Information for participation in medical-scientific research

A study in healthy subjects investigating the interaction between ceftobiprole and pitavastatin. Ceftobiprole is the compound studied and is an approved drug (not approved in The Netherlands) that is being used in the treatment of bacterial infections.

Official title: A Phase 1, single-center, open-label, non-randomized, fixed-sequence, drug-drug interaction study to assess the effect of repeated doses of intravenous ceftobiprole on the pharmacokinetics of oral pitavastatin (OATP1B substrate) and on plasma levels of coproporphyrin I (OATP1B biomarker) in healthy subjects

ICON project code: BSLBLB87-0H20C5 (0680/0062)
Sponsor code: BPR-CP-101
Study compound: ceftobiprole

Introduction

Dear Sir/Madam,

With this information letter, we would like to ask you to take part in a medical-scientific study.

Participation is voluntary. Based on brief information, you have shown interest in participating in medical-scientific research.

Here you can read about what the study involves, what it means for you, and what the advantages and disadvantages are. It is a lot of information. Could you please read the information and decide if you want to participate? If you want to participate, please fill in the form in **Appendix E**.

Ask your questions
You can take your decision based on the information in this information letter. In addition, we suggest to do the following:

- Ask questions to the investigator who gives you this information.
- Talk to your partner, family, or friends about this study.
- If necessary, ask questions to the independent expert. See **Appendix A** for contact details.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.
- You can also find more information about your stay at ICON in the information booklet ‘Your stay at ICON’.

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1.0 General information

Basilea Pharmaceutica International Ltd, Allschwil (Allschwil, Switzerland) has set up this study. Below, we always call Basilea Pharmaceutica International Ltd, Allschwil the 'sponsor'. The sponsor pays for this study. Researchers of the research center of ICON in Groningen will conduct the study. These can for example be doctors or nurses.

The Medical Research Ethics Committee [redacted] The Netherlands, has approved this study (see **Appendix A** for contact details).

You may participate in a drug study a maximum of 4 times a year. You may only participate in one study at a time. We will check this in a central system to which other research institutes are also connected. Data concerning your participation in studies is stored securely in this system.

Participants in medical-scientific research are often called subjects. Both patients and people who are in good health can be subjects.

For this study we are looking for 12 healthy men or women.

2.0 What is the purpose of the study?

In this study we will investigate the effect of administration of ceftobiprole on the elimination of pitavastatin.

We will also investigate how safe ceftobiprole is and how well ceftobiprole is tolerated by subjects when it is administered in combination with pitavastatin.

In addition, we will investigate the effect of ceftobiprole on a specific compound in the blood, called coproporphyrin I, which is naturally occurring in the body.

Please note that when the term 'study compound' is used in this document, we mean ceftobiprole, pitavastatin, or both.

3.0 What is the background of the study?

Ceftobiprole is not a new compound. It is a drug approved for the treatment of bacterial infections in humans in many countries worldwide. Ceftobiprole is not approved in The Netherlands. It is marketed under the brand names Zevtera®, Adaluzis® and Mabelio®. Ceftobiprole is an antibiotic that disrupts the formation of the bacterial cell wall leading to the death of the bacteria.

In this study, we investigate the effect of ceftobiprole on a specific type of proteins which are involved in the elimination of some drugs from the body. These proteins are called 'hepatic organic anion-transporting polypeptide 1B (OATP1B)'. This effect can be studied using pitavastatin. Pitavastatin is a drug which is approved for the treatment of increased levels of cholesterol in blood. It is known that OATP1B proteins are involved in the elimination of pitavastatin from the body. By measuring pitavastatin blood levels before and after administration of

ceftobiprole, we can see if blood levels of pitavastatin increase or not. In this way it can be examined whether ceftobiprole has an effect on OATP1B proteins. As a result, it can be predicted if ceftobiprole may have an effect on the elimination of drugs in which these OATP1B proteins are also involved.

4.0 What happens during the study?

Are you participating in the study? Then the study will take a maximum of 38 days from the screening until the follow-up visit.

The screening: are you eligible to participate?

