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A pivotal, international, randomised, double-blind, efficacy and safety trial of sodium valproate in paediatric and adult patients with Wolfram Syndrome

Submission date
16/04/2018

Recruitment status
No longer recruiting

Registration date
20/04/2018

Overall study status
Completed

Last Edited
27/11/2023

Condition category
Genetic Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Current plain English summary as of 24/11/2023:
Background and study aims
Wolfram syndrome is a rare genetic disease. It can cause diabetes and vision impairment in children, deafness, poor bladder function, balance problems, sleep disorders and sometimes depression. Life expectancy is reduced due to brain degeneration. There is currently no cure and nothing to prevent or slow down disease progression. The goal of this trial is to develop a treatment that will prevent or delay disease progression. Sodium valproate treats the disease in cell models of Wolfram syndrome and is already used to treat other conditions in children and adults, such as epilepsy. However, like all medicines, it has side effects. These include nausea, anaemia, tremor and mood disturbances. Sodium valproate must not be given to pregnant women. Therefore, the aim of this study is to show that sodium valproate is safe and effective at slowing disease progression in Wolfram syndrome patients.

Who can participate?
Patients aged 6 and older with Wolfram syndrome who have sufficient assessable vision (via visual acuity) during the course of the trial.

What does the study involve?
Participants are randomly allocated to be treated with either sodium valproate or placebo (dummy medicine). Participants are closely monitored for any side effects, for changes in vision and for changes in brain scans.

What are the possible benefits and risks of participating?
The potential benefit is to see whether sodium valproate can slow down or halt the disease process in Wolfram syndrome. If sodium valproate is taken by women who are pregnant, there is a high risk that it will harm the unborn child.

Where is the study run from?
1. Birmingham Children's Hospital NHS Foundation Trust (UK)
2. University Hospitals Birmingham NHS Foundation Trust (UK)
3. Montpellier University Hospital (France)
4. Hôpital Européen Georges Pompidou (France)
5. Medical University of Lodz (Poland)
6. Unidad de Gestión Clínica Almería Periferia (Spain)

When is the study starting and how long is it expected to run for?
December 2018 to October 2024

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Miss Amy Lamb
treatwolfram@trials.bham.ac.uk

Previous plain English summary from 07/02/2020 to 24/11/2023:
Background and study aims
Wolfram syndrome is a rare genetic disease. It can cause any of diabetes and vision impairment in children, deafness, poor bladder function, balance problems, sleep disorders, and sometimes depression. Life expectancy is reduced due to brain degeneration. There is currently no cure, and nothing to prevent or slow down the disease. The goal of this trial is to develop a treatment that will prevent or delay the disease progressing. Sodium valproate treats the disease in cell models of Wolfram syndrome and is already used to treat other conditions in children and adults. However, like all medicines, it has side effects. These include nausea, anaemia, tremor, and mood disturbances; and it must not be given to pregnant women. Therefore, the aim of this study is to show that sodium valproate is safe, and effective at slowing the disease process in Wolfram.

Who can participate?
People with Wolfram syndrome who have sufficient vision to be able to assess during the course of the trial.

What does the study involve?
Participants are randomly allocated to be treated with either sodium valproate or placebo (dummy medicine). Participants are closely monitored for any side effects, for changes in vision, and for changes in brain scans.

What are the possible benefits and risks of participating?
The potential benefit is to see whether sodium valproate can slow down or halt the disease process in Wolfram syndrome. If sodium valproate is taken by women who are pregnant, there is a high risk that it will harm the unborn child.

Where is the study run from?
1. Birmingham Children's Hospital NHS Foundation Trust (UK)
2. University Hospitals Birmingham NHS Foundation Trust (UK)
3. Montpellier University Hospital (France)
4. Hôpital Européen Georges Pompidou (France)
5. Medical University of Lodz (Poland)
6. Unidad de Gestión Clínica Almería Periferia, (Spain)

When is the study starting and how long is it expected to run for?
December 2018 to December 2023

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Mrs Amandip Malhi
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Previous plain English summary:
Background and study aims
Wolfram syndrome is a rare genetic disease. It causes diabetes and blindness in children, then deafness, loss of bladder control, loss of balance, sleep disorders, and sometimes depression. Death is in mid-life from damage to brain cells and brain shrinkage. There is no cure, and nothing to prevent or slow down the disease. The goal is to develop a treatment that will prevent or delay the disease progressing. Sodium valproate treats the disease in cell models of Wolfram syndrome and is already used to treat epilepsy in children. However, it should not be used in people with liver disorders, or in pregnancy, and it can cause side effects including nausea, anaemia, tremor, and mood disturbances. Therefore, its safety and effectiveness needs to be tested for Wolfram patients. The aim of this study is to show that sodium valproate is safe and effective at slowing the disease process.

