MUSTANG

Investigating the role of Miglustat in the management of a patient with Tangier's Disease: a single case experiment

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FUNDER

This trial is funded by the National Institute for Health Research (NIHR).

Protocol Information

This protocol describes the MUSTANG trial and provides information about procedures for entering the participant. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but the site entering the participant is advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
GCP	Good Clinical Practice
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SCTU	Southampton Clinical Trials Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee

KEYWORDS
Tangier Disease, Miglustat, Hypoalphalipoproteinaemia

TRIAL SYNOPSIS

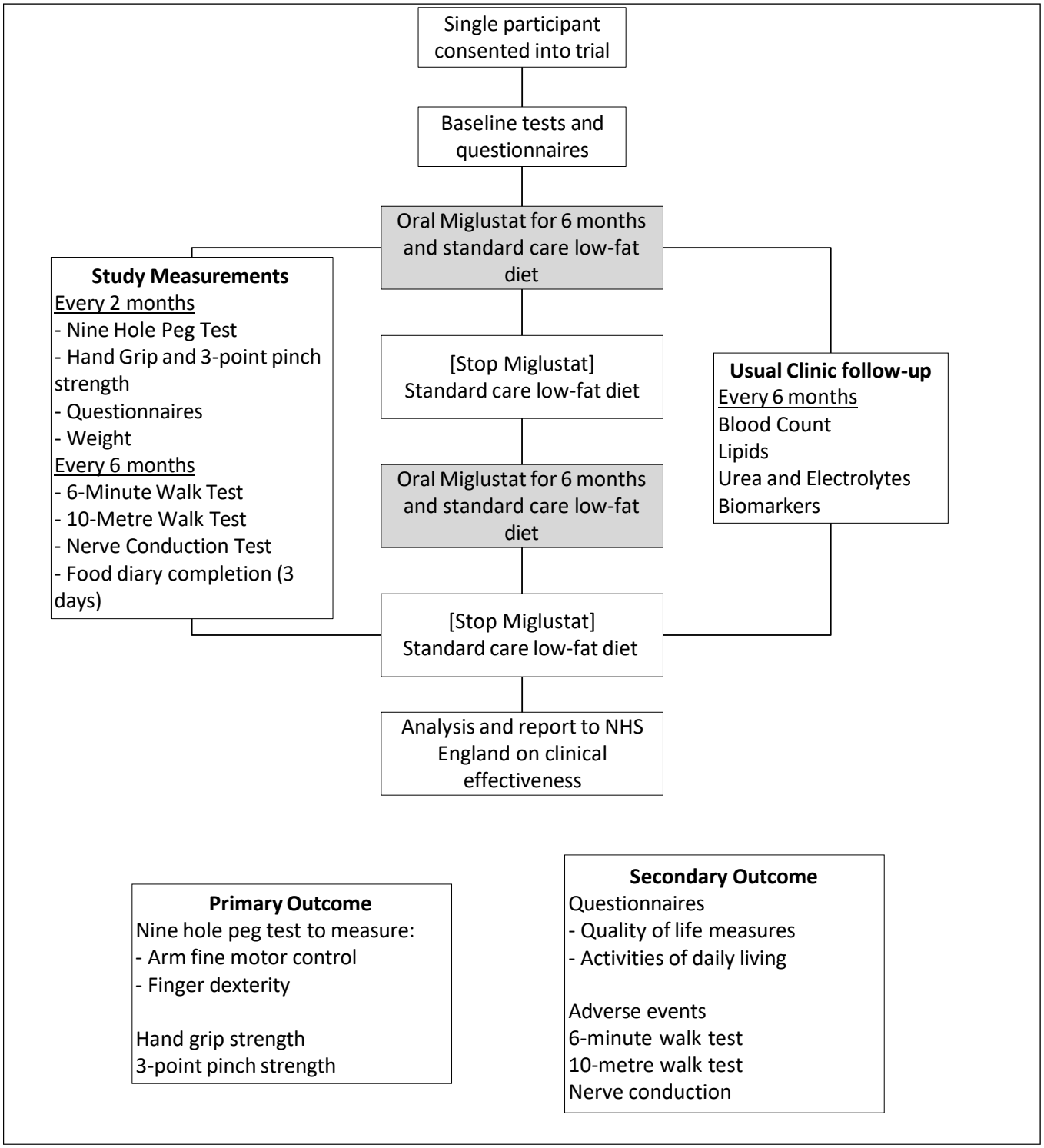
Short title:	MUSTANG – Miglustat in Tangier Disease
Full title:	Investigating the role of Miglustat in the management of a single patient with Tangier's Disease: a single case experiment.

