Subject information for participation in medical scientific research

A study to investigate the effect of FP-025 on the airways of asthmatic subjects with house dust mite allergy

Official title: The effect of FP-025, a MMP-12 inhibitor, on allergen-induced airway responses, airway inflammation and aspects of airway remodeling in subjects with mild eosinophilic house dust mite (HDM)-allergic asthma

Retain this information for future reference.

Participant number: |__|__| |__|__|__|__|

Dear Sir/Madam,

You are asked to take part in a medical scientific study. Participation is voluntary. Participation requires your written consent. You have received this letter because you have asthma and are allergic to house dust mite. You will receive a separate form with explanation about the measures QPS Netherlands B.V. takes to prevent contamination with COVID-19.

Before you decide whether you want to participate in this study, you will be given an explanation what the study involves. Please read this information carefully and ask the investigator for an additional explanation if you have any questions. You can also ask the independent physician, who is mentioned at the end of this document, for information. And you are also welcome to discuss your participation with your partner, friends or family. Additional information about participating in a medical scientific study can be found in the enclosed general brochure on medical scientific research. In case you decide not to participate in this study, please be ensured that this will not affect your medical treatment.

You may participate in maximally four (medicine) studies every year and only in one single study at a time. We will check this in a central registry that includes other research institutes. Information about participation in research is stored confidentially in this system.

1. General information

This research will be carried out in two centers, namely the independent research institute QPS Netherlands B.V. in Groningen and the Amsterdam UMC (location AMC) in Amsterdam. The research is performed at the request of Foresee Pharmaceuticals Co., Ltd. The sponsor pays for the costs of this study. The physicians, researchers and staff who are in charge of the trial are employed by QPS Netherlands B.V. or the Amsterdam UMC and have no (financial) relationship with Foresee Pharmaceuticals Co., Ltd. This is to ensure that there is no conflict of interest between the research physicians, researchers and the sponsor.

For this study male and female subjects aged 18 up to and including 55 years at the screening will be recruited and screened for eligibility. Thirty-two (32) to 36 of these subjects will ultimately be participating in the entire study.

The medical scientific research ethics committee “Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO)” in Assen (phone no.: +31 (0)592-405871) has approved this study. General information about the assessment of research can be found in the general brochure on medical scientific research.

2. Purpose of the study

During this study the effect of FP-025 on the lung function following an allergic response to inhaled house dust mite will be investigated by serial lung function measurements and other airway and blood tests in asthmatic subjects with house dust mite allergy. The safety, tolerability, absorption and breakdown of FP-025 will also be investigated in asthmatic subject who are allergic to house dust mite.

3. Background of the study

FP-025 is not yet registered for the treatment of asthma. It is a new drug that is currently being developed for the treatment of asthma and chronic obstructive pulmonary disease (COPD), being the most prevalent lung disorders worldwide. Patients with asthma and COPD may present with difficulties with breathing, as their airways are obstructed and inflamed. The causes of asthma and COPD are different. Their management and course of disease may also differ, depending for example on the type of airway inflammation a patient has. However, both airway disorders are characterized by inflammation and structural changes within the airways.

Evidence has been provided that the protein MMP-12 may play a role in the inflammation and structural changes of the airways. The study drug FP-025 developed by the sponsor is an inhibitor of MMP-12 and therefore possibly blocks certain aspects of the airway inflammation and improves some of the structural changes within the airways following house dust mite inhalation. In a mouse model, FP-025 has indeed been shown to have anti-inflammatory activity and a positive effect on the airways. In two previous studies this agent has been administered to healthy subjects. In these studies, FP-025 was given in single and multiple ascending doses. Both studies demonstrated that FP-025 is safe and well tolerated. The dose of FP-025 that will be used in this study is based on the doses used in the previous studies.

4. What participation involves

This study consists of two study periods. Prior to the study, your eligibility for the study will be tested on 3 screening days (S1, S2 and S3). You will come to QPS Netherlands B.V. for S1. If you satisfy the criteria during S1, you will come to the Amsterdam UMC for S2 and S3. If you participate, you will stay in the Amsterdam UMC for at least 5 days (3 nights) per study period (mandatory overnight stays in a hotel near the Amsterdam UMC: Day -1 until Day 1 and Day 10 until Day 12). Furthermore, you will come to the Amsterdam UMC for a visit on Day 5 and Day 9 in study period 1 and 2, and for a follow-up visit. Depending on your personal situation, the total number of overnight stays per study period may be increased with 3 more optional overnight stays (optional overnight stays: Day S2 until Day S3 and Day 9 until Day 10 in study period 1 and 2). In total, during the entire study you will stay in the Amsterdam UMC (hotel) for at least 10 days (6 nights) and at the most 14 days (9 nights). No visits are scheduled on Day 2-4 and Day 6-8 of each study period, however you may be asked to visit the Amsterdam UMC on these days upon assessment by the research physician. You are accessible for a phone call during these days when you will take study drug. In total, depending on your personal situation, during the entire study you will come to the Amsterdam UMC for a maximum of 22 times for a short visit or stay.

