BICS
Bisoprolol in COPD Study

Patient information leaflet

A study of the beta-blocker bisoprolol in Chronic Obstructive Pulmonary Disease (COPD).

Bisoprolol in COPD study (BICS).

We would like to invite you to take part in a research study into the treatment of COPD. In this study we are trying to find out if flare-ups of COPD can be prevented by using a tablet called bisoprolol. Bisoprolol is a beta-blocker that has been widely used for a long time to treat heart problems, but it now seems that bisoprolol might also reduce flare ups of COPD regardless of heart problems.

We believe that you might be eligible to take part in this study because you may have had two or more flare ups of your COPD in the last few years.

- Before you decide whether you would like to take part, 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 others if you wish.
- Ask us if there is anything that is not clear or if you would like more information.
- Take time to decide whether you wish to take part. If you are interested in taking part, you can make contact with us (our contact details are at the end of this leaflet).
- Thank you for reading this.

What is the purpose of the study?

COPD is a common lung condition and one of the features of COPD is that it can suddenly get worse. These 'flare ups' are known as exacerbations and are usually treated with antibiotics and steroids. Often flare ups result in people being admitted to hospital.

One of the aims of our research into COPD is to prevent flare ups occurring. Our study is trying to find out if the beta-blocker bisoprolol reduces the number of COPD flare ups. Beta-blockers have been used to treat heart conditions for over 30 years. There is now evidence that people taking beta-blockers who happen to have COPD are less likely to have flare-ups. In our study, we want to investigate whether people with COPD who are started on bisoprolol, are less likely to have flare ups.

In the past, doctors have been reluctant to use beta-blockers in people with COPD because of worries about narrowing the lung airways. The newer more targeted beta blockers such as bisoprolol are now known to be safe in COPD and have been widely used to treat heart conditions in people with COPD.

Why have I been chosen?

We are approaching you because we understand that you have COPD. We are approaching people with COPD who:

- Attend certain General Practices.
- Have been admitted to hospital with COPD.
- Attend chest clinics.
- Have been cared for in the community.
- Have attended pulmonary rehabilitation classes.

We are aiming to recruit 1574 people with COPD who have had two or more flare ups in the last year or so. In order to get 1574 people with COPD, the study is taking place in many hospitals and GP practices across the UK.

Do I have to take part?
No. It is up to you to decide whether to take part. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the NHS care you normally receive.

What will happen to me if I take part?
To find out if bisoprolol reduces the number of flare ups we are comparing the effects of bisoprolol against the effects of a placebo 'dummy treatment', which looks like the genuine medicine but contains no active ingredient.

To try to make sure the bisoprolol and placebo groups are the same to start with, each person is put into a group selected by chance (randomly by a computer). Half of the 1574 people will take bisoprolol and half will take the placebo for a year (as well as your usual medicines). To make sure that the true effects of bisoprolol are being studied neither you nor your doctor will know which treatment group you are in (although, if your doctor needs to find out he/she can do so).

To work out the best dose of bisoprolol (and placebo) for you we will slowly build up the dose over the first few weeks whilst checking each week how you feel, how your breathing is, and what your pulse and blood pressure is. You can read more about this below. This slow increase in dose is routine for beta blockers such as bisoprolol and ensures safety.

If you are interested in taking part, we will make an appointment to discuss the study with you at a time convenient to you.

The first appointment will take up to an hour. It can be done as a face-to-face appointment at your local GP practice or local hospital, or it can be done by telephone or video call.

During the appointment we will ask you:

- To sign a consent form saying that you are willing to take part in the study.
- To answer some questions about how COPD is affecting your life.
- To let us know what medicines and inhalers you are taking.
- If you come to a face-to-face appointment, we will check your pulse (at wrist) & blood pressure (inflatable cuff around arm). We will also give you a machine that measures pulse and blood pressure and show you how to use this. You can then take this home with you so that you can measure your pulse and blood pressure at home before your next appointment.
- If your first appointment is by telephone, we will send you a pulse and blood pressure monitor before the appointment so that you can measure your pulse and blood pressure during the appointment. This will come with instructions and we can tell you how to use it.

We will ask you to continue taking all of your usual medicines and tablets and if you have a flare up/ exacerbation of your COPD needing treatment that you make a note of the dates and treatment. You will be able to write these details down in a 'flare up/exacerbation' diary.

We will ask you to take one study tablet once a day until we speak to you again about one week later. There is a 50:50 chance that you will be taking bisoprolol or placebo 'dummy treatment.' It is important to realise that no immediate improvement in daily symptoms is likely to occur. Any improvement is likely to be in a reduction in the number of exacerbations.

