# A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING ACETAZOLAMIDE EFFICACY IN ATAXIA IN PMM2-CDG

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# *A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING ACETAZOLAMIDE EFFICACY IN ATAXIA IN PMM2-CDG*

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**Study Product:** Acetazolamide

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| ALT | Alanine Transaminase |
| AST | Aspartate Aminotransferase |
| BSAP | Bone-specific alkaline phosphatase |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CDG | Congenital Disorder of Glycosylation |
| CFR | Code of Federal Regulations |
| Cl | Chloride |
| CNS | Central Nervous System |
| CO2 | Carbon Dioxide |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTX | Carboxy-terminal collagen crosslinks |
| DSMB | Data and Safety Monitoring Board |
| EMR | Electronic Medical Record |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| Hct | Hematocrit |
| Hgb | Hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICARS | The International Cooperative Ataxia Rating Scale |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| K | Potassium |
| LFT | Liver Function Tests |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MVRD | Midsagittal Vermis Relative Diameter |
| Na | Sodium |
| NPCRS | Nijmegen Pediatric CDG Rating Scale |
| PTH | Parathyroid Hormone |
| pCO2 | Partial Pressure of Carbon Dioxide |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| Plt | Platelet |
| PMM2 | Phosphomannomutase deficiency |
| pO2 | Partial Pressure of Oxygen |
| PRO | Patient Reported Outcome |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SOP | Standard Operating Procedure |
| VBG | Venous Blood Gas |

| | |
|---|---|
| WBC | White Blood Cell Count |
| % | Percent |

## Study Summary

| | |
|---|---|
| Title | A randomized, double-blind, placebo-controlled study evaluating Acetazolamide efficacy in ataxia in PMM2-CDG |
| Running Title | Acetazolamide Trial in PMM2-CDG |
| Protocol Number | 20-000634 |
| Methodology | Randomized, double-blind, placebo-controlled, parallel |
| Overall Study Duration | 1 years (52 weeks) |
| Subject Participation Duration | Treatment period = 6 months (26 weeks); Open Label period = 6 additional months (26 weeks); Total of 1 year (52 weeks) |
| Single or Multi-Site | Multicenter – 3 sites (Seattle Children's Hospital, Children's Hospital of Philadelphia, Mayo Clinic) |
| Objectives | Objective 1 (Primary): To determine the efficacy of acetazolamide in improving ataxia in patients with PMM2-CDG.<br><br>Objective 2 (Secondary): To evaluate for any adverse events related to longer term acetazolamide administration.<br><br>Objective 3 (Secondary): To examine the effect of acetazolamide on PMM2 biomarkers including carbohydrate deficient transferrin results, electrolytes (Na, K, Cl, CO2), VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2, liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase), kidney function tests (BUN, Creatinine, Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio), growth (height, weight, head circumference), vital signs (blood pressure, respiratory rate, heart rate), PROMIS scores, dysarthria using the PATA score, and NPCRS score.<br><br>Objective 4 (Secondary): To explore characteristics of individuals with PMM2-CDG who do not respond to acetazolamide. |
| Number of Subjects | 26 total subjects |

| | |
|---|---|
| Diagnosis and Main Inclusion/Exclusion Criteria | Inclusion criteria:<br>1. Biallelic pathogenic or likely pathogenic variants in PMM2<br>OR<br>Biallelic variants of uncertain significance, pathogenic, or likely pathogenic variants in PMM2 AND Enzymatic confirmation of PMM2 enzyme deficiency<br>2. Age ≥4 years old, and<br>3. Affected with ataxia evidenced by mini International Cooperative Ataxia Rating Scale (Mini-ICARS) score >0 at baseline.<br><br>Exclusion criteria:<br>1. Hepatic impairment defined as AST/ALT >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal<br>2. Renal impairment defined as serum creatinine1.5-1.9 times ULN for age OR ≥ 26.5 umol/l increase from ULN for age<br>3. Hypokalemia<br>4. Hyponatremia<br>5. Hyperchloremic acidosis<br>6. Adrenal insufficiency<br>7. Hypersensitivity to acetazolamide<br>8. Hypersensitivity to any of the components of the placebo<br>9. History of treatment with experimental drug within 28 days of Visit 1<br>10. Currently taking Mecamylamine, Sodium Phosphates, Salicylates, Mefloquine, Methenamine and other Carbonic Anhydrase Inhibitors<br>11. Weight <10 kg |
| Study Product, Dose, Route, Regimen | Acetazolamide or Placebo<br>Acetazolamide capsules ≤30 mg/kg/day divided BID or matching placebo, divided BID daily, by mouth.<br>Due to the potential of subject intolerance, we will start patients on a lower dose divided BID and titrate up in a stepwise manner per table 1 if well tolerated with no AEs or abnormal pH. If the pH is <7.3 and/or bicarbonate <21, the dose will be reduced by 7mg/kg/day. |
| Duration of Administration | 12 months (52 weeks) total, 6 months (26 weeks) blinded, 6 months (26 weeks) open label extension |
| Reference therapy | Placebo |
| Statistical Methodology | The primary analysis will be conducted using the full analysis set, defined as all randomized patients who complete the baseline and 6-month visits. The between-arm mean difference in the change in Mini-ICARS score from baseline to 6 months will be evaluated via a two-sample t-test. The primary analysis will include all patients with a baseline and 6-month Mini-ICARS score. |

# 1 Introduction

This document is a protocol for a human research study. This study will be carried out as described in this protocol and comply with all principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 312 and the appropriate International Conference on Harmonization guidance documents.

## 1.1 Background

Phosphomannomutase deficiency, also known as PMM2-CDG, is the most common congenital disorder of glycosylation (CDG), with over 700 reported cases worldwide. It is an autosomal recessive disorder caused by biallelic pathogenic variants in the *PMM2* gene (Grunewald et al. 2002, Jaeken et al. 1980, 2014). Clinically, PMM2-CDG is characterized by multisystemic severe disease and cerebellar atrophy in infancy, neurologic disease including ataxia and developmental delay in childhood, and/or stable intellectual disability in adulthood (Freeze et al. 2012, Grunewald et al. 2009).

Cerebellar atrophy and cerebellar motor symptoms are common in patients with PMM2-CDG, typically more severe in the first decade of life (Barone et al. 2014, 2015, DeDiego et al. 2017). On a quality of life questionnaire administered to all families attending the 2019 World CDG conference, ataxia was identified as a major symptom impacting daily life in all age groups (unpublished data). Cerebellar dysfunction is a major cause of long-term disability, loss of autonomy, and limitations in daily life for patients with PMM2-CDG.

The International Cooperative Ataxia Rating Scale (ICARS) is a scoring system that has been validated to assess the severity of ataxia symptoms in children and adults with PMM2-CDG. (Serrano et al. 2015, 2017). The ICARS assessment was validated against cerebellar atrophy as calculated by the midsagittal vermis relative diameter (MVRD) on MRI (i.e., using a midsagittal section and measuring total posterior cranial fossa diameter in a linear segment from the posterior commissura to the opisthium and the largest sagittal diameter of the cerebellum parallel to the previous linear segment. The ratio of the cerebellum diameter over the total posterior cranial fossa diameter was used (Serrano et al. 2015)). ICARS showed significant negative correlation with MVRD ($r_s$ −0.87, p = 0.003).

Ataxia symptoms and stroke like episodes in CACNA1A-related disorder, a genetic channelopathy, are attributable to gain-of-function effects on channel gating in the $Ca_v2.1$ channel. Deficient N-glycosylation of $Ca_v2.1$ induce a similar gain-of-function effect on this channel (Izquierdo-Serra et al. 2018). Lowering of intracellular pH and thus transmembrane potential may decrease the activation of $Ca_v2.1$. This, in turn, may restore the excitability and resting activity of neurons. Thus lowering the intracellular pH may ameliorate the cerebellar symptoms of PMM2-CDG, given the hypothesis that cerebellar symptoms are partially due to dysfunctional hypo glycosylated channels such as $Ca_v2.1$.

## 1.2 Investigational Agent

## Acetazolamide

Acetazolamide is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion, in the treatment of certain convulsive disorders, and in the promotion of diuresis in instances of abnormal fluid retention. Acetazolamide is not a mercurial diuretic. Rather, it is a nonbacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides. Acetazolamide is an enzyme inhibitor that acts specifically on carbonic anhydrase, the enzyme that catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. Evidence seems to indicate that Acetazolamide has utility as an adjuvant in the treatment of certain dysfunctions of the central nervous system (CNS). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from CNS neurons. The diuretic effect of acetazolamide is due to its action in the kidney through the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. This reaction results in renal loss of HCO3 ions, which also carries out sodium, water, and potassium, leading to alkalinization of the urine and promotion of diuresis. Alteration in ammonia metabolism occurs due to increased reabsorption of ammonia by the renal tubules as a result of urinary alkalinization.

