Patient information and consent for participants in a scientific trial for patients with newly diagnosed chronic lymphocytic leukemia

Full title of the study: Short-term combined acalabrutinib and venetoclax treatment of newly diagnosed patients with CLL at high risk of infection and/or early treatment, who do not fulfil IWCLL treatment criteria for treatment. A randomized study with extensive immune phenotyping.

Short Title: PreVent-ACaLL

EudraCT NUMBER:	2019-000270-29
SPONSOR:	Rigshospitalet, Copenhagen, Denmark
HOSPITAL NAME:	
HOSPITAL ADRESS:	
NAME OF INVESTIGATOR:	

Dear Patient,

We are asking you if you would like to participate the medical study called PreVent-ACall, because you are newly diagnosed with Chronic Lymphocytic Leukemia (CLL) and are at high risk of developing infections.

You yourself decide whether you want to participate. Before you make your decision, it is important to know more about the study. Read through this information letter in your own time. Discuss it with your partner, friends or family. Also read the general brochure on 'Medical research' (Appendix 2) [insert local/national brochure, if relevant]. This contains a lot of general information about medical research. If you still have questions after reading the information, you can contact your doctor or the other doctors named in Appendix 1.

The study is supported financially by the Novo Nordisk foundation, and by the company Acerta Pharma. The medical companies Acerta Pharma and Abbvie are providing the study medication. The study is initiated by the Nordic CLL study groups and the HOVON CLL group and coordinated by Rigshospitalet, Copenhagen, Denmark

1. Study purpose

Many patients with CLL have a weakened immune system due to their disease. CLL increases the risk of developing serious infections requiring treatment or in the worst case CLL can result in fatalities.

The study will investigate whether three months treatment with a combination of two types of oral medication can reduce the risk of infection and the need for regular CLL treatment when it is given to newly diagnosed CLL patients.

A computer model can predict whether patients with CLL are at high risk of developing infections and/or require treatment. The two drugs will be given as preventive treatment prior to the patients needing any chemotherapy. In this way, it is tested whether the cancer disease can be "reset" and the immune system, which is inhibited by CLL, can be restored. The aim is thereby to reduce the risk of serious infections and the need for regular CLL treatment.

2. Study participation

Patients with Chronic Lymphocytic Leukemia (CLL) at high risk of developing infections can participate in this study. Several hospitals in Denmark, Sweden and the Netherlands participate in this medical study. A total of about 212 patients will be included in the study (50 patients in the first part and a total of 212 patients). In the first part, 30 patients are expected to be from Denmark. Patients will be followed for seven years after treatment initiation.

3. Study procedures

Screening and randomisation

To be part of the study, you have to be assessed by the computer model as high risk of infections and early chemotherapy, and you must sign the Informed Consent form before any study specific procedures and examinations are being done. Most of these examinations are standard of care for all patients with CLL, but some of the examinations are specific to this study. The study doctor will review your data during the screening period, to assess whether you are eligible for the study. The screening period can last up to 42 days.

If taking part in the study, you will be assigned by chance (like flipping a coin) to one of two treatment groups, so-called randomization. Your doctor has no influence on what group you will be in. You will have an equal (1 to 1) change of being assigned to either the study treatment group or the standard observation (no treatment) group.

Treatment for the treatment group

In this study, you will be treated with a combination of the drugs acalabrutinib and venetoclax. The treatment will be started within 14 days after you have been randomised.

You will be treated for three cycles, each cycle lasts 28 days.

Acalabrutinib is tablets that will be given for three cycles of 28 days with a dose of 100 mg twice daily. The tablets have to be taken approximately every 12 hours, at least eight hours apart. Acalabrutinib is approved for treatment of some types of lymphoma in the US, but not for treatment of CLL.

Venetoclax is tablets that will be given for cycles of 28 days. During cycle 1, the dose is increased weekly.The doses of 20 mg, 50 mg, 100 mg and 200 mg should be taken once daily for seven days at each dose level. For the last two cycles of 28 days, you will receive 400 mg of venetoclax once daily. The dosage is increased weekly to prevent side effects of venetoclax. To reduce the risk of side effects, you may receive additional medication and/or fluid therapy. Venetoclax is approved in the EU and the US for treatment of specific subgroups of patients with CLL.