The situation above regarding the location of the screening visits and the study are applicable during 2020 and may change depending on the situation in 2021. In the sense that the study including the screening and follow-up may be performed entirely in the QPS clinic. If this is the case, you will be informed about this by the screening team.

Between screening and the first study period there will be a washout (this is a treatment-free) period of 3 to 7 weeks during which no study procedures will take place. Both study periods will also be separated by a treatment-free period of 3 to approximately 7 weeks during which no study procedures will take place. In total, the study will last at minimum 13 weeks and at maximum approximately 26

weeks, depending on the exact duration of screening period and the periods without study procedures and depending on potential rescheduling of appointments in case your asthma is unstable.

The timing, visits and a summary of the study procedures are listed in Scheme 1. More information about the study procedures can be found in **appendix C**.

Scheme 1

Study Timeline →		
Screening (between screening and Study Period 1 will be a treatment-free period of 3-7 weeks)	**Study Period 1 & 2 (between study periods will be a treatment-free period of 3-7 weeks)**	**Follow-up**
Day S1: 1 visit Day S2: 1 visit (within 40 days after Day S1) Day S3: 1 visit (within 8 days after Day S2) If visits on Day S2 and Day S3 are scheduled on 2 sequential days, you may be asked to stay in the Amsterdam UMC for 1 optional overnight stay. Within 1 week before Day S2: phone call Within 48 hours after Day S3: phone call	Day -1 until Day 1: mandatory stay in the Amsterdam UMC (hotel) Day 2 until Day 4: no scheduled visit Day 5 (± 1 day): 1 visit Day 6 until Day 8: no scheduled visit Day 9:1 visit Day 10 until Day 12: mandatory stay in the Amsterdam UMC (hotel) Within 1 week before Day -1: phone call Twice daily telephone contact during study drug intake at home and completion of diary Within 72 hours after and within 1 week after Day 12: 2 phone calls If deemed necessary by the research physician: additional phone calls or, if needed, 1 short visit after each study period Note that you may be asked to also stay overnight at the Amsterdam UMC from Day 9 until Day 10.	12 to 16 days after final study drug administration in study period 2: 1 visit
Eligibility check	Administration of FP-025 or placebo (8 capsules, twice daily)	Check general health
Medical history Physical Examination Heart tracing (ECG) Height Weight BMI (Body Mass Index) Blood pressure Heart rate Respiration rate	Medical history Physical Examination Heart tracing (ECG) - Weight - Blood pressure Heart rate Respiration rate	Medical history Physical Examination Heart tracing (ECG) - Weight - Blood pressure Heart rate Respiration rate

Study Timeline →		
Screening (between screening and Study Period 1 will be a treatment-free period of 3-7 weeks)	**Study Period 1 & 2 (between study periods will be a treatment-free period of 3-7 weeks)**	**Follow-up**
Body temperature	Body temperature	Body temperature
Blood oxygen	Blood oxygen	Blood oxygen
Allergy test (if needed)	-	-
Blood tests	Blood tests	Blood tests
Urine tests	Urine tests	Urine tests
Alcohol breath test	Alcohol breath tests	-
-	Questionnaire asthma symptoms	-
Lung function test	Lung function tests	Lung function test
Methacholine/histamine provocation test	Methacholine/histamine provocation tests	Methacholine/histamine provocation test
House dust mite provocation test	House dust mite provocation test	-
Collecting coughed-up sputum	Collecting coughed-up sputum	Collecting coughed-up sputum
-	Breath analyses	Breath analyses
-	Nasal flushes and nasal brushes	Nasal flush and nasal brush
Dispensing of diary and patient instructions	-	-

During the study, we will regularly ask you how you are feeling. To this end, several phone calls are scheduled (see **Scheme 1**). Any complaints you report between visits will also be registered. We will ask you to record all complaints in a diary that will be provided to you on Day S3, as these complaints may be side-effects of the study drug. For the first screening visit you will have to come to the QPS clinic in a fasting state, and for your admittance on Day -1 and Day 10 and the Follow-up, you will have to come to the Amsterdam UMC in a fasting state. A fasting state means that you are not allowed to eat or drink anything (except water) for at least 4 hours before you arrive at the QPS clinic or the Amsterdam UMC.