Phase:	Phase II/III
Population:	A single patient with Tangier disease, who is already known to the chief investigator, and keen to try the intervention.
Overall Objective:	To determine, in a single patient, the efficacy of Miglustat to improve cholesterol metabolism and resulting neuropathy caused by Tangier disease.
Primary Objective:	To determine the efficacy of Miglustat to improve arm fine motor control, finger dexterity and grip strength.
Secondary Objective:	To determine the efficacy of Miglustat to improve Quality of Life, activities of daily living, aerobic capacity, endurance, ambulation and nerve conduction.
Mechanistic Objective:	To investigate the potential mechanisms by which Miglustat does, or does not, have an effect.
Rationale:	Tangier disease is an ultra-rare inborn error of metabolism, leading to neuropathy and cardiac disease. The only established treatment is low fat diet – but this slows the disease rather than curing it. No pharmaceutical intervention was known to have an effect. However, in 2010 in Italy a patient was diagnosed with Niemann-Pick type C disease and given Miglustat, a licenced treatment for the disease. The patient showed improvement after 4 months, however it was later shown through genetic assessment that she had been misdiagnosed, and the underlying issue was Tangier disease. Miglustat was discontinued, and when reviewed 7 months later her symptoms had worsened. Miglustat was then restarted and over the following six months she showed a progressive improvement in her symptoms. This suggests that Miglustat may have an effect in Tangier disease. A cellular study comparing Niemann-Pick type C and Tangier disease has further shown that the known cellular hallmarks of Niemann-Pick type C are present in Tangier disease, as it involves secondary inhibition of the Niemann-Pick type C disease cellular pathway. Furthermore, when cells from Tangier disease patients were treated in culture with Miglustat the Niemann-Pick type C phenotypes were corrected. Together, these provide evidence for the potential mechanism of action of Miglustat in Tangier disease. There is a 21 year old patient with Tangier disease who has developing progressive neuropathy, and may benefit from taking Miglustat. NHS England is willing to fund treatment with Miglustat for the patient, but only in a context where evidence of efficacy in this patient can be obtained. This trial therefore aims to investigate the efficacy of Miglustat to improve cholesterol metabolism and resulting neuropathy in a

	single patient, and to gain insight into the mechanism of Miglustat in Tangier disease.
Trial Design:	An n-of-1 study of ABAB design, with alternating periods of intervention and control.
Sample size:	One participant, with 4 crossover periods (i.e. 2 on drug, 2 off drug), and three points of observation within each condition (2, 4, and 6 months from the beginning of the period) will give 90% power at a 5% significance level to show the minimum detectable change between the on and off periods for 9-hold peg test and grip strength.
Investigational Medicinal Product/s:	Miglustat
Dosage Regimen / Duration of Treatment:	Alternating 6 months periods of (1) up to 200mg Miglustat by mouth three times a day, (2) no pharmacological intervention. Miglustat to be titrated up to 200mg three times a day, as tolerated by patient.

Co-Primary Trial Endpoints:	• Time on 9-hole peg test • Hand grip strength
Secondary Trial Endpoints:	• 6-minute walk test • 10-metre walk test • Quality of life (EQ-5D-5L) • Activities of daily living (Overall Neuropathy Limitations Scale and the Rasch-built Overall Disability Scale (R-ODS)) • Adverse events • Clinical assessment • Nerve conduction studies • Full blood count • Measurement of lipids • Urea • Electrolytes **Mechanistic evaluation** • Biomarker assessment
Total Number of Sites:	Single site

TRIAL SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

Month	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
On/Off Miglustat	Off	On						Off						On						Off					
Informed consent	X																								
Clinical Assessment - Physical examination - Blood Count - Lipids - Urea - Electrolytes	X						X						X						X						X
Weight	X		X		X		X		X		X		X		X		X		X		X		X		X
Mechanistic Evaluation - Biomarkers	X						X						X						X						X
Primary Physiotherapist Assessment - 9-hole peg test - Hand grip and 3-point pinch strength	X		X		X		X		X		X		X		X		X		X		X		X		X
Questionnaires - Quality of Life (EQ-5D-5L) - Activities of Daily Living "Neuropathy Limitations Scale" and "Rasch-built Overall Disability Scale" (R-ODS))	X		X		X		X		X		X		X		X		X		X		X		X		X
Adverse Events	X		X		X		X		X		X		X		X		X		X		X		X		X
Secondary Physiotherapist Assessment - 6-minute walk test - 10-metre walk test	X						X						X						X						X
Nerve Conduction Study	X						X						X						X						X
Patient Dietary diary							X						X						X						X

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected for the remainder of the sixth month intervention condition (unless the participant has specifically stated that they do not want this to happen).

1 INTRODUCTION

1.1 BACKGROUND

Tangier disease, also known as hypoalphalipoproteinemia is an ultra-rare autosomal recessive inborn error of metabolism caused by loss-of-function variant in the ATP-binding cassette transporter A1 (ABCA1) gene [1, 2]. This transporter plays a key role in the reverse transfer of free cholesterol from peripheral cells to lipid-poor Apo A-I particles [1, 3]. Tangier disease therefore is characterised by a severe reduction in high density lipoprotein in the bloodstream. It was first recognised in 1959 in a patient from Tangier Island, in Virginia USA. There are fewer than 100 patients described worldwide with only two adult patients currently known in the UK. It is likely underdiagnosed, particularly when presenting in adults.

As a consequence of deficiency of cholesterol metabolism, patients develop depositions of cholesterol esters. These deposits can be found throughout lymphoid tissues, bone marrow, liver and spleen and nervous system. Hepatosplenomegaly is common. The major issues noticed by adult patients are peripheral neuropathy and ischemic cardiovascular disease.