It is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for acetazolamide is N-(5-Sulfamoyl-1,3,4-thiadiazol-2yl)-acetamide. As a carbonic anhydrase inhibitor that changes the intracellular pH, acetazolamide affects the transmembrane potential and conductance of potassium and calcium channels (Bain et al. 1992, Sappey-Marinier et al. 1999). While it has been studied more extensively in adults, it has been safely administered to children for a variety of indications at doses that range from 4 mg/kg/day to the lower of 100 mg/kg/day or 4000 mg/day (Moffett et al. 2007, Distelmaier et al. 2006, Hacifazlioglu et al. 2012, Ko et al. 2010, Park et al. 2014, Per et al. 2013, Rangwala et al. 2007, Reiss et al.1996, Soler et al. 1998, Spennato et al. 2011, Standridge et al. 2010).

Acetazolamide is an FDA-approved drug for adults for treatment of glaucoma, epilepsy, altitude sickness, and edema. FDA approved doses are in adults 250 to 1000 mg/day divided once to four times daily. A documented off-label use is for treatment of familial periodic paralysis. While the regular-release capsule is not FDA approved in children, it is used commonly in clinical practice and recommended doses have been established in children for management of glaucoma and seizures, reversal of metabolic alkalosis, and prevention and treatment of altitude sickness at 10-30 mg/kg/day given in one to four divided doses. The extended released capsule is FDA-approved in children with a max dose of 30 mg/kg/day or 1000 mg/day (Acetazolamide, 2020).

Acetazolamide is contraindicated in cases of marked liver disease or dysfunction and in patients with cirrhosis because of the risk of development of hepatic encephalopathy and electrolyte imbalance. It is also contraindicated in patients with severe renal disease as it may potentiate acidosis and may cause CNS adverse effects in dialysis patients. It is contraindicated for individuals with carbonic anhydrase inhibitor hypersensitivity, sulfonamide hypersensitivity, electrolyte disturbances, and adrenal insufficiency. It has been reported to occasionally induce

bone marrow suppression and blood dyscrasias. It is an FDA pregnancy risk category C. These contraindications are reflected in our study exclusion criteria.

In this study, regular-release acetazolamide will be dispensed in compounded capsule and compounded liquid formulations.

### 1.3 Clinical Data to Date

Acetazolamide has previously been demonstrated to be efficacious in the treatment of ataxia symptoms in other genetic channelopathies including CACNA1A related disorder (Izquierdo-Serra et al. 2018). Acetazolamide has also been demonstrated to improve the cerebellar symptoms of PMM2-CDG over a six-month pilot study. This initial clinical trial in 24 patients ages 5 to 20 years (mean age 12.3 ± 4.5 years, 9 females, 15 males) demonstrated that acetazolamide is well-tolerated and effective for motor cerebellar syndrome over six months in patients with PMM2-CDG (EudraCT 2017-000810-44). Subjects had statistically significant improvements in ICARS and Nijmegen Pediatric CDG Rating Scale (NPCRS) scores, and lower PATA rates. The PATA rate is the number of "pa – tas" an individual is able to speak in ten seconds. In this study, treatment with acetazolamide coincided with the gain of ability for some patients to sit and stand independently for a longer period of time, which caretakers rated to be an important clinical gain that significantly improved their quality of life and autonomy. Even patients with severe cerebellar atrophy (i.e., low MVRD) showed significant improvement in ICARS, demonstrating a potential therapeutic effect independent of structural cerebellar anomalies and atrophy. In fact, larger gains were observed in individuals with more severe ataxia demonstrated by higher baseline ICARS scores. There were no serious AEs related to the drug during the treatment. There was also no control group comparison, long term follow-up, nor ability to accurately titrate dose by mg/kg. An efficacious dosage of 22 mg/kg/day was established for optimal treatment response, although not all subjects were able to tolerate this dosage, leading to subject drop-out (Martinez-Monseny et al. 2019).

Nine of the 18 items on the ICARS showed consistent improvement in patients on acetazolamide (items 1, 3, 5, 6, 8, 10, 13, 14, 15) (Martinez-Monseny et. al. 2019). These nine items constitute the "Mini-ICARS." Data from the initial validation study was reanalyzed looking at the items in the Mini-ICARS, and explored the internal consistency of the Mini-ICARS scale formed by the sum of the nine items in thirteen PMM2-patients. In collaboration with the authors of the initial clinical trial, we explored the internal consistency of the Mini-ICARS scale formed by the sum of the nine items in thirteen PMM2-patients and found that Cronbach's alpha was very high at 0.96 by analyzing this subset data from the 2015 and 2017 ICARS validation studies. Additionally, the agreement of scores between three different evaluators of the Mini-ICARS from analysis of the 2015 and 2017 ICARS validation studies again showed a correlation very close to 1, demonstrating the Mini-ICARS is also valid in PMM2-CDG (Serrano et. al. 2015, 2017, personal communication). The Mini-ICARS comprehensively captures the areas of clinically significant improvement, while being much shorter to implement, decreasing the likelihood of testing fatigue and inability to complete clinical testing in subjects. Thus, we chose the Mini-ICARS to be the primary endpoint for this trial.

## 1.4 Dose Rationale

Due to the potential of subject intolerance to the most efficacious dose of acetazolamide at 22 mg/kg/day as demonstrated by the initial clinical trial, which is well within the FDA-approved dosage, we will titrate up from a lower dose to increase tolerability, as is typical in clinical practice. The dose of study drug will be initiated at 7.58 mg/kg/day and increased to a maximum of 30 mg/kg/day (not to exceed 1000 mg/day) if well tolerated with no AEs or abnormal pH. If the pH is <7.3 and/or bicarbonate <21, the dose will be reduced per table 1. This is based on the cruder dose titration used by Martinez-Monseny et. al. 2019, as well as standard accepted doses for acetazolamide for other indications. Subjects will remain on their highest tolerated dose, not to exceed 30 mg/kg/day or 1000 mg/day. While 22 mg/kg/day was the goal dose in the Martinez-Monseny study, and there was a non-statistically significant trend towards greater ICARS improvement to higher doses, the mean tolerated dosage was 13 mg/kg/day with a range of 6.8-16.7 mg/kg/day, and subjects even on the lower end of this range derived some improvement in ICARS with doses as low as 7.58 mg/kg/day (Martinez-Monseny et al. 2019, personal communication – data summarized in Table 0a).

Table 0a

| ID | Gender/ Age* | Molecular findings | MVRD | ICARS V0 | ICARS V25 | Responder/ Withdrawal | ICARS V30 | Dose/ Kg 25wk |
|---|---|---|---|---|---|---|---|---|
| 1 | F 11.0 | c.338C>T c.353C>T+c.550C>A | 35 % | 63 | 58 | Yes/AZA | 56 | 16,67 |
| 2 | F 12.5 | c.470T>C c.484C>T | 46 % | 33 | 24 | Yes/NO | 27 | 12,82 |
| 3 | F 14.9 | C.95TA>GC C.256-1G>C | 52 % | 12 | 8 | Yes/AZA | 4 | 11,90 |
| 4 | F 8.8 | c.368G>A c.722G>C | 50 % | 16 | 12 | Yes/AZA | 8 | 16,67 |
| 5 | M 19.3 | c.278A>C c.422G>A | 69 % | 4 | 2 | Yes/NO | 4 | 15,31 |
| 6 | F 18.9 | c.367C>T c.458T>C | 29 % | 59 | 48 | Yes/AZA | 47 | 16,06 |
| 7 | M 8.9 | c.422G>A c.710C>T | 45 % | 56 | 50 | Yes/AZA | 50 | 16,30 |
| 8 | M 6.0 | c.338C>T c.710C>A | ND | PC | PC | Yes/NO | PC | 15,63 |
| 9 | M 16.9 | c.422G>A c.470T>C | 36 % | 56 | 51 | Yes/NO | 53 | 6,80 |
| 10 | M 18.4 | c.422G>A c.722G>C | ND | 12 | 7 | Yes/NO | 8 | 9,68 |
| 11 | M 14.3 | c.131T>C /Alu retrotrasp 28 kb deletion exon 8 | 37 % | 55 | 48 | Yes/AZA | 48 | 15,63 |
| 12 | M 8.3 | c.710C>T c.470T>C | 36 % | 69 | 52 | Yes/AZA | 50 | 16,45 |
| 13 | M 10.1 | c.95T>G c.422G>A | 51 % | 14 | 8 | Yes/NO | 13 | 7,58 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **14** | M<br>18.3 | c.710C>G<br>c.710C>G | 55 % | 8 | 4 | Yes/NO | 5 | 11,36 |
| **15** | M<br>20.0 | c.368G>A<br>c.548T>C | 34 % | 58 | 51 | Yes/AZA | 55 | 12,82 |
| **16** | M<br>6.0 | c.191A>C<br>c.422G>A | 48 % | 67 | 61 | Yes/NO | 68 | 15,15 |
| **17** | M<br>8.6 | c.193G>T<br>c.422G>A | 33 % | 76 | 65 | Yes/AZA | 64 | 16,74 |
| **18** | M<br>5.8 | c.415G>A<br>C.620T>C | 30 % | 66 | 60 | Yes/AZA | 58 | 16,67 |
| **19** | F<br>11.3 | c.470T>C<br>c.722G>C | 46 % | 15 | 11 | Yes/NO | 17 | 12,50 |
| **20** | M<br>13.2 | c.484C>T<br>c.523+3A>G | 56 % | 14 | 10 | Yes/NO | 18 | 10,71 |
| **21** | F<br>12.2 | c.193G>T<br>IVS-9T>G | 48 % | 56 | 55 | No/- | 57 | 8,47 |
| **22** | F<br>13.7 | c.640-9T>G<br>c.710C>T | 58 % | 46 | 48 | No/- | 47 | 8,43 |
| **23** | M<br>7.8 | c.44G>A<br>c.422G>A | ND | 79 | NC | No/- | NC | 8,06 |
| **24**† | F<br>13.5 | c.722G>C<br>c.470T>C | 31 % | NC | - | - | - | |

Additionally, longer term safety of acetazolamide in the pediatric population, while not formally assessed in a clinical trial, has accumulated, and been published post drug approval. This safety data is summarized in the below Table 0b.