Who can participate?
Patient aged 5 or older with Wolfram syndrome

What does the study involve?
Participants are randomly allocated to be treated with either sodium valproate or placebo (dummy medicine). Participants are closely monitored for any side effects, for changes in vision, and for changes in brain scans.

What are the possible benefits and risks of participating?
The potential benefit is to see whether sodium valproate can slow down or halt the disease process in Wolfram syndrome. If sodium valproate is taken by women who are pregnant, there is a high risk that it will harm the unborn child. Severe liver damage including liver failure, sometimes resulting in fatalities, has been very rarely reported. Early symptoms may include sudden onset of tiredness, lack of energy, and drowsiness.

Where is the study run from?
1. Birmingham Children’s Hospital NHS Foundation Trust (UK)
2. University Hospitals Birmingham NHS Foundation Trust (UK)
3. Institute des Neurosciences de Montpellier (France)
4. Hôpital Européen Georges Pompidou (France)
5. Medical University of Lodz (Poland)
6. Servicio Andaluz de Salud Área de Gestión Sanitaria Norte de Almeria (Spain)

When is the study starting and how long is it expected to run for?
December 2018 to December 2023

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Mrs Amandip Malhi
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Contact information

Type(s)
Scientific

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Additional identifiers

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Integrated Research Application System (IRAS)
222620

ClinicalTrials.gov (NCT)
NCT03717909

Protocol serial number
CPMS 37502, IRAS 222620

Study information

Scientific Title
A pivotal, international, randomised, double-blind, efficacy and safety trial of sodium valproate in paediatric and adult patients with Wolfram Syndrome

Acronym
Treat Wolfram

Study objectives

The aim of the trial is to show that Sodium Valproate is safe and effective at slowing the Wolfram syndrome disease process.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 19/03/2018, West of Scotland REC (Research Ethics, Clinical Research and Development, West Glasgow Ambulatory Care Hospital, Dalnair Street, Glasgow, G3 8SJ, United Kingdom; +44 (0)141 232 1808; WoSREC1@ggc.scot.nhs.uk), ref: 18/WS/0020
2. Approved 17/04/2018, Health Research Authority (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)207 104 8193; hra.approval@nhs.net), ref: 18/WS/0020

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Wolfram syndrome

Interventions
Current intervention as of 24/11/2023:
Patients will be randomized 2:1 to either treatment with sodium valproate or matching placebo (randomised preferably to sodium valproate). Thus using 70 patients as the assumed sample size, 47 patients would be randomised to receive sodium valproate and 23 to receive placebo.

Current intervention:
Treatment will initially commence at a dose based on the patient's body weight and increase over 4 weeks to a maximum of 800 mg/day for patients aged 6 to 12 years or 1600 mg/day for those aged 12 and over. For example:
Child under 45 kg: start dose up to 10 mg/kg/day in 1 or 2 divided doses in 200-mg or 400-mg increments, increasing to 40 mg/kg/day by week 4; maximum 800 mg per day, 400 mg per dose.
Child over 45 kg and 12 years or older, or adult: start dose 600 mg/day in 2 divided doses (week 1); 1000 mg/day in 2 divided doses (week 2); 1200 mg/day in 2 divided doses (week 3); 1600 mg/day in 2 divided doses (week 4).

The duration of this trial will be approximately 5 years. Patients will participate for a total of 37 months from the date of consent until the end of the trial.

Stage 1 is screening tests.
Stage 2 is the start of treatment, within 4 weeks of the screening tests.
Stage 3 includes follow-up visits 3, 6 and 12 weeks after starting treatment, for safety checks.
Stage 4 includes visits to the hospital at 6, 12, 18, 24, 30 and 36 months, for safety checks and measures of effectiveness. Tests of vision will be done every 6 months; and brain scans every 12

months.
Stage 5 is the final telephone call 4 weeks after the treatment has finished, for safety checks. Once the last participant has completed the last visit, the data collection will be closed and data analysed. The trialists anticipate a trial report within
6 months of the last participant completing the study.

Previous intervention from 07/02/2020 to 24/11/2023:
Patients will be randomized 2:1 to either treatment with sodium valproate or matching placebo (randomised preferably to sodium valproate). Thus using 70 patients as the assumed sample size, 47 patients would be randomised to receive sodium valproate and 23 to receive placebo.

Treatment will initially commence at a dose based on the patient's body weight and increase over 4 weeks to a maximum of 800 mg/day for patients aged 5 to 12 years or 1600 mg/day for those aged 12 and over. For example:
Child under 45 kg: start dose up to 10 mg/kg/day in 1 or 2 divided doses in 200-mg or 400-mg increments, increasing to 40 mg/kg/day by week 4; maximum 800 mg per day, 400 mg per dose.
Child over 45 kg and 12 years or older, or adult: start dose 600 mg/day in 2 divided doses (week 1); 1000 mg/day in 2 divided doses (week 2); 1200 mg/day in 2 divided doses (week 3); 1600 mg /day in 2 divided doses (week 4).

