Evaluation of biological and functional changes in healthy smokers

after switching from cigarettes to Tobacco Heating System (THS) 2.2 for 6 months

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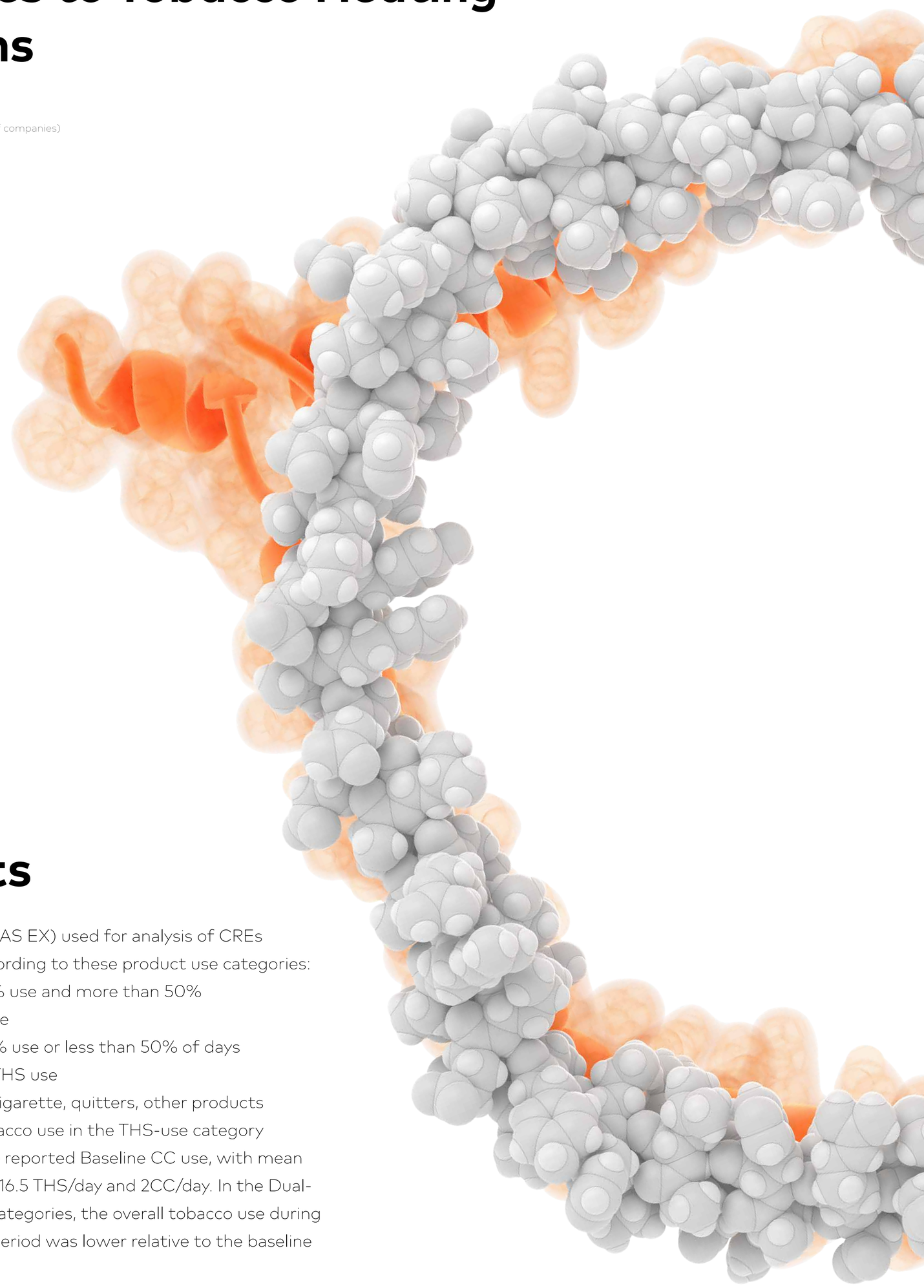


ApoA1 – key component of high density cholesterol particles

Introduction

The most effective way for cigarette smokers to reduce their risk of smoking-related diseases, resulting from long-term exposure to harmful and potentially harmful constituents (HPHCs) in cigarette smoke, is to quit smoking.

Tobacco harm reduction, replacing cigarettes (CC) with less harmful tobacco products, is a complementary approach for smokers who would otherwise continue smoking. THS 2.2 is a novel tobacco product that electrically heats tobacco at temperatures lower than cigarettes, producing substantially lower HPHC levels, while providing a taste, sensory experience, nicotine delivery that parallels smoking. Previous clinical studies demonstrated reduced exposure to HPHCs (approaching levels of smoking abstinence) for smokers who switched to THS 2.2 for up to 3 months.

This study was designed to further substantiate the harm reduction potential in smokers switching to THS, confirming similar changes in biological and physiological health effects (clinical risk endpoints — CREs) to those observed in smokers who stop smoking.

