Patient Information Sheet and Informed Consent Form

Study title:	An open-label, multicentre study to evaluate pharmacokinetics, safety and efficacy of zamicastat as adjunctive therapy in pulmonary arterial hypertension (PAH)
Protocol no.:	BIA-51058-201
EudraCT-Number:	2018-002448-10
Sponsor:	Bial - Portela & Cª, S.A. À Av. da Siderurgia Nacional 4745-457 Coronado (S. Romão e S. Mamede), Portugal Phone: +351 229866100 Fax: +351 229866192 http://www.bial.com

Your study doctor: _____

Your study site: _____

(Institution, address, phone number) _____

_____

Your study nurse: _____

*(may not be permitted in some countries)***Patient Number** |__|__|__|__|__|__|

Dear patient,

You are being invited to take part in a clinical research study because you have pulmonary arterial hypertension (PAH).

Clinical studies are necessary to obtain or increase knowledge on whether medications which have not yet been registered are effective and safe. According to the law, clinical studies must be carried out before a new medication is registered. This study is subject to international guidelines and regulations: The Declaration of Helsinki, the rules for Good Clinical Practice (GCP) and the national laws. Your rights as a volunteer in a clinical study are laid down in these regulations. The protocol for this study and this information sheet have been reviewed and approved by the national competent authority and by an Independent Ethics Committee.

Before you decide if you participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends or relatives if you wish. Ask the study doctor or nurse if there is something that is not clear or if you need more information. Take as much time as you need to decide whether you may take part or not.

Purpose of this study

Zamicastat is a medication which was developed by Bial - Portela & C[a], S.A. for PAH treatment. Zamicastat works by reducing the drive of the sympathetic nervous system. The sympathetic nervous system is part of the autonomic nervous system. The sympathetic nervous system can increase heart rate, make passages of the airways wider, decrease movement of the large intestine, make blood vessels narrower, cause widening of the pupils, goose bumps and sweating and raise blood pressure.

This clinical study is being conducted for research purposes. Zamicastat is an investigational medication for the treatment of PAH that will be used as adjunctive therapy (used along with other PAH medications). The word "investigational" means that zamicastat is still being tested and is not yet approved for sale. A total of 386 healthy volunteers received zamicastat in previous clinical studies.

With this study, researchers want to investigate the pharmacokinetics (what your body makes with zamicastat) and pharmacodynamics (how zamicastat affects your body) of different zamicastat doses (50 mg, 100 mg, 150 mg and 200 mg). They also want to know which side effects it causes and if treatment with zamicastat can reduce PAH related symptoms.

This study will be performed in about 15 hospitals in approximately nine European countries. It is planned to include approximately 32 patients who receive zamicastat. This clinical study will be organised and financed by Bial - Portela & C[a], S.A., the sponsor of this study. Please be informed that your study doctor and/or the study site will receive financial compensation for performing this study.

Voluntary participation and withdrawal from the study

It is entirely up to you if you will take part. If you decide to take part, you will be asked to sign a consent form before any study related procedures are performed.

If you agree to take part, you are still free to withdraw from the study at any time, for any reason without penalty or loss of benefits to which you are otherwise entitled. **If you do not wish to take part in this study or later withdraw from it, this will not affect your future care or your relationship with your study doctor in any way.**

In case of withdrawal, a final examination (early discontinuation visit [EDV]) within 10 days of discontinuation is recommended for your safety. However, you have the right to refuse additional examinations.

Your participation can also be terminated by the investigator or the sponsor due to the following reasons:

- Your health condition changes in a way that staying in the study is no longer medically justifiable.
- The entire study will be discontinued by the sponsor, any regulatory authority or ethics committee for safety or other reasons.
- Pregnancy.

In this case, a medical examination concluding your participation is necessary, for safety purposes. In addition, your study doctor will explain the reasons and will arrange for your care to continue.

In addition, at any time during or after withdrawal from the study, you will have the right to request the destruction of previously collected, stored and identifiable blood samples to prevent any further analysis. Please be informed that the data already collected until the time of withdrawal cannot be deleted with respect to the legal requirement to store the data.

