A ketone drink (ΔG®) to alleviate the symptoms of Parkinson's disease
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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:
TΔS® Ltd
30 Upper High Street, Thame, Oxfordshire, OX9 3EZ

Funder:
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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	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 alleviate the symptoms of Parkinson's disease	
Study Design	Longitudinal, single-blinded, randomized, placebo-controlled	
Study Participants	Patients with Parkinson's disease, Hoehn and Yahr stages 1 – 2	
Planned Sample Size	12	
Intervention Duration	One month, plus a two-week baseline and a two-week follow-up	
	Objective	Outcome Measures
Primary	To test the hypothesis that ΔG® will alleviate the symptoms of Parkinson's disease.	MDS-UPDRS, Axivity AX3, Smartphone application, Sniffin' Sticks, MoCA, Stroop, FSS, PDQ-39, PDQ-Carer, RBDSQ
Secondary	To test the hypothesis that ΔG® will improve the blood levels of metabolites associated with certain age-related diseases (Parkinson's disease, heart disease, and diabetes) in patients with Parkinson's disease.	Complete blood screen (including, but not limited to, uric acid, glucose, fructosamine, insulin, total cholesterol, HDL, TAG, CRP, TNF-α, IL-1β, and kynurenic acid)
	To assess participant compliance, study drink tolerability, and whether drink intake altered participants' dietary intake.	Study drink diary, compliance call, urine ketones, consumer questionnaire, food-intake record.
Investigational Product	Ketone ester drink (ΔG®)	
Dose, Administration	Four daily 25mL doses 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 (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 substantia nigra and manifests in a variety of progressive motor and nonmotor symptoms. While the exact causes of PD are not understood, it is believed that errors in energy metabolism contribute to the dysfunction and death of dopaminergic neurons and to the symptoms associated with PD. Evidence suggests that ketone bodies—a highly efficient source of fuel produced by the liver to feed the brain during starvation—may be able to rescue energy metabolism in dopaminergic neurons and alleviate the symptoms of PD.

Work *in vitro* and in mouse models of PD has demonstrated that ketone bodies increase ATP production in neurons,[1] prevent the death of dopaminergic neurons,[1,2] and protect against the development of PD motor symptoms.[1] Consistent with these *in vitro* and animal data, human PD patients who kept to a ketogenic diet for 28 days experienced marked symptom improvements as measured by UPDRS.[3] Unfortunately, ketogenic diets have limited clinical applicability because they are difficult with which to comply[4] and may increase cardiovascular risk.[5] Fortunately, the Clarke group at the University of Oxford has invented a ketone ester supplement (ΔG®) that can increase ketone body levels without the need for a diet. ΔG® is safe, well-tolerated,[6] and has already been demonstrated to improve peripheral tissue energy metabolism in human athletes.[7]

This placebo-controlled trial will build upon the literature summarized above by investigating whether ΔG®, the world's first commercially available ketone ester supplement, can be used to alleviate the symptoms of PD in human patients.

