A Multi-Center, Multi-Regional, Study on Biological and Functional Changes

in Healthy Adult Smokers during One Year of Continuous Smoking Abstinence

C. T. Tran, L. Felber Medlin, N. Lama, B. Taranu, E. Pierri, J. Ancerewicz, P. Picavet, G. Baker, C. Haziza, F. Lüdicke —
PMI R&D, Philip Morris Products S. A., Quai Jeanrenaud 5, CH-2000 Neuchâtel, Switzerland (Part of Philip Morris International group of companies)

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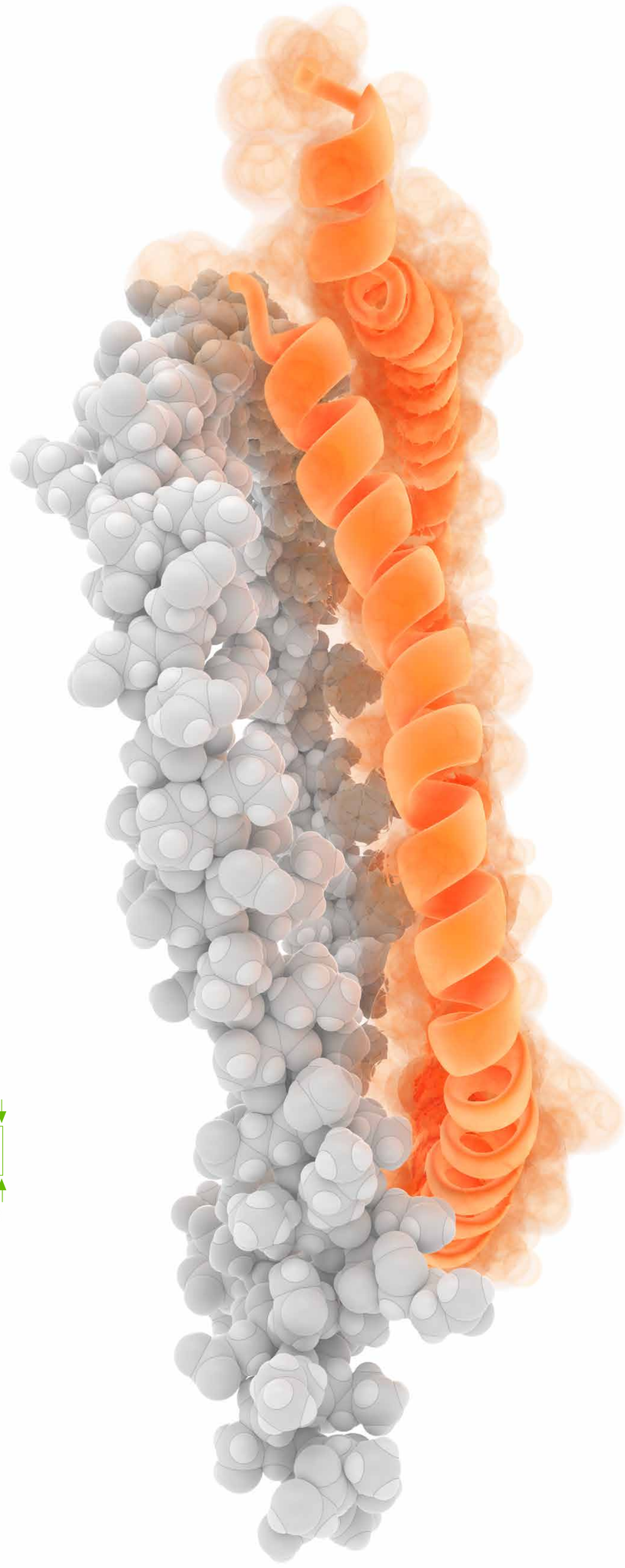


