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CASE REPORT

Miglustat as a Treatment for Adults with Tangier Disease Neuropathy: The MUSTANG N-of-1 Trial with 21 months Clinical Observation

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ABSTRACT

***Importance*:** Tangier disease (TD) is an ultra-rare disease, characterised by progressive peripheral neuropathy with no established treatment.
***Objectives*:** To determine whether miglustat improved the clinical status of a single patient with TD, and to investigate the possible mechanisms of miglustat in this patient.
***Design, Setting, and Participants*:** An n-of-1 ABAB study, alternating on and off treatment for 6-month periods, total study duration of 2 years with an additional compassionate-access period of 21 months.
***Exposure*:** Miglustat, an orphan drug licenced to treat Gaucher disease and Niemann–Pick disease, was repurposed.
***Main Outcomes and Measures*:** The study was designed with two co-primary endpoints: (a) time taken to complete the nine-hole peg test (fine motor control and finger dexterity), and (b) hand strength: grip and three-point pinch strength tests. Secondary endpoints were quality-of-life measures and biomarkers.
***Results*:** A 21-year-old (at baseline) left-handed male patient with TD, diagnosed at the age of 6 months, and disabling neuropathy was included in the study. Over 2 years, there was a small signal in our clinical measures that the drug may be beneficial. Compared with the 2 years prior to treatment, the patient had no relapse of neuropathy during his study period and further extension. During the 21-month treatment extension, he showed considerable improvement on primary endpoints. Biomarkers

Prior Publication and Presentation Abstracts based on the same study were submitted and accepted in the following conferences: (1) WORLDSymposium 2024 on Lysosomal Diseases. Tarekegn Geberhiwot, Antonio Ochoa-Ferraro, Andrew Cook, Frances Platt, Kerri-Lee Wallom, Nicola Condon, Investigating the role of miglustat in the management of a patient with Tangier disease: An n-of-1 study with alternating periods of intervention and control, Molecular Genetics and Metabolism, Volume 141, Issue 2, 2024,107837, ISSN 1096-7192. (2) SSIEM Annual Symposium 2023 between 29 August and 1 September 2023, Jerusalem, Israel. Investigating the Role of Miglustat in The Management of a Patient with Tangier's Disease: An N-Of-1 Study with Alternating Periods of Intervention and Control. Tarekegn Hiwot, Antonio Ochoa-Ferraro, Nicola Condon, Frances Platt, Kerri-Lee Wallom, Andrew Cook. (3) Scientific Program in 15th International Congress of Inborn Errors of Metabolism (ICIEM2025) from September 2nd to 6th, 2025, at the Kyoto International Conference Center. Miglustat as a treatment for adults with Tangier Disease Neuropathy: the MUSTANG N-of-1 trial with 21 months clinical observation.

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changed as expected based on the mechanism of action of miglustat. Nerve conduction studies showed a mild benefit. Importantly, the patient's reported experience suggested a meaningful benefit from miglustat.

Conclusions and Relevance: Miglustat may be used to treat neurological complications of TD. This study showed that an n-of-1 study to inform a policy decision is practical and may offer hope to patients with rare diseases.

Trial Registration: ClinicalTrials.gov Identifier: ISRCTN17945917. Registration date: 07/06/2021; 'retrospectively registered'.

Keywords: Miglustat; Tangier disease neuropathy; MUSTANG N-of-1 trial; Clinical trials

Key Summary Points

Why carry out this study?
A patient in the UK with Tangier disease had a manifestation of neuropathy that his clinician believed might benefit from Miglustat.
The service commissioner wanted evidence that this patient would benefit from miglustat before committing to funding lifelong treatment.

What was learned from the study?
While the patient appeared to benefit from miglustat, the clinical effects were not as dramatic as those shown in a previous Italian patient who had received this treatment. The patient's perceived benefit was much greater than clinical assessment would indicate.
The patient demonstrated continuous improvement in his perceived benefit upon extended follow-up while on medication.
N-of-1 studies can be effective in evaluating expensive treatments in rare diseases. Longer-term follow-up may however be necessary to investigate slowly arising effects.

