A randomised, double-blind, placebo-controlled, phase II clinical trial with a cross-over design assessing efficacy of a single dose of bumetamide in reducing focal attack severity in hypokalaemic periodic paralysis assessed using the McManis protocol.

Final Version 2

July 4, 2014

Thank you for reading this.
We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. We’d suggest this should take about 15 minutes. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Feel free to ask any questions if there is something that is not clear. Take your time to decide whether or not you wish to take part.

1. **What is the purpose of the study?**

Hypokalaemic periodic paralysis (HypoPP) is a very rare disorder and there is very little knowledge about the best way to treat patients’ attacks of weakness. The only treatment available at the moment for treating an acute attack is to administer potassium and so it is important to discover other effective medicines.

Bumetanide is a diuretic (a drug that increases the production of urine) also called a water tablet, and is normally used to treat high blood pressure and heart failure. It has therefore already been shown to be a safe drug in treating other diseases. This drug acts on an ion channel which can be found in your muscle. Ion channels are small pores controlling the passage of electrically charged particles. This ion channel may be important in contributing to attacks of weakness in HypoPP.

Bumetanide has been shown to stop attacks of weakness and increase muscle strength in mice with HypoPP. In these tests it was shown that bumetanide was even more effective than acetazolamide (Diamox). We therefore think it may be helpful in treating attacks of weakness in patients with HypoPP. However, so far no clinical studies have been done with bumetanide in patients with HypoPP to see if it reduces attacks.

The purpose of this research study is to see whether bumetanide has the potential as a drug treatment for acute attacks of weakness in patients with HypoPP. This study is part of a PhD student research. It will be performed by the MRC Centre for Neuromuscular Diseases. All participants will receive 2mg of bumetanide or a capsule of placebo (an inactive medication) during the neurophysiology exercise test (McManis test) to see if it reduces the severity and length of a localised attack in a small hand muscle.

2. **Why have I been invited?**
You are being asked to participate in this study because you have the rare muscle disorder, hypokalaemia periodic paralysis (HypoPP) and have regular attacks of weakness. It is estimated that 12 participants with HypoPP will take part in this study. All participants will come from the UK.

3. **Do I have to take part?**

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time without giving a reason. This would not affect the standard of care you receive.

4. **What will happen to me if I take part?**

The study will last from 2 to 5 months depending on your availability and how well you are. Overall the research study will last 1 year. The study will involve a screening visit with a member of the research team, two admissions for one day, two telephone calls before each admission, a monitoring phone call during the study and a follow up phone call at the end of the study.

Your first visit is called a screening visit. You will be asked to come to the National Hospital for Neurology and Neurosurgery for evaluation and investigations before the start of the study. This will be to ensure that it is safe for you to take part in the study and will last for approximately 2 hours. If you are eligible to proceed in the study you will be asked to make two further visits to the hospital: two admissions lasting one day each. These visits are for research purposes only and are not necessary to treat your disease. We will phone you the day before each of the admissions. If you have an attack at that time or have not fully recovered from a recent attack we will postpone the admission to a later date. You will also have a follow up phone call between your admissions to check how you are, and a follow up call at the end of the study. You may have a third visit if necessary.

At your screening visit, prior to the trial commencing, details of the trial will be discussed with you and you will have the opportunity to ask as many questions as you like. You will be asked questions about your medical background (any illnesses you have or have had). A blood sample will be taken to check your electrolyte levels (salt levels). If you are a woman of child bearing age you will be asked for a urine sample to perform a pregnancy test and you will be asked to practise an acceptable method of birth control for the duration of the trial. An electrocardiogram (ECG) will also be taken; this is a recording of your heart rhythm.

If you proceed in the study you will have two day-care admissions at the National Hospital for Neurology and Neurosurgery (NHNN). Each admission will last approximately 6 hours. During each admission, we will perform the McManis exercise test (neurophysiology evaluation). We will test a small
muscle in your non-dominant hand (i.e. if you are right-handed we will test your left hand). You will be asked to contract this muscle as strongly as possible for 5 minutes with brief (3-4 seconds) rest periods every 15 seconds. You will be asked to relax your hand completely for the next 4-5 hours. During this period, the response of your hand muscle to an electrical stimulus will be assessed on a regular basis. Once the muscle response has become significantly reduced (as commonly seen in HypoPP), we will give you either the drug or the placebo (similar capsule but with no action).

We will in addition infrequently check the response to an electrical stimulus in a hand muscle in the other (non-exercised) hand (in total 6 times during the admission). This will help us to identify a major attack of weakness at an early stage.

You will also be monitored with blood samples. Your potassium levels will be checked through blood samples drawn via a cannula (see below). You will be discharged approximately 4 hours after taking the treatment. There will be a 2-8 week gap between your first and second admission to ensure you are fully recovered.