The duration of this trial will be approximately 5 years. Patients will participate for a total of 37 months from the date of consent until the end of the trial.

Stage 1 is screening tests.
Stage 2 is the start of treatment, within 4 weeks of the screening tests.
Stage 3 includes follow-up visits 3, 6 and 12 weeks after starting treatment, for safety checks.
Stage 4 includes visits to the hospital at 6, 12, 18, 24, 30 and 36 months, for safety checks and measures of effectiveness. Tests of vision will be done every 6 months; and brain scans every 12 months.
Stage 5 is the final telephone call 4 weeks after the treatment has finished, for safety checks. Once the last participant has completed the last visit, the data collection will be closed and data analysed. The trialists anticipate a trial report within 12 months of the last participant completing the study.

Previous intervention from 18/01/2019 to 07/02/2020:
Treatment will initially commence at a dose based on the patient's body weight and increase over 4 weeks to a maximum of 800mg/day for patients aged 5- <12 years or 1600mg/day for those aged 12 and over.
For example:
Child under 45kg: Start dose: 10mg/kg/day in 1 or 2 divided doses, increasing in 200mg. increments to 40mg/kg/day by Week 4
Maximum dose: 5- <12 years - 800mg. per day (400mg per dose); 12 years and over – 1600mg. per day (800mg. per dose)
Child over 45kg or Adult: start dose 600mg/day (Week 1); 1000mg/day in in Week 2; 1200mg/day in Week 3 and 1600mg/day in Week 4. All daily doses are given as 2 divided doses. Maximum dose: 5 -<12 years - 800mg. per day (400mg. per dose); 12 years and over - 1600mg. per day (800mg per dose)

Original intervention:
Treatment will initially commence at 10mg/kg/day and be gradually increased by 10mg/kg/day to 40mg/kg/day (maximum 800mg/day 5-11 years; 1600mg/day 12 years of age and over) to ensure safety, for example:

Child under 45kg: start dose up to 10mg/kg/day in 1 or 2 divided doses in 200mg increments, increasing to 40mg/kg/day by week 4; maximum 800mg per day, 400mg per dose.
Child over 45kg or Adult: start dose 600mg/day in 2 divided doses (week 1); 1000mg/day in 2 divided doses (week 2); 1200mg/day in 2 divided doses (week 3); 1600mg/day in 2 divided doses (week 4).

The duration of this trial will be approximately 5 years. Patients will participate for a total of 37 months from the date of consent until the end of the trial.

Stage 1 is screening tests.
Stage 2 is the start of treatment, within 4 weeks of the screening tests.
Stage 3 is a follow-up visit 6 weeks after starting treatment, for safety checks.
Stage 4 includes visits to the hospital at 6, 12, 18, 24, 30 and 36 months, for safety checks and measures of effectiveness. Tests of vision will be done every 6 months; and brain scans every 12 months.
Stage 5 is the final telephone call 4 weeks after the treatment has finished, for safety checks.
Once the last participant has completed the last visit, the data collection will be closed and data analysed. The trialists anticipate a trial report within 12 months of the last participant completing the study. This will be the first quarter of 2023.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Sodium valproate gastro-resistant 200 mg oral tablets

Primary outcome(s)
Visual acuity is measured on the logMAR scale by sight tests in clinic using ETDRS charts at Day -28, Day 0 (baseline), Day 180, Day 360, Day 540, Day 720, Day 900, Day 1080

Key secondary outcome(s))
Current secondary outcome measures as of 24/11/2023:
1. Safety, measured by adverse events according to CTCAE v4 at days 0, 7, 21, 42, 90, 180, 270, 360, 450, 540, 630, 720, 810, 900, 990, 1080 and 1110.
2. Tolerability, measured by dose achieved, days of treatment, and treatment-related dose reductions and discontinuations. Treatment dose escalation period measured at day 0 to day 28.
3. Pons volume (PV), a surrogate marker for neurodegeneration, measured and recorded in mm3 by standardised analysis of MR images of the Pons, and brain substructure volumes. Measured at days -28, 360, 720 and 1080.
4. Brainstem volume, measured by MRI as with PV at days -28, 360, 720 and 1080.
5. Retinal nerve thickness, measured by Optical Coherence Tomography at days -28, 360, 720 and 1080.
6. Colour vision, measured using the Hardy Rand and Rittler (HRR) colour vision test at days -28, 360, 720 and 1080.
7. Contrast sensitivity (if available) at days -28, 360, 720 and 1080.
8. Visual fields measured by the local centre standard process (the same technique must be used throughout the patient participation to the study) at days -28, 360, 720 and 1080.
9. Data on cataracts measured by incidence and frequency of cataracts examination of the

patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080.
10. Afferent pupillary defects measured by incidence and frequency of afferent pupillary defects examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080.
11. Strabismus measured by incidence and frequency of strabismus examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080.
12. Nystagmus measured by incidence and frequency of nystagmus examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080.
13. Presence of changes in the inside of the eye, such as retinopathy, maculopathy and optic atrophy, assessed by fundoscopy at days -28, 360, 720 and 1080.
14. Visual evoked potentials measured by changes in visual evoked potentials (if available) measured by electrophysiology at days -28, 360, 720 and 1080.
15. Balance measured by Mini-BEST test measured at days -28, 360, 720 and 1080.
16. Hearing measured by pure tone audiometry measured at days -28, 360, 720 and 1080.
17. Severity of Wolfram syndrome symptoms assessed using the Wolfram Unified Rating Scale (WURS) at days -28, 360, 720 and 1080.
18. Mood assessed using the Kid-screen questionnaire for patients aged 8-18 years and the Hospital Anxiety and Depression Score (HADS) for adults at day -28 OR day 0 (depending on whether eligibility has been confirmed), and then days 21, 42, 90, 180, 360, 540, 720, 900 and 1080.
19. Insulin secretion assessed by mixed meal tolerance test and/or C-peptide measured at days -28, 360, 720 and 1080.
20. Glycated haemoglobin levels in blood measured at days -28, 360, 720 and 1080.
21. Quality of life measured by PedsQL (Paediatric quality of life inventory) for paediatric patients, by visual function questionnaires for children [VQoL-C and FVQ-C (8-12)], young people [VQoL-YP and FVQ-YP (13-18)], and adults [VFQ25 self-report or interviewer- administered for adults] at days -28, 180, 360, 540, 720, 900 and 1080.
22. Sleep, measured by the Sleep-related Breathing disorder scale extracted from the Pediatric Sleep Questionnaire (referred to as PSQ) parent report for those aged under 18 years, and Pittsburgh Sleep Quality Index (PSQI) Self-Report measured at Day-28, Day 180, Day 360, Day 540, Day 720, Day 900, Day 1080.

Other outcome measures:
23. Biomarkers of sodium valproate (SV) response in patients (proliferative capacity and CDKN1A expression) measured by change in the vitro proliferative capacity and CDKN1A expression of PBMCs (% baseline) measured at days -28, 180, 360, 720 and 1080.
24. Biomarkers of sodium valproate (SV) response in patients (effect of SV on cytokine production) measured by change in the vitro effect of SV on cytokine production in PBMCs (% of baseline) measured at days -28, 180, 360, 720 and 1080.
25. Biomarkers of sodium valproate (SV) response in patients (plasma) measured by change in plasma cytokine levels in patients (% of baseline) measured at days -28, 180, 360, 720 and 1080.
26. Fractional anisotropy of optic nerves measured using Diffusion Tensor Imaging (DTI) on MRI measured at days -28, 180, 360, 720 and 1080.
27. Global and regional brain volume measurements to assess atrophy of brain structures by MRI measured at days -28, 180, 360, 720 and 1080.
28. Change in urodynamic function measured by urodynamic function tests/flow ratio measured at days -28, 180, 360, 720 and 1080, and urology questionnaires [ICIQ-FLUTS (adult females), ICIQ-MLUTS (adult males) and ICIQ-CLUTS (children)] measured at days -28, 180, 360, 540, 720, 900 and 1080

Previous secondary outcome measures from 10/02/2020 to 24/11/2023:
1. Safety, measured by adverse events according to CTCAE v4 at days 0, 7, 21, 42, 90, 180, 270, 360, 450, 540, 630, 720, 810, 900, 990, 1080 and 1110

