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Changes in Biological and Functional Markers after Six Months, in Three Populations: THS 2.2 (*IQOS*®) Users, Continued Smokers, and Smoking Abstinence

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Clinical Assessment Program

Toxic cigarette emissions

Exposure → Molecular changes → Disruption of biological mechanisms → Cell/tissue changes → Disease → Population harm

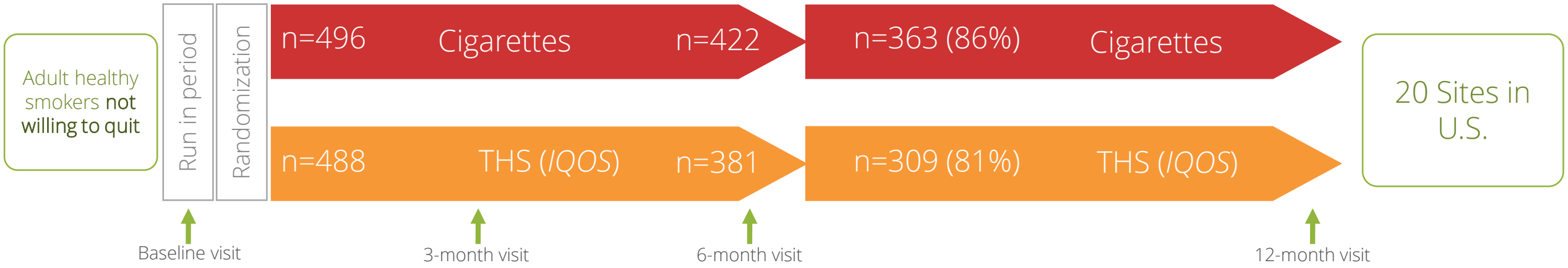
Reduced emissions → Reduced exposure → Reduced adverse health effects

Pharmacokinetics	5-day confinement reduced exposure	90-day ambulatory reduced exposure	Exposure response 6 months + 6 months ambulatory	Smoking cessation 12 months ambulatory
Nicotine absorption similar to cigarette	Exposure to toxicants is reduced Exposure to nicotine is similar		As actually used, exposure to toxicants is reduced, which leads to changes in clinical risk endpoints	

Study Design

Exposure Response Study

ZRHR-ERS-09-US (Clinical trials.gov: NCT026396381) ZRHR-ERS-09-EXT (Clinical trials.gov: NCT02649556)



Smoking Cessation Response Study

SA-SCR-01 (Clinical trials.gov: NCT02432729)

Exposure Response Study

Primary Objective and Co-Primary Endpoints

Smoking cessation

Epidemiologic link to smoking-related disease?

Affected by smoking status

Reversible upon smoking cessation

Co-Primary Endpoints Representative of Pathomechanisms	
Lipid metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial function	sICAM-1
Acute effect	COHb
Inflammation	WBC
Oxidative stress	8-epi-$PGF_{2\alpha}$
Lung function	FEV_1%pred
Genotoxicity	Total NNAL

Assess the changes across a set of the "8 co-primary clinical risk endpoints (CRE)" in smokers who switch from smoking cigarettes to using THS (*IQOS*) as compared with those continuing to smoke cigarettes for six months

Statistical Analysis

Success criteria:

To establish that the risk profile of THS (*IQOS*) is modified compared to cigarettes

1. All co-primary endpoints shift in the direction of cessation
2. ≥ 5 out of 8 CREs are statistically significant (Hailperin-Rüger Approach)

Primary analysis:
THS (*IQOS*) as actually used (> 70%)

Establish modification of risk

Smokers' health profile
Study-wise α=0.05
Test-wise α=1.5625%

Modification of risk is established if ≥ 5/8 significant CREs

Results of the study can be contextualized using the effects for smoking cessation