Your 2\textsuperscript{nd} admission will be identical to your first admission except that you will receive the capsule that you did not get the first time (either bumetanide or placebo). This is so that we can compare how bad the attack of weakness in your hand is when you are on bumetanide and placebo. Neither you nor the research doctor will know which medication you are receiving at each admission during the study.

During the admissions you will have:

- **History and Examination**: A study doctor will perform a physical exam including vital signs (blood pressure, pulse, height, weight). Your medications will be reviewed.

- **Muscle Strength Measurement**: A doctor will test the strength in your arms and legs to test how strong they are.

- **Intravenous Cannulation**: An intravenous cannula will be placed during each admission. This is a tube that is placed inside a vein in your arm. It will facilitate blood collection. It is also a safety measure as it may be used to give you treatment if needed. The cannula will be placed and removed during each admission.

- **Blood Tests**: All blood test sampling will be done via the cannula placed at the beginning of each admission. You will have a small amount of blood taken (approx. 30ml in total during each admission, which is equivalent to six teaspoons) to measure the levels of electrolytes levels (salt levels, in particular potassium levels) and kidney function. Samples will be taken at the beginning and at the end of each admission as well as six times during the assessment.
Urine pregnancy testing (women of child-bearing potential): During the screening visit and during both admissions, you will need to provide a urine sample to confirm that you are not pregnant if you are a woman. If the urine test is not conclusive, you will also need to have a blood test to confirm the result.

**Home Diary:** Participants will be asked to keep a home diary to record food intake, exercise and rest periods 24 hours before the first admission and will be encouraged to adhere to a similar pattern at the second visit.

**Adverse Events Diary:** Participants will be asked to keep a home diary to record any adverse events they experience.

**Studies of Nerve, Muscle, and Heart Electrical Activity:**

**Nerve conduction studies:** Responses of muscle to electrical stimulation of nerves are routinely used to diagnose muscle and nerve conditions. These studies will be done to determine how your muscles respond to stimulation of their nerves during an attack. Two electrodes will be taped to the skin of the hand for the nerve tested. Several small electrical pulses will be given to the nerve at the wrist (similar sensation to touching metal after walking on a carpet). Your hand will twitch in response to the stimulation. This may cause some mild discomfort.

**Electrocardiogram (ECG):** This test determines your heart rate and rhythm. You will be asked to expose your chest and electrodes will be taped onto your chest, wrists and feet. These will record your heart activity. This test takes approximately 10 minutes. An ECG will be performed during the screening visit and may be repeated during the admissions in the event of any adverse effects.

**Cross-over trial** – In a ‘cross-over trial’ the groups each have the different treatments in turn. There may be a break between treatments so that the first drugs are cleared from your body before you start the new treatment. In this study you will have a break between the two admissions to allow the drugs to clear and you to recover from your attack before you start the second treatment.

**Randomised Trial** – Sometimes we don’t know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each participant is put into a group by chance (randomly). Because this is a cross-over study you will be randomly given one drug in the first admission and given the other drug at your second admission.

**Blind trial** – In a ‘double blind trial’, neither you nor your doctor will know in which treatment group you are (although, if your doctor needs to find out he/she can do so).
Placebo – A placebo is a dummy treatment such as a pill, which looks like the real thing but is not. It contains no active ingredient.

5. Expenses and payments

You will not receive any payments for your participation in this study but study-related travel expenses such as parking, car fuel and public transport costs to the hospital will be reimbursed. If you live far away from the NHNN, you can stay in a hotel in London the night before each admission. This expense will also be paid.

6. What will I have to do?

If you decide to take part, you will be asked to discontinue carbonic anhydrase inhibitors (e.g. acetazolamide, dichlorphenamide) 72 hours prior to each admission. You will also be advised to stop any non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for 72 hours before the admission as these may interfere with the action of bumetanide. These can be recommenced the day after admission. If you routinely take oral potassium and potassium sparing diuretics you will be allowed to continue this throughout the trial. You will also be asked to fill a home diary 24 hours before the first admission. You will be encouraged to follow the same pattern of activity and food intake previously recorded at your home diary before the second admission.

You will be restarted on your regular treatment for HypoPP at the end of each admission.

During each admission, you will receive bumetanide or placebo. You will not need to take these medications in between your admissions.

If you choose to participate, it is essential that you keep all scheduled appointments and admissions and that you follow all instructions during the visits. Additionally, you will be expected to report any side effects to the researcher as soon as possible after they occur, whether you are in hospital or at home.

We will contact you by phone the day before each day-care admission. If you have any symptoms of an acute attack of weakness the day before or on the day of your admission or if you have not fully recovered from a recent attack, your admission will be postponed and rebooked.