Study medication

In this study, all patients will receive zamicastat in addition to their current PAH treatment. The study medication are tablets containing 100 mg zamicastat. You will receive the following zamicastat doses in this study if you are fine with the treatment and have no intolerable side effects:

- 50 mg zamicastat once daily (half a tablet of 100 mg)
- 100 mg zamicastat once daily (one tablet of 100 mg)
- 150 mg zamicastat once daily (one and a half tablet of 100 mg)
- 200 mg zamicastat once daily (two tablets of 100 mg)

The doses will be increased in sequential steps to your individual highest tolerated dose i.e. up to 200 mg zamicastat once daily.

You will start treatment with 50 mg zamicastat once daily and take the tablets for 14 days. If you should have intolerable side effects, you will be withdrawn from the study. If the study doctor confirms that you tolerate the dose, you will receive 100 mg zamicastat, 150 mg zamicastat and 200 mg zamicastat, each for 14 days (dose finding period). Afterwards, you will receive your highest tolerated dose for further 42 days.

A data monitoring board (a group of experts for PAH disease) will evaluate the safety of the used doses and will give a recommendation if the doses can be used as planned.

If you do not tolerate any of the next doses (i.e.100 mg, 150 mg or 200 mg zamicastat) at any time during the 14-day dose finding period you will come immediately to the study site or call the study doctor and the dose will be decreased to the previous tolerated dose. Then you will receive this dose for 42 days (the maintenance period). In case you should have intolerable side effects during the maintenance period, you will be withdrawn from the study.

You will take zamicastat for up to a maximum of 124 days.

You will have to take your study medication once daily in the morning after breakfast, orally to be swallowed. If required, the tablet can be divided at the brake score into equal halves. The study medication should be kept in the original packaging until administration and should be stored at temperatures up to 25 ºC in a dry place, out of reach from children. **Please do not take the study medication at home on the day of visit A3, B3, C3, D3, MPV1, MPV2 and MPV3 (for more information please see Section "Study visits and study procedures")**

Please make sure that you are familiar with the intake schedule after having received the tablets and feel free to ask your study doctor if anything remains unclear.

If you have forgotten to take the study medication after breakfast, you should take zamicastat after lunch and the next dose should be taken as scheduled. If you notice only later that you missed a dose, then you have to skip the dose for this day. Please report the missing dose to your study doctor on the next study visit.

In case more tablets have been forgotten, your study doctor will advise you how to further proceed.

Your study doctor will hand over the next bottles with study medication for administration during the course of the study. During the study you should bring the study medication with you at each on-site visit for inspection – also all empty bottles.

Study visits and Study Procedures

Your participation in this study will be between 12 and 21 weeks and you will have the following visits.

Visits	
V1 (on-site)	Your first visit; 9 to 7 days before A1. Your study doctor will check whether there is any medical or other reason that you may not participate.
<u>Dose finding period</u>	
A1 (on-site)	Day 1 of the study treatment, you will receive 50 mg zamicastat. You will come to the site in the morning and you will stay overnight; i.e. until 24 hours after zamicastat intake.
A2 (phone call)	8 days ±2 after A1
A3 (on-site)	14 days ±2 after A1 If you tolerate 50 mg, you will receive 100 mg and continue with B2.
B2 (phone call)	8 days ±2 after A3
B3 (on-site)	14 days ±2 after A3 If you tolerate 100 mg, you will receive 150 mg and continue with C2.
C2 (phone call)	8 days ±2 after B3
C3 (on-site)	14 days ±2 after B3 If you tolerate 150 mg, you will receive 200 mg and continue with D2.
D2 (phone call)	8 days ±2 after C3
D3 (on-site)	14 days ±2 after C3 <u>NOTE:</u> If you do not tolerate 100 mg, 150 mg or 200 mg zamicastat at any time during the dose finding period, your dose will be decreased to your previous tolerated dose. Please come immediately to the study site or call the study doctor, unless intolerance was detected during a scheduled visit.
<u>Maintenance period</u>	
MPV1 (on-site)	13 days ±2 after D3 (or after down-titration)
MPV2 (on-site)	27 days ±2 after D3 (or after down-titration)
MPV3 (on-site)	41 days ±2 after D3 (or after down-titration). You will come to the study site in the morning and you will stay overnight; i.e. until 24 hours after zamicastat intake.
<u>Follow-up period</u>	
Follow-up (down-titration) (phone call)	14 days ±2 after MPV3, only if you have taken 150 mg or 200 mg zamicastat and will not participate in the extension study.
Follow-up (on-site)	14 days ±2 after last zamicastat intake, only if you will not participate in the extension study.