Drug interactions might occur between the study medication and other drugs, including over-the-counter drugs, please tell your doctor if you are taking any other form of medication.

Observation group
If you are randomized to the observation group, you will receive no treatment for CLL. This is standard procedure for newly diagnosed CLL patients not requiring therapy according to current guidelines. Your doctor will follow you to assess whether you at some timepoint will require CLL treatment.

Follow-up period
No matter which group you are assigned to, you will have to return to the clinic for follow-up visits every month in the beginning and subsequently every 3 months. If you are randomized to the treatment group, for the first month you will have to come in for weekly visits to the clinic including additional blood testing the day before and after visits.

Data collected
The data for the study will be collected from your medical record, through interviews and from questionnaires you complete during the study. The data concerns information about your health, laboratory data, and medical history data, as well as information about the procedures and treatment you undergo.

During the study data will be collected as listed in appendix 3.

4. Expectations of you
During the study, we ask you to follow your doctor's instructions closely. It is important for your safety that you inform your treating physician if you need treatment anywhere else or take part in another study. In addition, it is important that you keep to your appointments.

If you are a woman:
If you are a woman of fertile age, you must agree to use contraception. This must be a combination of at least two approved contraceptive measures from the time of the first dose of the study medication and d during the whole study treatment period Hormonal contraception must not be the only contraceptive measure used.

You can use below mentioned approved and efficient contraceptive measures:

- IUD (all kinds) or hormonal IUD plus condom
- Hormonal contraception (tablet, depot, patch, injections or vaginal ring) plus condom
- Sexual abstinence

If you are pregnant or breastfeeding, you cannot participate in this study.

If you are a man:
If you are a man, you must agree to use a condom from the time of the first dose of study medication and for 30 days after the end of study treatment. Your female sex partners must also use a very efficient contraceptive measure, as described above in the paragraph “If you are a woman”. Your sex partner must use this form of contraception from the time you receive the first dose of study medication until after the last dose of study medication.
Other possible contraceptive measures:

- Vasectomy
- Sexual abstinence

Your doctor will discuss the most suitable contraceptive measures with you. If, despite this, you or your partner becomes pregnant during the study period, please contact your doctor immediately. The study treatment may have consequences for your unborn child. The effects of acalabrutinib and venetoclax on an unborn child are unknown and may be harmful. If you become pregnant, you will be withdrawn from the study, and at the same time kept under supervision.

5. Treatment(s) and care different and/or additional from the standard of care

Most tests are performed as part of your standard of care. You will have more appointments at the hospital when participating in the study and receive treatment at an earlier timepoint than outside of the clinical trial.

Supplementary tests

The following scientific examinations a part from standard of care tests are done specifically for this study:

- **Withdrawal of bone marrow.** During the study, a bone marrow examination will be performed minimal two times to determine very carefully the presence of leukemia cells. No more than 10 ml of bone marrow will be taken during the bone marrow puncture. An additional test will be done in case of progression of your disease.
- **Withdrawal of lymph node tissue**. If CLL disease does occurs during or after the treatment, lymph node tissue will be taken if there are enlarged nodes in a readily accessible site. For this puncture, a thin needle is inserted into the node or a biopsy is taken. This enables cells to be collected from the lymphoma and surrounding cells. In order to determine the puncture site as closely as possible and to perform the procedure with maximum safety, this puncture will take place under ultrasound guidance. Normally, it is not necessary to anaesthetise this beforehand, but local anaesthetic can be used.
- **CT scan**. CT scans will be taken to chart closely the spreading of your disease before treatment and the effect of the treatment on your disease. Not more than three CT scans will be taken during the whole of the research. Compared with the standard treatment, a maximum of two additional CT scans (10mSv per scan) will be done. If you were not to take part in the study, a scan would be made at the start of your treatment and in case of progression of your disease. For comparison, the annual natural background radiation exposure in Denmark (the amount of radiation in the air, etc.) is approx. 4 mSV. One scan corresponds to the radiation you will be exposed to during 2.5 years.
- **Quality of life questionnaires.** It is important to know whether the treatment improves your quality of life. For this reason, you will be asked to complete several questionnaires that provide an insight into the quality of life. You will be asked 9 times during the research to complete these questionnaires. It takes about 15 minutes to complete a questionnaire.
- **ECG**. You will have an electrocardiogram (ECG) done at screening to assess your heart rate and rhythm. This would also have been done if you were not in the study.
- **Pregnancy test.** If you are a woman of fertile age, a pregnancy test will be performed during the screening period. If you are in the study treatment group a negative pregnancy test is

needed within 7 days of start of treatment. A pregnancy test will be performed once a month until end of treatment.

