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English Translation of the German Original

Participant Information for the PAREXEL Clinical Trial 236073
EudraCT No.: 2017-003339-13

A Randomized, Open-label, Single-dose, Parallel-arm, Phase 1 Study to Investigate the Pharmacokinetic Profile of a Fixed-Dose Combination Tablet of Tesofensine and Metoprolol (Tesomet) and Co-Administration of Tesofensine Plus Commercial Metoprolol in Adult Healthy Subjects

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1. Preface

We thank you for your interest and your possible participation in this clinical trial.

This clinical trial is ethically justifiable only if it delivers evaluable results. If you decide to participate in this clinical trial, you must strictly adhere to the required behavior patterns. An infringement of the rules may endanger your health and can interfere with the results of the clinical trial concerning the investigational medicinal product.

PAREXEL International GmbH is a contract research organization, which will conduct this clinical trial at the request of Saniona and will be paid for it by Saniona.

This clinical trial is an investigation which involves research.

The information and the materials that are given to you in relation to the clinical trial are confidential information belonging to the Sponsor Saniona and should be kept private. However, you can discuss this information in confidence with your doctor or friends and family to decide whether to take part in this clinical trial and in discussing your healthcare.

This clinical trial will be registered in the European Clinical Trials Database (EudraCT). The sponsor of this clinical trial is also obliged to post the results of this clinical trial after its completion in EudraCT. A subset of data could be available to the public via the European Union Clinical Trials Register. The public data will not contain information that can identify you. At most, the Clinical Trial Register will include a summary of the results as well as possibly a description of the clinical trial.

A description of this clinical trial will be available on https://CinicalTrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Please read this Participant Information carefully. If you have further questions concerning this Participant Information, please refer them to our investigators who will be pleased to explain.

2. Introduction

The investigational medicinal product Tesomet is under development by Saniona for the treatment of a variety of conditions, for which a weight reducing effect is relevant to the treatment, such as obesity, type 2 diabetes and Prader-Willi Syndrome (an inborn disorder, which commonly causes obesity in children and adults).

Tesomet is a combination tablet, containing tesofensine and metoprolol. Tesofensine was originally under development as a treatment for Parkinson's and Alzheimer's disease. During a clinical trial, a significant weight loss was noticed in overweight participants, despite the fact that the subjects did not attempted to lose weight. It was therefore further developed for the treatment of obesity. Metoprolol has been approved in Germany and other countries for the treatment of heart conditions and high blood pressure.

The results obtained from previous clinical trials indicate that tesofensine is generally well tolerated. A slight increase in blood pressure (1 to 5 mmHg) and heart rate (8 beats per minute) has, however, been observed after being administered alone. As even a slight increase in blood pressure and heart rate may constitute an unacceptable safety risk after a while, tesofensine will be administered together with metoprolol, which mitigates these side effects. Metoprolol blocks certain beta receptors in the body ($beta_1$-selective beta receptor blocker) and through this leads to a slowing down of the heartbeat and a decrease in blood pressure.

Tesofensin and metoprolol have thus far been administered together, but in two separate tablets, in two clinical trials. The investigational medicinal product Tesomet is a tablet that contains both substances in a fixed dose combination. In this clinical trial the so-called "bioavailability" of Tesomet will be compared to that of a simultaneous administration of

tesofensine and metoprolol. The bioavailability indicates the amount of study drug that is available to the body after it reaches the blood circulation.

Tesofensine and metoprolol are being administered as a single combination tablet for the first time in this clinical trial.

Please be aware that this clinical trial has the purpose to investigate particular characteristics of an investigational medicinal product. Therefore, you will not have any benefit for your health if you chose to participate in this clinical trial.

3. Aim of the Clinical Trial and Overview

The main aim of this clinical trial is to investigate the bioavailability of a single dose of the fixed dose combination Tesomet tablet and a single dose of simultaneous administration of tesofensine together with commercial metoprolol. Therefore, it will be compared how much tesofensine and how much metoprolol is in your body over a certain period of time (pharmacokinetics). For this reason, blood samples will be collected at planned intervals after the single doses to measure the concentration of tesofensine and metoprolol.

It will also be investigated, how much a meal consumed before administration affects the amount of both substances that is taken up into the blood compared to a dose given under fasting conditions. Additionally, the pharmacokinetics of Tesomet will be investigated after a single administration of a higher dose and of a lower dose. Again for this reason, blood samples will be collected at planned intervals after the dose of Tesomet to measure its concentration.

Additionally, the safety and tolerability of a single dose of Tesomet as well as of the simultaneous dose of tesofensine and metoprolol will be investigated. The safety and the tolerability will be investigated by regularly assessing the vital signs (blood pressure, pulse, body temperature and respiratory rate) and the cardiac function (electrocardiogram [ECG]), by performing physical examinations and by questioning for adverse events. In addition, blood and urine samples will be collected for the determination of the safety parameters.