In case you withdraw prematurely, an EDV will be performed.

If considered necessary, the study doctor will ask you to come to additional visits or give you calls. **Please contact the study doctor immediately if you experience side effects.**

In case that you do not return for a scheduled visit and the site cannot contact you by telephone or certified letter, a family member or friend will be contacted. Please provide the name and telephone number in the consent form, at the end of this document. If you wish, you can change the contact person during the course of the study. Please inform the study doctor accordingly.

During the course of the study (V1 to FU visit), your study doctor will perform the following procedures:

Procedures	**Visit**
Discussion of your participation and asking for your consent.	V1
Documentation of your age, gender and race.	V1
Documentation of all illnesses, especially those related to PAH.	V1
Documentation of all medications/treatments you have been taking.	All visits
Measurement of your weight.	V1, MPV3/EDV
Measurement of your height.	V1
Your study doctor will rate the severity of your PAH.	V1, MPV3/EDV
Your study doctor will check if you fulfil all criteria for participation.	V1, A1
First intake of study medication.	A1
Please inform the study doctor about any changes in health condition or symptoms that occurred.	All visits
Blood samples up to a volume of 12 mL per visit and urine samples will be taken for standard assessments. A maximal total amount of 96 mL blood will be collected during the study for safety tests.	V1, A3, B3, C3, D3, MPV1, MPV3/EDV, FU
Blood pregnancy test if you are a woman able to become pregnant.	V1
Urine pregnancy test if you are a woman able to become pregnant.	A1, A3, B3, C3, D3, MPV1, MPV2, MPV3/EDV, FU
The amount of a certain protein (so-called biomarker) will be analysed from your blood plasma. A blood sample up to a volume of 6 mL per visit will be taken.	V1, MPV3
Blood gas analysis. The blood amount required to perform the blood gas analysis is approximately 1 drop.	A1, MPV3
Blood samples for pharmacokinetic and pharmacodynamic purposes. At A1 and MPV3 blood samples of 9 mL each will be taken before intake of zamicastat and 1 h, 2 h, 4 h, 8 h, 16 h and 24 h after intake. At A3, B3, C3, D3, MPV1 and MVPV2 one blood sample of 9 mL will be taken before intake of zamicastat.	A1, A3, B3, C3, D3, MPV1, MPV2, MPV3

Procedures	Visit
24-hour urine samples for pharmacodynamic purposes. Collection of the 24-hour urine sample will start at home one day before the respective visit in the morning.	A1, A3, B3, C3, D3, MPV3
Measurement of heart rate, blood pressure and body temperature. Heart rate and blood pressure will be measured twice in a laying position (separated at least be one minute) and then one more time in a standing position. At A1 and MPV3 heart rate and blood pressure will be measured before zamicastat intake, 4, 8 and 24 hours afterwards.	All on-site visits
A recording of the electrical activity of the heart (electrocardiogram). At visits A1 and MPV3 three measurements will be performed before zamicastat intake, 4 and 8 hours afterwards, respectively.	V1, A1, A3, B3, C3, D3, MPV1, MPV2 MPV3/EDV, FU
Ultrasound examination of your heart (echocardiography).	V1, MPV3
Routine physical examination e.g. listen to the heart, lungs etc.	V1, A3, B3, C3, D3, MPV1, MPV2, MPV3/EDV
Assessment for scars at the fingers and toes (in patients with scleroderma only).	V1, A3, B3, C3, D3, MPV1, MPV2, MPV3/EDV
Assessment of your skin (in patients with scleroderma only).	V1, MPV3/EDV
Measurement of the distance you can walk within 6 minutes. The measurement will be performed twice at visit V1.	V1, MPV3
A questionnaire rating your quality of life.	V1, MPV3
Right heart catheterisation A right-heart catheterisation will be performed to see how well or poorly your heart is pumping, and to measure the pressures in your heart and lungs. After injection of local anaesthetic into the skin, your study doctor guides a special catheter (a small, hollow tube) to the right side of your heart. He or she then passes the tube into your pulmonary artery. This is the main artery that carries blood to your lungs. Your study doctor observes blood flow through your heart and measures the pressures inside your heart and lungs. You may feel slight sensations as the catheter is moved about, but these are generally not uncomfortable.	A1, MPV3

It is not necessary to stop your previous PAH treatment but you should not start further PAH-specific or any other new treatment during the study without contacting your study doctor first.

