C4541003-1001	**A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACOKINETIC INTERACTION WITH MIDAZOLAM OF MULTIPLE ASCENDING ORAL DOSES OF PF-07258669 IN HEALTHY NON-JAPANESE, JAPANESE, AND OLDER ADULT PARTICIPANTS**

Pfizer Clinical Research Unit Brussels

EudraCT number:	2021-004037-36
Study medicine:	PF-07258669
Sponsor of the study:	Pfizer Inc.
Research organisation:	Pfizer Clinical Research Unit (PCRU), Route de Lennik 808, 1070 Brussels
Medical Ethics Committee:	Comité d'Ethique Hospitalo-Facultaire Erasme-ULB.
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Contents

C4541003-1001	**A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACOKINETIC INTERACTION WITH MIDAZOLAM OF MULTIPLE ASCENDING ORAL DOSES OF PF-07258669 IN HEALTHY NON-JAPANESE, JAPANESE, AND OLDER ADULT PARTICIPANTS**

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Pfizer Clinical Research Unit Brussels

I. Information vital to your decision to take part to the study

Introduction

You are being invited to take part in a clinical study to evaluate an investigational medicinal product. An investigational medicinal product is a medicinal product that is still being studied to evaluate its efficacy, safety or mode of action.

You will not personally derive any benefit from your participation in this study, but the results obtained could be very important for the development of medicines and treatments which will benefit other people.

Before you agree to take part in this study, we invite you to take note of its implications in terms of organisation and possible risks, to allow you to take a decision with full awareness of all the implications. This is called giving an “informed consent”.

Please read these few pages of information carefully and ask the investigator or his/her representative any questions you want. There are 3 parts to this document:

- the information essential to your decision,
- your written informed consent and
- supplementary information (appendices) detailing certain aspects of the basic information.

If you take part in this clinical study, you should be aware that:

- This clinical study is being conducted after having been reviewed and approved by one Ethics Committee and the federal agency for medicines and health products.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. However, even after having signed that document, you can stop participating in the study at any time, by informing the investigator of your decision.
- The data collected in the scope of the study are confidential and shall be processed in conformity with the General Data Protection Regulation and the Belgian law of 30 July 2018 relating to the protection of natural persons with regards to the processing of their personal data. Your anonymity is guaranteed during publication of the results.
- Insurance has been taken out in case you should suffer any damage in connection with your participation in this clinical study.
- You may contact the investigator or a member of his/her team at any time, should you need any additional information.
- If you have expressed a specific consent for this, your general practitioner will be informed of your participation in this study. He/she will also be informed when the study is complete.

Further information about the “Participant Rights” can be found in appendix (page 20).

Objectives and description of the study protocol

We are inviting you to take part in a clinical study involving PF-07258669 which will include around 150 participants. Of these, around 138 participants are planned in Part A and around 12 participants in Part B.

1. AIMS OF THE STUDY

PF-07258669 is a new medicine that is currently being developed as an oral treatment for metabolic diseases associated with unintended weight loss, such as geriatric anorexia (meaning the loss of appetite and/or decreased food intake in the elderly).

This research study will consist of 2 parts:

PART A:

If you participate in Part A of this study, you will receive multiple ascending doses of PF-07258669.

The purpose of part A of this research study is

- to evaluate the safety and tolerability of multiple, ascending, oral doses of PF-07258669 compared to placebo in healthy participants.
- to measure the amount of PF-07258669 in your blood and urine after you take multiple ascending doses of PF-07258669.
- to evaluate the effect of multiple, ascending doses of PF-07258669 administered for 14 days on body weight and body composition (e.g. total body water, fat mass, muscle mass, bone mass…)
- to evaluate the effect of multiple, ascending doses of PF-07258669 administered for 14 days on appetite, satiety and thirst.

If the results of Part A in healthy participants support further evaluation of PF-07258669, an optional cohort of approximately 8 Japanese adult participants may be enrolled in Part A of this study, to support enrolment of Japanese participants in future clinical studies with PF-07258669.

If the results of Part A and Part B in healthy participants support further evaluation of PF-07258669, an optional cohort of approximately 8-10 older adult participants may be enrolled in Part A of this study, to support enrolment of older adults in future clinical studies with PF-07258669. Older participants with chronic conditions (e.g., hypertension) that are controlled by either diet or stable doses of medications may be included in this optional cohort of older adult participants.

PART B:

If you participate in Part B of this study, you will receive the commercially available medicine midazolam with and without PF-07258669.

PF-07258669 might change the concentration and/or over time decrease the activity of certain liver enzymes that metabolize/change midazolam, so that it can be removed from the body. Taking midazolam together with PF-07258669 might therefore change the midazolam concentrations in the blood. This could change the effect of midazolam and/or the adverse reactions to this medicine.

The purpose of Part B of this research study is

- to compare how much midazolam is in your blood when you only take midazolam, and when you take midazolam after taking PF-07258669 for 10 days.
- to evaluate the safety and tolerability of midazolam alone and in combination with PF-07258669 in healthy participants.
- to evaluate the effect of multiple doses of PF-07258669 on hunger and thirst.

This will provide guidance for future dosing of PF-07258669 in combination with other medicines.
Part B will only be conducted if the results of Part A support further evaluation of PF-07258669.

2. LEGAL STATUS OF THE STUDY MEDICINES

PF-07258669 is a new investigational medicine. A new investigational medicine is one that is currently not approved for sale in Belgium.

Midazolam belongs to a group of medicines called benzodiazepines. They can be used for a number of medical purposes, including as a sedative for surgical procedures (anaesthesia), as well as to treat seizures, anxiety, and for sleeping disorders. The oral formulation used in this study is licensed in the EU for sedation prior to diagnostic, therapeutic or surgical procedures, and for short-term treatment of sleep disorders.

3. POSSIBLE SIDE EFFECTS

3.1. PF-07258669

PF-07258669 is a study drug given by mouth that has been shown to increase food intake and cause weight gain in animals. As of March 2022, there has been one completed clinical study of PF-07258669 in 29 healthy adult participants, of whom 20 were men and 9 were women of non-childbearing potential. These participants received single doses of PF-07258669 ranging from 0.1 mg to 300 mg, or a corresponding placebo (no drug). Based on data from these participants, single doses of PF-07258669 were well tolerated with an acceptable safety profile. All adverse events reported were “mild” in severity and there were no serious adverse events reported. Adverse events that were considered potentially related to PF-07258669 were a drop in blood pressure on standing that was not associated with symptoms in one participant and elevated levels of triglycerides in blood without associated symptoms in two participants.

There is a second, ongoing study in which repeated doses of either placebo (no drug) or PF-07258669 are administered to healthy participants for 14 days. One serious adverse event requiring hospitalization was reported during the follow up period in 1 participant (out of 10) in the first cohort of this study who received blinded study drug (PF-07258669 or placebo 3 mg every 8 hours, for a total daily dose of 9 mg per day, between study Day 1 and Day 14). This participant first reported polydipsia (excessive drinking due to excessive and inappropriate thirst) as well as excessive urination and increased appetite (when he could not drink) on Day 48 (34 days after last dose of study drug), at which point, he identified the date of onset of these symptoms as Day 30 (16 days after last dose of study drug). He required hospitalization for assessment and management of excessive and inappropriate thirst on Day 53 (39 days after last dose of study drug). These symptoms were not observed/reported during dosing or in the initial follow-up period after discharge from the clinical research unit. This participant also had a history of polydipsia during childhood that was not reported as medical history during the screening period. In the interval between last dose of study drug and the hospitalization for polydipsia, the participant tested positive for COVID-19 infection on Day 33. Blood tests during his hospital stay also showed that the participant had been infected with Epstein- Barr virus (EBV) in the weeks prior to hospitalization and had active disease during the hospital stay. The participant developed the following additional symptoms before or during the hospitalization: headache (MRI and CT imaging of brain were normal), visual impairment, balance disturbances, difficulty walking, sweating, dizziness, decreased appetite, nausea, transient low sodium levels in blood that required a 1-day stay in the intensive care unit, back pain, and a possible brief episode of loss of consciousness followed by single reports of low blood pressure, low body temperature, vomiting and diarrhea. As of March 2022, no final diagnosis is available and several of the symptoms (including thirst, headache, visual impairment, and balance disturbances), although improved, have not yet resolved. The cause of this serious adverse event is uncertain and while a potential role of study drug is considered unlikely (in the setting of prior past medical history of polydipsia, prolonged duration between last dose of blinded study medication and onset of symptoms and intervening medical issues such as COVID-19 infection and EBV infection), it cannot be excluded. Participants in this study will be monitored closely for any evidence of excessive or inappropriate thirst throughout the study.

