Supplementary Table 1. Sample size rationale and assumptions. AUC area under the concentration time curve, NRT nicotine replacement therapy, THP tobacco heating product, CV coefficient of variation, $C_{\text{max}}$ maximum plasma nicotine concentration, $T_{\text{max}}$ time of the maximum plasma nicotine concentration.

| Endpoint                              | Assumptions                                                                                                                                                                                                 | Power | Sample Size |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------------|
| AUC$_{\text{nic}}$ Log-normal         | THP is expected to reach a non-inferior AUC than the NRT where inferiority margin is set at geometric mean ratio of 0.8. At the same time the geometric mean ratio between the THP and usual brand cigarette is expected to not be above 1.25 ($\alpha = 0.1$). Based on a CV = 0.4 and correlation between pairs observations of 0.2, with observed mean ratio between THP and NRT of 1 and 0.8 between THP and usual brand cigarette. | 0.902 | 32          |
| $C_{\text{max}}$ Log-normal           | THP is expected to reach a non-inferior $C_{\text{max}}$ than the NRT where inferiority margin is set at geometric mean ratio of 0.8. At the same time the geometric mean ratio between the THP and standard cigarette is expected not to be above 1.25 ($\alpha = 0.1$). Based on group CVs = 0.58 and 0.44 for THP and standard cigarette. Correlation between pairs observations of 0.2, with observed mean ratio between THP and NRT is expected to be approximately 1.5 and 0.8 between THP and standard cigarette. | 0.917 | 14          |
| $T_{\text{max}}$ Normal               | Mean difference of $T_{\text{max}}$ for THP with respect to NRT is expected to be larger than 4 minutes, i.e. at least 4 min earlier for THP than for NRT. Assuming an observed difference of 7 and SD = 5 ($\alpha = 0.1$). | 0.907 | 31          |
| Overall intent to use again Log-normal| It is assumed that the overall intent to use the THP again is not inferior to NRT. There is no previous data available for this endpoint but assuming geometric mean ratio = 1 and CV = 0.4, with $\alpha = 0.1$. | 0.902 | 32          |
| Product liking Log-normal              | It is assumed that THP product liking is not inferior to NRT. There is no previous data available for this endpoint but assuming geometric mean ratio = 1 and CV = 0.4, with $\alpha = 0.1$. | 0.902 | 32          |
| Urge to smoke Log-normal               | Urge to smoke is assumed to be reduced by the THP compared to NRT. With observed geometric ratio of 0.8.                                                                                                      | 0.902 | 32          |
| Urge for product Log-normal            | Urge to use the product is assumed to be greater with the THP than with the NRT. With observed geometric ratio of 1.25.                                                                                           | 0.902 | 32          |
Supplementary Table 2. Summary of Product Evaluation Scale (PES) responses. THP tobacco heating product, *N* number of subjects.

| PES question | Timepoint | Statistic   | THP1.0 (RT) (N=32) | THP1.1 (RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|--------------|-----------|-------------|---------------------|---------------------|-----------------------------|-----------------------------|
|              | Pre-use   | Mean (SD)   | 3.1 (2.22)          | 3.1 (2.23)          | 1.9 (1.17)                  | 6.7 (0.87)                  |
|              |           | Median      | 2.5                 | 2.5                 | 1.0                         | 7.0                         |
|              |           | Min – Max   | 1–7                 | 1–7                 | 1–5                         | 3–7                         |
|              |           | Q1 – Q3     | 1–5                 | 1–5                 | 1–3                         | 7–7                         |
| 1. Was it satisfying? | 15 min | Mean (SD)   | 3.0 (2.14)          | 3.2 (1.97)          | 1.9 (1.20)                  | 6.3 (1.30)                  |
|              |           | Median      | 3.0                 | 2.5                 | 1.0                         | 7.0                         |
|              |           | Min – Max   | 1–7                 | 1–7                 | 1–5                         | 2–7                         |
|              |           | Q1 – Q3     | 1–5                 | 2–5                 | 1–3                         | 6–7                         |
|              | 240 min   | Mean (SD)   | 2.9 (2.08)          | 3.2 (1.89)          | 1.8 (1.08)                  | 6.4 (0.91)                  |
|              |           | Median      | 2.0                 | 3.0                 | 1.0                         | 7.0                         |