During the entire study, a total amount of approximately 288 mL blood will be collected over a period of approximately 12 to 21 weeks (as comparison, 450 to 500 mL of blood is taken at a typical blood donation).

What will happen at the end of this study?

Your study doctor will invite you to take part in an extension study. If you agree to participate, you will be asked to sign a new informed consent form. In the extension study, the sponsor will continue to provide you with study medication.

If you do not agree to take part in this extension study and you are taking 150 mg or 200 mg zamicastat at MPV3, you will decrease (down-titrate) your zamicastat dose by taking 100 mg for 14 days before stopping intake of zamicastat completely. The study doctor or another member of the study team will contact you by phone to ask you about any changes in health condition or symptoms that occurred and about all medications/treatments which you have taken. In case you are taking 100 mg or 50 mg zamicastat at MPV3, you will take the last tablet of zamicastat at MPV3.

If you do not continue with the extension study, no additional care apart from your standard treatment will be necessary due to your participation in the study at the end of the study. However, your study doctor will contact you by phone as soon as the last patient in this study has completed his/her last visit to obtain information about your health status.

Your responsibilities during your study participation

During your study participation, you will need to:

1. Follow the study doctor's instructions;
2. Provide your medical history and answer all questions truthfully;
3. Come to the site for the scheduled visits and be available for the telephone calls;
4. Stay overnight at the site at visits A1 and MPV3;
5. Take the study medication following the study doctor's instructions;
6. Not take any other prescribed or over-the-counter medicines, herbal products or vaccinations or change the regimen or dosage of any currently agreed concomitant therapy without talking to the study doctor first (excluding emergencies);
7. Return all unused study medication and empty bottles to the study doctor at each on-site visit;
8. Inform the study doctor or a study team member immediately about any changes in your health condition during the study;
9. Take your patient card with you at any time and show it in case a medical treatment at some other location may be necessary (e.g. in case of an accident);
10. Not participate in any other clinical study at the same time;
11. Not to eat grapefruits or to drink or eat products containing grapefruit;
12. For women able to become pregnant: follow the study doctor's instruction on contraception from the time of signing the informed consent until 30 days after the last zamicastat intake.
13. For man sexually active with a woman able to become pregnant: follow the study doctor's instruction on contraception from the time of signing the informed consent until 90 days after the last zamicastat intake.

For women: In case you gave birth to a child recently, you can only participate if you are not breastfeeding.

Risks and special warnings

Zamicastat is a new medication which is currently under investigation. Thus, even though proposed according to previous test results, it cannot be guaranteed to date that it will be as effective as other medications that are already on the market.

Zamicastat has been tested in 386 healthy volunteers and was generally well tolerated. The reported side effects were usually mild to moderate in intensity. The highest exposure to zamicastat was 1200 mg single-dose with food and 1200 mg once-daily for 10 days.

Like all medicines, zamicastat can cause side effects, although not everybody gets them. In previous clinical studies, the following side effects that were judged to be at least possibly related to zamicastat treatment.

In local versions, incidence in % can be deleted if not requested by national requirements.

Reported in more than 1 in 100 people:

Nervous system	headache (11.9%), feeling dizzy or sleepy (dizziness, 2.8%), dizziness postural (2.1%)
Gastrointestinal system	feeling sick (nausea, 5.2%), abdominal pain (1.6%), diarrhoea, (1.3%)
General:	fatigue (4.1%)
Blood vessels	circulatory problems due to low blood pressure (orthostatic hypotension, 1.8%)
Skin	rash (rash papular, 1.8%)

Reported in less than 1 in 100 people:

Nervous system	head discomfort (0.8%), numbness (hypoaesthesia, 0.5%), disturbance in attention, pricking (paraesthesia), and sleepiness (somnolence), 0.3% each
Gastrointestinal system	vomiting and abdominal discomfort, 0.5%, each, upper abdominal pain, impaired digestion (dyspepsia), soft faeces, stomach does not empty food as quickly as it should (impaired gastric emptying), toothache, flatulence and frequent bowel movements, 0.3% each
General	feeling drunk (0.8%), feeling abnormal (0.5%), weakness (asthenia), chest pain, feeling hot and discomfort (malaise), 0.3% each