Table 0b

| Study Author & Link to Pubmed | Year of Publication | Patients (n) | Indication; Age range (years) | Study Design | Route;Formulation; Dose (mg/kg/d); Duration of therapy | Adverse Events | Efficacy Endpoint, Magnitude of Change |
|---|---|---|---|---|---|---|---|
| **Lombroso et al. (13278187)** | 1956 | 126 (106 <=19 yr) | Epilepsy; 82 patients <12, 24 patients between 12-19 | Open label | Oral; tablets; 8-30 ; 3 months to 3 years | None – "side effects – drowsiness 19, anorexia 17, irritability 11, 2-5 for rest: rash, tingling, dizziness, poor behavior, enuresis, vomiting, ataxia, hyperpnea" | Seizure frequency, complete control 34/126, 90-99% reduction 12/126. |
| **Forsythe et al. (6797857)** | 1981 | 54 | Epilepsy; 3-14 | | 10-15; 2 years | None | |
| **Oles et al. (2492225)** | 1989 | 48 | Epilepsy; 6-64 | ?Open label | Oral; unspecified (Unspec); 3.8-22; 3-30 months (mean 12.9) | None | Seizure frequency, 50% decrease = responders – 44% = responders |
| **Futagi et al. (8972532)** | 1996 | 17 | Epilepsy or Febrile Seizures; 1.2 to 5.4 (mean 2.6) | Open label longitudinal | Unspec; unspec; 3.3-15.8 (mean 9.5); 1.2 to 6.9 years (mean 3.5 years) | Poor growth (weight and height) in 7/10 patients – not associated with bicarb level; resolved after drug withdrawal | None |
| **Katayama et al. (11934510)** | 2002 | 37 | Refractory Epilepsy; 1 to 17 (mean 8 years 1 month) | Open label | ?oral; unspec; 10-20; 10 months and 14 yrs 8 mo (mean 6 years 5mo) | Only one patient had a history of passing a stone at the age of 21 while he was taking AZA. No other serious side effects due to AZA. Some patients experienced transient drowsiness when starting on AZA | Seizure frequency, 50% decrease in frequency |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sharan et al. (20130709)** | 2009 | 22 | Glaucoma; 2 months to 15 years (mean 6.4 years), at end of study 2.0 to 18.8 years (mean 9.4 years) | Retrospective chart review | Oral; unspecified; 15–20; 5 months to 7.6 years (mean 1.5 years) | Two patients (9%) crossed 2 lines in percentile growth charts for weight, one was diagnosed with Sturge-Weber. Pt 1 (7.2yrs at time of discontinuation) pH 7.29, pCO2 38, bicarb 18. Pt 2 7.32, pCO2 32, bicarb 16. CBC normal.<br><br>Eleven patients (11/22, 50%) showed a decline in z score for weight over the follow-up period, and the remainder showed an increase, for an overall estimate of slope in this population of 0.01 (95% confidence limits [CL]: –0.08, 0.11), which was not significant (p 5 0.8). | None |
| **Markhorst et al. (25042881)** | 2014 | 3 | Nondystrophic myotonia; 10-17 | Open label case series | ?oral; unspecified; 200-1000 mg/d (unk weight); 4-10 years | Headache with high doses (1000 mg/d). | Improvement of muscle stiffness and speech, which recurred with withdrawal of treatment. |
| **Martinez-Monseny et al. (30873657)** | 2019 | 24 | Ataxia in PMM2-CDG; 6-20.0 (mean 12.4) | Open label; randomized withdrawal | Oral; tablets; 8-30; 25-30 weeks | 9 showed abnormally low bicarbonate, 2 showed asthenia, and 2 showed asthenia and paresthesia. | ICARS score; 3. |

## 1.5 Risks and Benefits

### Risks

In general, acetazolamide is considered a safe drug. Per the package insert, severe adverse reactions that have been reported with administration of acetazolamide include seizures, muscle paralysis, hepatic necrosis, hepatic failure, hepatic encephalopathy, toxic epidermal necrosis, agranulocytosis, anaphylaxis, aplastic anemia, hemolytic anemia, Stevens-Johnson syndrome, pancytopenia, acute generalized exanthematous pustulosis, renal failure, and renal tubular obstruction. The incidence of each reaction is unknown. It is likely that individuals who have significant baseline allergy to acetazolamide and other components, hepatic dysfunction, blood dyscrasias, and/or renal dysfunction would be at higher risk for these severe reactions. Thus we are assessing for hepatic dysfunction, renal dysfunction, allergy, and blood dyscrasias at baseline and excluding individuals with significant disturbances in their laboratory assessments or have a history of allergy to the components of the therapeutic agent or placebo (as defined by the exclusion criteria below). We will monitor complete blood count (CBC), liver function tests (LFT), venous blood gas (VBG or bicarbonate/CO2), electrolytes, and creatinine, and urinalysis with urine creatinine, calcium, and protein at baseline and regularly throughout the study, and if any individual meets exclusion criteria at any point during the study, we will terminate their treatment. Patients may develop acidosis on acetazolamide therapy, which may lead to inability to continue the therapy longer or a decrease in dosage. Acetazolamide has been associated with growth suppression in pediatric patients, although not all individuals have been reported to have poor growth and the dosages associated with growth suppression have not been consistent. Growth has been reported to resume and improve after discontinuation of acetazolamide. We will monitor growth parameters (height, weight, head circumference) regularly throughout the study and tailor their management and continuation in the study on a case by case basis. We will monitor patients' acid/base status and titrate acetazolamide accordingly. We will also obtain a one-time measurement of acetazolamide serum concentration at steady state at the six-month visit.

Other less severe side effects may include depression, confusion, ataxia, hyperglycemia, hypoglycemia, glycosuria, jaundice, elevated hepatic enzymes, hyperuricemia, hemolysis, thrombocytopenia, leukopenia, hyperchloremia, hyponatremia, crystalluria, hypokalemia, nephrolithiasis, hematuria, myopia, growth inhibition, melena, dizziness, paresthesias, fatigue, drowsiness, malaise, headache, photosensitivity, urticaria, fever, polyuria, diarrhea, anorexia, xerostomia, nausea, vomiting, dysgeusia, flushing, tinnitus, and purpura. These symptoms are also all monitored during each visit by history and laboratory studies. Subjects may voluntarily withdraw at any time from the trial.

### Benefits

We anticipate that subjects on active treatment will have improved quality of life due to lessening ataxia given the preliminary findings in previous studies. From a scientific standpoint, we anticipate that this study will evaluate the efficacy of acetazolamide as a therapeutic agent for ataxia in PMM2-CDG.

**Risk/Benefit Assessment**
The risks to subjects are reasonable in relation to the anticipated benefits because the major risks are not universal, closely monitored for, and would lead to study withdrawal. The majority of the risks can be treated medically and are likely to resolve after discontinuing therapy. The potential benefits for participating subjects and medical knowledge are clinically significant. Amelioration in ataxia will significantly improve the subject's quality of life, and possibly allow for downstream gains in learning and development. The gain in knowledge will allow for healthcare providers to make informed decisions about utilizing this therapeutic in this population. It may also be the groundwork needed to add an FDA-approved indication for the use of acetazolamide in PMM2-CDG. This would be the first FDA-approved therapeutic agent for PMM2-CDG, which would be a major breakthrough for this disease and other closely related ultra-rare genetic disorders.

# 2 Study Objectives

**Objective 1 (Primary):**
**To evaluate the efficacy of acetazolamide in improving ataxia in patients with PMM2-CDG.**
To achieve this goal, we will compare the change of Mini-ICARS score from baseline to after six months post-randomization of treatment between the placebo and active treatment groups.
**Objective 2 (Secondary):**
**To evaluate for any adverse events related to longer term acetazolamide administration.**
To achieve this goal, we will monitor changes on physical exam, laboratory studies that are likely to be affected by acetazolamide therapy including blood pH and electrolyte balance, and urine calcium excretion regularly through the duration of the trial. We will determine the percentage of patients treated with acetazolamide who experience (a) drug related adverse event(s) and (b) drug related serious adverse event(s) while they are on blinded therapy as well as for the duration they remain in the open label extension.