|              |           | Min – Max   | 1–7                 | 1–7                 | 1–5                         | 3–7                         |
|              |           | Q1 – Q3     | 1–4                 | 2–5                 | 1–2                         | 6–7                         |
| 2. Did it taste good? | Pre-use | Mean (SD)   | 2.8 (2.30)          | 3.0 (2.21)          | 1.4 (0.80)                  | 6.5 (0.88)                  |
|              |           | Median      | 1.0                 | 2.0                 | 1.0                         | 7.0                         |
|              |           | Min – Max   | 1–7                 | 1–7                 | 1–4                         | 4–7                         |
|              |           | Q1 – Q3     | 1–5                 | 1–5                 | 1–2                         | 6–7                         |
|              | 15 min    | Mean (SD)   | 2.8 (2.17)          | 3.0 (2.06)          | 1.7 (1.07)                  | 5.8 (1.28)                  |
|              |           | Median      | 1.5                 | 2.0                 | 1.0                         | 6.0                         |
|              |           | Min – Max   | 1–7                 | 1–7                 | 1–4                         | 3–7                         |
|              |           | Q1 – Q3     | 1–4                 | 1–5                 | 1–2                         | 5–7                         |
|              | 240 min   | Mean (SD)   | 2.6 (2.12)          | 2.8 (1.97)          | 1.7 (1.14)                  | 6.3 (0.95)                  |
|              |           | Median      | 1.5                 | 2.0                 | 1.0                         | 7.0                         |
|              |           | Min – Max   | 1–7                 | 1–7                 | 1–5                         | 4–7                         |
|              |           | Q1 – Q3     | 1–4                 | 1–5                 | 1–2                         | 6–7                         |
| PES question | Timepoint | Statistic | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|--------------|-----------|-----------|-------------------|-------------------|---------------------------|-----------------------------|
| 3. Did you enjoy the sensations in your mouth? | Pre-use | Mean (SD) | 2.8 (2.17) | 3.0 (2.06) | 1.4 (0.80) | 6.3 (1.00) |
|  | Median | 2.0 | 2.5 | 1.0 | 7.0 |
|  | Min – Max | 1 – 7 | 1 – 7 | 1 – 4 | 4 – 7 |
|  | Q1 – Q3 | 1 – 5 | 1 – 5 | 1 – 2 | 6 – 7 |
|  | 15 min | Mean (SD) | 2.7 (2.04) | 2.8 (1.97) | 1.6 (0.98) | 6.0 (1.31) |
|  | Median | 2.0 | 2.0 | 1.0 | 7.0 |
|  | Min – Max | 1 – 7 | 1 – 7 | 1 – 4 | 3 – 7 |
|  | Q1 – Q3 | 1 – 4 | 1 – 5 | 1 – 2 | 5 – 7 |
|  | 240 min | Mean (SD) | 2.6 (2.06) | 2.8 (1.70) | 1.7 (1.04) | 6.1 (1.13) |
|  | Median | 2.0 | 2.0 | 1.0 | 7.0 |
|  | Min – Max | 1 – 7 | 1 – 6 | 1 – 4 | 3 – 7 |
|  | Q1 – Q3 | 1 – 3 | 1 – 4 | 1 – 2 | 5 – 7 |
| 4. Did it calm you down? | Pre-use | Mean (SD) | 2.4 (1.74) | 2.6 (1.88) | 1.9 (1.39) | 5.8 (1.75) |
|  | Median | 1.5 | 2.0 | 1.0 | 7.0 |
|  | Min – Max | 1 – 7 | 1 – 7 | 1 – 7 | 1 – 7 |
|  | Q1 – Q3 | 1 – 4 | 1 – 5 | 1 – 3 | 5 – 7 |
|  | 15 min | Mean (SD) | 2.5 (1.87) | 2.3 (1.57) | 1.8 (1.35) | 5.3 (1.87) |
|  | Median | 2.0 | 1.5 | 1.0 | 6.0 |
|  | Min – Max | 1 – 7 | 1 – 6 | 1 – 6 | 1 – 7 |
|  | Q1 – Q3 | 1 – 3 | 1 – 4 | 1 – 3 | 4 – 7 |
|  | 240 min | Mean (SD) | 2.0 (1.59) | 2.3 (1.55) | 1.6 (0.95) | 5.3 (1.89) |
|  | Median | 1.0 | 2.0 | 1.0 | 5.5 |
|  | Min – Max | 1 – 7 | 1 – 7 | 1 – 5 | 1 – 7 |
|  | Q1 – Q3 | 1 – 3 | 1 – 3 | 1 – 2 | 4 – 7 |
| PES question                      | Timepoint | Statistic       | THP1.0 (RT) (N=32) | THP1.1 (RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|----------------------------------|-----------|-----------------|--------------------|--------------------|-----------------------------|-------------------------------|
| 5. Did it make you feel more awake? | Pre-use   | Mean (SD)       | 1.4 (0.95)         | 1.7 (1.17)         | 1.3 (0.67)                  | 4.0 (2.33)                    |
|                                  |           | Median          | 1.0                | 1.0                | 1.0                         | 4.0                          |
|                                  |           | Min – Max       | 1 – 5              | 1 – 5              | 1 – 4                       | 1 – 7                        |
|                                  |           | Q1 – Q3         | 1 – 1              | 1 – 2              | 1 – 1                       | 1 – 7                        |
|                                  | 15 min    | Mean (SD)       | 1.5 (0.98)         | 1.6 (1.13)         | 1.6 (1.34)                  | 3.2 (2.27)                    |
|                                  |           | Median          | 1.0                | 1.0                | 1.0                         | 2.0                          |