After this appointment, we will arrange for about 2 months supply of study tablets to be delivered to your house by courier.

We will give you a card to carry that explains that you are taking part in a study. You can show this card to any doctor or nurse that is treating you.

<u>At the second appointment 1-2 weeks later</u>, we will ask you:

- How you are feeling.
- If your breathing has changed.
- To check your pulse and blood pressure using the monitor we gave you.

Depending how you are feeling and on your breathing, pulse and blood pressure, we may ask you to take two study tablets once a day until we speak to you again about a week later.

The second, third, fourth and fifth appointments will take less than 30 minutes. It may not be necessary to have all these appointments.

At the third appointment 1-2 weeks later, we will ask you:

- How you are feeling.
- If your breathing has changed.
- To check your pulse and blood pressure using the monitor we gave you.

Depending how you are feeling, and, on your breathing, pulse and blood pressure, we may ask you to take three study tablets once a day until we speak to you again about a week later.

At the fourth appointment 1-2 weeks later, we will ask you:

- How you are feeling.
- If your breathing has changed.
- To check your pulse and blood pressure using the monitor we gave you.

Depending how you are feeling, and, on your breathing, pulse and blood pressure, we may ask you to take four study tablets once a day until we speak to you again about a week later.

At the fifth appointment 1-2 weeks later, we will ask you:

- How you are feeling.
- If your breathing has changed
- To check your pulse and blood pressure using the monitor we gave you.

Depending how you are feeling and, on your breathing, pulse and blood pressure, we will either ask you to keep taking four study tablets once a day for a year or to reduce the dose of study tablets for a year.

If, during the slow increase in dose over the second to fifth appointments, you start to have side effects then we will reduce the daily dose of tablets and you will remain on the reduced dose for a year.

If during the slow increase in dose you feel well but there are changes in breathing, pulse or blood pressure we will not increase the dose further and you will stay on this dose for a year. You can contact the study team at any time if you have questions about your dose of study tablets.

After 2 months and again after 5 months of treatment you will receive further supplies of study tablets delivered to your house by courier.

After 6 months of treatment we will arrange a telephone or video call at a time convenient to you and ask you:

- how you are getting on with the tablets.
- if you have had any flare ups of your COPD.
- how COPD is affecting your life.
- what medicines and inhalers you are taking.
- To check your pulse and blood pressure using the monitor we gave you.
  This appointment will take about an hour.

After 12 months of treatment we will arrange a telephone or video call at a time convenient to you and ask you:

- how you are getting on with the tablets.
- if you have had any flare ups of your COPD.
- how COPD is affecting your life.
- what medicines and inhalers you are taking.
- To check your pulse and blood pressure using the monitor we gave you.
  This appointment will take about an hour.

We will also tell you how to slowly reduce the dose of study tablets over the next 3 weeks by one tablet a week until you are taking no study tablets at all. Your research nurse will make contact to make sure you have successfully stopped the study tablets.

At the end of the study, we will ask you to take any unused study tablets to your local pharmacy and asking them if they can dispose of them safely.

Expenses and payments

If your first appointment is face-to-face, you can receive travel expenses to attend your local study centre. Please ask your research nurse for information about how to claim travel expenses.

What will I have to do?

We ask that you:

- Take the study tablet(s) once a day as directed, for a year.
- Participate in up to seven study appointments (first appointment, and then at about 1 week, 2 weeks, 3 weeks, 4 weeks, 6 months, and at 12 months) – most, if not all the appointments will be by telephone or video call.
- Make a record of any flare ups of your COPD whilst on the study tablets.
- Carry a card explaining you are in the study.
- Do not stop the study drug suddenly. People who stop the study drug suddenly can experience a reaction to this. If you do wish to stop, please contact your research nurse who can advise you how to stop more slowly.

Otherwise you should continue on your normal medicines and inhalers and carry on as normal. If you need to go to

your GP for treatment you should go, any flare ups/exacerbations of your COPD can be treated as they normally would.

What is the drug that is being tested?
The drug being tested is bisoprolol. Bisoprolol is licensed for people with COPD and heart disease but not for people who have COPD without heart disease. The maximum dose of bisoprolol in this study (5mg a day) is less than the dose usually used to treat heart conditions (10mg a day).

There are some drugs used mainly to treat heart conditions that are known to interact with bisoprolol.

