Clinical trial results:
Randomised, double-blinded, placebo-controlled, adaptive design trial of the efficacy of acipimox in patients with Mitochondrial Myopathy

Summary

EudraCT number	2018-002721-29
Trial protocol	GB
Global end of trial date	21 December 2021

Results information

Result version number	v1 (current)
This version publication date	07 June 2023
First version publication date	07 June 2023

Trial information

Trial identification

Sponsor protocol code	08486

Additional study identifiers

ISRCTN number	ISRCTN12895613
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1, Regent Point Regent Farm Road, Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Gillian Watson, Newcastle Clinical Trials Unit, 0044 0191208813, gillian.watson@newcastle.ac.uk
Scientific contact	Gillian Watson, Newcastle Clinical Trials Unit, 0044 01912088813, gillian.watson@newcastle.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2021
Global end of trial reached?	Yes
Global end of trial date	21 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary outcome is to establish if acipimox can increase energy (ATP content) in skeletal muscle in adult patients with mitochondrial disease and muscle involvement.

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

Patients with mitochondrial disease and muscle involvement will be treated with acipimox or matched placebo to determine what effect treatment has on the ATP content of muscle. Participants will also be treated with low dose aspirin to reduce the incidence of facial flushing, a known side effect of acipimox, and thus to maintain trial blinding.

Actual start date of recruitment	07 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was by clinic appointment, interrogation of the Wellcome Centre for Mitochondrial Research Patient Cohort followed by invitation, and advertisement. Cohort patients with mitochondrial disease may be related to one another; to minimise the risk of unblinding, patients with a familial relationship were not screened at the same time.

Pre-assignment

Screening details:

Patients' medical history was viewed, to assess eligibility. Screening procedures: obtaining consent and collection of medical history and information on demographics, medical history, prior procedures and current medication. Eligibility blood samples were taken, and a pregnancy test carried out and contraceptive counselling given, if appropriate.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The trial IMP (acipimox and placebo) were manufactured and packaged to ensure that the participants, PI, Pharmacy staff, clinical team and monitors were blinded to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Acipimox

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Acipimox
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects will be randomised at baseline on to receive either acipimox 250mg or matched placebo PO three times a day (TDS) for 12 weeks. Participants will be advised to take their medication with, or just after, a meal, with the first dose of the day taken 20 – 30 minutes after the nIMP (Section 10.8). No dose modifications are permitted during the treatment period.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsule, PO, three times daily

Number of subjects in period 1	Acipimox	Placebo
Started	10	11
Completed	6	6
Not completed	4	5
Consent withdrawn by subject	1	-
Withdrawn due to COVID-19	1	3
No baseline muscle biopsy	-	1
Unstable baseline muscle biopsy	2	1

Period 2	
Period 2 title	12 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Acipimox

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Acipimox
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects will be randomised at baseline on to receive either acipimox 250mg or matched placebo PO three times a day (TDS) for 12 weeks. Participants will be advised to take their medication with, or just after, a meal, with the first dose of the day taken 20 – 30 minutes after the nIMP (Section 10.8). No dose modifications are permitted during the treatment period.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsule, PO, three times daily

Number of subjects in period 2	Acipimox	Placebo
Started	6	6
Completed	6	6

Period 3	
Period 3 title	Change from baseline to 12 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Acipimox

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Acipimox
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects will be randomised at baseline on to receive either acipimox 250mg or matched placebo PO three times a day (TDS) for 12 weeks. Participants will be advised to take their medication with, or just after, a meal, with the first dose of the day taken 20 – 30 minutes after the nIMP (Section 10.8). No dose modifications are permitted during the treatment period.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsule, PO, three times daily

Number of subjects in period 3	Acipimox	Placebo
Started	6	6
Completed	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Acipimox
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Acipimox	Placebo	Total
Number of subjects	10	11	21
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	20
From 65-84 years	0	1	1
Gender categorical Units: Subjects			
Female	8	9	17
Male	2	2	4

End points

End points reporting groups

Reporting group title	Acipimox
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Acipimox
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Acipimox
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: ATP content in muscle at baseline (mean and sd)

End point title	ATP content in muscle at baseline (mean and sd)[1]
End point description:	
End point type	Primary
End point timeframe:	
Baseline	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of participants with both baseline and week 12 data for the primary outcome, the analyses are descriptive and no statistical comparison between the placebo and the acipimox groups are made.