Skin	inflammation of the skin due to allergens exposure (dermatitis contact) and increased sweating (hyperhidrosis), 0.5% each, sensitivity to light, itch (pruritus), redness of the skin or mucous membranes (rash erythematous) and irritation of the skin, 0.3% each
Blood vessels	hot flushes (0.5%)
Infections and infestations	cold (rhinitis) and inflammation of the gastrointestinal tract (gastroenteritis), 0.3% each
Breathing and chest area	sneezing (0.5%)
Heart	beating of the heart (palpitations, 0.5%)
Eye	Eye pain and blurred vision, 0.3% each
Investigations	blood tests showing high levels of creatine phosphokinase (an enzyme mainly found in the heart, brain, and skeletal muscle, 0.3%)
Metabolism and nutrition disorders	decreased appetite (0.6%)
Psychiatric	difficulty in sleeping (insomnia) and depressed mood, 0.3% each
Musculoskeletal	muscle pain (myalgia, 0.3%)
Kidney and urinary tract	abnormally frequent urination (pollakiuria, 0.3%)
Sexual organs and breast	irregular menstrual bleeding (0.3%)

Since zamicastat increases dopamine exposure, the following effects may be increased: hallucinations, nausea, and abnormal, uncontrollable, involuntary movements (dyskinesia), orthostatic hypotension and a temporary loss of consciousness usually related to insufficient blood flow to the brain (syncope). Therefore, please do not rise rapidly after sitting or lying down. Do not drive or use any tools or machines if you feel dizzy or drowsy or if your vision is affected.

Like other medicines also zamicastat may cause hypersensitivity/allergic reactions. If you have a rash, hives, itching, difficulty in breathing, swelling of the face, mouth, lips or tongue please contact your study doctor immediately. This can be a sign of an allergic reaction. Allergic reactions can happen immediately after the first intake of a medication or days or weeks after. If you have a rash, please take photos of the affected skin area(s) according the instruction provided on the photocard for rash and send the photos to the study site. In case the rash is noticed during an on-site visit, a member of the study team will take pictures of the affected skin area(s). All photos will be taken in a way that nobody will recognise you.

Zamicastat can potentially interact with other medicines (e.g. central nervous system depressants, catechol-structured medications or cardiovascular medications) and may affect your condition. There

are some medications that you cannot take at the same time while taking zamicastat due to potential interactions. Your study doctor will inform you about such medications.

If you do not understand the meaning of any of these side effects or if you wish to have a more detailed description of these conditions and the risks associated with each one, please ask your study doctor.

As with any medication at any stage of development, there is always a risk of rare or previously unknown side effects developing from treatment which are not known at this time.

If you experience any of the side effects listed above or any other signs or symptoms, please contact your study doctor to get medical help as required. All reported side effects will be noted and closely observed by your study doctor. He/she will also decide whether it is necessary to stop taking zamicastat. **In case of unusual or severe symptoms please consult your study doctor immediately.**

Right heart catheterisation

This assessment is considered as the only accurate way to measure the pressure in the pulmonary artery (vessel that conducts the blood from the heart to the lungs) and to diagnose PAH. It is also used to periodically monitor your disease during the treatment process. In this study it will be used to assess whether zamicastat reduced or not the pressure in your pulmonary artery and heart.

As with many medical tests there are some risks, although a right heart catheterisation is generally considered to be a safe test.

The following serious risks were reported in less than 1 in 100 people: low blood pressure (0.18%), bruising of the skin at the site where the catheter is inserted (0.14%), abnormal heart rhythms (e.g. fast heart rate in your lower heart chambers [0.14%]), partial collapse of your lung if your neck or chest veins are used to insert the catheter (0.07%), death (0.055%), and pulmonary artery rupture (a damage to the main artery in your lung, can result in serious bleeding, making it hard to breathe [0.03%]).

In local versions, incidence in % can be deleted if not required by national requirements.