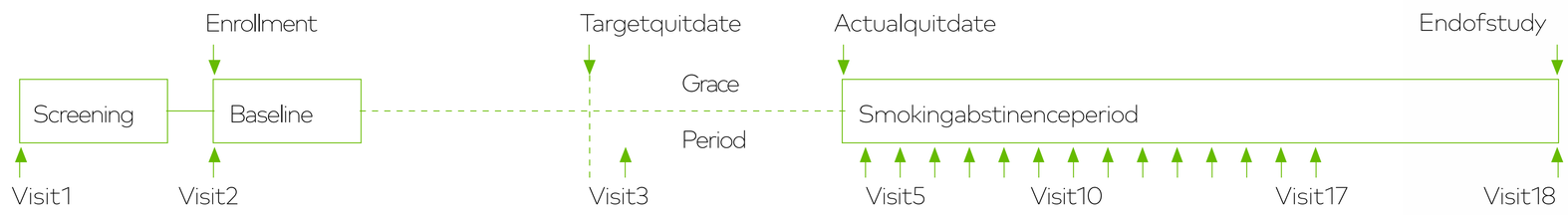
Introduction and Objectives

The harm from smoking mainly results from long-term exposure to Harmful and Potentially Harmful Constituents (HPHCs) contained in cigarette smoke generated by the combustion of tobacco. Smoking Cessation (SC) is the most effective way to reduce the harm and risk of smoking-related diseases to a relative risk level which may approach, overtime, that of never-smokers. In most SC studies, the main focus is on the successful quitting rate of the SC/approach treatment used. However, only limited information on short- to long-term functional/biological changes following SC is available in the literature.

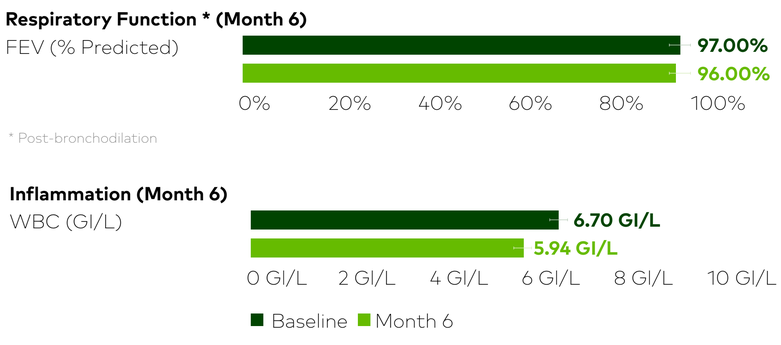
The overall aim of this study was to assess over a one-year period of continuous smoking abstinence the reversibility of the harm related to smoking by assessing changes of Biomarkers of Exposure to HPHCs (BoExp: CO in exhaled breath along with 8 urinary BoExp compounds) and Clinical Risk Endpoints (CREs) which are linked to pathophysiological pathways of smoking-related diseases. Selected CREs were associated with cardiovascular diseases (lipid metabolism, inflammation, platelet function, oxidative stress, endothelial dysfunction, metabolic syndrome, acute cardiovascular effect); respiratory diseases (spirometry); and genotoxicity (total NNAL). These BoExp and CREs were selected according to epidemiological evidence that the endpoints are associated with smoking-related diseases, sensitive to smoking status, and the expectation that these effects are reversed by SC over a period of time within the study duration.

