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The Short-Term Favorable Physiological Effects of Quitting Smoking are Preserved 6 Months after Switching from Cigarettes to Tobacco Heating System

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Background

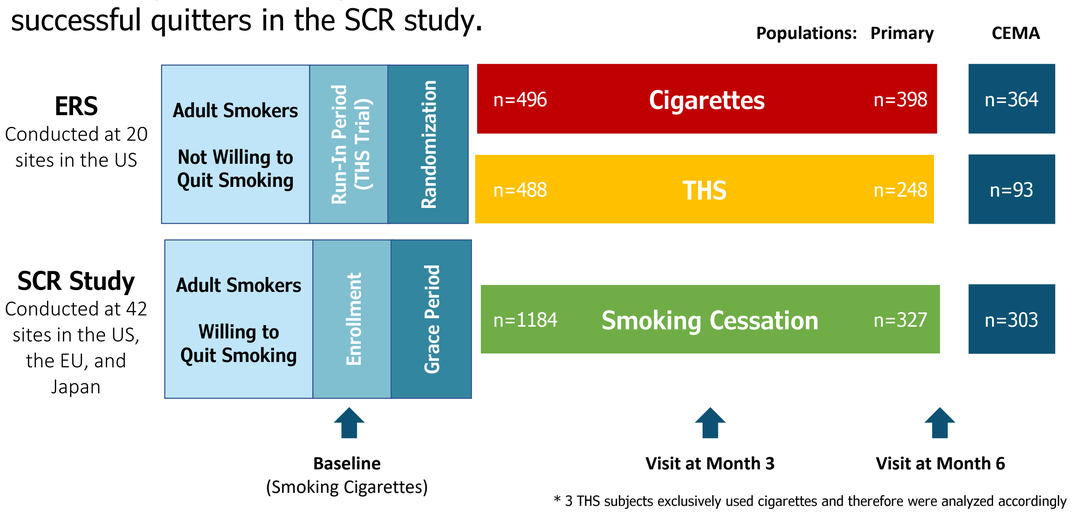
- Smoking cessation is the most effective way to reduce the harm and risks of smoking-related diseases. Therefore, the best choice for any smoker is to quit altogether. However, for those smokers who continue smoking cigarettes, there are now new alternative tobacco products that deliver nicotine without burning tobacco — "smoke-free products".
- Because these products do not burn tobacco, they emit substantially lower numbers and levels of the toxicants contained in cigarette smoke and, therefore, have the potential to reduce the risk of harm caused by smoking. This study looks at one such product, the Tobacco Heating System (THS), a heated tobacco product sold in over 50 markets as IQOS®.
- This research compares the effects observed in our Exposure Response Study (ERS - NCT02396381) with the results observed in our Smoking Cessation Response Study (SCR - NCT02432729).

Study Aim

Using the results from two studies to evaluate the relevance of the favorable changes in biomarkers of potential harm (BoPH) observed in the ERS by assessing how close these changes approach the effect observed following smoking cessation.

Methods

Data were pooled to compare the randomization set from the ERS with data from successful quitters in the SCR study.



* 3 THS subjects exclusively used cigarettes and therefore were analyzed accordingly

Primary Analysis Populations: Based on self-reported product use
- **THS**: defined by >70% of tobacco consumption from THS
- **Cigarettes**
- **Smoking Cessation**: Defined by successful quitting (based on self-reporting, CO breath test, urine cotinine test and total NNAL concentration)

CEMA Analysis Populations: Based on the level of CEMA (biomarker of exposure to acrylonitrile) at 6 months. To biochemically determine the level of cigarette exposure (adherence to THS).
- **THS**: randomized to THS with CEMA level <40 ng/mg creatinine
- **Cigarettes**
- **Smoking Cessation**

Baseline Comparability: Baseline comparability between the THS, cigarette, and cessation groups was assessed by using a propensity score approach based on demographics (sex, age, and race), lifestyle characteristics, baseline cigarette consumption, and BoPH and nicotine levels.
Note: A separate model was developed for each of the two different analysis sets.

Analysis: A repeated measures mixed model was used to evaluate the effects of THS use vs. cigarette smoking and cessation vs. cigarette smoking. The propensity scores were sub-classified on the basis of quintiles of cigarette users (reference product) and adjusted for the propensity scores for cigarettes and cessation.

Preserved effect of cessation following switching to THS was calculated as:

$$\text{Preserved Effect} = \frac{\text{THS vs. Cigarettes}}{\text{Smoking Cessation vs. Cigarettes}}$$

