



A 12-Month, Randomized, Controlled Study to Evaluate the Exposure to Smoke Constituents of an Electrically Heated Cigarette Smoking System in Healthy Adult Smokers

Biomarkers of Potential Harm

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Introduction

This second-generation electrically heated cigarette smoking system (EHCSS) comprises a special cigarette made of conventional tobacco filler rolled into a tobacco mat which is smoked in a battery-operated device that heats the tobacco during puffing. Reductions of 50% to 95% in several biomarkers of exposure (BOE) to cigarette smoke constituents were shown in an 8-day exposure evaluation in a controlled clinical setting.¹

The primary purpose of this study was to assess exposure to cigarette smoke constituents in adult smokers who switched to this EHCSS for 12 months in their normal life setting, as compared to adult smokers who continued to smoke a conventional cigarette. A proof-of-concept exploratory analysis was also conducted to evaluate whether this reduction in exposure was accompanied by changes in selected biomarkers of potential harm (BOPH).

Common pathophysiological mechanisms underlie many tobacco-associated adverse health effects: inflammation, oxidative stress, enhanced platelet activation, and abnormal lipoprotein metabolism. Compared to non-smokers or former smokers, cigarette smokers have increased biomarkers of:

- inflammation² (i.e., total white blood cells and subpopulations [i.e., neutrophils and lymphocytes], C-reactive protein, fibrinogen,
 - oxidative stress⁷ (i.e., urine 8-*epi*-prostaglandin F_{2α})
 - platelet activation (i.e., urine 11-dehydrothromboxane B₂)
 - red blood cell mass³ (i.e., hemoglobin, hematocrit, red blood cell count)
- and abnormal lipoprotein metabolism (i.e., decreased HDL-cholesterol).

still adding the refs as appropriate

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Objective

Comparison of biomarkers of potential harm (BOPH) in adult smokers of 1 to 7 mg tar (FTC) cigarettes who, for 12 months:

- were switched to EHCSS, or
- were switched to a 6 mg tar (FTC) conventional cigarette (CC)

