Your Guide to the P1-COPD-04-INT Study

A visit-by-visit overview of your participation in this research study

Thank You for Participating in the P1-COPD-04-INT Study

This guide provides information about participating in the P1-COPD-04-INT study and outlines the procedures you will have during each scheduled visit. Please take a few minutes to read through this guide before each visit so you know what to expect. If you have any questions, please do not hesitate to ask a member of our study team.

About the P1-COPD-04-INT Study

The P1-COPD-04-INT study seeks to demonstrate the slowing of the disease progression, including the improvement of COPD symptoms, in smoking subjects with mild and moderate COPD with a history of chronic bronchitis symptoms (sputum and cough) who switch to Tobacco Heating System (THS) as compared to those who continue to smoke cigarettes.

The THS consists of a rechargeable holder (THS device) and its corresponding Tobacco Induction Sticks (Sticks). The Sticks are compatible only with the THS holder and are heated by the THS device holder to generate an aerosol without combustion. The holder maintains a heating temperature below 350°C, significantly lower than the temperature observed for cigarettes, which reaches 900°C. Unlike cigarettes, the Sticks and do not burn, or combust, like regular cigarettes during use. The THS holder is designed to deliver 20 consecutive uses per charge without needing to recharge.

P1-COPD-04-INT Study Groups

Participants in the P1-COPD-04-INT study will choose to participate in one of 3 groups, based on their personal preference:

- Those who completely switch to the THS product (THS group)
- Those who are not willing to quit smoking nor to switch to the THS product but who will be willing to continue to smoke cigarettes of their choice (Cigarette group)
- Those who decide to stop smoking and using any tobacco and/or nicotine containing products (SA group)

Study Participation at a Glance

The P1-COPD-04-INT study lasts a maximum of 39 months and includes:

- **Screening Period:** up to 28 days
- **Run-in Period (ambulatory period, between Visit 2 and 3):** 2 weeks during which participants who are not willing to quit smoking will be invited to try the THS product
- **Grace Period (ambulatory period, between Visit 2 and 3):** 2 weeks during which participants who are willing to quit smoking will be invited to set a date from which they will begin their smoking abstinence journey
- **Study Visit Frequency:**
  - **Assessments (on-site visits):** at 6 months (V4), 11 months (V5), 12 months (V6), 24 months (V7), 35 months (V8) and 36 months (V9) after enrollment
  - **Product Resupply Visits:** monthly for those in the THS group
- **Safety Follow-up period:** 28 days after the last study visit

Screening and Baseline Visits (Visits 1 and 2)

During the screening visit, you will be given Informed Consent Forms that you will have to accept and sign before starting any study activity. These Informed Consent Forms are here to explain you in writing all the details of the study. You will also have the opportunity to discuss any question you may have with the Study Investigator or designee. Once you've signed the ICFs, you will go through a series of assessments and procedures to determine if you are eligible to participate in the P1-COPD-04-INT study.

Screening Visit: Visit 1

During this visit you will:

- Receive and sign Informed Consent Forms
- Have a COVID Test (as per site requirements)
- Receive information on the risks of smoking, advice on smoking cessation, and information about the THS
- Have assessment of your eligibility
- Discuss any medications you have been taking
- Discuss your medical and disease history
- Complete a series of questionnaires
- Have a physical examination
- Have your vital signs taken
- Have your body mass index (BMI) and waist hip ratio (WHR) measured
- Have a pregnancy test (for all biological female subjects, if applicable)
- Provide blood and urine samples for testing
- Have screening tests for Alpha-1 Anti-Trypsin Deficiency (AATD), HIV and Hepatitis B & C
- Have a chest X-ray, if applicable
- Have an electrocardiogram (ECG) test
- Have a lung function (spirometry) test
- Be asked whether you would consider quitting smoking, and
  - if yes, you will be immediately allocated to the SA group. Your target quit date will then be after the Baseline Visit (V2), which is also when the smoking cessation counselling will start for you.
  - If no, the Investigator, or designee, will show you the THS and how it works but you will not try it at this stage.

Baseline Visit: Visit 2

During the baseline visit, you will choose which group you would prefer to be in (cigarette, THS, or smoking abstinence group), have some screening tests repeated, and complete several questionnaires.

