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A ketone drink (ΔG°) to improve exercise performance in Parkinson's disease

IRAS ID: 257795

ISRCTN16599164

Date and Version No: May 21st, 2019. Version 1.12.

Chief Investigator:

Prof Michele Hu, Nuffield Department of Clinical Neurosciences
Department of Neurology, West Wing, Level 3
John Radcliffe Hospital, Headley Way, Oxford, OX1 3PT
Tel: +44 (0) 1865234337
Email: michele.hu@ndcn.ox.ac.uk

Investigators:

Nicholas Norwitz, Department of Physiology, Anatomy, and Genetics (DPAG)
Sherrington Building, Parks Road, Oxford OX1 3PT.
Tel: +44 (0) 7444054375
Email: nicholas.norwitz@dpag.ox.ac.uk

Sponsor:

TAS[®] Ltd
30 Upper High Street, Thame, Oxfordshire, OX9 3EZ

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Chief Investigators Signature:

Please declare any/no potential conflicts of interest:

None of the investigators has conflicts of interest to declare.

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee unless authorised to do so.

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1. KEY STUDY CONTACTS

Chief Investigator	Prof Michele Hu, Nuffield Department of Clinical Neurosciences Department of Neurology, West Wing, Level 3 John Radcliffe Hospital, Headley Way, Oxford, OX1 3PT Tel: +44 (0) 1865234337 Email: michele.hu@ndcn.ox.ac.uk
Sponsor	TΔS® Ltd 30 Upper High Street Thame Oxfordshire OX9 3EZ Email: info@tdeltas.com
Study Units	Oxford Brookes University Headington Campus, Oxford OX3 0BP Tel: +44 (0) 1865 741111
Committees	There are no Steering or Data Safety Monitoring Committees for this study.

2. SYNOPSIS

Study Title	A ketone drink (ΔG®) to improve exercise performance in Parkinson's disease	
Study Design	Single-blinded, randomized-crossover, placebo-controlled	
Study Participants	Patients with Parkinson's disease, Hoehn and Yahr stages 1 – 2	
Planned Sample Size	15	
Intervention Duration	Three 1-2-hour visits separated by one week	
	Objective	Outcome Measures
Primary	To test the hypothesis that ketone bodies improve exercise performance in patients with Parkinson's disease	Time (T) Average cadence Heart rate (HR) Oxygen intake (VO2) Respiratory exchange ratio (RER) Relative Perceived Exertion (RPE) Blood glucose, lactate, D-beta-hydroxybutyrate (βHB)
Secondary	There are no secondary objectives	N/A
Investigational Product	Ketone ester drink (ΔG®)	
Dose, Administration	Single dose of 25 mL ΔG® drink given orally	

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CPET	Cardiopulmonary Exercise Test
GP	General Practitioner
HRA	Health Research Authority
ICH	International Conference on Harmonization
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

4. BACKGROUND AND RATIONALE

Parkinson's disease is the world's most common neurodegenerative disease that affects motor function. These motor symptoms are progressive and inevitably impact all patients. Evidence in humans has demonstrated that exercise can alleviate the motor symptoms associated with Parkinson's disease¹⁻³ and data from animal models suggest that exercise can protect against the neurodegeneration of substantia nigra dopaminergic neurons.⁴ However, the effectiveness of exercise in protecting against the symptoms and progression of Parkinson's disease is confounded by the fact that Parkinson's disease itself limits patients' physical capabilities. Therefore, any intervention that could acutely boost patients' physical capabilities could, in theory, help to establish a positive feedback loop whereby increased exercise capacity leads to motor symptom improvements and so on.

The Clarke group at the University of Oxford has invented a ketone body dietary supplement (ΔG°) that can acutely boost physical capability. In a 2016 paper published in the journal *Cell*, the Clarke group provided strong evidence that ΔG° alters energy metabolism and increases exercise performance in human athletes.⁵ This study will investigate whether the results in athletes translate into individuals with Parkinson's disease and whether ΔG° may be used to increase exercise capacity in Parkinson's patients.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s)
Primary Objective To test the hypothesis that ketone bodies improve exercise performance in patients with Parkinson's disease	Time (T) Average cadence Heart rate (HR) Oxygen intake (VO ₂) Respiratory exchange ratio (RER) Relative Perceived Exertion (RPE)	During exercise
	Blood glucose, lactate, D-beta-hydroxybutyrate (β HB)	Before taking the study drink, 30 minutes after taking the study drink/before exercise, immediately after exercise
Secondary Objectives There are no secondary objectives	N/A	N/A