The following risks have been reported with an unknown frequency: excessive bleeding because of puncture of the vein during catheter insertion, cardiac tamponade (fluid build-up around your heart that affects its ability to pump blood effectively), infection, air embolism (air leaking into your heart or chest area), and blood clots at the tip of the catheter that can block blood flow.

For some people, having to lie still on the cardiac catheterisation table for the length of the procedure may cause some discomfort or back pain. There may be other risks, depending on your specific condition. Your study doctor will explain them to you.

After the procedure, you will be under close monitoring for bleeding, blood pressure changes, heart rate and breathing changes. The following symptoms should also be reported immediately to your study doctor:

- shortness of breath or trouble breathing
- fever or chills
- increased pain, redness, swelling, or bleeding or other drainage from the insertion site
- coolness, numbness or tingling, or other changes in the affected extremity
- chest pain or pressure, nausea or vomiting, profuse sweating, dizziness, or fainting

Pregnancy

For women: If you become pregnant in the period from first study medication intake until 30 days after last study medication intake, there may be risks to the unborn child, which are currently unknown. If you become pregnant or you suspect that you are pregnant during this period, please inform your study doctor immediately. If the pregnancy is confirmed, you have to stop zamicastat immediately and your study doctor will follow-up your pregnancy, the birth and the condition of your child.

For men: If your partner become pregnant in the period from first study medication intake until 90 days after last study medication intake, there may be risks to the unborn child, which are currently unknown. If your partner become pregnant during this period, please inform your study doctor immediately. Your study doctor will follow-up the pregnancy, the birth and the condition of your child.

Blood withdrawals

Risks associated with drawing blood may include pain, bruising, light-headedness and, on rare occasion, infection.

Benefits

We hope that if you receive zamicastat, you may experience an improvement of PAH symptoms. However, because the efficacy of this new medication is not yet confirmed, this cannot be guaranteed and it may happen that your participation in this study will not result in any clinical benefit for you.

Compensation for study participation

You do not have to pay for your participation in the study and for any procedure performed within the study. Your travel expenses which may arise due to your participation in this study will be compensated up to XXX € per visit. Please provide all receipts regarding travel costs to your study doctor. If you travel by car, you will receive mileage allowance of YYY €/km. Please ask your study doctor for more information.

In addition, for visits A1 and MPV3 you will receive a monetary compensation of ZZZ € per visit for the unproductive time while staying at the study site for more than 24 hours.

Apart from the reimbursements mentioned above, you will not receive any monetary compensation for participation in this study.

Alternative treatment

If you decide that you will not participate in this study, alternative treatments for PAH may include other approved treatments like ambrisentan, bosentan, macitentan, riociguat, selexipag, sildenafil, tadalafil, epoprostenol, iloprost or treprostinil.

The potential benefits of these treatments are an improvement of PAH symptoms. The potential risks are the side effects described in the package leaflet of these medications.

All mentioned medications differ in their effectiveness, their risks and their advantages. Please ask your study doctor if you need more information.

Insurance

Insurance coverage for all study participants has been taken out in accordance with the requirements in your country in the name of the sponsor.

In the event that an injury occurs as a result of this research, compensation will be available from this insurance. In case of an injury please inform the **insurance company directly or the study doctor** (see first page for contact details), who then will inform the insurance company in your name and provide you with a copy of the notification. The insurance company has to be informed immediately, otherwise you may lose the insurance coverage.

The insurance was taken out with:

<Company name>

<Address>

<Phone number or other contact details>

Insurance number: <Number>

In local versions, "if you wish," should be deleted, if it is mandatory to provide insurance documents.

If you wish, you will receive a copy of the insurance terms and conditions. Please pay special attention to the sections referring to insurance benefits, loss of coverage and obligations.

Confidentiality, data protection and authorised use of medical information

All information collected about you during the study will be kept strictly confidential in accordance to, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation, GDPR).

The information collected about you for BIAL or its designee will be used for the purposes of the study. It will be stored, both on paper and computer records, without identifying you by name or date of birth.

The data will be passed on in a pseudonymised (encrypted with a code number) form preventing your identification by the recipient:

a) to the sponsor of the clinical study and entities appointed by sponsor for the conduct of the study and the scientific evaluation of collected data,

b) in the event of an application for marketing authorisation: to the applicant and the competent authority for processing the application,

c) in the event of adverse events: to the competent ethics committees and the competent authorities, and from there to the European Database.