At each admission we will check your potassium in your blood and if the level is low (lower than 3.5mEq/L) your admission will be postponed and rebooked.

At each admission you will have a medical assessment to ensure that it is safe for you to proceed with the trial. If there is any medical concern we may need to postpone the admission.

7. What are the alternatives for diagnosis or treatment?
The current treatment for attacks of weakness in HypoPP is potassium either given as a tablet or in severe attacks given via an infusion. There are no other current treatments for acute attacks in this disease.

8. **What are the possible disadvantages and risks of taking part?**

During the insertion of a cannula, you may experience pain and/or bruising at the site on your arm where blood is taken. Localised clot formation and infections may occur, but this is rare. Fainting may occur rarely during or shortly after having blood taken. If you experience faintness, you should lie down immediately to avoid possible injuries and then notify study personnel.

During the studies of muscle and nerve, the electrical stimulation may cause brief discomfort or pain (similar to hitting your “funny bone” or snapping a rubber band against your skin). You may have mild skin irritation from the adhesive tape used to fix the electrodes to the skin of your hands for these tests.

You may experience a transient increase in your symptoms when you are asked to discontinue any medication that you currently take for HypoPP.

Before participating you should consider if this will affect any insurance you have and seek advice if necessary.

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

Participants will receive a single dose of bumetanide in a low dose (2mg). This drug is commonly used to treat heart failure and therefore many studies have been done to look at its safety. These studies showed that side effects during treatment with bumetanide are mild and usually associated with higher doses or prolonged treatment.

You should be aware of side effects that have been reported in association with different doses of Bumetanide. The commonest side effects reported in association with Bumetanide 1mg use are:

**Kidney and Bladder:** Increased production and passage of urine. Uncommon: kidney problems.
**Blood Pressure:** Low blood pressure (worsening when standing).
**Neurological Problems:** Dizziness / lightheadedness, vertigo (a sensation that you, or the environment around you, are moving or spinning), fatigue / tiredness and headache. Uncommon: fainting.
**Stomach / Bowels:** Stomach pain and/or discomfort and nausea. Uncommon: occasionally patients may develop vomiting, watery stools, constipation (not passing stools) or dry mouth and thirst.

**Nutrition:** Fluid and salt level imbalance (low potassium blood levels, high potassium blood levels, low sodium blood levels, low chloride blood levels). Uncommon: it may cause dehydration (when your body loses more fluid than you take in), abnormal sugar levels and gout (a type of joint inflammation that causes joint pain).

**Muscles:** Muscle contracture, pain and muscle pain.

Some rare side effects reported in association with Bumetanide 1mg use are:

**Blood:** Rarely patients may develop problems with their white or red blood cells and decreased number of platelets.

**Skin:** Occasionally patients may develop a rash or itching which can persist for few days.

**Breathing:** Occasionally patients may develop a cough or difficulties breathing.

**General:** Hearing disturbance is rare and reversible.

You will be asked to document and inform us of any side-effects or concerns you develop during the study. The side-effects will be addressed at each of the visits during the trial or the follow up phone call between admissions and at the end of the study. If any side effects occur between visits, you are also asked to contact us. During working hours you can contact the clinical trials co-ordinator, Gisela Barreto on 02073806851 or the trial researcher, Dr Renata Scalco on 02034484391. If you decide to participate in this research, you will receive a Participant Study Card with information regarding emergency situations and contact number for telephone calls outside working hours.

**Harm to the unborn child: therapeutic studies**

It is possible that if the treatment is given to a pregnant woman it will harm the unborn or breastfed child. **Pregnant women, women who plan to become pregnant during the study and breastfeeding women must therefore not take part in this study.**

Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive method during the course of this study.

Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor. Any pregnancy that occurs during the trial will be followed up by the study doctors in addition to your local obstetric care until the baby is born. **You will not be able to enter this study if you are already pregnant.**

If you have not been surgically sterilised, or have not undergone menopause in the last year, you must practice an acceptable method of birth control for
the duration of the trial. If you are a male participant, you and your partner must practice an acceptable method of birth control. Acceptable methods of birth control are:

1. Established use of oral, injected or implanted hormonal methods of contraception (pill, patch, ring, implant, injection).

2. Placement of an intrauterine device (IUD) or intrauterine system (IUS) often referred to as a coil.

3. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

10. **What are the possible benefits of taking part?**

We cannot promise the study will help you but the information we get from this study may help improve the treatment of patients with HypoPP.

The optimal treatment for attacks of weakness in HypoPP is not known. This study may provide information that supports bumetanide as an optional treatment that could be used to treat patients with HypoPP worldwide.

11. **What happens when the research study stops?**

At the end of the study period we will not recommend continuing the prescription of Bumetanide. Even if the study proves that Bumetanide can improve your symptoms, we still need to wait for a larger study to be performed before having Bumetanide as a treatment option for HypoPP.