Other than this participant, possible treatment-related adverse events reported for the remaining participants in this first cohort receiving blinded study drug were mainly reported as “mild”, except for areas of erythema (skin redness) and ecchymoses (bruising) in one participant that were graded as “moderate” and resolved spontaneously after discontinuation of study drug on the fifth day of dosing.

Otherwise, there are no other drugs (neither on the market nor in clinical trials) that work in a similar way to PF-07258669. As such, this summary is also based on information collected in animal studies. The study drug (PF-07258669) has been dosed in rats and in dogs for up to 1 month in duration. While animal studies do not always predict the adverse events humans may experience, the data that has been collected on PF-07258669 to date are summarized here. In rat and dog studies, decreases in heart rate and blood pressure were observed, and though those changes were observed at the doses potentially to be used in this study, heart rate and blood pressure decreases were relatively mild. The starting dose was selected to be significantly lower than the dose causing those effects in animals. Your heart rate and blood pressure will be monitored closely throughout the study.

At the highest dose level given in the 1-week dog study, convulsions were observed in one animal. This happened at the blood drug levels, which were 254 times higher than levels estimated to be needed in humans. Participants in this study will be monitored closely with serial physical exams directed at identifying any neurologic findings.

There was evidence of minimal to mild damage to the kidney in a rat study. The lowest dose at which this was observed was 117 times higher than levels estimated to be needed in humans. There were no kidney findings in dog studies at any doses used. Your kidney function will be monitored closely throughout this study using blood and urine tests. There were no serious findings in any other rats at this high dose level, or at any other dose level tested. Rats in the animal studies ate significantly more food, and many of those animals had larger internal organs, likely as a result of that. There were changes in blood chemical laboratory tests, including blood lipids including triglycerides; however, these were mild and not considered to be serious. Those effects also might have been influenced by increased food intake.

During this study, you will receive repeated doses of either placebo (no drug) or PF-07258669; this study is the first time that PF-07258669 will be given in repeated doses to humans. Though this remains to be determined based on the ongoing findings obtained from the study, the highest total daily dose of PF-07258669 that you will receive will be approximately 600 mg and will not exceed 2000 mg. All noteworthy adverse findings in animal studies were seen at high doses, higher than doses than you will receive, except for effects on heart rate and blood pressure.

At this time, there is no data on PF-07258669 regarding fertility, pregnancy, or breastmilk, so the study drug should not be administered to women of childbearing potential, pregnant women, or women who are nursing an infant. Appropriate precautions should be taken to prevent pregnancy in female partners of male study participants.

3.2. MIDAZOLAM SIDE EFFECTS

The following adverse effects have been reported following Midazolam administration, but their frequencies cannot be estimated from available data.

- Skin disorders (rash, pruritus (severe itching of the skin) and hives) and generalized allergic disorders (hypersensitivity reactions)
- Neurologic and psychiatric disorders: Drowsiness, reduced alertness, mental confusion, euphoria, hallucinations, fatigue, headache, dizziness, ataxia (lack of voluntary coordination of muscle movements), postoperative sedation, and anterograde amnesia (a condition in which a person is unable to create new memories after a memory-loss-inducing event), paradoxical reactions (treatment effects opposite to the effect which would normally be expected; agitation, involuntary movements, hyperactivity, hostility, anger, aggressiveness); physical dependence following prolonged administration, and withdrawal seizures following abrupt discontinuation of the drug.
- Gastrointestinal disorders: Nausea, vomiting, hiccups, constipation, dry mouth.
- Serious cardiorespiratory adverse effects: respiratory depression, apnea, respiratory arrest and/or cardiac arrest, hypotension, changes in the heart rate, vasodilation effects, dyspnea, laryngospasm.

Other currently unknown risks and discomforts could appear. It is therefore very important that any new health problem is quickly reported to the doctor, regardless of whether or not you think it has to do with the study.

As with any study medicines research, unexpected side effects may occur. These effects might be mild or serious. In some cases, these effects might be long-lasting or permanent, and might even be life-threatening. If any significant findings or side effects were to come to light during the course of this study, you would be notified.
In this case, you will be asked to sign either an addendum to the consent form or a new informed consent form.
The study medicines will not be available nor provided by the PCRU after the study has ended.

Course of the study

PART A
The study is planned to last for approximately 11 weeks.

Several examinations or procedures will be required in connection with the study:

- A screening examination
- A single treatment period organised of maximum 20 days and 19 nights in the PCRU.
    - In some cohorts, the first two participants might receive the study medicine for 48 hours, prior to the other participants. If the dose level of study medicine is judged to be safe, the remaining participants of that cohort will receive the study medicine as well. Participants of those cohorts might be admitted together at the same time or in separate groups.
- The check-up visit will take place approximately 7-10 days after the last administration of the study medicine.
- The follow-up phone call will take place approximately 28-35 days after the last administration of the study medicine.

PART B
The study is planned to last for approximately 11 weeks.

Several examinations or procedures will be required in connection with the study:

- A screening examination
- 2 consecutive treatment periods organised of 14 days and 13 nights in the PCRU.
    - The first two participants might receive the study medicine 48 hours prior to the other participants. If the study medicine is judged to be safe, the remaining participants will receive the study medicine as well. Participants might be admitted together at the same time or in separate groups.
- The check-up visit will take place approximately 7-10 days after the last administration of the study medicine.
- The follow-up phone call will take place approximately 28-35 days after the last administration of the study medicine.

1. SCREENING EXAMINATION

Before being allowed to take part in the study, you will undergo a medical examination, specifically an ECG as well as blood pressure and heart rate measurement both while lying down and standing up. Blood and urine samples (**for which you must have been fasting for at least 12 hours**) will be taken for laboratory tests and to screen for drugs. You will nevertheless be allowed to drink water.

For Part A: you will also be asked to also fill in a questionnaire that assesses your suicide risk.

A hormone test will be carried out for post-menopausal women.

You will also complete a questionnaire about your participation in clinical studies in the 365 days preceding this screening examination.

For hygiene reasons, you are requested to take a shower before this visit.
To make it easier for the ECG electrodes to adhere to the skin, we ask you not to apply a moisturizing cream on your body.

2. STUDY PERIOD

If you agree to take part in the study and meet all the conditions required to be enrolled in the study, you will undergo the tests and examinations described below:

PART A

- Physical examination: at admission.
- Neurological examination: 3 examinations.
- Detection of drugs in urine: at admission.
- Single 12-lead ECG: 1 measurement at discharge
- Triplicate 12-lead ECG: 26 measurements.
- Respiratory rate and oral temperature: 16 measurements
- Orthostatic blood pressure: 17 measurements
- Triplicate measurement of supine blood pressure, heart rate: 14 measurements
- Administration of the study medicine (see the section “Treatments administered during the study” page 9).
- 27 blood draws will be performed to collect the following samples (multiple samples can be collected during 1 blood draw)
    - Blood samples for safety laboratory tests: 7 samples (for which you will have to be fasting for at least 12 hours).
    - Blood samples for metabolite profiling: 7 samples
    - Blood samples to determine the amount of PF-07258669: 26 samples
    - Blood samples for biomarker assessment: 10 samples
- Urine samples for safety laboratory tests: 7 samples (for which you will have to be fasting for at least 12 hours).
- Continuous urine collection from dosing on Day 14 until 12 hours after dosing to determine the amount of PF-07258669: 1 sample
- Continuous 24-hour fluid intake assessment on Day -1, Day 7 and Day 14: 3 assessments
- Continuous 24-hour urine collection on Day -1, Day 7 and Day 14 for measurement of total amount of urine produced over 24 hours (Day -1, Day 7 and Day 14) and biomarker assessment (Day -1 and Day 14): 3 samples
- Continuous cardiac telemetry: 1 baseline assessment (2 hours) + 3 measurements (8 hours)
- Painless digital scale-based assessment of body composition using bio-electrical impedance: 5 measurements
- Suicide risk questionnaire: 3 measurements
- Eating related questionnaire: 29 eating related assessments, 18 after meal assessments and 1 exit survey.
- Thirst and Hunger questionnaire: 3 assessments.
- Retained research blood samples: 3 samples.