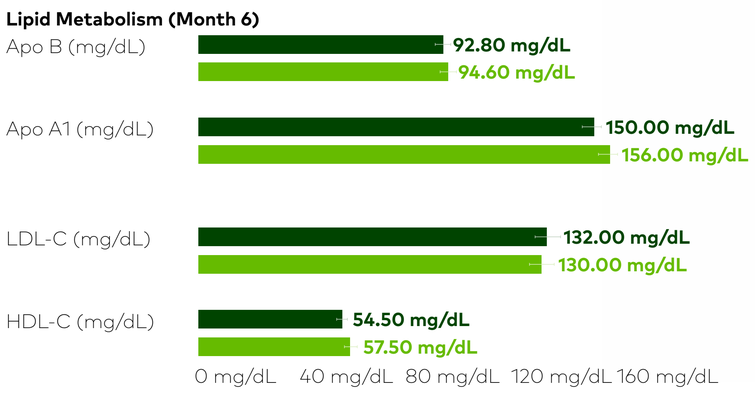
Methods

This was a multi-region, multi-center, ambulatory study conducted in the US, UK, Poland, Germany, and Japan, in healthy adult smokers who were willing to quit smoking and were asked to continuously abstain from smoking during a 52-week (1-year) period. To support the subjects to stop smoking, Nicotine Replacement Therapy (NRT) was provided at subjects' request and used as per country label for up to 3 months. Additionally, SC support, including counseling and behavioral support, was provided throughout the study and upon subjects' request. Data analysis of the full study (1 year continuous SC) is ongoing. This poster presents the data of an interim analysis from data extracted from a subset of 348 subjects of which 272 were continuously smoking abstinent until Month 6 based on the following criteria: self-reported use of tobacco/nicotine containing products, CO breath test ≤ 10 ppm, cotinine test < 100 ng/mL in spot urine (Month 5 onwards), free cotinine concentration < 50 ng/mL in 24-hour-urine (at Month 6). For the whole study, a total of 1,185 smokers willing to quit smoking were enrolled, and 436 successfully completed the study after one year (analysis ongoing).



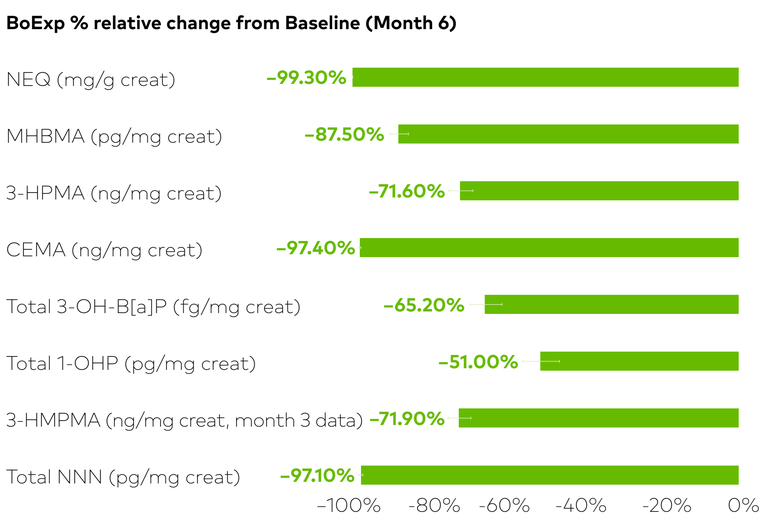
Results





ApoA1 – key component of high density cholesterol particles

Pathway	Endpoint	Relative change from baseline	95% CI
Inflammation	hs-CRP (mg/L)	1.33%	14.5, −10.3
	Homocysteine (µmol/L)	−10.4%	−7.58, −13.1
Platelet function	Platelet count (Gl/L)	5.13%	2.94, 7.36
	Fibrinogen (mg/dL)	−1.55%	0.653, −3.71
	11-DTX-B2 (pg/mg creat)	−26.8%	−20.9, −32.3
Oxidative stress	8-epi-PGF_{2a} (pg/mg creat)	−18.8%	−14.3, −23.1
	Myeloperoxidase (µg/L)	−6.73%	2.17, −14.8
Endothelial Dysfunction	s-ICAM-1 (ng/mL)	−12.3%	−10.0, −14.6
	Albumin urine (mg/g creat)	−0.665%	10.4, −10.6
Acute Cardiovascular Effect	COHb (%)	−74.4%	−71.6, −77.0
Genotoxicity	Total NNAL (pg/mg creat)	−96.5%	−97.0, −95.9