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INTRODUCTION

Tangier disease (TD, OMIM #205400) is an ultra-rare autosomal recessive inborn error of metabolism caused by a loss-of-function variant in the adenosine triphosphate (ATP)-binding cassette transporter A1 (*ABCA1*) gene (9q31.1) [1, 2]. ABCA1 plays a key role in the reverse transfer of free cholesterol from peripheral cells to lipid-poor Apo A-I particles [1, 3], and its dysfunction leads to severely reduced high-density lipoprotein (HDL) levels. First recognised in 1959 on Tangier Island, Virginia, USA, fewer than 100 cases are reported worldwide, with only two adult cases known in the UK, suggesting underdiagnosis, particularly when presenting in adults.

As a consequence of the defect in cholesterol metabolism, cholesterol ester deposits accumulate in lymphoid tissues, bone marrow, liver, spleen, and nervous system. The major issues experienced by adult patients are peripheral neuropathy and ischemic cardiovascular disease. Until recently, management was limited to a low-fat diet, without a significant impact on the course of disease progression. No pharmacological intervention has yet been reported.

In 2010, an Italian patient presented with a complex set of issues which had progressed over the previous 2 years, including splenomegaly,

dysarthria, dysphagia, ataxia, tongue and tonsil enlargement, prurigo nodularis, leg lymphedema, pancytopenia and bone marrow foam cells. She was initially misdiagnosed with Niemann–Pick disease type C (NPC) and treated with miglustat (300 mg/day), a substrate reduction therapy approved in the European Union for treating NPC [4]. After 6 months, neurological examination was significantly improved, and tonsils were normal in size and colour. However, genetic testing later confirmed TD, not NPC, and discontinuation of miglustat led to symptom relapse detected at 7-month review. Reintroduction of miglustat resulted in progressive amelioration of Tangier-related symptoms [5].

This case suggests that miglustat may have an effect in TD, further supported by a cellular study comparing NPC and TD [6]. The study hypothesis was that if miglustat, an NPC-modifying drug, also corrected TD, there may be mechanistic convergence between these two diseases. Given the expected natural progression to severe disability, we hypothesised that miglustat treatment could improve cholesterol metabolism, thereby enhancing mobility, fine motor skills, and neuropathy symptoms.

METHODS

Study Setting and Design

The study was conducted at the University Hospital of Birmingham NHS Foundation Trust between April 2021 and March 2023. The study was approved by the North East–Newcastle and North Tyneside 2 Research Ethics Committee (REC reference:21/NE/0048) and registered as Clinical Trials (ClinicalTrials.gov Identifier: ISRCTN17945917, Registration date: 07/06/2021). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Patient consent was received for publication.

Using an n-of-1 study with an ABAB design in a single patient, we compared his experience on and off drug [7, 8]. Each treatment period lasted 6 months, including up-titration and based on the drug's washout time, and the cycle was repeated twice with two on and two off phases, followed by a 21-month observation period with continuous treatment under compassionate use. The study was non-randomised, starting with an on-drug phase, as we had collected baseline data and the patient was keen to start the drug as soon as possible. The patient's performance was assessed during each period and analysed for a signal of an effect. The patient and most clinicians were unblinded, but the neurologist performing assessments was blinded. A placebo was not used, as miglustat's side effects typically compromise blinding.

Patient-reported outcomes, biomarkers, and neurophysiologic assessments were documented. The study was designed with two co-primary endpoints: (a) time taken to complete the nine-hole peg test (fine motor control and finger dexterity) and (b) hand strength (grip and three-point pinch strength tests). Secondary endpoints included the 6-minute walk test, EuroQol 5-Dimension, 5-Level (EQ-5D-5L) (Quality of life), Overall Neuropathy Limitations Scale and the Rasch-built Overall Disability Scale (R-ODS), adverse events, nerve conduction, clinical assessment and biomarker assessment (relative lysosomal volume in peripheral blood mononuclear cells [PBMCs] and circulating B cells, lipid analysis of circulating B cells and plasma palmitoyl phosphocholine serine).