PART B

- Physical examination: at admission.
- Detection of drugs in urine: at admission.
- Triplicate 12-lead ECG: 10 measurements
- Single 12-lead ECG: 1 measurement at discharge
- Respiratory rate and oral temperature: 9 measurements
- Triplicate measurements of supine blood pressure, heart rate: 10 measurements
- Orthostatic blood pressure: 11 measurements
- Continuous pulse oximetry (a non-invasive method for monitoring the oxygen levels in your blood): 3 measurements (6 hours)

- Administration of the study medicine (see the section “Treatments administered during the study” page 9).
- 39 blood draws will be performed to collect the following samples (multiple samples can be collected during 1 blood draw)
    - Blood samples for laboratory tests: 7 samples (for which you will have to be fasting for at least 12 hours).
    - Blood samples to determine the amount of Midazolam: 36 samples
    - Blood samples for biomarker assessment: 4 samples
- Urine samples for safety laboratory tests: 7 samples (for which you will have to be fasting for at least 12 hours).
- Painless digital scale-based assessment of body composition using bio-electrical impedance: 4 measurements
- Continuous 24-hour fluid intake assessment on Day -1 and Day 7: 2 assessments
- Continuous 24-hour urine collection on Day -1 and Day 7 for measurement of total amount of urine produced over 24 hours and biomarker assessment: 2 samples
- Thirst and Hunger questionnaire: 2 assessments
- Retained research blood samples: 3 samples.

For safety reasons, we may add procedures at any time during the study in order to check on your health status.

Approximately 7-10 days after the last administration of the study medicine, you will return to the PCRU for a check-up: medical examination, single 12-lead ECG, blood pressure and heart rate measurement both while lying down and standing up, bioelectrical impedance analysis, C-SSRS (for Part A only), Thirst and Hunger questionnaire, blood and urine samples – **for which you must have been fasting for at least 12 hours** – for laboratory tests.

Each participant will have a follow-up phone call 28-35 days after administration of the last dose of study medicine, during which the participant will provide an update on his/her general health status and again provide answers to the Thirst and Hunger questionnaire.

When participating to the study, you must be able to come to the PCRU within 24 hours if we need to call you in for a check-up. We therefore ask you not to make any travel plans that will prevent you from respecting this condition.

The remainder of your laboratory test samples and of the samples used to determine the study medicine and biomarkers levels may be retained for storage up to 1 year following completion of the study. These samples shall be destroyed after this timeframe or earlier if not used. The samples may be used for evaluation of exploratory safety biomarkers, bioanalytical method, as well as for other internal exploratory purposes related to this study medicine.

3. TREATMENTS ADMINISTERED DURING THE STUDY

The planned treatments are:

PART A

PF-07258669 or placebo will be administered as tablet(s).

From Day 1 until the morning of Day 14 inclusive, you will receive the study medicine either three times per day (every 8 hours) or two times per day (every 12 hours). The starting dose of PF-07258669 proposed for Cohort 1 of Part A of this study is 3 mg three times per day (9 mg total daily dose).

The planned PF-07258669 dose range to be evaluated in Part A of this study is shown in the table underneath. Currently a dosing of three times per day (every 8 hours) is planned for all cohorts.

Cohort	Food Regimen	Planned Dose (mg every 8 hours)
1	High Carbohydrate High Calorie	3
2	High Carbohydrate High Calorie	2
3	High Carbohydrate High Calorie	6
4	Standard Diet	6
5	Standard Diet	20
6	Standard Diet	60
7	Standard Diet	to be decided[1]
8	Standard Diet	to be decided[1]
Japanese (optional)	Standard Diet	to be decided[1]
Older adults (optional)	Standard Diet	to be decided[1]
Optional cohort	High Fat High Calorie	to be decided[1]
Optional cohort	High Fat High Calorie	to be decided[1]

1. Doses administered to Japanese participants (if enrolled) and/or older adult participants (if enrolled) will be less than or equal to the highest safe and well tolerated dose evaluated in previous cohorts in Part A.

The next dose regimen will be administered only if the previous dose regimen was safe and well tolerated, and if the amount of PF-07258669 in the blood was acceptable. The planned doses as well as the dosing frequency may change based on the results of the previous cohorts.

If the dose is changed based on the results of previous cohorts, the maximum daily dose will not exceed 2000 mg.

For Part A, neither you nor the Investigator site staff will know whether you are receiving PF-07258669 or placebo during the period in progress, but the staff will be able to obtain the study medicine identity if necessary.

For Part A, PF-07258669 will be administered in a random distribution determined by computer, which is also called randomization.

On Day 1 and Day 14, dosing will occur after an overnight fast of 12 hours. You may drink water until 1 hour prior to the morning dosing of the study medicine, and water may be consumed without restriction again beginning 1 hour after the morning dosing. Food may be consumed beginning 4 hours after the morning dosing of study medicine on Day 1 and Day 14.

For this study there will be three possible food regimens:

- Standard Diet: you will get standardized meals: you will be encouraged to consume a controlled amount of food, **or;**
- High Carbohydrate High Calorie: the amount of food you are consuming will not be restricted, and the nutritional composition of the meals will offer a higher carbohydrate than fat content. If desired, you will be offered second helpings during mealtimes and you will have access to snacks in between meals and after dinner. However, you are not obliged to eat all of the food that is offered to you during the meals or in the form of snacks, **or**;
- High Fat High Calorie: the amount of food will be restricted, and the nutritional composition of the meals and snacks will offer a higher fat than carbohydrate content. Second helpings and supplemental snacks will be available upon your request. However, you are not obliged to eat all of the food that is offered to you during the meals or in the form of snacks.

The PCRU staff will inform you which food regimen is assigned to you.

On all other days and for the afternoon and/or evening doses, other than the restrictions explained above and depending on the regimen that will be assigned to you, there are no food or drink restrictions, with the exception of days when blood sampling for safety laboratory tests is planned.

PART B

PF-07258669 or placebo will be administered as tablet(s).

Midazolam will be administered as an oral solution.

Dosing will occur on the following days:

Period 1:
- You will receive a single 1 mg dose of Midazolam on Day 1 after an overnight fast of 12 hours. You may drink water until 1 hour prior to the dosing of midazolam, and water may be consumed without restriction again beginning 1 hour after the dosing. Food may be consumed beginning 4 hours after the dosing of midazolam.

Period 2:
- You will receive PF-07258669 from Day 1 until Day 10. The dose and frequency will be based on the results from Part A, but will not exceed a total daily dose of 2000 mg.
- On Day 2 and Day 10, after an overnight fast of 12 hours and 5 minutes after ingesting PF-07258669, you will receive a single 1 mg dose of Midazolam. You may drink water until 1 hour prior to the dosing of midazolam, and water may be consumed without restriction again beginning 1 hour after the dosing. Food may be consumed beginning 4 hours after the dosing of midazolam.

For Part B, you will get standardized meals: you will be encouraged to consume a controlled amount of food.