Until recently management was limited to diet modification – a low fat diet can slow disease progression. No pharmaceutical intervention was known to have an effect. However, in 2010 in Italy a patient presented with a complex set of issues which had progressed over the previous 2 years including splenomegaly, dysarthria, dysphagia, ataxia, tongue enlargement, prurigo nodularis, legs lymphedema, pancytopenia and bone marrow foam cells. She was diagnosed with Niemann-Pick type C disease and given 300mg Miglustat a day (which is approved in the European Union for that condition). After 4 months she was considered to have improved. After 6 months of treatment her neurological examination was negative, skin lesions were very mild and both tonsils were normal in size and colour. Electromyography of upper and lower limbs was normal. It was later shown through genetic assessment that she had been misdiagnosed, and the underlying issue was Tangier disease. Miglustat was discontinued, and when reviewed 7 months later her skin lesions had worsened. The patient complained about reduced ability to focus attention, memory defects and slower thought processes. As a response to this the Miglustat was restarted and over the following six months she showed a progressive amelioration of the skin lesions and a subjective improvement of general and mental wellbeing, with less fatigue and faster thought processes [4].

This suggests that Miglustat may have an effect in Tangier disease.

This hypothesis was further strengthened by a cellular study comparing Niemann-Pick type C and Tangier disease. The study hypothesised that if the Niemann-Pick type C modifying drug Miglustat also corrected in Tangier Disease there may be mechanistic convergence between these two diseases. When Niemann-Pick type C and Tangier disease cells were compared all the known cellular hallmarks of Niemann-Pick type C were found to be present in Tangier disease as it involves secondary inhibition of the Niemann-Pick type C disease cellular pathway [5].

Furthermore, when cells from Tangier disease patients were treated in culture with Miglustat the Niemann-Pick type C phenotypes were corrected [5]. Miglustat is the only disease modifying therapy in Niemann-Pick type C. These findings greatly strengthen the scientific rational for treating Tangier disease patients with Miglustat.

One 21-year-old patient has Tangier disease in the UK with a level of severity where potential benefit could be gained from Miglustat. The patient presented with significant visual impairment and bilateral corneal opacity removed aged one. It was only at 6 years of age the diagnosis of TD came to light when the patient presented with the characteristic tonsil enlargement and pathological examination. Their HDL cholesterol was very low at 0.1 mmol/L with hypochromic microcytic anaemia. The diagnosis of tangier disease was confirmed by molecular genetic study showing homozygous variant of IVS35+1G>A in the ABCA1 gene. Despite the known risk of neuropathy, the patient has had no neurological symptoms till their teens and the nerve conduction study in 2014 was normal.

In the last four years the patient has developed a progressive neuropathy involving both upper and lower limbs with winging of the scapula, impaired hand function and foot drops. This has led to significant impairment in usual activity, higher education, and self-care. In addition, the patient is experiencing severe problems in walking which impinge on activities of daily living. In the last few years this has progressed to require walking aids and support for day to day needs with significant reduction in quality of life. The natural history from here is likely to result in severe disability.

We therefore designed an n-of-1 study, where the patient will participate in alternating periods of drug and no intervention, each lasting 6 months. The patient's performance will be assessed during each period and analysed for a signal of effect.

N-of-1 studies offer an opportunity to establish the efficacy of an intervention for a defined patient [6,7]. We thus need an approach which Perdices has described as a single subject design[8]. This is an approach which has previously been used to inform policy on access to expensive treatments [9] and for which robust guidance on conduct [6] and reporting [10] exists.

Mechanistically, as Tangier disease is a secondary lysosomal storage disease, circulating B cells can be used throughout the clinical study (from EDTA blood samples) to measure relative lysosomal volume as the Platt group have reported in a large cohort of Niemann- Pick type C patients [11]. This will allow this cellular biomarker to be monitored throughout this n-of-1 trial. Since the study can't be blinded, and is only conducted in one patient, the mechanistic elements will allow understanding of the plausibility of any clinical changes.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Miglustat is currently licensed in the UK and Europe for two indications. For Niemann-Pick type C the licensed dose is 200mg three times a day. For Gaucher Disease it is 100mg three times a day. The main adverse effect of Miglustat is gastrointestinal (GI) upset, in particular diarrhoea. This can be mitigated by dietary change and/or reduced dose. The other common side effect is low platelets which will require Full Blood Count (FBC) monitoring every 6 months. Other rare side effects may include transient neurological deterioration. The safety profile of this drug in this class of diseases is well established, despite the current lack of efficacy evidence.

The proof of concept for the clinical intervention in this study derives from the sole previous experience of this drug in Tangier disease, reported by Sechi and discussed in 1.1 [4, 5]. No other treatments are available, with a low-fat diet only being able to slow the progression of the disease. The natural history for Tangier disease is likely to result in severe disability. We hypothesise that Miglustat will improve cholesterol metabolism such that the patient's mobility, hand fine motor function and neuropathy will improve.

This patient is the only possible participant in the UK with this disease, at a stage which may be amenable to pharmaceutical treatment. The patient is keen to try this drug despite the current lack of evidence of efficacy beyond the single Italian case. The patient is prepared to risk the possibility of listed adverse effects, knowing he will be appropriately monitored through the study. Standard care, such as low-fat diet, will continue throughout the study, and will be monitored using a dietary diary.

Study endpoints have been selected in conjunction with the patient to identify a set of outcomes which address his perceived clinical problems.

NHS England are willing to fund treatment with Miglustat for this patient, but only if there is a robust process to assess the efficacy of the treatment for this patient. Experience in this patient may also inform commissioning policy for other future patients in England and perhaps set a benchmark for similar repurposing of drug for an ultra-rare disease.