This pragmatic trial assessed miglustat effects (if any) in one patient to inform a commissioning decision. One of the comparators therefore had to be usual care. This essentially consists of a low-fat diet. The novel intervention was a dose of miglustat, licensed for, and previously shown to have an effect in, NPC disease [9], alternating 6 months of (1) up to 200 mg miglustat orally three times daily, and (2) no pharmacological intervention for 6 months, with cycles over 2 years. At the start of each intervention period, the miglustat dose was titrated up to 200 mg three times a day, according to the patient's tolerance. Afterward, the patient continued miglustat 200 mg three times daily for 21 months under compassionate use.

Assessments by a delegated physiotherapist were performed at baseline and every 2 months thereafter, including a nine-hole peg test, three-point pinch test, and a hand grip strength test.

Medical reviews were conducted at baseline and every 6 months thereafter, covering physical examination, a neurological examination by a neurologist blinded to treatment status, a nerve conduction study, quality of life measures, 6-minute walk test, 10-metre walk test and collection of blood to assess biomarkers and drug safety.

Additional blood samples were analysed at baseline and every 6 months thereafter to evaluate whether the patient had an expanded lysosomal volume in their PBMCs, which is characteristic of NPC [10]. This test determined whether this patient had an expanded lysosomal compartment at baseline and whether this was reduced over time in response to treatment and relapsed off treatment. In parallel, biochemical measurements of stored glycosphingolipids (a feature of NPC and TD [6, 10]) were performed to give a quantitative read-out of stored lipids and their response to treatment.

Participant

The study participant was the only possible patient in the UK with TD, at a stage which may be amenable to pharmacological treatment.

Statistical Analysis

Sample Size

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 s, and a standard deviation of 2.69 s [11]. Using four crossover periods (i.e. two on drug, two 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, we would have 90% power at a 5% significance level to show the minimum detectable change between the on and off periods. Similarly, for grip strength test with a minimum clinically important difference of around 6 kg (standard deviation of 2.30) [12], using similar assumptions to the above, we would have 90% power to detect this difference.

Statistical Analysis Plan

In line with the CONSORT (Consolidated Standards of Reporting Trials) extension for n-of-1 trials (CENT), we presented the data graphically and descriptively for each period. We presented the mean difference between treatments with 95% confidence intervals and conducted a paired *t*-test. We also documented any harms or adverse events due to the treatment medication.

RESULTS

Patient, Treatment and Primary Endpoint

A 21-year-old (at baseline) left-handed male patient with TD and disabling neuropathy, with a level of severity where potential benefit could be gained from miglustat, was enrolled in this study. At the age of 6 months, he presented with significant visual impairment, bilateral corneal opacities (removed at age 1), and large tonsils, leading to a diagnosis of TD confirmed by a homozygous variant of IVS35+1G>A in the *ABCA1* gene. Despite the known risk of neuropathy, the patient had no neurological symptoms until his teens, with normal nerve conduction at age 14. Over the 4 years before the study, he developed a progressive neuropathy that worsened, with relapsing–remitting episodes, affecting lower and upper limbs with winging of the scapula, impaired hand function, foot drops, and severe walking difficulties. This led to reliance on walking aids, significant functional impairment, and reduced quality of life. He was followed over a 2-year period on and off miglustat treatment, with a further 21 months of drug continuation as part of his clinical care. He tolerated treatment with no adverse events. Figure 1A shows the patient's performance on a three-point pinch strength test. There was no statistically significant difference in average pinch strength at the end of the trial period. However, performance gradually increased in