First, we want to know if you are eligible to participate. The investigator will go over this document with you first. If you decide to participate in this study, the investigator will sign this document with you. Thereafter, the investigator will start the screening. This will consist of the following assessments:

- Physical examination. The investigator will for example listen to your heart and lungs, and measure your weight and height.
- Vital signs. For this, your blood pressure, heart rate, number of breaths per minute, and body temperature will be measured.
- Heart tracing (ECG).
- Blood and urine tests. For this, blood will be drawn, and a small volume of urine will be collected.
- Tests for the use of alcohol and drugs of abuse (hard and soft drugs). For this, blood will be drawn, and a small volume of urine will be collected.
- Tests for the diseases HIV, hepatitis B and hepatitis C. For this, blood will be drawn. If the tests show that you have any of these diseases, we will tell you, and you cannot participate in this study. If you do not want to know, you cannot participate in this study either.
- A pregnancy test for women. For this, blood will be drawn. Women cannot participate in the study if they are pregnant or breastfeeding.

In **Appendix C** it is explained what these assessments and measurements entail.

In addition, we collect your demographic data, such as your age, sex, race, and ethnic origin. This is to gain insight into the population in which the study compound is being studied, as these factors can influence how well a drug works and how safe it is. The investigator will discuss the results, your medical history, and medication use with you. All these factors are important for the study because they can influence the effects of the study compound.

It can happen that you are healthy, but still are not eligible to participate. For example, because your body weight is too high or too low according to the requirements of the study. The investigator will tell you more about this.

Just before administration of the study compound, we will decide based on the latest test results if you are eligible for participation or not.

How often will you visit the research center?

In total, you will visit the research center 3 times:

- once for the screening as described before.

- once for a stay in the research center of 10 days (9 nights). You are expected at the research center 2 days (Day -2) before the first administration of the study compound on Day 1. You have to be at the research center between 9:30 hrs and 14:00 hrs on Day -2. Before coming to the research center, you will be notified of the exact time. You will leave the research center on Day 8 of the study.
- once for the follow-up visit, which takes place on a day between Day 13 and Day 17.

Below is an overview of the days you stay at the research center, or when you visit the research center.

Screening	**Stay in the research center**			**Follow-up visit**
	Arrival	**In-house stay**	**Departure**	
On a day between Day -21 and Day -3	Day -2	Day -2 until Day 8	Day 8	On a day between Day 13 and Day 17

How will the study compound be given?

You will receive ceftobiprole as an intravenous infusion (solution of the compound that will be administered directly in a blood vessel). The infusion takes 2 hours.

You will receive pitavastatin as a tablet which you have to swallow with 240 milliliters (mL) of water.

After each dose of the pitavastatin tablet, one of the investigators will check if you have taken the tablet .

How much and how often will the study compound be given?

You will receive the following doses:

- Ceftobiprole: 500 milligrams (mg) every 8 hours from Day 4 to Day 7 (thus an infusion of 2 hours 3 times per day from Day 4 to Day 7)
- Pitavastatin: 2 mg once on Day 1 and once on Day 6

Please refer to the table below for an overview of when you will receive ceftobiprole and pitavastatin during your stay in the research center:

Day →	-2	-1	1	2	3	4	5	6	7	8
Ceftobiprole						X	X	X	X	
Pitavastatin			X					X		

In the mornings of Day 4 to Day 7, you will receive the ceftobiprole infusion after an overnight fast (no food or drinks, except water) of at least 10 hours.

You will receive pitavastatin as a tablet in the mornings of Day 1 and Day 6 after an overnight fast (no food or drinks, except water) of at least 10 hours.

Which assessments and measurements will we do?

During the study, we will do the following assessments and measurements:

- Physical examination, only if considered necessary by the investigator. The investigator will then for example listen to your heart and lungs.
- Vital signs. For this, your blood pressure, heart rate, number of breaths per minute, and body temperature will be measured.

- Blood and urine tests. For this, blood will be drawn, and we will take a urine sample.
    - On certain days, blood will be collected regularly. On these days, an indwelling cannula (a tube in a vein in the arm) will be temporarily inserted. In **Appendix C** you can see on which days this is and how long the indwelling cannula will remain in place.
- Heart tracings (ECGs).
- Questions about your wellbeing and if there are details about your health.
- Questions about your medication use.
- Taking photos (if necessary). In certain situations, for example in the case of a skin reaction or reactions at an injection/cannula site, it may be necessary to take a photo of the affected area. You cannot be recognized on the photo. These photos can then be used for assessment and follow-up of the reaction or for remote assessment by a doctor. Photos will only be taken if the investigator considers this necessary. You can ask questions prior to the photos being taken and indicate whether you agree with this.
- Tests for the use of alcohol and drugs of abuse (hard and soft drugs). For this, blood will be drawn once, and a small volume of urine will be collected once.
- A pregnancy test for women. For this, blood will be drawn once.

