Appendix 17: ZRHR_ERS_09_US Study Protocol Summary

PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

ZRHR-ERS-09-US

Study Title:	A randomized, controlled, 2-arm parallel group, multi-center study, to evaluate biological and functional changes in healthy smokers switching to Tobacco Heating System 2.2 (THS 2.2) compared to continuing smoking conventional cigarettes for 26 weeks in an ambulatory setting.
Short Title:	Evaluation of biological and functional changes in healthy smokers after switching to THS 2.2 for 26 weeks.
Registration Number:	Not assigned
Study Number	ZRHR-ERS-09-US
Product Name:	Tobacco Heating System 2.2 (THS 2.2)
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version Number:	Final Version 5.0
Revision Date:	19 January, 2017
Authors:	S. Michael Ansari, Clinical Scientist Nicola Lama, PhD, Study Statistician Nicolas Blanc, MD, Medical Safety Officer

SYNOPSIS

Sponsor:

Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Product Name:

Tobacco Heating System 2.2 (THS 2.2)

Study Title:

A randomized, controlled, 2-arm parallel group, multi-center study, to evaluate biological and functional changes in healthy smokers switching to Tobacco Heating System 2.2 (THS 2.2) compared to continuing smoking conventional cigarettes for 26 weeks in an ambulatory setting.

Study Number:

ZRHR-ERS-09-US

Short Study Title:

Evaluation of biological and functional changes in healthy smokers after switching to THS 2.2 for 26 weeks.

Primary Objective and Endpoints:

The primary objective of this study is:

1. To demonstrate favorable changes of the "smokers' health profile" in smokers switching from conventional cigarettes (CC) to THS 2.2 as compared to those continuing to smoke CC.

   Endpoints included in the "smokers' health profile" measured at V10 (Week 26):

   - High density lipoprotein cholesterol (HDL-C) in serum.
   - White blood cell total count (WBC) in blood.
   - Soluble intercellular adhesion molecule-1 (sICAM-1) in serum.
   - 11-dehydrothromboxane B2 (11-DTX-B_2) in urine (expressed as concentration adjusted for creatinine).

- 8-epi-prostaglandin F2α (8-epi-$PGF_{2\alpha}$) in urine (expressed as concentration adjusted for creatinine).
- Carboxyhemoglobin (COHb) in blood.
- Forced expiratory volume in 1 second (FEV_1 post-bronchodilator, expressed as % predicted [FEV_1 %pred]).
- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) in urine (expressed as concentration adjusted for creatinine).

Secondary Objectives and Endpoints:

The secondary objectives of this study are:

2. To evaluate self-reported product use (THS 2.2 and/or CC) over the duration of the study.

   Endpoint:

   - Number of CC or THS Tobacco Sticks used daily as reported in the product use electronic diary.

3. To determine short-term changes of the "smokers' health profile" in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoint measured at V7 (Week 13):

   - All components of the "smokers' health profile" (defined in the primary objective).

4. To demonstrate the reduction of exposure to harmful and potentially harmful constituents (HPHCs) in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoints measured at V7 (Week 13) and at V10 (Week 26):

   - Biomarker of exposure (BoExp) to carbon monoxyide (CO):
     - CO in exhaled breath (expressed as ppm).
   - BoExp to various HPHCs in urine (expressed as concentration adjusted for creatinine):
     - BoExp to 1,3-butadiene: monohydroxybutenylmercapturic acid (MHBMA).
     - BoExp to acrolein: 3-hydroxypropylmercapturic acid (3-HPMA).
     - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (total NNN).
     - BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).
     - BoExp to benzo[a]pyrene: 3-hydroxybenzo(a)pyrene (3-OH-B[a]P).

- BoExp to crotonaldehyde: 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA).
- BoExp to pyrene: total 1-hydroxypyrene (total 1-OHP).

5. To describe the levels of nicotine exposure in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoints (BoExp to nicotine) over the duration of the study:

   - Nicotine equivalent (Neq): molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide in urine (expressed as concentration adjusted for creatinine).
   - Nicotine and cotinine in plasma.