|                                  |           | Min – Max       | 1 – 5              | 1 – 5              | 1 – 6                       | 1 – 7                        |
|                                  |           | Q1 – Q3         | 1 – 2              | 1 – 2              | 1 – 2                       | 1 – 5                        |
|                                  | 240 min   | Mean (SD)       | 1.6 (1.11)         | 1.6 (1.18)         | 1.5 (1.02)                  | 3.5 (2.05)                    |
|                                  |           | Median          | 1.0                | 1.0                | 1.0                         | 3.0                          |
|                                  |           | Min – Max       | 1 – 5              | 1 – 6              | 1 – 6                       | 1 – 7                        |
|                                  |           | Q1 – Q3         | 1 – 2              | 1 – 2              | 1 – 2                       | 2 – 5                        |
| 6. Did it make you feel less irritable? | Pre-use   | Mean (SD)       | 1.8 (1.52)         | 1.9 (1.27)         | 1.5 (0.92)                  | 4.9 (1.81)                    |
|                                  |           | Median          | 1.0                | 1.0                | 1.0                         | 5.0                          |
|                                  |           | Min – Max       | 1 – 6              | 1 – 5              | 1 – 5                       | 1 – 7                        |
|                                  |           | Q1 – Q3         | 1 – 2              | 1 – 3              | 1 – 2                       | 4 – 7                        |
|                                  | 15 min    | Mean (SD)       | 1.7 (1.35)         | 2.0 (1.56)         | 1.6 (1.13)                  | 4.2 (2.14)                    |
|                                  |           | Median          | 1.0                | 1.0                | 1.0                         | 4.0                          |
|                                  |           | Min – Max       | 1 – 6              | 1 – 6              | 1 – 5                       | 1 – 7                        |
|                                  |           | Q1 – Q3         | 1 – 2              | 1 – 3              | 1 – 2                       | 2 – 6                        |
|                                  | 240 min   | Mean (SD)       | 1.7 (1.26)         | 1.7 (1.17)         | 1.5 (0.92)                  | 4.1 (2.30)                    |
|                                  |           | Median          | 1.0                | 1.0                | 1.0                         | 4.0                          |
|                                  |           | Min – Max       | 1 – 6              | 1 – 5              | 1 – 5                       | 1 – 7                        |
|                                  |           | Q1 – Q3         | 1 – 2              | 1 – 2              | 1 – 2                       | 2 – 7                        |
| PES question | Timepoint | Statistic | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|--------------|-----------|-----------|-------------------|-------------------|---------------------------|-----------------------------|
| 7. Did it help you concentrate? | Pre-use | Mean (SD) | 1.6 (1.21) | 1.7 (1.15) | 1.2 (0.66) | 3.7 (2.32) |
| | | Median | 1.0 | 1.0 | 1.0 | 4.0 |
| | | Min – Max | 1–6 | 1–5 | 1–4 | 1–7 |
| | | Q1 – Q3 | 1–2 | 1–2 | 1–1 | 1–6 |
| | 15 min | Mean (SD) | 1.7 (1.38) | 1.8 (1.26) | 1.4 (0.80) | 3.5 (2.09) |
| | | Median | 1.0 | 1.0 | 1.0 | 3.5 |
| | | Min – Max | 1–6 | 1–5 | 1–4 | 1–7 |
| | | Q1 – Q3 | 1–2 | 1–2 | 1–2 | 2–5 |
| | 240 min | Mean (SD) | 1.6 (1.31) | 1.8 (1.49) | 1.3 (0.78) | 3.5 (2.24) |
| | | Median | 1.0 | 1.0 | 1.0 | 3.0 |
| | | Min – Max | 1–6 | 1–7 | 1–5 | 1–7 |
| | | Q1 – Q3 | 1–2 | 1–2 | 1–1 | 2–5 |
| 8. Did it reduce your hunger for food? | Pre-use | Mean (SD) | 1.8 (1.36) | 2.1 (1.57) | 1.3 (0.80) | 4.4 (2.30) |
| | | Median | 1.0 | 1.0 | 1.0 | 4.0 |
| | | Min – Max | 1–6 | 1–7 | 1–5 | 1–7 |
| | | Q1 – Q3 | 1–3 | 1–3 | 1–1 | 3–7 |
| | 15 min | Mean (SD) | 1.7 (1.12) | 2.1 (1.40) | 1.7 (1.31) | 4.0 (2.19) |
| | | Median | 1.0 | 2.0 | 1.0 | 4.0 |
| | | Min – Max | 1–4 | 1–7 | 1–6 | 1–7 |
| | | Q1 – Q3 | 1–3 | 1–3 | 1–2 | 2–6 |
| | 240 min | Mean (SD) | 1.8 (1.14) | 2.0 (1.40) | 1.5 (0.72) | 3.8 (2.07) |
| | | Median | 1.0 | 2.0 | 1.0 | 4.0 |
| | | Min – Max | 1–5 | 1–7 | 1–4 | 1–7 |
| | | Q1 – Q3 | 1–3 | 1–3 | 1–2 | 2–6 |
| PES question          | Timepoint | Statistic     | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|-----------------------|-----------|---------------|-------------------|-------------------|-----------------------------|-------------------------------|
| 9. Did it make you dizzy? | Pre-use   | Mean (SD)     | 1.3 (0.93)        | 1.3 (0.73)        | 1.8 (1.60)                  | 2.0 (1.62)                    |