Bumetanide is currently not a licensed medication for HypoPP in the UK, although it is licensed for the treatment of high blood pressure and heart failure. If analysis of the trial results suggest that bumetanide is effective, these results would be used to justify performing further clinical trials required to make bumetanide a licensed medication for the treatment of attacks in HypoPP. You may be invited to participate in further studies of Bumetanide. In this specific case, you may receive the treatment in a clinical research setting.

You will revert to your usual clinical care following the end of the trial.

12. **What if there is a problem?**

Any complaint about the way you have been dealt with during the clinical trial or any possible harm you might suffer will be addressed. The detailed information concerning this is given in Part 2 of this information sheet. If you have any concerns or complaints you should contact your study doctor in the first instance.
13. **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. The details are included in Part 2.

14. **Contact Details**

**Your Doctor**

Name: Dr Doreen Fialho  
Tel. Number: 0845155 5000 ext 83114  Fax 02077137743

**Your Research Fellow**

Name: Dr Renata S. Scalco  
Tel. Number: 0203 448 4391

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

**Part 2**

15. **What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this happens, we will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study we will ask you to sign an updated consent form.

16. **What will happen if I don’t want to carry on with the study?**

You can withdraw from treatment at any time but we would ask that you keep in contact with us to let us know about your progress. We may ask you to come in for a follow up visit if it is in your best interest for your clinical care. Information collected during the trial may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.
You are free to decline to participate or to withdraw without needing to give a reason and with no effect on the standard of care you receive.

17. What if there is a problem?

If you have concerns about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Dr Renata Scalco Tel: 020 3448 4391). If you remain unhappy and wish to complain formally, you can contact the UCLH Patient Advice and Liaison Service (PALS) in person between 9.00 and 16.00 Monday to Friday (excluding public holidays) at the PALS Office, Ground Floor Atrium, University College Hospital, 235 Euston Road, London, NW1 2BU or by telephone. From within the hospital dial extension 73018 or 73002, from outside the hospital ring the direct line 02034473011 or email PALS@uclh.nhs.uk Jacintha.crudden@uclh.nhs.uk.

Every care will be taken in the course of this clinical trial. However in the unlikely event that you are injured by taking part, compensation may be available.

If you suspect that the injury is the result of the Sponsor’s (University College London) or the hospital’s negligence then you may be able to claim compensation. After discussing with your study doctor, please make the claim in writing to Dr Doreen Fialho who is the Chief Investigator for the clinical trial and is based at UCLH. The Chief Investigator will then pass the claim to the Sponsor’s Insurers, via the Sponsor’s office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your study doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal National Health Service complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website: http://www.dh.gov.uk.

18. Will my taking part in this study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at
the National Hospital for Neurology and Neurosurgery under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the Sponsor (UCL), who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised.

Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Sponsor, which is the organization responsible for ensuring that the study is carried out correctly. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority (the Medicines and Healthcare Products Regulatory Authority); this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis.

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 20 years. Arrangements for confidential destruction will then be made.

19. Will my GP be informed of my involvement?

With your permission, your GP, and other doctors who may be treating you, will be notified that you are taking part in this study. Information, for instance the results of any tests, may be exchanged if necessary.

20. What will happen to any samples I give?

Blood samples will be taken specifically to assess your eligibility and treatment during this study. They will be processed routinely with all NHS samples. No samples will be stored outside of the standard procedures used for samples collected as part of routine clinical practice. No samples will be used or stored for future research.

21. Will any genetic tests be done?

No genetic tests will be done as part of this study
22. What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the participants involved in the trial will be identified in any report or publication.

The data may also be evaluated by a specialised commission as part of the Good Clinical Practice. The audit process is performed to make sure the research was performed properly according to standardised parameters.

Should you wish to see the results, or the publication, please ask your study doctor.

23. Who is organizing and funding the research?

This study is being funded by Clinical Research and Development Committee Research Funding from the UCLH Charities - Fast Track Grant.

The study is sponsored by University College London.

The study investigators have no financial relationships with the regulatory authorities, other than the funds that they receive for carrying out research.

24. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called Research Ethics Committee, to protect your interests. This study has been reviewed by UCLH Research Ethics Committee based at the Directorate of Research and Development at the University College London Hospitals NHS Trust.

25. Further information and contact details

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the drug(s)/procedure(s) involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor. If you require any further information or have any concerns while taking part in the study please contact one of the following people:

Your Doctor

Name Dr Doreen Fialho Tel. Number: 0845155 5000 ext 83114

Your Research Fellow / PhD Student

Name Dr Renata S. Scalco Tel. Number: 020 3448 4391
If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure. Thank you for taking the time to read this information sheet and to consider this study.