6. To describe the changes of clinical risk endpoints associated with respiratory diseases, cardiovascular diseases, and xenobiotics in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoints associated with respiratory diseases measured at V7 (Week 13) and V10 (Week 26):

   - Lung function (spirometry post-bronchodilator): FEV_1, forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow (FEF 25-75).
   - Lung function (lung volume pre-bronchodilator): forced residual capacity (FRC), vital capacity (VC), total lung capacity (TLC), inspiratory capacity (IC) and residual volume (RV).
   - Cough symptoms (intensity and frequency), and amount of sputum production, and bothersomeness of cough symptom from the cough questionnaire.

   Endpoints associated with respiratory diseases measured at V10 (Week 26):

   - Lung function (spirometry pre-bronchodilator): FEV_1, forced vital capacity (FVC), FEV_1/FVC, FEF 25-75.
   - Lung function (spirometry pre and post-bronchodilator): bronchodilator reversibility in FEV_1.

   Endpoints associated with cardiovascular diseases measured at V7 (Week 13) and V10 (Week 26):

   - Myeloperoxidase (MPO), apolipoprotein A1 and B (Apo A1 and Apo B), low density lipoprotein cholesterol (LDL-C), and high sensitivity C-reactive protein (hs-CRP) in serum.

- Fibrinogen, and homocysteine in plasma.
- Platelet count, and hemoglobin glycosylated (HbA1c) in whole blood.
- Albumin in urine (expressed as concentration adjusted to creatinine).
- Blood pressure (BP), weight, waist circumference.

Endpoint associated with xenobiotics measured at V7 (Week 13), and V10 (Week 26):

- Cytochrome P450 2A6 (CYP2A6) activity: molar metabolic ratio of 3-hydroxycotinine/cotinine in plasma.

7. To describe the changes in subjective effects of smoking in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC:

   Endpoint:

   - Product evaluation over the duration of the study: subscales from the modified cigarette evaluation questionnaire (MCEQ).

8. To evaluate the safety profiles associated with THS 2.2 and CC.

   Endpoints over the duration of the study:

   - Adverse events (AEs), serious adverse events (SAEs) and device events including THS 2.2 malfunction/misuse.
   - Vital signs, body weight and BMI
   - Respiratory symptoms (cough assessment VAS and Likert scales)
   - Spirometry (clinical interpretation and COPD categories)
   - Electrocardiogram (ECG).
   - Clinical chemistry, hematology and urine analysis safety panel.
   - Physical examination.
   - Concomitant medications.

Exploratory Objectives and Endpoints:

The exploratory objectives of this study are:

9. To evaluate the relationship between the levels of urinary BoExp and Neq in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

   Endpoint measured at V7 (Week 13), and V10 (Week 26):

- MHBMA, 3-HPMA, total NNN, CEMA, 3-OH-B[a]P, 3-HMPMA, total NNAL, total 1-OHP, and Neq (expressed as concentration adjusted for creatinine).

10. To describe the effect of combined product use (dual use) over the study on the components of the "smokers' health profile".

    Endpoint:

    - The levels of the components in the "smokers' health profile" and the number of CC and THS Tobacco Sticks used daily as reported on the self-reported product use electronic diary.

11. To describe the intention to use THS 2.2 in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC:

    Endpoint:

    - Intention to use associated with THS 2.2 at V10 (Week 26): item scores from intent to use questionnaire for THS 2.2 (ITUQ).

12. To describe the change in tobacco dependence at V10 (Week 26) in smokers switching from CC to THS 2.2 as compared to those continuing to smoke CC.

    Endpoints:

    - Score from the Fagerström test for nicotine dependence (FTND) questionnaire.
    - Time to first cigarette from the FTND questionnaire.

Study Hypothesis:

THS 2.2 modifies the risk of smoking related diseases as demonstrated by favorable biological and functional changes on the "smokers' health profile", in comparison to continued smoking of CC (shifting in the direction as they would upon smoking cessation).