|                       |           | Median        | 1.0               | 1.0               | 1.0                         | 1.0                          |
|                       |           | Min – Max     | 1 – 5             | 1 – 4             | 1 – 7                       | 1 – 6                        |
|                       |           | Q1 – Q3       | 1 – 1             | 1 – 1             | 1 – 2                       | 1 – 3                        |
|                       | 15 min    | Mean (SD)     | 1.5 (1.16)        | 1.9 (1.66)        | 1.4 (0.95)                  | 3.0 (2.43)                   |
|                       |           | Median        | 1.0               | 1.0               | 1.0                         | 2.0                          |
|                       |           | Min – Max     | 1 – 6             | 1 – 7             | 1 – 5                       | 1 – 7                        |
|                       |           | Q1 – Q3       | 1 – 1             | 1 – 2             | 1 – 2                       | 1 – 5                        |
|                       | 240 min   | Mean (SD)     | 1.3 (0.62)        | 1.6 (1.32)        | 1.4 (0.91)                  | 2.7 (2.35)                   |
|                       |           | Median        | 1.0               | 1.0               | 1.0                         | 1.0                          |
|                       |           | Min – Max     | 1 – 3             | 1 – 7             | 1 – 5                       | 1 – 7                        |
|                       |           | Q1 – Q3       | 1 – 1             | 1 – 2             | 1 – 2                       | 1 – 5                        |
| 10. Did it make you nauseous? | Pre-use   | Mean (SD)     | 1.2 (0.54)        | 1.3 (1.18)        | 1.4 (1.16)                  | 1.1 (0.30)                   |
|                       |           | Median        | 1.0               | 1.0               | 1.0                         | 1.0                          |
|                       |           | Min – Max     | 1 – 3             | 1 – 7             | 1 – 6                       | 1 – 2                        |
|                       |           | Q1 – Q3       | 1 – 1             | 1 – 1             | 1 – 1                       | 1 – 1                        |
|                       | 15 min    | Mean (SD)     | 1.2 (0.45)        | 1.2 (0.49)        | 1.2 (0.64)                  | 1.8 (1.86)                   |
|                       |           | Median        | 1.0               | 1.0               | 1.0                         | 1.0                          |
|                       |           | Min – Max     | 1 – 3             | 1 – 3             | 1 – 4                       | 1 – 7                        |
|                       |           | Q1 – Q3       | 1 – 1             | 1 – 1             | 1 – 1                       | 1 – 2                        |
|                       | 240 min   | Mean (SD)     | 1.1 (0.42)        | 1.2 (0.75)        | 1.3 (0.80)                  | 1.4 (1.34)                   |
|                       |           | Median        | 1.0               | 1.0               | 1.0                         | 1.0                          |
|                       |           | Min – Max     | 1 – 3             | 1 – 5             | 1 – 4                       | 1 – 7                        |
|                       |           | Q1 – Q3       | 1 – 1             | 1 – 1             | 1 – 1                       | 1 – 1                        |
| PES question | Timepoint | Statistic | THP1.0 (RT) (N=32) | THP1.1 (RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|--------------|-----------|-----------|---------------------|---------------------|-----------------------------|-----------------------------|
| 11. Did it immediately relieve your craving for a cigarette? | Pre-use | Mean (SD) | 2.7 (1.81) | 3.3 (2.18) | 2.3 (1.85) | 5.2 (2.48) |
|               |           | Median    | 2.0          | 3.0          | 1.5          | 7.0          |
|               |           | Min – Max | 1 – 7        | 1 – 7        | 1 – 7        | 1 – 7        |
|               |           | Q1 – Q3   | 1 – 4        | 1 – 5        | 1 – 3        | 4 – 7        |
|               | 15 min    | Mean (SD) | 2.7 (1.80) | 3.0 (2.00) | 2.3 (1.80) | 5.5 (2.09) |
|               |           | Median    | 2.0          | 2.0          | 1.5          | 7.0          |
|               |           | Min – Max | 1 – 7        | 1 – 7        | 1 – 7        | 1 – 7        |
|               |           | Q1 – Q3   | 1 – 4        | 1 – 5        | 1 – 3        | 5 – 7        |
|               | 240 min   | Mean (SD) | 2.5 (1.78) | 3.1 (1.83) | 2.4 (1.43) | 5.3 (2.18) |
|               |           | Median    | 2.0          | 3.0          | 2.0          | 6.0          |
|               |           | Min – Max | 1 – 7        | 1 – 7        | 1 – 7        | 1 – 7        |