Mechanistic evaluation

The biochemical mechanistic studies will determine whether this patient has an expanded lysosomal compartment at baseline (in line with studies published on four Tangier patients [5]) and whether this is reduced over time in response to treatment and relapses off treatment. In parallel, biochemical measurements of stored glycosphingolipids will give a quantitative read out of stored lipids and their response to treatment. Our hypothesis is that they will be reduced with similar kinetics to the relative lysosomal volume measurements. This will aid interpretation of the, possibly subjective, clinical outcomes. If biochemical and nerve conduction changes align with clinical response, then we can have far more confidence that any reported clinical change is causally related to drug administration.

2 TRIAL OBJECTIVES

	Objective	Endpoint used to evaluate
Primary:	To determine the efficacy of Miglustat to improve arm fine motor control, finger dexterity and grip strength.	• Time on 9-hole peg test • Hand grip strength • 3-point pinch strength
Secondary:	To determine the efficacy of Miglustat to improve Quality of Life, activities of daily living, aerobic capacity, endurance, and ambulation.	• 6-minute walk test • 10-metre walk test • EQ-5D-5L • Overall Neuropathy Limitations Scale • R-ODS • Adverse events • Clinical Assessment • Nerve conduction study
Mechanistic:	To investigate the potential mechanisms by which Miglustat does, or does not, have an effect.	• Biomarker assessment

3 TRIAL DESIGN

A N-of-1 trial, of ABAB design, in a single patient comparing their experience both on and off drug. The patient will receive alternating periods of drug and no-drug. Each treatment period is 6 months long.

The study will start with an 'on-drug' period (following baseline assessment), then alternate every 6 months until the end of the study.

3.1 TRIAL ENDPOINTS

3.1.1 Co-Primary endpoints

- Time taken to complete 9-hole peg test (fine motor control and finger dexterity)
- Hand strength: grip and 3-point pinch strength

3.1.2 Secondary endpoint

- 6-minute walk test (aerobic capacity and endurance)
- 10-metre walk test (gait, ambulation and leg strength)
- EQ-5D-5L (Quality of life)
- Overall Neuropathy Limitations Scale and the Rasch-built Overall Disability Scale (R-ODS) (Activities of daily living)

- Adverse events
- Nerve conduction
- Clinical assessment
    - Physical Examination
    - Full blood count
    - Measurement of lipids
    - Urea
    - Electrolytes
- Biomarker assessment
    - Relative lysosomal volume in circulating B cells
    - Lipid analysis of circulating B cells
    - Oxysterols
    - Lyso-SM-509, lyso-sphingomyelin
    - Bile acid derivatives

3.2 DEFINITION OF END OF TRIAL

The trial will end once the participant has completed the last visit.

4 SELECTION AND ENROLMENT OF PARTICIPANT

4.1 CONSENT

Consent to enter the trial must be sought from the participant only after a full explanation has been given, a Participant Information Sheet offered and time allowed for consideration. Signed participant consent must be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participant remain within the trial for the purposes of follow-up and data analysis. Follow up would be continued for the remainder of the sixth month intervention period the participant is in at the time. The participant is free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes and the original filed in the Investigator Site File. With informed consent from the participant, a copy of the Informed consent form will be scanned and securely transferred to SCTU to allow for central monitoring of consent forms. Secure transfer is by means of SafeSend https://safesend.soton.ac.uk/, encrypted email, or secure nhs.net email.

4.2 INCLUSION CRITERIA

There are limited inclusion and exclusion criteria as the single participant for the trial has already been identified.

- Diagnosis of Tangier Disease
- Patient aged 18 and above
- The participant must be willing and able to provide informed consent.
- The participant must be using effective contraception

4.3 EXCLUSION CRITERIA

- Severe renal impairment.
- Contraindications to Miglustat treatment, as detailed in the SmPC (see Appendix 3)

4.4 REGISTRATION PROCEDURES

The patient will be given the Participant Information Sheet prior to the baseline outpatient clinic visit. The patient will provide informed consent at the baseline clinic visit.

4.5 CONTRACEPTION

Effective contraception must be used during treatment. The participant should avoid conceiving a child during the trial.

A male participant must use a condom as method of contraception if sexually active, in line with CTFG guidance on contraception:
(https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf).

The study participant must follow contraception advice during the treatment period and up to 3 months after the last IMP dose, in line with Miglustat SmPC.

5 TRIAL OBSERVATIONS AND PROCEDURES

5.1 SCREENING PROCEDURES

No screening procedures will be used as the single participant is already known to the Chief Investigator.

5.2 TRIAL PROCEDURES

Informed consent

Informed consent to be taken by PI or delegated trial team member during the patient's baseline appointment. The patient will be sent the Patient Information Sheet at least one day before attending the appointment.

IMP dispensing

During on treatment periods Miglustat will be dispensed by University Hospitals Birmingham pharmacy. The patient will be able to pick this up in person, or this can be supplied directly to the patient's home via the University Hospitals Birmingham pharmacy patient transport system (for example, in the case of COVID-19 restricitons). The participant will be given 2 months supply at a time.

Clinical assessment

Conducted by Principal Invesitgator, Sub-Principal Investigator, or other delegated qualified person, as part of regular patient follow-up at outpatient clinic at baseline and every 6 months thereafter (treatment as usual). This will include physical examination, and the below samples being taken by a Research Nurse:

- Full blood count (EDTA)
- Lipids (Gold-top tube)
- Urea (Urine sample)
- Electrolytes (Gold-top tube)

Mechanistic evaluation

Additional study assessment, to be conducted as part of outpatient clinic at baseline and every 6 months thereafter. Blood samples will be taken to measure the following biomarkers:

- Relative lysosomal volume in circulating B cells
- Lipid analysis of circulating B cells
- Oxysterols
- Lyso-SM-509, lyso-sphingomyelin

- Bile acid derivatives

See 'Mechanistic evaluation blood sample storage and processing' below.