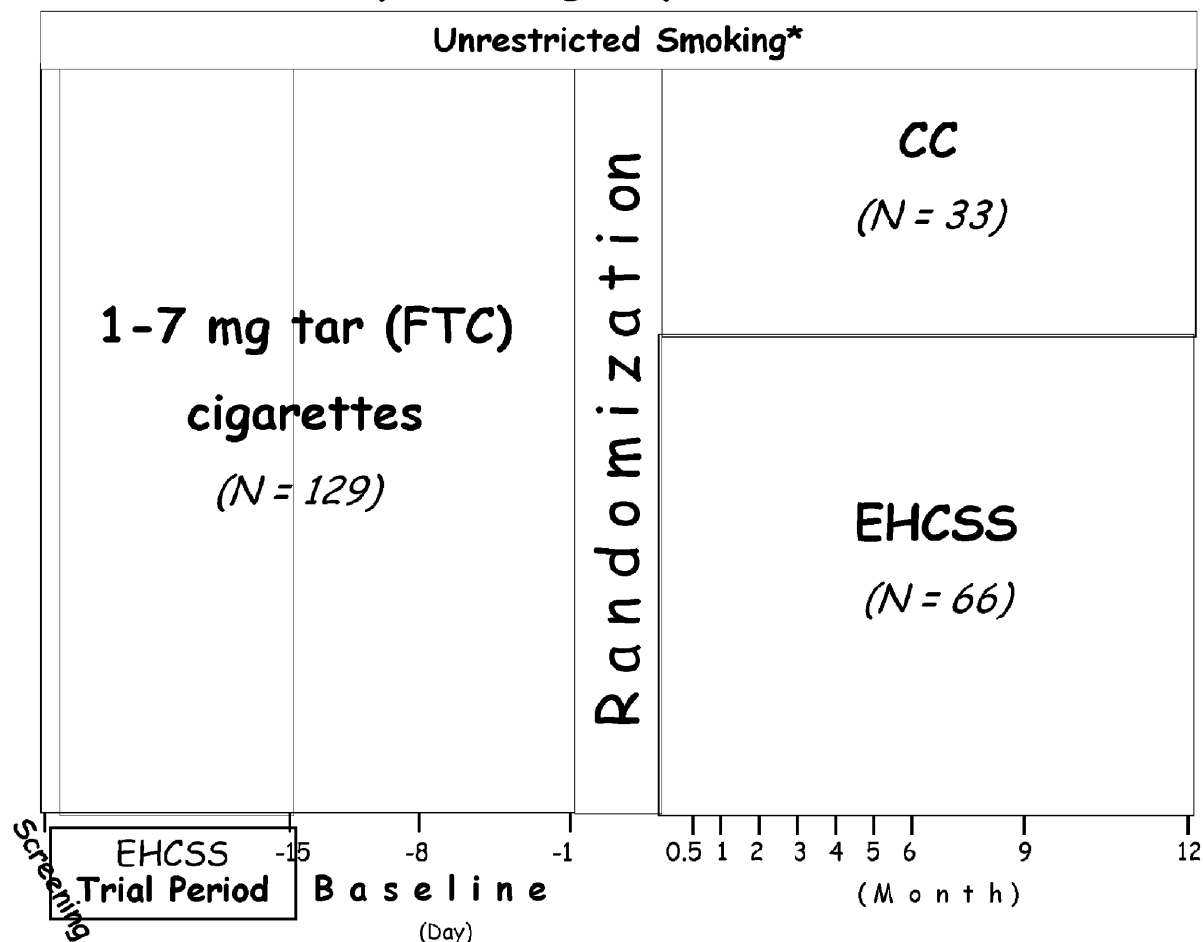
Study Products

EHCSS		CC	
Tar	2.6 mg	Tar	6.1 mg
Nicotine	0.2 mg	Nicotine	0.5 mg
CO	0.2 mg	CO	7.2 mg

*mainstream smoke delivery, Federal Trade Commission (FTC)
method*

METHODS: Study Design

Randomized, controlled, forced-switching, open-label,
parallel-group, two-center



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The last available Baseline measurement was defined as the Baseline if no statistical difference was found among the three Baseline measurements.

METHODS: Study Design

Subjects lived in their normal life setting except during the investigational visits when they stayed in a clinical research center for ~36h which included collection of a 24h urine sample and recording all cigarettes smoked during the urine collection.

*Unrestricted smoking: Cigarette smoking in a subject's normal life setting with no restrictions on time of smoking or number of cigarettes smoked. Cigarette smoking was limited to the study-assigned product.

The study was conducted in compliance with Good Clinical Practice.

METHODS: Study Population

➤ Key Inclusion Criteria

- Healthy adult (25-65 years old) male and female smokers
- Smoke 10 to 40 non-menthol cigarettes per day (1 to 7 mg tar [FTC] delivery) ≥ 10 years

➤ Key Exclusion Criteria

- Pregnant or nursing females
- Use of other nicotine or tobacco products
- FEV₁ or FVC $< 70\%$ predicted

METHODS: Biomarkers of Potential Harm (BOPH)

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Biomarker	Matrix	Method	Health Effect
Hemoglobin, Hematocrit, RBC count	whole blood	Automated cell counter	Oxygen-carrying capacity
White Blood Cell Count (total and differential)	whole blood	Automated cell counter	Inflammation
11-Dehydrothromboxane B ₂	24-hr urine	EIA	Platelet activation, Cardiovascular disease
Fibrinogen	plasma	Photometric	Cardiovascular disease
hs C-Reactive Protein	serum	Nephelometry	Inflammation
HDL-cholesterol	serum	Hitachi Analyzer	Atherosclerosis

pls add a column after Method w/ the following LLOQ: H,H,RBC, WBC (N/A), 11DHTx 14 pg/mL, fibrinogen 10 mg/dL, hs CRP 0.021 mg/L, HDL 13 mg/dL ???also add ref ranges for as appropriate

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METHODS: Analysis of Data

- Linear mixed-model repeated measures ANOVA of difference in mean change from baseline over all 12 months between EHCSS and CC groups
- Level of significance: $\alpha < 0.05$ (two-sided test)