Screening

During screening, we will assess whether you may participate based on the measurements listed in Scheme 1. On Day S1, you will come to the QPS clinic, on Day S2 and S3 you will come to the Amsterdam UMC. On Day S1, we will ask you about your medical history and blood will be drawn to test your general health and (in female subjects) to determine if you are pregnant. If you are postmenopausal, your hormone level will be checked with a blood test. Urine will be collected to determine if you have used drugs or if you have smoked. An alcohol breath test is used to check if you have been drinking alcohol. An allergy test, to determine what you are allergic to, will be performed (see **appendix C**), except when an allergy test has already been performed in the past 12 months. You will also be tested for HIV (AIDS-test), hepatitis B and hepatitis C. If you have any of these diseases, we will tell you. If you do not want to know, you cannot participate in this study. If deemed necessary by the research physician, some measurements of Day S1 may be moved to Day S2 or Day S3 and/or may be repeated on Day S2 and/or Day S3.

The screening sometimes reveals findings that require further medical examination. We will always inform you about these findings, while further medical analysis will be done by your own general practitioner or medical specialist. The costs of these extra investigations will be charged to your own insurance.

On Day S2, a lung function test and a so-called methacholine/histamine provocation test will be performed. These tests will provide information on certain aspects of your asthma and how sensitive

your airways are. These tests will determine your eligibility in the study. In addition, you will inhale a salty aerosol and will be asked to cough up sputum for the analysis of airway cells and their products.

On Day S3, you will be asked to inhale several ascending concentrations of house dust mite. With this house dust mite provocation test, it will be determined at which concentration house dust mite an allergic airway reaction is provoked that is suitable for the remainder of the study. More information about the lung function test, the methacholine/histamine provocation test, the collection of coughed up sputum and the house dust mite provocation test can be found in **appendix C**.

When you leave the Amsterdam UMC on Day S3, we will provide you with Ventolin MDI (aerosol), including instructions. You may use Ventolin as needed throughout the study. The use of other asthma medications is not allowed during the study. You will be asked to write the use of Ventolin in your diary on a daily basis (date, time point and number of puffs). If you do not use Ventolin on a certain day, you can write '0'.

In the event you asthma temporarily worsens during the study, it is allowed to temporarily increase the use of Ventolin. But if you need more than 4 times a day during 2 consecutive days, you have to inform the study physician. You can find their telephone numbers in **appendix A** or in your diary. Furthermore we are asking you to take with you all other medication you are using, including Ventolin during every visit to the QPS clinic or the Amsterdam UMC.

Study Period 1 and 2

During Study Period 1 and 2, you will come to the Amsterdam UMC. During each study period, asthma stability will be checked on Day -1 (by a questionnaire, laboratory tests and ECG) and on Study Day 1 (lung function tests and methacholine/histamine test). If your asthma is still stable and protocol criteria are still met, you can participate in the study.

The participants will be divided in 2 groups. One half of the subjects will receive 400 mg of FP-025 (the study drug) as 8 capsules of 50 mg, twice per day in Period 1, the other half will receive a placebo (8 capsules to be taken twice per day). A placebo is a 'fake drug' without effect on your body. In Period 2, it will be the other way around, the group that received the study drug in Period 1 will now receive placebo. The group that received placebo in Period 1 will now receive study drug. It will be determined by chance (like flipping a coin) in what order you will receive the study drug or placebo.

Please store all study drugs in the refrigerator. After receiving the study drugs, put the study drugs in your refrigerator as soon as you arrive at home. Please make sure that only you will take the study drugs and please make sure that children do not have access. The study drugs can be kept outside the refrigerator for up to 24 hours. Please do not keep the study drugs under direct sun light.

This is a so-called double-blind study, which means that neither you nor the investigator will know which treatment you receive. This can be found out, should it be important to your health. General information about this can be found in the general brochure on medical scientific research.

You will ingest 8 capsules of study drugs with 240 ml water one time a day on Day 1 and Day 12 and two times a day – 8 capsules of study drug in the morning (in the Amsterdam UMC: between 7:00 and 9:00 am; at home: between 6:00 and 10:00 am) and 8 capsules in the evening (in the Amsterdam UMC: between 7:00 and 9:00 pm; at home: between 6:00 and 10:00 pm) - from Day 2 to Day 11. The first time you will use the study drug, it will be taken under supervision of a nurse or research physician. On Day 2 and up to and including Day 9, you will take the study drug at home. When you visit the Amsterdam UMC on Day 5 you can take your study drugs in the morning or in the evening in the Amsterdam UMC. It will be checked if you have taken the study drug using a diary and with a phone call. During the study drug intake at home, you will be contacted daily by study staff. You will be asked how you are feeling, how many capsules you have taken, to indicate your asthma symptoms, if you used Ventolin, if there have been any complaints and if you have any other question or concern.

Every time you visit the Amsterdam UMC, you have to bring your study drug including empty packages, your patient instructions, Ventolin, any other concomitant medications and your completed diary which will be reviewed.