**Objective 3 (Secondary):**
**To examine the effect of acetazolamide on PMM2 biomarkers including carbohydrate deficient transferrin, electrolytes (Na, K, Cl, CO2), VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2, liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase), kidney function tests (BUN, Creatinine, Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio), growth (height, weight, head circumference), vital signs (blood pressure, respiratory rate, heart rate), PROMIS scores, dysarthria using the PATA score, and NPCRS score.**
We will collect these data at baseline and after 6 months of placebo or treatment and identify changes from baseline. We will analyze if there is a difference of changes between the treatment and placebo group. We will also compare baseline measurements to the last measurement obtained as part of the open label extension and determine if there are changes to these measurements.

**Objective 4 (Secondary):**

**To explore characteristics of individuals with PMM2-CDG who do not respond to acetazolamide.**
In addition to analyzing our data for effect, we will perform subgroup analysis based on genotype, ataxia severity, baseline NPCRS score, sex, concomitant therapies, results of transferrin isoform analysis, concomitant medical problems/diagnoses, number of previous hospitalizations, ages at diagnosis, baseline laboratory test results, age at developmental milestones achievement, baseline developmental/educational achievement, baseline frequency and type of therapies, and baseline support needed for activities of daily living to determine if there are particular subgroups that are less responsive to therapy.

# 3 Study Design

## 3.1 General Description

This study is a double-blind, placebo-controlled, 1:1 randomized clinical therapeutic trial of acetazolamide for the treatment of ataxia in patients with PMM2-CDG. Clinical history and screening data will be reviewed to determine subject eligibility. Potential subjects who have biallelic pathogenic or likely pathogenic variants in PMM2 OR biallelic variants of uncertain significance, pathogenic, or likely pathogenic variants in PMM2 AND Enzymatic confirmation of PMM2 enzyme deficiency will be consented. Baseline data will be collected prior to randomization and at treatment initiation. Subjects who meet all inclusion criteria and none of the exclusion criteria will be enrolled into the study. Each subject who meets all the inclusion and none of the exclusion criteria will then be randomized to placebo or acetazolamide. They will be administered weight-dependent doses of acetazolamide or an equivalent dose of placebo twice daily by mouth. Initial dose of acetazolamide is at least 7.58 mg/kg/day per Table 1 . If the pH is <7.3 and/or bicarbonate <21, a value associated with mild metabolic acidosis, the dose will be reduced per table 1. Subjects will be randomized after Visit 1, will initiate blinded therapy within the first week, and will continue on prescribed/adjusted blinded treatment until Visit 4. Of note, the volume or number of capsules will be adjusted based on tolerance as assessed by symptoms and laboratories. If an individual is randomized to the placebo arm, the initial number of capsules will be as per Table 1, and number of capsules will also be adjusted based on symptoms and laboratory values each time dose adjustment is planned. Open label period will then begin after Visit 5 up to Visit 9 (see Figure 1 and Table 3). As both the subject and investigator do not know if the subject received placebo or acetazolamide, the dose of acetazolamide will be started at Visit 5 per table 1 and titrated upwards in the same manner in Visits 6, 7 and 8 (remote) as in Visits 2, 3 and 4 (remote). Subjects will have the option to withdraw from the study any time after Visit 5 if they do not wish to proceed onto or continue with the open label phase.

## 3.2 Number of Subjects

We aim to enroll 26 evaluable patients. Up to 7 additional patients will be enrolled to account for a 20% loss in sample size due to ineligibility, major treatment violation, cancellation, or withdrawal prior to completion of the 6-month blinded phase of the study. Maximum projected accrual is, therefore, 33 patients. Enrollment will continue until the 26$^{th}$ evaluable patient completes the blinded phase. Enroll will pause when 26 patients have either completed or are

actively completing the blinded phase; enrollment will reopen if any of these patients withdraw before completing the blinded phase.

### 3.3 Duration of Participation

The duration of participation is a maximum of approximately 1.75 years as outlined in Figure 1 below.

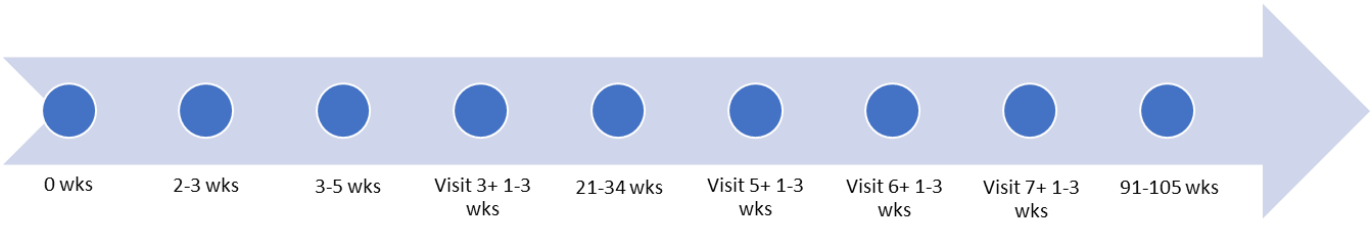


Figure 1. Study Timeline for visits 1 through 9

### 3.4 Primary Study Endpoints

Primary Endpoint: Change in Mini-ICARS score from baseline to 6 months.

### 3.5 Secondary Study Endpoints

Secondary Endpoints: Biomarkers, testing scores, and rating scales at 6 months. These biomarkers and scores include carbohydrate deficient transferrin results (Mono/Di, A/Di, Apo CIII1/Apo C III2, Apo CIII0/Apo CIII2), electrolytes (Na, K, Cl, CO2), VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2, liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase), coagulation factors (prothrombin time, coagulation factor XI, and antithrombin), kidney function tests (BUN, Creatinine, Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio), bone mineral metabolism markers (serum bone-specific alkaline phosphatase (BSAP) and carboxy-terminal collagen crosslinks (CTX), Calcium, Phosphorus, Vitamin D, and parathyroid hormone (PTH)), growth (height, weight, head circumference), vital signs (blood pressure, respiratory rate, heart rate), PROMIS scores, the PATA score, and NPCRS score.

### 3.6 Primary Safety Endpoints

The primary safety endpoint is incidence of (a) drug related adverse event(s) and (b) drug related serious adverse event(s) while patients are on blinded therapy as well as for the duration they remain in the open label extension.

### 3.7 Identification of Source Data

The following data will be collected:

- Date of visit
- Age at visit (Years, Months, Days)
- Vital signs: systolic and diastolic blood pressures (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), temperature (degrees C)
- Growth Data: length/height (cm), weight (kg), head circumference (cm)
- Physical Exam: brief neurologic exam, cardiovascular exam, abdominal exam, (HEENT) head ears eyes nose throat exam, dermatologic exam, pulmonary exam, musculoskeletal exam (Normal/Abnormal with text field to explain abnormality)
- PATA score
- AE and SAEs defined by the CTCAE version 5 (specific AE/SAE and date; see Appendix D)
- PROMIS Questionnaires (Appendix C)
- Mini-ICARS (Appendix B)
- NPCRS (Appendix A)
- Drug volume prescribed (ml/day or number of capsules/day)
- Laboratory values, normal ranges, and units: CBC (WBC, Hgb, Hct, Plt, % Neutrophils, % Lymphocytes, % Eosinophils, % Basophils, % Monocytes, %Bands, MCV, MCHC, MCH), electrolytes (Na, K, Cl, CO2), VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2, liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase), coagulation factors (prothrombin time, coagulation factor XI, and antithrombin), kidney function tests (BUN, Creatinine, Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio)
- BSAP, CTX, calcium, phosphorus, vitamin D, and PTH at baseline and visit 5.
- Plasma/Serum Acetazolamide level at visit 5.
- Physical therapy, Occupational therapy, Speech therapy, Feeding therapy – (yes/no if ongoing, number of sessions per month)
- Annual screening ophthalmological exam including intraocular pressure testing.

The following source data will be captured in supportive documentation (e.g. study source documents, EMR):

- Clinical interpretation of laboratory values
- Medication review and adherence
- Video of the Mini-ICARS assessment

# 4 Subject Selection Enrollment and Withdrawal

## 4.1 Inclusion Criteria

- At minimum, 4 years of age at Visit 1
- Biallelic pathogenic or likely pathogenic variants in PMM2
  OR
  Biallelic variants of uncertain significance, pathogenic, or likely pathogenic variants in PMM2 AND Enzymatic confirmation of PMM2 enzyme deficiency
- Affected with ataxia evidenced by Mini International Cooperative Ataxia Rating Scale (Mini-ICARS) score >0 at baseline
- Parent or legal guardian available to provide consent on behalf of minor subjects or adult subjects who are unable to give informed consent due to developmental disabilities. Willingness of subject or legal guardian to provide consent.
- If female and >10 years old, willing to practice abstinence or using an effective contraceptive regimen that is constituted by two acceptable effective methods of contraception, including a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device (IUD), or intrauterine system for the entire duration of the treatment period and for at least 28 days after receiving the last study drug dose. Sterilized or infertile subjects (defined as having undergone surgical sterilization, ie, bilateral tubectomy, hysterectomy and bilateral ovariectomy or as being postmenopausal, defined as at least 12 months of amenorrhea prior to enrollment) will be exempted from the requirements to use contraception in this study.