Your study doctor will keep a list which links the code number to your name. Regulatory authorities, members of the ethics committee, study site personnel and representatives of the sponsor or sponsor's designees may access this list and review your medical records. This is necessary to check that the study is being performed correctly and that the information is accurate. All personnel having access to your records are required to respect your confidentiality also after the end of this study.

In accordance with GDPR you have the right to access your collected information via your study doctor, and ask to correct any errors in the information. To obtain detailed information on your personal data the study site has stored, you may contact the study site in writing or via email. You may also request the study site to transfer the data that have been collected about you as indicated above to you or to forward such data to a third party designated by you. If you find that any information stored about you is inaccurate or incomplete, you may request immediate correction or completion of such information at any time. Access to your information may be postponed if it would hinder the conduct of the study. If you do not want to be any longer in the study, your information collected so far may still be used by the sponsor or sponsor's designee, if permitted by law.

Your data will be retained for the period required in accordance with compulsory applicable law <study-specific retention periods, e.g. contractual periods, need to be specified here, if applicable>. At the expiration of such terms your personal data will be deleted.

If you agree, your general practitioner will be informed about your participation in this study.

This clinical study will only be performed by collecting and using data related to your health. National and international data protection regulations give you the right to control the use of your medical information. Therefore, by signing this form you specifically authorise your medical information to be checked, transferred and processed as follows:

The authorised representatives of the sponsor, and its designees, study site personnel, the ethics committee and regulatory authorities' inspectors in various countries may review your medical information by direct access to your medical records.

Study data, including your medical information, and information on any medical samples taken, may be processed, which means it will be collected, entered into computer databases, verified, analysed, printed and reported as necessary for legitimate scientific purposes, as outlined above.

A transfer of your personal encrypted data to countries outside the European Union or the European Economic Area ("third countries") may take place, incl. to such countries which do not guarantee an equivalent level of data protection as the European Union.

Contact:

In the event of questions about the processing of your personal data by the study site, you may contact the person responsible for data processing of the study site:

_____

Name and telephone number of the employee responsible for the data processing, e. g. data protection officer

If you do not agree with the data processing activities carried out by the study site or the information provided by it, you have the right to lodge a complaint with the competent supervisory authority *<insert the specific competent supervisory authority, if possible; otherwise add "competent supervisory authority">*

Samples of biological material

Blood and urine samples will be collected and used for purposes of this study only. Blood samples for safety analysis and biomarker assessment will be analysed centrally at LKF, Laboratory for Clinical Trials GmbH, Lise-Meitner-Strasse 25, 24223 Schwentinental, Germany. Blood samples for pharmacokinetic and pharmacodynamic purposes will be analysed centrally at SYNLAB Analytics & Services Switzerland AG, Sternenfeldstrasse 14, CH-4127 Birsfelden, Switzerland (pharmacokinetic samples) and at Anapharm, Encuny 22, 2nd floor, 08038 Barcelona, Spain (pharmacodynamic samples). Urine samples for pharmacodynamic analysis will be analysed at The Doctors Laboratory, Halo Building, 1 Mabledon Place, London WC1H 9AX, United Kingdom.

Future scientific research may reveal further naturally occurring biological substances in the blood (biomarkers) that may help to better understand your disease PAH. By analysing stored plasma samples after the end of this study, new biological substances which allow to predict if a patient will benefit most from treatment with zamicastat, could be identified. You will be asked at the end of this document for your consent to store those plasma samples for a maximum of 10 years.

The samples will be stored until 6 months after the study report is finalised and will be destroyed afterwards (apart from the biomarker samples). No genetic analyses will be performed on your samples.

Identifiable samples can be destroyed at any time at your request in order to prevent any further analysis.

New findings

New information may become available during the course of the study that might affect your willingness to agree to your further study participation. If this happens, your study doctor will explain it to you in a timely manner and discuss with you your participation in the study.

Publicly accessible information on this clinical study

A description of this study and the results will be available on the internet, e.g. on *http://www.clinicalstudysregister.eu*, and may be published in specialised medical journals. A summary of the results of the study presented in terms understandable to a layperson will be made available in the EU database. For details please ask your study doctor. This will not include information (text or photo) that can identify you.