|               |           | Q1 – Q3   | 1 – 3        | 2 – 5        | 1 – 3        | 4 – 7        |
| 12. Did you enjoy it? | Pre-use | Mean (SD) | 3.0 (2.28) | 3.1 (2.25) | 1.7 (1.12) | 6.6 (1.16) |
|               |           | Median    | 2.0          | 2.5          | 1.0          | 7.0          |
|               |           | Min – Max | 1 – 7        | 1 – 7        | 1 – 4        | 1 – 7        |
|               |           | Q1 – Q3   | 1 – 5        | 1 – 5        | 1 – 3        | 7 – 7        |
|               | 15 min    | Mean (SD) | 2.9 (2.12) | 3.1 (2.15) | 1.8 (1.22) | 6.2 (1.20) |
|               |           | Median    | 2.0          | 2.0          | 1.0          | 7.0          |
|               |           | Min – Max | 1 – 7        | 1 – 7        | 1 – 5        | 2 – 7        |
|               |           | Q1 – Q3   | 1 – 4        | 1 – 5        | 1 – 3        | 6 – 7        |
|               | 240 min   | Mean (SD) | 2.8 (2.05) | 3.1 (2.02) | 1.6 (0.98) | 6.3 (1.06) |
|               |           | Median    | 2.0          | 2.5          | 1.0          | 7.0          |
|               |           | Min – Max | 1 – 7        | 1 – 7        | 1 – 4        | 3 – 7        |
|               |           | Q1 – Q3   | 1 – 4        | 1 – 5        | 1 – 2        | 6 – 7        |
| PES question                                      | Timepoint | Statistic   | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|-------------------------------------------------|-----------|-------------|-------------------|-------------------|---------------------------|-----------------------------|
| 13. Did it relieve withdrawal symptoms?         | Pre-use   | Mean (SD)   | 2.5 (1.80)        | 3.2 (2.11)        | 2.5 (1.88)                | 6.3 (1.26)                  |
|                                                 |           | Median      | 2.0               | 3.0               | 2.0                       | 7.0                         |
|                                                 |           | Min – Max   | 1 – 7             | 1 – 7             | 1 – 7                     | 2 – 7                       |
|                                                 |           | Q1 – Q3     | 1 – 3             | 1 – 4             | 1 – 4                     | 6 – 7                       |
|                                                 | 15 min    | Mean (SD)   | 2.7 (1.87)        | 3.6 (2.11)        | 2.7 (1.69)                | 6.2 (1.42)                  |
|                                                 |           | Median      | 2.0               | 3.0               | 2.0                       | 7.0                         |
|                                                 |           | Min – Max   | 1 – 7             | 1 – 7             | 1 – 7                     | 2 – 7                       |
|                                                 |           | Q1 – Q3     | 1 – 4             | 2 – 6             | 1 – 4                     | 6 – 7                       |
|                                                 | 240 min   | Mean (SD)   | 2.8 (1.93)        | 3.6 (1.87)        | 2.3 (1.28)                | 6.3 (1.40)                  |
|                                                 |           | Median      | 2.0               | 4.0               | 2.0                       | 7.0                         |
|                                                 |           | Min – Max   | 1 – 7             | 1 – 7             | 1 – 5                     | 1 – 7                       |
|                                                 |           | Q1 – Q3     | 1 – 4             | 2 – 5             | 1 – 3                     | 6 – 7                       |
| 14. Did it relieve the urge to smoke?           | Pre-use   | Mean (SD)   | 2.6 (1.91)        | 3.3 (2.18)        | 2.5 (1.81)                | 5.6 (2.37)                  |
|                                                 |           | Median      | 2.0               | 3.0               | 2.0                       | 7.0                         |
|                                                 |           | Min – Max   | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                 |           | Q1 – Q3     | 1 – 4             | 1 – 5             | 1 – 4                     | 6 – 7                       |
|                                                 | 15 min    | Mean (SD)   | 2.8 (1.97)        | 3.5 (2.11)        | 2.6 (1.72)                | 6.5 (1.41)                  |
|                                                 |           | Median      | 2.0               | 3.0               | 2.0                       | 7.0                         |
|                                                 |           | Min – Max   | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                 |           | Q1 – Q3     | 1 – 5             | 2 – 5             | 1 – 4                     | 7 – 7                       |
