PARTICIPANT INFORMATION SHEET

Can a ketone drink (ΔG®) alleviate the symptoms of Parkinson's disease?

You (and possibly a care partner) are being invited to take part in a research study as you have expressed an interest in doing so. Before you decide to participate, it is very important for you to understand why the research is being done and what it will involve. You can decline to participate in this study at any point.

Please take time to read the following information carefully.

This participant information leaflet is split into two parts:

Part 1

Describes the purpose of this study and what will happen to you if you decide to take part.

Part 2

Has more detailed information about how we will conduct the study.

Please make sure you ask us if there is anything that is not clear or if you would like more information.

Part 1

The purpose of the study and what will happen to you if you take part.

1. Why have I been invited?

You have been identified as an indivudal who may meet the eligability criteria for our study. We hope that you will consider participating in our study and, thereby, make a contribution to the advancement of Parkinson's research.

2. What is the purpose of the study?

To investigate the hypothesis ketone bodies may improve the symptoms of Parkinson's.

3. Do I have to take part?

No, it is up to you to decide whether to take part. If you do, you will be given this information sheet to keep and will be asked to sign a consent form. You are free to withdraw at any time without giving a reason. A decision to withdraw, or a decision not to take part, will not affect the standard of any medical care that you may need in the future.

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

Your participation in this study would involve fortnightly visits over the course of 2 months to the John Radcliffe Hospital. Visits may also occur at the Sherrington Building of the Department of Physiology, Anatomy and Genetics at Oxford University, or your own home. Each visit will likely last 1-2 hours but can last longer under special circumstances.

During the first visit we will ask you some questions to check whether you are eligible for the study and, if you agree to participate, we will ask you to sign a consent form and randomly assign you to either the experimental/ketone group or the placebo control group (see more below).

The first 2 weeks of the study will constitute a baseline period. The following 4 weeks constitute the actual intervention. During the intervention, you will be asked to ingest your respective drink (ketone or control) 4 times daily. You will also be asked to come in for a follow-up assessment 2 weeks after the conclusion of the intervention.

At each fortnightly visit (excluding the enrollment visit) you will undergo a series of noninvasive motor and nonmotor tests and be asked to provide blood samples. The motor and nonmotor tests include minimally burdensome easy-to-perform tasks such as standing, walking, smelling, reading, naming colors, and filling out brief questionnaires. We will take blood samples through a small needle inserted into one of your arms to measure levels of various metabolites.

5. What else do I have to do?

Apart from the tests described above, you will be asked to wear a small no-maintenance continuous activity monitor on your lower back for 7 days before and 7 days during the intervention. You will also be asked to use a 7-minute smartphone app 4 times every day throughout the trial. To assess compliance, we will ask you to record each time you consume a study drink in a diary. We will also

call you once per week at random to ask you when you last consumed a study drink, to ask you about your energy level, and request that you measure you ketones by urine stick. We will provide a smartphone preloaded with the app and a ketone monitor and show you how to use both.

6. If my partner/carer is involved what will s/he have to do?

During the visits that occur at the beginning and end the of the intervention period (second and fourth visits) your partner/carer will be asked to fill out two questionnaires. (1) The first questionnaire is used to assess whether you may have a sleep disorder. You and your partner/carer will fill this out together as s/he may be able to provide information about which you are unaware, such as if you occasionally act out your dreams. This information will be used to categorize your data into a subgroup for the purposes of some of our analyses. (2) The second questionnaire is a quality of life questionnaire your partner/carer will fill out at the same time you fill out a similar quality of life questionnaire. We ask this of partners/carers because we recognize that the impact of Parkinson's disease can extend beyond the individual.

7. What is the drink that is being tested?

The ketone ester is called ΔG® and is transformed into ketone bodies after being digested. These substances are not naturally found in the human diet but are produced by the liver during carbohydrate starvation as an alternative energy source for the brain.

ΔG® is produced by the parent company TΔS, a spin-out company from the University of Oxford's Department of Physiology, Anatomy and Genetics. ΔG® was first invented by Oxford's own Professor Kieran Clarke using a $10 million grant she received from the United States military to create a product that would enhance soldiers' physical and cognitive performance.

8. What are the potential side effects drinking the ketone ester ΔG®?

ΔG® is generally well tolerated. You may experience none, some, or all mild episodes of the symptoms listed below:

- Diarrhoea
- Abdominal distension
- Nausea
- Headache
- Dizziness

Published studies, in rodents and healthy human subjects, support ΔG®'s safety and tolerability for longer-term use. In collaborations with UK Sport, numerous studies have been performed on ~250 athletes to determine the effects of single drinks on physical endurance and cellular metabolism without problems. The HVMN ΔG® drink has FDA approval and is commercially available in the United States as a sports supplement.