- **Microbiome samples (feaces, saliva, skin swab and buccal swab):** Samples will be collected up to 4 times during the study to examine the types of bacteria present.
- **Withdrawal of additional blood**. During the research blood (100 ml) will be taken for a biobank at a maximum of 10 different times over a period of 3 years.
  For every visit blood test will be taken (20 ml). This is similar to what patients would get if they were not in the study.
  For the treatment group additional 10 blood samples will be taken for tumor lysis syndrome (TLS) risk.

A schedule of all the examinations is given in Appendix 3.

6. Other treatment options

Your doctor will discuss any other treatment options with you.

7. Side effects from the study treatment

You can find information about side effects of acalabrutinib and venetoclax in Appendix 4. However, not all side effects are mentioned or known. The side effects mentioned may not occur in all patients. It is also possible that side effects may occur which are not yet known. If you develop symptoms, please tell your doctor, even if you do not consider it a side effect of the study. In the event of severe symptoms, you must contact your doctor immediately. In addition, you will be asked regularly during visits to the outpatient department whether you have had any symptoms and, if so, how severe they were.

8. Possible benefits and disadvantages of participating in this study

We do not know whether being in the study will be a direct benefit to you. About half of the patients in the study will get the study treatment.
If you are in the treatment group, you will receive a treatment not usually used for newly diagnosed CLL patients. The treatment might decrease the risk of infections and postpone the need for chemotherapy. The treatment may also cause side effects, which you would not have experienced with the standard of care where no medication is given.
If you are in the observation group there is no direct benefit for you to be in the study. What we learn from this study may help improve the treatment for future CLL patients.

If you are participating in the study, additional tests and procedures may impose risks including minor bleeding or infection from blood drawings and radiation due to CT scans, which equals approximately the background radiation that you would otherwise be exposed to in a few years. The CT scans performed as part of the study will expose you to approx.10 mSv per scan. For comparison, the annual natural background radiation exposure (the amount of radiation in the air, etc.) is approx. 4 mSV.

An independent Data and Safety Monitoring Board (DSMB) will have the oversight of results during the study. The DSMB consists of doctors and other experts in CLL and clinical trial management. They will help keep the study safe for all study participants.

9. Participation in and withdrawal from the study

It is up to you to decide whether to participate in this study. Participation is voluntary. If you decide not to participate, you do not have to do anything else. You do not have to sign anything. You do not have to say why you do not want to participate. If you decide not to participate, you will receive the standard of care.
If you do participate, you can always change your mind and stop participation, even during the course of the study.
If you want to withdraw from the study, tell your doctor, who will advise and supervise how you safely stop the use of the study medicines.

Your participation in the trial may, under certain circumstances, terminate without you having any influence on the decision. This may happen if:

- Your investigator decides that your continued participation in the trial could harm you;
- The trial is stopped for administrative or safety reasons.

10. End of study

The study ends for you when you have received the full study treatment and all the follow-up visits are completed. You will be followed in the study for seven years after treatment initiation. Afterwards, information about your health may still be retrieved through medical records and registries until 2045 and then your data will be destroyed.
It may happen that your doctor or the sponsor of the trial decides to stop your participation or the full trial earlier than this if new information about your disease or your treatment has become available.

11. Insurance

It is important that you tell the doctor if you think you are injured because of your participation in this study
[Site instruction: Please insert site/country specific information regarding insurance]

12. New information of relevance during the study

The study will proceed according to plan as far as possible. However, the situation may change, for example due to the way you respond to the treatment, or due to new information. If that is the case, your doctor will discuss this directly with you. You then decide yourself whether you want to withdraw from or continue your participation in the study. If your safety or health are at risk, you will be withdrawn from the study immediately.

13. Personal data and bodily material

Your personal data and bodily material will be collected, used and stored for this study. All study participants are assigned a study number, which is used for identification of all samples and data. Personal data such as name, and any information that can directly identify you, will not be included.