## 4.2 Exclusion Criteria

- Hepatic impairment defined as AST/ALT >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormalin the last 12 months
- Renal impairment defined as serum creatinine 1.5-1.9 times ULN for age OR ≥ 26.5 umol/l increase from ULN for age
- Hypokalemia
- Hyponatremia
- Hyperchloremic acidosis
- Adrenal insufficiency
- Hypersensitivity to acetazolamide
- Hypersensitivity to any of the components of the placebo
- History of treatment with experimental drug within 28 days of Visit 1
- Currently taking Mecamylamine, Sodium Phosphates, Salicylates, Mefloquine, Methenamine, other Carbonic Anhydrase Inhibitors, Phenytoin, Primidone, folic acid antagonists, antidiabetic agents, quinidine, lithium, cyclosporine, sodium bicarbonate.

- Participation in another therapeutic trial - the subject will not be permitted to participate in any other drug trial during the blinded phase and during the 28 days prior to Visit 1
- Pregnant (positive urine beta-HCG test) or nursing (by history) women
- Weight <10 kg

### 4.3 Subject Recruitment, Enrollment and Screening

- Patients seen clinically by genetics at Seattle Children's, CHOP, and Mayo Clinic with molecularly and/or enzymatically-confirmed diagnosis of PMM2-CDG will be approached for consent. Additional patients may be consented if referred by an external provider to the genetics clinic. If an individual fails screening, they can be rescreened 4 or more months after their initial screening. Subjects' treatment may be paused or discontinued if the study drug is found to be harmful such as development of kidney or hepatic failure or insufficiency as measured by renal and hepatic function labs, respectively. If abnormal values are noted as defined in section 8.1 and no other cause for these laboratory changes are likely, then drug will be stopped, and repeat labs will be obtained at reasonable intervals per investigator's clinical judgement after discontinuation until labs have normalized to stabilized. Treatment may be restarted if labs have returned to baseline using the same ramp up schedule as described for visits 2, 3 and 4.

### 4.4 Subject Withdrawal Criteria

- Failure of subject to adhere to protocol requirements
    - If a patient is unable to adhere to study procedures, they may be withdrawn from the study by the investigator per investigator discretion.
- Subject decision to withdraw from the study (withdrawal of consent)
    - A patient or patient's family/guardian may withdraw consent at any time and cease administration of study drug or placebo. They may be asked to return for follow up testing to ensure that laboratory values are satisfactory (see schedule of events table (SOE)) and please refer to section 6.10.

## 5 Study Drug

### 5.1 Description

Name and detailed description of the investigational product(s)

- Acetazolamide is an inhibitor of the enzyme carbonic anhydrase. It is a white to faintly yellowish white crystalline, odorless solid, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for acetazolamide is N-(5-Sulfamoyl-1,3,4-thiadiazol-2yl)-acetamide. The acetazolamide formulations used in our study will be capsules.

  - Acetazolamide 250 mg oral capsules: will be compounded by over-encapsulating acetazolamide 250 mg tablet within a gelatin capsule and filled with lactose powder.
- Placebo (to match Acetazolamide)
  - Placebo capsules: to be compounded by filling empty gelatin capsules with lactose powder to match Acetazolamide capsules.

## 5.2 Treatment Regimen

Acetazolamide dosages will be calculated based on weight and will be administered orally or enterally (i.e., via gastric-tube, nasogastric tube, etc.) as capsules with food in gradually increasing dosages according to Table 1 below. Subjects <10 kg will be excluded from the study. Missed doses will be documented but will not be re-dosed. Patients will resume their original scheduled dosing per protocol. Blinding will be maintained by having specifically affected laboratory markers (e.g., bicarbonate level, pH) being monitored by an unbiased clinician who is not part of the study.

Table 1. Capsule formulation Acetazolamide Dosages, oral administration divided BID

| **Subject weight (kg)** | **Dose 1** | | **Dose 2** | | **Dose 3** | |
|---|---|---|---|---|---|---|
| | **mg/day** | **mg/kg/day** | **mg/day** | **mg/kg/day** | **mg/day** | **mg/kg/day** |
| **>10 - <16.4** | 125 | 6.3-12.5 | 250 | 12.5-25 | 250 | 12.5-25 |
| **16.4 - <33** | 250 | 7.1-12.5 | 375 | 10.7-18.75 | 375 | 14.4-25 |
| **33 - <41** | 250 | 5.6-7.1 | 500 | 11.1-14.3 | 750 | 16.6-21.4 |
| **≥41** | 375 | <8.3 | 750 | <16.7 | 1000 | <22.2 |

Initially individuals will be started on Dose 1 or the volume equivalent of placebo after randomization. The therapy will be mailed to the subject after randomization or the subject will pick it up at the site designated by the investigational pharmacy. Subjects should start the therapy by week 1.5 after visit 1. At Visits 2, 3 and 4 doses will be adjusted for both acetazolamide and placebo (volume equivalent in placebo for dosages either in ml or # caps) as follows:

- If no related or likely related AE or SAE and pH is ≥7.3 and/or bicarbonate ≥ 21,
  - if current dose is at dose 1, dose will be advanced from dose 1 to dose 2;
  - if current dose is at dose 2, dose will be advanced from dose 2 to dose 3;
  - if current dose is at dose 3, dose will remain at dose 3.
- If no related or likely related AE or SAE and pH is ≥7.3 and/or bicarbonate < 21,
  - dose will remain at current dose.
- If pH is <7.3 and/or bicarbonate <21 and no related or likely related AE or SAE
  - if current dose is at dose 1, drug or placebo will be discontinued;
  - if current dose is at dose 2, dose will be decreased from dose 2 to dose 1;
  - if current dose is at dose 3, dose will be decreased from dose 3 to dose 2 or dose 1 if dose 2 and 3 are the same.

- If the investigator becomes aware of a likely related or related SAE, based on clinical judgement, the subject may be discontinued from placebo or drug. If an SAE occurs, the investigator will report the SAE to the DSMB. The DSMB will decide whether unblinding is necessary and convey their decision to the local study team, who will then implement the decision.

At Visit 5 (26 weeks) a discussion with the subject regarding whether they would like to proceed into the open label extension with acetazolamide will occur. If continuation is preferred, they will be restarted on dose 1 since we are not certain if they were on treatment or placebo. At subsequent visits after visit 5, acetazolamide will be modified in the same manner as above. If not, then neither drug nor placebo will be given to the patient. As this is an open label continuation, acetazolamide will be dispensed by a clinical pharmacy.

## 5.3 Method for Assigning Subjects to Treatment Groups

- After informed consent, randomization will occur as a tiered approach based on age (group 1 <12 years, group 2 ≥ 12 years) and Mini-ICARS score (group a score <25, group b ≥ 25 points) to give 50/50% to placebo/drug, respectively. If a Mini-ICARS was performed and recorded <1 year prior to enrollment, randomization can be based on that historic score. The randomization scheme will be generated by a statistician that is not part of the study team and will be provided to the applicable research pharmacy.

## 5.4 Preparation and Administration of Study Drug

- The study drug and placebo will be compounded by the research pharmacy at each institution.
- A member of the study team will pick up the drug/placebo from the pharmacy and deliver it to the investigator meeting with the patient. The investigator will educate the patient on proper administration of the drug/placebo (number of times per day to take the drug, amount for each administration) and answer any questions or concerns the patient/patient's parent or guardian may have. The study drug may also be mailed to subjects at their address of residence.
- The research pharmacy will obtain the study drug and have the production lab over encapsulate the drug and placebo for blinding purposes.

Table 2: Formulation of Acetazolamide and Placebo

| ORAL CAPSULE FORMULATION | Acetazolamide 250 mg Capsules | Placebo Capsules |
|---|---|---|
| Active ingredient | Acetazolamide 250 mg tablets (any commercially available generic brand) | N/A |
| Empty Gelatin Size 0 capsules | TBD | TBD |

| | | |
|---|---|---|
| Lactose USP powder | Quantity sufficient to fill capsule | Quantity sufficient to fill capsule |

## 5.5 Subject Compliance Monitoring

Subjects and/or their caregivers will be asked to keep a patient diary noting the date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

If a subject is significantly non-compliant, as per the investigator's discretion, with the study drug regimen, the investigator will discuss with the patient the reasons that the drug is not being taken as requested. Missed doses will be recorded. If this discussion does not improve the subject's compliance to greater than 50% of the doses taken per week by the next study visit, they are encouraged to adhere to the study medication schedule.