Evaluation Criterion:

The study will substantiate that THS 2.2 modifies risk of smoking related diseases if the following criteria are met in smokers switching from CC to THS 2.2 as compared to smokers continuing to smoke CC:

- All co-primary endpoints of the "smokers' health profile" shift in the same direction as they would upon smoking cessation.
- At least 5 of 8 components of the "smokers' health profile" are statistically significantly improved as compared to CC using a two-sided test with the Hailperin-Rüger adjusted α

level, with the point estimates showing that the majority of the effect of smoking cessation is preserved.

Study Design:

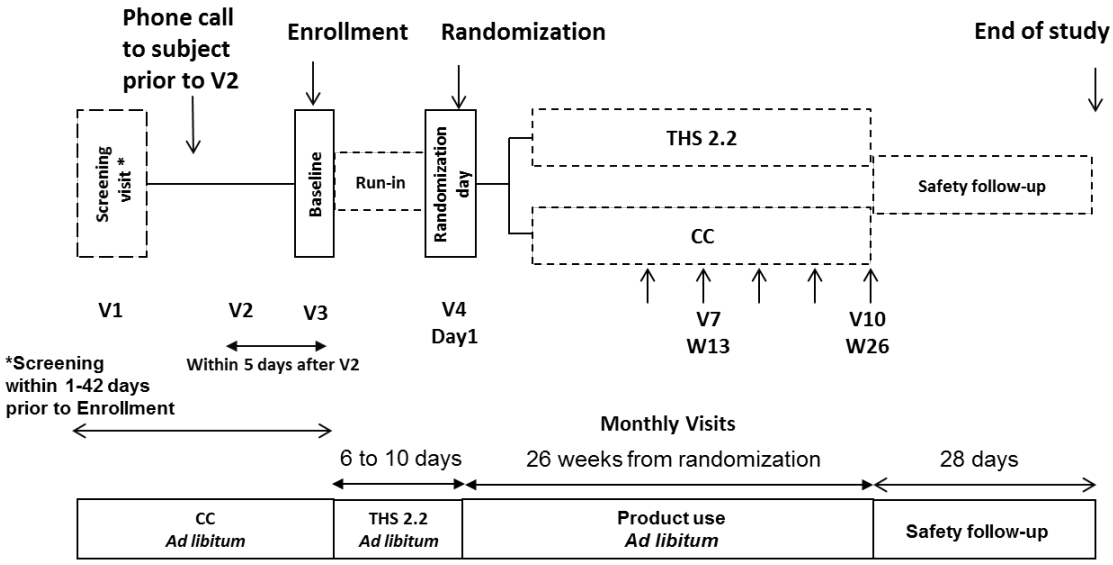
This study will be conducted as a multi-center study in the US. Subjects who are smoking non-menthol CC, and who are not motivated to quit smoking within the next 6 months will be randomized (950 subjects).

This is an *ad libitum* smoking study with unrestricted product use (THS 2.2 and CC) for the duration of the study (including site visits). Starting with visit V2, subjects will capture the number of used THS Tobacco Sticks, CCs (menthol and non-menthol), and other nicotine/tobacco containing products on a daily basis in a product use electronic diary. Smoking of menthol CCs will be allowed during the study.

Upon the judgment of the Principal Investigator(s) (PI(s)) or designee(s), subjects who do not meet entry criteria after signing the informed consent form (ICF) and prior to enrollment at V3 will be considered as screen failures.

End of Study for whole study is the last subject individual EOS.

Subjects that terminate the study after enrollment and prior to completion of the study will undertake early termination procedures (section 9.5).



V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	Safety follow-up
Screening		Enrollment / Baseline	Day 1	Week 4	Week 9	Week13	Week 17	Week 22	Week 26	28 days

Figure 1 Study Design

The Screening Period (from the ICF Signature to the Enrollment at V3):

V3 will be organized within 42 days after screening visit (V1), with the last day of the Screening period being the day before V3. At V1, eligibility criteria of the subject will be checked and a demonstration of THS 2.2 will be done. If the inclusion and exclusion criteria are satisfactorily met, the site staff will call the subject to arrange his/her next visit (V2) to the site.