During each study period, blood will be collected to check your general health, to determine the amount of FP-025 and its breakdown products and to determine the response of your body to the study drug. Urine, exhaled breath, lung mucous, fluid from your breath and nasal cells and liquid will also be collected to determine the response of your body to the study drug. Furthermore, the provocation test with house dust mite test will be performed once during each study period (Day 11) using those concentrations of house dust mite that produced an adequate airway response during screening.

After completion of each period, within one week after the last intake of the study drug your general health will be checked. This may be done with a phone call, but if needed you may be asked to come to the Amsterdam UMC for a short visit.

Follow-up
The follow-up will take place 12 to 16 days after the last intake of the study drug or placebo in Period 2 in the Amsterdam UMC. A number of final tests will be performed (see **Scheme 1**).

5. What is expected of you

In order to carry out the study properly and for your own safety, it is important that you follow the following rules.

The most important rules are:

- You are expected to be present at pre-arranged times and accessible for a phone call during dosing days at home.
- During the study you must follow instructions given to you by the nursing staff or research physician.
- You are willing to take the study drug as directed.
- You will not participate in another medical study.
- The only asthma medication you will use during the study is the Ventolin provided to you during the screening.
- In the QPS clinic and the Amsterdam UMC you will be given food, drinks and snacks at fixed times. You are not permitted to bring or eat your own food, drinks or snacks.
- Smoking is not allowed from 12 months before screening until follow-up. The use of any other tobacco- or nicotine-containing products is prohibited from screening up to and including follow-up. This will be regularly checked. Furthermore, you should prevent second-hand smoking as much as possible.
- From screening until the follow-up, you are not allowed to take any of the drugs specified in **appendix C**. Infrequent use of paracetamol or short-acting beta-2 agonists is permitted, but please notify the research physician if you use these drugs.
- The use of drugs is not permitted from screening until the follow-up. This will be checked.
- From 48 hours before Day -1 and up to and including Day 11 of each period, you are not allowed to drink alcohol. In the treatment-free periods it is allowed to drink 1 unit of alcohol per 24 hours.
- From 12 hours prior to any visit to the QPS clinic or the Amsterdam UMC until all tests during that visit are finished, you may not consume any xanthine containing drinks or food (coffee, tea, cola, chocolate or energy drinks (e.g. red bull)). This restriction is not applicable during the

treatment-free periods. Decaffeinated drinks including green tea or rooibos tea are allowed during the study

- From 48 hours prior to any visit to the QPS clinic or the Amsterdam UMC until all tests during that visit are finished, you must avoid strenuous physical effort (endurance sports, competition sports, heavy lifting). It is furthermore advised to avoid strenuous physical effort for at least 48 hours after the inhaled allergen challenges.
- From Day 1 up to and including Day 12 of each period, you are not allowed to work irregular night shifts and you must ensure you get a good night rest. This restriction is not applicable during the treatment-free periods.
- Please inform study staff if you have plans to travel, taking into consideration that the study drugs should be stored in the refrigerator.
- If you are allergic to animals (such as cats), you may not be exposed to these animals during the study. If you are allergic to pollen, you will be challenged outside the relevant pollen season.
- During the study until 90 days after the last administration of study drug, it is important to use 2 reliable contraceptive methods when having intercourse to avoid (potential) harm to an unborn child (see **appendix C**).
- If you disobey the rules or fail to keep appointments, measures will be taken and you may be excluded from further participation.
- You will carry your participant card for the study with you. This card states that you are participating in this study. It also states whom to contact in the event of an emergency. Show this card if you visit a doctor.

It is important that you contact the investigator if one of the following situations occurs:

- You start using other medicines. Even if they are homeopathic or natural remedies, vitamins and/or over-the-counter medicines.
- You are admitted to hospital or are going for treatment there.
- You suddenly develop any health problems.
- You no longer want to participate in the study.
- Your contact details change.
- You or your partner become(s) pregnant during the study.

6. Possible side effects

The study drug has previously been administered to humans and was generally well tolerated. A number of side effects possibly linked to the study drug have been reported. These were: diarrhea, fatigue, dizziness, headache, coughing, a sore throat, eye irritation, redness of the skin and rash.

The risk to health at this dose level is limited but you may experience one of the above mentioned side-effects or other symptoms not previously reported. Your health will be closely monitored during the trial to minimize these risks.

Doctors will monitor your health and possible side effects of the study drug closely. If you develop any complaints, the research physician will treat these if necessary. Should new information become known concerning the safety of the study drug, we will tell you as soon as possible.

If you notice changes in your physical or mental condition or if you experience side effects, we ask you to tell the research physician immediately. The research team will also collect blood samples to monitor for abnormal values. This is important for your own safety as well as for the quality of the research.