2. Tolerability, measured by dose achieved, days of treatment, and treatment-related dose reductions and discontinuations. Treatment dose escalation period measured at day 0 to day 28
3. Ventral pons volume (VPV), a surrogate marker for neurodegeneration, measured and recorded in mm3 by standardised analysis of MR images of the pons measured at days -28, 360, 720 and 1080
4. Brainstem volume, measured by MRI as with VPV at days -28, 360, 720 and 1080
5. Retinal nerve thickness, measured by Optical Coherence Tomography at days -28, 360, 720 and 1080
6. Colour vision, measured using the Hardy Rand and Rittler (HRR) colour vision test at days -28, 360, 720 and 1080
7. Visual fields measured by the local centre standard process (the same technique must be used throughout the patient participation to the study) at days -28, 360, 720 and 1080
8. Data on cataracts measured by incidence and frequency of cataracts examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080
9. Afferent pupillary defects measured by incidence and frequency of afferent pupillary defects examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080
10. Strabismus measured by incidence and frequency of strabismus examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080
11. Nystagmus measured by incidence and frequency of nystagmus examination of the patient's eyes by an ophthalmologist at days -28, 360, 720 and 1080
12. Presence of changes in the inside of the eye, such as retinopathy, maculopathy and optic atrophy, assessed by fundoscopy at days -28, 360, 720 and 1080
13. Visual evoked potentials measured by changes in visual evoked potentials (if available) measured by electrophysiology at days -28, 360, 720 and 1080
14. Balance measured by Mini-BEST test measured at days -28, 360, 720 and 1080
15. Hearing measured by pure tone audiometry measured at days -28, 360, 720 and 1080
16. Severity of Wolfram syndrome symptoms assessed using the Wolfram Unified Rating Scale (WURS) at days -28, 360, 720 and 1080
17. Mood assessed using the Kidscreen questionnaire for patients aged 8-18 years and the Hospital Anxiety and Depression Score (HADS) for adults at day -28 OR day 0 (depending on whether eligibility has been confirmed), and then days 21, 42, 90, 180, 360, 540, 720, 900 and 1080
18. Insulin secretion assessed by mixed meal tolerance test and/or C-peptide measured at days -28, 360, 720 and 1080
19. Glycated haemoglobin levels in blood measured at days -28, 360, 720 and 1080
20. Quality of life measured by PedsQL (Paediatric quality of life inventory) for paediatric patients, by visual function questionnaires for children [VQoL-C and FVQ-C (8-12)], young people [VQoL-YP and FVQ-YP (13-18)], and adults [VFQ25 self report or interviewer- administered for adults] at days -28, 180, 360, 540, 720, 900 and 1080
21. Sleep, measured by Sleep-related Breathing disorder scale extracted from the Pediatric Sleep Questionnaire (referred to as PSQ) parent report for those aged under 18 years, and Pittsburgh Sleep Quality Index (PSQI) Self-Report measured at Day-28, Day 180,Day 360, Day 540, Day 720, Day 900, Day 1080

Other outcome measures:
22. Biomarkers of sodium valproate (SV) response in patients (proliferative capacity and CDKN1A expression) measured by change in the vitro proliferative capacity and CDKN1A expression of PBMCs (% baseline) measured at days -28, 180, 360, 720 and 1080
23. Biomarkers of sodium valproate (SV) response in patients (effect of SV on cytokine production) measured by change in the vitro effect of SV on cytokine production in PBMCs (% of baseline) measured at days -28, 180, 360, 720 and 1080
24. Biomarkers of sodium valproate (SV) response in patients (plasma) measured by change in

plasma cytokine levels in patients (% of baseline) measured at days -28, 180, 360, 720 and 1080
25. Fractional anisotropy of optic nerves measured using Diffusion Tensor Imaging (DTI) on MRI measured at days -28, 180, 360, 720 and 1080
26. Global and regional brain volume measurements to assess atrophy of brain structures by MRI measured at days -28, 180, 360, 720 and 1080
27. Change in urodynamic function measured by urodynamic function tests/flow ratio measured at days -28, 180, 360, 720 and 1080, and urology questionnaires [ICIQ-FLUTS (adult females), ICIQ-MLUTS (adult males) and ICIQ-CLUTS (children)] measured at days -28, 180, 360, 540, 720, 900 and 1080

Previous secondary outcome measures from 18/01/2019 to 10/02/2020:
1. Safety, measured by adverse events according to CTCAE v4 at Day 0, Day 7, Day 21, Day 42, Day 90, Day 180, Day 270, Day 360, Day 450, Day 540, Day 630,
Day 720, Day 810, Day 900, Day 990, Day 1080, Day 1110
2. Tolerability, measured by dose achieved, days of treatment, and treatment-related dose reductions and discontinuations. Treatment dose escalation period measured at Day 0 to day 28
3. Ventral Pons Volume (VPV), a surrogate marker for neurodegeneration, measured and recorded in mm3 by standardised analysis of MR images of the Pons measured at Day -28, Day 360, Day 720, Day 1080
4. Brainstem volume, measured by MRI as with VPV measured at Day -28, Day 360, Day 720, Day 1080
5. Retinal nerve thickness, measured by Optical Coherence Tomography at Day -28, Day 360, Day 720, Day 1080
6. Colour vision, measured by Farnsworth plates measured at Day -28, Day 360, Day 720, Day 1080
7. Visual fields measured by Humphrey Perimetry measured at Day -28, Day 360, Day 720, Day 1080
8. Data on cataracts measured by incidence and frequency of cataracts measured at Day -28, Day 360, Day 720, Day 1080
9. Afferent pupillary defects measured by incidence and frequency of afferent pupillary defects measured at Day -28, Day 360, Day 720, Day 1080
10. Strabismus measured by incidence and frequency of strabismus measured at Day -28, Day 360, Day 720, Day 1080
11. Nystagmus measured by incidence and frequency of nystagmus measured at Day -28, Day 360, Day 720, Day 1080
12. Visual evoked potentials measured by changes in visual evoked potentials (if available) measured at Day -28, Day 360, Day 720, Day 1080
13. Smell, measured by Smell Test (UPSIT) measured at Day -28, Day 360, Day 720, Day 1080
14. Balance, measured by Mini-BEST test measured at Day -28, Day 360, Day 720, Day 1080
15. Hearing, measured by pure tone audiometry measured at Day -28, Day 360, Day 720, Day 1080
16. Wolfram Unified Rating Scale (WURS) measured at Day -28, Day 360, Day 720, Day 1080
17. Mood, measured by Questionnaires measured using the Kidscreen (Patients aged 8-18), Hospital Anxiety and Depression Score (HADS) for Adults measured at Day 0, Day 21, Day 42, Day 90, Day 180, Day 360, Day 540, Day 720,Day 900, Day 1080
18. Pancreatic beta cell reserve–tolerance test measured by mixed meal tolerance test measured at Day -28, Day 360, Day 720, Day 1080
19. Pancreatic beta cell reserve-glycated haemoglobin measured by percentage glycated haemoglobin measured at Day -28, Day 360, Day 720, Day 1080
20. Urodynamic assessment is measured using the Urodynamics bladder flow rates and urology questionnaire (ICIQ-FLUTS) measured at Day -28, Day 180, Day 360, Day 540, Day 720, Day 900, Day 1080