Main Analysis Population

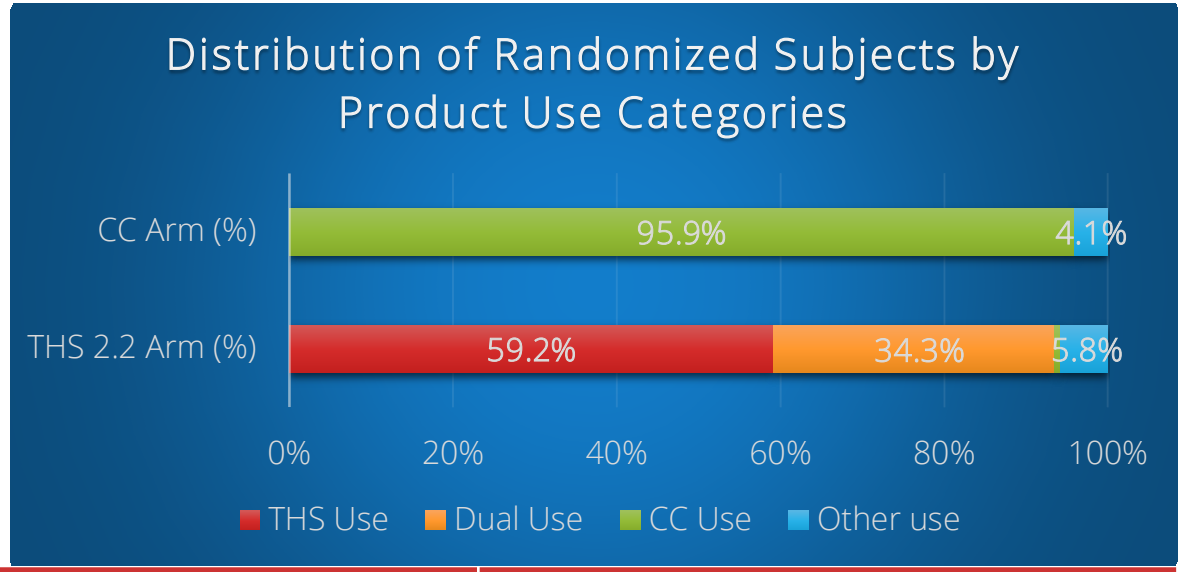
THS Use

- Randomized product use
- ≥ 70% THS use*

CC Use

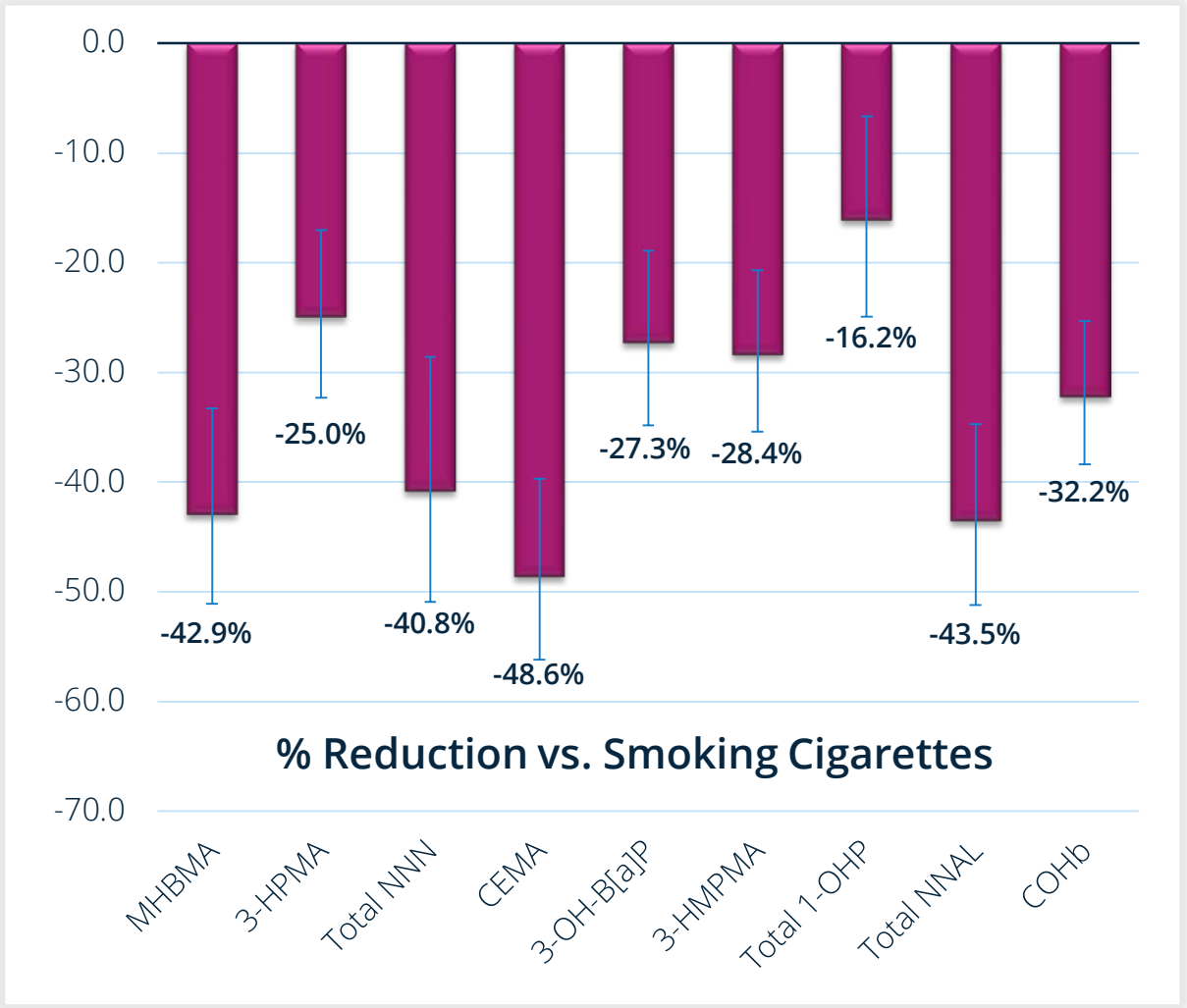
- Randomized product use
- ≤ 1% THS use*