Based on results from Part A the dose of midazolam can be decreased or increased to up to 8 mg.

Other than the restrictions explained above and depending on the regimen that will be assigned to you, there are no food or drink restrictions, with the exception of days when blood sampling for safety laboratory tests is planned.

Contraception, pregnancy and breast-feeding

1. FOR WOMEN ONLY:

Women of non-childbearing potential:

You may participate in this study provided that:

- You are between 18 and 60 or between 65 and 90 (for the optional cohort of older adult participants only) and
- You are post-menopausal (meaning that your last period was at least one year ago).
- OR ELSE you have been surgically sterilised (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
- OR you have an ovarian failure.

If you do not fall into one of these categories (described above), you will be considered as capable of having children. In this case, you will not be allowed to participate in this study.

2. FOR MEN ONLY:

At each visit to the PCRU, we will check that you are using the appropriate contraception.

If you are abstinent from heterosexual intercourse with a female of childbearing potential as your preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent, you do not have to use additional contraception.

If you have a female partner of childbearing potential and you are not abstinent, you may take part in this study on condition that you use condoms during your participation in the study and for 28 days following the last administration of the medicine.
In addition to that, if your partner is a woman of childbearing potential, she will have to use one of the following contraception methods:

- IUD or IUS
- hormonal contraception

If you have had a vasectomy more than six months ago, or if your partner is post-menopausal or surgically sterilised OR has had bilateral tubal occlusion**, she will not need to use the contraception methods set forth above.**

Taking the study medicine could bring about an unknown risk for an embryo, foetus or could negatively affect the quality of the sperm. It is important that you tell us if your partner is pregnant or if you plan to conceive during the study and up to at least 90 days after the last administration of the medicine. You commit to inform your partner about your taking part in this study and the potential risks for an embryo or foetus.

You cannot donate sperm until at least 28 days after the last administration of the medicine.

3. PREGNANCY FOLLOW UP

Any pregnancy during the study, from the female partner of a male participant, or within at least 90 days after the treatment with the study medicine stopped, should be reported to the study doctor or his/her representative immediately. The study doctor will ask if your partner or your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If your partner agrees, this information will be provided to the study sponsor for safety monitoring follow-up.

Risks associated with the evaluation procedures specific to the study

1. BLOOD DRAWS

Blood draws may cause faintness, dizziness, inflammation of the vein (blood vessel), pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.

2. ECG

The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches or shaving. If anything abnormal on ECG is seen, it may be necessary for you to have continuous ECG monitoring for some time for your own safety. This might mean that you are not able to move around very easily.

3. FASTING

Fasting could cause symptoms such as: dizziness, headache, stomach discomfort, fainting, and/or possibly hypoglycemia (low blood sugar).

4. TESTING OF DNA AND/OR RNA

Genes are pieces of DNA that, through material called RNA, give instructions for building the proteins that make our bodies work. These instructions are stored in the form of a code. This is the code that you inherit from your parents and that you pass on to your children. DNA, RNA, and proteins can be studied as part of genetic research. This study may involve studying your biology and whether a particular biological feature (including genes) is related to the effects or action of the study medicine or to a disease. This may include analysing all of your genetic information (called "whole genome sequencing"). Sequencing a gene is like reading a book one letter at a time. This is a very thorough way to learn about genes. The genetic analysis is for research purposes only and is not a medical test. This means that the medical importance of the results may not be known, or that they may not be related to any medical condition.
The results of tests on your sample will not be given to you or the study doctor.
If you do not want genetic testing to be done on your samples, you should not agree to participate in the research described in this document.

Benefits

You will not personally derive any benefit from your participation in this study, but the results obtained could be very important for the development of drugs and treatments which will benefit other people.

Withdrawal from the study

Your participation is voluntary and you are entitled to withdraw from the study for any reason, without having to justify your decision. Nevertheless, it may be useful for the investigator and for the sponsor of the study to know if you are withdrawing from the study because the constraints or discomfort of the treatment are too great (too many uncomfortable side effects, for example).

You may be asked if this decision to withdraw is just to stop receiving the study medicine or also to stop taking part in study procedures and/or post treatment study follow-up. If you agree to continue with the follow up part of the study, information about your health will continue to be collected as described above in the procedures.

If you disagree to continue with the follow up part of the study, you must inform the study doctor in writing.

The sponsor will use information and samples already collected from you in the study before your withdrawal.

It is also possible that the investigator withdraws you from the study because he/she thinks it is better for your health or because he/she finds out that you are not following the instructions given to participants.

Finally, the competent national or international authorities, the ethics committee that initially approved the study or the sponsor may decide to interrupt or discontinue the study because the information gathered shows that the investigational treatment causes more side effects or more serious side effects than anticipated, or for any other reason, such as, for example, the decision to stop research and development of the study medicine.

Samples of biological material collected during the study

The sponsor of the study undertakes that the samples will only be used as defined in this section.

1. RETAINED RESEARCH SAMPLE

Two 10 mL blood samples and one 2 mL blood sample will be collected at (Period 1) Day 1. This sample will be used to study biological substances in your sample(s), including your genes. This will help us learn more about the study medicine.
These samples are called "Retained Research Samples"

The sample will be held by Pfizer for up to 50 years. Research results will not be communicated to you or your doctor.
Specimens will be stored in a Pfizer-designated facility, which is currently located at 2910 Fortune Circle West, Suite E, Indianapolis, Indiana, 46241 in the United States.

The sample taken of your biological material is considered to be a “donation” and you should know that, as a matter of principle, you will not receive any financial benefit (royalties) related to the development of new therapies derived from the use of your donation of biological material and that could have commercial value.

If you withdraw your consent for participation in the study, you may contact the investigating physician to have the unused portion of your sample destroyed. The results obtained based on your samples before the withdrawal of your consent will remain the property of the sponsor of the study.

If you take part in this clinical study, we ask you:

- To cooperate fully in the smooth running of this study.
- Not to conceal any information relating to your state of health, the medication you are taking or the symptoms you are experiencing.
- Not to take part in other clinical study involving an investigational treatment, be it a medicinal product, a medical device or a procedure, while taking part in this study.
- To carry the "emergency card" with you at all times. This is imperative for your safety in the event of emergency care in an institution that does not know you. This card states that you are taking part in a clinical study. It also mentions a telephone number that you may call in an emergency. You should return this card to us at the end of the study.

Contact

If you need further information, but also if you have problems or concerns, you can contact the Pfizer Clinical Research Unit on the following telephone number +32(0) 2/556 70 02.

II. Supplementary information

Restrictions

Phototoxicity
You will be advised to avoid direct sunlight exposure (skin and eyes) or any high intensity ultraviolet light exposure, from the first day of dosing with study medication until the follow-up visit.
You will be asked to report any reaction. You will be instructed to apply a cream/sunscreen with a high sun protection factor (50+), as appropriate and wear sunglasses, for up to seven days after the last dose of study medicine.

Medication
You should avoid all medications including non-prescription medicines bought, including vitamins, extracts of plants, homeopathic medicines and medicinal herbal teas, in the four weeks before the study, throughout the study and up to the day of final payment.
For the optional cohort of older adult participants only: Older participants that suffer from chronic conditions that require treatment (e.g. hypertension), should be on a stable dose of permitted medications, as determined by the study physician. You should continue to take your permitted daily prescription or non-prescription medications at approximately the same time each day in the four weeks before the screening visit, throughout the study and up to the follow-up phone call. In case of a change in the dose or dosing regimen of your medication, you should contact the PCRU immediately to inform the study physician.
If you fall ill and require treatment, please contact the PCRU immediately. You will be told what treatment you may undergo or whether it is possibly preferable to discontinue the study.

Lifestyle considerations
You must also avoid consuming any alcoholic drinks, stimulants (such as coffee, tea, chocolate or beverages containing caffeine or theine), bread or cakes containing poppy seeds:

- from 24 hours before the screening examination until the results of your tests are known,

then

- from 24 hours before the start and throughout each study period, **and lastly**
- from 24 hours before the check-up visit.