RESULTS: Baseline Demographic Characteristics and Smoking History

		EHCSS-JLI	CC	Overall
Gender (n)	FEMALE	35	17	52
	MALE	29	16	45
Race (n)	BLACK	1	0	1
	CAUCASIAN	61	32	93
	HISPANIC	2	1	3
Smoking Duration (Years)	10 to 15 years	14	6	20
	16 to 19 years	16	4	20
	20 to 29 years	19	15	34
	30 years or more	15	8	23
Age	N	64	33	97
	Mean	41.3	42.9	41.8
	SD	9.1	10	9.4
Body Mass Index	N	64	33	97
	Mean	25.3	26.1	25.6
	SD	2.89	3.31	3.05

At Baseline, all subjects smoked cigarettes in the 1-7 mg tar (FTC) range. Both groups were comparable at Baseline for most BOE and BOPH levels.

Will include N randomized and completed study by group and (97 and 82) overall

RESULTS: Cigarette Consumption* (cigarettes/24h)

unrestricted smoking

Table 6: Daily Cigarette Consumption by "Treatment" at Baseline* and Study Week
(Arithmetic Mean for Baseline Through Overall, LS Means for Overall % Change from Baseline,
and p-values for "Treatment" Comparison)

	Cigarettes/24h (mean \pm SD)		p-value
	EHCSS	CC	
Baseline	24 \pm 10	23 \pm 7	0.99 ^a
Overall	46 \pm 25	29 \pm 13	
Overall % Change from Baseline	95 \pm 95	27 \pm 48	0.0001 ^b

* Self-documented cigarettes smoked during the 24h urine collection at investigational study visits. In at least some subjects in the EHCSS group, "dual smoking" (i.e., EHCSS and conventional cigarettes) occurred during the ambulatory intervals between these investigational study visits as determined by inspection of biweekly spot urine NNAL/creatinine and responses to questionnaires.

^a p-values for difference in median values were obtained from non-parametric (Kruskal-Wallis) test.

^b p-values for difference in LS mean % change from Baseline over all Study Months (0.5 through 12) were obtained by repeated measures ANOVA.

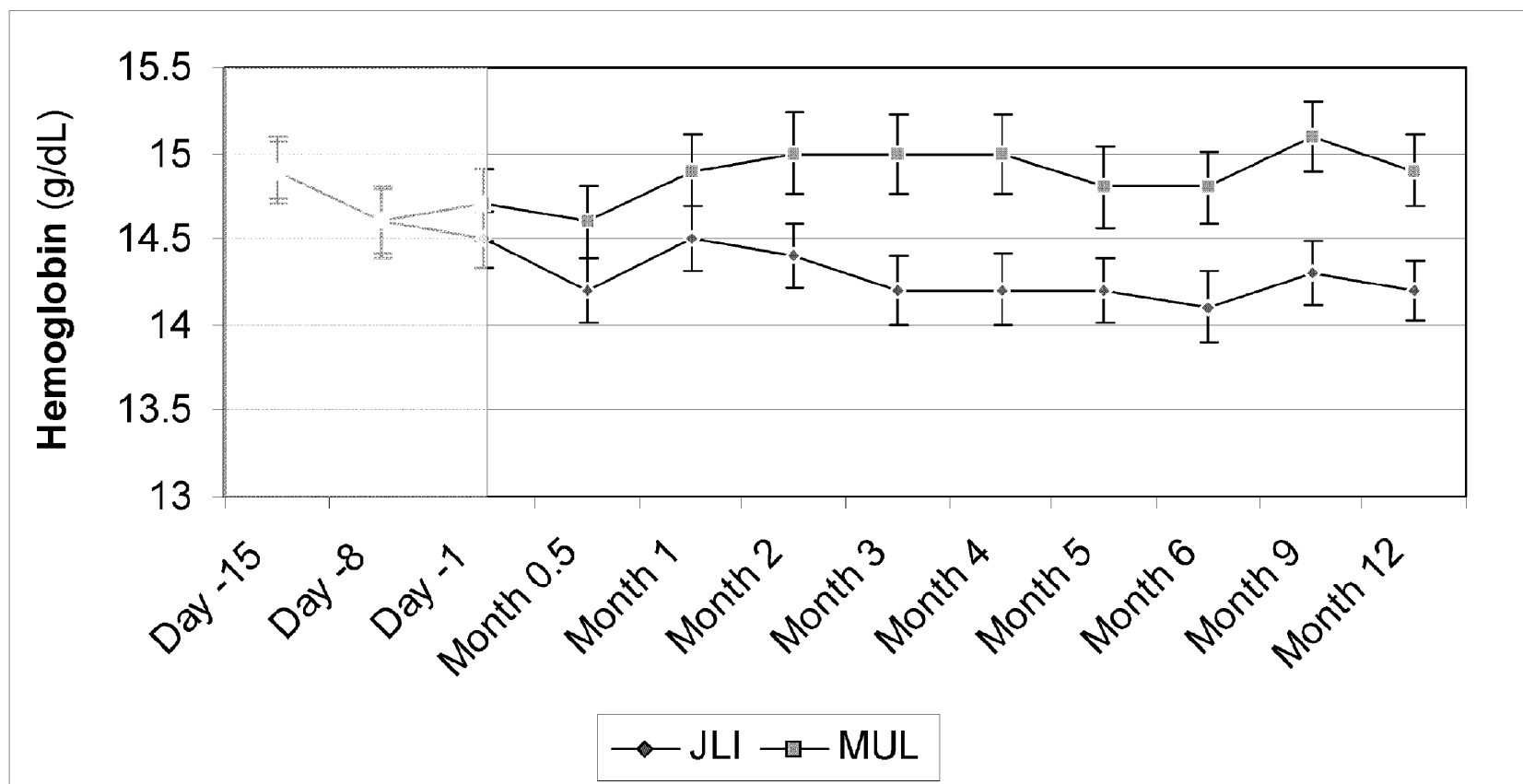
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Red Blood Cells