What to do after a provocation or challenge test?
After a bronchial provocation or challenge test, during which irritating particles will be inhaled (for example methacholine, histamine, hypertone saline or allergen) your airway will respond with constriction similar to what you will recognize and experience as your asthma symptoms. Methacholine, histamine and hypertonic saline are commonly used in clinical practice, while allergen challenge tests are mainly used to test clinical effectiveness of new drugs with asthma. After all these tests you will always receive Ventolin to treat the airway constriction and your pulmonary function will be checked to ensure you are safe to leave the Amsterdam UMC. Depending on your personal situation (health/place of residence), the study physician may advise you to stay an extra night in the Amsterdam UMC. After each allergen challenge test you have to make sure you always have Ventolin with you and you will follow the patient instructions. In case of any concern you have to contact the study physician (the contact details can be found in the patient instructions). The first night after each allergen challenge test you will take Ventolin before you go to sleep. During the night you should not be alone.

Blood Collection
The blood collection procedure may cause discomfort or bruising. In total, approximately 365 ml of blood will be taken from you. This amount does not cause any physical problems in adults. To compare: a blood donation involves 500 ml of blood being taken each time.

7. Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide to join. If you participate in this study, this does not mean that your disease will be cured or that you will suffer less from your disease.

The study drug may relieve your airway complaints, but this is not certain. Your symptoms may return or worsen at any time during this study.

Disadvantages of participation in the study may be the possible discomforts of the tests performed in the study or possible side effects. All these aspects have been described above under point 6 and in **appendix C**.

8. If you do not want to participate or you want to stop participating in the study

It is up to you to decide whether or not to participate in the study. Participation is voluntary. If you decided to stop your participation, this will not affect your medical treatment

If you do participate in the study, you can always change your mind and decide to stop, at any time during the study. You do not have to say why you are stopping, but you do need to tell the investigator immediately. The data collected until that time will still be used for the study. If you want, any collected bodily material can be destroyed. If you stop, there will be no impact on your standard medical care.

If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to continue your participation.

9. End of the study

Your participation in the study stops when:
- All visits according to Scheme 1have been completed.
- You yourself choose to stop.
- You become pregnant.
- The investigator considers it best for you to stop.

- Foresee Pharmaceuticals Co., Ltd., the government or Medical Research Ethics Committee, decides to stop the study.

The entire study is concluded once all the participants have completed the study. The study drug you have used during the study will not be available once the study has ended. The investigator will discuss the options for further medical care with you.

10. Usage and storage of your data and bodily material

Your personal data and bodily material will be collected, used and stored for this study. This concerns the following data: your name, address, date of birth (month and year) and data about your health. The collection of blood, urine, exhaled breath, lung mucous, fluid from your breath and nasal cells and liquid is required for this study. The collection, use and storage of your data and your bodily material is required to answer the questions asked in this study and to publish the results. It is also required to put the investigated product on the market. We ask your permission for the use of your data and bodily material.

Confidentiality of your data and bodily material

To protect your privacy, your data and your bodily material will be given a code. Your name and other information that can directly identify you, will be omitted. Data can only be traced back to you with the encryption key. The encryption key remains safely stored in the local research institute. The data and bodily material that is sent to the sponsor and any other involved parties will only contain the code, not your name or other data with which you can be identified. The data cannot be traced back to you in reports and publications about the study.

Access to your data for verification

Some people can access all your data at the research locations, including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable manner. Persons who have access to your data for review are: the study team, a monitor working for the sponsor of the study or who has been commissioned by the sponsor of the study, national and international supervisory authorities, for example, the Healthcare and Youth Inspectorate and Medical Research Ethics Committee. They will keep your data confidential. We ask you to consent to this access.

Retention period of your data and bodily material

Your data must be kept for 15 years at the research locations and at the sponsor. Your bodily material will not be destroyed immediately after use. It will be kept in order to be able to perform new assessments in connection with this study, in the course of this study.

We will also extract DNA from your blood sample that may in future reveal genetic differences between participants that may further explain some of the results of the study. You can indicate on the consent form if you agree with this genetic research.

Storage and use of bodily material for additional research

Your bodily material may also be of importance to further investigate the effect of FP-025 on the airways of asthmatic subject who are allergic to house dust mite. To this end, your bodily material will be stored for15 years. You can indicate on the consent form whether or not you agree with this. If you do not agree with this, you can still participate in the current study. By signing the consent form, you agree to this.

Information about unexpected findings

During this study, something may be found by chance that is not important to the study, but may be important to you. If this is important for your health, you will be informed. You can then discuss with your doctor or specialist what needs to be done. You also consent to this.

Withdrawing consent

You can withdraw your consent to the use of your personal data at any time. This applies to this study and also to storage and use for future research. The study data collected until the moment you withdraw your consent will still be used in the study. Your bodily material will be destroyed after your consent has been withdrawn. If measurements have already been made with that bodily material, then this data will still be used.

