7.3.1 Executive Summary: Clinical Studies

The THS clinical development program was developed to substantiate that THS reduces the risk of developing smoking related diseases as compared to continuing smoking conventional cigarettes (CC). Quitting is the best and most effective way for smokers to minimize their health risks, and in accordance with the opinion of the institute of medicine (IOM), smoking cessation was used as a benchmark for assessing the risk reduction potential of THS.
The clinical development program included studies in a confined and ambulatory setting and were conducted on healthy smokers in US, Japan and Europe with four types of clinical study designs.

Pharmacokinetics (PK)/Pharmacodynamic (PD) Studies: Single Product use (ZRHR-PK-01-EU; ZRHR-PK-02-JP; ZRHM-PK-05-JP, ZRHM-PK-06-US)

The randomized cross-over, relative bioavailability PK/ PD studies aimed to determine the nicotine absorption profile following single use of THS as compared to CC and NRT use. Multiple blood samples were drawn pre and post product use over 24-hours and nicotine concentration was measured in plasma. PK parameters including maximum concentration (C_{max}), area under the curve from the start of product use to time of last quantifiable concentration (AUC_{∞}), and time to maximum concentration (t_{max}) were calculated. In addition, subjective effects related to smoking (e.g. suppression of urge-to-smoke, product evaluation) were assessed and safety was monitored during these studies. The studies were conducted in Europe (ZRHR-PK-01-EU), in Japan (ZRHR-PK-02-JP and ZRHR-PK-05-JP) and in US (ZRHM-PK-06-US).
These studies showed that nicotine absorption profile following single use of THS was comparable to smoking one CC.

Reduced Exposure (Confinement Setting): *ad Libitum* Product Use for Five Days (ZRHR-REXC-03-EU and ZRHR-REXC-04-JP)

These randomized, open-label, parallel group reduced exposure studies included THS (*ad libitum* use), CC (*ad libitum* use), and smoking abstinence (SA) arms with a five day investigational exposure period which was subsequent to a 2 day baseline period during which all the subjects smoked their own brand of CC. The aim of these studies was to demonstrate reduction in the levels of biomarkers of exposure (BoExp) to selected harmful and potentially harmful constituents (HPHCs) following switching to THS in an optimal, clinical setting where compliance to arm allocation was controlled by the site staff. Exposure to nicotine and subjective effects related to smoking (urge-to-smoke, withdrawal symptoms, and product evaluation) were assessed and safety monitored. These studies were conducted in Europe (ZRHR-REXC-03-EU) and Japan (ZRHR-REXC-04-JP).

Reduced Exposure (Confinement and Ambulatory Setting): *ad Libitum* Product Use for Five days in confinement followed by Eighty-five Days in ambulatory setting (ZRHM-REXA-07-JP, ZRHM-REXA-08-US)

These randomized, open-label, parallel group reduced exposure studies included THS (*ad libitum* use), CC (*ad libitum* use), and smoking abstinence (SA) arms and had two distinct periods: a five day confinement investigational exposure period to investigational product in confinement followed by an eighty-five-day ambulatory investigational exposure period. The ambulatory extended study period was set to assess if reductions in exposure observed in a confined setting were sustained in an ambulatory period, more "real-life" setting where confounding factors such as environment, diet, passive smoking, use of CC in combination with THS (dual-use) could influence the levels of exposure to HPHCs. Furthermore, these studies provided continued insights in the understanding of product use and acceptance and the safety associated with product use over a prolonged period of time.

The clinical study reports of the studies ZRHR-PK-01-EU; ZRHR-PK-02-JP; ZRHM-PK-05-JP, ZRHM-PK-06-US, ZRHR-REXC-03-EU and ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US are presented as part of Module 7. The studies were conducted between 2013 and 2015 and were disclosed on clinical trial.gov as presented in Table 1.

Table 1. Duration, Location and Type of Studies

Study Code	THS Variant	Country	Exposure Duration	Study Type	ClinicalTrial.gov Identifier
ZRHR-PK-01-EU	THS 2.2, Regular THS Tobacco Stick	UK	Single use	PK/PD	NCT01967732
ZRHR-PK-02-JP	THS 2.2, Regular THS Tobacco Stick	JP	Single use	PK/PD	NCT01959607
ZRHM-PK-05-JP	THS 2.2, Menthol THS Tobacco Sticks	JP	Single use	PK/PD	NCT01967706
ZRHM-PK-06-US	THS 2.2, Menthol THS Tobacco Sticks	US	Single use	PK/PD	NCT01967719
ZRHR-REXC-03-EU	THS 2.2, Regular THS Tobacco Stick	PL	5 days	Reduced Exposure (Confinement Setting)	NCT01959932
ZRHR-REXC-04-JP	THS 2.2, Menthol THS Tobacco Sticks	JP	5 days	Reduced Exposure (Confinement Setting)	NCT01970982
ZRHM-REXA-07-JP	THS 2.2, Menthol THS Tobacco Sticks	JP	90 days	Reduced Exposure (confinement and ambulatory settings)	NCT01970995
ZRHM-REXA-08-US	THS 2.2, Menthol THS Tobacco Sticks	US	90 days	Reduced Exposure (confinement and ambulatory settings)	NCT01989156