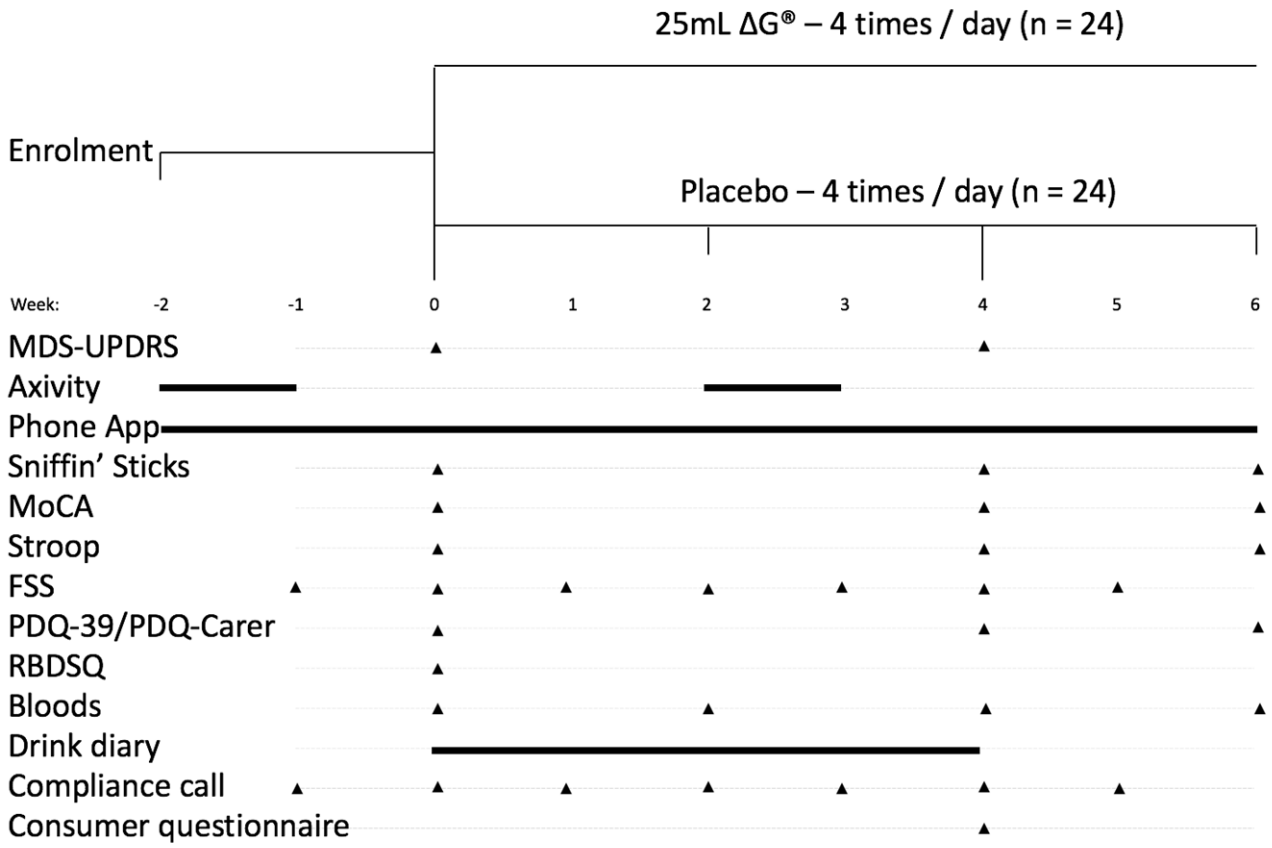
5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Descriptions	Timepoints (Weeks)
Primary Objective To test the hypothesis that ΔG® will alleviate the symptoms of Parkinson's disease.	MDS-UPDRS	Standard clinical test ("off" medications)	0, 4 (both before and after consuming drink)
	Axivity AX3	Continuous activity monitor	-2 – -1, 2 – 3 (continuous)
	Smartphone application	Tasks performed on a phone	-2 – 6 (4x daily)
	Sniffin' Sticks 16	Odour identification	0, 4, 6
	MoCA	Montreal Cognitive Assessment	0, 4, 6
	Stroop	Colour-word selective attention test	0, 4, 6
	FSS	Fatigue Severity Survey	-1, 0, 1, 2, 3, 4, 5
	PDQ-39/PDQ-Carer	Quality of life questionnaires	0, 4, 6
	RBDSQ	REM Behaviour Sleep Disorder Screening Questionnaire	0
Secondary Objectives To test the hypothesis that ΔG® will improve the blood levels of metabolites associated with age-related diseases in patients with Parkinson's disease.	Bloods	Complete blood screen (including, but not limited to, uric acid, glucose, fructosamine, insulin, total cholesterol, HDL, TAG, CRP, TNF-α, IL-1β, and kynurenic acid)	0, 2, 4, 6
Pharmacokinetics To assess participant compliance, study drink tolerability, and whether drink intake altered participants' dietary intake.	Bloods	βHB, acetoacetate, FFA, TAG, glucose, and kynurenic acid	0
	Study drink diary	Participant record of drink and food consumption	0 – 4 (4x daily)
	Compliance call	Randomly timed call	-1, 0, 1, 2, 3, 4, 5
	Consumer questionnaire	Study drink likeability	4

6. STUDY DESIGN

This longitudinal, single-blind, randomized, placebo-controlled trial will include 12 patients with Parkinson's disease divided equally into ketone ester (ΔG®) and a placebo-control groups. Each participant will be involved in the study for a total of two months, a time period consisting of a two-week baseline (weeks -2 to 0), a one-month intervention (weeks 0 to 4), and a two-week follow-up (weeks 4 to 6). Throughout the one-month intervention, participants will be asked to drink 25mL of ΔG®, or a taste-matched placebo control, four times daily. The drinks will be individually packaged and delivered to the participants' homes by a member of the research team.