In **Appendix C** it is explained what these assessments and measurements entail.

What happens during the follow-up visit?

On a day between Day 13 and Day 17, your health will be checked for the last time during the follow-up visit. The appointment for this follow-up visit will be made during the study. The follow-up visit will consist of the following assessments and measurements:

- Vital signs. For this, your blood pressure, heart rate, number of breaths per minute and body temperature will be measured.
- A heart tracing (ECG).
- Several blood and urine tests. For this, blood will be drawn and a small volume of urine will be collected.
- A pregnancy test for women. For this, blood will be drawn.
- Questions about your wellbeing and if there are new details about your health.
- Questions about your medication use.

What does it mean if you are a reserve?

To make sure we have enough suitable subjects, we always invite additional potential subjects to come to the research center. It is therefore possible that you will be assigned the position of reserve, even if you have been approved during the screening and based on that you have been invited to come to the research center. It is never known in advance whether you will be a subject or a reserve. Based on the latest test results of all potential subjects who have come to the clinical research center and just prior to administration of the study compound, the investigator determines if you can participate in the study or not. If you have been given the reserve position after entering and have not been involved in the study, you can often be given a priority position if you are interested in participating in another group of the same study or a new study. As a reserve subject you will receive a part of the fee. If you replace a subject who is withdrawn from the study, you will be eligible for the full compensation as defined in Section 11.

5.0 What agreements do we make with you?

We want the study to go well and safely. Therefore, it is important that you adhere to the agreements presented in the below table. In the table you can also see when these agreements apply.

Agreements

What is not allowed?	When?

Food and drinks (water is allowed)	• At least 4 hours prior to:
	  o the screening.
	  o entry into the research center on Day -2.
	  o the follow-up visit.
	• 10 hours prior to administration of ceftobiprole in the mornings of Day 4 to Day 7.
	• 10 hours prior to administration of pitavastatin in the mornings of Day 1 and Day 6.
	• At least 4 hours after administration of pitavastatin on Day 1 and Day 6 until lunch.
	• At least 1 hour after the end of the administration of ceftobiprole in the mornings of Days 4, 5 and 7.

Drinking water	• 1 hour prior until 1 hour after administration of pitavastatin on Days 1 and 6. • 1 hour prior to the start of administration of ceftobiprole until 1 hour after the end of administration of ceftobiprole in the mornings of Day 4 to Day 7.
Caffeine and caffeine-like beverages (coffee, tea, cola, energy drinks) or food (chocolate)	• Within 48 hours (2 days) prior to entry into the research center on Day -2. • During your stay in the research center.
Grapefruit and grapefruit juice	• During your stay in the research center.

Alcohol*	• Within 48 hours (2 days) prior to:
	  o the screening.
	  o entry into the research center on Day -2.
	  o the follow-up visit.
	• Intake of alcohol is also not allowed during the stay in the research center.

Foods containing poppy seeds (as this could cause an incorrect drug screen result)	• Within 48 hours (2 days) prior to:
	  o the screening.
	  o entry into the research center on Day -2.

Strenuous physical activity (e.g. sports, activities which make you out of breath, cause muscular pain, or make you sweat)	• Within 96 hours (4 days) prior to:
	  o the screening.
	  o entry into the research center on Day -2 until the follow-up visit.

Prescribed medication	• From 30 days prior to entry into the research center on Day -2 until the follow-up visit.