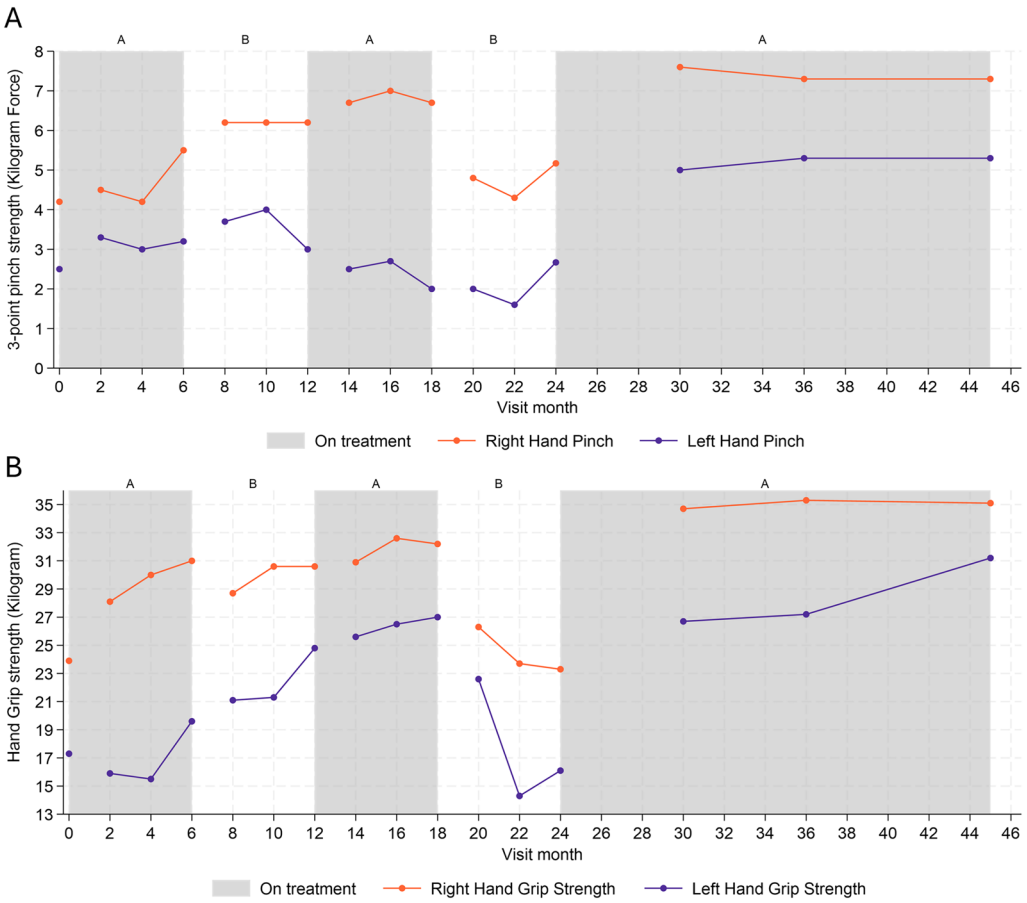

Fig. 1 Change in hand muscle strength over time across the on and off treatment periods. On these tests, higher numbers reflect a better clinical state. **A** Right-hand and left-hand three-point pinch. **B** Right-hand and left-hand grip strength over time

both hands over the extension period of 21 months, in which the patient was treated continuously with miglustat without interruption. Similarly, for grip strength, there was no statistically important difference in the mean results at the end of the trial period. However, during the 21-month extension, a gradual increase in performance over time was observed (Fig. 1B).

The co-primary endpoint, the nine-hole peg test for each hand across the 2 years of on- and off-drug periods, is shown in Fig. 2. Looking at the trend over the entire study period, it appeared that the patient's performance improved over time. The right hand showed no statistically significant difference between on- and off-drug periods. The left hand was statistically significantly worse on treatment by an average of 1.48 s (95% CI 0.0009–2.95). However, both hands showed some improvement in performance at the end of the 21 months of drug continuation compared to the baseline values.

