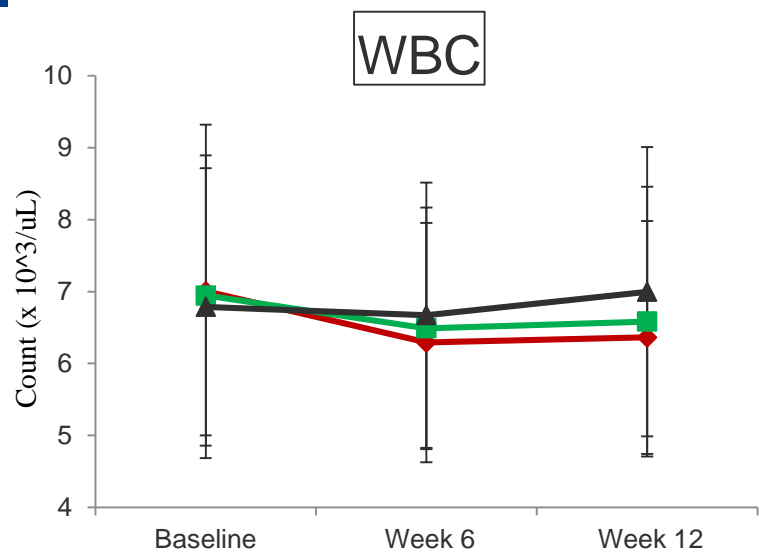
Classic Bold
Menthol Bold
Control

Arithmetic Means ±SD

Biomarkers of Potential Harm

Urine 8-epi-PG F2α

Urine 11-DTX B2

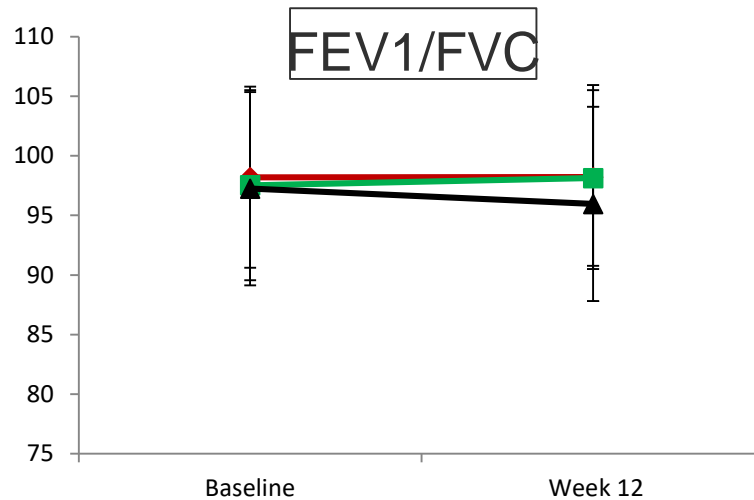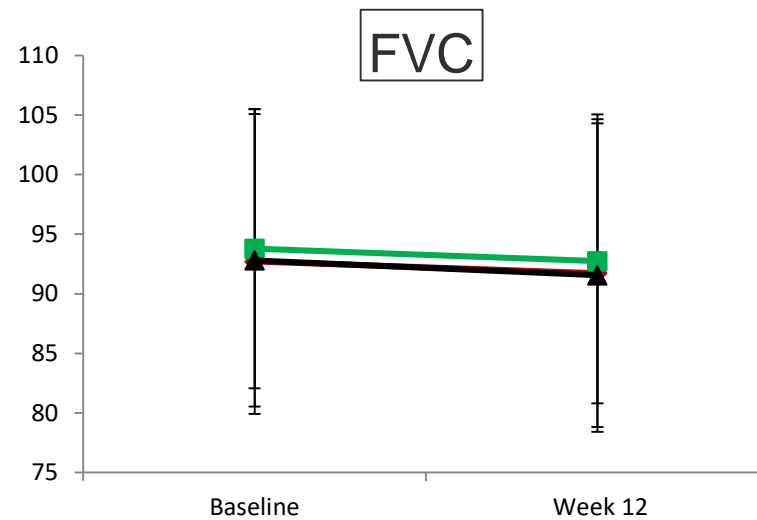Legend:
- Classic Bold
- Menthol Bold
- Control