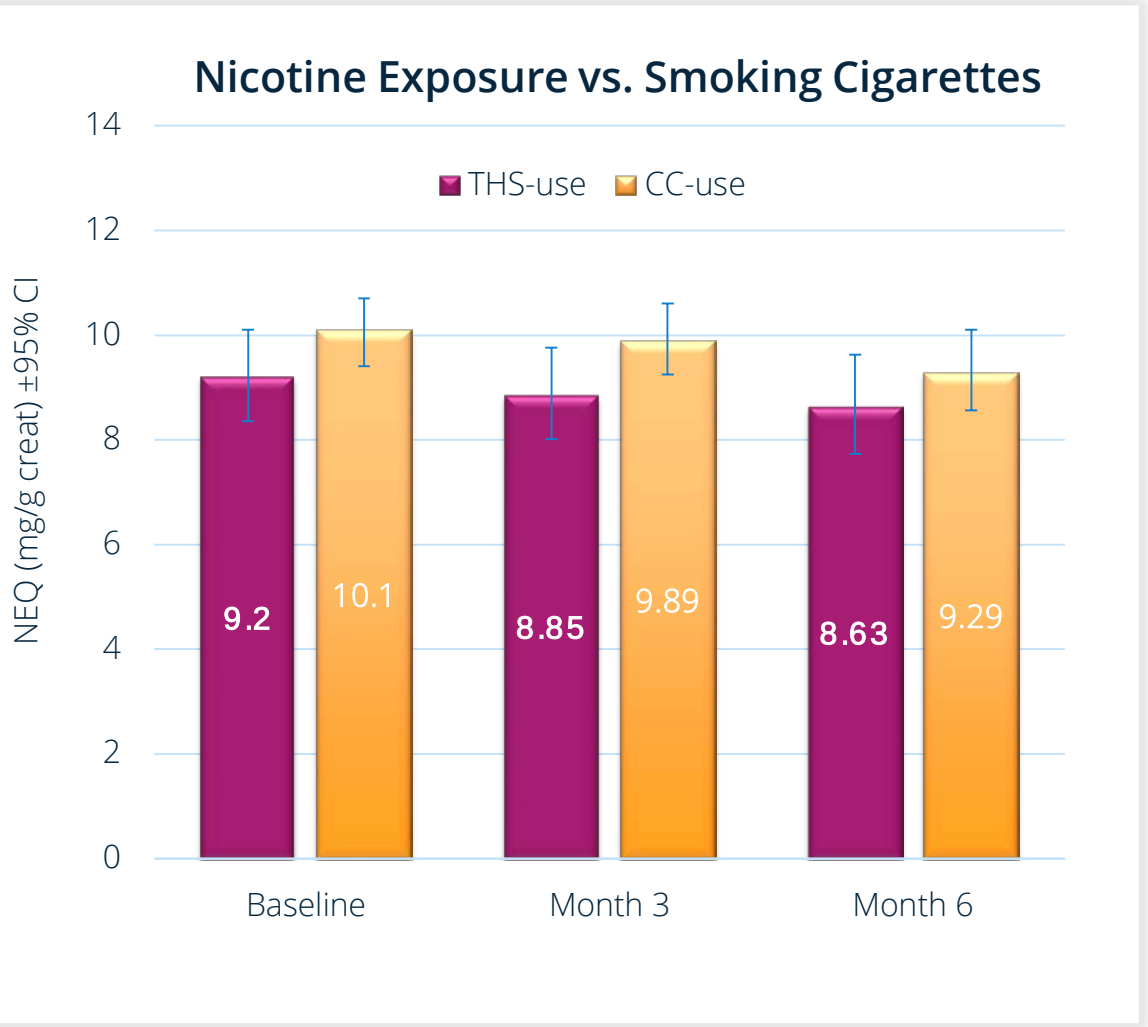
* Calculated over the study and on at least 50% of the study days