Passing on to countries outside the European Union (EU)

In this study, your encoded data and bodily material will also be sent to countries outside the EU because the sponsor and facility institutions are located outside the EU. In those countries, the EU rules on the protection of your personal data do not apply. However, your privacy will be protected at an equal level. If you do not approve of this, you cannot participate in the study.

More information about your rights when processing data

For general information about your rights when processing your personal data, you can consult the website of the Dutch Data Protection Authority.

If you have questions about your rights, please contact the person responsible for the processing of your personal data. For this study, that is QPS Netherlands B.V. (see **appendix A** for contact details).

If you have questions or complaints about the processing of your personal data, we advise you to first contact the research location. You can also contact the Data Protection Officer of the institution (see **appendix A**) or the Dutch Data Protection Authority.

Registration of the study

Information about this study is included in a list of medical-scientific studies namely www.toetsingonline.nl (CCMO register). You can find this study under the EudraCT number 2017-005164-17. This website does not contain any information that can be traced to you. After the study, the website may display a summary of the results of this study.

11. Study subject insurance

Insurance has been taken out for everyone participating in this study. This insurance covers damage caused by the study. The insurance does not cover all damages. **Appendix B** contains more information about the insurance. It also tells you who to report damage to.

12. Informing general practitioner and/or treating specialist

We will always send your general practitioner and/or treating specialist a letter to inform them about your participation in the study. This is for your own safety. If you do not agree to this, you cannot participate in this study.

It is possible that, during the study, a previously undisclosed and serious disease is discovered, such as hepatitis B, hepatitis C, cancer or HIV infection. If this occurs, you and your doctor will be informed.

You cannot participate in the study if you do not have a general practitioner.

13. Compensation for participation

For your participation in this study you will receive a remuneration fee of € 3126,- for participation in the entire trial. If you only participate in the screening (Day S1 until Day S3), you will receive a remuneration fee of € 432,-. Travel expenses will be refunded on the basis of kilometers traveled calculated based on your home postal code (the fastest route by car, as given by the route planner on www.anwb.nl). Your home postal code is taken from the personal details submitted by you during enrolment. Travel expenses will be reimbursed at € 0.19 per kilometer irrespective of mode of transport and irrespective of distance traveled. The remuneration payment will be reported to the tax

office as income. The (gross) remuneration fee will be paid within 1 month of completion of the study and after receiving your expenses form.

If you withdraw your participation before completion of the trial, the remuneration fee you receive will be adjusted accordingly. If you have to leave the trial because you have contravened the rules, you will forfeit a part of your fee.

If the research physician withdraws you from the trial e.g. because of complications or because the sponsor has decided to stop the trial, you will be reimbursed for the period during which you were a participant and a reasonable compensation for the reserved days will be paid.

14. Any questions?

If you have any questions, please contact the research physician. If you would like any independent advice about participation in this study, you may contact the independent doctor. He knows about the study but is not involved in it in any way.

If you have any complaints, you may contact QPS Netherlands B.V or the Amsterdam UMC. In addition, you may contact QPS Netherlands B.V. or the Amsterdam UMC should you have any questions with regard to your rights as a volunteer.

All the relevant details can be found in **appendix A**: Contact details.

15. Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide whether you will participate in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the information and consent to participate in the study.

The signature sheet is kept by the research physician. You will get a copy or a second copy of this consent form. We advise you to keep this copy until at least 3 months after the last visit.

16. Appendices to this information

A. Contact details for QPS Netherlands B.V and Amsterdam UMC
B. Insurance information
C. Additional and specific background information

Informed Consent Form

Appendix A: contact details for QPS Netherlands B.V. and Amsterdam UMC

Research physician

Dr. Zuzana Diamant
Tel: +31 (0) 50-8200483

Dr. Khalid Abd-Elaziz
Tel: +31 (0) 50-8200483

QPS Netherlands B.V.
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9713 GZ, Groningen

For emergencies outside of office hours
Tel: +31 (0) 6-12737834

Sponsor

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Locations where the study takes place

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www.qpsvrijwilliger.nl

* QPS Netherlands B.V. is an independent company situated on the UMCG grounds

AND

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Dr. Rudi Stellema, phone no.: +31(0)6-12685007

Data Protection Officer

Mr. Martijn van Dijk, QPS Netherlands B.V., phone no.: +31 (0) 50-8200483, email: privacy@qps.com

Complaints

You can request a complaint form via QPS Netherlands B.V. using the general telephone number: +31 (0) 50-8200483.

You can also contact QPS Netherlands B.V. via the general telephone number +31 (0) 50-8200483 for questions regarding your rights as a volunteer.

Appendix B: Insurance information

Insurance has been taken out by Foresee Pharmaceuticals Co., Ltd for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within four years of the end of the study. You must notify the insurance company about the damage within those four years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text.