What is not allowed?	When?
	• An exception is made for hormonal contraceptives which are allowed throughout the study.
Over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g. St. John's Wort, which is used for depression, anxiety, and sleeping problems)	• From 14 days prior to entry into the research center on Day -2 until the follow-up visit. • An exception is made for paracetamol which is allowed up to 2 grams (4 tablets of 500 mg) per day for no more than 3 consecutive days throughout the study.
Smoking or use of other tobacco products	• Within 48 hours (2 days) prior to entry into the research center on Day -2. • During your stay in the research center.
Drugs of abuse (hard or soft drugs)*	• No use of drugs of abuse (hard or soft drugs) during or prior to participation in this study. Please note that after (incidental) drug use, drugs can be detected in blood for a long period. Subjects with a positive drug test cannot participate in the study.
Blood donation/blood loss of more than 450 mL	• From 60 days prior to administration of the first dose of pitavastatin on Day 1 until the follow-up visit.
Blood donation/blood loss of more than 1.5 liters (for men)/1 liter (for women)	• From 10 months prior to administration of the first dose of pitavastatin on Day 1 until the follow-up visit.
Unprotected sex, egg and sperm donation	• See **Appendix D** for more information about the contraceptives to be used and the period in which they should be used.

*Tests and spot checks will be done on the use of alcohol and/or drugs of abuse.

What are the most important conditions for participation?

The most important conditions for participation are:

- You are willing to participate in this study.
- You take the study compound according to the instructions.
- You keep to the appointments for visits.
- You are a healthy man or woman.
- You are at least 18 and not older than 65 years of age.
- You have a body mass index (BMI) of at least 18.0 and not higher than 30.0 kilograms/meter^2 (for more explanation, see **Appendix C**).
- You do not smoke more than 5 cigarettes, 1 cigar or 1 pipe daily and you have not smoked or used other tobacco products within 48 hours (2 days) prior to entry into the research center on Day -2. You also adhere to the conditions for smoking as described above in the table with 'Agreements'.
- You have not participated in any other drug study within 30 days prior to administration of the first dose of pitavastatin on Day 1 (calculated from the follow-up visit of the previous study).
- At screening your state of health must satisfy the entry requirements of the study.

Furthermore, in the protocol of the study additional criteria for participation are included; these will be discussed with you during screening.

During participation in this study, it is important that you contact the investigator:

- Before you start using other medicines. Even if they are homeopathic or natural remedies, vitamins and/or over-the-counter medicines.
- If you are admitted to a hospital or treated in a hospital.
- If you suddenly develop any health problems.
- If you no longer want to participate in the study.
- If you or your partner becomes pregnant.
- If your contact details change.

6.0 What side effects, adverse effects, or discomforts may you experience?

What side effects can ceftobiprole have?

Like all medicines, ceftobiprole may cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some people may experience serious side effects and may require treatment.

Based on clinical studies with ceftobiprole, the most common side effects occurring in 1 in 100 or more of the patients were:

- nausea
- diarrhea
- vomiting
- headache
- taste disorder
- rash
- infusion site reaction (including inflammation of a vein)
- increased levels for liver enzymes in the blood (this says something about the functioning of the liver).

Other potential side effects reported in adults include decreased sodium levels in the blood, hypersensitivity (allergic reaction) including life-threatening allergic reaction (such as difficulty in breathing, low blood pressure and/or organ failure), seizures (an episode of spasms and reduced consciousness), antibiotic-associated inflammation of the bowel, low number of platelets which may cause bleeding and bruising and changes in red and white blood cell counts (if white blood cell count becomes very low, the risk of severe infections increases and may become life threatening).

If you suffer any of these side effects (or any others not mentioned above) or think you are experiencing a side effect during this study, please tell the investigators immediately. You may receive treatment for side effects, if considered necessary by the responsible doctor.

The study compound may also have (serious) side effects that are still unknown.

If during the study more information becomes available regarding side effects that may be related to the study compound, the responsible doctor will inform you about this.

What side effects can pitavastatin have?

Pitavastatin may also cause side effects. The most common side effects occurring in less than 1 in 10 users are:

- joint pain
- muscle pain
- constipation
- diarrhea
- indigestion
- nausea
- headache.

More information about pitavastatin can be found in the package leaflet, which will be provided to you.

If you suffer any of these side effects (or any others not mentioned above) or think you are experiencing a side effect during this study, please tell the investigators immediately. You may receive treatment for side effects, if considered necessary by the responsible doctor.

What possible discomforts can you expect due to measurements?

Blood draw

Drawing blood may be painful or cause some bruising. The use of the indwelling cannula (a tube in a vein in the arm) can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bruising around the puncture site. In some individuals, a blood draw can cause pallor, nausea, sweating, low heart rate, and/or drop in blood pressure with dizziness or fainting.

In total, we will take about 233 milliliters (mL) of blood from you from screening to follow-up. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time at once. If the investigator thinks it is necessary for the safety of a subject, extra blood samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be more than the amount indicated above.