6. STUDY DESIGN

This single-blinded, randomized-crossover, placebo-controlled experimental study will be performed in 15 patients with Parkinson's disease Hoehn and Yahr stages 1-2, aged 40 – 80 (inclusive). Participants will come into the lab after an overnight fast in a drug "off" state and be asked consume a drink containing 25 mL ΔG and 45g carbohydrates or a isocaloric taste-matched control containing 75g carbohydrates and Symrise bitter flavor (product code: SY648352) 30 minutes prior to performing an exercise test on a fixed-Watt cycle ergometer. The exercise test will consist of measuring the maximum average cadence that a participant can hold for a set time period of time at a fixed wattage (e.g. X rpm for 1 minute at 105 Watts) and/or measuring how long a participant can hold a fixed cadence and wattage (e.g. 90 rpm for X minutes at 80 Watts).

Time (T), average cadence, heart rate (HR), oxygen intake (VO₂), respiratory exchange ratio (RER), and relative perceived exertion (RPE) will be measured during the exercise test. The Borg scale and a set script will be used to assess RPE. Blood levels glucose, lactate, and βHB will be measured before participants take the study drink, 30 minutes after they take the study drink/before exercise, and immediately after they stop exercising.

7. PARTICIPANT IDENTIFICATION

The population will consist of 15 patients with Parkinson's disease, Hoehn and Yahr stages 1 – 2, aged 40 – 80 (inclusive).

7.1 Inclusion Criteria

- Diagnosis of Parkinson's disease
- Hoehn and Yahr stages 1 – 2
- Aged 40 – 80 (inclusive)
- Fluent in English
- Capable of giving informed consent

7.2 Exclusion Criteria

- Communication impairments
- History of cardiovascular disease
- Any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the study, or may influence the result of the experiment, or the participant's ability to participate in the study.

8. STUDY PROCEDURES

8.1 Recruitment

Participants will be identified and referred to the research team by the John Radcliffe Hospital, which will act as the Participant Identification Centre (PIC) for this study. After participants have been referred to the research team, a study invitation pack will be sent to potential participants. This will include a letter of invitation, a Participant Information Sheet, a reply-paid envelope and a reply slip to indicate whether the participant is willing to attend an initial recruitment visit or would like to speak to one of the research team for further information.

With appropriate approvals in place, potential participants may also be identified and recruited via advertising posters in the University of Oxford and an advertisement on the Oxford Parkinson's Disease Centre's webpage.

The research team will schedule a follow-up call with potential participants one week after the invitation pack has been issued to ensure the packs were received and to ascertain their interest in attending a screening visit. Individuals responding positively to the invitation will then be pre-screened for the study by the investigators according to the eligibility criteria.

8.2 Informed Consent

Sufficient time will be provided between the participant receiving the information pack and the visit. Participants will be encouraged to discuss all queries with the research team.

The participant must personally sign and date the latest approved version of the Informed Consent Form before any study-specific procedures are performed. Participant Information and Informed Consent Form will be presented to the participants detailing no less than the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the confidentiality of personal data; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained using participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorized to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

8.3. Study Schedule

Number of visit	Procedures
1	<input type="checkbox"/> Screening interview (check eligibility criteria). <input type="checkbox"/> Informed consent. <input type="checkbox"/> Practice/familiarization exercise test

<p>2 & 3</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Blood tests (-30 minutes, 0 minutes, end of exercise). <input type="checkbox"/> Ketone or control drink (0 minutes). <input type="checkbox"/> Exercise test with cardiopulmonary testing.
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8.4 Sample Handling

The samples taken for biochemical data will be analysed at the Oxford Brookes University or the Department of Physiology, Anatomy and Genetics of the University of Oxford. Samples will be identified using the study participant number and, immediately after their analysis, all samples will be destroyed.

8.5 Discontinuation of Participants from Study

Each participant has the right to withdraw from the study at any time. Any participants who withdraws from the study may be replaced if necessary. The reason (if provided) for withdrawal will be recorded. If the participant is removed due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved.

8.6 Definition of End of Study

The end of the study is defined as the moment when the last participant completes the planned procedures.

9. SAFETY AND REPORTING

9.1 Definitions

- *Adverse Event (AE)*: Any untoward medical occurrence in a participant to whom an investigational product has been administered, including incidents which are not necessarily caused by or related to that product.

- *Adverse Reaction (AR)*: An untoward and unintended response in a participant to an investigational product which is related to any dose administered to that participant. The phrase "response to an investigational product" means that a causal relationship between the study food supplement and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study's investigational product qualify as adverse reactions.