Conclusions

The 6-month interim study results indicate that continuously stopping smoking leads to a substantial reduction in exposure to HPHCs, subsequently resulting in favorable changes in CREs reflecting improvements of multiple mechanisms and biological functions including lipid metabolism, inflammation or oxidative stress. All of these changes are likely to be contributing to the reduction of the risk of developing smoking-related diseases

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Introduction and Objectives

Background

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Main Objectives

The overall aim of this study was to assess over a one-year period of continuous smoking abstinence the reversibility of the harm related to smoking by assessing changes of Biomarkers of Exposure (BoExp) to HPHCs and Clinical Risk Endpoints (CREs) which are linked to pathophysiological pathways of smoking-related diseases. These BoExp and CREs were selected according to epidemiological evidence that the endpoints are associated with smoking-related diseases, sensitive to smoking status, and the expectation that these effects are reversed by SC over a period of time within the study duration.

Study conduct

The study was approved by Independent Ethics Committees and Institutional Review Boards in all participating countries and was initiated in May 2015. The study was conducted according to the principles of ICH-GCP and registered on ClinicalTrials.gov (NCT02432729)

BoExp to HPHCs

Constituents	Biomarker	Biomarker abbreviation
Carbon Monoxide	Carboxyhemoglobin	COHb
Nicotine	Nicotine equivalents: free nicotine, nicotine N-glucuronide, free cotinine, cotinine-N-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-O-glucuronide	NEQ
1,3-Butadiene	Monohydroxy-3-butenyl mercapturic acid	MHBMA
Acrolein	5-(3-hydroxypropyl)-mercapturic acid	3-HPMA
Acrylonitrile	2-cyanoethylmercapturic acid	CEMA
Benzo[a]pyrene	Total 3-hydroxybenzo[a]pyrene	Total 3-OH-B[a]P
Pyrene	Total 1-hydroxypyrene	Total 1-OHP
Crotonaldehyde	3-hydroxy-1-methylpropylmercapturic acid	3-HMPMA
N-nitrosonornicotine	Total N-nitrosonornicotine	Total NNN

Clinical Risk Endpoints

Associated with		Clinical Risk Endpoints	Abbreviation
Cardiovascular diseases:	Lipid Metabolism	High density lipoprotein cholesterol	HDL-C
		Low density lipoprotein cholesterol	LDL-C
		Apolipoprotein A1	Apo A1
		Apolipoprotein B	Apo B
	Inflammation	White blood cell count	WBC
		High sensitivity C-reactive protein	hs-CRP
		Homocysteine	
	Platelet function	Platelets	
		Fibrinogen	
		11-dehydrothromboxane B2	11-DTX-B2
	Oxidative stress	8-epi-prostaglandin F2alpha	8-epi-$PGF_{2\alpha}$
		Myeloperoxidase	MPO
	Endothelial dysfunction	Soluble intercellular adhesion molecule-1	sICAM-1
		Albumin	
	Metabolic Syndrome	Glycosylated hemoglobin	HbA1c
	Acute Cardiovascular effect	Carboxyhemoglobin	COHb
Respiratory diseases:	Spirometry (pre- and post-bronchodilator):	Forced expiratory volume in 1 second	FEV1
Genotoxicity:	Total NNAL	Total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol	Total NNAL

Methods

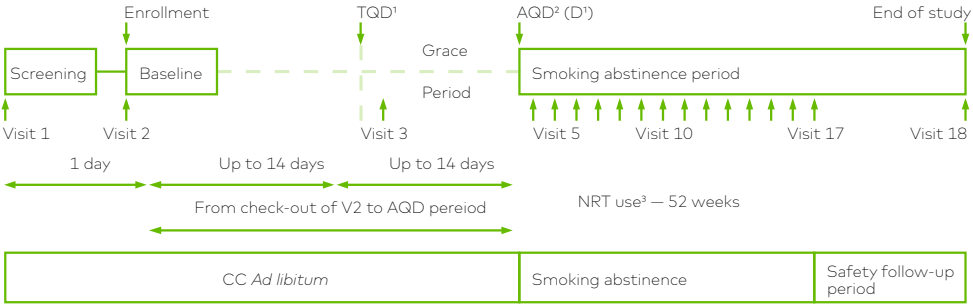
Design

This was a multi-region, multi-center (43 sites), ambulatory study conducted in the US, UK, Poland, Germany, and Japan, in healthy adult smokers who were willing to quit smoking and were asked to continuously abstain from smoking during a 52-week (1-year) period in an ambulatory setting followed by a 28-day Safety Follow-Up period.