Heart tracing

To make a heart tracing, electrodes (small, plastic patches) will be placed on your arms, chest and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

7.0 What are the advantages and disadvantages if you participate in the study?

Taking part in the study can have advantages and disadvantages. We will list them below. Think about this carefully and talk to other people about it.

You yourself will not benefit from participation in this study. But your participation will help the investigators to increase the knowledge about the effects of ceftobiprole on the elimination of drugs in which OATP1B proteins are involved.

Participation in the study may have these disadvantages or consequences:

- Possible side effects.
- Possible adverse effects or discomforts of the evaluations in the study.
- That you will spend time on the study.
- That you have to undergo measurements.
- That you have to comply with agreements.

All these aspects have been described before in Sections 4, 5 and 6. You will receive some compensation for time spent in this study and a contribution for any travel expenses (see **Section 11**).

It is possible that during the study something is discovered by accident that is not important for the study but may be important for your health or the health of members of your family. See **Section 10** what will be done if this happens.

You do not want to participate?

It is up to you to decide if you wish to participate in the study or not. Participation is voluntary.

8.0 When does the study end?

The investigator will let you know if there is any new information about the study that is important for you. The investigator will then ask you if you still want to participate.

In the following situations the study will stop for you:

- You have completed all the visits.
- You choose to stop. This can be at any time. Report this to the investigator immediately. You do not have to explain why you stop. The investigator will still invite you for a follow-up visit.
- You became pregnant.
- The investigator thinks it is better for you to stop. The investigator will still invite you for a follow-up visit.
- One of the following organizations decides to stop the study:
    - the sponsor,
    - the government or
    - the Medical Research Ethics Committee.
- You do not follow the instructions of the study.
- You need a treatment which is not allowed according to the study protocol.

What happens if you stop participating in the study?

If you withdraw or the administration of the study compound is stopped prematurely, you will be asked to visit the research center to complete the study. During this visit, follow-up assessments may be done, such as laboratory tests, a physical examination and vital signs to help you withdraw from the study safely. We advise you to always have the planned follow-ups.

The investigators use the data and bodily material (blood and urine) that have been collected up to the moment that you stopped. If you wish, the collected bodily material can be destroyed. Inform the investigator about this.

The entire study ends when all subjects have completed the study.

9.0 What happens after the study has ended?

Will you get the results of the study?

After processing all data, and upon request from you, the investigator may inform you about the most important results of the study.

10.0 What do we do with your data and bodily material?

Are you participating in the study? Then you also give your consent to collect, use and store your data and bodily material.

What data do we store?

We store these data:

- Your name
- Your address
- Your contact details
- Your date of birth
- Your sex
- Your race and ethnic origin
- Information about your health
- (Medical) data that we collect during the study, such as ECG, vital signs, measurement results, and possibly photos.

What bodily material do we store?

For this study we collect, use and store your blood and urine.

Why do we collect, use, and store your data and bodily material?

We collect, use, and store your data and your bodily material to answer the questions of this study. And to publish the results. Data and/or bodily material can be used by the sponsor and companies that help the sponsor with the study. We also need these data and the material to be able to market the study compound.

How do we protect your privacy?

To protect your privacy, we give a code to your data and bodily material. We only put this code on your data and bodily material. Your name and other personal data that could directly identify you will be stored separately. Only the key to the code of the data can be used to identify you. The research center (ICON) stores this key in a safe place. We only send your data and bodily material to the sponsor and other parties involved in this study using that code. Also, in reports and publications about the study, nobody will be able to see that it was about you.

Who can see your data?

Some people can see your name and other personal information without a code. This could include data specifically collected for this study, but also data from your medical file. These are people checking whether the investigators are carrying out the study properly and reliably. These persons can access your data:

- Someone who checks the data and works for the sponsor or investigator (ICON) or someone who checks the data and has been hired by the sponsor or the investigator (ICON).
- National and international supervisory authorities (such as for example the European Medicines Agency [EMA] and 'Food and Drug Administration' [FDA]).

These people will keep your information confidential. If you sign the consent form, you will give consent to these people and authorities having access to your data. The Health and Youth Inspectorate can access your personal information without your permission.

For how long do we store your data and bodily material?

Your data will be stored for 25 years at the research center and 25 years with the sponsor after completion of the study.

