EVIDENCE RELATED TO THE IMPACT ON TOBACCO USERS

EVALUATION OF CLINICAL AND BEHAVIORAL PHARMACOLOGICAL STUDIES

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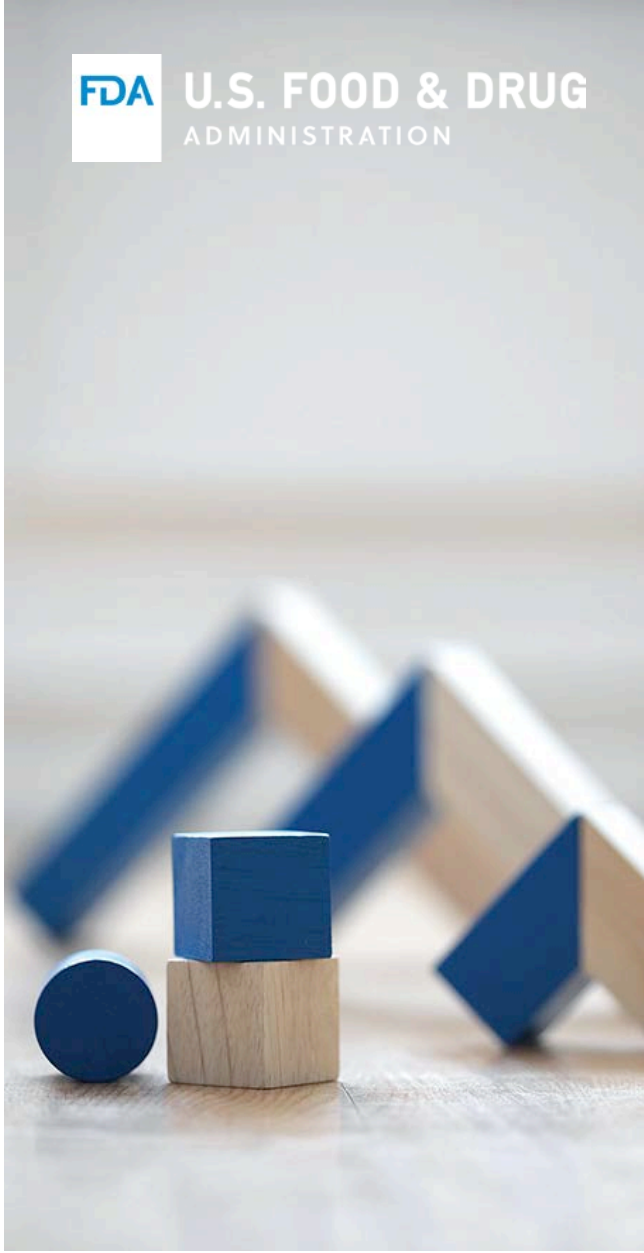

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OUTLINE

Study Overview

- Pharmacokinetic and Pharmacodynamic (PK/PD) Studies
- Reduced Exposure (REX) Studies
- Actual Use Study

Results

- Nicotine Exposure
- Product Use/Consumption
- Abuse Liability

Summary and Conclusions

ACRONYMS

- PK/PD: Pharmacokinetic and Pharmacodynamic
- REX: Reduced Exposure
- QSU-Brief: Questionnaire of Smoking Urges
- MCEQ: Modified Cigarette Evaluation Questionnaire
- MNWS: Minnesota Nicotine Withdrawal Scale
- FTND: Fagerström Test for Nicotine Dependence
- NEQ: nicotine equivalents
- IQOS = THS2.2 (The applicant uses different terms to describe the products tested in the studies presented below, including the Tobacco Heating System [THS]. In a March 2017 amendment to the applications, the applicant stated that THS2.2 is the investigational product name for the product they plan to market as the *IQOS* system.)