At V2, the urine containers (with equipment to keep the urine cooled) and electronic diaries will be distributed, and subject will be trained on 24-hour urine home collection and on the use of the electronic diary. The site will program the electronic diary for the date of the next visit (V3). Twenty-four hour urine collection will start the day before V3 and will end in the morning of V3.

During this period, all subjects will continue smoking their own preferred brands of CC.

The Baseline (from the Enrollment to the Check-out of V3):

Enrollment of the subject will take place at V3 after the subject checks-in on site with the cooled container(s) filled with his/her 24-hour urine, confirmation of a negative pregnancy test (for female subjects only), and check of exclusion criteria 5 and 6. All other procedures and data collection will be completed following the enrollment of the subject. The data collected at V3 will correspond to Baseline values. V3 should be organized within 5 days after V2.

After enrollment and prior to check-out at V3, all the subjects will be distributed THS 2.2 to be used during the run-in period and will receive training on how to use THS 2.2. Only female subjects with a negative pregnancy test at V3 will be allowed to try the product during the run-in period.

During the visit, all subjects will continue to smoke their CC.

The Run-in Period (from the Check-out of V3 to the Check-in of V4):

Subject will use THS 2.2 *ad libitum* in an ambulatory setting. The interval between V3 and V4 will be 8 days ± 2 days. Smoking of other tobacco/nicotine containing products will be tolerated and recorded in the electronic product use diary.

The Randomization Day (from the Check-in to the Check-out of V4):

On V4, subjects will return all the components of THS 2.2 including the unused THS Tobacco Sticks back to the site staff. Subjects will be asked if they are willing to comply with study procedures and willing to use THS 2.2 for the next 26 weeks, if they agree they will be randomized to one of the two study arms. Subjects will be randomized as follows:

- THS 2.2 arm: ~475 subjects, use of THS 2.2 *ad libitum*.
- CC arm: ~475 subjects, use of their own CC brand *ad libitum*.

At V4, following randomization, subjects will be informed of their randomized study arm, distributed THS 2.2, if allocated to the THS 2.2 study arm, and checked-out from the clinic.

Until randomization, subjects can be replaced. However, subjects discontinued prematurely after randomization will not be replaced and will not be allowed to re-enter the study.

The Randomized Exposure Period (from the Check-out of V4 (Day 1) until the Check-out of V10 (Week 26)):

From the check-out at V4, subjects will use their assigned product in an ambulatory setting for 26 weeks *ad libitum*, including during the visits. Subjects in the THS 2.2 and CC arms will be instructed to exclusively use their assigned product.

Subjects will be required to make 6 visits, each on a monthly basis (from V5 to V10), to the investigational site. V5 (Week 4), V6 (Week 9), V7 (Week 13), V8 (Week 17), V9 (Week 22), and V10 (Week 26) will be organized 4 weeks (28 days), 9 weeks (63 days), 13 weeks (91 days), 17 weeks (119 days), 22 weeks (154 days), and 26 weeks (182 days) respectively, after the V4 (Day 1) with a time window of +/- 5 days respective to V4.

The monthly visits will be organized for safety checks. During these visits, subjects in the THS 2.2 arm will be re-supplied with a sufficient amount of THS Tobacco Sticks to cover their needs until the next visit. Additional visits to replace THS 2.2 components and to re-supply THS Tobacco Sticks may be accomodated.

The V7 and V10 (section 9.3) visits will correspond to the main visits where blood and 24-hour urine will be collected for assessments of BoExp and clinical risk endpoints. Twenty four-hour urine collection will start at subjects' home in the morning of the day before the visits V7 and V10, and will end 24 hours later in the morning on the day of the visit.

Any subject randomized, who wants to make a quit attempt from using tobacco-containing products (e.g. THS 2.2 and CC) during the study will be encouraged to do so and will be referred to appropriate medical services. The subject will not be discontinued from the study, will come to all scheduled visits for assessments, and his/her financial compensation will not be affected.

After the check-out on V10, subjects completing the study will be offered to enter into an extension study. During this extension study, safety will be monitored and additional endpoints will be collected as defined in a separate clinical study protocol. Subjects who

enter in the extension study will not enter in a Safety Follow-up Period until the end of the extension study.