Some of your blood samples may be sent to the United States for analyses assessing response to treatment, as these analyses are not currently available within the EU. It concerns 30 mL of blood, bone marrow and lymph node tissue. This will not include samples where extensive mapping of genetic material is part of the analyses.

Confidentiality

All your data will be treated confidentially. Only the study doctors and the participating staff at the hospital know the study number you have. Your samples and data are sent to the study sponsor,

but marked only with your study number, never with your name or any other personal identifier. The key to the trial number remains with the local trial doctor. The data cannot be traced back to you from reports and publications about the study.

Access to your data for verification
Authorized personnel monitoring and overviewing the trial for the sponsor can access all your medical and personal data at the study location. This is necessary to check whether the study is being conducted in a good, ethical and reliable manner. They will all keep your data confidential. Personnel who have access to your data for review beside your study doctors and the participating staff are:

- Study sponsor and monitors appointed by the sponsor
- National and international authorities, for example Medical Agency or Data protection Agency.
- Ethics Committee

If you sign the consent page, you consent to collection, storage and inspection of your medical and personal data.

Your samples
The extra samples taken in connection with the study (samples for biobank) will be sent to a central laboratory facility in Copenhagen, Denmark (Rigshospitalet).

We would like to store your data and samples to use the for research with the purpose of increasing the knowledge of your disease and improve the diagnose and treatment. This includes immune system characteristics (immunophenotyping), immune response and analyses of the microbiome (bacterial and microbial flora) as well as genetic analyses, explained in detail below. The samples will be kept in a research biobank as long as study analyses are ongoing.
The amount of material taken for the research biobank can be seen above in the section *Supplementary Tests*. Any remaining material in the research biobank will be destroyed after all study analyses have been completed. The study will run for many years and it might take a long time to analyse all samples, but the study materials will be destroyed no later than 2035.

14. Information about genetic analyses

In the study we will perform genetic analyses. This means that we are investigating the significance of genetic material for disease development.

What are chromosomes and genes?

All the cells of the body contain chromosomes. Chromosomes are small structures that hold our heritable characteristics, called genes. The information carried in the genes is important for our characteristics and controls the development of the organs, e.g. the brain, heart and kidneys. The cells of the body normally contain 46 chromosomes arranged in 23 pairs. In a pair of chromosomes, one comes from the mother and the other from the father. The first 22 pairs of chromosomes are similar in men and women. The 23rd pair is called sex chromosomes. This pair is called XX in women and XY in men.

The chromosomes contain DNA. A gene forms a piece of our DNA. There are about 20,000 genes in each cell. All genes have specific functions, but the functions of all genes are not yet known. We carry the genes with us through life and the information about our genes is therefore different from

most other health information that typically is a snapshot of the present situation. There are changes in the genes of all persons. Sometimes these changes result in disease. A genetic disease occurs if the function of one or more genes is abnormal. The cause can be the gene missing a piece or an alteration of information in the gene. An alteration in a gene, also called a mutation, can be recent or inherited from one or both parents.

Why perform an extensive mapping of the genetic material?
Previously, it was only possible to examine one gene at the time. Therefore, it could take many years to find the genetic cause for a heritable disease or development of cancer. By doing an extensive mapping of the genetic material it is now possible to examine all of the 20,000 human genes all at once. Among other things, this means that it is possible to find the cause of a heritable genetic disorder or development of cancer much earlier that before. The research is expected to provide us with new knowledge and make it possible to target patient treatment for the good of public health. The genetic analyses result in a large amount of surplus information, so called genome data. These genome data will be stored in the study in compliance with the General Data Protection Regulation and the Data Protection Act.

By sequencing the whole genome in this study, we will characterize the changes in the cancer cells characterizing the disease in each patient to better understand the development of the disease and the effect of a possible treatment.

After end of study, genome data will be stored according to the General Data Protection Regulation and the Data Protection Act. In case of new research, we will request the ethics committee for approval.

The whole genome sequencing will be performed in collaboration with the Department for Genomic Medicine at Rigshospitalet. Financial support for this is included in the funding of the study (see item 17 below).

Feedback to you?
This is a research study, not a patient examination. We do not expect that you will benefit personally from the study and therefore will we not give you any feedback concerning results of the genetic test.
From the extensive mapping we might obtain knowledge we did not expect.

