EVIDENCE RELATED TO THE IMPACT ON TOBACCO USERS

EVALUATION OF CLINICAL AND BEHAVIORAL PHARMACOLOGICAL STUDIES

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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.)
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

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

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

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

- **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)
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
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
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
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.

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)
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

**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)

*Source: Section 6.2.2 of MPRTA*
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.
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)
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.
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.
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.
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?