(mean \pm SEM)

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Asha, legends for groups should use EHCSS and CC only.

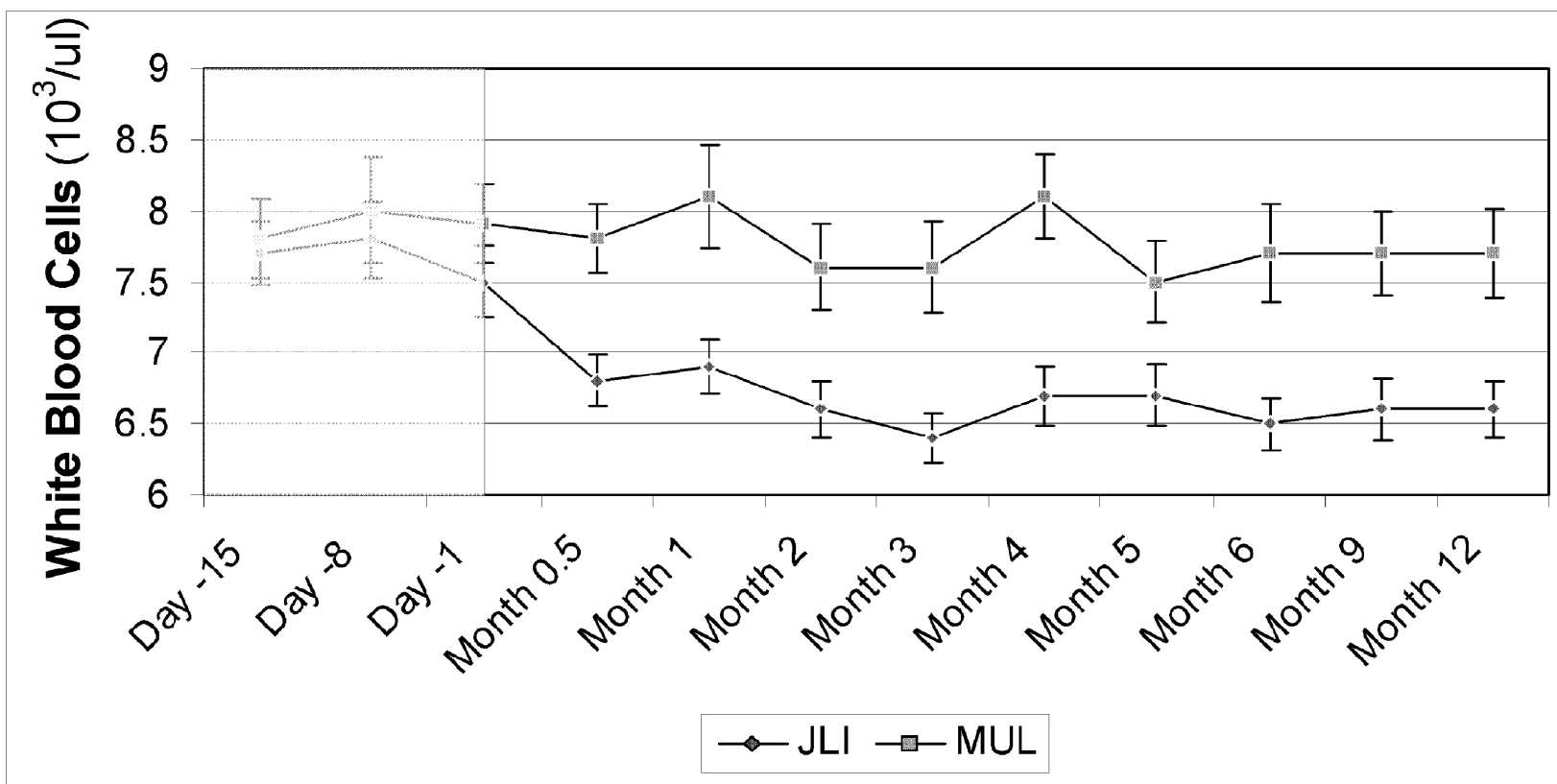
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Inflammation