|                                                 | 240 min   | Mean (SD)   | 2.7 (1.86)        | 3.4 (1.86)        | 2.5 (1.65)                | 6.0 (1.86)                  |
|                                                 |           | Median      | 2.0               | 3.0               | 2.0                       | 7.0                         |
|                                                 |           | Min – Max   | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                 |           | Q1 – Q3     | 1 – 3             | 2 – 5             | 1 – 3                     | 6 – 7                       |
| PES question | Timepoint | Statistic | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|--------------|-----------|-----------|-------------------|-------------------|--------------------------|-----------------------------|
| 15. Was it enough nicotine? | Pre-use | Mean (SD) | 3.2 (2.09) | 4.3 (2.35) | 4.7 (2.38) | 6.5 (1.19) |
| | | Median | 3.0 | 4.5 | 4.5 | 7.0 |
| | | Min – Max | 1 – 7 | 1 – 7 | 1 – 7 | 3 – 7 |
| | | Q1 – Q3 | 1 – 5 | 2 – 7 | 3 – 7 | 7 – 7 |
| | 15 min | Mean (SD) | 3.6 (2.29) | 4.7 (2.07) | 4.5 (2.08) | 6.7 (0.69) |
| | | Median | 3.5 | 5.0 | 4.0 | 7.0 |
| | | Min – Max | 1 – 7 | 1 – 7 | 1 – 7 | 4 – 7 |
| | | Q1 – Q3 | 1 – 5 | 3 – 7 | 3 – 7 | 7 – 7 |
| | 240 min | Mean (SD) | 3.4 (2.27) | 4.5 (2.31) | 4.4 (2.23) | 6.6 (0.95) |
| | | Median | 3.0 | 4.0 | 4.0 | 7.0 |
| | | Min – Max | 1 – 7 | 1 – 7 | 1 – 7 | 3 – 7 |
| | | Q1 – Q3 | 1 – 6 | 3 – 7 | 3 – 7 | 7 – 7 |
| 16. Was it too much nicotine? | Pre-use | Mean (SD) | 1.4 (0.98) | 2.4 (1.98) | 3.8 (2.57) | 1.8 (1.61) |
| | | Median | 1.0 | 1.0 | 3.0 | 1.0 |
| | | Min – Max | 1 – 5 | 1 – 7 | 1 – 7 | 1 – 6 |
| | | Q1 – Q3 | 1 – 1 | 1 – 4 | 1 – 7 | 1 – 1 |
| | 15 min | Mean (SD) | 1.4 (0.91) | 2.7 (1.69) | 3.4 (2.43) | 1.8 (1.34) |
| | | Median | 1.0 | 2.0 | 2.5 | 1.0 |
| | | Min – Max | 1 – 4 | 1 – 6 | 1 – 7 | 1 – 5 |
| | | Q1 – Q3 | 1 – 1 | 1 – 4 | 1 – 6 | 1 – 2 |
| | 240 min | Mean (SD) | 1.6 (1.01) | 2.7 (1.77) | 3.5 (2.51) | 1.7 (1.43) |
| | | Median | 1.0 | 2.0 | 3.0 | 1.0 |
| | | Min – Max | 1 – 4 | 1 – 6 | 1 – 7 | 1 – 6 |
| | | Q1 – Q3 | 1 – 2 | 1 – 4 | 1 – 7 | 1 – 1 |
| PES question                  | Timepoint | Statistic | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|-------------------------------|-----------|-----------|-------------------|-------------------|---------------------------|------------------------------|
| 17. Was it easy to use?       | Pre-use   | Mean (SD)| 6.5 (1.16)        | 6.4 (1.39)        | 6.7 (0.73)                | 7.0 (0.18)                    |
|                               |           | Median   | 7.0               | 7.0               | 7.0                       | 7.0                          |
|                               |           | Min – Max| 2 – 7             | 2 – 7             | 4 – 7                     | 6 – 7                        |
|                               |           | Q1 – Q3 | 7 – 7             | 7 – 7             | 7 – 7                     | 7 – 7                        |
|                               | 15 min    | Mean (SD)| 6.2 (1.48)        | 6.0 (1.96)        | 6.3 (1.61)                | 6.8 (0.78)                    |
|                               |           | Median   | 7.0               | 7.0               | 7.0                       | 7.0                          |
|                               |           | Min – Max| 2 – 7             | 1 – 7             | 1 – 7                     | 3 – 7                        |
|                               |           | Q1 – Q3 | 6 – 7             | 6 – 7             | 7 – 7                     | 7 – 7                        |
|                               | 240 min   | Mean (SD)| 6.2 (1.60)        | 6.2 (1.43)        | 6.3 (1.65)                | 6.8 (0.75)                    |
|                               |           | Median   | 7.0               | 7.0               | 7.0                       | 7.0                          |
|                               |           | Min – Max| 1 – 7             | 2 – 7             | 1 – 7                     | 4 – 7                        |
|                               |           | Q1 – Q3 | 7 – 7             | 6 – 7             | 7 – 7                     | 7 – 7                        |
| 18. Were there bothersome side effects? | Pre-use   | Mean (SD)| 1.5 (1.50)        | 1.5 (1.52)        | 1.4 (1.19)                | 1.1 (0.39)                    |
|                               |           | Median   | 1.0               | 1.0               | 1.0                       | 1.0                          |
|                               |           | Min – Max| 1 – 7             | 1 – 7             | 1 – 5                     | 1 – 3                        |
|                               |           | Q1 – Q3 | 1 – 1             | 1 – 1             | 1 – 1                     | 1 – 1                        |