You must also avoid any strenuous physical exercise:

- from 48 hours before the screening examination until the results of your tests are known,

and

- from 48 hours before the start and throughout each study period, **and lastly**
- from 48 hours before the check-up visit.

You must also avoid consuming tobacco-or nicotine-containing products from 24 hours before the start and throughout each study period.

Furthermore, you may not consume red wine, grapefruits or grapefruit juice or citrus fruit of the grapefruit type (pomelos, « Seville » oranges or bitter oranges) from 7 days before the start of the first period until the last day of the last period.

Exclusions

You may not take part in this study if:

- You are actively following a calorie-restricted diet for purposes of intentional weight loss.
- You have a history of eating disorders (e.g., anorexia nervosa, bulimia nervosa, binge-eating disorder, avoidant/restrictive food intake disorder).
- You have a history of low blood pressure or low heart rate associated with symptoms.
- You have a positive test result by PCR for SARS-CoV-2 infection at the time of Screening or at admission.
- For Japanese cohort only: you don't have 4 biological Japanese grandparents who were born in Japan
- Part B only: You have a history of sensitivity reactions to midazolam, or you would be at increased risk if dosed with midazolam.
- You are outside of the age limits (18-60 years) or weight limits (minimum of 50 kg), or you are outside of the limits of the Body Mass Index (17.5 - 28.5 kg/m^2). For the optional cohort of older adult participants only: You are outside of the age limits (65-90 years) or weight limits (minimum of 50 kg), or you are outside of the limits of the Body Mass Index (17.5-32.4 kg/m^2).
- You are regularly taking medications or you are suffering from a chronic illness. For the optional cohort of older adult participants only: Participants with chronic conditions (e.g. hypertension), that are controlled by either diet or stable doses of allowed medications, may be included.
- You have an illness or you have received treatment that may affect absorption of the medicines (for example a gastrectomy or bariatric surgery).
- You are suffering from asthma or from any allergy to a medicine.
- You are suffering from any treated or symptomatic, seasonal allergies (hay fever).
- You smoke more than 5 cigarettes a day or consume an equivalent quantity of tobacco / nicotine-containing products.
- You have taken part in another clinical study involving investigational medicines within the last 30 days. In case the investigational medicines are expected to be present in the body longer than 30 days, you will not be able to participate in this study until these products have been eliminated from your body. This period of elimination is specific for each medicine and depends on its half-life, the time required for a quantity of medicine to reduce to half of its initial value. An elimination period of 5 times the half-life should be respected.
- You have given blood or constituent elements of blood (platelets) during the two months preceding the study or you intend to be a donor in the two months following the end of the study (Red Cross standard to guarantee blood cells regeneration). Giving plasma is allowed.
- You have taken or you are taking drugs.
- You think you are at risk of being infected with the AIDS virus, hepatitis B or C.
- You have a history of regular alcohol consumption exceeding 14 drinks/week (1 drink = 90 mL of wine or 240 mL of beer or 30 mL of spirit).

Supplementary information on the risks associated with participation in the study

Specific features of the study

1. BLOOD VOLUME

The total quantity of blood taken during the study will be approximately 260 mL (Part A) and 250 mL (Part B).
The times for taking blood may change. Additional blood samples may be added provided the total volume of 550 mL is not exceeded.

Your body will quickly build up again this quantity of blood during the study.

2. QUESTIONNAIRE ABOUT SUICIDAL BEHAVIOUR

By using the Columbia Suicide Severity Rating Scale (C-SSRS), your risk of experiencing a suicidal state of mind will be evaluated with the clinical team before you may be included in the study as well as after taking the medication during the study. The questions contained in the Columbia Suicide Severity Rating Scale (C-SSRS) have been developed as a consistent indication to measure the suicide risk (i.e. dark thoughts such as the wish to die, to go to sleep and never wake up, thinking of a suicide strategy, drafting a will or a suicide letter) and the intensity of the suicidal thoughts, as well as suicidal behaviours (suicide attempts, failed or interrupted attempts, purchase of drugs or firearms).

3. TELEMETRY

Telemetry consists of a painless recording of your heart activity. For this, you will wear a small case which will be linked to 10 electrodes (similar to ECG electrodes) placed on your chest. The apparatus itself is connected by a wireless link to a central computer that analyses your heart activity and enables us to monitor it in real time. Telemetry will generally be recorded for a minimum of 8 hours.
There will also be a recording for 2 hours, in the same conditions at the start of the study, that will be used as the starting point for comparisons with the telemetries taken after administration of the study medicine.

4. CONTINUOUS PULSE OXIMETRY

We will ask you to wear an electrode on your finger. This electrode will enable us to determine the levels of oxygen circulating in your blood. This analysis is completely painless.

5. BIOELECTRICAL IMPEDANCE ANALYSIS

Bioelectrical impedance analysis (BIA) is a method for estimating body composition. A small electric current is sent through your body. As the current flows through your body, the voltage is measured in order to calculate impedance (electrical resistance) of your body. By measuring the impedance, your body composition (e.g. total body water, fat mass, muscle mass, bone mass, …) can be ascertained.

Glossary

Anterograde amnesia: a condition in which a person is unable to create new memories after a memory-loss-inducing event.

Ataxia: lack of voluntary coordination of muscle movements

Bilateral oophorectomy: Ablation (surgical removal) of the ovaries.

Bilateral salpingectomy: Surgical removal of the fallopian tubes.

Bioanalytical method: Techniques used to measure the quantity of study medicine, metabolite, biomarkers or proteins.

Biobank: Reserve of biological samples.

Biomarker: A biomarker is a characteristic objectively measured and evaluated as an indicator of a disease or of the action of a medicine. Thus, for example, glucose is a biomarker for diabetes, and blood pressure is a biomarker for arterial hypertension (high blood pressure).

Body Mass Index: The Body Mass Index is calculated by dividing your weight (in kg) by your height (in m) squared. In practice, you just need to divide your weight by your height and then once again divide the result by your height. For example, if you are 1.70 m tall and you weigh 70 kg, your BMI index will be 24. This is calculated as follows: 70 kg / 1.70 m = 41 and 41 / 1.70 m = 24.

Continuous pulse oximetry: a non-invasive method for monitoring the levels of oxygen in your blood.

DNA: A molecule that is present in all cells, and which comprises the entire set of information necessary to the development and working of an organism. It is also the support of the heredity, because it is wholly or partly transmitted in the course of reproduction. It therefore carries the genetic information (the genotype) and constitutes the genome of living beings.

Dyspnea: difficult or laboured breathing

Enzyme: Protein produced by the body which enables the activation or acceleration of chemical reactions.

Hysterectomy: Ablation (surgical removal) of the uterus.

Laryngospasm: spasm of the vocal cords that temporarily makes it difficult to speak or breathe

Metabolite: Compound resulting from the transformation of a medicine in a cell, in a tissue or in blood.

Pharmacokinetics (PK): Assessment of the evolution of study medicine concentrations in the blood before and after administration.

Plasma: The liquid portion of the blood that bathes the other blood components (red blood cells, white blood cells, platelets).

Protein: Biological molecule composed of amino acids brought to the body through food processing by digestion followed by assimilation by the intestines, among others.

QTc: Is a specific electrocardiogram (ECG) measurement. This measurement strongly depends on the heart rate. Certain medicines are known to lengthen the QTc interval, which may upset the heart rate in rare cases. An electrocardiogram is a painless recording of the electrical activity of the heart.

RNA: A biological molecule that is present in practically all living organisms, including certain viruses. The RNA is a molecule that is chemically very similar to DNA and it is also in general synthesised in the cells based on a DNA matrix of which it is a copy. Living cells use RNA in particular as an intermediary support for the genes to generate the proteins they need. The RNA can fulfil numerous other functions and in particular intervene in chemical reactions taking place in the cell.