Arithmetic Means ±SD

Biomarkers of Potential Harm

Biomarker	Group	Absolute Change from Baseline to 12 Weeks			LS Mean Difference (Test - Control)	p-value^
		LS Means				
		Test (n)		Control (n)		
Whole Blood WBC Count (x 10^3/uL)	Classic Bold	-0.686 (110)		0.111 (128)	-0.797	0.0002
	Menthol Bold	-0.342 (119)		0.111 (128)	-0.453	0.0639
	Both e-Vapor Groups	-0.514 (229)		0.111 (128)	-0.625	0.0001
Urine 11-DTX B2 (ng/g Cr)	Classic Bold	-74.904 (110)		-2.635 (125)	-72.269	0.4543
	Menthol Bold	-62.755 (120)		-2.635 (125)	-60.120	0.6061
	Both e-Vapor Groups	-68.830 (230)		-2.635 (125)	-66.194	0.1242
Plasma sICAM-1 (ng/mL)	Classic Bold	-25.921 (111)		-5.902 (129)	-20.019	0.0005
	Menthol Bold	-26.899 (120)		-5.902 (129)	-20.997	0.0002
	Both e-Vapor Groups	-26.410 (231)		-5.902 (129)	-20.508	<.0001
Serum HDL-C (mg/dL)	Classic Bold	3.468 (110)		1.778 (128)	1.690	0.3934
	Menthol Bold	3.329 (119)		1.778 (128)	1.552	0.4576
	Both e-Vapor Groups	3.399 (229)		1.778 (128)	1.621	0.0849
Urine 8-epi-PG F2α (ng/g Cr)	Classic Bold	-31.350 (111)		-4.759 (128)	-26.591	0.5234
	Menthol Bold	-18.096 (120)		-4.759 (128)	-13.337	0.9331
	Both e-Vapor Groups	-24.723 (231)		-4.759 (128)	-19.964	0.2444

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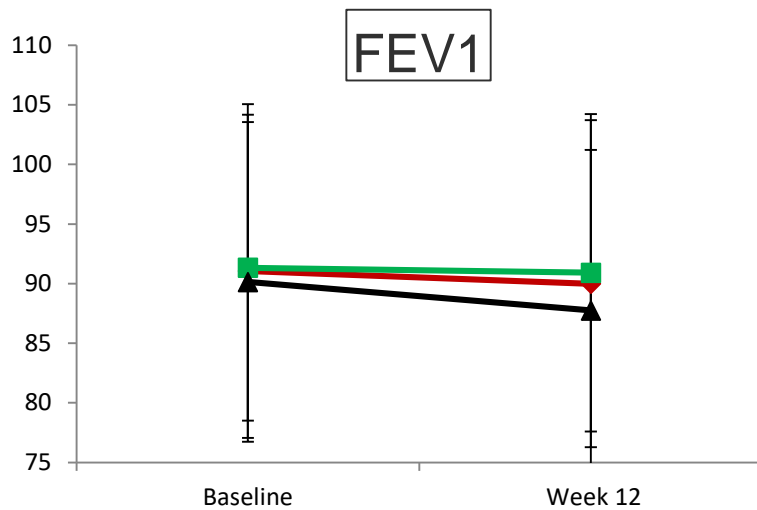
Spirometry (percent predicted)

Arithmetic Means ± SD

Spirometry (percent predicted)

Absolute Change from Baseline to 12 Weeks					
		LS Means			
Pulmonary Function Parameter	Comparison	Test (n)	Reference (n)	LS Mean Difference (Test - Reference)	p-value
Percentage of Predicted FEV1 (%)	Classic Bold	-1.04 (100)	-2.46 (115)	1.42	0.0839
	Menthol Bold	-0.37 (112)	-2.46 (115)	2.10	0.0089
	Both e-Vapor Groups	-0.71 (212)	-2.46 (115)	1.76	0.0119
Percentage of Predicted FVC (%)	Classic Bold	-1.00 (100)	-1.26 (115)	0.26	0.7101
	Menthol Bold	-1.03 (112)	-1.26 (115)	0.24	0.7325
	Both e-Vapor Groups	-1.01 (212)	-1.26 (115)	0.25	0.6781
Percentage of Predicted FEV1/FVC (%)	Classic Bold	0.12 (100)	-1.36 (115)	1.48	0.0136
	Menthol Bold	0.58 (112)	-1.36 (115)	1.94	0.0009
	Both e-Vapor Groups	0.35 (212)	-1.36 (115)	1.71	0.0008

Overall Summary

Subjects switching to MarkTen® products demonstrated:

- Reduction in cigarette consumption by ~98%

- Significant reduction in BOE (NNAL & COHb)

  - Nicotine exposure remained the same as for cigarettes

- Favorable changes in BOPH

  - WBC and sICAM significantly reduced ($p<0.001$)

  - HDL, 11-dehydro and 8-epi all showed favorable changes

  - Favorable changes in lung function

Comparable outcomes were observed between the Menthol and Classic Bold MarkTen® products

Conclusions

- Complete switching from cigarettes to MarkTen® should reduce the risks of smoking related diseases

- Flavor does not appear to have an impact on the risk reduction potential.

- A 12-week study with the currently available biomarkers along with exclusive use should be sufficient enough to assess the potential health effects of a new tobacco product