We store your bodily material for a maximum of 12 months after completion of the study to be able to perform new analyses that are related to this study. As soon as this is no longer needed, we will destroy your bodily material.

What happens if there are unexpected discoveries?

It is possible that during the study we discover something coincidentally that is not important to the study, but that is important to you or to members of your family. If this concerns information that can be important for your health, we will tell you this. The investigator will also contact your general practitioner or other healthcare providers. You can then discuss with your general practitioner or other healthcare providers what needs to be done. Any further medical examination will be done by them. The costs of this will be charged to your own insurance. With the consent form you give permission to inform your general practitioner or other healthcare providers.

Can you take back your consent for the use of your data?

You can take back your consent for the use of your data and bodily material for this study at any time. Please tell the investigator if you wish to do so. But please note: if you take back your consent, and the investigators have already collected data for a study? Then they are still allowed to use this data. If you wish, collected bodily material can be destroyed. Inform the investigator about this. But if assessments with bodily material have been carried out? Then the investigator can continue to use the results.

We send your data to countries outside the European Union (EU)

For this study, we send your coded data and/or bodily material also to countries outside the EU. This may also involve storing data on servers outside the EU. The privacy rules of the EU do not apply in those countries. However, your privacy will be protected at a similar level. If you do not consent to this, you cannot participate in this study.

Do you want to know more about your privacy?

Do you want to know more about your rights when processing personal data? Visit https://autoriteitpersoonsgegevens.nl/en.

Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the ones responsible for the processing of your personal data. For your study, these are:

- The sponsor and ICON.

If you have complaints about the processing of your personal data, we advise you to first contact the research center. You can also contact the data protection officer of ICON. Or you can submit a complaint to the Dutch Data Protection Authority.

See **Appendix A** for contact details.

Where can you find more information about the study?

The study will be listed in registries like:

- Registration of studies in Europe (https://euclinicaltrials.eu/)
- Registration of studies in the USA (http://www.ClinicalTrials.gov)

After the study, these websites may contain a summary of the results of this study. These websites do not contain any information that can identify you. You can find this study under BPR-CP-101.

11.0 What compensation will you receive if you participate in this study?

Section 4.0 explains that just prior to administration of the study compound, you will be told if you can participate in the entire study or that you will be a reserve subject and thus cannot participate in the entire study. It may also be that you are not eligible for participation in this study based on the latest screening results on the day of arrival in the research center or on Day 1 (for example the laboratory test results). The day on which this decision is taken determines the amount of compensation that you will receive. The compensation is as follows:

Participation	Compensation
For full participation (up to the follow-up)	[redacted]
If you are a reserve*	[redacted]
If you are not eligible at screening**	[redacted]
If you are not eligible on Day -2	[redacted]
If you are not eligible on Day -1 after arriving on Day -2	[redacted]
If you are not eligible on Day 1	[redacted]

* If, as a reserve, you replace a subject who is withdrawn from the study, you will be eligible for the compensation for full participation.

** If the screening needs to be repeated you will not receive additional compensation.

In addition, your travel expenses will be reimbursed based on the travel distance. This compensation is [redacted] per round trip, whatever the mode of transport. Parking fees are not reimbursed. If you stop before the study is over, your compensation will be reduced. Except for the travel expenses, the compensation you receive will be communicated to the Tax Authorities as 'income from other sources'. If necessary, ask the Tax Authorities.

Payment will take place after the follow-up examination, including any necessary repeat measurements. However, you will not receive any payment for participation or travel expenses if the test on the use of drugs of abuse or alcohol is positive, or if you do not show up at the research center without having notified the investigator. In the latter case you will only receive compensation for the screening and travel expenses for the screening visit.

12.0 Are you insured during the study?

Insurance has been taken out for everyone participating in this study. The insurance covers damage caused by the study. But not for all damages. You can find more information about the insurance in **Appendix B**. It also says who you can report damage to.

13.0 We will inform your general practitioner

We will send your general practitioner a letter to let him or her know that you are participating in the study. This is for your own safety. We will also request medical data from your general practitioner; the General Data Protection Regulation (GDPR) applies here. This means that your data will be processed and protected as described in the GDPR.

14.0 Do you have any questions?

You may address your questions to the screening physician or other employees of the screening center during screening. The medical supervision is provided by the responsible doctor. After office hours you can contact the doctor on duty.