|                               | 15 min    | Mean (SD)| 1.4 (1.27)        | 1.4 (1.16)        | 1.5 (0.92)                | 1.9 (1.76)                    |
|                               |           | Median   | 1.0               | 1.0               | 1.0                       | 1.0                          |
|                               |           | Min – Max| 1 – 7             | 1 – 7             | 1 – 5                     | 1 – 7                        |
|                               |           | Q1 – Q3 | 1 – 1             | 1 – 1             | 1 – 2                     | 1 – 2                        |
|                               | 240 min   | Mean (SD)| 1.1 (0.42)        | 1.4 (1.21)        | 1.4 (1.21)                | 1.8 (1.87)                    |
|                               |           | Median   | 1.0               | 1.0               | 1.0                       | 1.0                          |
|                               |           | Min – Max| 1 – 3             | 1 – 7             | 1 – 7                     | 1 – 7                        |
|                               |           | Q1 – Q3 | 1 – 1             | 1 – 1             | 1 – 1                     | 1 – 1                        |
| PES question                                                                 | Timepoint | Statistic  | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|------------------------------------------------------------------------------|-----------|------------|-------------------|-------------------|---------------------------|------------------------------|
| 19. Were you comfortable using the product in public?                        | Pre-use   | Mean (SD)  | 6.2 (1.56)        | 6.0 (1.96)        | 5.4 (2.29)                | 6.5 (1.54)                   |
|                                                                              |           | Median     | 7.0               | 7.0               | 7.0                       | 7.0                         |
|                                                                              |           | Min – Max  | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                                              |           | Q1 – Q3    | 7 – 7             | 7 – 7             | 4 – 7                     | 7 – 7                       |
| 15 min                                                                       | Mean (SD) | 6.1 (1.67) | 6.2 (1.71)        | 5.2 (2.47)        | 6.3 (1.53)                |                             |
|                                                                              | Median    | 7.0        | 7.0               | 7.0               | 7.0                       |                             |
|                                                                              | Min – Max | 1 – 7      | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                                              | Q1 – Q3   | 6 – 7      | 7 – 7             | 3 – 7             | 7 – 7                     |                             |
| 240 min                                                                      | Mean (SD) | 5.9 (1.87) | 6.0 (1.80)        | 5.3 (2.40)        | 6.3 (1.62)                |                             |
|                                                                              | Median    | 7.0        | 7.0               | 7.0               | 7.0                       |                             |
|                                                                              | Min – Max | 1 – 7      | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                                              | Q1 – Q3   | 5 – 7      | 6 – 7             | 3 – 7             | 7 – 7                     |                             |
| 20. Did you still have a craving for a cigarette after using the product?    | Pre-use   | Mean (SD)  | 4.2 (2.54)        | 4.3 (2.29)        | 4.2 (2.47)                | 2.3 (1.94)                  |
|                                                                              | Median    | 4.0        | 5.0               | 4.0               | 1.0                       |                             |
|                                                                              | Min – Max | 1 – 7      | 1 – 7             | 1 – 7             | 1 – 7                     | 1 – 7                       |
|                                                                              | Q1 – Q3   | 1 – 7      | 2 – 7             | 2 – 7             | 1 – 3                     |                             |
| 15 min                                                                       | Mean (SD) | 4.0 (2.09) | 3.4 (1.79)        | 4.2 (2.02)        | 2.0 (1.60)                |                             |