There was no statistically significant difference between on-drug and off-drug performance on the 6-minute walk test and 10-metre walk test. It should be noted that, compared to the primary outcome measures being assessed every 2 months, these outcome measures were only assessed at the end of each treatment period, so there are far fewer observations. There was no statistically significant difference between on-drug and off-drug performance on

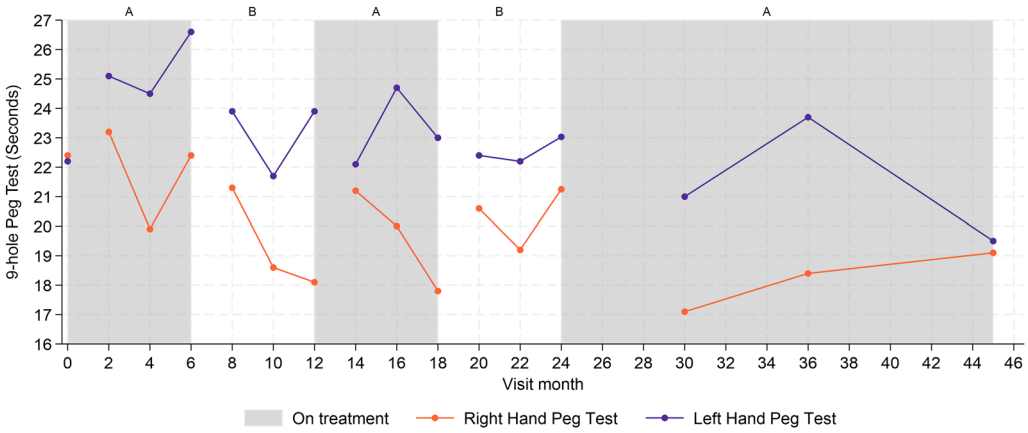

Fig. 2 Nine-hole peg test over time for both hands during the on- and off-treatment periods. On this test, lower numbers reflect a better clinical state

quality of life measures, EQ-5D-5L or Neuropathy Limitation Scale.

Clinical Global Impression and Patient-Reported Experience

The patient became able to open his house door with a key, whereas prior to the first course of treatment he could not do this, and needed to wait for someone to let him in. Similarly, on treatment, he could manage his shirt buttons and hold objects without dropping them, whereas previously he could not. It was also observed that while he is naturally left-handed, he changed to using mainly his right hand due to his neuropathy being more severe in the left upper limb. On treatment, he is now able to use his favoured left hand. A clear discrepancy was observed between the patient's ability in daily task performance and the primary outcome measures while on and off drug. However, the patient-reported experience is in line with the objective assessment of the primary endpoint during the extension period.

Nerve Conduction Studies

At baseline, there was a loss of sensory axons in the upper and lower limbs; this was not a completely length-dependent process, with the ulnar sensory potentials being preserved but with dominant involvement of the superficial radial nerve. There was evidence of conduction blocks at the below-elbow stimulation sites at both ulnar nerves, which is inconclusive whether due to another process (such as coexistent ulnar nerve lesion) or genuine. Specifically, in the left ulnar nerve, the most dominant slowing was seen across the forearm, and there was evidence of chronic denervation throughout the territories. After 6 months of miglustat therapy, there was a marginal improvement in sensory axons, and there was no further deterioration in motor block across the forearm segment of both ulnar nerves and the left median nerve, and this has been maintained throughout the 'on' and 'off' periods of the study.

Biomarkers

Figure 3 shows that the LysoTracker biomarker (relative lysosomal volume) in lymphocytes decreased in both 'on' periods (and increased in both 'off' periods). On the other hand, B-cell glycosphingolipid (GSL) levels only decreased in the second 'on' period but increased in both 'off' periods. The second 'on' period had the most effect. LysoTracker seems to be a more dynamic biomarker for miglustat effects in blood samples, and the biomarkers support the concept that the treatment was reducing lysosomal