Primary Physiotherapist assessment

In person/remote assessment completed by a delegated physiotherapist at baseline and every 2 months thereafter. This consists of:

- 9-hole peg test
- Hand grip and 3-point pinch test

These should be completed in person whenever possible, however if the patient is unable to attend (for example, due to COVID-19 restrictions), the handgrip dynamometer and 9-hole peg test can be sent to the patient's home, and tests administed remotely via telephone or video call, with permission from the patient, by delegated physiotherapist.

Secondary Physiotherapist assessment

In person assessment completed by a delegated physiotherapist at baseline and every 6 months thereafter (at the end of each treatment condition).

- 6-minute walk test
- 10-metre walk test

With the patient's consent, walk tests will be video recorded to help observe if there are any Gait changes. If the patient is unable to do the tests in person (for example, due to COVID-19 restrictions), these tests cannot be completed remotely. The reason for them being missed should be recorded on the CRF.

Questionnaires

To be administered by Research team in clinic, by post, or telephone at baseline and every 2 months thereafter.

- EQ-5D-5L (Quality of life)
- Overall Neuropathy Limitations Scale and the Rasch-built Overall Disability Scale (R-ODS) (Activities of daily living)

These should be completed in person whenever possible, however if the patient is unable to attend (for example, due to COVID-19 restrictions), these can be sent by post and administered over the phone/via video call, with permission from the patient, by the SCTU Mustang Research Team or Birmingham NHS Trust Research Nurse. Consent must be provided by the patient for contact from the SCTU Mustang Research Team.

Adverse Events

Review of adverse events (if any) to be undertaken every two months by the Principal Investigator.

Nerve Conduction Study

A nerve conduction study will be completed at baseline and every 6 months thereafter at the Queen Elizabeth Hospital Birmingham.

The responsible neurologist/delegated person completing the test should be blinded to treatment phase (on/off Miglustat).

Weight

The participants weight (measured as part of usual care) will be recorded on the CRF at each trial visit (every 2 months). If the participant cannot attend the visit in person (for example, due to COVID-19 restrictions), they will be asked to complete this measurement at home. A set of scales will be posted to the participant to facilitate this, if required.

Dietary diary
The patient will be asked to complete a dietary diary for three days every 6-month intervention condition. They will be asked to complete this for the three days prior to their regular clinic visit (in month 6 of each condition).The patient will be instructed how to keep the dietary diary at baseline, and will be supplied with a copy of the diary.

GP Letter
A letter will be sent to the participant's GP informing them of their patient's participation.

Treatment as usual, which primarily consists of following a low-fat diet, will be maintained thorughout the trial.

Mechanistic evaluation blood sample storage and processing
A blood sample (EDTA, 10ml) for the evaluation of Relative lysosomal volume in circulating B cells and lipid analysis of cirulating B cells (from the mechanistic evaluation) will be transported to the Platt Lab, University of Oxford for anlaysis. This must be received by the laboratory within 3 days, however ideally within 48 hours of the sample being taken. Samples should not be shipped on a Friday, unless using same day delivery. The lab must be notified, via email, in advance of the sample date to ensure receipt. The sample is to be inverted 8-10 times and stored at ambient temperature. A blood sample (EDTA, 2ml) for the evaluation of oxysterols will be sent on dry ice to the Willink Lab, Manchester. A blood sample (EDTA, 2ml) for the evaluation of Lyso-SM-509 will be sent on a filtercard to Centogene AG, Schillingallee 68, 18055 Rostock, Germany.
A blood sample (li-heparin, 6ml) and a random urine (5ml) for the evaluation of bile acid derivatives will be sent to the Insitute of Child Health, Great Ormond Street Hospital.

All samples should be processed, stored and shipped according to instructions provided in the Lab Manual.

5.3 FOLLOW UP
The participant will be regularly monitored throughout the trial, as outlined in 5.2. No further follow-up is to be completed beyond end of trial.

5.4 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at the site should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

5.5 TRIAL DISCONTINUATION

In consenting to the trial, the participant has consented to the trial intervention, follow-up and data collection. The participant may be discontinued from the trial procedures at any time.

5.5.1 Reasons for trial discontinuation
The participant may be discontinued from the trial in the event of:

- Clinical decision, as judged by the CI
- Termination of trial by sponsor
- Participant choice

Full details of the reason for trial discontinuation should be recorded in the CRF and medical record.

5.6 WITHDRAWAL

The participant/legal representative is free to withdraw consent from the trial at any time without providing a reason. Should the participant decide at any point that they no longer want to take the study drug, the participant will be given the option to stay in the trial for follow-up only for the remainder of the 6-month treatment period. Should the participant decide they do not want to stay in the trial for follow-up, the trial will end.

Investigators should explain the value of remaining in trial follow-up and allowing this data to be used for trial purposes to the participant. Where possible, if the participant withdraws from trial treatment, they should remain in follow-up as per the trial schedule for the remainder of the 6-month treatment period. If participants additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect standard follow-up data and unless the participant explicitly states otherwise, follow-up data will continue to be collected.