A total of 60 healthy male participants will participate in this clinical trial. The participants will be divided into 4 groups of 15 participants each. Each group will be assigned to one of the following treatments:

	Treatment	**Amount of tesofensine**	**Amount of immediate release metoprolol**	**Amount of extended release metoprolol**	**Fasting condition or after meal**
Group 1	1 Tesomet tablet („higher Dose“)	1 mg	20 mg	80 mg	Fasting
Group 2	1 Tesomet tablet („lower Dose “)	0,2 mg	5 mg	20 mg	Fasting
Group 3	Tesofensine and metoprolol tablets	1 mg (2 tablets)	25 mg (1 tablet)	75 mg (2 tablets)	Fasting
Group 4	1 Tesomet tablet („higher Dose“)	1 mg	20 mg	80 mg	After meal

It will be randomly determined, which of the possible treatments you will receive; it will be like drawing a lot. The possibility that you are assigned to a specific group will be 25% or 1:4.

This is an open-label trial. Therefore, both you and the Investigator will know which treatment you are receiving.

The total duration of the clinical trial for each participant is up to 38 days (including the screening period).

It cannot be excluded that health impairment or disturbances in your well-being might occur during the clinical trial. It is necessary that you comply with the instructions given in this Participant Information and with the instructions given by the investigators. Please contact the Investigator or the trial staff directly if any symptoms occur.

4. Risks of the Investigational Medicinal Products

The evaluation of side effects is based on the following frequencies:

Very common	more than 1 out of 10 patients
Common	less than 1 out of 10 but more than 1 out of 100 patients
Uncommon	less than 1 out of 100 but more than 1 out of 1,000 patients
Rare	less than 1 out of 1,000 but more than 1 out of 10,000 patients
Very rare	less than 1 out of 10,000 patients, including single cases
Not known	frequency cannot be estimated based on available data

Risks of Tesofensine

To date, 25 clinical trials with tesofensine have been completed, with 289 healthy participants, 167 obese patients and 849 patients with Parkinson's and Alzheimer's disease. The following adverse events were observed in the clinical trials:

Very common:

- Headache, insomnia, dizziness, sleepiness, loss of appetite, lack of energy, dry mouth, attention disturbances, cold-like symptoms, diarrhea, constipation.

Common:

- Nausea, vomiting, fast pulse, muscle spasms, sweating, palpitations, vertigo, blurry vision, flatulence, abdominal pain or discomfort, tooth pain, fatigue.

Rare:

- Altered state of consciousness, sensory disturbance. Agitation and persecutory delusion were found in a subject that received multiple doses of 4 mg tesofensine per day.

To date, tesofensine and metoprolol have been administered together in 2 clinical trials to a total of 42 participants (12 healthy participants and 30 overweight or obese type 2 diabetes patients). The most common adverse events from the trials with 30 type 2 diabetes patients were: Nausea (7 participants), excessive sweating (6 participants), headache (5 participants), dry mouth (4 participants), impaired emptying of stomach, fatigue, muscle spasms, dizziness and restlessness (3 participants each).

Risks of Metoprolol

Extended release metoprolol (Metoprolol-ratiopharm® Succinat Retardtabletten)

Like all medicines, this medication may have side effects, although not everybody gets them.

Very common:

- Significant decrease in blood pressure, especially when standing up, very rarely with a loss of consciousness
- Tiredness.

Common:

- Decreased heartrate (bradycardia), impaired balance (very rarely with a loss of consciousness), irregular heartbeat or palpitations
- Dizziness, headache
- Shortness of breath under physical strain
- Nausea, stomach pain, diarrhea, constipation
- Cold hands and feet.

Uncommon

- Temporary worsening of complaints related to a heart muscle insufficiency, a specific form of heart arrhythmia (Grade 1 AV-block), pain around the heart
- Abnormal sensations such as tingling (paresthesia)
- Spasm of the airways
- Vomiting
- Skin alterations, psoriasis-like skin rash
- Increased sweating
- Muscle spasm
- Weight gain
- Fluid trapped in tissue (edema)
- Depression, difficulty concentrating, lightheadedness or insomnia

Rare:

- Functional heart complaints, such as irregular heartbeat or racing heart, certain heart arrhythmias (impaired conductivity)
- Impaired vision, dry or agitated eyes, conjunctivitis
- Common cold
- Dry mouth
- Hair loss
- Worsening of diabetes
- Abnormal values in liver function tests
- Impotence and other sexual disorders, hardening of the connective tissue in the cavernous body of the penis (induratio penis plastica)
- Nervousness, anxiety

Very rare:

- Decrease in blood platelets (thrombocytopenia), decrease in white blood cells (leukopenia)
- Tinnitus, hearing disturbance
- Taste disorder
- Light sensitivity, Worsening of psoriasis, emerging psoriasis, psoriasis-like skin alterations
- Joint pain, muscle weakness
- Tissue death (necrosis) in patients with severe blood flow impairment in the arms and/or legs before treatment, increased complaints of intermittent blood flow problems in the legs (intermittent claudication) or blood vessel spasms in the toes and fingers (Raynaud syndrome)
- Liver inflammation
- Forgetfulness or memory difficulties, confusion, hallucinations, personality changes (e. g. mood changes)

Immediate release metoprolol (Egilok metoprolol tartrate)

The following side effects may occur during the treatment: Tiredness, headache, feeling unwell, abdominal pain, diarrhea or constipation, dizziness, sleeplessness, cold feeling in the extremities, excessive sweating, blurred vision, shortness of breath.