21. Quality of Life measured by PedsQL (Paediatric quality of life inventory) for paediatric patients, by Visual function questionnaires for children and for young people [VQOL_C/YP (children) and VFQ25 (adults)] measured at Day-28, Day 180,Day 360, Day 540, Day 720, Day 900, Day 1080
22. Sleep, measured by Paediatric Sleep Questionnaire (PSQ) Parent Report for those under 18, and Pittsburg Sleep Quality Index (PSQI) Self-Report measured at Day-28, Day 180,Day 360, Day 540, Day 720, Day 900, Day 1080

Other outcome measures:
1. Biomarkers of sodium valproate (SV) response in patients (proliferative capacity and CDKN1A expression) measured by change in the vitro proliferative capacity and CDKN1A expression of PBMCs (% baseline) measured at: Day-28, Day 360 ,Day 720, Day 1080
2. Biomarkers of sodium valproate (SV) response in patients (effect of SV on proliferative capacity and CDKN1A expression) measured by change in the vitro effect of SV on proliferative capacity and CDKN1A expression measured at Day-28, Day 360 ,Day 720, Day 1080
3. Biomarkers of sodium valproate (SV) response in patients (effect of SV on cytokine production) measured by change in the vitro effect of SV on cytokine production in PBMCs (% of baseline) measured at Day-28, Day 360, Day 720, Day 1080
4. Biomarkers of sodium valproate (SV) response in patients (plasma) measured by change in plasma cytokine levels in patients (% of baseline) measured at Day-28, Day 360, Day 720, Day 1080
5. Fractional anisotropy of optic nerves measured using Diffusion Tensor Imaging (DTI) on MRI measured at Day-28, Day 360 ,Day 720, Day 1080
6. Global and regional brain volume measurements to assess atrophy of brain structures by MRI measured at Day-28, Day 360 ,Day 720, Day 1080

Original secondary outcome measures:
1. Safety, measured by adverse events according to CTCAE v4 at Day 0, Day 7, Day 21, Day 42, Day 90, Day 180, Day 270, Day 360, Day 450, Day 540, Day 630, Day 720, Day 810,Day 900, Day 990, Day 1080, Day 1110
2. Tolerability, measured by dose achieved, days of treatment, and treatment-related dose reductions and discontinuations. Treatment dose escalation period (Day 0 to day 42)
3. Ventral Pons Volume (VPV), a surrogate marker for neurodegeneration, measured and recorded in mm3 by standardised analysis of MR images of the Pons at Day -28, Day 360, Day 720, Day 1080
4. Brainstem volume, measured by MRI as with VPV at Day -28, Day 360, Day 720, Day 1080
5. Retinal nerve thickness, measured by Optical Coherence Tomography at Day -28, Day 360, Day 720, Day 1080
6. Colour vision, measured by Farnsworth plates at Day -28, Day 360, Day 720, Day 1080
7. Visual fields, measured by Humphrey Perimetry at Day -28, Day 360, Day 720, Day 1080
8. Smell, measured by Smell Test (UPSIT) at Day -28, Day 360, Day 720, Day 1080
9. Sleep, measured by Sleep questionnaire and Visual function questionnaires (VQOL_CYP (children) and VFQ25 (adults) at Day -28, Day 42, Day 180, Day 360, Day 540, Day 720, Day 900, Day 1080
10. Balance, measured by Mini-BEST test measured at Day -28, Day 360, Day 720, Day 1080
11. Hearing, measured by pure tone audiometry at Day -28, Day 360, Day 720, Day 1080
12. Wolfram Unified Rating Scale measured at Day -28, Day 360, Day 720, Day 1080
13. Mood, measured by questionnaires measured using the Kidscreen (Patients aged 5-18), Hospital Anxiety and Depression Score (HADS) at day of treatment Day 0, Day 21, Day 42, Day 90, Day 180, Day 270, Day 360, Day 450, Day 540, Day 630, Day 720, Day 810,Day 900, Day 990, Day 1080, Day 1110
14. Quality of life, measured by PedsQL questionnaire (Paediatric patients) at Day -28, Day 42,