(mean \pm SEM)

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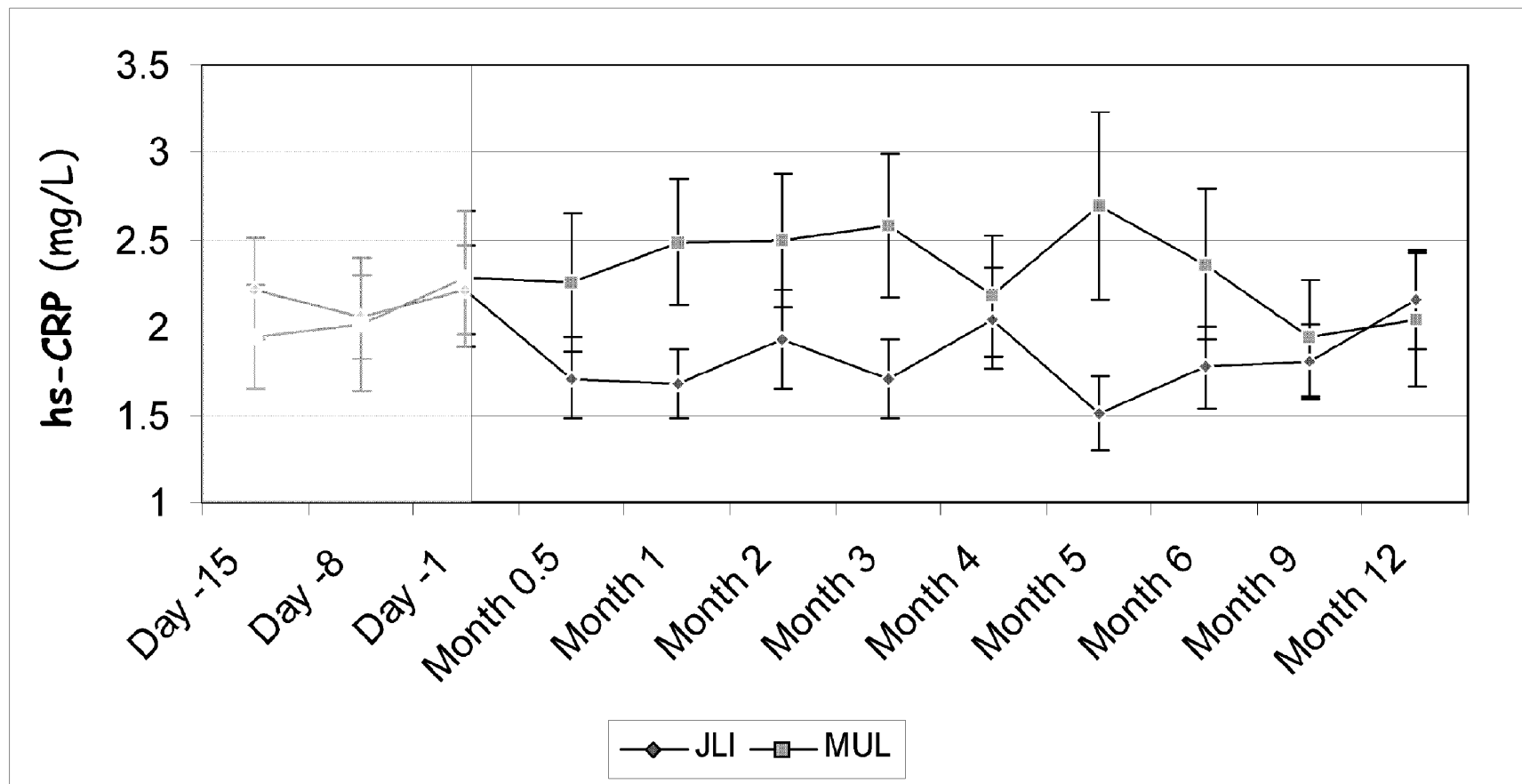
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Inflammation