Details of trial discontinuation (date, reason if known) should be recorded in the CRF and medical record.

5.7 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

The trial is not blinded. A placebo would need to induce GI tract side effects, which is deemed unethical and inappropriate.

6 TREATMENTS

6.1 TREATMENT SCHEDULE

Alternating 6-month long periods of (1) up to 200mg Miglustat by mouth three times a day, (2) no pharmacological intervention. This will be repeated for a total duration of 2 years as per section 6.3.

At the start of each intervention period the Miglustat dose can be titrated up to 200mg three times a day, according to patient tolerance, in line with the below guidelines. The treating clinician is able to titrate the dose (up to a maximum of 200mg three times a day) according to clinical judgement. Any changes in the dose should be recorded in the CRF.

1st Intervention period	Dose
4 weeks	100mg twice a day*
4 weeks	100mg three times a day
4 weeks	200mg three times a day

* If this dose is not tolerated by patient, down titrate to 100mg once/day.

At the start of the second intervention period, Miglustat dose can be titrated up to 200mg three times a day after four weeks of treatment at a dose of 100mg three times a day.

2nd Intervention period	Dose
4 weeks	Up to 100mg three times a day*
Week 5 onwards	Up to 200mg three times a day

* If this dose is not tolerated by patient, down titrate as per 1st Intervention Period.

6.2 IMP SUPPLY

IMP will be supplied through the pharmacy at University Hospitals Birmingham, who will acquire it through their usual purchasing channels. As this drug is prescribed for other patients in the trust with other indications there are established suppliers, and a pharmacy stock. The pharmacy is responsible for ordering, re-ordering, storage and distribution.

IMP will either be paid for by NHS England or donated by the manufacturer. NHS England will base their decision on whether to continue funding the drug for the patient beyond the end of the trial, based on the trial's findings.

The IMP will be supplied in its original packaging with the standard NHS dispensing label and in additon an IMP label which will specify:
'For Clinical Trial use only',
The trial name: MUSTANG Trial, Sponsor Identification number: RRK7088,
Include the Patient Trial ID, EudraCT Number: 2020-005505-13
Chief Invesitgiator Name, Dr Tarek Hiwot
Sponsor and Trial Site: University Hospitals Birmingham
NHS Foundation Trust
Birmingham, B15 2TH Tel & Sponsor telephone contact number.

6.3 ADMINISTRATION

Months 1-6
Up to 200mg Miglustat by mouth three times a day.

Months 7-12
No IMP, or non-IMP administration.

Months 13-18
Up to 200mg Miglustat by mouth three times a day.

Months 19-24
No IMP, or non-IMP administration.

6.4 ACCOUNTABILITY

The study drug provided for this study will be used only as directed in the study protocol.

The patient will be asked to return unused study medication at the end of each 6-month schedule. Returned tablets will be counted and recorded on the CRF and Drug Accountability Log.

Clinical Trials Pharmacy ITM, Pharmacy - University Hospitals Birmingham NHS Foundation Trust (Queen Elizabeth Hospital) have an establish system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from Janssen-Cilag are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- The Patient returns all unused medication and empty containers to the investigator.

All unused or returned medication, after drug accountability, should be destroyed and documented according to local procedures at the study site.

6.5 CONCOMITANT MEDICATIONS

Information on any treatment received by the participant, along with dose, frequency and therapeutic indication, from the baseline visit up to the end of the trial will be recorded in the case report form (CRF). This includes periods where Miglustat is not being administered (off-drug).

6.6 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

There are no prohibited or restricted therapies during the trial.

Co-enrollment in another interventional trial is allowed, subject to approval from the CI.

6.7 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY

Not Applicable

7 SAFETY

7.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered.
All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).
When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected. Reports which add significant information on specificity or severity of a known documented adverse event are to be considered unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** – *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*
- **Requires hospitalisation, or prolongation of existing hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.
** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: *It is the responsibility of the PI or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).*

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

7.2 SERIOUSNESS

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All adverse events that fulfil the criteria definition of 'serious' in protocol section 7.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

All SAEs must be reported immediately by the PI or delegate at the participating centre to the SCTU.

7.2.1 Exceptions

There are no relevant exceptions. All SAEs require reporting to the SCTU using the Serious Adverse Event Report Form.

7.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the MHRA will be informed of both parties' points of view.

Relationship	Description	Denoted
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	SAR/ SUSAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

7.4 EXPECTEDNESS

Expectedness assessments are made against the approved Reference Safety Information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	IB/SmPC	Section /Table No.	Manufacturer	Last updated on eMC
Zavesca (miglustat) 100 mg hard capsules	SmPC	4.8 Undesirable effects	Janssen-Cilag Ltd (United Kingdom)	18-Nov-2020 Located in Appendix 1

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AE should be recorded as 'unexpected'.

7.5 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the SCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

7.5.1 Reporting Details

For all SAEs, SARs and SUSARs an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and faxed/emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

Or

Contact SCTU by phone for advice and then fax or email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Fax: 0844 774 0621 or Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

The SAE report form asks for nature of event, date of onset, severity, outcome, causality and expectedness. The responsible investigator (or delegate) should assign the seriousness, causality and expectedness of the event with reference to the approved IMP IB/SmPC and provide version used for the assessment.
The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the NCI CTCAE v5.

Additional information should be provided as soon as possible if all information was not included at the time of reporting, but no more than 7 days after initial report.

