

HITHARD trial: A large medical trial in which very ill patients are divided into groups to test if a short course of antibiotics with a higher dose works just as well as the usual longer treatment with standard dosing.

Official title of the trial: A phase III cluster randomised controlled, cross-over, non-inferiority Trial of a short course, High dose Antimicrobials vs conventional dose and Duration in critically ill patients (HIT-HARD)

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THE TRIAL AT A GLANCE

1. Why did I receive this document to read?

We are inviting you to take part in a trial because you are admitted on the intensive care unit with a pneumonia, infection of the abdomen or bloodstream infection (Also called sepsis in medical terms) and for which a bèta-lactam antibiotic named ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem was prescribed. These are all antibiotics which are already available on the Belgian and Dutch market. It is important to know that further in this study document 'investigational medical product' will be mentioned when talking about the routinely prescribed antibiotic.

The main goal of the study is to determine if a short course (3-5 days) with higher dosing of one of the abovementioned antibiotics works just as good as the standard course (6-9 days) for critically ill patients admitted to the intensive care unit.

There will be 1282 patients in Belgium and The Netherlands taking part in the trial.

2. What is the purpose of this document?

To conduct a trial correctly, the patients or legal representative must be informed in a correct way about the details of this trial, therefore this document is provided. This way the patient/lawful representative can decide about participation. This is called giving 'informed consent'.

This chapter will give the patient/lawful representative an idea about the trial entails. Nevertheless, we want to ask to read all the pages, even if it will take a lot of time. It is important that the patient/lawful representative reads and understands everything. Ask all your questions to the trial staff.

3. How will the investigational medical product be administered?

The investigational medical product will be administered via a small tube in the bloodstream that is already placed during the standard treatment of patients admitted with a pneumonia, infection of the abdomen or bloodstream infection on the intensive care unit.

The investigational medical product itself was already prescribed routinely and not determined by the trial, the way it is administered namely via continuous infusion in higher dose and shorter course or standard course and standard dosing is determined by the trial.

Continuous infusion means at constant rate without interruptions.

4. What are the main procedures that will be conducted?

In the hospitals mentioned below 1 blood sample will be taken 36-96h after start of the treatment to determine the antibiotic exposure, in the hospitals which are not mentioned, no blood sample will be taken, all the other procedures are the same for all hospitals:

- University hospital Ghent
- CHU Liège
- AZ Sint Lucas Gent
- AZ Delta Roeselare
- Hôpital Erasme Brussel
- Clinique Saint-Pierre Ottignies

The blood sample will be taken from a tube already inserted in the bloodstream. This will cause no pain and won't require additional punctures.

Routinely acquired information will be gathered by the trial staff.

An example of this information are lab results, which other medication you are receiving, length, weight.

For a detailed list of all the study procedures that will take place, see chapter 4.

5. What is the duration of the trial?

You will take part for about 90 days in this trial. After you discharge out of the hospital, you will be contacted by telephone call on day 28 and day 90 by someone of the trial staff to gather information about your health and general wellbeing, this happens using a short questionnaire. The telephone call will ask about 10 minutes of your time.

6. Will the investigational medical product have any side effects?

At the administration of every medicine, side effects can arise, this can be the same for the administration of antibiotics. Some of the known side effects are diarrhea, hypersensitivity reactions, nausea, vomiting, skin rash. A detailed list can be found in chapter I § 6 page 13.

7. Is there an insurance cover in case something goes wrong within the trial?

For this trial, the sponsor took out an insurance with Allianz (further details are described on page 2 and chapter I § 7 page 18). The insurance covers damage by the trial. Therefore, the patient must understand well that these side effects or every new health problem must be reported to the treating physician or someone of the trial staff.

8. May the participant get pregnant during the trial?

Women who are pregnant or are breastfeeding, cannot partake in this trial.

9. Who pays the trial specific costs and what does the participant have to or not have to pay?

The investigations specific to the trial will not be charged to the participant. All other investigations or treatment that the patient would otherwise receive if they would not participate, must be paid by the health insurance or yourself.

10. Are the data treated confidentially?

The data of the participant will be treated confidentially and stored in a secure database.

11. Is the participant free to partake in the trial?

It is the free choice to participate in the trial, the participant can decide at every moment to (not) continue in participating. Participation is voluntary.

12. Who has reviewed and approved the trial documents?

These trial documents are reviewed and approved by the government and independent Commission for Medical Ethics.

13. Will the participant receive the investigational medical product after their participation in the trial?

The investigational medical product that will be prescribed in this trial was prescribed as per standard to treat your infection. If you withdraw from the trial, the trial ends, and this does not affect which medicine you receive. The trial only investigates the way in which the investigational medical product is administered. Via short, high dosing or standard dosing and course.

14. Which commitments are expected from the participant?

From every participant it is expected:

- to agree that the investigator informs the treating physicians of participation in the trial
- not simultaneously participate in another clinical trial (unless the sponsor agrees)
- to share relevant information about their health status, other medication taken or symptoms experienced.

15. Who can give more information to the participant?

The content of the trial will be explained by the treating physician, principal investigators and/or trial staff.

If a participant agrees to participate, you sign the form of informed consent. This document will also be signed by the person/physician who provided you with the necessary information about the trial. You will receive a signed and dated copy of the form.

CHAPTER I – DESCRIPTION OF THE TRIAL AND YOUR RIGHTS WHEN PARTICIPATING

1. Why is this study being conducted?

This clinical trial (further on referred to as “trial”) will evaluate the investigational medicinal product (IMP), Ceftriaxone, Cefotaxime, Cefuroxime, Piperacillin-Tazobactam or Meropenem for the treatment of pneumonia, abdominal infections or bloodstream infections.

The purpose of this trial is to learn about:

Sepsis is a potentially life-threatening reaction to an infection. Sepsis is caused by toxic substances (toxins) of bacteria and other organisms that enter the bloodstream from the site of infection. In some people, the infection can progress to sepsis and septic shock, in which the function of the organs in the body are affected.