9. What are the other possible disadvantages and risks of taking part?

Some participants find venepuncture painful or have difficult to access veins. To minimise these problems, all venepunctures will be performed by NHS-certified personnel.

10. What are the possible benefits of taking part?
You may experience improvements in motor symptoms, cognitive function, sleep, smell, and mood. It is also possible that you will experience no noticeable benefits.

11. Will ΔG® be available after the study ends?
If would like to purchase ΔG® for yourself after the study is complete, it is currently commercially available as a sports supplement from the biotech company HVMN. The following is a link to the company's website: https://hvmn.com/ketone. It is currently very expensive, although the price is expected to come down as the synthesis process streamlined and scaled up.

12. What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Contact information is provided below.

13. Will my taking part in this study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. More details about this are included in Part 2.

14. Will I receive reimbursement for taking part in this research?
Yes. Participants who complete the study will receive £150 and reasonable travel expenses.

15. Who do I contact if I have problems?
If you wish to complain about any aspect of the way in which you have been approached or treated during this study, you should contact the investigators directly at 07444 054375 or nicholas.norwitz@dpag.ox.ac.uk. You may also contact the University of Oxford Clinical Trials and Research Governance (CTRG) office at 01865 572224 or the head of CTRG at ctrg@admin.ox.ac.uk. Alternatively, you can contact Chief Investigator, Professor Michele Hu, at michele.hu@ndcn.ox.ac.uk.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study.

If you wish to contact the PALS team, please contact:
PALS Office
Churchill Hospital
Old Road, Headington
Oxford OX3 7LE
Tel: 01865 235855
Email: PALSCH@ouh.nhs.uk

TΔS® Ltd, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

More detailed information about how we will conduct of the study

1. Who is organising, sponsoring, and funding the research?
The Department of Physiology, Anatomy and Genetics (DPAG) of the University of Oxford is organizing the research, TΔS® Ltd is sponsoring the research, and a private benefactor is funding the research through the sponsor via a designated donation.

2. What will happen if I don't want to carry on with the study?
You can withdraw from the study at any point.

3. Will my taking part in this study be kept confidential?
All the information is confidential. None of the information stored on computers will be identifiable with your name. We will replace your name, initials, and date of birth with a participant number to make sure you remain anonymous.

4. What will happen to the samples that I give?
The samples you provide will be anonymised using a study specific de-identification code. They may be transferred to the University of Oxford for analysis or analysis may occur at the John Radcliffe Hospital's laboratories. Before analysis is complete, your data will remain de-identified and secure in a locked drawer, when it is not being actively analysed by a member of the research team. After the samples have been analysed, they will be immediately destroyed.

5. What if my samples reveal an abnormal finding?
All clinically relevant information will be relayed to your General Practitioner.

6. Will any genetic tests be done?
No genetic tests will be performed as part of this study.

7. Who is responsible for and what will happened with my information?
TΔS Ltd. is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as data as the data controller for this study. This means that we are responsible for looking after your information and using it properly. TΔS will keep your information for 5 years after the study has finished. 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. If you withdraw from the study, we will keep the data we have already obtained. To safeguard your rights, we will use the minimum possible personally identifiable information. The John Radcliffe Hospital will collect information from you and/or your medical records for this research study in accordance with our instructions.

The John Radcliffe Hospital will use your name, NHS, number, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from TΔS, the University of Oxford, and regulatory organisations, may look at your medical and research records to check the accuracy of the research study. The John Radcliffe Hospital will pass these details to TΔS along with the information collected from you and/or your medical records. The only people at TΔS who will have access to information that identifies you will be people who need to contact you if any health issues arise or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, or contact details.

The John Radcliffe Hospital will keep identifiable information about you from this study for up to 5 years after the study has finished.

8. What will happen to the results of the research study?
At the end of the study, the results will be presented at regional, national, and international meetings and published in medical journals. All published results and information will be anonymised.

9. Who has reviewed the study?
This study has been given a favourable ethical opinion for conduct in the NHS by South Central – Oxford B Research Ethics Committee.

This study is part of an educational project that will contribute towards doctoral degrees in Physiology, Anatomy, and Genetics for DPhil (PhD) candidates Nicholas Norwitz and Dr. Adrian Soto.

If you would like to be part of this study, or would like more information, please contact Nicholas Norwitz.
Email: nicholas.norwitz@dpag.ox.ac.uk
Mobile number: 07444 054375