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Elevations in liver biochemistry that meet Hy's Law criteria are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

7.5.2 Follow Up and Post-trial SAEs

The reporting requirement for all AEs and SAEs affecting the participant applies for all events occurring up to the end of the trial. This includes months 18-24 where the participant is not taking the trial treatment.

All unresolved adverse events should be followed by the investigator until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At the last scheduled visit, the investigator should instruct the participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

7.5.3 Non-serious AEs

All adverse events (unless specified as exceptions in this protocol) should be recorded in the relevant CRF and submitted to SCTU.

7.5.4 Pre-existing Conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions the conditions worsens during the trial. The condition, however, must be reported on the Medical History CRF. Any adverse events that occur after Informed Consent should be recorded on the AE CRF as per safety reporting section.

7.5.5 Pregnancy

If the participant's partner becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP/NIMP, the investigator must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy.

Follow-up is of course, dependent on obtaining informed consent for this from the participant's partner.

If the participant leaves the area, their new healthcare professional should also be informed.

7.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the necessary REC of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit all safety information to the REC in annual progress report and in the annual Development Safety Update Report.

7.7 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit the Developmental Safety Update Reports to MHRA annually.

8 STATISTICS AND DATA ANALYSES

8.1 METHOD OF RANDOMISATION

The study will not be randomised.

8.2 SAMPLE SIZE

The overarching concern in considering the sample size (number of periods on and off the drug) was what is reasonable to ask of the patient. An ABAB design already runs to 2 years. Whilst extending this to include further periods would increase the power, this was not felt to be acceptable by the patient nor the clinical team.

The nine-hole peg test has a minimum detectable change (which was also judged to be the minimum clinically important change) in the non-dominant hand of 7.46 seconds, and a standard deviation of 2.69 seconds[1] [12]. Using 4 crossover periods (i.e. 2 on drug, 2 off drug) each with three points of observation (i.e. 2, 4, and 6 months from the beginning of the period), assuming an alpha of 0.05 and a correlation between repeated measures of 0.6[2] we would have 90% power at a 5% significance level to show the minimum detectable change between the on and off periods.

In a systematic review, Roberts and colleagues describe a protocol for testing grip strength, and identified a minimum clinically important difference of around 6kg with a standard deviation of 2.3 [13]. Using similar assumptions to above we would have 90% power to detect this difference.

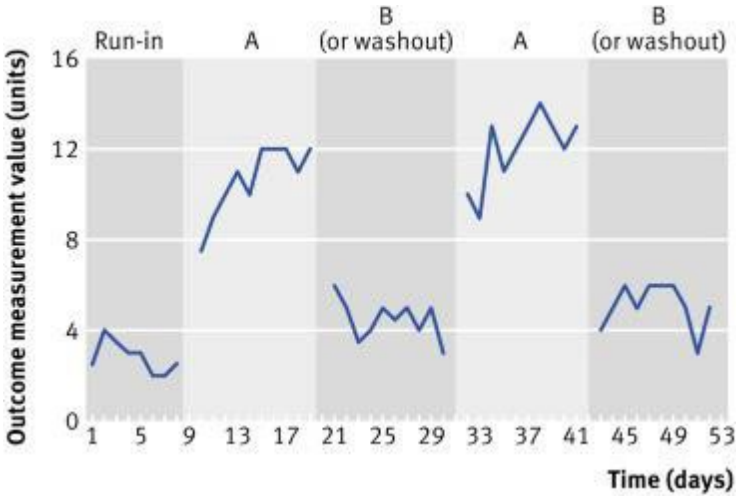
Both of these effects might be viewed as large [14, 15], but they have been seen on studies of other diseases; and the experience of the Italian patient makes them appear plausible.

In such a rare condition, it is difficult to estimate appropriate standard deviations and correlations because there is no literature on this particular condition and what literature there is in other conditions tend to look at between rather than within person measures. Moreover, the standard deviation might vary considerably from patient to patient and we are only interested in this one individual, for whom the values are unknown. We will therefore carefully monitor assumptions with the DMEC to ensure that we retain adequate power to still answer the research question.

8.3 STATISTICAL ANALYSIS

In line with the CONSORT extension for N-of-1 trials (CENT) we will present the data graphically (see recommended graph below) and descriptively for each period [10].

[1]



[1] This work was done in patients with Multiple Sclerosis – there is no work on this in patients with Tangier or similar disorders. It seems to us however reasonable that the clinically important differences would be similar

We will present the mean difference between treatments with 95% confidence intervals and conduct a paired t-test. We will also document any harms or adverse events due to the treatment medication.

9 REGULATORY

9.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

10 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

10.1 SPECIFIC ETHICAL CONSIDERATIONS

None.

10.2 ETHICAL APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee.

10.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

between the patient groups.

[2] Frisson [16] [12] suggests the plausible range is 0.5 – 0.7, we have taken the middle of the range.

10.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

10.5 INDEPENDENT PATIENT SUPPORT

The patient will be provided with contact details for Metabolic Support UK, a patient organisation for Inherited Metabolic Disorders.

11 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

11.1 INDEMNITY

The University Hospitals Birmingham NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

11.2 FUNDING

The National Institute for Health Research (NIHR) are funding this trial.

11.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

This trial is adopted onto/ automatically eligible for the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

11.4 PARTICIPANT PAYMENTS

The participant will not be paid for participation in this trial. The participant will be reimbursed for reasonable travel expenses to attend additional study visits. Travel expenses will not be reimbursed for attending their usual clinic visits.