(mean \pm SEM)

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Method LLOQ = 0.021 mg/L

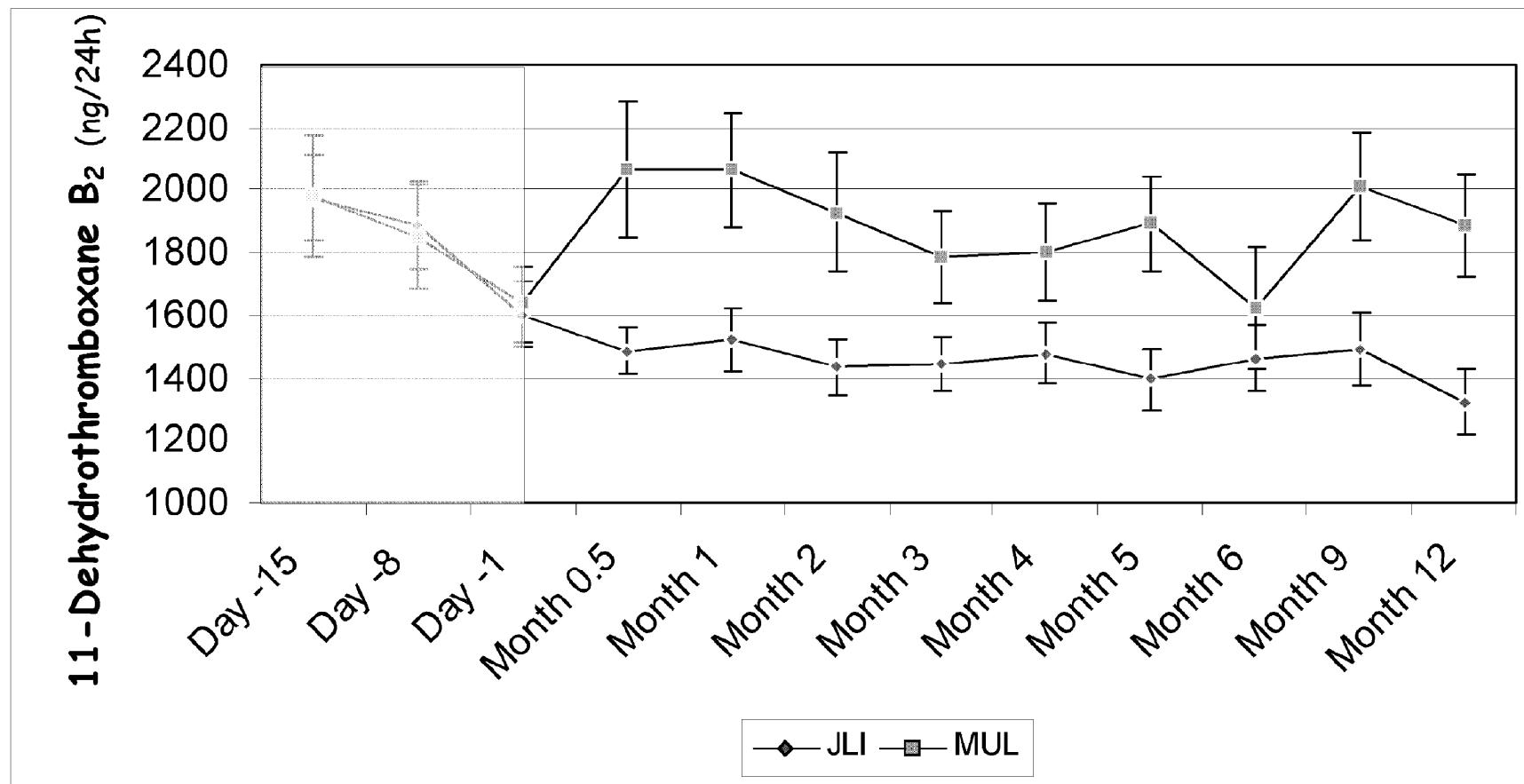
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Platelet Activation