In both Belgium and the Netherlands, the most common infections on the intensive care unit are pneumonia acquired outside the hospital, pneumonia acquired in the hospital, pneumonia due to mechanical ventilation and infections in the abdomen or the bloodstream.

Most of these bacterial infections are treated with bèta-lactam antibiotics, as the standard choice on the intensive care unit.

The growing problem of antibiotic resistance makes these challenges even greater, especially in patients with severe infections, because the intensive care units are often hotspots for antibiotic resistance within hospitals. This is mainly due to the use of invasive medical devices, exposure to antibiotics, the vulnerability of patients and the intensive care which increase the risk of spreading resistant microorganisms.

The HIT-HARD trial focuses on two major challenges: improving the use of antibiotics in critically ill patients admitted to the intensive care unit for one of the abovementioned infections and the reduction of antibiotic resistance. The aim of this investigation is to optimize the treatment and limit the development of antibiotic resistance. Previous research has suggested that this may be achieved by administering higher doses of antibiotics, and also by shorter treatment durations.

We focus mainly on mortality within 90 days after the treatment. Additionally, we investigate the levels of antibiotics in the body, the development of antibiotic resistance, recovery of the patient, safety and the costs.

All used antibiotics in this trial (Ceftriaxone, Cefotaxime, Cefuroxime, Piperacillin-Tazobactam or Meropenem) are all registered medicines that are currently being used in the treatment of sepsis.

2. Why am I being asked to take part?

You have been diagnosed with pneumonia, abdominal infection or bloodstream infection (in medical terms also called sepsis).

You are being asked to take part in this trial because you are admitted to the intensive care unit with a pneumonia, infection of the abdomen or bloodstream infection (in medical terms also called sepsis) for which you are prescribed a beta-lactam antibiotic called Ceftriaxone, Cefotaxime, Cefuroxime, Piperacillin-Tazobactam or Meropenem. These are all antibiotics which are already available on the Belgian and Dutch markets.

The main aim of the trial is to determine if a short course (3-5 days) with a higher dosing of one of the abovementioned antibiotics works as good as a standard course (6-9 days) in critically ill patients admitted to the intensive care unit.

Before you can participate to the trial, we want to confirm that you are eligible to partake. This is way some aspects are being reviewed by the researcher. The most important aspects are listed below:

- Information about your infection and which medications you are using
- Determining the severity of the infection using a scoring system
- Confirmation that you are 18 years of age or older and that it is expected that you stay at least 2 days on the intensive care unit.
- Confirm that you do not have a severe allergy for the prescribed antibiotic, that there are no limitations in the treatment, that you have not previously participated in the HIT-HARD trial, and that you are not on kidney dialysis.

The investigator or trial staff will discuss with you the requirements to be allowed to enter the trial.

3. Do I have to take part in a trial?

Your participation in a trial is voluntary and must remain free of any coercion. This means that you have the right not to take part in the trial or to withdraw at any time without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or your treating physician, nor will it affect the quality of your future medical care.

If other treatments are available for your pneumonia, infection of the abdomen or bloodstream infection, the investigator or his/her delegate will discuss these treatments with you.

4. What will happen during the trial?

This trial will include 1282 participants in Belgium and the Netherlands, of which about 641 in Belgium and 641 in the Netherlands.

This trial is a phase III cluster randomised controlled, cross-over, non-inferiority trial of a short course, high dose antimicrobials versus conventional dose and duration in critically ill patients.

Below, some trial terms are explained to better understand the trial.

A phase III trial is a large investigation in which a new treatment is compared to the current standard treatment to evaluate if the new treatment is better or as effective. This is the last step before a treatment can be approved for general use. In this phase a lot of patients are included to ensure that the treatment is safe and effective for a larger group of people.

Cluster-randomized means that not the individual patients, but entire groups (in this case hospitals) are randomly assigned to a treatment. This helps investigators to determine which treatment works better in a real practice situation, without confusion arising within one hospital about which treatment a patient receives.

For this trial the intensive care units will be randomized, and not the patients.

Cross over means that the intensive care units in the trial will administer both treatments to the patients, but at different moments. The units that start with the HIT-HARD strategy will afterwards be assigned to 15 months of the Control strategy.

Those that start with the Control strategy will end with the HIT-HARD strategy.

A non-inferiority trial investigates whether a new treatment strategy (shorter and higher dosing) work as well as the existing standard treatment, but is not necessarily better. The aim is to demonstrate that the new treatment is not less effective, but may provide advantages such as less side effects or a shorter course. In other words, the new treatment is 'not worse' than the standard treatment.

4.1. Study duration

Your participation to the trial will take 90 days in total.

4.2. Study visits

Screening

The investigator reviews certain information to determine if you are eligible for the trial. This process is called the 'screening'.

The investigator:

- Gathers information about your health, medical history and/or potential medication that you use or have used.
- Confirms you have an infection for which you are prescribed a beta-lactam antibiotics.

Baseline/inclusion

- To determine the severity of your illness, they will use a scoring system
- Your length, weight, age and sex will be gathered
- Information about your infection and which medication you use is gathered

All these data will be gathered during standard care of the patient who is admitted to the intensive care unit.

Study specific

Your health status before hospital admission will be assessed using a questionnaire. This questionnaire is called an EQ-5D-5L.

Treatment phase until end of therapy

Choice of antibiotics, hereby described as the investigational medical product, is part of the standard therapy and is therefore not determined by the trial.

Further, data will be collected about organ support, e.g. need for oxygen, mechanical ventilation, blood-pressure-supporting medication and whether or not kidney dialysis is required.