Solution: A homogeneous mixture composed of two or more substances.

Triglycerides: a type of fat (lipid) in your blood. The body converts calories it doesn't need into triglycerides.

Vasodilation: the widening of blood vessels, which decreases blood pressure.

Additional information on protecting participants and their rights in each clinical study

You must inform the study doctor or his/her representative of:

- Any medicine or substance that you have taken in the last 28 days, that you are currently taking or that you intend to take;
- Any change in treatment that has taken place during the study;
- Any study exclusion criteria that would apply to you according to the information given by the doctor in charge;
- Any significant illness, past or present, including any consultation you have had with any doctor during the last six months, whether or not it resulted in medication or a medicine prescription;
- Your history of drug taking, alcohol consumption or smoking tobacco;
- Your participation in other clinical studies during the last 12 months.

Assistance or advice

This study has been submitted to an independent Ethics Committee 'Comité d'Ethique Hospitalo-Facultaire Erasme-ULB', which has issued a favourable ethical opinion as regards to its implementation. The Ethics Committees are responsible for the protection of the subjects who take part in clinical research in accordance with the Law of 7 May 2004 concerning experiments on humans.
However, the decision as to whether or not to participate in this study must be your own personal decision. Under no circumstances should you take the Ethics Committee's favourable opinion as an incentive to take part in this study.

If you have any questions, concerns or complaints concerning the role of the Ethics Committee or your rights as a participant in a clinical study, you may contact the Ethics Committee 'Comité d'Ethique Hospitalo-Facultaire Erasme-ULB', during office hours, dialling the following number: 02/555 37 07.

A description of this clinical study will be available on http://www.ClinicalTrials.gov, as required by legislation. This website will not contain information that can identify you. It will be no more than a summary of the general results of the study. You can check this website at any time. However, it may take several years before the research results are available online.

The ClinicalTrials.gov website is in English only. If you would like any help in understanding the contents of this website, please talk to your study doctor or his/her representative.

Participant rights

Before signing, do not hesitate to ask any questions that you consider useful. Take the time to discuss it with a person you trust if you so wish.

Your participation in this study is voluntary and you must remain free from any constraint. This means that you have the right not to take part to the study or withdraw from it, at any time, without giving any justification and without losing your legal rights, even if you previously agreed to take part to it.

If you decide to withdraw from the study, we ask you to inform the study doctor and to undergo some follow-up examinations so that we can be sure that you are in good health.
The doctor in charge of the study can decide to remove you from the study, if she/he deems that it would be harmful for you to continue to take part to it.
The study may also be discontinued further to the discovery of new information concerning the product or in the event that the Ethics Committee takes a new decision on the study.

You will be informed of any new data that may influence your decision to take part or not in the study.

If you agree to take part in the study, you must sign the informed consent form. The study doctor, or designee, will also sign this form and will thereby confirm that she/he has provided you with all the necessary information on the study. You shall receive a paper copy of that document.

Compensation and insurance

Your compensation for the inconveniences caused by your participation to the study will be available three weeks after the last contact (see point 12 of the "Participant Agreement and Consent Form").

Any clinical study carries a risk, however small it is. If you suffer damage as a result of your participation in this study, you (or in the event of death, your dependants) will be compensated for this damage by the study sponsor in accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004). You do not have to prove a fault for this. In this regard, the sponsor has taken out an insurance policy.

You are therefore asked to report any new health problem to the investigator before consulting another doctor, taking any other medication or receiving any other medical treatment. If, for any reason, you consult another doctor during this clinical study, you must inform him/her that you are taking part in a clinical study and present your clinical study participant card. This could be important in establishing a diagnosis and treating your complaints.

If the investigator believes that a link with the study is possible (the insurance does not cover the natural progression of your disease or the known side effects of your normal treatment), he/she will inform the study sponsor, which will initiate the declaration procedure to its insurance company. The latter will appoint an expert - if it considers it necessary - to assess whether there is a link between your new health problems and the study.

In the event of disagreement either with the investigator or with the expert appointed by the insurance company and also whenever you feel it is appropriate, you or - in case of death - your dependents may bring proceedings against the insurer directly in Belgium (Insurer: Chubb European Group SE, policy number: BECANA07085, Tel: +32 (2) 516 97 11).

The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer's registered offices.

Provision has been made for insurance to cover research injury liability of the sponsor established in relation to the clinical trial.

Protection of your personal data

Your participation in the study means that you accept that the study doctor will collect data related to you (the "Personal Data") such as your name, postal address, email address, phone number, your date and place of birth, sex, age, your general practitioner's name (with your consent), bank details, as well as ethnic origin and data relating to your health status, and that the study sponsor (Pfizer) will use this Personal Data for research purposes as specified in this document, and for scientific and medical publications on that research (fully anonymously).

Your Personal Data will be collected, stored, accessed and otherwise processed in compliance with the applicable EU and Belgian laws on clinical trial, and with the applicable EU and Belgian privacy legislations as they may be amended or repealed and replaced from time to time (collectively referred to as "Data Privacy Laws") and as specified in the annex "Supplement related to personal data protection" (p. 27).

You have the right to consult, correct or request deletion of your Personal data by writing to the following address: Participants Recruitment Department, Pfizer Clinical Research Unit, route de Lennik 808, 1070 Brussels. Should communicating your Personal Data potentially jeopardise the results of the study, we may ask you to wait until the end of the study to access these Personal Data.

If you want to ask for removal of Your Personal Data, please send a signed and dated letter to Participants Recruitment Department, Pfizer Clinical Research Unit, route de Lennik 808, 1070 Brussels. Your data will be deleted by Pfizer and will no longer be stored or processed by us (except for your letter requesting the removal – see point G of the "Supplement related to personal data protection"). You will therefore not be able to participate in any of our future studies.

However, if you have taken part to a study or a screening, we will not be able to delete your data, but your file will be inactivated, and you will not be contacted again.

Monitoring of non-participation in other clinical studies

Our Pfizer Clinical Research Unit, located on route de Lennik 808, 1070 Anderlecht (Brussels) takes part in the « Verified Clinical Trials LLC ("VCT") programme.

The aim of this database is to enable us to ensure that participants are not taking part in several phase I clinical studies at the same time. In addition, this system will enable us to enhance your protection, as well as the quality of the data for the study that you will be taking part in.
For more information regarding VCT, please refer to the separate VCT consent form.

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PARTICIPANT AGREEMENT AND CONSENT FORM

Principal Investigator	Dr. Laure Mendes da Costa

1. I freely agree to take part in this study.
2. I have received full explanations from the staff in charge of the study about the nature, purpose and likely duration of the study, and about what is expected of me. I have also been informed of all the possible side effects. The information document, which was sent to me, is attached hereto and is an integral part thereof. I have informed the study doctor of my medical history, of the medications I may have taken, and of any other studies I may have participated in. In this regard, I was given the Study Information Leaflet pertaining to the abovementioned study.
3. I have been given the opportunity to question the study doctor on all aspects of the study and have understood the advice and information given as a result.
4. I have been informed that a blood sample will be taken for HIV, Hepatitis B and C screening. I have also been informed that a blood sample will be taken, to study biological substances including my genes, to help us learn more about the study drug. The sample will be held in a Pfizer-designated facility for up to 50 years.
   Research results will not be communicated to me or my doctor.
5. I agree to comply with any instruction given during the study and to co-operate faithfully with the study doctor and to tell him/her immediately if I suffer any change of any kind in my health or well-being or any symptoms of whatever kind.
6. I undertake to be present on the premises of the Pfizer Clinical Research Unit for the whole period spent in hospital, and also for the outpatient visits scheduled within the context of this study. I am aware of the fact that non-compliance with this obligation could be detrimental to my health if I experienced an undesirable effect and could not immediately gain access to the appropriate medical care.
7. I shall not donate blood during the study, nor for two months before or after the trial.
8. I undertake to comply with the study restrictions as they are mentioned under “II. Supplementary information” (page 15). If a violation of these commitments were confirmed by laboratory tests, I could be excluded from the study.
9. I understand that data about me will be collected throughout my participation in this study and that the Investigator and the Sponsor of the study will guarantee the confidentiality of these data.