For the documentation of possibly occurring side effects, affected body parts may be photographed. The photos are stored in pseudonymised (encoded) form, which means that your personal identification attributes (such as name, birthday, address) will be replaced by a number.

The Investigator will explain all important points about the investigational medicinal products Tesomet and tesofensine to you during the information meeting. In addition, together with this Participant Information you will receive the package leaflet of metoprolol immediate release tablet (Egilok) and metoprolol extended release tablets (Metoprolol-ratiopharm® Succinat Retardtabletten).

Serious adverse reactions and hospitalization:

Although all possible precautions are taken to prevent serious adverse reactions (side effects), such events cannot be completely excluded. It might be necessary that during a possible treatment at the hospital medical information from the clinical trial at PAREXEL is shared with the treating clinician so that he/she can provide the appropriate therapeutic measures. Similarly, it is necessary to make the data collected during the medical treatment accessible the Investigator at PAREXEL, in order to transfer insights about the safety of the investigational medicinal product. The exchange of this information is not possible without your prior written consent.

Clear criteria are defined for this clinical trial, which lead to stopping of the clinical trial in a single participant as well as the whole clinical trial. These criteria may comprise abnormal laboratory values, defined adverse events or clinically relevant ECG recordings, as judged by the Investigator.

You will be informed immediately if during the course of this clinical trial any new findings from this clinical trial or other clinical trial, including animal experiments, become known about the investigational medicinal products Tesomet or tesofensine and metoprolol, which could influence your decision to further participate in this clinical trial. Subsequently, you decide anew about your participation. You will be informed immediately in case of any changes or additions to the protocol of the clinical trial, as applicable, and you will receive an updated Participant Information and will then decide again on your consent to participation.

In this clinical trial the current formulation of the investigational medicinal product is administered in humans for the first time. Therefore, you should also be aware that adverse events other than those mentioned may occur. Clinical trials with new investigational medicinal products generally bear the risk that you may experience adverse events that are currently unknown and unforeseeable.

5. Risks of the Clinical Trial

During the regular course of the entire clinical trial, no more than 144 ml of blood will be drawn. This blood amount may increase accordingly by unanticipated control blood samples for safety monitoring and by repeated examinations at the Screening Visit or on days immediately before the administration of the investigational medicinal product. For comparison: at a single blood donation, up to 500 ml of blood are drawn.

To take a single blood sample, a disposable needle will be used. To take multiple blood samples, an intravenous cannula will be inserted, to avoid repeated puncturing of the vein

with a disposable needle. An intravenous cannula is a short thin plastic tube, which will be inserted through a steel cannula into a forearm vein or a cubital vein (bend of the arm) by the Investigator or qualified trial staff and will remain there for the respective blood-sampling day or until the next morning. Puncturing a vein with a disposable needle or a cannula does not generally entail any risks. In rare cases, bleeding into the surrounding tissue (bruising), and very rarely inflammation of the vein or thrombosis (formation of blood clots) may occur. In rare cases a nerve may be hit, which may cause pain and temporary tingling in the arm.

The further examinations, such as ECG recordings, measurements of blood pressure, pulse, body temperature and respiratory rate are of no health risk to you.

In case any changes occur in your well-being, in laboratory values or other findings, which indicate an impairment of your health, we are obliged to undertake all necessary medical measures to restore your initial condition or to monitor your findings until they have normalized again.

6. Conditions for Participation

To participate in this clinical trial you must fulfill several criteria. Your Investigator will assess your eligibility for participation in this clinical trial from the examinations at the Screening Visit. In any case, the responsible Investigator will inform you about the results of the examinations and the possible need for any further clarification.

The examinations at the Screening Visit can only take place after you have signed the written Informed Consent Form attached to this Participant Information. You will sign the Informed Consent Form after you have clarified all aspects of the clinical trial that are of interest to you from this Participant Information and by additional verbal explanations by the Investigator.

Prior to the information meeting, you will be, in accordance with the law, handed the confirmation of insurance, the Participant Information, as well as the Informed Consent Form.

You may only be enrolled in the clinical trial after you have fulfilled all requirements assessed during the Screening Visit, and also there are no concerns immediately before the (first) administration of the investigational medicinal product. If you are not enrolled in the clinical trial after the Screening Visit or immediately before the (first) administration, you cannot put forward any claim from your consent for participation.