Depending on which group (HIT-HARD strategy or Control strategy) the intensive care unit is assigned, you will receive the routinely prescribed investigational medical product as follows:

HIT-HARD strategy:

- Ceftriaxone: Loading dose 2000mg + 4000mg daily
- Cefotaxime: Loading dose 4000mg + 12000mg daily
- Cefuroxime: Loading dose 3000mg + 6000mg daily
- Piperacillin-Tazobactam: Loading dose 8000/1000 + 20000/2500mg dialyse
- Meropenem: Loading dose 2000mg + 6000mg daily

During 3-5 days

Control strategy

- Ceftriaxone: Loading dose 2000mg + 2000mg daily
- Cefotaxime: Loading dose 2000mg + 4000mg daily
- Cefuroxime: Loading dose 1500mg + 4500mg daily
- Piperacillin-Tazobactam: Loading dose 4000/500 + 16000/2000mg dialyse
- Meropenem: Loading dose 1000mg + 3000mg daily

During 6-9 days

A loading dose is the starting dose which is administered over 30 to 60 minutes or according to the usual standard treatment of the hospital where you are admitted. . After the loading dose the antibiotic will be administered by continuous infusion. Continuous infusion means at constant rate without interruptions.

If (severe) side effects should arise, these will be reported in detail.

In the following centers at timepoint 36 to 96 hours after start of the antibiotic treatment a blood sample will be taken to evaluate and measure the level of antibiotics in the blood. This helps us to evaluate if the amount of antibiotics says something about how good the treatment works.

- University hospital Ghent
- CHU Liège
- AZ Sint Lucas Ghent
- AZ Delta Roeselare
- Hôpital Erasme Brussel
- Clinique Saint-Pierre Ottignies

There is a strict follow up by the trial staff if everything goes according to the study protocol.

Follow-up period

Overall, your participation in the trial will last 90 days and involve 2 telephone calls visits. The trial is expected to last a total of 30 months.

During your stay in the hospital, the investigator will regularly see you until your discharge or day 14 (depending on which is first).

On day 28 and day 90 you will be contacted by telephone call by some of the trial staff to ask about your health condition using a questionnaire. This telephone call will not take longer than

10 minutes of your time. If on day 28 or 90 you are (still) unconscious or for any other reason unable to respond yourself, the EQ-5D-5L questionnaire may be completed by a close relative.

If you meet all the conditions required to be enrolled in the trial and agree to take part in the trial, you will undergo the above-mentioned tests and examinations.

5. Will I benefit from the trial?

The information obtained during a trial may contribute to a better understanding of the use of the investigational medicinal product (referred to as “IMP”) or to the development of a new medicinal product for the treatment of yourself or future patients.

The IMP may or may not be beneficial in treating your pneumonia, abdominal infection or bloodstream infection or relieving your symptoms. Even if it is beneficial to you, a potential return or worsening of symptoms, illness or disease is still possible.

6. What are the possible risks and discomforts of taking part?

6.1. What are the possible side effects of Ceftriaxone, Cefotaxime, Cefuroxime, Piperacillin-Tazobactam and Meropenem?

Participation in a trial involves some risk.

In this study NO new medication is being used, but a higher dosing and shorter course may be applied (HIT-HARD strategy). Higher doses are already being applied in current practice. We therefore don't expect any other side effects than those mentioned in the tables below. However, in the trial arm with higher dosing, the chance of side effects is potentially higher than in the trial arm with conventional dosing.

Because this IMP is still under investigation, other currently unknown risks and discomforts could occur. **Therefore, it is very important that you report any new or worsened health problems immediately to the investigator, regardless of whether or not you think it has to do with the trial (or to ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam and meropenem), and even when it is already described in this document. If you need to use other medication, discuss this with the investigator beforehand. If, for any reason, you consult another treating physician during the trial you must inform him/her that you are taking part in a trial and present your emergency card. This could be important in determining a diagnosis and giving you the correct treatment if needed.**

If you need to use other medication, please discuss this with the investigator before you take them. In case you consult another physician during the trial, for whatever reason, you must inform them that you are partaking in a clinical trial. This could be important to make a correct diagnosis and give correct treatment if necessary.

Even though previous trials have shown that Ceftriaxone, Cefotaxime, Cefuroxime, Piperacillin-Tazobactam and Meropenem are well tolerated, you can still experience side effects.

The following is used in classifying the occurrence:

Very common ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Less common ($\geq 1/1.000$, $< 1/100$)

Rare ($\geq 1/10.000$, $< 1/1.000$)

Unknown (could not be determined with available data)

- **Ceftriaxone**

Very common	/
Common	Diarrhea, reduced white blood cell or platelet count, increased liver enzymes, skin rash
Less common	Genital fungal infections, anemia, impaired coagulation, headache, dizziness, nausea, vomiting, inflammation at the catheter site
Rare	Narrowing of the airways, urticaria, blood in the urine, sugar in the urine, fluid retention, cold shivers
Unknown *	Development of a new infection, anemia, allergic reaction, epileptic seizure, dizziness, inflammation of the pancreas, inflammation of the tongue and/or oral mucosa, accumulation of substances in the gallbladder, inflammation of the liver, severe skin reaction with painful skin rash, reduced urine production

* Side effects identified after marketing.

- **Cefotaxime**

Very common	/
Common	/
Less common	Reduced white blood cell or platelet count, symptoms of fever, cold shivers, headache, muscle pain, diarrhea, increased liver enzymes, skin rash, decreased kidney function, inflammatory reaction at the insertion site
Rare	/

Unknown *	Development of a new infection, anemia, reduced white and red blood cell count, hypersensitivity reaction, headache, dizziness, arrhythmia after rapid bolus, nausea, vomiting, abdominal pain, inflammation of the large intestine, inflammation of the liver, severe skin reaction with painful skin rash, blistering with skin peeling, pus-filled bumps (pustules), acute kidney failure
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* Side effects identified after marketing.