STUDY OVERVIEW

Four **Pharmacokinetic/Pharmacodynamic (PK/PD) Studies**

- Objective: compare the rate and extent of nicotine uptake
- Design: Single use, randomized, 2-period, 4-sequence, cross-over study with *ad libitum* use after 24-hour abstinence

Study ID	Location	Tobacco Flavor	THS2.2 vs. Own-Brand Cigarette	THS2.2 vs. Nicotine Replacement Therapy
ZRHR-PK-01-EU	Ireland	Regular	n=42	n=18 (NRT: nasal spray)
ZRHR-PK-02-JP	Japan	Regular	n=42	n=18 (NRT: nicotine gum)
ZRHM-PK-05-JP	Japan	Menthol	n=43	n=18 (NRT: nicotine gum)
ZRHM-PK-06-US	U.S.	Menthol	n=41	n=17 (NRT: nasal spray)

- Outcome Measures: nicotine PK in plasma (C_{max} and $AUC_{0\text{-last}}$), craving (QSU-Brief), reinforcing effects (MCEQ)

STUDY OVERVIEW

Four **Reduced Exposure (REX) Studies**

- Objective: investigate systemic exposure to 16 biomarkers of HPHCs
- Design: Randomized, open-label, 3-arm parallel group study, with *ad libitum* use (recruitment: 80 THS2.2, 40 own-brand cigarettes, 40 smoking abstinence)

Study ID	Location	Tobacco Flavor	# Randomized	Duration
ZRHR-REXC-03-EU	Poland	Regular	n=160	5 days confinement
ZRHR-REXC-04-JP	Japan	Regular	n=160	5 days confinement
ZRHM-REXA-07-JP	Japan	Menthol	n=160	5 days confinement, 85 days ambulatory
ZRHM-REXA-08-US	U.S.	Menthol	n=160	5 days confinement, 85 days ambulatory

- Outcome Measures: biomarkers of exposure (BOE), biomarkers of potential harm (BOPH), exposure to nicotine, tobacco product consumption, topography, subjective effects (e.g., QSU-Brief, MNWS, FTND, MCEQ)

STUDY OVERVIEW

One **Actual Use Study**

- Study ID: THS-PBA-07-US
- Objective: investigate how smokers use THS2.2 in naturalistic setting
- Design: Single group, prospective, observational study (n~1000)
  - 1 week baseline (own-brand cigarette), 6 weeks THS2.2
  - Can request regular, menthol, or both flavors
- Location: U.S.
- Outcome measures: tobacco product consumption, hypothetical purchase question, product misuse

Note: patterns of use will be discussed in a separate presentation

LIMITATIONS OF STUDY DESIGNS

PK/PD Studies

- Participants are a convenience sample of ≥10 cpd smokers with no quit intent in the next 6 months (not generalizable, not nationally representative)

REX Studies

- Participants are a convenience sample of ≥10 cpd smokers with no quit intent in the next 6 months (not generalizable, not nationally representative)
- Longer-term studies were only conducted in menthol smokers (not generalizable)
- THS2.2, but not cigarettes, are provided free of charge (may inflate use rates)

Actual Use Study

- Participants are convenience sample with no quit intent in the next 30 days (not generalizable, not nationally representative)
- THS2.2, but not cigarettes, are provided free of charge (may inflate use rates)