Would you like to get advice from someone who is independent of the study? Then please contact the independent expert. This expert knows about the study but is not involved in the study.

If you have any complaints, you may contact the complaints committee of ICON.

All contact details can be found in **Appendix A**.

15.0 How do you consent to this study?

You can first think carefully about this study. Then you tell the investigator if you understand the information and if you want to participate or not. Do you want to participate? Then you can fill in the consent form that you can find with this information sheet (**Appendix E**). The signature sheet is kept by ICON. You will get a copy of the signed consent form.

Thank you for your time.

16.0 Appendices to this information

A. Contact details
B. Insurance information
C. Overview of tests
D. Contraception and pregnancy reporting
E. Subject consent form

You will also receive the information booklet ‘Your stay at ICON’ together with this document. Further, you will receive the package leaflet for pitavastatin.

Appendix A: Contact details

ICON
Van Swietenlaan 6
9728 NZ Groningen, The Netherlands
The Netherlands: 0800-0292044
Belgium: 0800-89036
Germany: 0800-0713579

Responsible doctor:
[redacted]
BIG registration numbe PPD [redacted]
Telephone number: PPD [redacted]

Outside office hours a doctor on duty can be reached on:
Telephone number: PPD [redacted]

Independent expert:
PPD [redacted]
BIG registration number: PPD [redacted]
University Medical Center Groningen, Groningen, The Netherlands
Telephone number: PPD [redacted]

Medical Research Ethics Committee
[redacted]

Data protection officer of ICON:
Data_Privacy_Officer@iconplc.com

Dutch Data Protection Authority
PO Box 93374
2509 AJ The Hague, The Netherlands

Sponsor:
Basilea Pharmaceutica International Ltd, Allschwil
Hegenheimermattweg 167b
4123 Allschwil
Switzerland
dataprotection@basilea.com

Complaints:
Complaints Committee ICON
P.O. Box 8144
9702 KC Groningen, The Netherlands
info@geneesmiddelenonderzoek.nl

Appendix B: Insurance information

Insurance has been taken out by the sponsor for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting itself during the study or within 4 years after you participated in the study. You must notify the insurance company about the damage within those 4 years.

In the event of damage please contact the insurance company directly.

The insurance company for the study is:	
Name of insurer:	[redacted]
Address:	[redacted]
Telephone:	[redacted]
E-mail:	[redacted]
Policy number:	[redacted]

The insurance offers a maximum cover of € [redacted] per subject and € [redacted] for the entire study.

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

- Damage as a result of a risk that we informed you about in the written information. But this does not apply if the risk appeared to be bigger than we anticipated. Or if the risk was very unlikely to occur.
- Damage to your health that would also have occurred if you had not participated in the study.
- Damage that occurs because you did not or not well follow the directions or instructions.
- Damage to the health of your children or grandchildren.

These provisions are in the Compulsory Insurance Decree in Medical Research Involving Human Subjects 2015 (https://www.overheid.nl/english). This decision can be found in the government's Law Database (https://wetten.overheid.nl).

Appendix C: Overview of tests

Recording of side effects	During the entire study we will document all side effects.
Recording of medication use	During the entire study we will document all medication that you use.
Blood sampling, indwelling cannula (tube in an arm vein)	An indwelling cannula will be inserted twice to draw blood on Days -1, 1 and 2, and on Days 5, 6 and 7. This indwelling cannula will stay in your vein for approximately 48 hours. Other blood samples between screening and the follow-up visit will be drawn by direct puncture of a blood vessel. Blood will be drawn: ○ for routine laboratory tests. ○ to check for side effects. ○ to measure to what extent ceftobiprole and pitavastatin are absorbed in your blood. ○ to measure to what extent coproporphyrin I has changed in your blood. Note: in most studies, reserve subjects do not have an indwelling cannula for blood sampling inserted. However, for this study, reserve subjects will have an indwelling cannula inserted on Day -1 for multiple blood sampling for the determination of coproporphyrin I levels on Day -1.
Administration by intravenous infusion (in an arm vein)	For the intravenous administration of the study compound on Days 4 to 7, an extra indwelling cannula will be inserted on Day 4 in addition to the indwelling cannula used for blood sampling. This extra indwelling cannula remains in place for as long as possible and is replaced when necessary. Thus, you will have a cannula inserted in both arms at certain times.
Collection of urine	Urine will be collected for routine laboratory tests.
Vital signs	Blood pressure, heart rate, number of breaths per minute, and body temperature will be measured regularly when you have been lying down on your back for at least 5 minutes.
Heart tracing (ECG)	ECGs will be made regularly. In this test, electrodes (small, plastic patches) will be placed on your arms, chest and legs. These electrodes are connected to a machine that shows your heartbeat based on the electrical activity of your heart. The ECG will be made after you have been lying down on your back for at least 5 minutes.
Physical examination	A few times, a physical examination will be done, including at screening and the follow-up visit.
Body weight and height including Body Mass Index (BMI) calculation	Body weight and height will be measured and used to calculate your BMI. The BMI represents the ratio between the body weight in kilograms and the body height in meters. You can calculate your BMI by dividing your weight in kilograms by the square of your height in meters. For example, if you weigh 80 kilograms and you are 1.75 meters in height, your BMI is: $80 / (1.75)^2 = 26.1$ kg/m^2.