There is a very small change that during the subsequent research done on your samples, medical information might emerge that can be of importance to you personally or to your family, in case you are bearer of a genetic heritable disorder. If this situation arises, Rigshospitalet will contact the study doctor keeping the key to the study number and who knows your name. Your treating doctor can then inform you. It may also be necessary to inform your family members if a result can prevent death or serious deterioration of health. In the consent form, it is specified whether you wish or to be informed or not.

15. Information for your GP or specialist

If you have a GP and/or treating specialist, your doctor will inform him or her in writing that you are participating in the research. This is for your own safety. You give your consent to this on the consent form. If you do not give your consent, you cannot participate in the research.

16. Costs

There are no additional costs for you associated with participation in this research. You will receive no compensation for participation in the research and no travel expenses will be covered, except for what is covered as part of the standard of care.

17. Financial conditions

The study is carrried out by (sponsored by) Rigshospitalet in Denmark.
The finanacial sponsors are Novo Nordisk Foundation with DKK 10.5 million for the study and the medical company Acerta Pharma with € 1.19 million for the first part of the study. The medical companies Acerta Pharma and Abbvie provides the study medication. Financial support is given to the participating departments. The Danish research sites will receive a lump sum of € 7,000 and will then receive about € 10,000 per participant, in average. This also covers visits, data collection, tests and procedures.
The investigators in the study will not receive any financial compensation for their participation in the study. The research responsible and the primary investigator have no financial affiliations to the financial sponsors

18. Ethics Committee approval

[insert information about local ethics committee]

19. Additional study information

If you have any additional questions, you can ask your doctor or other doctors at your hospital.

If you have questions before or during the study that you would rather not ask your doctor, you can contact an independent doctor who is not involved in the study.
If you are not satisfied with the study or the treatment, you can submit a complaint.
You will find all the contact details in Appendix 1

When the results of the study, positive, negative or inconclusive, become known, one or more scientific papers and presentations will be published about the study results. You can receive information about the published results at your local hospital.

Informed consent

If you decide to participate in the research, we ask you to sign the consent form (Appendix 5). By signing this informed consent, you agree to participate in this research.
You can decide to stop participating at any time.
Your doctor will also sign the form and thereby confirm that you have been informed about the study, and that you have received this information letter.

Appendices:

1. Contact details
2. Medical research brochure (insert local/national brochure, if relevant)
3. Treatment regimen and schedule of examinations
4. Side effects of acalabrutinib and venetoclax
5. Informed consent

Appendix 1 Contact details

Further information or questions
You can ask questions or obtain further information about the study from the study investigator:

<Name Telephone number>

Or from:

Independent doctor
You can consult the following as an independent doctor:

<Name Telephone number>

Complaints
You can submit a complaint to
<Independent complaints committee or other procedure>

Appendix 2 Medical research brochure

(insert local/national brochure, if relevant)

Appendix 3 Schedule of examinations

	At screening[1]	Cycle 1 day 1 (start of treatment/ observation)	Cycle 1 day 8	Cycle 1 day 15	Cycle 1 day 22	Cycle 2 day 1	Cycle 3 day 1	12 weeks after treatment/ observation start	24 weeks after treatment/ observation start	Every 3 months until 2 years	1 year after treatment/ observation start	2 years after treatment/ observation start	Follow-up every 6 months, until 7 years[2]	On any increase / return of the disease
			Treatment group only											
Visit window			+/-4 days	+/-4 days	+/-4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	
Informed consent	X													
Outpatient check-up	X	X	X	X	X	X	X	X	X	X	X	X		X
Medical history	X	X				X	X	X	X	X	X	X	X	X
Adverse Events[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X				X	X	X	X	X	X	X		X
Blood samples	X	X	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X	X		X
ECG	X													
CT scan	X								X					X
Disease evaluation	X	X				X	X	X	X	X	X	X	X	X
Quality of life questionnaire	X					X	X	X	X	X[5]	X	X		
Pregnancy test	X	X[6]				X[7]	X[7]	X[7]						
Sampling for PreVent-ACaLL biobank														
Blood	X		X[8]	X[8]		X	X	X	X		X	X		X
Flow MRD	X							X	X		X	X		X
Bone marrow	X								X					X
Microbiome samples	X							X	X			X		
Lymph node biopsy														X