STUDY RESULTS

NICOTINE EXPOSURE

PK/PD Studies

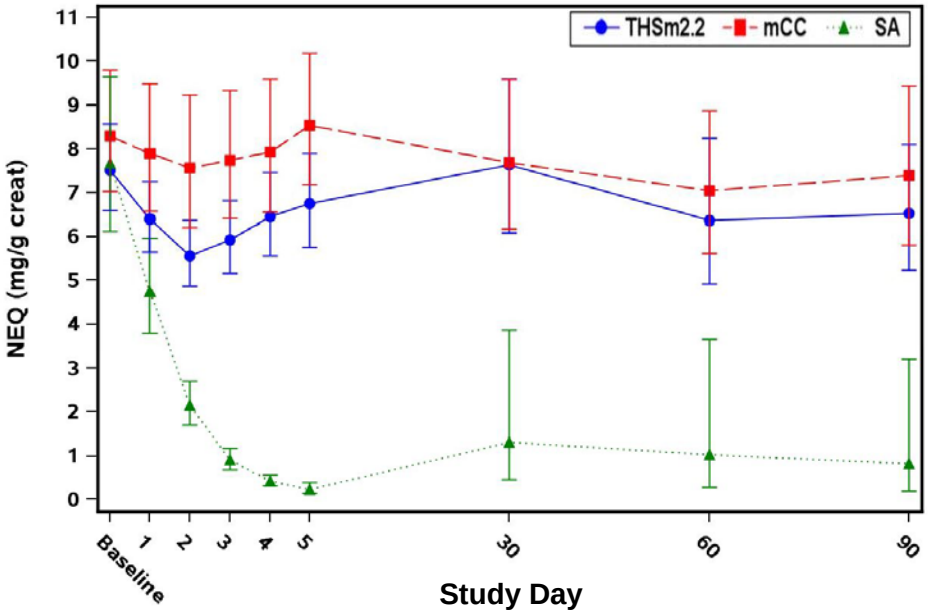
- After a single use, systemic exposure to nicotine was lower for THS2.2 relative to cigarette smoking in two studies (U.S. & Ireland), but similar for THS2.2 relative to cigarette smoking in two studies (Japan)

- These differences may be explained by:
  - Different nicotine yields of cigarette comparators used in different countries
  - Greater THS2.2 experience in Japanese population
  - Genetic differences in nicotine metabolism

NICOTINE EXPOSURE

REX Studies

- Urinary nicotine equivalents (NEQ) were measured in 24-hour urine daily (Days 1-5, 30, 60, and 90).
- Systemic exposures to nicotine (NEQ) were similar between the THS2.2 and cigarette arms during the ambulatory periods.



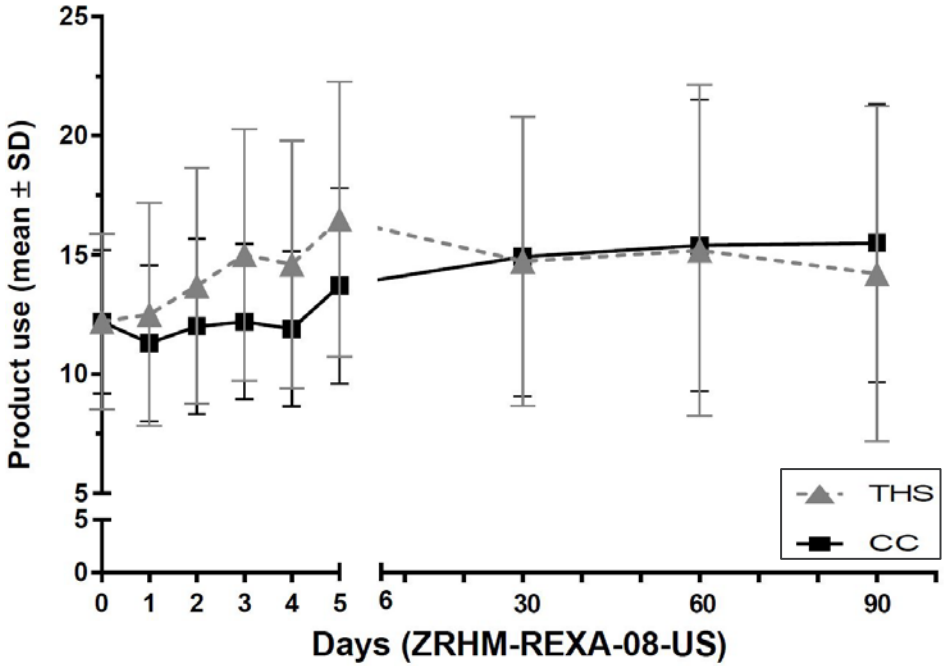
Source: ZRHM-REXA-08-US

Outcome Limitations: Dual use was evident in ambulatory studies, but there was no stratification of complete vs. incomplete switchers (limits interpretation for nicotine/ biomarker exposure)