(mean \pm SEM)

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EIA method with LLOQ = 14 pg/mL

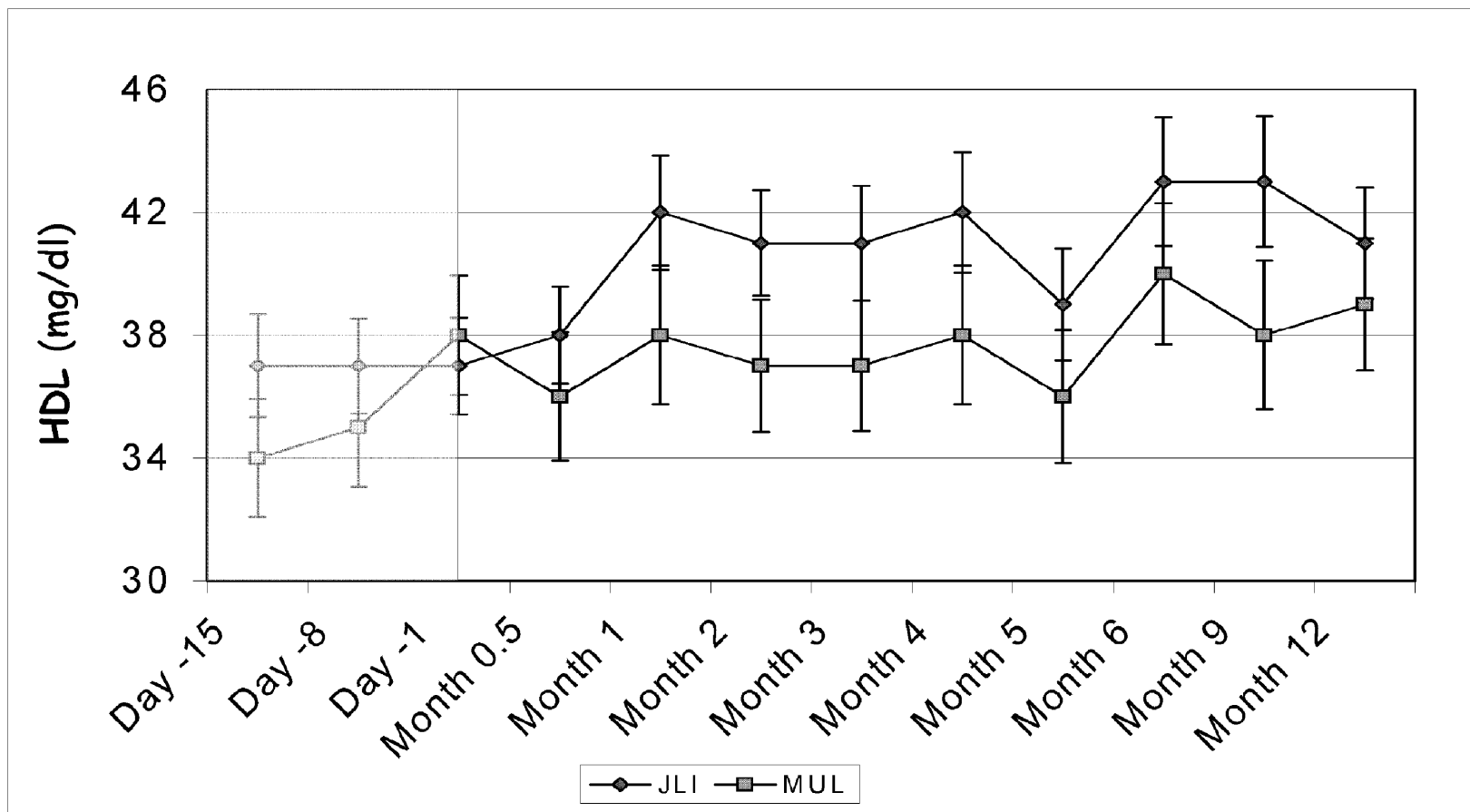
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HDL-Cholesterol