[1] Up to 42 days prior to randomization, a max of 14 days from randomization until start of treatment/observation (Cycle 1 day 1)
[2] Registry based or only as data collection at site to assure information about survival status, infections, adverse event and new CLL treatment
[3] Including information about new CLL treatment and all infections
[4] Blood samples will be drawn the day before visit, 6 hours after intake of venetoclax tablets and the day after visit for TLS samples.
[5] Only every 6 months for two years
[6] Seven days before treatment start a negativ pregnancy test must be presented from women of fertile age
[7] Only applies to women of fertile age in the treatment arm
[8] Only in treatment arm

Appendix 4 Side effects

You may have some or no side effects from the treatment. Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

Acalabrutinib
As with any drug, there may be unknown and potentially serious or life-threatening side effects that could occur with Acalabrutinib. The full side-effect profile of Acalabrutinib is not yet known. Side effects can vary from mild to very serious and may vary from person to person.

Serious side effects that may occur with Acalabrutinib include:
Hemorrhage (Bleeding)
Events of bleeding have occurred in subjects treated with Acalabrutinib. These include minor events such as nose bleed, bruising, or ecchymosis (bleeding in skin) and major events which could be fatal such as internal bleeding in the bowel or bleeding in the brain. If you are using any blood thinners (drugs that prevent your blood from clotting e.g. aspirin or warfarin) your risk for bleeding may be increased.

Infections
Infections have been reported to occur in subjects receiving Acalabrutinib. The most commonly reported infections were upper respiratory infection, sinus infection, and pneumonia (lung infection). Infections that are uncommon or rare, but which can result in severe disability or death, have also occurred in subjects receiving Acalabrutinib. These infections include hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML). Reactivation of HBV is where a type of liver virus infection becomes active again if you had a previous infection with that virus. PML is a rare, serious brain infection caused by a virus, usually in subjects with weakened immune systems, and can result in severe disability or death.
Tell your study doctor right away if you experience any symptoms of an infection such as fever, runny nose, sore throat, cough, and feeling tired. If you have previously had HBV or any other viral liver infection, your study doctor may need to monitor you closely.

Cytopenias (Low Blood Cell Counts)
Subjects receiving Acalabrutinib can experience low blood cell counts. Your study doctor will do blood tests while you receive Acalabrutinib to check your blood cell counts, which include:

- White blood cells - cells that fight against infections
- Red blood cells – cells that carry oxygen throughout your body
- Platelets – cells that help your blood to clot

Second Primary Malignancies
The development of a second cancer has been reported to occur in some subjects who receive Acalabrutinib. Majority of these cancers were skin cancers. If you develop a second cancer, you may need to stop the study drug, and your doctor may need to do further tests to diagnose what the cancer is.

Atrial Fibrillation/Atrial Flutter
Atrial fibrillation and atrial flutter are abnormal heart rhythms which have been reported to occur in some subjects who receive Acalabrutinib. Atrial fibrillation or flutter may occur more commonly in subjects with other risk factors for cardiac (heart) disease, such as hypertension (high blood pressure), diabetes mellitus, acute infections, or a previous history of atrial fibrillation. While atrial fibrillation or

flutter often may not cause symptoms, some subjects may experience palpitations (feeling like your heart is beating too hard or too fast), fainting, chest pain, or shortness of breath. If you have any of the symptoms described above, tell your doctor.

Side effects considered to be caused by the Acalabrutinib are provided in the table below.

Very Common (at least 10% of subjects)	Common (at least 1% but less than 10% of subjects)
• Headache • Bruising events (including bruises, petechiae (pinpoint red or purple spots on the skin)), and increased tendency to bruise • Bleeding • Diarrhea (frequent or loose stools) • Nausea • Constipation (bowel movements that are infrequent or hard to pass) • Vomiting • Abdominal pain • Rash	• Nose bleeds • Severe bleeding

Tumor Lysis Syndrome (TLS)

A case of TLS was reported in a subject with chronic lymphocytic leukemia. TLS occurs when a drug kills a large amount of cancer cells at the same time causing the contents of the cancer cells to spill into the blood stream. This can lead to severe organ malfunctions that can be life-threatening if not monitored and treated promptly. If your study doctor deems you are at risk for tumor lysis syndrome, you will be closely monitored during the study.