To support the subjects to stop smoking, Nicotine Replacement Therapy (NRT) was provided at subjects' request and used as per country label for up to 3 months. Additionally, SC support, including counseling and behavioral support, was provided throughout the study and upon subjects' request.

Participants

① Subjects understood the information provided for the study and signed the Informed Consent Form.
② Subjects were judged healthy by the Investigator.
③ Subjects had no disorders or other conditions that would have jeopardized the subjects' safety or affect the validity of the study results as judged by the Investigator.
④ Subjects were 30 to 65 years old (inclusive).
⑤ Subjects smoked ≥10 commercially available cigarettes per day for the last 12 months and had been smoking for ≥10 years.
⑥ Subjects had negative alcohol and drug tests.
⑦ Female subjects were not pregnant or breast feeding.
⑧ Subjects were willing to quit smoking within the next 30 days.
⑨ Subjects accepted continuous smoking abstinence for 52 weeks.



① Target quit date was within 1–14 days of check-out of visit 2
② Actual quit date was within 14 days of target quit date (grace period with occasional CC use)
③ Use of NRT was only allowed for up to 3 months (+2 weeks) after the start date of NRT.
NRT could be started at any time between target quit date and 1 week after the aqtual quit date
④ Follow-up Phone Call was conducted 4 weeks after visit 17

Results

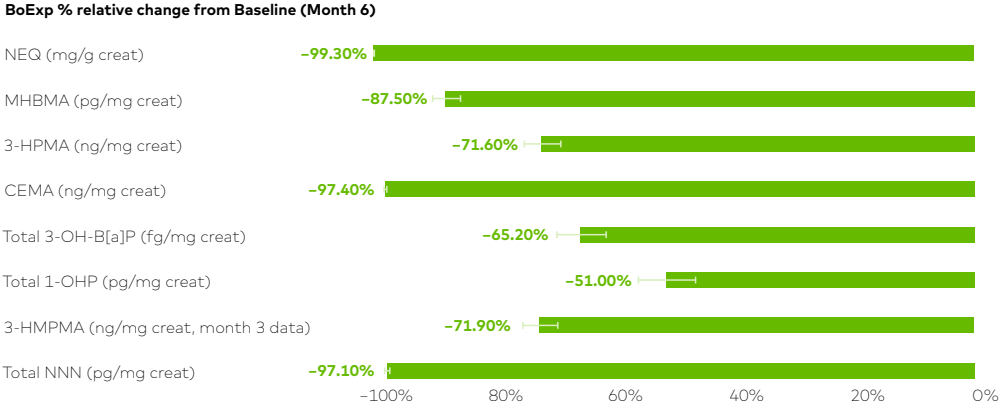
Interim Data Extraction (6 months)

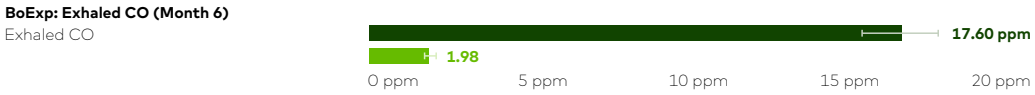
Data analysis of the full study (1 year continuous SC) is ongoing. This poster presents the data of an interim analysis from data extracted from a subset of 348 subjects of which 272 were continuously smoking abstinent until Month 6 based on the following criteria: self-reported use of tobacco/nicotine containing products, CO breath test ≤10 ppm, cotinine test < 100 ng/mL in spot urine (Month 5 onwards), free cotinine concentration < 50 ng/mL in 24-hour-urine (at Month 6).