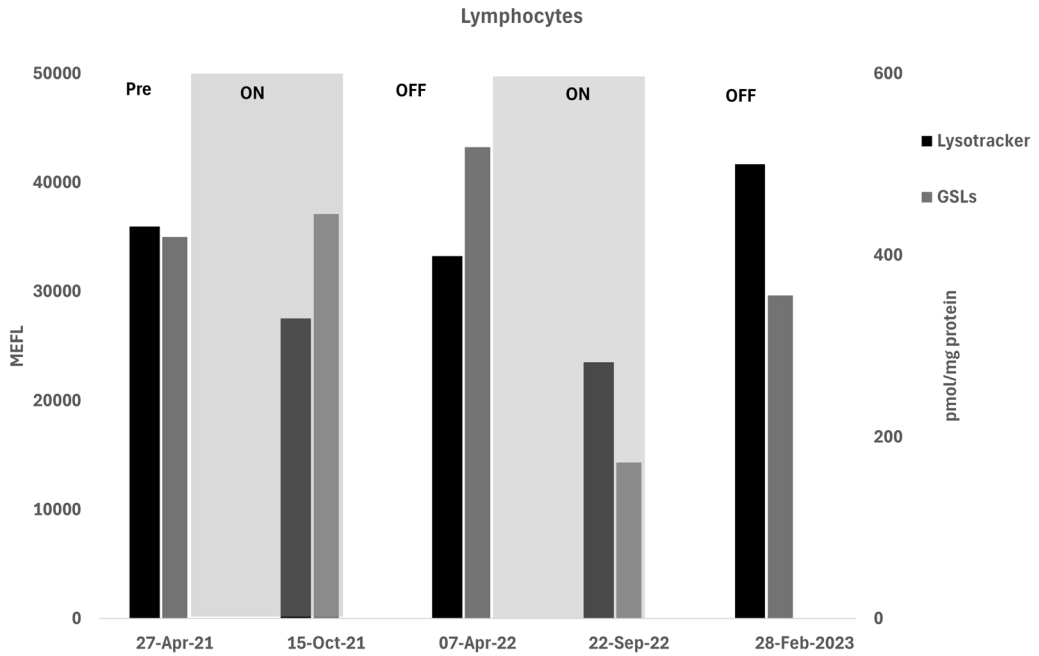

Fig. 3 Lysosomal volume and GSL measurements in lymphocytes. On this chart, the left-hand *y*-axis shows the mean equivalentof fluorescence (MEFL), which is an index of relative lysosomal volume measured by LysoTracker using fluorescence-activated cell sorting (FACS) analysis. The right-hand *y*-axis is pmol GSLs/mg protein

storage. Changes in lymphocytes show a similar pattern to changes in total peripheral blood mononuclear cells. In addition, Lyso-SM-509 is a marker of lipid metabolism, which decreases in patients with NPC administered miglustat [13]. This appeared to have happened in the first treatment period, and the effect extended into the first off-treatment period.

DISCUSSION

Rare diseases affect 1 in 2000 people; yet, with more than 6000 types of rare diseases in existence, approximately 300 million people live with rare diseases worldwide. Around 80% of rare diseases have a genetic cause, and about 95% lack approved treatment [14]. Addressing the treatment needs of rare and ultra-rare conditions cannot be met with the traditional individually randomised parallel-group controlled clinical trial design to show the safety and efficacy of treatment benefit. This study resulted from a difficult commissioning decision facing the English National Health Service (NHS) for high-cost drugs. NHS England were willing to fund miglustat to treat a patient with neuropathy due to TD, but only if there was 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 drugs for ultra-rare diseases worldwide.

TD is an ultra-rare inborn error of metabolism; only two adult patients are currently diagnosed with this progressive neuropathy in the UK. Several attempts were made to increase the number of study participants, including recruiting international patients, but no other patients met the recruitment criteria or were willing or able to travel to England. Hence, our study was designed as an n-of-1 study of ABAB design, with alternating on- and off-drug periods of 6-month durations, with the total study duration being 2 years. The rationale for the study was the discovery that TD and NPC unexpectedly show convergent cellular pathogenesis [6], and NPC is treated with miglustat as standard of care.

When NPC and TD cells were compared, all the known cellular hallmarks of NPC were found to be present in TD, as it involves secondary inhibition of the NPC disease cellular pathway [6]. Furthermore, when cells from patients with TD were treated in culture with miglustat, the NPC phenotypes were corrected [6]. These findings strongly support the scientific rationale for treating patients with TD using miglustat.