During this visit you will:

- Arrive fasting (for blood draw)
- Have a COVID Test (as per site requirements)
- Receive information on the risk of smoking, advice on smoking cessation
- Receive result of your Alpha-1 Anti-Trypsin Deficiency (AATD) test
- Discuss any medications you have been taking
- Discuss any adverse events (side effects) you may be experiencing
- Receive an eDiary to complete the questionnaires during the study or will be explained how to do it from your own smartphone
- Complete a series of questionnaires
- Receive behavioral support counseling
- Receive information about the Tobacco Heating System (THS) if you are not willing to quit smoking
- Choose which group you prefer to be in (use THS, smoke cigarettes, quit smoking)
- Have a physical examination
- Have your vital signs taken
- Have your body mass index (BMI) and waist-hip ratio (WHR) measured
- Have a pregnancy test (for all biological female subjects, if applicable)
- Provide blood and urine samples for testing
- Have an electrocardiogram (ECG)
- Complete a 6-minute walking test
- Complete Sit to Stand test
- Have a lung function (spirometry) test
- Receive a rescue medication sensor (to count how often you use your rescue medication) and a training on how to use them
- Receive a THS device, Sticks and training on how to use them (if you are not willing to quit smoking)

Run-In/Grace Period (between Visit 2 and 3)

At the end of this Baseline Visit, and if you do not want to quit smoking or using tobacco products, you will enter a 2-week "Run-In Period", during which you will be asked to use THS ad libitum, meaning as much as you wish, to get familiar with the THS product. During this 2-week period, you can continue to smoke your regular brand of cigarettes. The device and any unused product should be returned to the study site at Visit 3 (after the run-in period).

If you who are willing to stop smoking you will enter a 2-week "Grace Period" to quit smoking and using tobacco products. If you have chosen to stop using tobacco products, and if you request for it, you can begin nicotine replacement therapy during this period and use it throughout the study.

Investigational Period (Visit 3 to Visit 9)

At the end of the run-in/grace period described above, you will have then to decide at Visit 3 whether you wish to continue to smoke during the study and enter the cigarette group or to switch to the THS and enter the THS group. If you chose at Visit 2 to stop smoking you will enter the SA group.

Whatever your decision is, meaning continue smoking or switch to THS, you will be asked to exclusively use your self-selected product (cigarette or THS, respectively). If you choose to stop smoking and not to use any other tobacco and nicotine containing products, you will be encouraged to remain abstinent for the study duration.

During the Investigational Period you will record information in the eDiary you received.

Self-Selected Group Allocation Visit: Visit 3

During this visit you will:

- Arrive fasting (for blood draw)
- Have COVID test (as per site requirements)
- Receive information on the risk of smoking, advice on smoking cessation
- Discuss any concomitant disease, including COVID infection(s)
- Discuss any side effects that you may have experienced
- Discuss any medications you have been taking
- Report event/complaints related to THS, if applicable
- Have your use of the eDiary checked
- Complete a series of questionnaires
- Declare the final preference for product group selection after the run-in period, if applicable
- Receive behavioral support counseling
- Have your vital signs taken
- Have a pregnancy testing (for all biological female subjects, if applicable)
- Provide blood and urine samples for testing
- Have an electrocardiogram (ECG)
- Return of THS device and unused Sticks if you choose to continue to smoke cigarettes
- Return unused Sticks, and receive new Sticks if you choose the THS group for the rest of the study

Remote Follow-up (between Visit 3 and Visit 4)

On top of the behavioral support provided during on-site visits (if you are in the THS or SA group), you will have additional follow-up sessions at Weeks 6, 7, 8, 12, 16 and 20. These visits are mandatory and will be fully remote for a duration of up to 15 minutes.

Between Visit 4 and Visit 9, additional in person and/or remote behavioral support can be provided upon you request.

Also, to encourage you to abstain from smoking (if you are in the SA group) or to sustain using exclusively THS, automated motivational Short Message Service (SMS) messages will be provided from V2 onwards. You will receive three text messages a week for the first month and then once per week for the following two months. You will be able to opt out of this additional support at any time.

Main Site Visits - Visit 4, Visit 6, Visit 7

You will be required to come for 3 main site visits at 6 months (V4), at 12 months (V6) and at 24 months (V7) after V2 (Baseline) . During these site visits, you will:

- Arrive fasting (for blood draw)
- Have COVID test (as per site requirements)
- Receive information on the risk of smoking, advice on smoking cessation
- Discuss any medications you have been taking
- Report event/complaints related to THS, if applicable
- Discuss any adverse events (side effects) you may be experiencing
- Have your use of the eDiary checked
- Complete a series of questionnaires
- Receive behavioral support counseling (SA and THS groups; only if requested by you)
- Have a physical examination
- Have your vital signs taken
- Have your waist to height ratio measured
- Have your body mass index (BMI) and waist-hip ratio (WHR) measured
- Have pregnancy testing (for all biological female subjects, if applicable)
- Provide blood and urine samples for testing
- Have an electrocardiogram (ECG)
- Have a lung function (spirometry) test
- Complete a 6-minute walking test
- Complete Sit to Stand test
- Return unused Sticks, and receive new Sticks if you chose the THS group