AVERAGE PRODUCT CONSUMPTION

Number of products used per day

- **REX Studies**: small changes in # cigarettes or *HeatSticks* used for both study arms
- **Actual Use Study**: small decrease in # cigarettes and *HeatSticks* used per day



Source: Section 6.2.2 of MPRTA

Outcome Limitations: Consumption data during the REX ambulatory period and during the Actual Use Study are based on self-report (potential for missing/incorrect data)

COMPLIANCE

Compliance to THS2.2:
Rates of near-exclusive (e.g., >95% THS2.2) use, in the last study period:

- **REX Studies**
  - REX-07-JP: 85.9%
  - REX-08-US: 63.8%
- **Actual Use Study**
  - PBA-07-US: 7.5%

Outcome Limitations: Consumption data are based on self-report (potential for missing/incorrect data); in the REX studies, non-compliance may be under-reported; in the Actual Use study, subjects do not receive exclusive use instructions and do not use product exclusively in short-term confinement setting.

TOPOGRAPHY

REX Studies

- Cigarette arm: topography measures generally stable over time
- THS2.2 arm: differences on a variety of topography metrics, explained as adaptation to the new product (intrinsic properties and differences in nicotine delivery, flavor, etc.)

Considerations:

- THS2.2 limits smoking to a maximum of 14 puffs & 6 minutes of use
- Average puff number exceeded 14 puffs due to higher measurement sensitivity by study topography device (HPT SODIM SPA/M) vs. THS2.2 holder (measures differences in flow rate vs. differences in temperature)
- Applicant states that participants may overcome 14-puff limit by using a “multipuff” technique (varying puff intensity)

ABUSE LIABILITY: DEPENDENCE (QSU-BRIEF, MNWS, FTND)

PK/PD Studies

- Relief from craving (QSU-Brief) was similar between THS2.2 and cigarettes over time

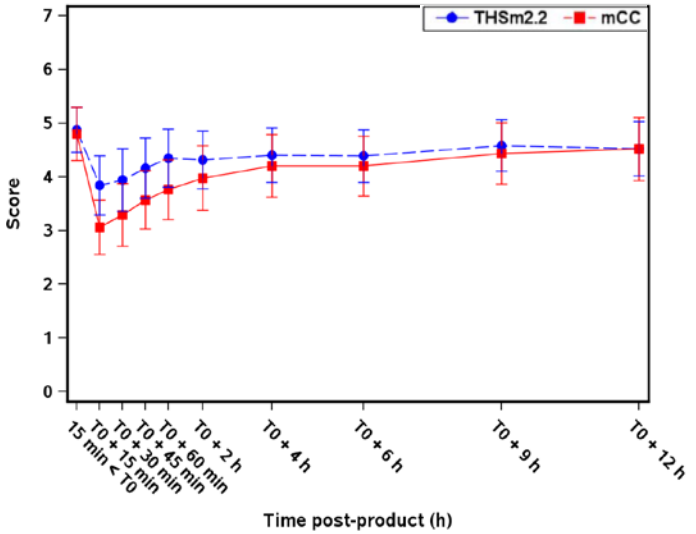
REX Studies

- Relief from craving (QSU-Brief) & withdrawal (MNWS) were similar between THS2.2 and cigarette study arms
- No difference in dependence severity (FTND) between study arms at Day 90