Participants will be assessed at the study site on a fortnightly basis by a series of motor and non-motor tests. These include the MDS-UPDRS for overall symptom severity, MoCA for cognition, Stroop for selective attention, and Sniffin' Sticks for olfaction. Participants will also have bloods drawn. In addition to the standard bloods drawn for all participants on the dates of their visits, we will offer each participant the option to opt in to an additional single blood test in which they come into the lab fasted, consume a standard dose of the study drink, and have small 1-2.5 mL blood samples taken from an IV cannula placed by a trained research nurse at 0, 10, 20, 30, 60, 90, 120, 150, 180, and 240 minutes post-drink. From the samples we will measure βHB, acetoacetate, free fatty acids, triglycerides, glucose, and kynurenic acid. These measurements will allow us to confirm that the pharmacokinetic profile of the ketone ester is consistent between individuals with and without Parkinson's disease, the latter having being previously reported by other members of our team[8], and, secondarily, whether levels of a potentially neuroprotective metabolite (kynurenic acid) are affected by ingestion of the ketone drink.[9–12] Whether or not a participant decides to opt in will not affect his/her enrollment in the rest of the study. Participants will also be asked to fill out three questionnaires: the PDQ-39/PDQ-Carer will be used to assess quality of life, the RBDSQ will be used to screen for REM sleep disorder, and a consumer



questionnaire will be used to assess the study drink's likeability. Finally, participants will also be responsible for completing tasks at home. First, participants will be asked to wear a no-maintenance continuous activity monitor (Axivity) on their wrists before and during the intervention. Second, they must complete a short series of tests using a smartphone four times each day. Third, they will keep a diary of each time they consume a study drink and several participants will keep a detailed record of their dietary intake (the latter will be done on an opt-in basis). Fourth, they will receive weekly surprise compliance calls. The caller will ask participants when they last consumed the study drink and to measure their ketone levels by urine stick. During the call, participants will also be asked to verbally complete a fatigue survey. Further details about the timing and duration of each task can be found in section 5 and in the flowchart above.

7. PARTICIPANT IDENTIFICATION

The population will consist of 12 paitents with Hoehn and Yahr stage 1 or 2 Parkinson's disease who are taking L-dopa, who are between the ages of 40 and 80, and who are fluent in English.

7.1 Inclusion Criteria

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

7.2 Exclusion Criteria

- Communication impairments
- 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, and a prepaid reply envelope 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 sign and date the latest version of the Informed Consent before any study-specific procedures are performed. Participant Information and Informed Consent will be presented to the participants detailing 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; 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

Visit Week	Procedures
-2	Screening interview (check eligibility criteria) Informed consent
0	MDS-UPDRS (“off” medication, before consuming study drink) MDS-UPDRS part III (“off” medication, one-hour after consuming study drink) Sniffin’ Sticks MoCA Stroop PDQ-39/PDQ-Carer RBDSQ Blood draw (plus pharmacokinetics for a subset of volunteers)
2	Blood draw
4	MDS-UPDRS (“off” medication, before consuming study drink) MDS-UPDRS part III (“off” medication, one-hour after consuming study drink) Sniffin’ Sticks MoCA Stroop PDQ-39/PDQ-Carer Blood draw Consumer questionnaire

6	□ Sniffin' Sticks □ MoCA □ Stroop □ PDQ-39/PDQ-Carer □ Blood draw

8.4 Sample Handling

The samples taken for biochemical data will be analysed at the John Radcliffe Hospital 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.

9.7 COVID-19 Pandemic

In light of the recent Covid 19 viral pandemic, routine research visits being conducted at the John Radcliffe Hospital will be cancelled in line with current OUHFT advice until further notice. During this time to minimise potential risk of Covid 19 exposure, research assessments will be conducted where appropriate following participant agreement either in the patient's own home, or in the Sherrington Building, Department of Physiology, Anatomy and Genetics, Oxford University (Parks Road, OX1 3PT). Prior to the home or Sherrington Building research visit, each research participant will be pre-screened by the research team the day prior, and will not be seen if:

1. They or the research team member assessing the patient are deemed to have significant symptoms in the previous 5-10 days that would suggest Covid 19 virus infection (including dry cough, temperature, other respiratory symptoms).
2. They have significant existing disease comorbidity that could result in a worse outcome following potential Covid 19 infection including asthma, COPD, immunosuppressive medications or disorders.

If appropriate, research team members will also wear recommended protective equipment in compliance with existing OUHFT policy for hospital visits at the time of the research visit.

10. STATISTICS

10.1 Description of Statistical Methods

All quantitative data will be compared using paired t-tests, independent sample t-tests, and ANOVA as appropriate. 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 may be included.

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, clinical test results, blood sample results, and questionnaire responses.