Pre-Confirmatory Visits – Visit 5 and Visit 8

You will be required to come for 2 pre-Confirmatory site visits at 11 months (V5) and at 35 months (V8) after V2 (Baseline). During this site visit, you will:

- Have COVID test (as per site requirements)
- Receive information on the risk of smoking, advice on smoking cessation
- Discuss any medications you have been taking
- Report event/complaints related to THS, if applicable
- Discuss any adverse events (side effects) you may be experiencing
- Have your use of the eDiary checked
- Complete a series of questionnaires
- Receive behavioral support counseling (SA and THS groups; only if requested by you)
- Have your vital signs taken
- Have pregnancy testing (for all biological female subjects, if applicable)
- Provide urine sample for testing
- Have a lung function (spirometry) test
- Return unused Sticks, and receive new Sticks if you chose the THS group

Visit 9 – End of Study Visit

You will be required to come for the last study visit at 36 months (V9) after V2 (Baseline). During this site visit, you will:

- Arrive fasting (for blood draw)
- Have COVID test (as per site requirements)
- Receive information on the risk of smoking, advice on smoking cessation
- Discuss any medications you have been taking
- Discuss any adverse events (side effects) you may be experiencing
- Report event/complaints related to THS, if applicable
- Have your use of the eDiary checked
- Complete a series of questionnaires
- Receive behavioral support counseling (SA and THS groups; only if requested by you)
- Have a physical examination
- Have your vital signs taken
- Have your waist to height ratio measured
- Have your body mass index (BMI) and waist-hip ratio (WHR) measured
- Have pregnancy testing (for all biological female subjects, if applicable)
- Provide blood and urine samples for testing
- Have an electrocardiogram (ECG)
- Have a lung function (spirometry) test
- Complete a 6-minute walking test
- Complete Sit to Stand test
- Return your THS device and all unused Sticks if you chose the THS group
- Return your rescue medication sensor
- Return your handheld device (eDiary) if you were given one for this study

Safety Follow-up

After you have left the site, you will be monitored for 28 days to assess any possible effect on your health. If you end your participation in the study with an adverse event (side effect) still in progress, you will be contacted via phone by the study investigator to follow-up on this event.

If you do not experience any adverse events prior to the end of your participation in the study, the study Investigator will instruct you to report any health problems or discomfort experienced during this period.

If you were enrolled in the THS or cigarette group, you will be free to smoke your preferred own brand of cigarette.

If you were enrolled in the smoking abstinence group, you will be encouraged to continue abstaining from smoking.

Withdrawal From the Study

You may decide to stop taking part in the P1-COPD-04-INT study at any time and without providing any reason. If you withdraw from the study before the end of the study period or if you are discontinued by the study Investigator, you will be asked to return to the study site for an early termination visit, within 5 days of your withdrawal or discontinuation.

During this visit, you will:

- Arrive fasting (for blood draw)
- Have COVID test (as per site requirements)
- Receive information on the risk of smoking, advice on smoking cessation
- Discuss any medications you have been taking
- Discuss any adverse events (side effects) you may be experiencing
- Report event/complaints related to THS, if applicable
- Have your vital signs taken
- Have a pregnancy test (for all biological female subjects, if applicable)
- Return your device and non-used products (if you were in the THS group)
- Provide blood and urine samples for testing
- Have an electrocardiogram (ECG)
- Have your use of the eDiary checked (return of your eDiary)
- Return your handheld device (eDiary) if you were given one for this study
- Return your rescue medication sensor

Resupply Visits

If you are in the THS group, you will keep the THS device for use during the investigational period and will be supplied with Sticks in sufficient quantities for your needs until the next supply visit. These visits are on a monthly basis but can be adapted based on your needs and availabilities, but this must be discussed and agreed with the study Investigator.

At the next supply visit, you will have to return to the site staff all unused Sticks and you will receive a new supply of Sticks.

Site Visit Reminders

Attending each study visit allows the study staff to monitor your health and well-being on a regular basis. It is important that you keep all scheduled study visits. If you will be unable to attend a scheduled visit, please call the study site as soon as possible to reschedule.

P1-COPD-04-INT Study Contact Info

Study Doctor: _____

Study Coordinator: _____

Study Clinic/Address: _____

Phone Number: _____

Please do not hesitate to ask a member of the study team if you have any questions.

To make it easier, you may list out your appointment information here:

Visit Date: _____ Time of Appointment: _____

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Notes

Use this page to keep track of any questions you might have for the study team or to note anything you have observed about your health during the study.

Thank You for Your Participation

Thank you for taking part in the P1-COPD-04-INT study. If you need to reschedule an appointment, please contact our study staff at your earliest convenience and we will work with you to make arrangements. If you have any questions, please contact a member of our study staff.

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