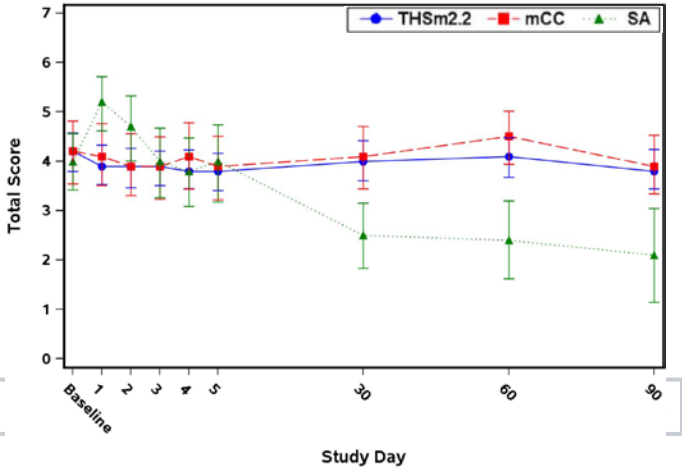
Outcome Limitations: no validation of translated questionnaires, questionnaires were not modified to replace references to cigarettes with *HeatSticks/IQOS*, no assessment of relationship between subjective measures and behavior

QSU Brief Total Score

A. Source: ZRHM-PK-06-US



B. Source: ZRHM-REXA-08-US



ABUSE LIABILITY: REINFORCEMENT (MCEQ)

PK/PD Studies

- After single use: THS2.2 scored lower on four of five MCEQ subscales: *Smoking Satisfaction* (4 studies), *Enjoyment of Respiratory Tract Sensations* (4 studies), *Psychological Reward* (2 studies), *Craving Reduction* (2 studies) compared to own-brand cigarettes
- Cigarettes and THS2.2 did not differ on the *Aversion* subscale.

REX Studies

- End of 5 Days: THS2.2 scored lower on four of five MCEQ subscales: *Smoking Satisfaction* (3 studies), *Enjoyment of Respiratory Tract Sensations* (1 study), *Psychological Reward* (1 studies), *Craving Reduction* (2 studies)
- End of 90 Days: no differences on any subscales between study arms

Outcome Limitations: no validation of translated questionnaires, no assessment of relationship between subjective measures and behavior

ABUSE LIABILITY: PRODUCT VALUATION

Actual Use Study

Participants were asked about their likelihood to purchase *IQOS* "if the iQOS device were available for $79.99 and a pack of Marlboro HeatSticks were available at a price comparable to a pack of Marlboro cigarettes."

Results

- Full sample (n=987): ~20% reported that they "probably would" or "definitely would" buy *IQOS*
- Subsample of participants using product at least 70% of the time (n=138): ~50% reported that they "probably would" or "definitely would" buy *IQOS*

Outcome Limitations: unclear if participants assumed that they had already purchased the *IQOS* system and were being asked about buying *HeatSticks* only, or if they were being asked about buying both the *IQOS* system and *HeatSticks*.

ABUSE LIABILITY: MISUSE

Misuse of a product, which may increase nicotine exposure and/or use rates (i.e., abuse potential), was low.

Actual Use Study (n=985)

- 47 (4.8%) participants reported using *HeatSticks* without the *IQOS* device: the majority (97.9%) lit the *HeatSticks* like a cigarette; one participant chewed the *HeatStick*.
- 2 (0.2%) participants reported using the *IQOS* device without *HeatSticks*: one participant used the *IQOS* device with marijuana; one participant used it with conventional cigarettes.

Outcome Limitations: misuse data are based on self-report (potential for missing/incorrect data)

CONCLUSIONS

- Systemic nicotine exposure was similar after single and multiple uses of THS2.2 and combusted cigarettes (both regular and mentholated). Nicotine exposures appear sufficient to provide user satisfaction.

- THS2.2 use rates were similar to cigarettes. THS2.2 produces reinforcing effects and is expected to have an abuse potential that is similar to cigarettes.

CLARIFYING QUESTIONS?