(mean \pm SEM)

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Asha, can you change y-axis label from HDL to HDL-Cholesterol?

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Summary: Biomarkers of Potential Harm

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Biomarker	Units	Mean Absolute Change from Baseline		
		Overall (Months 0.5 thro 12)		p-value*
		EHCSS	CC	
Hemoglobin	g/dL	-0.16	0.25	0.0009
Hematocrit	%	-0.44	0.88	<.0001
Red Blood Cells	10 ⁶ /uL	0.05	0.15	0.0172
White Blood Cells	10 ³ /uL	-0.78	-0.19	0.0035
Neutrophils	10 ³ /uL	-0.82	-0.31	0.0096
Lymphocytes	10 ³ /uL	-0.15	0.05	0.0050
Monocytes	10 ³ /uL	-0.01	0.01	0.23
Platelets	10 ³ /uL	-9.56	-3.58	0.23
11-Dehydrothromboxane B ₂	ng/24h urine	-374	9	0.0031
Fibrinogen	mg/dL	-13	1	0.22
hs-CRP	mg/dL	-0.3	0.2	0.17
8-epi-Prostaglandin F _{2α}	ng/24h urine	164	266	0.33
HDL-Cholesterol	mg/dL	5	1	0.0080
LDL-Cholesterol	mg/dL	-2	1	0.14
Heart Rate	bpm	-1	3	0.0102

*P-value for difference in LS mean absolute change from Baseline overall (Months 0.5 through 12) between the 2 groups was obtained by repeated measures ANOVA.

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Conclusions: Biomarkers of Potential Harm

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Over all 12 months after switching from cigarettes with 1 to 7 mg tar (FTC) to EHCSS, there were statistically significant and pathophysiologically favorable differences in change from baseline for the EHCSS group (compared to the group that continued to smoke a CC), in:

- *hemoglobin, hematocrit, RBC count*
- *total WBC count; neutrophil and lymphocyte counts*
- *24h urine 11-dehydrothromboxane B₂*
- *HDL-cholesterol*
- *heart rate*

In this 1-year study, substantial reductions in exposure to several tobacco smoke constituents in the adult smokers switched to EHCSS, compared to those who continued to smoke a CC*, were accompanied by rapid, sustained, measurable, and favorable changes in several surrogate markers of adverse health effects. This occurred despite "dual smoking" (i.e., EHCSS and conventional cigarettes) in at least some subjects in the EHCSS group, during the ambulatory intervals between the investigational study visits.

** Here will cite the EHCSS-JLI BOE poster also being presented*

BOPH References *Still needs a fair amt of clean-up.*

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