• Cefuroxime

Very common	/
Common	Reduced white blood cell or platelet count, temporary increase of liver enzymes, inflammatory reaction at the insertion site
Less common	Stomach-and intestine complaints, skin rash, urticaria, itching
Rare	/
Unknown *	Reduced platelet count, anemia, drug fever, inflammation of the kidneys, hypersensitivity reaction, inflammation of the blood vessels, allergic reaction, inflammation of the large intestine, severe skin reaction with painful skin rash, acute kidney failure

* Side effects identified after marketing..

• Piperacilline- tazobactam

Very common	Diarrhea
Common	Fungal infection, reduced platelet count, anemia, insomnia, headache, abdominal pain, vomiting, constipation, nausea, stomach discomfort, skin rash, inflammatory reaction at the injection site, increased liver values
Less common	Reduced white blood cell count, reduced potassium, epileptic seizure, low blood pressure, inflammatory reaction at the insertion site, hot flushes, skin rash, muscle pain, chills, reduced amount of sugar in the blood (blood glucose), increased bilirubin (a substance that can indicate whether the liver and bile ducts are functioning properly)

Rare	Inflammation of the intestine, inflammation of the oral mucosa, low white blood cell count, nosebleed, severe skin reaction
Unknown *	Reduced white blood cell or platelet count, heart attack related to allergy, allergic reaction, hypersensitivity, acute confusion, pneumonia, jaundice, severe skin reaction with painful skin rash, blistering of the skin, muscle breakdown (rhabdomyolysis), prolonged bleeding time

* Side effects identified after marketing..

- **Meropenem**

Very common	/
Common	Reduced platelet count, diarrhea, abdominal pain, vomiting, nausea, skin rash
Less common	Fungal infection, anemia, anaphylaxis (acute reaction of the body's immune system, usually occurring due to an allergy), angioedema (swelling of the skin or mucous membranes), delirium (acute confusion), colitis, increased blood LDH, urticaria, pain at the injection site, low potassium levels, drug-induced liver injury.
Rare	Headache, paresthesia, convulsions
Unknown *	Increased blood creatinine (a substance that can indicate whether the kidneys are functioning properly), increased blood urea (a substance that can indicate whether the kidneys are functioning properly), inflammation, pain, inflammation of the veins

*Side effects identified after marketing.

6.2. What are the possible risks or discomforts of the examinations during the trial?

There are no known risks of the examinations during the trial.

In the trial centres listed in section 4.2 a blood sample will be taken (1 tube of blood of circa 3mL). This is necessary to determine the level of antibiotics in the blood. It will be taken from a tube (catheter) that is placed in a large blood vessel. Therefore, the blood draw will not cause pain.

The drawing of the blood is study specific.

The placement of the catheter in the large blood vessel is routine practice.

6.3. Can I take other medicines during the trial?

For your safety you must inform the investigator of which treatments you are using or could use during the trial (e.g. prescription medicines, vitamins, non-prescription medicines, herbal supplements, etc.) Some of these medications may need to be avoided, interrupted or the dose need to be lowered.

Do not hesitate to ask your investigator for more explanation about the use of other medicines and food supplements (including aromatherapy, phytotherapy, homeopathy..).

6.4. Will my participation to the trial have an impact on my daily activities?

You will be asked to comply with the following important study requirements throughout the entire study:

- You must be able and willing to take the necessary time to attend scheduled follow-up appointments after you have been discharged from the hospital, specifically the telephone follow-up calls on Day 28 and Day 90.
- You must report any new problems, illnesses, injuries, hospital visits, medical procedures, or changes in medication that occur during the study (especially after you have left the hospital). It is very important that you report these events to the study staff as soon as possible.

6.5. Can I get pregnant, conceive a child, or can I breastfeed during the trial?

Pregnancy or breastfeeding is a reason not to partake in the trial.

We are not worried about a participant becoming pregnant after the trial, because beta-lactam antibiotics are not stored in the body, but excreted via the urine.

Female participant: It is a precaution measure that pregnant women and women who are breastfeeding cannot partake in the study. There are no adverse effects in pregnancy known for meropenem, piperacillin-tazobactam, ceftriaxone, cefotaxime and cefuroxime. They are classified under 'most safe cephalosporines' during pregnancy. Cephalosporines is a group name for this type of antibiotics.

You don't need to take any precaution measures regarding contraception to avoid becoming pregnant during your participation in the trial. Your total participation is until 90 days after you are included in the study.

Male participant: You don't need to take any precaution measures regarding contraception to avoid your partner becoming pregnant during your participation in the trial.

7. What if something goes wrong within the trial?

Even if there is no fault, the sponsor is liable for harm caused to you whether directly or indirectly related to your participation in the trial. The sponsor has taken an appropriate insurance (a so called "NO FAULT INSURANCE" at Allianz Global Corporate & Specility SE, Branch Office Belgium, Uitbreidingstraat 86, BE-2600, Berchem, number BEL001889) for this liability in accordance with the current European and Belgian legislation on clinical investigations. A copy of the insurance certificate can be obtained from the investigator or trial staff.

If you (or in the event of death, your rightful claimants) seek compensation for a harm to your health as a direct or indirect result of participating in the trial, you must inform your investigator or trial staff promptly.

If the investigator believes that a link between the new or worsened health problem(s) and the trial is possible, he/she will inform the trial sponsor. The sponsor will then immediately initiate the declaration procedure to its insurance company. If the company considers it necessary, it will appoint an expert to assess whether there is a link between your reported health problem(s) and the trial. The insurance does not cover the natural progression of your disease/condition or the known side effects of the treatment you would have received without taking part to the trial (*that is* your standard treatment).

Whenever you feel it is appropriate or if you or your rightful claimants disagree either with the investigator or with the expert appointed by the insurance company, you may contact the insurance company or proceedings may be brought against the insurance company. You will find the contact details on the front page of this form.

8. What if other treatment options or new information on the IMP or the study become available during the course of the trial?