End point values	Acipimox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nmol/mg				
arithmetic mean (standard deviation)	5.47 (± 1.37)	4.78 (± 0.74)		

Statistical analyses

No statistical analyses for this end point

Primary: ATP content in muscle at Week 12 (mean and sd)

End point title	ATP content in muscle at Week 12 (mean and sd)[2]
End point description:	
End point type	Primary

End point timeframe:

12 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of participants with both baseline and week 12 data for the primary outcome, the analyses are descriptive and no statistical comparison between the placebo and the acipimox groups are made.

End point values	Acipimox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nmol/mg				
arithmetic mean (standard deviation)	4.51 (± 1.13)	4.91 (± 1.24)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in ATP content in muscle from baseline to Week 12 (mean and sd)

End point title	Change in ATP content in muscle from baseline to Week 12 (mean and sd)[3]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to 12 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of participants with both baseline and week 12 data for the primary outcome, the analyses are descriptive and no statistical comparison between the placebo and the acipimox groups are made.

End point values	Acipimox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nmol/mg				
arithmetic mean (standard deviation)	-0.97 (± 1.47)	0.128 (± 1.618)		

Statistical analyses

No statistical analyses for this end point

Primary: ATP content in muscle at baseline (median and range)

End point title	ATP content in muscle at baseline (median and range)[4]

End point description:

End point type	Primary

End point timeframe:

Baseline

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of participants with both baseline and week 12 data for the primary outcome, the analyses are descriptive and no statistical comparison between the placebo and the acipimox groups are made.

End point values	Acipimox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nmol/mg				
median (full range (min-max))	5.47 (3.27 to 7.17)	4.86 (3.46 to 5.54)		

Statistical analyses

No statistical analyses for this end point

Primary: ATP content in muscle at Week 12 (median and range)

End point title	ATP content in muscle at Week 12 (median and range)[5]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of participants with both baseline and week 12 data for the primary outcome, the analyses are descriptive and no statistical comparison between the placebo and the acipimox groups are made.

End point values	Acipimox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nmol/mg				
median (full range (min-max))	4.73 (2.72 to 5.79)	4.81 (3.3 to 6.94)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in ATP content in muscle from baseline to Week 12 (median and range)

End point title	Change in ATP content in muscle from baseline to Week 12

	(median and range)[6]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to 12 weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small number of participants with both baseline and week 12 data for the primary outcome, the analyses are descriptive and no statistical comparison between the placebo and the acipimox groups are made.

End point values	Acipimox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nmol/mg				
median (full range (min-max))	-0.565 (-2.87 to 0.55)	0.395 (-2.24 to 2.33)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events are reported as they happen, throughout the trial.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	2.1

Reporting groups	
Reporting group title	Acipimox
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Acipimox	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Acipimox	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	10 / 11 (90.91%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Burning sensation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Impaired healing			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Choking			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	3 / 11 (27.27%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Sinonasal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Investigations			

Blood magnesium decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Head injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Wound haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	5 / 11 (45.45%)	
occurrences (all)	1	4	
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Eructation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Contusion			
subjects affected / exposed	2 / 10 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Dermatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Hypoaesthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			

subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin discolouration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Myopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Alveolar osteitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Bacterial vaginosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Nasopharyngitis			

subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Oral infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Post-acute COVID-19 syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2019	Substantial Amendment 01 This amendment relates to two additional documents not previously submitted as part of the initial REC approval process. These documents include: • AIMM Sleep Wake Diary (attached) – This is a diary to be used for the subset of participants who will undergo activity monitoring as part of the trial. It is detailed in the approved trial protocol but was not included in the original application • Pregnancy Follow-up Consent Form - To formally obtain consent for follow-up for trial participants or their partner should a pregnancy occur during their participation in the trial
08 July 2020	Substantial Amendment 02 Inclusion criteria updated to include patients (≥ 16 years) with clinician-confirmed, genetically proven mitochondrial myopathy. Protocol, PIS, Brief PIS and Lily wording adverts updated to reflect change Assay analysis of primary outcome measure changed following assay validation work Secondary outcome measure of cycle ergometry made optional due to COVID-19 and access to facilities Frequency of follow-up phone calls reduced from weekly to Weeks 1, 2, 4 and 8, and optional at Week 10 Options for participants wishing to withdraw from trial or from active treatment clarified and refined to withdrawal from active treatment with continued follow-up by trial team, or withdrawal with no further data collection; protocol updated and Participant Withdrawal Form and Discontinuation of Treatment Form created Protocol updated to allow use of routine bloods taken in previous three months period to be used for screening, to minimise visit length participant burden Protocol updated to provide more contraceptive guidance for participants and their partners while on the trial Protocol updated to include signposting of participants via Patient Identifying Centres (PICs) Staffing and contact detail changes: • Protocol, GP letter, Hospital Consultant letter, Thank you letters, invitation letter and consent form - Update of Chief Investigator's title and role • Protocol updated to include: additional trial management and data management staff, updated Sponsor Pharmacy email and Sponsor address, and to remove Prof Turnbull as a Co-investigator Information sheets created to provide participants with information prior to, and following, muscle biopsy Pregnant Partner Information sheet created to provide information formally to a pregnant partner of a trial participant, prior to obtaining their consent for pregnancy follow-up and to accompany previously approved Consent to Follow up Form

16 December 2020	Substantial Amendment 03 Dr Naomi Thomas replaced Professor Gráinne Gorman as Principal Investigator at the single trial site PIC Site Invitation Letter created for PIC sites to give to potential participants Patient Information Sheet, brief Patient Information Sheet, invitation letter and adverts updated to correct timings of follow-up phone calls
11 June 2021	Substantial Amendment 04 Change of Trial Manager Transfer of Physical Examination and assessment of Vital Signs from Baseline to Screening Addition of Oxygen saturations to Vital Signs tests ECG only to be performed in patients undergoing exercise testing Removal of laboratory analyses in trial protocol: Investigation of potential molecular markers of mitochondrial biogenesis, and metabolomic analysis to identify novel biomarkers in blood and urine Alteration of laboratory analyses: use of an assay kit forNAD+/NADH ratio via metabolomics in muscle, and quantitative proteomics analysis made optional Correction of typographical errors in protocol Addition of box for witness details to Informed Consent Form, and amendment of wording in Patient Information Sheet and protocol to allow for oral consent, with independent witnessing and signature of the Consent Form, for patients with weakness/ataxia due to their condition Addition of information relating to site procedures to manage potential non-availability of web-based randomisation system Change of individual performing expectedness assessment of SARs, due to change in Sponsor process Avoidance of unblinding during recruitment process, in this cohort of patients Update to Contraception Guidance to include exclusively same-sex relationships Protocol updated to state that eligibility bloods analysed in Newcastle Laboratories in previous three months are acceptable for screening Clarification of which staff members can carry out follow-up phone calls Separation of Chief Investigator (CI) and Principal Investigator (PI) responsibilities Addition of information relating to filing withdrawal forms at site Clarification of: SAE, site pregnancy reporting, and Statistics procedures, and timing of dispensing and fitting of wearable activity monitor, and provision of sleep-wake diary
29 July 2021	Substantial Amendment 05 This amendment was submitted for the formal halt of trial recruitment. A temporary recruitment pause was necessary as the trial IMP reached the end of its shelf life as a result of COVID-19 and delays to the second IMP campaign.
02 December 2021	Substantial Amendment 06 Change of definition of end of trial, from Last Patient Last Visit (LPLV) date, to date of last data collection for last participant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	The interruption involved the withdrawal from trial treatment of the five participants that were participating at the trial at the time. The interruption was due to the COVID-19 pandemic, and the decision was made in the best interests of the participants, as mitochondrial patients are considered vulnerable and as such, at the time, were subject to shielding measures.	01 December 2020

Notes:

Limitations and caveats

None reported