Subjects who do not enroll in the extension study will enter in a 28 days Safety Follow-up Period.

The Safety Follow-up Period (from the Check-out of V10 (Week 26) plus 28 days):

During the Safety Follow-up Period AE/SAEs can be spontaneously reported by the subjects and ongoing AEs will be actively followed-up by the site. AEs will be followed-up until they have been resolved, stabilized (*i.e.*, no worsening of the event), or until a plausible explanation of the event has been found. The end of study (individual) is defined as the check-out of V10 or the date of early termination of the subject plus a 28 days Safety Follow-up Period, if applicable.

Study Population and Main Criteria for Inclusion/Exclusion:

Female or male currently smoking, healthy adult subjects meeting the following main criteria without any restriction on race and ethnicity.

Inclusion Criteria:

- Healthy current smoker as judged by the Principal Investigator(s) or designee(s).
- Minimum age: 30 years old.
- Have smoked for the last 10 years.
- Have smoked ≥ 10 non menthol CC/day on average (no brand restriction) over the past year prior to screening.
- Not intending to quit smoking within the next 6 months, as assessed by the Prochaska's stages of change questionnaire.

Exclusion Criteria:

- Clinically relevant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric or cardiovascular disorders or any other conditions that in the opinion of the investigators would jeopardize the safety of the participant or affect the validity of the study results.
- Abnormal findings on physical examination, in the medical history, or in clinical laboratory results deemed clinically relevant by investigators (as per the common terminology criteria for adverse events [CTCAE]).
- Acute illness (*e.g.*, upper-respiratory-tract infection, viral infection etc.) requiring treatment within 30 days prior to enrollment in the study.
- Use of any prescribed or over-the-counter systemic medication with an impact on the endpoints of the "Smokers' Health Profile" within 5 half-lives of the medication prior

to study enrollment except over-the-counter vitamin supplements, hormonal contraceptives and hormone-replacement therapy (see Appendix 2 for examples).

- Subject who has (FEV_1/FVC) < 0.7 and FEV_1 < 80% predicted value at post-bronchodilator spirometry.
- Subject with asthma condition (post-bronchodilator FEV_1/FVC < 0.75 and reversibility in $FEV_1 \geq 12\%$ and > 200 mL from pre- to post-bronchodilator values).
- Pregnant or breast feeding female.
- Female who does not agree to use an acceptable method of effective contraception.

Investigational Products; Dose; and Mode of Utilization:

Test Product:

Tobacco Heating System 2.2 (THS 2.2) which has three major parts: the THS Tobacco Stick (Tobacco Stick), the THS Tobacco Stick Holder (Holder), and the Charger.

Reference Product:

Subject's own supply of commercially available own brand CC (manufactured and hand-rolled). Cigarettes will not be provided by the Sponsor.

Duration of Study:

The entire study duration per subject will be between 32 to 38 weeks, including a Screening period of up to 42 days prior to enrollment (at V3), a 6 to 10 day run-in period prior to randomization (at V4), followed by a 26 week randomized ambulatory period. The end of study (individual) is defined as the check-out of V10 or the date of early termination of the subject plus a 28 days Safety Follow-up Period, if applicable.

Statistical Methods:

The confirmatory analysis of the "smokers' health profile" at V10 (Week 26) will compare the two study arms according to subjects' exposure (THS 2.2 or CC) with respect to:

- Mean difference in each of the following endpoints FEV_1 %pred, HDL-C, and WBC at V10.
- Ratio of the geometric mean levels of each of the following endpoints the 11-DTX-B_2, sICAM-1, 8-epi-$PGF_{2\alpha}$, COHb, and total NNAL at V10.

The endpoints will be tested individually with a two-sided Type I error probability of 0.03125. The endpoints will be analyzed using a generalized regression model adjusting for site, sex, Baseline value of the endpoint and other endpoint specific covariates. The test will be declared significant if the contrast of THS 2.2 versus CC is significant and the change

following the switch to THS 2.2 is directionaly the same as would be observed following smoking cessation.

FEV_1, HDL-C, and WBC will be analyzed in the real scale. Other markers will be analyzed in the logarithmic scale and will be back-transformed to provide relative effects.