During the course of the trial, important new information might become available, possibly affecting your decision to (further) participate. For example, other treatments for your disease or important new information on the IMP may become available. It is the duty of the investigator to discuss this new information with you and to give you the opportunity to reconsider your participation in the trial.

If you decide to stop taking part in the trial or if you are no longer able to participate, your investigator will see to it that you continue to receive the best possible medical care.

9. Can my participation in the trial end prematurely?

As explained in detail below, your trial participation may end prematurely when

- you decide to withdraw your consent or to discontinue treatment with the study drug,
- the investigator decides to end your trial participation, or to discontinue your treatment with the IMP, or
- other entities interrupt or end the trial.

In any case, if your trial participation ends prematurely, the investigator will discuss your future medical care with you. Data collected before you terminate your participation will continue to be used as described in this form. This is to avoid skewing / biasing results of the trial (as described in chapter I. § 12.3.).

Depending on your situation, the investigator will discuss with you whether follow-up visits or procedures are needed.

If you experience a side effect at the time you stop taking the IMP, the investigator may contact you afterward to determine whether or not the side effect disappeared after your participation in the study ends.

If you experience a new side effect after stopping your participation in the trial, you may contact the investigator and ask for follow up.

9.1. You decide to withdraw your consent

You are entitled to withdraw your consent for any reason, at any time, without having to justify your decision. However, for your safety, you should inform the investigator of your decision. Although it is not mandatory, it may be useful for the investigator and for the sponsor to know the reason of this decision (for example side effects, frequency of clinical visits,...).

If you withdraw your consent, this means you decide to stop

- the treatment with the IMP, and
- all trial-related visits and examinations.

No new data will be collected and sent to the sponsor.

If your biological samples (e.g. blood samples, urine samples) have already been used or analysed before the withdrawal of your consent, the sponsor still has the right to use the results from those tests.

The biological samples that have been collected (but not tested) before the withdrawal of your consent and the data obtained from it, can also still be used by the sponsor. You may ask for a destruction of those samples. If this impacts the validity of the trial, the destruction may be postponed till the end of the trial.

9.2. The investigator decides to end your trial participation or to discontinue your treatment with the IMP

The investigator may end your trial participation because

- he/she thinks it is better for you (e.g. based on your test results, when you develop certain health problems, when the protocol defines that you should not get pregnant and you get pregnant anyway, ...),
- he/she determines that you are not following the instructions given to participants, or
- any other reason that will be explained,
- the entire study should be discontinued for all participants (see next paragraph).

If that happens, the trial staff will explain why and ensure appropriate follow-up.

9.3. Other entities may interrupt or end the trial

The sponsor and the competent Belgian health authorities may interrupt or end the trial because

- the information gathered shows that the IMP is not effective (does not deliver a sufficient level of improvement in the health of the trial participants),
- the IMP causes more (serious) side effects than anticipated, or
- any other reason that will be duly motivated by such party.

10. Which treatment will I get after my participation in the trial?

If you stop the study, the investigator will assess your health. If necessary, he/she will prescribe you the best standard treatment available or refer you to another treating physician of your choice.

11. Will my participation in the trial involve extra costs for me?

11.1. Examinations and treatments paid by the sponsor

As described in section 4, the treatments and examinations that are trial specific will not be charged to you. The standard procedures or examinations for your condition (i.e. standard of care) will be charged to you or reimbursed by your mutual insurance fund (Belgian social security).

The sponsor has arranged to compensate the hospital for

- the time devoted to the trial by the investigator and the trial staff,
- the visits/consultations and all scheduled examinations specific to the trial,
- the investigational treatment (IMP and any other medication and material specifically used for the trial).

12. Which data are collected about me during the trial and what will happen with them?

12.1. Which data are collected and processed during the trial?

The collected and processed personal data concern information about your health and medical condition. This includes your medical history, some of your background information (for example your age and sex) and the results of examinations required by the trial.

12.2. How will the investigator treat my personal data?

The investigator (and the trial staff) is bound by professional secrecy or by a confidentiality agreement about the data collected.

This means that he/she will never reveal your identity, including in a scientific publication or a lecture and that he/she will encode your data (Ref. ¹) (*that is* by replacing your identity by an identification code in the trial) before sending them to the sponsor. In other words, this code will not contain any personal identifier or combination of identifiers such as name, first name, initials, full or partial date of birth, file number, etc.

Therefore, the investigator and the trial staff under the responsibility of the investigator, will be the only ones able to establish a link between your identity and the data transmitted during the trial, with the exceptions listed under section 12.5.

The data transmitted to the sponsor will not allow the sponsor to identify you.

12.3. How will my data be handled?

Your participation in the study means that your personal data will:

- be collected by the researcher; and
- be used in coded form by the sponsor of the study.

The procedure used to code your personal data is the same as the procedure used for your biological samples.

The researcher and the sponsor may use the coded personal data only for research purposes related to scientific publications within the framework of the study in which you are participating.

If broader use of the coded data is planned, this will be stated below.

In addition, the sponsor may grant external researchers (who are not involved in this study) access to the coded data. If an external researcher wishes to use the data for research that is not described in this document, that research must be approved by an Ethics Committee. If your coded data are sold, you will not receive any compensation for this.

12.4. Do I have access to my data collected and processed during the trial and can I rectify them?

You are entitled to ask the investigator what data are being collected about you and how those data will be used in connection with the trial.

Your study data will be processed in accordance with the General Data Protection Regulation (GDPR) (Ref. 2) and the Belgian Data Protection Act of 30 July 2018 (Ref. 3). The sponsor is responsible for this processing.

The national register number of Belgian patients will be collected in order to perform a cost-effectiveness analysis after completion of the study. This analysis will be carried out by the KCE (Belgian Health Care Knowledge Centre) in collaboration with the researchers. A cost-effectiveness analysis examines whether the costs of a treatment are proportionate to the health benefits it provides, in order to determine whether the treatment is worth its cost.