- **Your participation in this clinical trial is voluntary. You have the right to withdraw your consent to participate in this clinical trial at any time. If you decide not to participate in the clinical trial, you may do so without giving any reason. No new information will be collected after you have withdrawn from the clinical trial.**
- **Withdrawing from participation in this clinical trial or a premature termination of the clinical trial has no detrimental effects for you.**
- **You are asked to report to the Investigator your withdrawal from participation in the clinical trial immediately. You can withdraw from the clinical trial without giving any reason. We would appreciate, though, if you would tell us if you withdraw your consent due to an adverse event or any other reason (e.g. illness).**
- **Your withdrawal from the clinical trial by the Investigator or the Sponsor must be justified. These may include, in addition to medical reasons, also deliberate infringements of the rules of the house or misbehavior during the clinical trial, which may endanger your safety or the evaluability of collected data. Regardless of the reasons for the withdrawal, you will be asked to attend a Follow-up Visit for an examination, for your own health benefit.**
- **You have the right to access your data through the Investigator and to have them corrected in case of errors.**
- **After administration of Tesomet or tesofensine and metorpolol a mouth and hand check will be performed. You will be asked to open the mouth and stick the tongue out after you have swallowed the tablets. The Investigator will examine the mouth**

with a light source. You will be asked to lift the tongue and then move it from side to side so that the Investigator can examine the areas.

- **You must have private or statutory health insurance of unlimited duration. If you hold private health insurance you are advised to check with the insurance company before you agree to take part in this clinical trial, as your coverage may be affected.**

The following circumstances may lead to withdrawal from the clinical trial or to the termination of the clinical trial:

- Occurrence of adverse events, which, in the interest of your health, do not allow the clinical trial to proceed;
- Protocol deviations that imply a health risk or jeopardize the clinical trial in a relevant way;
- Your own wish;
- New results become known, including from this clinical trial that indicate unacceptable risks for the participants of this clinical trial.

7. Handling of Samples and Data Obtained from the Samples

Blood samples collected during the course of this clinical trial will be sent to external laboratories for further processing. Your samples will be handled only in encoded form (refer to Section 11: Protection of Personal Data). Sponsor Saniona and third parties that cooperate with Sponsor Saniona will investigate your samples only for the purposes specified in this clinical trial Blood and urine samples, which are investigated by PAREXEL, or third parties that cooperate with PAREXEL, for safety laboratory tests will be handled also only in encoded form (refer to Section 11: Protection of Personal Data). No genetic investigations will be performed with these samples.

Certain values cannot individually independently be measured with some of the technical devices used for the determination of safety laboratory values in blood and urine samples. Therefore, it may happen that in some cases values are issued by the device, which are not necessary for the clinical trial and hence, are in addition to the required values. The external safety laboratory responsible for the blood test will neither provide these additional values to the Investigator nor to the Sponsor. Should the urinalysis conducted at the PAREXEL-Laboratory show abnormal results in the unintended values, then these will be send to the Investigator for assessment.

Your samples will be sent to the below listed laboratories for storage or analysis, but may also be sent to third parties. You will not receive an additional notification if there is a change of laboratories during the trial or if your samples will be sent to third parties. The laboratories listed below and the Sponsor Saniona remain responsible to ensure that all institutions adhere to the appropriate standards regarding the handling of the samples and data protection.

Laboratories assigned to the different assessments are:

- Safety laboratory for blood: synlab pharma institute, Turmstraße 21, 10559 Berlin.
- Safety laboratory for urinalysis: PAREXEL International GmbH, EP Labor, Spandauer Damm 130, 14050 Berlin.
- Blood for concentration measurement of tesofensine and metoprolol: Envigo CRS Limited, Woolley Road, Alconbury, Huntingdon, Cambridgeshire PE28 4HS, United Kingdom

If you decide later on not to participate in the clinical trial, you have the right to request the destruction of your samples. For this purpose please contact the Investigator. The Sponsor is the single owner of all data and inventions, which result from the investigation of these samples, so long as the rights of the donor of the sample are not affected. Results obtained from samples that were collected prior to the time of withdrawal of consent may still be used further under specific conditions (refer to Section 11: Protection of Personal Data). The

Sponsor or third parties will destroy your samples after the end of the clinical trial; data obtained from these samples must be stored for at least 10 years according to applicable law (refer to Section 11: Protection of Personal Data). In case of commercial use of any product which is a result of this clinical trial, the Sponsor is the single owner of this product and you do not have the right to participate in the financial profit. PAREXEL stores personal data for a period of 15 years.

8. Conduct of the Clinical Trial

The clinical trial consists of an ambulatory Screening Visit, a treatment period of 3 days and a Safety Follow-up phone call. The total duration of the clinical trial for each participant is up to 38 days.

Screening Visit

After giving your written consent for participation in the clinical trial, within a period of 30 to 2 days before the start of the clinical trial you will take part in the Screening Visit, where your eligibility for participation will be assessed.

Your personal data such as age, weight, height, body mass index, sex and medical history will be assessed and the following assessments and procedures will be performed:

- Physical examination
- Measurement of blood pressure, pulse, body temperature and respiratory rate
- ECG recording
- Blood samples will be taken for safety laboratory, including HIV and hepatitis test (serology)
- Collection of a urine sample for safety laboratory test, for drugs of abuse (illegal drugs), nicotine and alcohol
- Recording of complaints and concomitant medication.