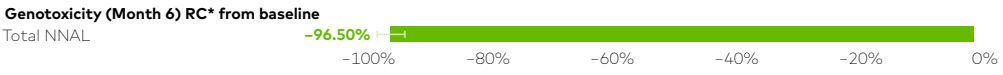
Demographics

For the whole study, a total of 1,185 smokers willing to quit smoking were enrolled, and 436 successfully completed the study after one year (analysis ongoing). The table below presents the demographic characteristics of subjects' data extracted for the interim analysis

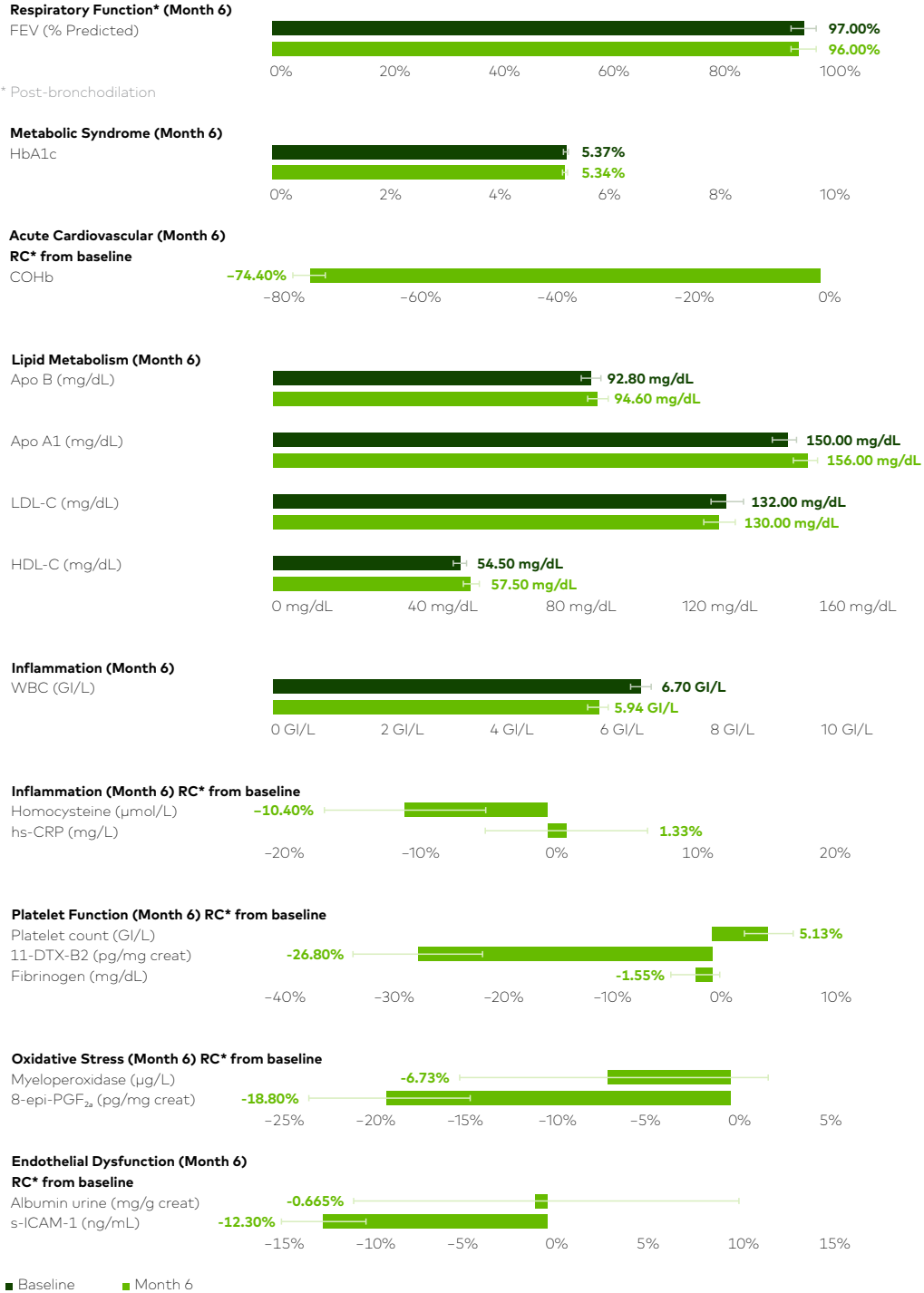
Baseline Characteristics	Abstinent Subjects at Month 6 (N=272)
Male (n; %)	122 (44.9)
Female (n; %)	150 (55.1)
Age (years; Mean [SD])	43.3 (9.13)
BMI (kg/m2; Mean [SD])	25.8 (3.69)
Caucasian (n; %)	230 (84.6)
Not Caucasian (n; %)	42 (15.4)
Smoking intensity over the past year (cig/day; Mean [SD])	17.0 (5.54)
Smoking duration (years; Mean [SD])	22.5 (8.71)