Unknown/Unexpected Side Effects

In addition to the side effects listed above, there are side effects that are not known or do not happen often when subjects take these study drugs, including severe or life-threatening allergic reactions, or interactions with another medication, including those that are fatal.

There may also be side effects that we cannot predict. Other drugs can give side effects that occur less often and are less uncomfortable. Many side effects go away shortly after the study drug or procedure is stopped, but in some cases side effects can be serious, long lasting or permanent.

For more information about side effects, ask the study doctor and/or the research staff.

Venetoclax

Very common (> 10%)	Common (1-10%)	Rare (0,01-0,1%)
• Anemia • Reduced number of blood cells, low number of platelets • Diarrhoea • Nausea • Cold	• Reduced number of white blood cells, fungal infection • Bacterial skin infection (shingles, a painful skin disease caused by herpes virus), flu, pneumonia or bronchitis, infection in nose or throat • Fungal or virus infection in the mouth or other parts of the body, sepsis, urinary tract infection. • Tumor lysis syndrome (see below), seen only rarely at the dose used in this study.	• Infection • Inflammation in the gastric system, virus, infection. • Lung infection caused by a type of bacteria called pseudomonas.

In some cases, the treatment of your disease (particularly with venetoclax) can cause the tumor cells to be destroyed very rapidly. When your body tries to eliminate these breakdown products, this can have some harmful effects as a result. This is known as tumor lysis syndrome. To minimize the risk of tumor lysis syndrome the following are being done:

- Venetoclax is started at a low dose and increased weekly for the first 5 weeks until the full dose.
- You will receive additional medicines from one day prior to the first dose of venetoclax and at least until the start of the full dose of venetoclax. The treating physician will decide if you will continue the additional medicine until end of study treatment.
- We advise you to drink a lot, at least 2 liters a day during study treatment.

Tumor lysis syndrome can lead to severe problems such as consequences for your kidneys and heart (including an abnormal heart rhythm), or seizures. These side effects can result in you needing renal dialysis (a special machine removes the waste materials from your blood). Your doctor will keep a close eye on you, and treat you with fluids and medicines to reduce the risk of severe laboratory changes, or complications of tumor lysis syndrome.

There is a caution that male fertility may be compromised.

Risk of the study procedures

In addition to the risks of acalabrutinib and venetoclax, the routine punctures for blood samples and bone marrow biopsies can cause pain, bruises and, in rare cases, infection. The CT scans performed as part of the study will expose you to approx.10 mSv per scan. For comparison, the annual natural background radiation exposure (the amount of radiation in the air, etc.) is 4 mSV

Appendix 5

Informed Consent

to participation in a scientific study including extensive mapping of genetic material:

PreVent-AcaLL: Short-term combined acalabrutinib and venetoclax treatment of newly diagnosed patients with CLL at high risk of infection and/or early treatment, who do not fulfil IWCLL treatment criteria for treatment. A randomized study with extensive immune phenotyping.

I sign this consent of free will. I understand that by signing this consent I will not lose any right that I would otherwise be entitled to.

I have read and understood the participant information and have received answers to all my questions. I understand that I will receive a signed and dated copy of this consent. I have had the time needed to familiarize myself with the purposes and procedures, the potential risks and the benefits of the study, and other available treatments for my condition. I agree to cooperate with the medical staff and to take the medicine and follow the treatments according to the instructions.

I have been informed verbally and in writing that this is a research study including extensive mapping of genetic material. I have also been informed that in rare cases, heritable genetic disorders might emerge that might lead to serious disease which can be prevented or treated. In this case I can be informed.

As the study complies with the rules of Good Clinical Practice access to your medical record it is required with the purpose of monitoring, control and inspection (quality control)
___ Yes ___ No

If important information about my health, including heritable genetic disorders, emerges during the trial, I would like to be informed of them
___ Yes ___ No (if you reply ´No` you will receive further information about the right not to know)
[Correct or delete according to local requirement]

When the trial is completed, I would like to see the results of the study and find out what consequences it may have for me.
___ Yes ___ No

_____
Name of participant (printed)

_____
Signature of the participant

_____
Date

The doctor signing below has fully informed this patient about the above-mentioned study.

_____
Name of the doctor informing the patient (printed)

Signature of the doctor informing the patient

_____
Date