Day 180, Day 360, Day 540, Day 720, Day 900, Day 1080
15. Urodynamic assessment using the Urodynamics bladder flow rates and urology questionnaire (ICIQ-FLUTS) at Day -28, Day 42, Day 180, Day 360, Day 540, Day 720, Day 900, Day 1080

Completion date
31/10/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/11/2023:
1. Definitive diagnosis of Wolfram syndrome, as determined by the presence of both of the following:
1.1. Documented diabetes mellitus diagnosed under 16 completed years according to WHO or ADA criteria and/or documented optic atrophy diagnosed under 16 completed years.
1.2. Documented functionally relevant mutations on one or both alleles of the WFS1 gene based on historical test results (if available) or from a qualified laboratory at screening.
2. Aged 6 years or older and weighing at least 20 kg.
3. Visual acuity assessed as either the right eye or left eye having a LogMAR score of 1.6 or better on an ETDRS chart, with or without corrected vision.
4. Written informed consent.
5. Females of childbearing potential will only be included after a negative pregnancy test as per the national valproate pregnancy prevention programme or equivalent. If sexually active, they must agree to use a highly effective contraception measure and to pregnancy testing at each clinic follow-up visit.
6. Sexually active men with a female partner of childbearing potential must agree to the use of condoms and the use of a highly effective method of contraception by the female partner.
7. Patient willing and able to meet all protocol-defined visits for the duration of the trial. The definition of protocol defined visits includes all visits except MRI visits when a patient is not suitable for the procedure (e.g. patient with cochlear implants/braces would still be eligible for the study) or declines the procedure (patient’s own decision).

Previous inclusion criteria from 07/02/2020 to 24/11/2023:
1. Definitive diagnosis of Wolfram syndrome, as determined by the presence of both of the following:
1.1. Documented diabetes mellitus diagnosed under 16 completed years according to WHO or ADA criteria and/or documented optic atrophy diagnosed under 16 completed years
1.2. Documented functionally relevant mutations on one or both alleles of the WFS1 gene based on historical test results (if available) or from a qualified laboratory at screening
2. Aged 5 years or older
3. Visual acuity assessed as either the right eye or left eye having a LogMAR score of 1.6 or better on an ETDRS chart, with or without corrected vision
4. Written informed consent
5. Females of childbearing potential will only be included after a negative pregnancy test as per the national valproate pregnancy prevention programme or equivalent. If sexually active, they must agree to use a highly effective contraception measure and to pregnancy testing at each clinic follow-up visit
6. Sexually active men with a female partner of childbearing potential must agree to the use of condoms and the use of a highly effective method of contraception by the female partner
7. Patient willing and able to meet all protocol-defined visits for the duration of the trial. The definition of protocol defined visits includes all visits except MRI visits when a patient is not

suitable for the procedure (e.g. patient with cochlear implants/braces would still be eligible for the study) or declines the procedure (patient's own decision).

Previous inclusion criteria from 18/01/2019 to 07/02/2020:
Patients must meet all of the following criteria to be eligible for enrolment:
1. The patient has a definitive diagnosis of Wolfram syndrome, as determined by the following:
1.1. Documented diabetes mellitus diagnosed under 16 completed years according to WHO or ADA criteria plus documented optic atrophy diagnosed under 16 completed years AND
1.2. Documented functionally relevant mutations on one or both alleles of the WFS1 gene based on historical test results (if available) or from a qualified laboratory at screening
2. The patient is aged 5 years or older
3. The patient's visual acuity assessed as either the right eye or left eye having a LogMAR score of 1.6 or better on an ETDRS chart, with or without corrected vision
4. Written informed consent
5. Females of childbearing potential will only be included after a negative highly sensitive urine pregnancy test. If sexually active, they must agree to use a highly effective contraception measure and to pregnancy testing at each clinic follow-up visit- see 4.1.1 for further information
6. Sexually active men with a female partner of childbearing potential must agree to the use of condoms and the use of a highly effective method of contraception by the female partner
7. Patient willing and able to meet all protocol-defined visits for the duration of the Trial

