Impact of Switching to a Heat-Not-Burn Tobacco Product on CYP1A2 Activity: A Review of Four Clinical Studies

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Introduction and Objectives

The cytochrome P450 1A2 (CYP1A2) enzyme is involved in the metabolism of about 9% of marketed drugs [1]. Cigarette smoking, through exposure to polycyclic amino hydrocarbons (PAH), has been shown to induce CYP1A2 enzyme activity [2], which has been quantified to be 1.72-fold higher in heavy smokers compared to non-smokers [3]. On the other hand, sudden smoking cessation and the subsequent abolishment of CYP1A2 induction has been documented by numerous case reports to be associated with adverse drug reactions [4].

Philip Morris International (PMI) has developed a range of Reduced-Risk Products (RRP) that present, are likely to present, or have the potential to present less risk of harm to adult smokers who switch to these products versus continuing smoking. One of these products is the Tobacco Heating System – THS 2.2 – currently marketed in various markets under the brand name *IQOS*® with *HEETS*®, a candidate Modified Risk Tobacco Product (MRTP) for which PMI has implemented an assessment program which follows the FDA's MRTP Applications Draft Guidance [5].

PMI assessment studies have evaluated both Cyp1a2 gene expression in animal models and CYP1A2 activity in humans. This is due to the fact that switching to THS 2.2 has been shown to reduce the exposure to harmful and potentially harmful smoke constituents (HPHC) by 90%, on average [6], including PAHs.

The aims of this poster are to describe the effects of switching to THS 2.2 on *Cyp1a2* gene expression in pre-clinical and CYP1A2 activity in clinical studies carried out by PMI.

Methods

The pre-clinical exposure studies evaluated protein and mRNA expression changes for *Cyp1a2* in liver across two ApoE $^{-/-}$ mouse studies and two Sprague-Dawley rat exposure studies [7].

In the mouse studies, female ApoE $^{-/-}$ mice were exposed for up to six or eight months to 3R4F cigarette smoke (CS), Sham, or THS 2.2 at matched nicotine concentrations [12,13]. The rat studies represent 90-day inhalation toxicology studies according to OECD TG 413, complemented with systems toxicology methods.

The clinical studies included two five-day [8,9] and two 90-day reduced exposure studies [10-12].

- The five-day studies described the changes in CYP1A2 enzymatic activity on Day 5 in smokers i) switching from regular cigarettes to THS 2.2 with regular (non-menthol) heatsticks, ii) continuing to smoke regular cigarettes, and iii) smoking abstinence (SA).
- The 90-day studies described the change in CYP1A2 enzymatic activity (on Days 5 & 90) in smokers i) switching from mentholated cigarettes to THS 2.2 with menthol heatsticks (M), ii) continuing mentholated cigarette smoking, and iii) SA. The results presented refer to the full analysis set (FAS) populations.
- The measurement of enzyme activity was assessed through paraxanthine and caffeine (CAF) plasma molar concentrations approximately six hours (± 15 minutes) after the intake of either a cup of coffee made from 4.2 g (± 10%) regular instant coffee (Nescafé Gold Instant; Nestlé; Germany; CAF content: 72 mg/2 g) with 150 ml ±10 ml water, or, after the intake of one Tomerumin® CAF tablet with 150 ml ± 10 ml of water.

Results

A summary of the studies assessing protein and mRNA expression changes for CYP1A2 in liver across two ApoE$^{-/-}$ mouse and two Sprague-Dawley rat exposure studies are described in Table 1.

- Across the four *in vivo* studies, CS resulted in a significant upregulation of *Cyp1a2* levels in three of the studies. The significant fold changes compared to Sham-exposed animals had a maximum of 1.76 for protein and 1.45 for mRNA expression changes.
- In contrast to CS, THS 2.2 (M) aerosol exposure did not result in significant differential expression of *Cyp1a2* across the four studies.
- In addition, the ApoE $^{-/-}$ mouse studies included cessation (CESS) groups, exposing the mice for two or three months to 3R4F CS before changing the exposure to fresh air (Table 1, Figure 1).
- The first ApoE $^{-/-}$ mouse study also included a group switching from 3R4F CS to THS 2.2 aerosol (SWITCH). Upon both cessation and switching to THS 2.2, the upregulation of *Cyp1a2* observed upon CS exposure reverted to levels close to Sham.

Table 1. *Cyp1a2* expression in mouse and rat liver upon CS and THS 2.2 (M) exposure.