After this the Investigator will assess your eligibility for this clinical trial.

Treatment period

You will come to the institute on Day –1 in the morning and will remain there until the morning of Day 3.

In addition, the following assessments will be performed:

Day –1:

- Physical examination
- Measurement of blood pressure, pulse, body temperature and respiratory rate
- Test for drugs of abuse, nicotine and alcohol, from a urine sample
- Blood sampling and collection of a urine sample for the safety laboratory before dosing
- ECG recording
- Complaints and concomitant medications will be recorded.

Day 1:

Participants of Groups 1, 2 and 3 must not eat and drink anything except for water from 10 hours before the administration of Tesomet or tesofensine and metoprolol until 4 hours afterwards. From 1 hour before until 1 hour after the administration the participants must not drink anything except for the water for swallowing the tablets. Four (4) hours after dosing the participants will receive lunch – a breakfast will not be served.

Participants of Group 4 will be served a high-fat breakfast approximately 30 minutes before dosing of Tesomet, which they are required to eat within a period of 30 minutes. The

breakfast consists of 2 scrambled eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 120 g of fried potatoes and 240 ml of whole milk. The participants may not eat and drink anything except for water until 4 hours after their breakfast. From 1 hour before until 1 hour after the administration the participants must not drink anything except for the water for swallowing the tablets and the 240 ml milk as part of the breakfast.

On this day you will be allocated to a certain treatment sequence. In the morning of Day 1 you will receive a dosing of Tesomet or tesofensine and metoprolol, which must be taken together with 240 ml of water. Following dosing you will be required to sit upright on the edge of your bed for 20 minutes and must not lie down during this time. You will be required to sit or walk upright for the first 2 hours following dose administration with the exception of supine rest period prior to certain measurements. You will receive standardized meals at set times during your stay at the institute.

The following assessments and procedures will be performed:

- Measurement of blood pressure and pulse pre-dose and 1, 2, 4, 8, 12 and 16 hours post-dose
- Measurement of body temperature and respiratory rate in the morning
- ECG recording pre-dose and 1, 6 and 12 hours post-dose
- Blood sampling for determination of the concentration of tesofensine and metoprolol pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 20 hours post-dose
- Complaints and additional intake of medications will be recorded.

Day 2:

- Measurement of blood pressure and pulse 24, 30 and 36 hours post-dose
- Measurement of body temperature and respiratory rate in the morning
- Blood sampling and collection of a urine sample for the safety laboratory
- ECG recording 24 hours after dosing
- Blood sampling for determination of the concentration of tesofensine and metoprolol 24, 30 and 36 hours after dosing
- Complaints and additional intake of medications will be recorded.

Day 3:

- Physical examination
- Measurement of blood pressure and pulse 48 hours after dosing
- Measurement of body temperature and respiratory rate in the morning
- ECG recording 48 hours after dosing
- Blood sampling for determination of the concentration of tesofensine and metoprolol 48 hours after dosing
- Complaints and additional intake of medications will be recorded.

If you are in good health and if there are no safety concerns, as judged by the Investigator, you will be discharged from the institute after all assessments have been completed on Day 3.

Safety Follow-up phone call (Day 8):

Seven (7) days after dosing of Tesomet or tesofensine and metoprolol you will receive a phone call and you will be asked for complaints and additional drugs you might have taken.

Please refer to the table at the end of this Participant Information for details of the clinical trial course and please contact your Investigator at any time if you wish more detailed explanations about this. Please note that PAREXEL reserves the right to perform additional alcohol urine tests, nicotine tests (cotinine test) or tests for drugs of abuse without advance notice during the clinical trial. A positive result in one of these tests may lead to your exclusion from the clinical trial.