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 £150.00 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

1. Tieu K, Perier C, Caspersen C, et al. D-β-Hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease. *J Clin Invest*. 2003;112:892-901. doi:10.1172/JCI200318797
2. Kashiwaya Y, Takeshima T, Mori N, Nakashima K, Clarke K, Veech RL. D-Hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. *Proc Natl Acad Sci*. 2000;97:5440-5444. www.pnas.org.
3. Vanitallie TB, Nonas C, Rocco AD, Boyar K, Hyams K, Heymsfield SB. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. *Neurology*. 2005;64:728-730. doi:10.1212/01.WNL.0000152046.11390.45
4. Payne NE, Cross JH, Sander JW, Sisodiya SM. The ketogenic and related diets in adolescents and adults-A review. *Epilepsia*. 2011;52:1941–1948. doi:10.1111/j.1528-1167.2011.03287.x
5. Kwiterovich PO, Vining EPG, Pyzik P, Skolasky R, Freeman JM. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. *J Am Med Assoc*. 2003;290:912-920. doi:10.1001/jama.290.7.912
6. Clarke K, Tchabanenko K, Pawlosky R, et al. Kinetics, safety and tolerability of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate in healthy adult subjects. *Regul Toxicol Pharmacol*. 2012;63:401-408. doi:10.1016/j.yrtph.2012.04.008
7. 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
8. Stubbs BJ, Cox PJ, Evans RD, et al. On the metabolism of exogenous ketones in humans. *Front Physiol*. 2017;8(OCT). doi:10.3389/fphys.2017.00848
9. Chmiel-Perzyńska I, Kloc R, Perzyński A, Rudzki S, Urbańska EM. Novel aspect of ketone action: β-Hydroxybutyrate increases brain synthesis of kynurenic acid in vitro. *Neurotox Res*. 2011;20(1):40-50. doi:10.1007/s12640-010-9220-0
10. Zádori D, Klivényi P, Vámos E, Fülöp F, Toldi J, Vécsei L. Kynurenines in chronic neurodegenerative disorders: Future therapeutic strategies. *J Neural Transm*. 2009;116(11):1403-1409. doi:10.1007/s00702-009-0263-4
11. Zarnowski T, Chorągiewicz T, Tulidowicz-Bielak M, et al. Ketogenic diet increases concentrations of kynurenic acid in discrete brain structures of young and adult rats. *J Neural Transm*. 2012;119(6):679-684. doi:10.1007/s00702-011-0750-2
12. Żarnowska I, Wróbel-Dudzińska D, Tulidowicz-Bielak M, et al. Changes in tryptophan and kynurenine pathway metabolites in the blood of children treated with ketogenic diet for refractory epilepsy. *Seizure*. 2019;69:265-272. doi:10.1016/j.seizure.2019.05.006

18. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date Issued	Author(s) of changes	Details of Changes made
1	1.7	June 24th, 2019	Nicholas Norwitz	For the compliance test, ketones will be measured by urine stick rather than fingerprick (pages 4 and 8)
2	1.8	November 9th, 2019	Nicholas Norwitz	On a single visit, a subset of willing 6 participants will be asked to undergo a test in which bloods (βHB, acetoacetate, free fatty acids, triglycerides, glucose, and kynurenic acid) are drawn over four hours so that we can perform pharmacokinetics and also measure levels of a neuroprotective metabolite.
3	1.9	February 18th, 2020	Nicholas Norwitz	On an opt-in basis, researcher Nicholas Norwitz will work with willing participants to develop personalized libraries/menus of items that individual participants actually consume with serving sizes that make sense to the participant. These source data will then be fed into a program that will do an in-depth nutritional analysis of the participants' intakes, including not only macronutrient breakdown, but fat profile analyses, and micronutrient analyses as well. These data will be used to assess whether the drink impacts dietary intake, which could be a confound in this nutritional supplementation study.
4	1.10	March 12th, 2020	Nicholas Norwitz	In light of the recent Covid 19 viral pandemic, routine research visits being conducted at the John Radcliffe Hospital will be cancelled in line with current OUHFT advice until further notice. During this time to minimise potential risk of Covid 19 exposure, research assessments will be conducted where appropriate following participant agreement either in the patient's own home, or in the Sherrington Building, Department of Physiology, Anatomy and Genetics, Oxford University (Parks Road, OX1 3PT). Prior to the home or Sherrington Building research visit, each research participant will be pre-screened by the research team the day prior, and will not be seen if: 1. They or the research team member assessing the patient are deemed to have significant symptoms in the previous 5-10 days that would suggest Covid 19 virus infection (including dry cough, temperature, other respiratory symptoms). 2. They have significant existing disease

				comorbidity that could result in a worse outcome following potential Covid 19 infection including asthma, COPD, immunosuppressive medications or disorders. If appropriate, research team members will also wear recommended protective equipment in compliance with existing OUHFT policy for hospital visits at the time of the research visit.

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