A ketone drink (ΔG®) to increase cerebral ATP in Parkinson's disease

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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

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Study Units	Department of Physiology, Anatomy, and Genetics (DPAG) Sherrington Building, Parks Road, Oxford OX1 3PT. Tel: +44 (0) 1865 272500.
Committees	There are no Steering or Data Safety Monitoring Committees for this study.

2. SYNOPSIS

Study Title	A ketone drink (ΔG®) to increase cerebral ATP in Parkinson's disease	
Study Design	Crossover study	
Study Participants	Patients with Parkinson's disease, Hoehn and Yahr stages 1 – 2	
Planned Sample Size	12	
Intervention Duration	One 1-2-hour visits	
	Objective	Outcome Measures
Primary	To test the hypothesis that ketone bodies increase ATP levels in the brains of patients with Parkinson's disease	Cerebral P_i/βATP ratio and other cerebral metabolite ratios, at baseline and one hour after ingesting ketone ester (ΔG®)
Secondary	To test the hypothesis that ketone bodies favorably alter levels of insulin and circulating energy metabolites in patients with Parkinson's disease	Blood insulin, glucose, free fatty acid (FFA), D-beta-hydroxybutyrate (βHB), at baseline and one hour after ingesting ketone ester (ΔG®)
Investigational Product	Ketone ester drink (ΔG®)	
Dose, Administration	Single 25mL dose of ΔG® drink given orally	

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
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 (PD) is the second most common neurodegenerative disease in the world, affecting 2-3% of individuals >65. It is biologically characterized by the death of dopaminergic neurons within the midbrain's substantia nigra. The death of these dopaminergic neurons is caused, at least in part, by errors in energy metabolism, including a decrease in respiratory chain complex I activity.[1] These errors in energy metabolism contribute to the 44% decrease in cerebral ATP levels (P_i/β-ATP ratio as measured by magnetic resonance imaging) that has been observed in the brains of PD patients as compared to age-matched controls.[2] This ATP depletion constitutes an energy crisis within dopaminergic neurons (one of the most energetically demanding cell types in the body), initiating a cascade of events that lead to cell death and the progression of PD.

Providing the brain with ketone bodies as a source of fuel may alter brain metabolism in such a way as to increase ATP levels and rescue dopaminergic neurons. Ketone bodies are a highly efficient source of fuel, providing more ATP per molecule than glucose. Furthermore, ketone bodies may be able to circumvent complex I dysfunction in the context of Parkinson's disease, thus helping to rescue normal oxidative metabolism in neurons.[3] Indeed, work *in vitro* and in animal models of PD has shown that ketone bodies increase ATP levels in neurons,[3] protect dopaminergic neurons against cell death in the context of complex I dysfunction,[3,4] and prevent the development of Parkinsonian motor symptoms.[3]

Until recently, the only way to effectively increase ketone body levels in human patients was through endogenous mechanisms prompted by starvation or pseudo-starvation ketogenic diets. One small feasibility study even demonstrated that PD patients who adhered to a ketogenic diet for 28-days experienced improvements in their motor symptoms.[5] However, ketogenic diets are difficult with which to comply and may confer cardiovascular risk. Fortunately, the Clarke group at the University of Oxford has recently invented a nutritional ketone ester (ΔG®) that can be consumed as a supplement. Data in healthy humans has already demonstrated that ΔG® is a tolerable and safe way to increase ketone body levels[6] and favorably alter energy metabolism, at least in peripheral tissues.[7] The aim of this study is to investigate whether ΔG® can be used to increase ATP levels in the brains of patients with PD and, thereby, ameliorate the energy crisis that leads to dopaminergic neuron cell death.

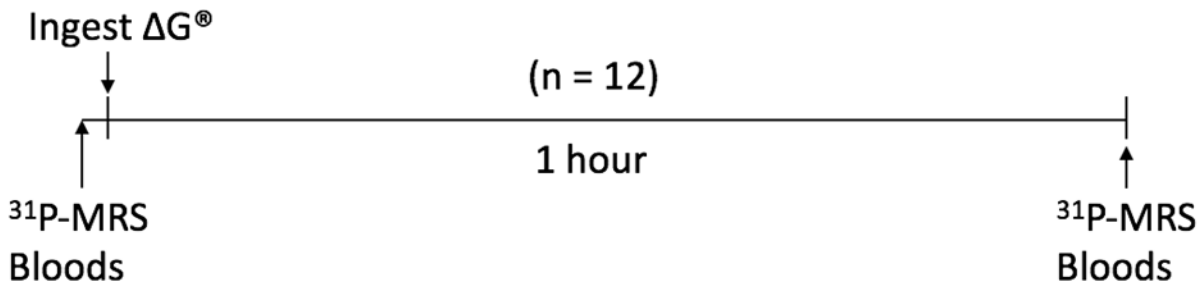
5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s)
Primary Objective To test the hypothesis that ketone bodies increase ATP levels in the brains of patients with Parkinson's disease	Cerebral P_i/βATP ratio and other cerebral metabolite ratios	Baseline (before taking the study drink) and one hour after taking the study drink
Secondary Objectives To test the hypothesis that ketone bodies favorably alter levels of insulin and circulating energy metabolites in patients with Parkinson's disease	Blood insulin, glucose, free fatty acid (FFA), D-beta-hydroxybutyrate (βHB)	Baseline (before taking the study drink) and one hour after taking the study drink

6. STUDY DESIGN

This study will be performed in 12 patients with Parkinson's disease Hoehn and Yahr stages 1-2, aged 40 – 80 (inclusive). Participants will come into the John Radcliffe Hospital after an overnight fast and undergo 31-phosphorus magnetic resonance imaging (^{31}P-MRS) and have their blood drawn from one of their arms. Standard MRI will also be collected for anatomical localization. Blood samples will be used to measure insulin, glucose, FFA, and βHB levels. Participants will then be asked consume a drink containing 25 mL of ΔG and wait for one hour prior to having the ^{31}P-MRS scan and blood draw repeated.

Study Flowchart:



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7. PARTICIPANT IDENTIFICATION

The population will consist of 12 paitents 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
- Contraindications for undergoing magnetic resonance imaging (certain metal implants, claustrophobia)
- 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

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 will be 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	☐ Screening interview (check eligibility criteria). ☐ Informed consent.
2	☐ Blood tests (Baseline). ☐ ^{31}P-MRS (Baseline). ☐ Ketone drink (0 minutes). ☐ Blood tests (1 hour). ☐ ^{31}P-MRS (1 hour).

8.4 Sample Handling

The samples taken for biochemical data will be analysed at the John Radcliffe Hospital and at 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
12 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 and ^{31}P-MRS results.

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 geneous 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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18. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date Issued	Author(s) of changes	Details of Changes made

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