Although we are obliged to tell you about this, you do not need to remember them because:

- We would check whether you are already taking any of these drugs.
- We would let your GP know that you are in the study, which drugs to avoid and what to do if (s)he wants to put you on one of these drugs.
- We would give you a small card to show to nurses or doctors, this will direct them to a list of the drugs to avoid and tell them what to do if they want to put you on one of these drugs.
- If your doctor wants to start you on one of these drugs, then they will tell you to stop taking the study tablets whilst on these drugs. This may mean that you have to stop taking the study tablets permanently.

For reference, the list of drugs to avoid is:

- *Blood pressure/angina tablets called calcium antagonists*; verapamil and diltiazem.
- *Angina tablet*: Ivabradine.

- *Heart rhythm drugs*: quinidine, disopyramide; phenytoin; flecainide, propafenone.
- *Certain blood pressure tablets*: clonidine, methyldopa, moxonodine, rilmenidine.

What are the side effects of any treatment received when taking part?

Although most people tolerate bisoprolol well, some people can develop side effects. *We hope to reduce these by slowly increasing the dose of study tablets at the start of the study to find the best dose for you.* If side effects do develop then they should stop when the dose of study tablets is reduced or stopped.

Side effects of bisoprolol

Common (affect between 1 in 10 to 1 in 100 people)
Dizziness, headache, nausea, vomiting, diarrhoea, constipation, cold hands & feet, tiredness.

Uncommon (affect between 1 in 100 to 1 in 1000 people)
Breathlessness, muscle weakness & cramps, unsettled sleep, low mood.

Rare (affect between 1 in 1000 to 1 in 10,000 people)
Blackouts, congested nose, nightmares, hallucinations, dry eyes, reduced hearing, itchy rash, inflamed liver, erectile dysfunction.

Very rare (affect less than 1 in 10,000 people)
conjunctivitis, psoriasis, hair loss.

If you decide to take part in our study, we will give you another information leaflet with your medicine that will tell you more about the study tablets, how to take them, and the

possible side effects. Please read all the information contained in this leaflet.

If you feel unwell at any point, please seek medical help as you would do usually. If you are concerned that you may have developed side effects, you should contact your local study centre, or your GP and they will provide help and advice.

What are the possible disadvantages of taking part?
Other than the potential side effects described above, we do not think there are other risks associated with taking part in BICS. Taking part may affect your travel insurance or private health insurance – there is more information about this below. The study involves extra appointments as described in the section "What will happen to me if I take part?", but most (if not all) of these can be done by telephone or video call.

What are the possible benefits of taking part?
We cannot promise the study will help you but we expect the information we get from this study will help improve the treatment of people with COPD, reduce the need for antibiotics and steroids and reduce hospital admissions for COPD.

We will investigate whether bisoprolol reduces the number of flare ups in people with COPD, and if it does, whether it reduces the need for antibiotics and steroids and reduce hospital admissions for COPD.

Travel and private health insurance

Taking part in a clinical research study such as BICS may affect any travel insurance or private health insurance cover you have. If your insurer asks you, you need to tell them that you are taking part in a clinical trial. You must answer all their questions as fully and accurately as you can. If you do not, your insurer may refuse to pay any claims and could cancel your policy. We can provide more information to your insurer.

What happens when the research study stops?

When you have stopped the study tablets in the weeks after the 12-month appointment, we will not give you any more study tablets. We would not advise taking bisoprolol for your COPD until we know whether bisoprolol makes a difference in COPD. We will know this in 2023 when the study has finished. If, at the end of your 12 months in the study, you feel that the study tablets have improved your COPD we can let your GP know and advise that the dose of bisoprolol would need to be slowly increased. You would need to discuss this with your GP though.

Involvement of the General Practitioner (GP)

We will ask your permission to let your GP know that you are taking part in the study. At the end of the study, again with your permission, we may ask your GP if we can look at your GP records to count up the number of times you have visited your GP and the number of flare ups you have had whilst on the year of study treatment.

What if relevant new information becomes available?
If we get any important new information about the use of bisoprolol in people with COPD, your local study team will tell you and discuss with you whether you should continue in the study. If you decide not to carry on, arrangements will be made for your usual NHS care to continue. This may be with your GP or may be with the chest clinic at the hospital. If you decide to continue in the study, you may be asked to sign an updated consent form.

What will happen if I don't want to carry on with the study?
You are still free to withdraw at any time and without giving a reason and this will not affect the NHS care you normally receive. Study information collected up to that point may still be used.

If you do wish to stop the study tablets, please contact your local study team and they will advise on how to reduce the dose safely to zero. We will ask you to take any unused study tablets to your local pharmacy and asking them if they can dispose of them safely.