The reason we are allowed to process your personal data is that we are conducting scientific research and are performing a task carried out in the public interest.

12.5. Who, other than the Investigator and his trial staff, has access to my personal data?

To verify the quality of the trial, it is possible that your personal **uncoded** data or information in your medical records relevant for the trial, will be examined by people outside the trial staff but under the responsibility of the investigator. These persons must be subject to professional secrecy or a confidentiality agreement. The following might be considered:

- the personnel designated by the sponsor of the trial (MONITORS and AUDITORS), and people or organisations providing services for or collaborating with the sponsor. They will however never transfer your name and contact details to the sponsor.
- inspectors of competent health authorities worldwide

- an independent audit group
- people designated by the Ethics Committee

For the needs of the trial, the encoded trial data may be sent to other EU and non-EU countries and may be reviewed by

- personnel (other than the inspectors) of competent health authorities of Belgium (Federal agency for medicines and health products, FAMHP) and other EU and non-EU countries,
- the evaluating Belgian Ethics Committee(s),
- external researchers,
- the sponsor of the trial, personnel designated by the sponsor, and people or organisations providing services for or collaborating with the sponsor, and/or
- group companies of the sponsor in Belgium, and in other EU and non-EU countries.

The European regulation and the Belgian legislation on data protection have requirements for transferring data to non-EU countries. The sponsor must ensure equivalent guarantees regarding personal data protection standards before transferring the encoded data to non-EU countries. If for this purpose, there is a data protection agreement, a copy of this agreement may be obtained via the investigator. You can always contact your investigator to obtain more information about any such transfers.

12.6. Except the investigator and his trial staff, who else has access to my data in this autologous ATMP trial?

To ensure the quality of the study, it may be necessary for your non-coded personal data or other study-relevant information from your medical record to be inspected by individuals other than the study staff. This access will take place under the supervision of the researcher, and these individuals are bound by professional secrecy or a confidentiality agreement. This may include:

- personnel designated by the sponsor (MONITORS and AUDITORS) and persons or organizations providing services to or collaborating with the sponsor. However, they will never share your name or contact details with the sponsor;
- inspectors from competent health authorities worldwide;
- an independent audit group;
- persons designated by the Ethics Committee.

If necessary for the study, **coded study data** may be transferred to and reviewed in other countries within and outside the European Union (EU) by:

- personnel (other than inspectors) of the competent health authorities of Belgium (Federal Agency for Medicines and Health Products, FAMHP) or of other countries within and outside the EU;
- the Belgian reviewing Ethics Committee(s);
- external researchers;
- the study sponsor, personnel designated by the sponsor, and persons or organizations providing services to or collaborating with the sponsor; and/or
- companies belonging to the sponsor's group in Belgium and in other countries within and outside the EU.

European regulations and Belgian data protection legislation impose restrictions on the transfer of data to countries outside the EU. The sponsor must always ensure that your coded study data are afforded an equivalent level of protection when transferred to a non-EU country. If the sponsor enters into a data protection agreement for this purpose, a copy of this agreement may be obtained via the researcher.

You may always contact your researcher for more information about such data transfers.

12.7. What will happen to the results of the trial?

After trial closure, a description and the results of this clinical trial will be published in specialised medical journals. A copy of the scientific publication or a summary for laypersons can be obtained from the investigator or the trial staff or via <https://kce.fgov.be/nl>

A description of the trial will also be available on <https://clinicaltrialregister.eu/>. You can search these websites at any time using the information on the front page of the informed consent form. Within 1 year after the study's completion, the website will contain a summary of the results in accordance with the European Commission's guidelines.

These websites or publications will not include information that can identify you.

12.8. Will my data be used for other purposes than for the trial in which I take part?

The results of the trial will be used to answer the scientific questions of the trial. In addition, the sponsor would like to use your data obtained from this trial, in connection with other research and development activities (and the associated scientific publications). These activities may only concern

- the way β -lactam antibiotics called ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem work
- the disease/condition for which ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem is evaluated in this trial or
- other diseases and health problems which could benefit from ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem, or from related diagnostic tests.

Any additional research outside of the trial and therefore not described in the above points, must be approved by a Belgian recognized Ethics Committee.

At the end of this form, you agree or disagree to the use of your trial data for other purposes by ticking the appropriate checkbox in Chapter II, page 30.

12.9. How long will my data be kept?

After the end of the trial your encoded data will be retained for at least 25 years in accordance with the European clinical trial regulation to ensure the validity of the research. This will also be the case if you stopped trial participation prematurely.

13. Which biological samples are collected from me during the trial and what will happen with them?

13.1. Which biological samples are collected from me during the trial?

Biological samples are samples of human body material (e.g. blood).

In selected centres, as outlined in the summary “The study at a glance,” **one blood sample (approximately 3 ml)** will be taken in both treatment strategy groups to measure antibiotic exposure.

In this trial, the following biological sample(s) will be taken: a blood sample at 36 hours to 96 hours after start of the antibiotics.

The procedure to encode your biological samples is the same as that used for your personal data in accordance with Belgian legislation on the use of human body material (see I § 12.2). Samples sent to the sponsor or to organisations working in collaboration with the sponsor, will only be labelled with your trial identification code. The sponsor ensures that the location of your biological samples is always tracked. The use of your biological samples is linked to the processing of the associated coded personal data.

Your biological samples are deemed to be a “donation”. You will not receive any financial benefit associated with the development of new therapies derived from the use of your biological samples, and which may have commercial value.

13.2. What will happen to the collected biological samples?

The collected biological samples will be analysed at the study's central laboratory: Radboudumc Pharmacy, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands.

After analysis of antibiotic exposure, the biological samples will be stored at Radboudumc Pharmacy, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands for a period of 5 years.

After this period, the samples will be destroyed.

These biological samples will be analyzed solely for the purposes of the objectives of the study.