|                                                                              | Median    | 4.0        | 3.0               | 4.0               | 1.0                       |                             |
|                                                                              | Min – Max | 1 – 7      | 1 – 7             | 1 – 7             | 1 – 7                     |                             |
|                                                                              | Q1 – Q3   | 2 – 6      | 2 – 5             | 2 – 6             | 1 – 2                     |                             |
| 240 min                                                                      | Mean (SD) | 3.6 (1.95) | 3.8 (2.10)        | 4.4 (2.11)        | 3.0 (2.24)                |                             |
|                                                                              | Median    | 3.0        | 3.5               | 4.0               | 2.0                       |                             |
|                                                                              | Min – Max | 1 – 7      | 1 – 7             | 1 – 7             | 1 – 7                     |                             |
|                                                                              | Q1 – Q3   | 2 – 4      | 2 – 5             | 3 – 7             | 1 – 5                     |                             |
| PES question                                      | Timepoint | Statistic | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) |
|--------------------------------------------------|-----------|-----------|-------------------|-------------------|---------------------------|-----------------------------|
| 21. Are you concerned that you would become      | Pre-use   | Mean (SD) | 1.2 (0.79)        | 1.1 (0.39)        | 1.2 (0.72)                | 3.3 (2.60)                  |
| dependent on this product?                       |           | Median    | 1.0               | 1.0               | 1.0                       | 1.5                         |
|                                                  |           | Min – Max | 1 – 5             | 1 – 3             | 1 – 5                     | 1 – 7                       |
|                                                  |           | Q1 – Q3   | 1 – 1             | 1 – 1             | 1 – 1                     | 1 – 7                       |
|                                                  | 15 min    | Mean (SD) | 1.3 (0.96)        | 1.1 (0.34)        | 1.2 (0.75)                | 3.0 (2.44)                  |
|                                                  |           | Median    | 1.0               | 1.0               | 1.0                       | 1.0                         |
|                                                  |           | Min – Max | 1 – 6             | 1 – 2             | 1 – 5                     | 1 – 7                       |
|                                                  |           | Q1 – Q3   | 1 – 1             | 1 – 1             | 1 – 1                     | 1 – 5                       |
|                                                  | 240 min   | Mean (SD) | 1.3 (0.99)        | 1.4 (1.16)        | 1.2 (0.75)                | 2.7 (2.32)                  |
|                                                  |           | Median    | 1.0               | 1.0               | 1.0                       | 1.0                         |
|                                                  |           | Min – Max | 1 – 6             | 1 – 7             | 1 – 5                     | 1 – 7                       |
|                                                  |           | Q1 – Q3   | 1 – 1             | 1 – 1             | 1 – 1                     | 1 – 5                       |
**Supplementary Table 3.** Summary of treatment emergent adverse events (Safety Population). THP tobacco heating product,  *N* number of subjects,  *TEAE* treatment emergent adverse event. Data are number of subjects affected (% of subjects affected) [total number of events reported].

|                      | THP1.0(RT) (N=32) | THP1.1(RT) (N=32) | Nicorette Inhalator (N=32) | Usual brand cigarette (N=32) | Overall (N=32) |
|----------------------|-------------------|-------------------|-----------------------------|-------------------------------|----------------|
| TEAEs                | 2 (6.3%) [2]      | 2 (6.3%) [2]      | 1 (3.1%) [1]                | 3 (9.4%) [3]                 | 6 (18.8%) [8]  |
| Serious TEAEs        | —                 | —                 | —                           | —                            | —              |
| TEAEs Related to Investigational Product | — | — | — | 1 (3.1%) [1] | 1 (3.1%) [1] |
| Severe TEAEs         | —                 | —                 | —                           | —                            | —              |
| TEAEs Leading to Study Product Discontinuation | — | — | — | — | — |
| TEAEs Leading to Death | — | — | — | — | — |