Time Period	Product	THS Use Mean/Day (Min, Max)	CC Use Mean/Day (Min, Max)
Baseline	Cigarettes	18.5 (10.0, 65.0)	19.5 (10.0, 90.0)
Post-randomization	THS	16.5 (3.2, 63.0)	< 0.01 (0.0, 0.44)
	Cigarettes	1.95 (0.0, 14.0)	16.8 (3.0, 43.7)
	Overall Tobacco	18.5 (3.2, 63.5)	16.9 (3.1, 43.7)

Reduction of Exposure





Co-Primary Endpoints – Direction of Change

Change from Baseline	THS - Use		Cigarette-Use	
	Mean (95% CI)	Direction	Mean (95% CI)	Direction
HDL – C (mg/dL)	0.74 (-0.95, 2,42)	↑	-2.54 (-3.59,-1.49)	↓
WBC Count (GI/L)	-0.381 (-0.615, -0.148)	↓	0.032 (-0.135, 0.198)	↑
sICAM – 1	-2.87% (-5.22, -0.47)	↓	0.18 (-1.63, 2.01)	↑
11-DTX-B2	-15.6% (-23.0, -7.43)	↓	-9.73% (-16.4, -2.49)	↓
8-epi-PGF2a	-10.6% (-16.2, -4.64)	↓	-4.22% (-8.28, 0.02)	↓
COHb	-34.1% (-41.3, -26.2)	↓	-3.32% (-7.87, 1.45)	↓
FEV1 %pred	-1.34 (-2.15, -0.53)	↓	-2.63 (-3.28, -1.97)	↓
Total NNAL	-51.9% (-59.0, -43.7)	↓	-12.5% (-19.0, -5.63)	↓

All CRE shifted in the same direction as smoking cessation effect

As observed in the literature

Primary Analysis Results – Comparison with Smoking

	Type of Change	Observed Change*	Halperin-Rüger Adjusted CI	1-sided *p*-value (0.0156)	Statistical Significance
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	< 0.001	✓
WBC Count	Difference	–0.420 GI/L	–0.717, –0.123	0.001	✓
sICAM-1	% Reduction	2.86%	–0.426, 6.04	0.030	
11-DTX-B2	% Reduction	4.74%	–7.50, 15.6	0.193	×
8-epi-$PGF_{2\alpha}$	% Reduction	6.80%	–0.216, 13.3	0.018	
COHb	% Reduction	32.2%	24.5, 39.0	< 0.001	✓
FEV_1%pred	Difference	1.28%pred	0.145, 2.42	0.008	✓
Total NNAL	% Reduction	43.5 %	33.7, 51.9	< 0.001	✓