9. Behavior of Participants during the Clinical Trial

- Please come to the unit at Screening in a fasted state.
- Please do not consume poppy-seed containing food (e.g. poppy-seed cake) up to 3 days before the Screening Visit and up to 3 days before Day -1 because this can lead to a positive result of your urine test for drugs of abuse.
- Please do not consume alcohol containing beverages within 48 hours before the Screening Visit and from 48 hours before Day -1 until you are discharged from the institute.
- Please abstain from caffeine-containing food and beverages (chocolate, coffee, tea, cola, cocoa, mate, guarana, energy drinks) from 48 hours before Day -1 until you are discharged from the institute.
- Only non-smokers may participate in this clinical trial. You are not allowed to smoke/use cigarettes or similar products containing nicotine during the preceding 6 months and are not allowed to do this during the trial. Please also avoid passive smoking as it may lead to a positive cotinine (=metabolite of nicotine) test in your urine.
- Please abstain from strenuous physical activities (including sporting events) for 48 hours before Day -1 until discharge. After discharge, mild physical activity can be resumed.
- In order to enable proper functioning of the ECG electrodes and a correct and failure-free ECG recording, participants may be shaved on the affected areas. Participants must disrobe from the waist up in order to ensure correct ECG recording.
- Please note that you are not allowed to remove equipment attached to you (i.e. ECG) without being instructed by the trial staff.
- During your in-house stay you will receive standardized meals and standardized beverages. You are asked to finish these meals completely since different food amounts can influence the results of the clinical trial. You are not allowed to consume additional food.
- You will receive an emergency card confirming that you are participating in a clinical trial with a new investigational medicinal product. The address of the clinical trial institute and an emergency telephone number are given in this card. Please carry this card with you during the entire duration of the clinical trial, especially when you are not at the clinical trial institute.
- Under no circumstances should you have participated in another clinical trial within the last 3 months before the clinical trial or (in more than 3 clinical studies within 12 months) and during the entire clinical trial! Otherwise, you might seriously damage your health, since it is not foreseeable what kind of interactions might occur between the investigational medicinal products in the different clinical trials.
- You should not have donated one or more units (≥450 mL) of blood or had any significant blood loss within 60 days before clinic admission on Day -1, or have donated plasma within 7 days before clinic admission on Day -1 and you must not donate blood or plasma during the participation in the clinical trial. You may not donate any blood within 3 months after discharge from the institute
- CONCOMITANT MEDICATIONS (i.e. prescription or over the counter drugs, including natural and herbal remedies [including St. John's Wort], vitamins and dietary supplements), must not be taken within 2 weeks prior to the administration of the investigational medicinal product and until the Safety Follow-up phone call. The occasional intake of paracetamol (not more than 2 g daily) or other non-steroidal anti-inflammatory drugs (NSAIDs, such as Aspirin [acetylsalicylic acid] or Ibuprofen) is

permitted if agreed by the Investigator. You must inform the Investigator of a medical treatment beforehand. Emergencies are an exemption.

- Should an illness occur or a medical treatment is required, the responsible Investigator will decide whether you may continue to participate in the clinical trial.
- DRUGS OF ABUSE: Under no circumstances are you allowed to take drugs of abuse for the duration of the clinical trial. This could lead to unpredictable risks, which can seriously damage your health.
- During your stay at the institute you must rest from 23:00 until 06:00.
- We would like to inform you that all corridors and the dining room of the institute are under video surveillance.
- Access to the toilet area is controlled by an electronic chip card system.
- You are not allowed to bring food or beverages with you. Please note that PAREXEL staff may check your bags, rucksacks etc. at admission. If there is reasonable ground for suspicion your personal belongings may also be checked at unannounced time points during your in-house stay at the institute.
- You can meet your visitors in a designated room only between 12:00 and 19:00. Visitors will be asked to leave their bags in lockers at the reception.
- Should you have difficulty in keeping an appointment at the institute, please report this in advance, if possible, in order not to endanger the regular course of this clinical trial.
- IN-HOUSE STAYS: You are explicitly instructed that you are not allowed to leave the institute during in-house stays for insurance reasons. Visiting the park of the institute is allowed only if you are accompanied by PAREXEL staff.
- TRANSPORT TO/FROM THE INSTITUTE: Please use public transport when coming to and when returning from our trial institute. Please note that your ability to participate in road traffic and your capacity of reaction time may be impaired temporarily even after you have left the trial institute.
- We would like to ask you not to bring any valuable articles for your in-house stay; PAREXEL is not liable for any lost property.

You must always follow the instructions of the Investigator and staff and always adhere to PAREXEL rules of the house.

10. Medical Care

A physician-on-call service will be available for the entire duration of the clinical trial. You can contact one of our investigators by telephone should any adverse events occur or if you wish to do so for any other reason.

On weekdays, your responsible Investigator or one of his or her deputies will be present in the trial institute between 08:00 and 17:00 and can be contacted under the following phone numbers:

Phone: 030 30685–4254 (Dr. med. Astrid Breitschaft)
or
030 30685–4225 (Dr. Tommaso Fadini)

After 17:00 and on Saturdays, Sundays and on public holidays the following phone number is available:

Phone: 030 30685–347
(Responsible Employee on Duty at PAREXEL)

You will be immediately connected with the Investigator on duty.

Should you have questions concerning your participation in this clinical trial, the course of this clinical trial or your rights as a participant in a clinical trial, please contact the following phone number from your admission day to the institute:

Phone: 030 30685–5100

You should also inform your general practitioner about your participation in a clinical trial.

Furthermore, you can contact the *Bundesinstitut für Arzneimittel und Medizinprodukte* (*BfArM* – Federal Institute for Drugs and Medicinal Products) to obtain information about the conduct of a clinical trial. The contact address is:

Bundesinstitut für Arzneimittel und Medizinprodukte
Fachgruppe Klinische Prüfung / Inspektionen
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn
Phone: 0228 207-43 18
Fax: 0228 207-43 55

11. Protection of Personal Data

During the clinical trial medical findings and personal information (as age, gender, race and ethnical origin) will be collected from you through the Investigator and written down in the institute in your personal file or stored electronically.