This is set out in the Medical Research (Human Subjects) Compulsory Insurance Decree. This decree is listed on the website of the Central Committee on Research Involving Human Subjects www.ccmo.nl (see "Library" and then "Legislation and regulations").

You can report any damage to the insurance company directly.

The insurance company for the study is:	
Name:	HDI Global SE, The Netherlands
Address:	P.O.box 925, 3000 AX Rotterdam, The Netherlands
Telephone number:	+31(0)10-4036100
E-mail:	info@nl.hdi.global
Policy number:	V-058-430-867-8
Contact person:	Mr. M. Wijnsma (+3120 5650654)

The insurance covers €650.000,- per study subject and at least € 5.000.000,- for the entire study.

The insurance policy does **not** cover the following damage:

- damage as a result of a risk that you were informed about in the written information. This does not apply if the risk occurs in a more severe form than envisaged, or if the risk was very unlikely to occur;
- damage to your health that would also have occurred if you had not participated in the study;
- damage resulting from not or not (entirely) following directions or instructions;
- damage to your descendants as a result of a negative effect of the study on you or your descendants;
- damage as a result of an existing treatment method for research into existing methods of treatment.

Appendix C: Additional background information

Physical examination
During a physical examination, the research physician will examine your entire body.

Body Mass Index (BMI)
Your BMI will be calculated based on your height and weight.

Blood sampling
During the study, especially on Day 11 of each period, a sizeable amount of blood will be drawn. Therefore, a cannula (a thin, flexible tube) will be inserted into a vein in you lower arm on Day 10. After the last blood sample on Day 11 of each period the cannula will be removed. At other moments, blood will be taken from a vein in your arm using a needle. In total, we will take approximately 365 ml blood from you.

Heart Tracing (ECG)
An ECG will register the electrical activity of you heart. Stickers connected with wires to an ECG computer will be applied to your chest. This will measure your heart function. During this measurement you will lie on your back for a couple of minutes.

Blood pressure and heart rate
Your blood pressure and heart rate will be measured while you are lying down and have rested for 5 minutes.

Body temperature
Your body temperature will be measured with an ear thermometer.

Blood oxygen measurement
On some days and time points, the amount of oxygen in your blood will be measured by clipping a probe onto one of your fingers. This measurement will last a few minutes at most.

Allergy test
Blood will be drawn to check which allergens you are allergic to.

Alcohol breath test
You will be asked to take a deep breath, after which you will exhale into a testing apparatus for several seconds.

Questionnaire asthma symptoms
We will ask you to complete a questionnaire about your asthma symptoms.

Breath analysis
You will first be asked to completely expire and then breathe in deeply through an apparatus. Then you will be asked to slowly exhale into the same apparatus for online measurement of exhaled nitric oxide, a biomarker of airway inflammation.

Using another apparatus, fluid from your breath will be collected. To this end, you will be asked to breathe normally into an apparatus for 10 to 20 minutes.

Nasal flush and nasal brush
For the nasal wash, you will be asked to sit down with your head resting on a table. One nostril will be closed by a small tube connected to a small balloon. The other nostril is slowly filled with a saline solution via the tube. This solution will remain in your nostril for 5 minutes, after which it is removed from the nostril through the tube. During removal of the saline solution, this solution is used to briefly flush the nasal cavity twice. During this procedure, you are not allowed to blow your nose.

The nasal swab will be performed in the other nostril. During this test, a small brush is brushed on the inside of your nostril for 3 seconds.

Lung function test

You will be asked to blow hard in and out of a hollow tube while having a clip on your nose according to instructions given to you by the nurse. This test measures the volume of your lungs and provides information on how well your lungs are functioning.

Methacholine/histamine provocation test

This is a standard test in clinical practice to test the twitchiness of the airways. You will inhale several concentrations of nebulized methacholine or histamine solutions. Based on its availability, the investigator will determine if you will inhale methacholine or histamine. Methacholine is an irritating but harmless substance. Histamine is a harmless substance found in the body. The use of histamine can lead to a brief headache and/or blushing, particularly with higher doses.

Using several long function tests, it will be determined how your airways respond to the inhalation of methacholine or histamine.

House dust mite provocation test

You will inhale several concentrations of house dust mite. Using several measurements, it will be determined how your airways respond to the inhalation of house dust mite. Your airway response to house dust mite will be measured repeatedly using the previously described lung function test and by a specialized lung function test measuring small airways function called impulse oscillometry (IOS). For this test you will be asked to breathe through a mouthpiece connected with an analyzer for a couple of minutes.

Collecting coughed-up sputum

After inhalation of salbutamol, a lung function test is performed (see earlier point). With a clip on your nose, you will then breathe in a nebulized saline solution during 3 periods of 5 minutes (at approximately 15 minutes intervals). You will be asked to calmly breathe through your mouth. Once every minute, you will be asked to breathe in deeply. After every period of 5 minutes, you will be asked to blow your nose and to rinse your mouth with water, after which you will be asked to cough up sputum into a plastic container. After collecting lung sputum, your lung function will be checked.