* Observed change presented as LS Mean Difference / Relative Reduction

5 of 8 CREs were statistically significant compared with continued smoking

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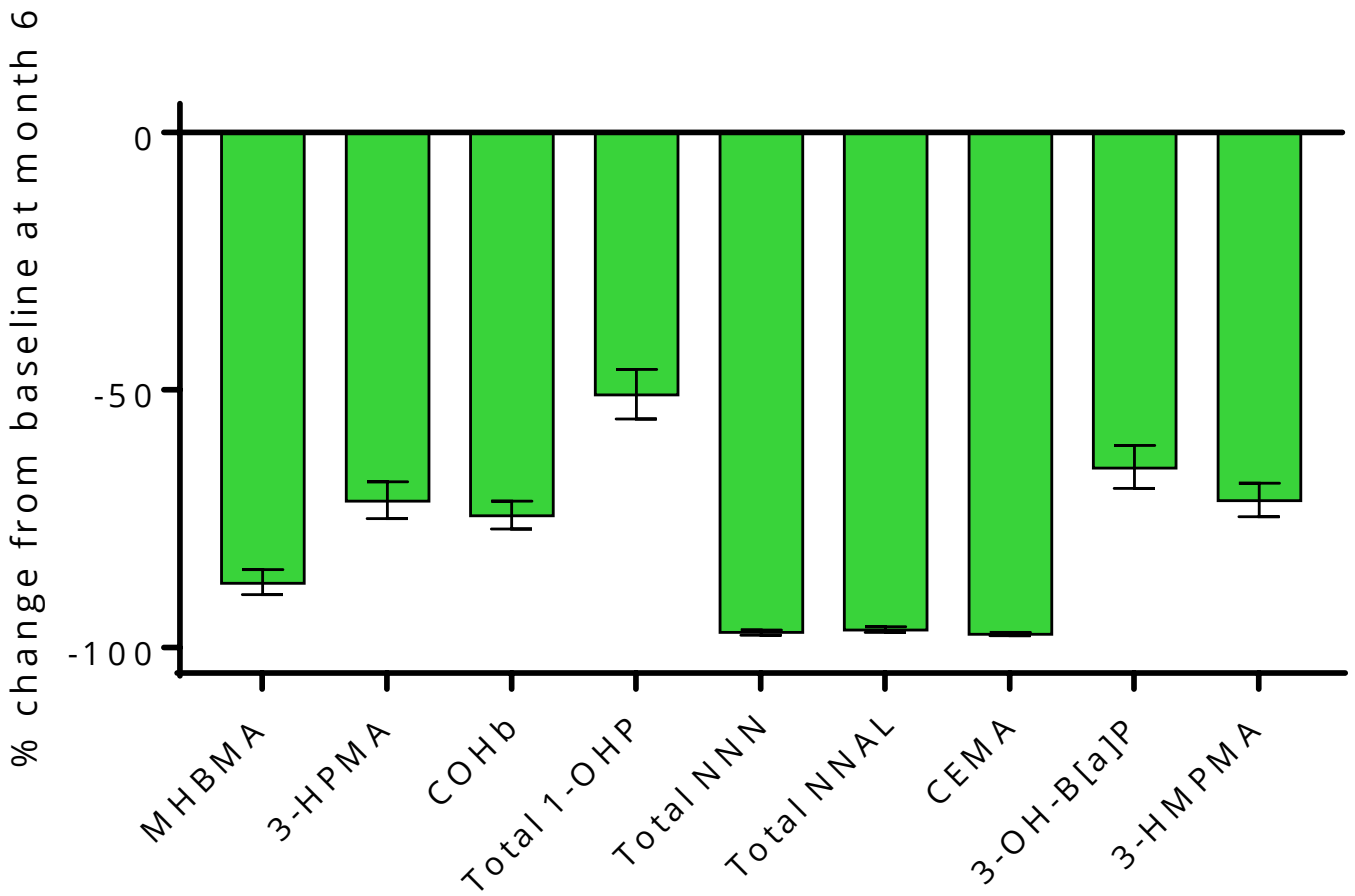
Smoking Cessation Study

Exposure Reduction



After six months of smoking cessation, all biomarkers of exposure to harmful and potentially harmful constituents (HPHC) were reduced with reductions from baseline ranging between 51% and 97.4%.

Endpoint Changes upon Smoking Cessation

Endpoint	Change from Baseline after 6 Months Cessation	95% CI	Directional Change vs. SA (literature)
HDL-C	2.58 mg/dL	1.38, 3.78	↑
Total WBC Count	–0.773 GI/L	–0.960, –0.587	↓
sICAM-1	12.3% reduction[1]	10.0, 14.6	↓
11-DTX-B2	26.8% reduction[1]	20.9, 32.3	↓
8-epi-$PGF_{2\alpha}$	18.8% reduction[1]	14.3, 23.1	↓
COHb	74.4% reduction[1]	71.6, 77.0	↓
FEV_1	–1.24%pred	–2.05, –0.424	↓
Total NNAL	96.5% reduction[1]	95.9, 97.0	↓

[1] % relative change from baseline

Takeaways

THS (*IQOS*), as actually used, reduces exposure to HPHCs

THS (*IQOS*), as actually used, changes CREs in the same direction as cessation

THS (*IQOS*) significantly changes the profile of CREs associated with the risk of smoking-related diseases compared with continued smoking

Although smoking cessation is the best option for smokers to reduce their risk of smoking-related disease, switching to THS (*IQOS*) is a better option than continuing to smoke