To the best of our knowledge, this is the first formal n-of-1 study conducted to investigate a potential treatment for rare and ultra-rare conditions. None of the co-primary endpoint differences reached our pre-determined level of clinical difference. There were small and slow effects in the initial period on drug which appeared to continue through the initial off period, then wearing off in the final off period. This may suggest that the drug had an effect much slower than anticipated. This delayed effect was further supported by the lipid metabolism biomarker, Lyso-SM-509, which decreased in the first treatment period, and the effect was extended into the first off-drug period. This appears to lend credence to the suggestion that miglustat has a potentially significantly delayed effect in this patient relative to that experienced in NPC disease. This is further supported by the results from the 21-month drug continuation period that showed a continuous improvement, highlighting the potential long-term effectiveness of the drug treatment. In retrospect, although based on clinical experience elsewhere (with a patient who experienced a 6-month 'on' period followed by a 7-month 'off' period) [5], it may be that the crossover period of the study was too short. Therefore, study on the long-term effect of the drug is warranted to identify the anticipated long-term favourable outcome.

Clinical, neurophysiological and lysosomal markers were consistent in showing the benefit of treatment. The clinical observation can be summarised by the patient's own words when asked by a journalist about his experience of taking part in the study, to which the patient said:

> *The treatment made a huge difference in my day-to-day life. Before I started to take miglustat, I struggled to pick up heavy objects, eat with a knife and fork, and once I came home from college I couldn't turn my key in the door. My dad had to come home and let me in. The weakness would often move around, so just as one hand was regaining some dexterity, one of my legs would get weak. My quality of life is much improved now and I am so grateful for all the team who have supported me.*

There have been no relapsing neurological events during the 2 years of the study period, whereas these did occur in the 2 years prior. Furthermore, he has had no relapse for 21 months after completion of the study in which he continues to receive miglustat.

Similarly, objective measures—the lipid and cellular biomarkers and the nerve condition studies—have shown improvements and are consistent with the hypothesis that there is an underlying pathophysiological process in TD which has been affected by the drug. Miglustat inhibits glycosphingolipid (GSL) biosynthesis, and GSLs are stored in NPC and TD [6].

Study limitation: We acknowledge the potential for subjective bias, as the study was not blinded for the primary care physician and the participant. However, the participant's overall care was not compromised by enrolment in the clinical trial.

The overall picture appears that miglustat may be used to treat neurological complications of TD, consistent with the published case report [5]. This study has shown that an n-of-1 study to inform a policy decision is practical and may offer hope to patients with rare and ultra-rare diseases.

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and Jess Doyle from Metabolic Support UK, who contributed to our trial management group. The study was sponsored by the University Hospitals Birmingham NHS Foundation Trust and funded by the National Research Collaboration Programme.

Author Contributions. Andrew Cook and Tarekegn Hiwot conceived the need for this research and wrote the first draft of the protocol paper. Fran Webley and Tom Oliver were trial managers on the project, and Claire Forbes coordinated the trial. Beth Stuart designed the statistical plan, and Megan Lawrence carried out the analysis. Frances Platt and Kerri-Lee Wallom led the cellular mechanism and biochemical work. Nicholas Davies provided neurological expertise. Nicola Condon, Charlotte Dawson, Vishy Veeranna, and Antonio Ochoa-Ferraro worked clinically with the patient. Subadra Wanninayake drafted the manuscript. All authors reviewed and approved the final manuscript.

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Data Availability. Requests for access to study data should be made to the Southampton Clinical Trials Unit in the first instance. Due to the nature of the data collected in this study, it is unlikely we will be able to share data without the active consent of the participating patient.

Declarations

Conflict of Interest. All authors, Andrew Cook, Beth Stuart, Antonio Ochoa-Ferraro, Nicola Condon, Megan Lawrence, Fran Webley, Kerri-Lee Wallom, Claire Forbes, Vishy Veeranna, Subadra Wanninayake, Tom Oliver, Nicholas Davies, Charlotte Dawson, Frances Platt, and Tarekegn Hiwot declared that there is no conflict of interest for this work.

Ethical Approval. The study was approved by the Northeast–Newcastle and North Tyneside 2 Research Ethics Committee (REC reference:21/NE/0048) and registered as Clinical Trials (ClinicalTrials.gov Identifier: ISRCTN17945917, Registration date: 07/06/2021), and the study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Patient consent was received for publication.

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