If you stop taking the study tablets you can still have the study appointments at 6 and 12 months.

What if there is a problem?
If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek compensation through the research sponsors of the study - the University of Aberdeen and NHS Grampian. Contact details for both research sponsors are available through the research team.

As a patient of the NHS if you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

If you have a concern about any aspect of this study, you should ask to speak to the study doctors who will answer your questions (contact details are at the end of this information leaflet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints mechanisms (or Private Institution). Contact details can be obtained from your local hospital. In addition to this, you may contact the chairman of the BICS Trial Steering Committee (who is independent from the study) through the BICS study office.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information which is collected about you during the research will be kept strictly confidential and will be held securely for 25 years in accordance with the latest Data Protection legislation.

The University of Aberdeen will be the data controller for this study and is responsible for looking after your information and using it properly. You can find more about this at www.abdn.ac.uk/privacy.

The local research team at the hospital or GP practice that you were recruited in will have access to your information. They will use your name and contact details to contact you about the study, to make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

The study is being co-ordinated by the Centre for Healthcare Randomised Trials (CHaRT), a registered clinical trials unit at the University of Aberdeen. The study team in CHaRT will have access to your information and will keep this confidential. They will have access to your information to contact you about the study and for quality control purposes.

We will ask you to give us the name and address of someone that you know who we can contact if we cannot get in touch with you. This might be a family member, friend or neighbour. Again, with your permission, we will tell this person that you are taking part in the study.

With your permission we will need to pass on your name and address to Clinical Trials Pharmacy who will organise the study tablets for you and the courier company who will deliver the study tablets to your home. These details will be kept strictly confidential and be used only to send you the tablets.

We will keep the study data for at least 25 years. It will be kept confidential at all times.

The statistical analysis of the study is being conducted at the University of Aberdeen, and to maintain confidentiality, the statistical team will only analyse completely anonymous data. (Anonymous data does not include names or addresses, and it is not possible to identify individual participants from anonymous data). Any reports or publications arising from the study will contain totally anonymous data so that you cannot be recognised from it.

Other researchers may wish to access anonymous data from this study in the future. If this is the case, they would be expected to follow legal, data protection and ethical guidelines. It will not be possible to identify you from this data.

If you join the study, the data collected for the study, together with any relevant medical records, may be looked at by authorised persons from the University of Aberdeen, the Research and Development Department of your local NHS Organisation and the Regulatory Authorities to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant.

We will ask you whether you would like to be approached about other research studies. If you agree to this, we would not share your name or address with the researchers who are running these studies. Instead, a member of the BICS research team would tell you about the other study and give you details of how to contact the study team if you wanted to take part. If you do not want to be approached about other research studies, please tell us.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate.

What will happen to the results of the research study?
The results of the study will be published in scientific journals and presented at scientific meetings. In addition, with the help of the British Lung Foundation and Chest Heart & Stroke Scotland we will pass on the results to other people with chest disease. It will not be possible to identify you from the results of the study. We will also send you a summary of the results. This will be when all the people taking part in the study have completed their follow-up in the study (this may be later than when you would finish your follow-up in the study) and all the information collected in the study has been analysed. When we send you the results of the study, we can let you know whether you were taking the beta-blocker tablets or the placebo tablets. But we will not tell you this at the end of your follow-up unless you or your doctor need to know this information to plan future treatment.

Who is organising and funding the research?
This study is being organised by the University of Aberdeen and chest doctors in Aberdeen, Birmingham, Dundee, Edinburgh, Glasgow, Hull, Liverpool, London, Manchester, Newcastle, and Norwich. The research is being funded by the National Institute for Health Research, Health Technology Assessment programme: NIHR-HTA.

The study is being co-ordinated by the Centre for Healthcare Randomised Trials (CHaRT), a registered clinical trials unit at the University of Aberdeen.

Who has reviewed the study?

The study has been reviewed by an NHS Research Ethics Committee, which has responsibility for scrutinising proposals for medical research on humans. In this case, the reviewing committee was Scotland A REC, who have raised no objections to the study.

In addition, the study has also been reviewed and approved by the Medicines and Healthcare Products Regulatory Agency. The Research and Development Department of your local hospital and/or local primary care organisation has also reviewed and approved the study.

Contact for further information

If you have any questions or would like more information, please contact us. Our contact details are below.

If you are interested in taking part in this research, please let us know. You can telephone us, email us, or use the reply slip and freepost envelope. Our contact details are below.

<<insert local contact details>>

Thank you for taking the time to read this information leaflet. We hope that you have found it useful in deciding whether or not to take part in the BICS study.