Cyp1a2 expression in liver	CS Group[1]	FC[2] mRNA	FC[2] protein	THS 2.2 (M) Group[1]	FC[2] mRNA	FC[2] protein	CESS/SWITCH Group[1]	FC[2] mRNA	FC[2] protein
ApoE $^{-/-}$ mouse study #1	3R4F 6m	1.39	**1.60***	THS 2.2 6m	1.05	0.96	CESS 6m	1.04	1.01
	3R4F 8m	1.44	**1.76***	THS 2.2 8m	1.11	1.00	CESS 8m	1.07	1.00
							SWITCH 6m	1.05	1.02
							SWITCH 8m	1.09	1.01
ApoE $^{-/-}$ mouse study #2	3R4F 6m	**1.35***	**1.38***	THS 2.2 6m	1.06	1.05	CESS 6m	1.02	0.97
OECD 90-day rat (regular)	3R4F 23-F-90d	1.11		THS 2.2 23-F-90d	1.07				
	3R4F-23-M-90d	1.90		THS 2.2 23-M-90d	1.25				
OECD 90-day rat (menthol)	3R4F 23-F-90d	1.37	1.33	THS 2.2 M 23-F-90d	0.86	1.07			
	3R4F 23-M-90d	1.58	1.23	THS 2.2 M 23-M-90d	1.19	1.12			
	1XMIS 23-F-90d	1.44	1.38						
	1XMIS 23-M-90d	1.52	**1.30***						
	2XMIS 23-F-90d	**1.45***	**1.33***						
	2XMIS 23-M-90d	1.59	1.25						

LEGEND
1: Group comparisons versus Sham-exposed animals labeled as item – ; 2: Expression fold changes versus Sham-exposed animals; *, False discovery rate-adjusted p-value < 0.05; Included studies: ApoE $^{-/-}$ mouse study #1 (32, 33), ApoE $^{-/-}$ mouse study #2, OECD 90-day rat THS 2.2 (34), and OECD 90-day rat THS 2.2. Group labels: Item – Time point [mouse studies]; Item – Concentration (µg nicotine/L) – Sex (M, male; F, female) – Time point [rat studies]; CESS, cessation; SWITCH, switching from 3R4F CS to THS 2.2 (M) aerosol.

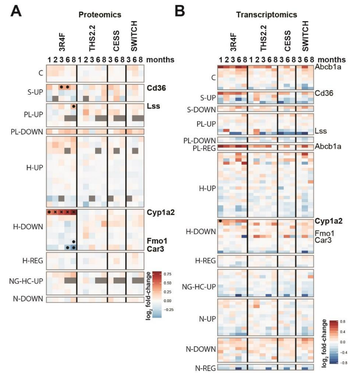

Figure 1. *Cyp1a2* expression in mouse liver upon CS and THS 2.2 exposure.

Within a broad liver toxicity panel, CS (3R4F) particularly affected expression levels of *Cyp1a2* compared with Sham-exposed animals. In contrast, *Cyp1a2* levels were not affected upon THS 2.2 exposure or upon cessation (CESS) or switching (SWITCH). Included liver toxicity categories: C, cholestasis; S-UP/DOWN, steatosis (up/down); PL-UP/DOWN, phospholipidosis (up/down); H-UP/DOWN/REG, hepatotoxicity (up/down/regulated); NG-HC-UP/DOWN, nongenotoxic hepatocarcinogenicity (up/down); N-UP/DOWN, necrosis (up/down).

Figure adapted from [15].

- A summary of the demographic characteristics of the clinical study participants can be found in Table 2, and a summary of the clinical study findings is described in Table 3.
- All clinical studies found a decreased activity of CYP1A2 in smokers who switched to THS 2.2 and to SA compared to continued smoking. These changes were seen at both five days and 90 days of follow up. There were no differences in the levels of CYP1A2 activity between smokers who switched to THS 2.2 and those who were abstinent.

Table 2. Demographic characteristics of clinical study participants.

	5-day study in Poland	5-day study in Japan	90-day study in Japan	90-day study in US
Number of participants				
THS 2.2 arm (N)	80	80	78	80
CC arm (N)	41	40	42	41
SA arm (N)	39	40	40	39
Sex				
THS 2.2 arm (men %/women %)	48.8/51.2	50/50	57.7/42.3	60/40
CC arm (men %/women %)	51.2/48.8	50/50	59.5/40.5	58.5/41.5
SA arm (men %/women %)	51.3/48.7	50/50	55/45	61.5/38.5
Mean age				
THS 2.2 arm (SD)	35.4 (9.4)	37.6 (11.7)	37.1 (10.6)	39.2 (11.7)
CC arm (SD)	32.6 (10.1)	37.2 (11.7)	37.4 (11.2)	33.7 (10.2)
SA arm (SD)	33.6 (11.5)	35.9 (10.6)	37.0 (10.0)	38.8 (11.4)

Table 3. CYP1A2 activity in smokers, switchers to THS 2.2, and abstainers in PMI's clinical studies (FAS).