## 5.6 Prior and Concomitant Therapy

- All concomitant medication and concurrent therapies (physical therapy (PT)/occupational therapy (OT)/speech therapy (ST)/feeding therapy (FT)) will be documented at baseline and at each visit (from 30 days prior to the first dose).
    - Medication trade name;
    - Indication for which the medication was given;
    - Dose/strength, route, and frequency of administration;
    - Date started and date stopped (or continuation at study exit).
- All medications that do not have a high risk of serious reactions will be permitted while on the study. Any medication listed as an exclusion criterion is not permitted while on the study (i.e., Mecamylamine, Sodium Phosphates, Salicylates, Mefloquine, Methenamine and other Carbonic Anhydrase Inhibitors).
- If a subject has started taking a prohibited medication on the exclusion criteria, they will be discontinued from the study. If a subject is started on a medication that has a high risk of serious reaction, continued participation in the study will be decided on a case-by-case-basis.

## 5.7 Packaging

Packaging, labeling, taste, and appearance of test and control treatments will be very similar to maintain the blind. Active drug concentrations will be prepared by the pharmacy prior to handoff to clinicians or families for administration. Both the study drug and comparator will be labeled with the same label "Acetazolamide or Placebo" or per institution standards as well as "Limited by Federal Law to Investigational Use Only." Drug products will be packaged in standard pharmacy containers with child resistant closures for outpatient use (e.g. amber HDPE bottles or prescription vials).

### 5.7.1 Blinding of Study

- Investigators, study staff in contact with patients, and subjects will be blinded. The research pharmacy will then dispense acetazolamide or placebo to the patient or study staff. Access to the randomization code will be strictly controlled by the research pharmacy and DMCC. Packaging, labeling, and appearance of the test and control treatments will be similar to maintain the blinding. Active drug concentrations will be prepared by the pharmacy prior to handoff to clinicians or patients/caretakers for administration. The study will proceed to open label continuation at Visit 5 (Week 40-56). During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management. If the blind is broken for a subject, that individual will be removed from the blinded portion of the study. If a subject experiences an adverse event warranting unblinding procedures, the pharmacy will inform the physician of the prescribed treatment.

  After all data are collected for the blinded portion of the study and all data cleaning is completed for these data, the data base for the blinded portion of the study will be locked and the study will be unblinded for analysis.

## 5.8 Receiving, Storage, Dispensing and Return

### 5.8.1 Receipt of Drug Supplies

Acetazolamide is an FDA-approved, commonly available drug. The research pharmacy will order the drug and prepare the proper dosage.

### 5.8.2 Storage

- The research pharmacies are in secure locations only accessible to credentialed staff members with badge access.

### 5.8.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated by the study team/research pharmacist.

### 5.8.4 Return or Destruction of Study Drug

In accordance with federal regulations (21CFR 312.62), all Investigators are required to keep accurate records showing final disposition of all investigational drugs and placebo.

Investigational drugs are to be used only in accordance with this protocol and under supervision of the Study Pharmacist or a duly designated person. An accurate drug disposition record will be kept at each site, specifying the amount dispensed and the date of dispensation. This inventory record must be available for inspection at any time. Copies of this record will be available for monitoring boards upon request.

After the study is completed, the Study Pharmacist must account for all drug used, unused and partially used. Unused study medication from the study site will be returned to either the investigator or Study Pharmacist and destroyed. Drug destroyed on site will be documented in the study files.

# 6 Study Procedures

Prior to participating in the study, written approval of the protocol and informed consent must be obtained from the IRB.

Informed consent:
The investigator or designated study coordinator will explain the study to the patient and/or parents/guardian of the patient. Study purpose, procedures, risk, and benefits will be discussed. Patient/parents/guardians willingness and ability to meet the follow up requirements will be determined and written informed consent will be obtained. The investigator/study coordinator will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the patient/parent/guardian. Informed consent will be obtained prior to any procedures or data collection.

Subject Identification:
Ethical and confidential research standards will be maintained. The minimum necessary protected health information will be used in study records. Computer records of data will be password protected behind institutional information technology security firewalls. All information will be treated with strict adherence to professional standards of confidentiality.

The following is a detailed list of study visits from screening to final follow-up and the required procedures/tests.

## 6.1 Visit 1 – Week 0

- Screening for eligibility
- Informed consent; no procedures will occur until informed consent and eligibility criteria are confirmed.
- Interview elements:
    - Medical history (past and current medical conditions, past surgical history)
    - Clinical history (history of present illness, any assessments)
    - Concomitant medication review
    - Ongoing therapies (physical therapy (PT), occupational therapy (OT), speech therapy (ST), feeding therapy (FT))
- Procedural elements:
    - Physical exam: Vital signs – temperature, systolic and diastolic blood pressures (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), Growth Data* - length/height (cm), weight (kg), head circumference (HC in cm), Exam by systems – (normal/abnormal) brief neurologic exam, cardiovascular exam,

abdominal exam, (HEENT) head ears eyes nose throat exam, dermatologic exam, pulmonary exam, musculoskeletal exam
    - Mini-ICARS
    - PATA
    - NPCRS
    - Blood collection** (CBC (WBC, Hgb, Hct, Plt, % Neutrophils, % Lymphocytes, % Eosinophils, % Basophils, % Monocytes, % Bands, MCV, MCHC, MCH), electrolytes (Na, K, Cl, CO2), VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2, liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase, calcium, phosphorus, vitamin D, parathyroid hormone), coagulation factors (prothrombin time, coagulation factor XI, and antithrombin) kidney function tests (BUN, Creatinine), CTX, BSAP
    - Urine collection (Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio, HCG for females)
- Survey given to families to complete and returned to site at or after visit by mail or electronically
    - PROMIS
- Performed after visit once inclusion and exclusion criteria are met and Mini-ICARS score established
    - Randomization
    - Dose Initiation – Investigational pharmacy to dispense to patient/caregiver by mail or in person at previously designated location by pharmacy. Investigator or pharmacist to instruct patient/caregiver regarding administration of drug or placebo via phone call, telehealth, or in person.

*Growth data including length/height (cm), weight (kg), head circumference (HC in cm) will be measured or measured at home and reported by subjects at least every 12 weeks.
**Total blood volume drawn will not exceed 5% of total blood volume of the child over 24-hour period, and 10% of total blood volume of the child over 8 weeks.

## 6.2 Visit 2 (Remote)– Week 2-3

- Procedural elements
    - Blood collection (CBC, electrolytes and/or VBG, liver function tests, kidney function tests)
    - Urine collection (same as section 6.1)
- Medication adherence questionnaire (appendix E): family to send this to us electronically or via mail.
- Interview elements
    - AE assessment
    - Concomitant medication review
    - Ongoing therapies (same as section 6.1)
- Dose Adjustment (see section 5.2) – After venous blood gas and electrolytes have resulted, partnering clinician will instruct patient/caregiver regarding administration of drug or placebo via phone call, telehealth, or in person.

### 6.3 Visit 3 (Remote)– Week 3-5

- Procedural elements
  - Blood collection (same as section 6.2)
  - Urine collection (same as section 6.1)
- Medication adherence questionnaire (appendix E): family to send this to us electronically or via mail.
- Interview elements
  - AE assessment
  - Concomitant medication review
  - Ongoing therapies (same as section 6.1)
- Dose Adjustment (see section 5.2) – After venous blood gas and electrolytes have resulted, partnering clinician will instruct patient/caregiver regarding administration of drug or placebo via phone call, telehealth, or in person.

### 6.4 Visit 4 (Remote)– Visit 3 +1-3 weeks

- Procedural elements
  - Blood collection (same as section 6.2)
  - Medication adherence questionnaire (appendix E): family to send this to us electronically or via mail.
- Interview elements
  - AE assessment
  - Concomitant medication review
  - Ongoing therapies (same as section 6.1)
- Dose Adjustment (see section 5.2) – After venous blood gas and electrolytes have resulted, partnering clinician will instruct patient/caregiver regarding administration of drug or placebo via phone call, telehealth, or in person. At this visit, the dose can only be adjusted downwards. If the dose needs to be adjusted, repeat CBC, electrolytes and/or VBG will be checked within 4 weeks of the dose adjustment. Repeat downward dose adjustments based on labs and repeat CBC + VBG or electrolytes will occur until either the dose does not need to be adjusted downwards or the subject is off therapy.

### 6.5 Visit 5 – Week 21-34

- Interview elements:
  - Concomitant medication review
  - Ongoing therapies (same as section 6.1)
  - Medication adherence questionnaire (see section 6.2)
  - AE assessment
- Procedural elements:
  - Physical exam (see section 6.1)
  - Mini-ICARS
  - PATA
  - NPCRS
  - Blood collection (see section 6.1) In addition, random blood level of acetazolamide will be collected.

    - Urine collection (see section 6.1)
- Survey given to families to complete and returned to site at or after visit by mail or electronically
    - PROMIS
- Open Label Extension (OLE) or discontinuation – investigator will discuss with family option of rolling over into an open label extension of the study where the patient will receive the drug. If patient/caregivers decide to proceed with OLE, the patient will be started on dose 1 of acetazolamide.

### 6.6 Visit 6 (Remote)– Visit 5 +1-3 weeks

- Procedural elements
    - Blood collection (same as section 6.2)
    - Urine collection (same as section 6.1)
- *Medication adherence questionnaire (see section 6.2)
- Interview elements
    - AE assessment
    - Concomitant medication review
    - Ongoing therapies (same as section 6.1)
- *Dose Adjustment (see section 5.2) – After venous blood gas and electrolytes have resulted, investigator will instruct patient/caregiver regarding administration of drug via phone call, telehealth, or in person.