It is possible that the analysis of your biological samples may incidentally (and beyond the objectives of the study) reveal information that could be relevant to your health or that of your blood relatives. Such information is referred to as "incidental findings" and will be handled as described in Chapter I, §15, page 28.

13.3. How will my biological samples be handled?

The procedure for coding your biological samples is the same as the procedure used for your personal data (see Section I §12.3, page 22, Ref.). Samples that are sent to the sponsor, or to organizations collaborating with the sponsor, will therefore be identified only by your study identification code.

As part of the research conducted within the study, the sponsor may transfer (part of) your samples to a collaborating laboratory. That laboratory may use your samples only as described in this document.

Your biological samples are a gift. You will not receive any financial benefit related to the development of new therapies that may result from the use of your biological samples and that could have commercial value.

13.4. What happens to the remaining biological samples once the analyses described in this document have been completed?

These biological samples will be analysed for the objectives of the trial.

You may also request that the remaining biological samples be returned to you, if they could still be usable for your own benefit. For this, please contact the investigator or the study staff.

Since scientific progress in this area is constant, the sponsor would like to, with your consent retain the remainders of your biological samples for 5 years. The sponsor will use them for additional research that remains within the context of the current clinical trial and thus with the same disease or the same treatment/drug as in this study.

13.5. Will biological samples be used for research outside the context of the current trial?

Not applicable.

14. What if the trial reveals meaningful information about your health?

We may discover new information about your health during the course of the trial. If this information may be important to your health, the sponsor will inform the researcher. With your consent, the researcher will inform you and your treating physician about your results and the possible consequences. If necessary, the researcher and/or the treating physician will advise you on what to do next.

You can let the researcher know whether or not you agree to be informed about meaningful information discovered about your health by ticking the relevant checkbox in Chapter II, page 30. The researcher/your treating physician will inform you about this information in any case where not being informed may cause serious harm to your health or that of third parties.

15. Who has reviewed and approved the trial documents?

The documents of the trial have been reviewed by

- The Belgian competent health authorities (FAMHP) or, if applicable, by the competent national health authorities of other EU members states and
- An independent Belgian Ethics Committee

It is the task of the competent health authorities and the Ethics Committees to protect people who take part in a trial. The health authorities will ensure that the trial is conducted in accordance with the applicable legislation.

You should not under any circumstances take their approval as an incentive to take part in the trial.

CHAPTER II - INFORMED CONSENT

PARTICIPANT

PREREQUISITES FOR YOUR PARTICIPATION IN THE TRIAL

- I declare that I have read this form and understood its information.
- I declare that I have been informed of and that I understand the purpose of the clinical trial, its duration and consequences, possible risks and discomforts, and what is

expected of me. My rights have been explained to me and I have understood those rights.

- I have had enough time to think about taking part in this trial and to discuss it with a trusted person (for example friends, relatives, treating physician, ...).
- I have had the opportunity to ask any questions that came to mind and have obtained a satisfactory response to my questions.
- I understand that my participation in this trial is voluntarily and free from any coercion and that I am free to stop at any time my trial participation.
- I understand that data about me will be collected and that they will be treated confidentially as described in Chapter I, §12.2.
- I agree to my personal data being processed as described in Chapter I, § 12.
- I understand that representatives of the sponsor, the ethics committee, and competent health authorities have access to my medical record if authorised to do so (as described in Chapter I, §12.5).
- I understand that the sponsor has taken out an insurance in case I should suffer any damage in connection with my participation in this trial.
- I understand that when participating in this trial, I will not have any costs except those related to the standard of care treatment of my disease.
- I am aware that my treating physician(s) being informed of my participation in this trial.
- If I take part in another interventional trial, I must inform the investigator or trial team about this. I agree not to take part in any other interventional trial (e.g. with a study drug, medical device, experimental surgical technique) at the same time without first informing the investigator or the trial staff, who might not permit me to participate for a good reason.
- I understand that I need to cooperate and follow the investigator's and trial staff's instructions regarding the trial.
- I understand that participation to the trial might end for me without my consent if I need other treatment, do not follow the trial plan, have a trial-related injury, or for any other justified reason.
- I certify that all the information I have given about my medical history is correct, to the best of my knowledge. I understand that it may be harmful to me if I do not inform the investigator of possible reasons why I could not participate in the study.

OPTIONAL CONSENTS WHICH ARE NO PREREQUISITE FOR YOUR PARTICIPATION IN THIS TRIAL.

DATA OBTAINED FROM THIS TRIAL

1. As specified in Chapter I, § 12.8 page 25 the sponsor would like to be able to use your data obtained from this trial for other research and development activities (and the associated scientific publications) on the condition that such research purposes have been approved by a Belgian recognized Ethics Committee.

Do you agree with the use of your data obtained in this trial for other research purposes?

(Tick as appropriate, if this question is left unanswered, we assume that the answer is ‘I do not agree’.)

☐ I agree	☐ I do not agree
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MEANINGFUL INFORMATION

2. As specified in Chapter I, §14 page 27, it may occur that meaningful information is discovered that may be important for your health or that of third parties.

If this were to occur, would you like the researcher/your treating physician to inform you of this result?

(Tick as appropriate, if this question is left unanswered, we assume the answer is “yes, I wish to be informed”.)

☐ No, I do not wish to be informed.	☐ Yes, I wish to be informed.
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I consent to take part in the trial, with the above restrictions and I have received a signed and dated copy of all pages of this document.

Participant’s surname and first name:

Date (DD/MMM/YYYY):

Time:

Participant’s signature:

LEGAL REPRESENTATIVE (REF. 2)

I declare that I have been informed that I am being asked to take a decision on whether or not to take part in the clinical trial for the person I represent, considering his/her best interests and taking into consideration his/her likely wishes. My consent applies to all the items listed in the consent of the participant.

I have also been informed that as soon as the clinical situation allows, the person I represent will be made aware of his/her participation in a clinical trial and from that point will be free to continue with this participation or end it by signing or refusing to sign this consent form.