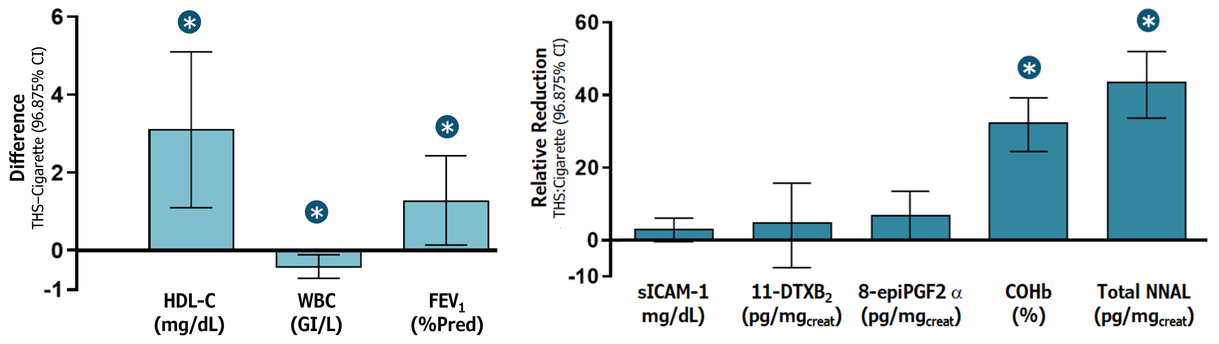
- Assumes a maximum preserved effect of 100% because the THS effect cannot be greater than the smoking cessation effect.
- A non-parametric bootstrap method was used to compute the 95% confidence intervals.

Study Population

	Primary Analysis Population			CEMA Analysis Population		
	THS (n=245)	Cigarettes (n=401)	Cessation (n=327)	THS (n=93)	Cigarettes (n=364)	Cessation (n=303)
% Female	38.4%	41.4%	49.5%	26.9%	37.9%	44.2%
Age (Mean ± SD)	44.2 (9.64)	45.2 (9.52)	44.4 (8.88)	42.5 (9.56)	44.8 (9.65)	44.2 (8.96)
% Caucasian	73.9%	74.1%	77.7%	73.1%	73.4%	76.9%
Smoking Duration Years (Mean ± SD)	25.7 (9.49)	26.9 (10.0)	24.5 (8.86)	24.1 (9.69)	26.4 (10.2)	24.4 (9.06)
Number of cig/day at Baseline (Mean ± SD)	18.5 (7.09)	19.3 (7.68)	18.3 (7.05)	16.9 (7.46)	18.9 (7.60)	17.8 (7.25)

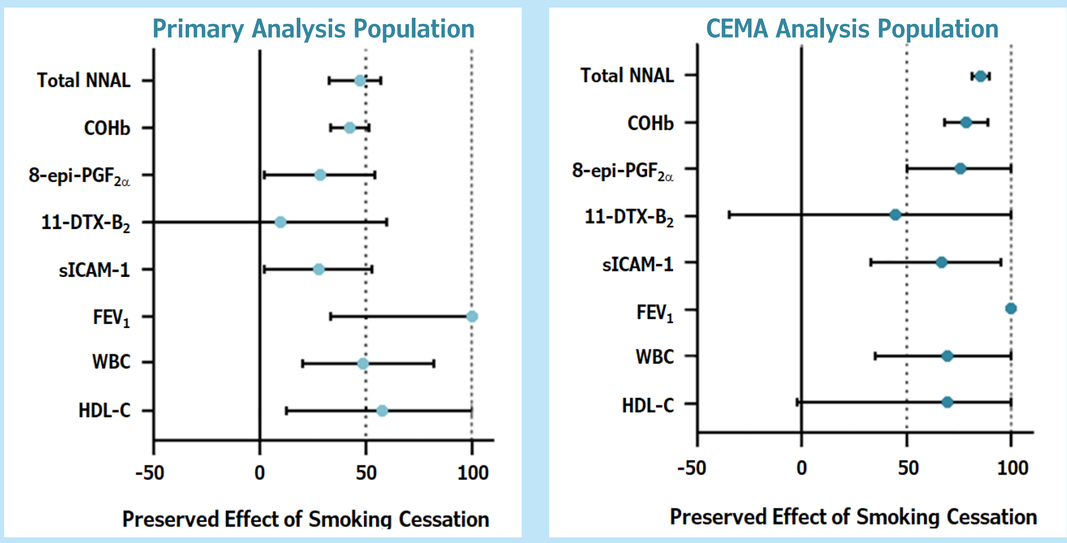
Results

- The results of the ERS showed that smokers who switched from cigarettes to THS had favorable changes for all 8 BoPH, with 5 of the 8 BoPH showing statistically significant improvement relative to continued cigarette smoking.



* Statistically significant (p-value < 0.015625), Hailperin-Rüger adjusted p-value for ≥ 5 of 8 BoPH

- **Primary Analysis Population** (Self-Reported ≥70% THS Use):
  40% of the cessation effect was preserved for 5 of the 8 co-primary BoPH, with the majority (>50%) of the cessation effect being preserved in 2 of the key BoPH (FEV_1 & HDL-C).
- **CEMA Analysis Population** (With Biologically Verified Product Use):
  More than $^2/_3$ of the cessation effect was preserved for all but 1 of the 8 co-primary BoPH.



Conclusions

- Although both quitting smoking and switching to THS resulted in favorable changes in all 8 co-primary BoPH (indicative of smoking-related diseases), the changes were greater following smoking cessation.
- Smokers switching to THS showed a substantially preserved effect of cessation even when the analysis was performed with self-reported product use data, which allows up to 30% concomitant cigarette use. Upon using the biologically verified THS use data (CEMA levels), the majority of the cessation effect was preserved.
- This is additional evidence that smokers who switch to THS have the potential to reduce the risk of smoking-related diseases relative to continued cigarette smoking.

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