* Will only be performed for those individuals who opted to continue in the OLE.

### 6.7 Visit 7 (Remote)– Visit 6 + 1-3 weeks

- Procedural elements
    - Blood collection (same as section 6.2)
    - Urine collection (same as section 6.1)
- *Medication adherence questionnaire (see section 6.2)
- Interview elements
    - AE assessment
    - Concomitant medication review
    - Ongoing therapies (same as section 6.1)
- *Dose Adjustment (see section 5.2) – After venous blood gas and electrolytes have resulted, investigator will instruct patient/caregiver regarding administration of drug via phone call, telehealth, or in person.

* Will only be performed for those individuals who opted to continue in the OLE.

### 6.8 Visit 8 (Remote)– Visit 7 +1-3 weeks

- Procedural elements
    - Blood collection (same as section 6.2)
    - *Medication adherence questionnaire (appendix E): family to send this to us electronically or via mail.

- Interview elements
  - AE assessment
  - Concomitant medication review
  - Ongoing therapies (same as section 6.1)
- *Dose Adjustment (see section 5.2) – After venous blood gas and electrolytes have resulted, partnering clinician will instruct patient/caregiver regarding administration of drug or placebo via phone call, telehealth, or in person. At this visit, the dose can only be adjusted downwards. If the dose needs to be adjusted, repeat CBC, electrolytes and/or VBG will be checked within 4 weeks of the dose adjustment. Repeat downward dose adjustments based on labs and repeat CBC + VBG or electrolytes will occur until either the dose does not need to be adjusted downwards or the subject is off therapy.

* Will only be performed for those individuals who opted to continue in the OLE.

## 6.9 Visit 9 – Week 49-105

- Interview elements:
  - Concomitant medication review
  - Ongoing therapies (see section 6.1)
  - *Medication adherence questionnaire (see section 6.2)
  - AE assessment
  - Reason for discontinuation of study treatment and discontinuation of study
- Procedural elements:
  - Physical exam (see section 6.1)
  - Mini-ICARS
  - PATA
  - NPCRS
  - Blood collection (see section 6.1)
  - Urine collection (see section 6.1)
  - Annual screening ophthalmological exam including intraocular pressure testing.
- Survey given to families to complete and returned to site at or after visit by mail or electronically
  - PROMIS

## 6.10 Visit – Early Termination

- Procedural elements
  - Blood collection (same as section 6.1)
  - Urine collection (same as section 6.1)
- Medication adherence questionnaire (see section 6.2)
- Interview elements
  - AE assessment
  - Concomitant medication review
  - Ongoing therapies (same as section 6.1)
  - Reason for discontinuation of study treatment and discontinuation of study

- Study withdrawal – investigator will discuss with the patient and caretakers the reason for withdrawal from the study. Investigator will also attempt to consent/assent subject and/or caretaker family to collect follow up information whenever possible through review of medical records. Data to be collected include lab data to look at urinalysis values, chemistries in serum, hematology, physical exam data (including vital signs and reviewing concomitant medications), ICARS scoring, NPCRS scoring and any other adverse events if available. These evaluations will be obtained as part of their clinical care.

| Table 3: Schedule of Events | Visit 1 (Wk 0) | Visit 2 (Wk 2-3) | Visit 3 (Wk 3-5) | Visit 4 (Visit 3 + 1-3 wks) | Visit 5 (Wk 21-34) | Visit 6 (Visit 5 + 1-3 wks) | Visit 7 (Visit 6 + 1-3 wks) | Visit 8 (Visit 7 + 1-3 wks) | Visit 9 (Wk 49-105) | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | x | | | | | | | | | |
| Medical History | x | | | | | | | | | |
| Clinical History | x | | | | | | | | | |
| Physical Exam* | x | | | | x | | | | x | |
| HC | x | | | x | x | | | x | x | |
| Height | x | | | x | x | | | x | x | |
| Weight | x | | | x | x | | | x | x | |
| Vital Signs (Temperature, BP, RR, HR) | x | | | | x | | | | x | |
| Ophthalmological exam including intraocular pressure testing** | | | | | | | | | x | |
| NPCRS[a] | x | | | | x | | | | x | |
| Mini-ICARS[b] | x | | | | x | | | | x | |
| PATA | x | | | | x | | | | x | |
| Blood[c] collection | x | x | x | x | x | x | x | x | x | x |
| Urine[d] Collection | x | x | x | | x | x | x | | x | x |
| PROMIS[e] | x | | | | x | | | | x | |
| I/E review; Randomization | x | | | | | | | | | |
| Dose Initiation | x | | | | | | | | | |
| Dose Adjustment | | x | x | x | | x | x | x | x | |
| Open label continuation or discontinuation | | | | | x | | | | | x |
| Medication adherence questionnaire | | x | x | x | x | x | x | x | x | x |
| AE Assessment | | x | x | x | x | x | x | x | x | x |
| Concomitant Medication Review | x | x | x | x | x | x | x | x | x | x |
| Ongoing therapies (PT, OT, ST, FT)[f] | x | x | x | x | x | x | x | x | x | x |

[a]Appendix A [b]Appendix B [c]Blood labs: see sections 6.1 and 6.2 [d]Urine labs: see section 6.1. [e]PROMIS: Subset of patient reported outcomes as for natural history trial based on PROMIS questionnaire. See Appendix C. [f]PT = physical therapy, OT = occupational therapy, ST = speech therapy, FT = feeding therapy – collecting information regarding if

| | | |
|---|---|---|
| | | therapy ongoing (yes/no), number sessions per month. Grey shading: only for subjects who continue in OLE.*head circumference, height, and weight will be measured at least every 12 weeks. **to be done offsite as part of routine clinical care.<br>Abbreviations: Wk = week, I/E inclusion and exclusion criteria, HC = head circumference, BP = blood pressure, RR = respiratory rate, HR = heart rate |

# 7 Statistical Plan

## 7.1 Sample Size Determination

Given that the improvement in ICARS, which is highly correlated to the Mini-ICARS, was 5.6 points over roughly 20 months (Serrano, 2015), if we assume a linear change, then we have 5.6*(6/20) = 1.68 points decrease over 6 months. The expected effect size in the experimental group is 6 points decrease, whereas it is 1.68 in the placebo. Using a standard deviation of the change in scores of 4, two-sided alpha 0.05, and power 75%, the sample size required to detect a true difference of 4.32 units is 26 patients total (13 per arm) based on the two-sample t-test.

## 7.2 Statistical Methods

**Descriptive Statistics**

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the treatment groups. These analyses will help identify potential confounding variables to be used as covariates in sensitivity analyses. Distributions across subgroups used in randomization will be qualitatively compared to assess whether the randomization was successful in equalizing distributions of these prognostic variables across treatment groups. Putative prognostic variables that will be investigated through these descriptive analyses include variables such as sex, baseline Mini-ICARS score, age, and baseline NPCRS score.

**Primary Endpoint Analysis Approach:**

**Primary Hypothesis:** The administration of acetazolamide will improve the ataxia symptoms in patients with PMM2-CDG. **Primary Endpoint:** Change in Mini-ICARS score from baseline to 6 months.

The primary analysis will be conducted using the full analysis set (see Section 7.3). The between-arm mean difference in the change in Mini-ICARS score from baseline to 6 months will be evaluated via a two-sample t-test. The primary analysis will include all patients with a baseline and 6-month Mini-ICARS score. As a sensitivity analysis, all patients with a missing Mini-ICARS score at 6 months will be assumed to have no change in Mini-ICARS score between baseline and 6 months. A per-protocol analysis will also be conducted using the per-protocol set (see Section 7.3). A nominal significance level of $\alpha$=0.05 will be used for all analyses.

**Exploratory Analysis:** To explore characteristics of individuals with PMM2-CDG who do not respond to acetazolamide (objective 4), we will define the subgroup of individuals who received at least 6 months of acetazolamide and did not have an improvement in ataxia. These individuals could have received acetazolamide during either the blinded period or open label extension period for at least 6 months. In addition, their Mini-ICARS score difference after being on acetazolamide for at least six months was at or less than the mean Mini-ICARS score change for the placebo group. A correlation analysis for change in Mini-ICARS from baseline to 6 months will be performed with each of the baseline characteristics. These baseline characteristics include age, sex, weight, height, head circumference, NPCRS score, Mini-ICARS score, PATA score, concomitant medication list, allergies, current ability with activities of daily living, laboratory

data (carbohydrate deficient transferrin results (Mono/Di, A/Di, Apo CIII1/Apo C III2, Apo CIII0/Apo CIII2), electrolytes (Na, K, Cl, CO2), VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2, liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase), kidney function tests (BUN, Creatinine, Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio)), growth (height, weight, head circumference), vital signs (blood pressure, respiratory rate, heart rate), ongoing therapies (physical, occupation, speech therapy yes/no and sessions/month), physical exam elements (normal/abnormal for each examined system including neurologic exam, cardiovascular exam, abdominal exam, HEENT exam, dermatologic exam, pulmonary exam), prior or existing medical conditions within the standard body systems (present/absent – general, dermatologic, HEENT, cardiovascular, respiratory, GI, GU, musculoskeletal, neurologic, allergic, immunologic, hematologic, endocrine), and number of past hospitalizations.