- *Serious Adverse Event (SAE)*: Is any untoward medical occurrence that:

- results in death.
- is life-threatening.
- requires inpatient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability/incapacity.
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- *Serious Adverse Reaction (SAR)*: An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

- *Suspected Unexpected Serious Adverse Reaction (SUSAR)*: A serious adverse reaction, the nature and severity of which is not consistent with the information about the investigational product in question:
 - in the case of a product with a marketing authorization, in the summary of product characteristics (SmPC) for that product
 - in the case of any other investigational product, in the investigator's brochure (IB) relating to the study in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe the intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Causality

The relationship of each adverse event to the study supplement must be determined by a medically qualified individual according to the following definitions:

- *Related*: The adverse event follows a reasonable temporal sequence from study investigational product administration. It cannot reasonably be attributed to any other cause.
- *Not Related*: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

9.3 Procedures for Recording Adverse Events

All AEs occurring during the study that are observed by the Investigator or reported by the participant will be recorded, whether attributed to the study's investigational product or not. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study supplement, other suspect drug or device and action is taken. Follow-up information should be provided as necessary. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

AEs considered related to the study's investigational product as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the participant's removal from treatment or not.

A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

9.4 Reporting Procedures for Serious Adverse Events

All SAEs will be reported to the Sponsor or delegate within 24 hours of the research team becoming aware of the event being defined as serious.

9.5 Expectedness

Expectedness will be determined according to the Investigators' Brochure.

9.6 SUSAR Reporting

All SUSARs will be reported to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than seven calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report.

10. STATISTICS

10.1 Description of Statistical Methods

All quantitative data will be compared using a t-paired test. All analysis and calculations will be done using SPSS software.

10.2 Sample size

15 patients with Parkinson's disease will be recruited.

10.3 The Level of Statistical Significance

All statistical significance will be assessed using a p-value of 0.05 or 95% confidence interval.

10.4 Procedure for Accounting for Missing, Unused, and Spurious Data

Data from withdrawing or non-compliant participants will be excluded.

11. DATA MANAGEMENT

11.1 Source Data

Source documents are where data are first recorded, and from which participants data are obtained. These include, but are not limited to, blood sample results and cardiopulmonary test reports.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent and the screening/enrolment log, the participant will be referred to by the study participant number/code, not by name.

11.2 Access to Data

Direct access will be granted to authorized representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

11.3 Data Recording and Record Keeping

The participants will be identified by a unique study specific number. The name and any other identifying detail will NOT be included in any study data electronic file.

12. QUALITY ASSURANCE PROCEDURES

The study will be conducted by the currently approved protocol, GCP, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted by the principles of the Declaration of Helsinki.

13.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted by relevant regulations and with GCP.

13.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC). The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, except for the enrolment log. All documents will be stored securely and only accessible by study staff and authorized personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical.

13.5 Expenses and Benefits

Reimbursement will be £50.00 GBP conditional on completing all the measurements and procedures. Reasonable travel expenses for any visits additional to standard care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

14. ARCHIVING

Archiving of study documentation will be the responsibility of the Chief Investigator. Documentation will be stored for a minimum of 5 years in secure purpose-designed archive facilities.

15. FINANCE AND INSURANCE

15.1 Funding

Funding is being provided through TΔS® Ltd by a generous donation from a private benefactor. The donation has been designated for this research specifically.

15.2 Insurance

Insurance for the study (including participant liability cover) will be provided by TΔS® Ltd.

16. PUBLICATION POLICY

No intellectual property will be produced in this study. Data will be available for all investigators for educational purposes and all investigators will be acknowledged in the publication. The Chief Investigator will provide a summary of the study within one year of the end of the trial to the REC and the sponsor.

17. REFERENCES

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3. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair*. 2009;23:600-608. doi:10.1177/1545968308328726
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5. Cox PJ, Kirk T, Ashmore T, et al. Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes. *Cell Metab*. 2016;24:256-268. doi:10.1016/j.cmet.2016.07.010

18. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date Issued	Author(s) of changes	Details of Changes made
1	1.11	24-02-2019	Nicholas Norwitz (sponsor approved)	Modified design of actual exercise test to make it more appropriate for persons with Parkinson's disease
2	1.12	TBD	Nicholas Norwitz (sponsor approved)	Added the John Radcliffe Hospital as a Participant Identification Centre (PIC)

Protocol amendments must be submitted to the Sponsor for approval before submission to the REC.