   I agree to my personal data being processed as described under “Protection of your personal data” in the section “Additional information on protecting participants […]” (page 20). I also consent to these data being transferred to and processed in countries other than Belgium.
10. Although my name must never appear in the report of the study disclosed to third parties, I expressly authorise the company Pfizer to pass on the results of this study to the competent medical or pharmaceutical authorities, both Belgian and foreign, to technical advisers, whether or not linked to the company, and to publish the results.
11. It is understood that I am free to leave the study at any time without having to justify my decision and without losing my legal rights. However, I shall, in that case, continue to benefit from all treatments and check-ups my condition may require.

12. The company sponsoring the study confirms that:

i)

I shall receive the sum of **€ 4 087.00** (four thousand and eighty-seven euros) for my participation in the whole Part A of the study.

I shall receive the sum of **€ 2 945.00** (two thousand nine hundred and forty-five euros) for my participation in the whole Part B of the study.

If I need to withdraw from the study for medical reasons evaluated by the Investigator as related to the study, I shall however receive a full payment of the above-mentioned amount for my participation.
If the investigator allows me to leave the Unit earlier because my study assessments were all completed before the end date mentioned in the calendar of the study as provided at the time of first dosing, I shall receive a full payment of the above-mentioned amount for my participation.
If I withdraw from the study for other medical reasons or other reasons not associated with my participation in the study, I shall receive a compensation proportional to the duration of my participation.
If I enter the study at a later stage than the beginning of the study, I shall receive a compensation proportional to the duration of my participation.

If changes are made to the original calendar of the study as provided at the time of first dosing, the compensation amount will be reviewed proportionally to the duration of the new calendar.

If my participation is ended for not respecting the restrictions, I shall be removed from the study, and my compensation amount shall be reviewed proportionally to the duration of my participation.

In addition, **I will be compensated for my travel expenses** (a lump sum) based on the journey from the address where I officially reside, and the number of journeys made.

ii) The sponsor has subscribed a no-fault insurance to cover injuries or significant deterioration in health or well-being in connection to my participation in the study.

13. I have been made aware of the reasons for which personal data will be processed and/or transferred as part of the study and of my legal rights concerning these personal data as described in the Participant Information Sheet.

Signatures:

In agreement, the participant:

_____
Printed name of participant

_____ _____
Signature of participant Date of signature§

§Participant/ impartial witness must personally date their signature.

Person Obtaining Consent:

I hereby confirm having provided the participant with all the necessary information about the study, without exercising any pressure to cause the subject to participate. I further confirm that I have handed over a copy of the Information and Consent Leaflet signed by the participant and by me, and that I am willing to answer any additional questions if necessary. I state that I work in compliance with the ethical principles set out in the "Helsinki Declaration" and the Belgian Law of 7 May 2004 concerning experiments on humans.

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____
Signature of the Person Conducting the Consent Discussion † Date of Signature

†The investigator, or an appropriately qualified and trained person designated by the investigator to conduct the informed consent process, must sign and date the consent document during the same discussion when the participant signs the consent document.

Consent for Participant Who Cannot Read:

The study participant has indicated that he/she is unable to read. One or more members of the study team read the consent document to the study participant, discussed it with the study participant, and gave the study participant an opportunity to ask questions.

_____
Printed name of impartial witness ‡

_____ _____
Signature of impartial witness Date of signature§

☐ Not applicable (*Check this box if the Signature of an impartial witness is not required. Signature of an impartial witness is required if the participant cannot read.*)

§Participant /impartial witness must personally date their signature.

‡ Impartial Witness: A person, who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the participant o cannot read, and who reads the informed consent and any other written information supplied to the participant. *See* Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.

SUPPLEMENT RELATED TO PERSONAL DATA PROTECTION

This **Supplement related to personal data protection** describes how we will collect, use, and share your personal data. It also describes your rights as data subject of whom personal data are being collected and processed. Your personal data shall be processed in compliance with the General Data Protection Regulation and the Belgian law of 30 July 2018 relating to the protection of natural persons with regards to the processing of their personal data.

A. What personal data may we collect about you during this study?

The study team and others assisting you with study-related care will collect information related to you (personal data), in the framework of the study. Amongst these personal data; some are sensitive data. These data may include:

- **Information that directly identifies you** such as your name, address, telephone number, e-mail address, date and place of birth, national ID number.
- **Your bank details.**
- **With your consent, the identification of your general practitioner.**
- **Sensitive personal data** such as your medical history, data from this study (including study results from tests and procedures), demographics (for example, age and gender) and other sensitive personal data that is needed for this study such as ethnic origin, genetic information, sexual orientations, HIV/AIDS, tuberculosis, dietary preferences.
- **Data from testing and analysis of biological samples** (such as blood or urine) **and images** (such as X-rays, CT-Scans, and medical photographs). This may also include genetic information.
- **Data captured from electronic devices,** if you complete the consent process using the eConsent tablet or if you use a mobile application or other digital tool during the study. This information may include data about your use of the eConsent tablet, application or tool, such as the length of time it takes you to complete the consent process, the number of times you scroll between pages or click on the hyperlinked items, your electronic signature. Mobile applications and other digital tools used in the study may have their own privacy policies. Those policies provide additional information about the data processing activities performed by the digital tools.

B. Who will use my personal data, how will they use it, and where will it be stored?

Any personal data collected about you during this study will be stored by the study team at your study site. The study team must ensure the confidentiality of your personal data.

Your personal data shall be accessed by:

- The study doctor and other study team members;
- The Sponsor and its representatives (including its affiliated companies);
- People or organizations providing services for, or collaborating with, the Sponsor;
- Any organization that obtains all or part of the Sponsor's business or rights to the product under study;
- Government or regulatory authorities (including those in other countries); and
- Institutional Review Board(s) (IRB) or Independent Ethics Committee(s) (IEC) overseeing this study.

The individuals and groups listed above will use your personal data to conduct this study, and to comply with legal or regulatory requirements, including to:

- determine if you are eligible for this study;
- provide you with reimbursement for your time, effort and certain expenses related to your participation;
- verify that the study is conducted correctly, and that study data are accurate;
- answer questions from IRB(s), IEC(s), or government or regulatory agencies;
- assess your use of electronic devices in the study, for example, to determine how long it takes you to complete any eConsent module used for the study and your comprehension of the eConsent process;
- contact you during and after the study (if necessary);
- follow-up on your health status, including using publicly available sources should the study team be unable to contact you using information held on file;
- protect your vital interests and/or the interests of your pregnant partner (for example, a critical medical situation, such as providing information to an emergency department of a hospital where you are being treated); and
- answer your personal data protection requests (if any).

The study site will retain your personal data for the period necessary to fulfil the purposes outlined in the consent document(s). This period could be up to 25 years after the end of the study.

If you provide someone else's personal data (for example, an emergency contact or details of family medical history) you should make them aware that you have provided the information to us. We will only use such personal data in accordance with this informed consent and applicable law.

C. What happens to my personal data that is sent outside the study site?

Before the study team transfers your personal data outside the study site, the study site will replace your name with a unique code and remove all information that directly identifies you. We call this "**Coded Information**." The study site will keep the link between the unique code and your personal data confidential, and the Sponsor will not have access to that link. The Sponsor's employees and representatives are required to protect your Coded Information and will not attempt to re-identify you.

Your Coded Information will be used by the following persons:

- The Sponsor and its representatives (including its affiliated companies);
- People and/or organizations providing services to or collaborating with the Sponsor;
- Any organization that obtains all or part of the Sponsor's business or the rights to the product under study;
- Other researchers;
- The IRB or IEC that approved this study;
- Government or regulatory authorities, if necessary;

The above parties may use your personal data for the following purposes:

- **Conducting the study**, including:
  - Examining your response to PF-07258669;
  - Understanding the study and the study results; and
  - Assessing the safety and efficacy of PF-07258669.