All employees of the companies Saniona and PAREXEL International GmbH, Berlin, involved in the above mentioned clinical trial, are subject to professional secrecy. The employees of Competent Authorities are officially obliged to discretion. This guarantees that your personal data will be handled absolutely confidentially and will not be available to the public, i.e. your name will not appear in any report and in any publication. Important data for the clinical trial will be additionally stored, transferred and evaluated in a pseudonymous manner.

The procedure of pseudonymisation (encoding) of your data means that your personal identification attributes (such as name, birthday, address) will be replaced by a number. The data are protected against unauthorized access. The Investigator creates and files a decoding list, which helps to reassign the pseudonymised data to your person, to an allowed extent and as appropriate. A decoding only takes place in compliance with the requirements regulated by law.

Without your consent to the processing of your data you cannot participate in the clinical trial mentioned above.

Personal data collected from you and stored in the course of the above mentioned clinical trial will be, if required, held available for viewing by the Competent Authority or representatives of the Sponsor to verify the proper conduct of the clinical trial.

Where required, your data will be transferred in a pseudonymous manner

a) to the Sponsor or to an agency commissioned by it for the purpose of scientific evaluation or publication,

b) in case an application for marketing authorization is filed, to the applicant and the concerned higher authority,

c) in case of adverse events of the investigational medicinal product to the Sponsor, to the responsible Ethics Committee and the concerned Higher Federal Authority which then transfers them to the European Database,

d) to companies in European and non-European foreign countries which are affiliates of the Sponsor and, if necessary, from these companies to the responsible foreign competent authorities.

The consent to the processing of your data is irrevocable. In case of withdrawal of your consent to participate in the above mentioned clinical trial, the data stored up to this point may be used further, if required, to

1. determine the effects of the investigational medicinal product,

2. ensure that legitimate interests of the concerned person are not compromised,

3. comply with the requirement to provide complete marketing authorization documents.

In addition, PAREXEL International GmbH sometimes receives requests by job centers, employment agencies, social welfare authorities, and other authorities (e. g. tax office) with regard to the expense allowance paid to you. In such a case, PAREXEL International GmbH will provide data about the expense allowance paid to you in the course of this trial to the requesting authority.

The Sponsor will archive all of your data for at least 10 years after completion or discontinuation of the clinical trial. Personal data are archived at PAREXEL for 15 years. You may request the disclosure of your data, provided this is technically not impossible as a result of a deletion of identifying attributes and keywords for decoding that has been made in

the meantime. In this case please contact the Investigator or the Sponsor. Inaccurately processed data concerning you will be corrected on your request.

12. Insurance

For this clinical trial an insurance policy has been taken out as defined in § 40 para. 1 sentence 3 No. 8 and paragraph 3 of the German Pharmaceuticals Act (*Arzneimittelgesetz*, AMG). This insurance covers damage to the health of the participants, which occurs during the conduct of the clinical trial. In case a person dies, the body or the health of the participant is harmed during the conduct of the clinical trial; insurance coverage will also take over liability, if no other party will assume responsibility.

The insurance does not apply to already existing damage to the health and its worsening, which would have occurred or persisted also without your participation in this clinical trial. Genetic damage, i.e. changes of the genetic material (genome), of the chromosomes, of the genes or of single nucleotides, is also excluded from the insurance coverage. However, insurance coverage will be provided in case organic health damage of the insurant with effects on the clinical picture (phenotype) is the consequence.

The insurance coverage is only guaranteed, if you have not violated the instructions of the Investigator and the conditions in the Participant Information. In particular, you are obliged:

- not to undergo any other medical treatment – **except in an emergency** – unless it is in agreement with the Investigator
- to notify the insurer (the insurance company) immediately about any damage to your health, which could have occurred as a consequence of the clinical trial

Please inform the Investigator immediately about possible emergency treatments.

The “General Insurance Conditions for Clinical Studies” and the confirmation of insurance coverage will be handed out to you.

PAREXEL has taken out the insurance policy for this clinical trial with the ‘Allianz Versicherungs-AG’, P.O. Box 10900 Berlin, Phone: 040.69469-33406, Fax: 0800.440 01 01 (Policy No. AS-0243360732) to the amount of EURO 500,000 per participant, which is the legally obligatory minimal amount. Accordingly, you are insured up to a maximum of EURO 500,000 in case of health damage, death or permanent occupational disability.

13. Ethical and Legal Regulations

This clinical trial will be conducted in accordance with the German Pharmaceuticals Act and the German Guidelines on the implementation of Good Clinical Practice (GCP-Guidelines – GCP-V) – according to the directives of the European Community, the Declaration of Helsinki for biomedical research in humans (revised version of 1996) and the International Council for Harmonisation. The clinical trial protocol as well as the Participant Information and the Informed Consent Form have been submitted to the Ethics Committee of the Land Berlin and to the Competent Authority *(Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)* for the required reasoned opinion and authorization, respectively. The clinical trial will be conducted only if these agencies raised no reservations against it.

This information is part of the Informed Consent for the participation in the clinical trial with the investigational medicinal product specified in Section 2. You also will be informed by an Investigator or a member of the investigator group, who are physicians, about the clinical trial in an information meeting. If you have any further questions, please discuss them with the responsible Investigator or the Investigator Dr. med. Astrid Breitschaft.