Study	Baseline			Day 5			Day 90		
	THS 2.2	CC	SA	THS 2.2	CC	SA	THS 2.2	CC	SA
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
5-day Poland	112.4 (104.4-120.4)	110.3 (100.7-119.8)	113.1 (98.4-127.9)	91.7 (85.2-98.2)	123.0 (112.1-134.0)	94.5 (82.6-106.3)	NA	NA	NA
5-day Japan	81.3 (73.9-88.8)	78.2 (69.8-86.6)	77.6 (69.6-85.6)	56.6 (52.3-60.8)	76.5 (68.7-84.3)	52.3 (47.4-57.1)	NA	NA	NA
90-day Japan	76.2 (70.8-81.5)	73.3 (66.6-80.0)	78.0 (70.0-86.0)	58.3 (54.4-62.2)	79.8 (72.0-87.7)	58.5 (52.7-64.3)	58.6 (54.6-62.6)	83.9 (73.8-94.1)	64.3 (56.5-72.1)
90-day US	124.7 (115.7-133.6)	128.5 (116.6-140.4)	128.5 (115.1-141.8)	82.1 (75.3-88.9)	129.3 (118.5-140.1)	91.5 (79.6-103.3)	83.2 (74.7-91.6)	111.6 (97.3-125.9)	101.3 (87.1-115.5)

Discussion

The pre-clinical studies showed that being exposed to THS 2.2 aerosol did not result in significant differential expression of *Cyp1a2* across the four studies. The clinical studies assessing CYP1A2 enzymatic activity in smokers switching to THS 2.2 and after smoking cessation showed reductions in CYP1A2 in switchers to THS 2.2 comparable to those seen in those who quit smoking.

Smoking of 10–20 cigarettes per day appears to be a weak to moderate inducer of CYP1A2, depending on the contribution ratio values for CYP1A2 (CRCYP1A2) of the substrate drug. In smokers, drugs that are primarily metabolized by CYP1A2 will have faster systemic clearance as a result of enzyme induction [2].

On the other hand, there is substantial evidence showing that smoking cessation results in downregulation of the CYP1A2 enzyme, as it has been shown to reverse induced hepatic enzyme levels to normal [4]. After sudden smoking cessation, initial caffeine clearance decreased, and the apparent half-life of CYP1A2 activity was 38.6 hours (27.4–54.4 hours). Therefore, after smoking cessation, there might be a need for dose adjustment of drugs metabolized by CYP1A2.

Data from case reports of smokers switching to e-cigarette use have shown a similar decrease in CYP1A2 activity.

There are multiple cases of elevations of CYP1A2-metabolized drug levels in those who stopped smoking, in particular in those who were taking Clozapine. The same was observed in those who switched to e-cigarettes.

Nicotine replacement treatment to assist smoking cessation will not improve this effect, because the effect on hepatic microsomal enzymes is related not to nicotine but rather to PAHs.

Even though current cessation guidelines do not mention the need to adjust the dosage of CYP1A2-metabolized drugs after smoking cessation, this is recommended in clinical practice, especially for drugs with a narrow therapeutic index. Particularly, increased plasma concentrations of these drugs after smoking cessation may cause serious clinical consequences [16]. Due to the short turnover time of CYP1A2, empirical dose reduction may be necessary within two to three days after smoking cessation.

Because both CYP1A2 expression and activity reductions have been shown to be comparable in quitters and those switching to THS 2.2 due to reduction in exposure to PAHs [6], the same recommendations for dosage adjustment for CYP1A2-metabolized drugs that guarantee a reduction in the exposure to PAHs should be made upon switching to RRPs.

Conclusions

Switching to RRPs reduces CYP1A2 activity to a similar extent as smoking cessation. The same recommendations for dose modification made for smokers upon cessation should be extrapolated to smokers switching to THS 2.2 or other RRPs.

End-users and quitters should be made aware of any unwanted effects associated with smoking cessation that might affect a smoker's attempt to quit as well as the potential effects of switching to RRPs.

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