12 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group and a combined Trial Steering Committee and Data Monitoring and Ethics Committee.

12.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the trial, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the trial.

The MUSTANG TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.2 COMBINED TRIAL STEERING COMMITTEE (TSC) AND INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC))

(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).

The combined TSC-DMEC will perform both of the below roles:

The TSC-DMEC will act as the oversight body on behalf of the Sponsor and Funder. The TSC-DMEC will meet in person or by video conference at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The aim of the TSC-DMEC is to safeguard the interests of the trial participant, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

The MUSTANG TSC-DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC/DMEC, including the timing of meetings, methods of providing information to and from the TSC/DMEC, frequency and format of meetings and relationships with other trial committees.

13 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning the participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the case report forms (CRF). CRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the CRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the CRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will be generated manually & raised by the SCTU trial team, if required. All alterations made to the CRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by signing the CRF. The CRF will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

14 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

15 MONITORING

15.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within the participant over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). The site will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU within the required timeframe. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

The consent form received by SCTU staff will be checked following the TMP and relevant SCTU SOPs.

15.2 CLINICAL SITE MONITORING

Site monitoring will occur where required, as detailed in the TMP. However due to COVID-19 being a highly contagious pandemic it is expected that no or very limited site monitoring will be conducted - including Source Data Verification (SDV). The Mustang trial will use an enhanced central monitoring process as detailed in the Mustang Trial risk assessment and trial monitoring plan, until safe and viable to resume on-site monitoring

15.2.1Source Data Verification

Upon receipt of a request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the CRF (taking into account data protection regulations). Access should also be given to trial staff and departments (e.g. pharmacy).

The participant's medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the Competent Authority. Details will remain confidential and participant's name will not be recorded outside the trial site without informed consent.

15.3 SOURCE DATA

Source documents are where data are first recorded, and from which participant's CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

15.4 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University Hospitals Birmingham NHS Foundation Trust (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

16 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 25years following the end of the trial.

Sites are responsible for archiving the ISF and participant's medical records.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

17 PUBLICATION POLICY

Data will be analysed and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the

basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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19 APPENDICES

APPENDIX 1 EXPECTED SIDE EFFECTS

Expected Adverse Events are recorded in the SmPC as versions specified in Section 7.4. Please refer to these approved documents for full list of expected side effects.

Summary of the safety profile

The most common adverse reactions reported in clinical studies with Zavesca were diarrhoea, flatulence, abdominal pain, weight loss and tremor. The most common serious adverse reaction reported with Zavesca treatment in clinical studies was peripheral neuropathy.

In 11 clinical trials in different indications 247 patients were treated with Zavesca at dosages of 50-200 mg t.i.d. for an average duration of 2.1 years. Of these patients, 132 had type 1 Gaucher disease, and 40 had Niemann-Pick type C disease. Adverse reactions were generally of mild to moderate severity and occurred with similar frequency across indications and dosages tested.

Tabulated list of adverse reactions

Adverse reactions from clinical trials and spontaneous reporting, occurring in >1% of patients, are listed in the table below by system organ class and frequency (very common: ≥ 1/10, common: ≥ 1/100 < 1/10, uncommon: ≥1/1,000 to <1/100, rare: ≥1/10,000 to <1/1,000, very rare: <1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders	
Common	Thrombocytopenia
Metabolism and nutrition disorders	
Very common	Weight loss, decreased appetite
Psychiatric disorders	
Common	Depression, insomnia, libido decreased
Nervous system disorders	
Very common	Tremor
Common	Peripheral neuropathy, ataxia, amnesia, paraesthesia, hypoaesthesia, headache, dizziness
Gastrointestinal disorders	
Very common	Diarrhoea, flatulence, abdominal pain
Common	Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia
Musculoskeletal and connective tissue disorders	
Common	Muscle spasms, muscle weakness
General disorders and administration site reactions	
Common	Fatigue, asthenia, chills and malaise
Investigations	
Common	Nerve conduction studies abnormal

Description of selected adverse reactions

Weight loss has been reported in 55% of patients. The greatest prevalence was observed between 6 and 12 months.

Zavesca has been studied in indications where certain events reported as adverse reactions, such as neurological and neuropsychological symptoms/signs, cognitive dysfunction and thrombocytopenia could also be due to the underlying conditions.

APPENDIX 2 CTCAE VERSION 5

Please go to the following website to access the CTCAE Version 5.

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX 3 MIGLUSTAT CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed:

List of excipients
Capsule contents
Sodium starch glycolate type A
Povidone K30
Magnesium stearate Ph. Eur. [vegetable]
Capsule shell
Titanium dioxide (E171)
Gelatin

20 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V1, 21-Dec-2020	Initial document
V2, 12-Aug-2021	- Addition of exclusion criteria: Contraindications to Miglustat treatment - Clarification of contraception requirements - Additional requirement for person conducting nerve conduction study to be blinded - Updated Mechanistic evaluation blood sample storage and processing details - Dietary diary to be kept for 3 days, instead of 7 days. - Additional requirement for patient's weight to be recorded at each trial visit (measured as part of usual care). - Additional IMP supply option added (donation from manufacturer) - Correction of minor typographical errors
V3 03-Mar-2022	- Inclusion of Video recording of patient walk tests - Inclusion of 2nd Intervention Period guidance dosing schedule table