14. Expense Allowance

For the participation in this clinical trial each participant will receive an expense allowance. It consists of a partial installment for the clinical trial course and a second installment payable at the end of the clinical trial (i.e. after the Safety Follow-up phone call and possible control

examinations). A claim for the entire amount of the expense allowance is only possible if you have participated in all planned examinations, including the examinations at the Safety Follow-up phone call and have also fulfilled the conditions for trial participation during the clinical trial.

The check for the first installment of the expense allowance will be issued at the earliest on the day of the Safety Follow-up phone call or later, if necessary, only on presenting a valid official identity card. No interim payments will be made.

You will receive the second installment of the expense allowance after the Investigator has assessed all findings and no further control examinations are necessary (i.e. within one week after Safety Follow-up phone call or a control examination, respectively). In case of changes to your medical results compared to screening, PAREXEL is obliged to monitor these changes even after the follow-up until they have returned to their initial level or, where necessary, to take appropriate medical measures. Therefore, should it be necessary to perform additional control examinations / additional visits prescribed by a doctor, you will receive an expense allowance of EURO 20 for each additional visit to the trial institute (this does not apply for screening).

In the event of an infringement of the duties detailed in this Participant Information (in particular concerning the intake of other medicines, alcohol or drugs of abuse), you will relinquish your rights to an expense allowance, if the respective data cannot be used for evaluation. Deliberate infringements of the rules of the house or serious misbehavior may lead to your withdrawal from the clinical trial, followed by the cancellation of the second installment of your expense allowance.

Once again, we would like to emphasize the fact that the clinical trial course and the planned number of single examinations to be performed are described according to current status. It is possible that shortly before the start of the clinical trial or during the clinical trial the number of single examinations may be increased or reduced based upon new scientific evidence or requirements, which could result in changes to the expense allowance. You will be informed of any substantial changes, which are to be notified to the Ethics Committee.

For the sake of completeness, we would also like to point out that we do not make any deductions for tax or social security contributions, because no contract of employment between you and PAREXEL exists. Expense allowances are generally subject to income tax. Tax needs not to be paid only if the entire annual income, including the expense allowance, does not exceed the tax exemption limit specified in the tax scale.

If the clinical trial is terminated prematurely, either as a whole or for single participants, or if single trial days are canceled, the participants will receive a proportional amount of the expense allowance.

You will receive EURO 30 for the participation in the screening. This amount covers additional visits, for example for controls of blood and/or urine during the entire screening period. This sum is only paid out separately if you are not suitable for the clinical trial; otherwise it is included in the first instalment (see below).

If you are invited to the admission but receive no medication, you will receive an amount of up to EURO 150 (depending on the time spent).

You will not receive a separate reimbursement of your travel expenses; these are covered by the expense allowance.

Please claim the check immediately after you have received it. If you have not collected or claimed the checks your entitlement to the expense allowance expires 6 months after the Safety Follow-up phone call.

The first installment of the expense allowance is EURO 480, the second installment is EURO 192. Thus, the total amount of the expense allowance is EURO 672, if you complete the entire clinical trial course.

15. HIV- and Hepatitis-Examination

With the participation in this clinical trial you will be asked to give your consent to blood examinations for a HIV test, Hepatitis B test, Hepatitis A test and Hepatitis C test during the Screening Visit. The following precautions will be taken to protect the anonymity of your test results:

Your blood sample will be labeled in a pseudonymous manner as described in Section 11, i.e. the laboratory staff doing the test cannot connect your blood sample with your name. The laboratory will transfer the results of the examination electronically to that part of the internal database system at PAREXEL, to which only authorized persons have access, who are obliged to confidentiality (according to §13 of the *Bundesdatenschutzgesetz*, German Data Protection Law). The Investigator or a medical designee will inform you about the finding in a confidential, personal conversation.

A positive result of the HIV test will be reported **anonymously** according to the German „*Infektionsschutzgesetz*" §7 (3), i.e. without giving your name, to the Robert Koch Institute (Berlin). The reporting of a positive result to third parties indicating your name is not possible without your written consent.

We want to point out explicitly the following: Your participation in the clinical trial is only possible in case of a negative result of the HIV test. In no case should you draw consequences from the inclusion in a clinical trial regarding your sexual behavior, e.g. refraining from protective measures just because you assume that your test result is negative.

A positive test result from the Hepatitis B, Hepatitis A or the Hepatitis C test will be reported according to the German „*Infektionsschutzgesetz*" §7 (1) **by name** to the responsible health authority (*"Gesundheitsamt")*.

Only a newly acquired infection will be reported, for example, a known chronic Hepatitis C disease is exempted from this.

Your participation in the clinical trial is only possible in case of a negative result from the Hepatitis B-, Hepatitis A- and the Hepatitis C-tests.

Should you have further questions about this, please contact the responsible Investigator at PAREXEL, an independent medical examiner or a competent outreach clinic.