Descriptive statistics (number of subjects [n], number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation [SD], median, first and third quartiles, minimum and maximum for continuous data; geometric mean and coefficient of variation (CV) for data analyzed in the log scale; frequency counts and percentages for categorical data) will be presented at each timepoint, where applicable.

Analyses over time will be descriptive statistics of parameters at each assessment timepoint, together with mean difference from Baseline and 95% confidence intervals (CI).

Safety will be summarized for the safety population according to randomization arm and according to product exposure.

Sample Size:

A total of 950 smokers (475 THS 2.2 and 475 CC) will be randomized. This is sufficient to attain a statistical power of more than 99% to show at least 5 out of 8 statistically significant favorable changes in the "smokers' health profile", using the Hailperin-Rüger [1, 2] approach, where a two-sided type I error probability of 0.03125 is used to test each component while preserving the overall 0.05 family-wise error rate.

The sample size has been calculated to ensure an overall study power of at least 90% while maintaining at least 80% power to detect the expected effect of THS 2.2 as compared to CC for each individual endpoint. The sample size/power assumptions for each endpoint test are summarized in the table below. A sample size of 950 subjects provides 82.2% power to detect 1.6%pred difference between THS 2.2 and CC on FEV_1 (%pred) at Visit 10 (26 weeks), using a two sided test of the mean difference with an anticipated standard deviation of 6.0%pred.

Table 1 Power for Singular Endpoints of the "Smokers' Health Profile" Assuming a Success Criteria of at Least 5 out of 8

Endpoint	Preserved Effect of Cessation	Change from CC	Variability	Test-Wise Power [3]	Updated Test-wise Power[3]
HDL-C	80%	3.3 mg/dL	10.0 mg/dL	99.6%	91.6%
WBC	70%	-0.6 10^9/L	1.6 10^9/L	98.5%	84.5%

FEV_1	75%	1.6%pred	6.0%pred	82.2%	80.3%
sICAM-1	60%	12%reduction [1]	CV = 23% [2]	99.9%	99.5%
11-DTX-B_2	80%	18%reduction [1]	CV = 27% [2]	99.9%	99.9%
8-epi-$PGF_{2\alpha}$	50%	16%reduction [1]	CV = 36% [2]	99.9%	93.3%
COHb	80%	65% reduction [1]	CV =39% [2]	99.9%	99.9%
NNAL	80%	70% reduction [1]	CV = 60% [2]	99.9%	99.9%

Note: THS = Tobacco Heating System; CC = Conventional cigarettes

1. Effect is reported as ratio of the THS 2.2/CC effects
2. Variability reported as geometric coefficient of variation (CV)
3. Test-wise power using a Type I error of 0.03125 (0.05 * 5/8)

The initially planned sample size accounted for an anticipated 75% of the THS 2.2 arm will be Mostly THS 2.2 users (*i.e.*, report at least 70% use of THS 2.2). All clinical risk endpoints preserve the majority of the effect seen with cessation as detailed in the table above, following Mostly THS 2.2 use. Sample size considerations were made assuming that the effect size in the THS 2.2 arm will be diluted due to non-Mostly THS 2.2 product use.

Based on our current understanding of product use data, the definition of the product use categories was redefined and the underlying assumptions re-evaluated so that approximately 60% of the subjects in the THS 2.2 arm are expected to be in the THS-use category, with an anticipated 20% of subjects drop-out or reporting insufficient product use data in the two arms. The planned sample size is sufficient to attain an overall statistical power of more than 99% to show at least 5 out of 8 statistically significant effects on the primary endpoints using the same Hailperin-Rüger approach described previously, with a testwise power indicated in Table 1 ("Updated Test-wise Power"). In the revised calculation of the statistical power, no dilution of the THS 2.2 effect is accounted for in the comparison between THS-use and CC-use in accordance with the as-exposed analysis approach planned.

The assumptions in this table are based on the current status of our knowledge with respect to the effects and use patterns of THS 2.2. During the ongoing review of product use data these assumptions may be revised and updated as appropriate.