Original inclusion criteria:
1. The patient has a definitive diagnosis of Wolfram syndrome, as determined by the following:
1.1. Documented diabetes mellitus diagnosed under 16 completed years according to WHO or ADA criteria plus documented optic atrophy diagnosed under 16 completed years AND
1.2. Documented functionally relevant mutations on one or both alleles of the WFS1 gene based on historical test results (if available) or from a qualified laboratory at screening
2. Patient aged 5 years or older
3. The patient's visual acuity assessed as either the right eye or left eye having a LogMAR score of 1.6 or better on an ETDRS chart, with or without correction
4. Written informed consent
5. Females of childbearing potential will only be included after a negative highly sensitive urine pregnancy test. If sexually active, they must agree to use a highly effective contraception measure and to pregnancy testing at each clinic follow-up visit- see 4.1.1 for further information
6. Sexually active men with a female partner of childbearing potential must agree to the use of condoms and the use of a highly effective method of contraception by the female partner
7. Patient willing and able to meet all protocol-defined visits for the duration of the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
6 years

Sex

All

Total final enrolment
63

Key exclusion criteria
Current exclusion criteria as of 18/01/2019:
Patients who meet any of the following criteria are not eligible for this Trial:
1. The patient has clinically significant non-Wolfram related CNS involvement which is judged by the Investigator to be likely to interfere with the accurate administration and interpretation of protocol assessments
2. The patient has a diagnosis of a mitochondrial myopathy
3. The patient has active liver disease, has a personal or family history of liver dysfunction related to known genetic disorders, or patient has porphyria
4. The patient has received treatment with any investigational drug within the 30 days prior to Trial entry
5. The patient is currently taking sodium valproate; or has a known hypersensitivity to sodium valproate or its excipients
6. Any other acute or chronic medical, psychiatric, social situation or laboratory result that, based on investigator's judgment, would jeopardize patient safety during trial participation, cause inability to comply with the protocol, or affect the Trial outcome
7. The patient is currently breastfeeding
8. The patient has known urea cycle disorders
9. The patient has one of the following disorders: Lactose intolerance, the Lapp lactase deficiency, or glucose- galactose malabsorption

Previous exclusion criteria:
1. The patient has clinically significant non-Wolfram related Central Nervous System (CNS) involvement, which is judged by the Investigator to be likely to interfere with the accurate administration and interpretation of protocol assessments
2. The patient has a diagnosis of a mitochondrial myopathy
3. The patient has active liver disease, has a personal or family history of liver dysfunction, or has porphyria
4. The patient has a mutation in the POLG gene that is known to be associated with sodium valproate induced liver injury
5. The patient has received treatment with any investigational drug within the 30 days prior to study entry
6. The patient is currently taking sodium valproate; or has a known hypersensitivity to sodium valproate or its excipients
7. Any other acute or chronic medical, psychiatric, social situation or laboratory result that, based on investigator's judgment, would jeopardize patient safety during trial participation, cause inability to comply with the protocol, or affect the study outcome
8. The patient is currently breastfeeding
9. The patient has Known urea cycle disorders
10. The patient has one of the following disorders: lactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

Date of first enrolment
08/01/2019

Date of final enrolment

01/11/2021

Locations

Countries of recruitment
United Kingdom

England

France

Poland

Spain

Study participating centre
Birmingham Children's Hospital NHS Foundation Trust
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
CHU de Montpellier - Hôpital Gui de Chauliac
Département de Neurologie Pédiatrique
80 Rue Augustin Fliche
Montpellier
France
34295

Study participating centre
Hôpital Européen Georges Pompidou
Functional Unit of Ophthalmology
Ophthalmological Rare Diseases Reference Center

Assistance Publique Hôpitaux de Paris
20, Rue Leblanc
Paris
France
75015

Study participating centre
Medical University of Lodz
Department of Paediatrics, Oncology and Haematology
36/50 Sporna Street
Lodz
Poland
91-738

Study participating centre
Unidad de Gestión Clínica Almería Periferia
Servicio Andaluz de Salud
Distrito Sanitario Almería
Unidad de Gestión Clínica Almería Periféria
Almeria
Spain
04600

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/P007732/1

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The CRCTU has a defined procedure in place for data sharing which ensures that the necessary legal and ethical requirements are met. For more information please read their Data Sharing Policy which is based on guidelines published by the Information Commissioners Office, the Medical Research Council (MRC) Methodology Hubs called “Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials” and is compliant with Cancer Research UK Policy on Data Sharing and Preservation.

Application for access to data is made via completion of data request form from the interested parties (stating the reason for the request, type of data requested, how the data will be stored /used and other information like ethical approval etc) and the request will be reviewed by the Trial management group. The data will be stored on University of Birmingham (Sponsor) servers and the data retained as per the study protocol and current regulatory approval authorisation (data will be stored for at least 25 years after the end of the study).

The patient consent form states “ I understand that anonymised data and samples from the trial may be provided to other 3rd parties (e.g. pharmaceutical companies or other academic institutions) for research, safety monitoring or licensing purposes. This data will be provided to countries inside and outside the European Economic Area. My identity will remain anonymous.” This consent allows the clinical data to be accessed for research and safety monitoring drug licensing purposes.

Website for more information: https://www.birmingham.ac.uk/research/crctu/data-sharing-policy.aspx

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No