I have received a signed and dated copy of this document.

Participant's surname and first name:

Legal representative's surname and first name:

Relationship to the participant:

Date (DD/MMM/YYYY):

Time:

Legal representative's signature:

IMPARTIAL WITNESS / INTERPRETER (REF. 3)

I, the undersigned (Tick as appropriate),

☐ Impartial Witness

☐ Interpreter

was present during the entire process of informing the participant and I confirm that the information on the objectives and procedures of the trial was adequately provided, that the participant (or his/her legal representative) apparently understood the trial and that consent to participate in the trial was freely given.

I declare furthermore that acting as an impartial witness/interpreter, I am independent of the sponsor and the investigator.

Participant's surname and first name:

Impartial Witness / Interpreter surname and first name:

Impartial Witness / Interpreter qualification:

Date (DD/MMM/YYYY):

Time:

Impartial Witness / Interpreter signature:

INVESTIGATOR

I, the undersigned investigator, confirm that

- the participant has been verbally provided with the necessary information about the trial, has been explained the content and has been given an original signed document.
- I have verified that the participant has understood the trial.
- I have given the participant sufficient time to agree to take part and to ask any questions.
- no pressure was applied to persuade the participant to agree to take part in the trial.
- I operate in accordance with the ethical principles set out in the latest version of the “Helsinki Declaration”, the “Good Clinical Practices” and the Belgian Law on clinical trials.

Investigator’s delegate, surname and first name:

Investigator’s delegate, qualification:

Date (DD/MMM/YYYY):

Time:

Investigator’s delegate signature:

Investigator’s, Surname and first name:

Date (DD/MMM/YYYY):

Time:

Investigator’s signature:

CHAPTER III

TO BE COMPLETED ONLY IN CASE OF REFUSAL TO PARTICIPATE IN THE STUDY AND THE WISH
TO DISCONTINUE THE STUDY INTERVENTION

PARTICIPANT

I wish to **withdraw** from participation in this trial and I understand that this will have no effect on my further treatment, my relationship with those providing my care, or my relationship with the study center.

I have received a signed and dated copy of this document.

Participant's surname and first name:

Date (DD/MMM/YYYY):

Time:

Participant's signature:

LEGAL REPRESENTATIVE (REF. 4)

As the legal representative of _____ (name of the patient)
I wish to discontinue from participation in this trial and I understand that this will have no effect on the further treatment of the participant, the relationship with those providing care, or the relationship with the study center.

I have received a signed and dated copy of this document.

Participant's surname and first name:

Legal representative's surname and first name:

Relationship to the participant:

Date (DD/MMM/YYYY):

Time:

Legal representative's signature:

IMPARTIAL WITNESS / INTERPRETER (REF. ⁵)

I, the undersigned (Tick as appropriate),

☐ Impartial Witness

☐ Interpreter

was present during the entire process of informing the participant and I confirm that the information on the objectives and procedures of the trial was adequately provided, that the participant (or his/her legal representative) apparently understood the trial and that the withdrawal of consent to participate in the trial was freely given.

I declare furthermore that acting as an impartial witness/interpreter, I am independent of the sponsor and the investigator.

Participant's surname and first name:

Impartial Witness / Interpreter surname and first name:

Impartial Witness / Interpreter qualification:

Date (DD/MMM/YYYY):

Time:

Impartial Witness / Interpreter signature:

GLOSSARY

FAMHP: Federal agency for medicines and health products

DPA: The Data Protection Authority ensures that personal data are handled with care and thoroughly protected, and that your future privacy also remains guaranteed.

NO FAULT INSURANCE:

The sponsor is liable for any injury or any damage that the participant has suffered, and which is directly or indirectly related to the clinical trial. You do not have to prove any mistake in this respect.

MONITOR and AUDITOR

Both the monitor and auditor work for the sponsor. The monitor takes care of a continuous quality check during the entire process of the trial. The auditor performs an independent, one-time quality check at some time during the trial. They verify if the trial is being/was conducted according to the protocol, if the reported data are liable and if the clinical trial was conducted according to the applicable rules.

REFERENCES

¹ Throughout the document, the term “encoding” is used as a synonym for “pseudonymisation”, the term used in General Data Protection Regulation No 2016/679.

² When a person of full age is incapable of expressing his will, legal representation must be used which is determined in successive order (person whom the patient has previously designated to act in his place, administrator, or failing that, cohabitating spouse, the legal cohabiting partner, de facto cohabiting partner, an adult child, a parent, an adult brother or sister). If that person does not wish to do so or is absent, the professional concerned, where appropriate in multidisciplinary consultation, represents the interests of the patient. The regulation is laid down in article 31 of the law of 7 May 2017 on clinical trials for medicinal products for human use and articles 12 and 14 of the Law of 22 August 2002 on patients' rights.

³ The use of an impartial witness is necessary when the subject or their legal representative speaks and/or fully understands the language of the approved informed consent form but cannot read and write due to a physical disability or is visually impaired. An interpreter is necessary when the investigator does not speak the patient's language.

⁴ When a person of full age is incapable of expressing his will, legal representation must be used which is determined in successive order (person whom the patient has previously designated to act in his place, administrator, or failing that, cohabitating spouse, the legal cohabiting partner, de facto cohabiting partner, an adult child, a parent, an adult brother or sister). If that person does not wish to do so or is absent, the professional concerned, where appropriate in multidisciplinary consultation, represents the interests of the patient. The regulation is laid down in article 31 of the law of 7 May 2017 on clinical trials for medicinal products for human use and articles 12 and 14 of the Law of 22 August 2002 on patients' rights.

⁵ The use of an impartial witness is necessary when the subject or their legal representative speaks and/or fully understands the language of the approved informed consent form but cannot read and write due to a physical disability or is visually impaired. An interpreter is necessary when the investigator does not speak the patient's language.