- **Complying with legal and regulatory duties,** such as:
  - Ensuring the study is conducted according to good clinical practice;
  - Making required disclosures to IRB(s), IEC(s), or government or regulatory authorities;
  - Seeking approval from government or regulatory authorities to market PF-07258669 (it is possible that these government or regulatory authorities may disclose your Coded Information to other researchers for the conduct of future scientific research); and
  - Sharing study data with other researchers not affiliated with the Sponsor or the study team (including through publication on the internet or other media). However, information that could directly identify you will not be made available to other researchers.
- **Publishing summaries of the study results** in medical journals, on the internet or at educational meetings of other researchers. You will not be directly identified in any publication or report of the study. However, some journal representatives may need access to your Coded Information to verify the study results and ensure the research meets the journal's quality standards. Moreover, journals may require that genetic and other information from the study that does not directly identify you, be made available to other researchers for further research projects.
- **Improving the quality, design and safety** of this study and other research studies.

The Sponsor will retain your Coded Information for the period necessary to fulfil the purposes outlined in the consent document(s). This period could be up to 25 years after the end of the study.

D. How are my biological samples and images handled?

If biological samples or images of you are taken during the study, those samples and images will be handled in the same way as your Coded Data. All samples will be treated as required by law. Sometimes your study site may be unable to remove information that can identify you from your images before sending images to the Sponsor and its representatives.

E. Can my personal data be used for other research?

Your Coded Information may be used to advance scientific research and public health in other projects that will occur in the future. At this time, we do not know the specific details of these future research projects.

This other research may be conducted (1) in combination with data from **other sources**, (2) for **additional scientific research purposes** beyond objectives of this study, and (3) subject to **specific safeguards**.

- **Other sources**: Coded Information may be combined with data from other sources that are taken from outside typical research settings. These sources may include: coded electronic health records, claims and health care cost and payment data or databases, product and disease registries, data gathered through your phone, tablet, or other devices and mobile applications, social media, pharmacy data, biobanks, or patient engagement programs.
- **Additional scientific research:** Coded Information may be used to understand how to make new medicines, devices, diagnostic products, tools and/or other therapies that treat diseases and to improve future research. It may also be used to inform value, cost-effectiveness and pricing, and to optimize access to medicines.
- **Specific safeguards** will be used to protect your Coded Information, which may include:

    - Limited access to Coded Information to specific individuals who will be bound to keep this information confidential and will be prohibited from attempting to re-identify your Coded Information.
    - Use of security measures to avoid data alteration, loss and unauthorized access.
    - Anonymisation of the data by removing and/or replacing information from the Coded Information and/or destroying the link to the Coded Information.
    - Assessment of data protection systems to identify and mitigate privacy risks, if any, associated to each additional scientific research purpose.
    - When required by applicable law, verification that the scientific research has obtained the approval of IECs, IRBs, or other similar review groups.

F. How will my personal data be protected when transferred from the study site to the Sponsor?

Your personal data will be treated in compliance with applicable data protection laws. The Sponsor and Pfizer Clinical Research Unit (PCRU), part of Pfizer SA, are the data controllers of your personal data. The PCRU will be the data controller of your personal data and the Sponsor, will be the data controller of your Coded Information.

Some of the people using your personal data, including your Coded Information, may be based in countries other than those of the European Union (EU) and of the European Economic Area (EEA), including the United States. Data protection laws may be different in these countries. The European Commission has decided that some of these countries provide a level of data protection equivalent to the one available in the EU (the full list of these countries is available at this website: https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/adequacy-decisions_en or and people working with the Sponsor will take steps to maintain the confidentiality of your personal data. If your personal data is transferred by the Sponsor from the EU, EEA, and/or Switzerland to other countries that have not yet been found by European Commission to meet requirements for the protection of personal data, the Sponsor has put in place standard EU data transfer agreements to protect your personal data. Please contact your study team to obtain a copy of these standard data transfer agreements.

G. What are my data protection rights? Whom may I contact about these rights or any concerns or complaints?

If you wish to exercise any of the rights described below or have concerns about how your personal data is being handled, it is best to contact the PCRU and not the Sponsor of the study. Generally, the Sponsor will not know who you are (by name) because the Sponsor only holds your Coded Information, which does not include your name or other information that can identify you. Please contact the PCRU, the study team representative or Data Privacy Steward, at the following address: Participants Recruitment Department, Pfizer Clinical Research Unit, route de Lennik 808, 1070 Brussels, Phone: 0800/99.256 or +32 2/556.70.02; Email: werespectyourprivacy@pfizer.com.

- You have the right to access your personal data that is held about you by the study team. To ensure the integrity of the study, you will not be able to review some of the data until after the study has been completed.
- You have the right to correct or update your personal data.
- You have the right to limit the collection and use of your personal data under certain circumstances (for example, if the information is inaccurate).
- You have the right to receive your personal data in a in a structured, commonly used and machine-readable format (for example, in a readable text electronic file or chart) for your own purposes or for giving it to others. *You do not have the right to receive your personal data that have been used for public interest purposes (for example, for reporting incidents of disease to public health officials) or in the exercise of official authority vested in the Sponsor or the PCRU (for example, responding to information requests from public agencies or monitoring drug safety).*
- You have the right to request the deletion of your personal data if you are no longer participating in the study and you have withdrawn your consent to process your personal data as described in this document. *However, there are limits to the ability to honour a request to delete your personal data. Some or all of your personal data may be kept and used if deletion would seriously impair the study (for example, if deletion would affect the consistency of study results) or if your personal data is needed to comply with legal requirements.*
- You have the right to file a complaint with the data protection authority:

  Data Protection Authority
  Rue de la Presse 35, 1000 Brussels
  Tel.: +32 (0)2 274 48 00
  Fax: +32 (0)2 274 48 35
  Email: contact@apd-gba.be
  https://www.dataprotectionauthority.be/contact-us

H. What happens if I do not wish to continue with the study?

As noted in the main consent document, you are free to stop taking part in this study at any time by informing the study team of it.

If you stop taking part in the study and you do not inform the study team about your withdrawal, your contact information may be used by the study team to contact you and check whether you wish to continue in the study. If the study team is unable to reach you, the Sponsor may use publicly available records about your health to monitor the long-term safety of the study medicine. This will only be done if allowed by the law.

If you stop taking part in the study but do not withdraw your consent for the processing of your personal data, your personal data will continue to be used in accordance with this document and applicable law.

If you decide to withdraw your consent:

- You will no longer be able to participate in the study;
- No new information or samples will be collected about you or from you by the study team.
- The study team may still need to report any safety event about the medicine related to the study that you may have experienced due to your participation in the study;
- Your personal data, including your Coded Information, that has already been collected up to the time of your withdrawal of consent, will be kept and used by the Sponsor to guarantee the integrity of the study, to determine the safety effects of PF-07258669, to satisfy legal or regulatory requirements and/or for any other purposes permitted under applicable data protection laws.;
- Your personal data, including your Coded Information, will not be used for further scientific research. However, if your personal data has been anonymized so that the information does not identify you personally, that information may continue to be used for further scientific research (as described in Section E of this document), as permitted by applicable law; and
- Biological samples that have been collected but not analysed will no longer be used, unless permitted or required by applicable law.

  You have the additional right to request that any remaining samples that have been collected from you as part of the study be destroyed. You may exercise this right by communicating to the study team your wish to have the samples destroyed. The study team will then send your coded request to the Sponsor. In some countries, local laws or regulations may require that your samples be destroyed or de-identified if you withdraw from the study, regardless of whether you specifically make such a request.

  However, we cannot guarantee the destruction of all samples because some of the samples may no longer be traceable to you, they may have been entirely used up, or they may have been released to a third party. In those cases, it would not be possible to remove and destroy your biological samples and any related data.