Methods

This was a randomized, controlled, two-arm parallel group, multicenter US study in healthy adult smokers, not willing to quit smoking, who switched from CC to THS 2.2 relative to continuing to smoke CC over 6 month (Figure 1). The primary objective was to demonstrate statistically significant favorable changes (comparable to smoking cessation) in predominant THS 2.2 switchers (THS use category), for at least 5 out of the 8 CREs tested, with THS-use vs CC-use effect evaluated for each CRE, and with all of the CREs moving into the direction of smoking cessation. The analysis was performed using a 1-sided test with the Hailperin–Rüger adjusted type I error (a=1.5625%). These CREs are linked to smoking-related diseases, representative of multiple pathomechanistic pathways that are sensitive to smoking and reversible within 1 year of smoking cessation in the literature

Results

The population (FAS EX) used for analysis of CREs was analyzed according to these product use categories:

① THS-use: >70% use and more than 50% of days THS use
② Dual-use: <70% use or less than 50% of days
③ CC-use: < 1% THS use
④ Other-use: E-cigarette, quitters, other products

The overall tobacco use in the THS-use category was similar to the reported Baseline CC use, with mean of approximately 16.5 THS/day and 2CC/day. In the Dual-use and CC-use categories, the overall tobacco use during the randomized period was lower relative to the baseline CC use.

Exposure to nicotine, as measured by urinary nicotine equivalents, nicotine and cotinine in plasma, was comparable between THS-use and CC-use categories.

Figure 1: study design

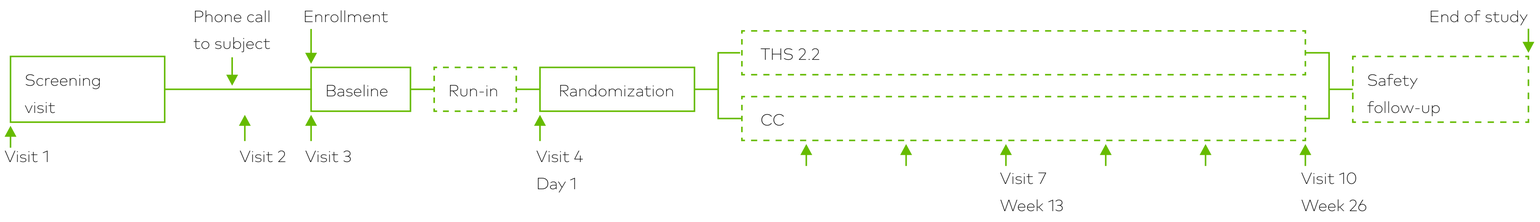


Figure 2: Distribution of randomized subjects by product use categories (FAS-EX) over 6 month

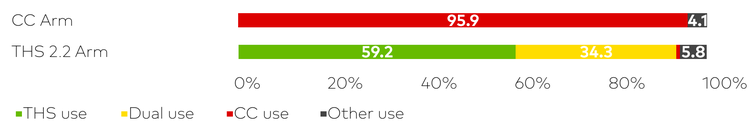
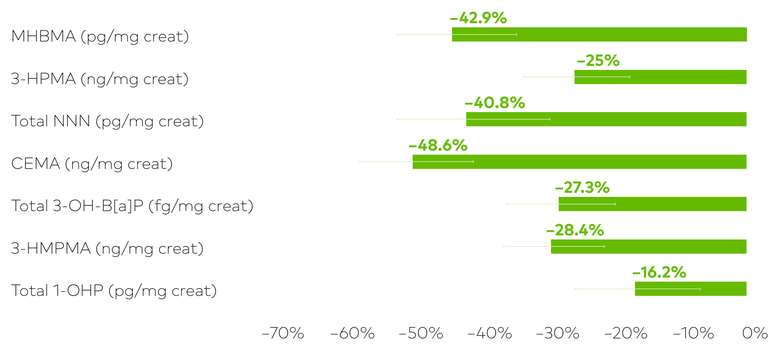


Table 1: Primary analysis of «Smokers' Health Profile» endpoints between THS-use and CC-use categories at month-6 (FAS-EX)

Endpoint	Change from CC-use	LS mean difference/ Relative reduction	96.875% CI	1-sided p-value
HDL-C	Difference	3.09 mg/dl	1.10, 5.09	<0.001*
WBC count	Difference	−0.420 Gl/L	−0.717, −0.123	0.001*
sICAM-1	% reduction	2.86%	−0.426, 6.04	0.030
11-DTX-B_2	% reduction	4.74%	−7.50, 15.6	0.193
8-epi-PGF_{2a}	% 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*

Figure 3: Analysis of the BoExp: Comparison Between THS-use and CC-use Categories at Month 6 BoExp % reduction (Month 6)



Conclusions

This study demonstrated that switching to THS 2.2 results in favorable changes in CREs representative of patho-mechanistic pathways underlying the development of smoking-related diseases. These results indicate a lower risk profile in smokers switching from CC to THS 2.2, an alternative candidate modified risk tobacco product.

* Denotes significant p value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach

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