Preventing pregnancy

Male participants

The effects of the study drug on an (unborn) child are unknown. We therefore expect male participants to use 2 types of reliable contraceptive methods to prevent pregnancy in their partner.

Male subjects must agree to use a condom with spermicide or to abstain from sexual intercourse throughout the trial (including the treatment free periods) and until 90 days after the last administration of study drug. Surgical sterilization can be accepted as a form of birth control if the sterilization procedure took place at least 4 months prior to the trial. You must agree to not donate sperm during the trial and until 90 days after the last administration of study drug.

Acceptable methods of birth control for female partners of male participants are the following: hormonal contraceptives (oral contraceptives, an implant or an injection), an intrauterine device (which should be placed at least 1 month before the start of the trial), or a diaphragm. Surgical sterilization of the partner of a male participant can be accepted as a form of birth control if the sterilization procedure took place at least 6 months prior to the trial.

Female participants

The effects of the study drug on an (unborn) child are unknown. It is therefore not allowed for female subjects to become pregnant or breastfeed a baby from screening until 90 days after study drug

administration. We therefore expect female participants to use 2 types of reliable contraceptive methods to prevent pregnancy or to abstain from sexual intercourse throughout the study (including the treatment free periods) and until 90 days after the last administration of study drug.

Acceptable forms of birth control are:

- Male or female condom;
- Hormonal contraceptives (oral contraceptives, an implant or an injection)
- Diaphragm;
- Cervical cap;
- Intrauterine device (IUD);
- Vasectomy of the sexual partner (performed at least 90 days prior to screening).

In order to participate in the study, a pregnancy test must be performed to confirm that you are not pregnant. This test will be repeated just before the study drug is administered in each study period and will be rechecked after the study.

If a pregnancy test during the study shows that you may be pregnant, you will be withdrawn from the study. You will be asked for the results of any tests and procedures carried out during your pregnancy and up to a birth. You may also be asked for the results from any evaluation of the baby after the birth.

Postmenopausal female participants

You are considered postmenopausal if you have not had a menstrual period for at least 12 months and if the concentration follicle stimulating hormone in your blood is higher than 30 mIU/mL.

Surgical sterilization can be accepted as a form of birth control if the sterilization procedure took place at least 6 months prior to the trial. Examples of sterilization procedures (that make you not able to become pregnant) are: surgical removal of the womb and/or both ovaries or bilateral tubal occlusion/ligation. If you are not able to become pregnant, you should show documentation supporting this.

Subject consent form

A study to investigate the effect of FP-025 on the airways of asthmatic subject who are allergic to house dust mite

- I have read and understood the subject information form. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my general practitioner and/or treating specialist to be informed about my participation in this study. It is possible that, during the study, a previously undisclosed and serious disease is discovered, such as hepatitis B, hepatitis C, cancer or HIV infection. If this occurs, you and your doctor will be informed.
- I give permission for information to be requested from my general practitioner and/or treating specialist concerning my medical details, if relevant to my participation in this study.
- I know that some people may have access to all my data to verify the study. These people are listed in this information sheet. I consent to the inspection by them.
- I am aware that FP-025 is not registered as a medicine.
- I consent to my data, blood samples and bodily material being used in the way and for the purpose stated in the information sheet.
- I consent to my data being stored at the research locations for another 15 years after this study.
- I consent to my bodily material being stored at the sponsor for another 15 years after this study and know that it may be used for additional research in the future as stated in the information sheet.
- Male subjects: I know that I must not impregnate my partner during the study and up to 90 days after final administration.
- Female subjects: I know that I must not become pregnant from screening until 90 days after study drug administration.
- The investigator has discussed the most suitable contraceptives for me and/or my partner with me.
- I □ **do**
  □ **do not** consent to my blood sample being stored for another 15 years after this study to perform genetic research.
- I know that my data and bodily material will be transferred to countries outside the European Union where the privacy rules of the European Union are not applicable.
- I consent to have my data and all research results exchanged between all the involved investigators and research locations.
- I want to participate in this study.

Surname: _____

First name (as mentioned on ID card):_____

Date: DD / MMM / YYYY (dd/mmm/yyyy) Signature _____

I have provided verbal and written explanations of this clinical research trial. I am prepared to answer any further questions arising over the trial to the best of my ability. If information comes to light during the course of the study that could affect the study subject's consent, I will inform him/her of this in a timely fashion. I will give a signed copy of the declaration of consent to the participant.

Name: _____
On behalf of QPS Netherlands B.V./ Amsterdam UMC

Date: DD / MMM / YYYY (dd/mmm/yyyy) Signature _____

Time: ____:____ (hr:min)