Whom to contact with questions

For questions concerning this study, please contact your study doctor (see first page). For further information regarding your rights as a study patient, or in case of study-related injury, you can contact:

Name:

Phone: <phone number>

Address: <National contact, address>

Email address: <email>

Thank you for reading this information.

Name of the patient: _____
(This can be entered by the site or patient)

INFORMED CONSENT FORM

Study title:	An open-label, multicentre study to evaluate pharmacokinetics, safety and efficacy of zamicastat as adjunctive therapy in pulmonary arterial hypertension (PAH)
Protocol no.:	BIA-51058-201

I, _____

(Print patient's name. This can be entered by the site or patient)

declare by signing this informed consent form that:

1. I have read the patient information sheet for this study. I have received an explanation of the nature, purpose, duration, and foreseeable effects and risks of the study and what I will be expected to do. My questions have been answered satisfactorily. I have been given ample time and opportunity to enquire about details of the study and to make my decision.
2. I agree to take part in this study. I agree to cooperate fully with the study doctor and will contact him/her immediately if I suffer any unexpected or unusual symptoms or ─ for female patients ─ if I think that I am pregnant during the study or ─ for male patients ─ if I think that my partner is pregnant during the study. For the duration of the study, I will notify the study doctor of any other medical treatments that may be necessary for me to undergo.
3. I have informed the study doctor of all my previous or present illnesses and medication and of any consultation that I have had with any doctor in the last months.
4. I have further informed the study doctor of any participation in other studies in the past months.
5. I am aware that if I do not cooperate fully with the study doctor's requests and directions, I may harm myself by participating in the study.
6. I understand that my participation is voluntary. I understand if I do not sign this form, I will not be able to participate in this study. I also understand that I may withdraw from the study:
   - Whenever I wish
   - Without having to explain why
   - Without this affecting my medical care
7. I further understand that any information that becomes available during the course of the study that may affect my willingness to take part will be disclosed to me in a timely manner.
8. Also, I agree that authorised representatives of sponsor and competent regulatory authorities, bound by professional secrecy, may inspect my personal data held by the investigator, in particular my health records, to the extent necessary to verify the proper conduct of the study. For this purpose, I release the investigator from his/her duty of secrecy.
9. I agree that my general practitioner _____ (insert name) will be notified of my involvement in the clinical study (strike-through, if not desired).
10. I agree that health data from attending physicians be collected to the extent necessary for the proper conduct and monitoring of the study. For this purpose, I release these physicians from their duty of secrecy.

Name of the patient: _____
(This can be entered by the site or patient)

11. I agree that my plasma samples will be stored for a maximum of 10 years for further analysis for other scientific purposes as specified above (outside this study). Yes ☐ __ No ☐
12. I agree that the following person(s) may be contacted in case that I do not return for a scheduled visit and the site cannot contact me by telephone or certified letter (strike-through, if not desired).

_____
(name and telephone number of the specified person)

_____
(name and telephone number of the specified person)

I have spoken to_____
(print full name of the person who carried out the consent discussion)

I hereby freely consent that I will take part in the study.

Signature of the patient _____ Date _____
(Personally signed and dated) (dd-mm-yyyy)

Study doctor:

I, the undersigned, have fully and carefully explained the details of the study to the patient and certify that to the best of my knowledge, the patient clearly understand the nature, objectives, benefits, implications, risks and inconveniences of participation in this study.

I herewith declare that currently no financial or other ties to the sponsor currently exist other than receiving financial compensation for performing this study (this is also valid for any of my institutional affiliations).

Signature of the study doctor _____ Date _____
(Personally signed and dated by the person who carried out the consent discussion) (dd-mm-yyyy)

Name of the patient: _____
(This can be entered by the site or patient)

If this consent form is read to the patient because the patient is unable to read the form, an impartial witness not affiliated with the research or study doctor must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient. The patient freely consented to be in the study.

_____
(Print full name of the impartial witness)

Signature of the impartial witness _____ Date _____
(Personally signed and dated) (dd-mm-yyyy)

The signed patient information sheet and consent form must be stapled. A copy <replace "A copy" by "An original" as applicable acc. to local law> of the signed patient information sheet and consent form will be given to the patient.