* RC: relative change


Respiratory Function* (Month 6)
FEV (% Predicted)
97.00%
96.00%
0%
20%
40%
60%
80%
100%
* Post-bronchodilation
Metabolic Syndrome (Month 6)
HbA1c
5.37%
5.34%
0%
2%
4%
6%
8%
10%
Acute Cardiovascular (Month 6)
RC* from baseline
COHb
-74.40%
-80%
-60%
-40%
-20%
0%
Lipid Metabolism (Month 6)
Apo B (mg/dL)
92.80 mg/dL
94.60 mg/dL
Apo A1 (mg/dL)
150.00 mg/dL
156.00 mg/dL
LDL-C (mg/dL)
132.00 mg/dL
130.00 mg/dL
HDL-C (mg/dL)
54.50 mg/dL
57.50 mg/dL
0 mg/dL
40 mg/dL
80 mg/dL
120 mg/dL
160 mg/dL
Inflammation (Month 6)
WBC (GI/L)
6.70 GI/L
5.94 GI/L
0 GI/L
2 GI/L
4 GI/L
6 GI/L
8 GI/L
10 GI/L
Inflammation (Month 6) RC* from baseline
Homocysteine (µmol/L)
hs-CRP (mg/L)
-10.40%
1.33%
-20%
-10%
0%
10%
20%
Platelet Function (Month 6) RC* from baseline
Platelet count (GI/L)
11-DTX-B2 (pg/mg creat)
Fibrinogen (mg/dL)
5.13%
-26.80%
-1.55%
-40%
-30%
-20%
-10%
0%
10%
Oxidative Stress (Month 6) RC* from baseline
Myeloperoxidase (µg/L)
8-epi-PGF2a (pg/mg creat)
-6.73%
-18.80%
-25%
-20%
-15%
-10%
-5%
0%
5%
Endothelial Dysfunction (Month 6)
RC* from baseline
Albumin urine (mg/g creat)
s-ICAM-1 (ng/mL)
-0.665%
-12.30%
-15%
-10%
-5%
0%
5%
10%
15%
Baseline
Month 6
* RC: relative change

Conclusions

The 6-month interim study results indicate that continuously stopping smoking leads to a substantial reduction in exposure to HPHCs, subsequently resulting in favorable changes in CREs reflecting improvements of multiple mechanisms and biological functions including lipid metabolism, inflammation or oxidative stress. All of these changes are likely to be contributing to the reduction of the risk of developing smoking-related diseases.

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Our RRPs

Reduced-risk products («RRPs») is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. We have a range of RRPs in various stages of development, scientific assessment and commercialization. Because our RRPs do not burn tobacco, they produce an aerosol that contains far lower quantities of harmful and potentially harmful constituents than found in cigarette smoke.

Competing financial interest

The research described in this brochure was sponsored by the Philip Morris International group of companies

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