Appendix D: Contraception and pregnancy reporting

For men

For male subjects, there is no need to use contraception during the study. There is also no restriction regarding sperm donation during the study.

For women

If you are sexually active and you have a male partner, you will have to ensure that you cannot get pregnant from at least 4 weeks prior to first administration of pitavastatin on Day 1 until after you leave the research center on Day 8 of the study. Donation of egg cells is also not permitted during this period.

To prevent a pregnancy, you and your partner have to use a combination of 2 of the following methods of contraception, including at least one so-called 'barrier' method:

- Hormonal contraceptives (oral, transdermal patches, vaginal or injectable),
- Intrauterine device with or without hormones,
- Condom ('barrier' method),
- Diaphragm or cervical cap ('barrier' method).

The above does not apply to women who are post-menopausal (not having menstruated for at least 1 year) or have undergone surgical sterilization. The above also does not apply to male partners who have undergone surgical sterilization (ie, vasectomy with a post-vasectomy semen analysis negative for sperm) at least 6 months before screening.

If you still become pregnant during the study before you leave the research center on Day 8, you should immediately tell the responsible doctor. The pregnancy can then be monitored more closely and reported to the sponsor of this study. We will separately ask you and your partner permission for the additional checks (and for collecting of information from other healthcare providers on the clinical course and the outcome of pregnancy).

Appendix E: Subject consent form

A study in healthy subjects investigating the interaction between ceftobiprole and pitavastatin. Ceftobiprole is the compound studied and is an approved drug (not approved in The Netherlands) that is being used in the treatment of bacterial infections.

- I have read and understood this subject information form. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all. Or to withdraw from the study. I do not need to give a reason for this.
- I give the investigators permission for my general practitioner to be informed about my participation in this study.
- I give the investigators permission for information to be requested from my general practitioner and other healthcare providers about my health.
- I give the investigators permission to give my general practitioner and other healthcare providers information about unexpected discoveries made during the study that are important for my health.
- I consent to be informed of unexpected findings which may be discovered by chance and may be important for my health.
- I give the investigators permission to my data being collected, used and stored in the way and for the purposes stated in Section 10.
- I give the investigators permission to my bodily material being collected, used and stored in the way and for the purposes stated in Section 10.
- I know that some people and authorities can get access to my data to review the study. These people and authorities are listed in this subject information sheet. I give consent to let these people see my data for this review.
- I agree to my coded data and bodily material for this study being forwarded to countries outside the EU, where European rules for personal data protection do not apply. I am informed that my privacy is protected under separate agreements in these countries.
- I know that I must not become pregnant from at least 4 weeks prior to first administration of pitavastatin on Day 1 until after I leave the research center on Day 8 (for women).
- The investigator has discussed with me how I can prevent becoming pregnant (for women) / my partner becoming pregnant (for men).

- I want to participate in this study.

Signature subject:

_____	_____	_____	_____
Name	Date	Time	Signature

V- ☐ ☐ ☐ ☐

- I hereby declare that I have fully informed this subject about this study.
- I hereby declare that the subject speaks and understands English sufficiently.

Signature responsible doctor (or his/her representative):

_____	_____	_____	_____
Name	Date	Time	Signature

The subject will receive the full subject information document, together with a copy of the signed consent form.