**Secondary Endpoint Analysis Approach:**
**Secondary Endpoint 1:** Incidence of (a) drug related adverse event(s) and (b) drug related serious adverse event(s) while they are on blinded therapy. The maximum grade for each type of adverse event will be summarized using the CTCAE v5.0. Using the safety set (see Section 7.3), the frequency and percentage of patients with a grade 1+ adverse event or serious adverse event classified as possibly, probably, or definitely related to the study treatment will be summarized by treatment arm. The frequency and percentage of patients who discontinue study treatment due to adverse events will also be reported by treatment arm. This analysis will be repeated to evaluate incidence of (a) drug related adverse event(s) and (b) drug related serious adverse event(s) for the duration that patients remain in the open label extension.
**Secondary Endpoint 2:** PMM2-Biomarker and other scores including:

- carbohydrate deficient transferrin results (Mono/Di, A/Di, Apo CIII1/Apo C III2, Apo CIII0/Apo CIII2),
- electrolytes (Na, K, Cl, CO2),
- VBG (pH, pCO2, PO2, CO2, Base excess) or bicarbonate/CO2,
- liver function tests (AST, ALT, GGT, indirect and direct bilirubin, total protein, albumin, alkaline phosphatase),
- kidney function tests (BUN, Creatinine, Urinalysis, urine calcium/creatinine ratio, urine protein/creatinine ratio),
- growth (height, weight, head circumference),
- vital signs (blood pressure, respiratory rate, heart rate),
- PROMIS scores,
- the PATA score,
- and NPCRS score.

As these endpoints are all numeric, and to identify if the post blinded therapy or final measurement of the open label extension is different from the baseline value, we will use a linear regression model to test if there is a change from baseline. Using the full analysis set (see Section 7.3), the between-arm mean difference in 6-month scores will be evaluated via a linear regression model predicting 6-month scores from baseline scores and treatment arm. This analysis will be repeated based on the final measurement of the open label extension. A nominal significance level of $\alpha$=0.05 will be used for all analyses.

**Handling of Intercurrent Events**
Per the E9(R1) guidance (*Statistical Principles for Clinical Trials; Addendum: Estimands and Sensitivity Analysis in Clinical Trials*), a treatment policy strategy will be used to address intercurrent events. That is, for the primary analysis, each patient's change in Mini-ICARS score from baseline to 6 months will be used regardless of whether an intercurrent event occurs.

**Handling of Missing Data**
Attempts to minimize missing data will be made through site training and data monitoring (e.g., form delinquency notifications, data queries). Patients who prematurely discontinue study treatment will be encouraged to remain in the study for their scheduled efficacy and safety assessments. The primary analysis evaluating the between-arm mean difference in the change in Mini-ICARS score from baseline to 6 months will include all patients with a baseline and 6-month Mini-ICARS score. For patients with a missing Mini-ICARS score at 6 months, imputation will be used as part of a sensitivity analysis. Specifically, all patients with a missing Mini-ICARS score at 6 months will be assumed to have no change in Mini-ICARS score from baseline to 6 months (i.e., 0 imputed for all missing change scores).

**Multiplicity**
No adjustment for multiplicity will be made, though interpretation will take into consideration that the type I error is strictly controlled for the primary endpoint only. Overall interpretation will also take into consideration consistency of results across analyses.

**Interim Analysis**
No interim analysis will be conducted.

### 7.3 Subject Populations for Analysis

- *Intent-to-treat set*: All randomized patients, regardless of whether they received their assigned study treatment.
- *Full analysis set*: All randomized patients who complete the baseline and 6-month visits.
- *Safety set*: All randomized patients who receive at least one dose of acetazolamide or placebo.
- *Per-protocol set*: All randomized patients who report taking at least 4 weeks of their assigned study treatment and complete the baseline and 6-month visits.

## 8 Safety and Adverse Events

Blood will be collected at regular intervals to assess electrolytes level, kidney function, coagulation factor, and measure of base. Urine will also be collected at regular intervals to assess calcium and protein levels. Routine urinalysis will also be performed to monitor for any significant changes in body fluids as a result of acetazolamide function. Monitoring for thrombocytopenia, electrolyte disturbances, and metabolic acidosis should be completed within 4 weeks of a dose increase. If significant changes occur in blood or urine tests, risk will be re-evaluated by the principal investigator to determine if acetazolamide should be continued as per below. The AE reporting period will encompass visits 0 to 9 of the study. If a subject withdraws early, we will attempt to assess AEs up to 91 weeks after enrollment through review of medical records.

## 8.1 Definitions

**Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)**
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the acetazolamide package insert, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

**Adverse Event**
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) or placebo in a patient or research subject. AEs may also be problems/events that in the opinion of the investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

**Serious Adverse Event**
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

**Adverse Event Reporting Period**

The study site will document all AEs that occur (whether or not related to study drug) within one week of the investigator becoming aware of the event. The collection period for all AEs will begin after informed consent is obtained and end after procedures for the final study visit have

been completed. In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB.

**Pre-existing Condition**
A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

**General Physical Examination Findings**
At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new or worsening clinically significant findings/abnormalities that meet the definition of an adverse event must also be documented and reported as an adverse event.

**Post-study Adverse Event**
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report, to the investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

**Abnormal Laboratory Values**
A clinical laboratory abnormality should be documented as an adverse event if they meet the following criteria:

- Hepatic impairment defined as AST/ALT >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
- Renal impairment defined as serum creatinine 1.5-1.9 times ULN for age OR ≥ 26.5 umol/l increase from ULN for age

If these values are noted and no other cause for these laboratory changes are likely, then drug will be stopped, and repeat labs will be obtained at reasonable intervals per investigator's clinical judgement after discontinuation until labs have normalized to stabilized. Treatment may be restarted if labs have returned to baseline using the same ramp up schedule as described for visits 2, 3 and 4. These changes in treatment will be documented.

**Hospitalization, Prolonged Hospitalization or Surgery**
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse

event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

## 8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

The most up to date National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual (appendix D). If the experience is not covered in the modified criteria, the guidelines shown in Table below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

**Table 4. AE Severity Grading**

| Severity (Toxicity Grade) | Description |
|---|---|
| Mild (1) | Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well. |
| Moderate (2) | Mild to moderate limitation in activity, no or minimal medical intervention/therapy required. |
| Severe (3) | Marked limitation in activity, medical intervention/therapy required, hospitalizations possible. |
| Life-threatening (4) | The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe. |

### AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table .

**Table 5. AE Relationship to Study Drug**

| Relationship to Drug | Comment |
|---|---|
| Definitely | Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis. |
| Probably | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions. |
| Possibly | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors. |
| Unrelated | An event that can be determined with certainty to have no relationship to the study drug. |

## 8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study subject and then complete the Study Adverse Event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

### 8.3.1 Investigator reporting: notifying the IRB

The investigator will report to the IRB any UPIRTSOs and Non-UPIRTSOs according to the IRB Policy and Procedures.

Information collected on the adverse event worksheet:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:

- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

### 8.3.2 Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

The sponsor-investigator must also notify the FDA (and sponsors must notify all participating investigators) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i)-(iv).

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

## 8.4 Unmasking/Unblinding Procedures

In the event that a subject needs to be unblinded for safety reasons, a member of the study team will contact the research pharmacy to learn the treatment the subject is on in order to provide

necessary care. If a subject needs to be unblinded for safety reasons, this may be documented in the subject's file, and may need to be documented as an SAE. Regardless of if the event is classified as an SAE or not, the event will be reported within 1 week of learning about the event. Each study site's PI will be responsible for reporting the unblinding and SAE to the IRB and DSMB for the subjects enrolled at their site. They will also notify the lead investigator of the SAE as well as the DSMB.

## 8.5 Stopping Rules

Any SAEs greater than grade 3 (severe) as defined as "marked limitation in activity, medical intervention/therapy required, hospitalizations possible" will qualify as study stoppage for the rest of the study. The central Data and Safety Monitoring Board (DSMB) will be notified and they will determine if the study would need to be placed on hold with IRB. The study may be restarted if the SAE resolves or is deemed unrelated to the study.

Additionally, if clinical laboratory results show:

- Hepatic impairment defined as AST/ALT >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
- Renal impairment defined as serum creatinine 1.5-1.9 times ULN for age OR ≥ 26.5 umol/l increase from ULN for age

If no other cause for these laboratory changes are likely, then drug will be stopped, and repeat labs will be obtained at reasonable intervals per investigator's clinical judgement after discontinuation until labs have normalized to stabilized. Treatment may be restarted if labs have returned to baseline using the same ramp up schedule as described for visit 2 and 3. The DSMB will also be notified.

## 8.6 Medical Monitoring

It is the responsibility of the Investigator at each site to oversee the safety of the study at his/her site. Any SAE will be reported to the DSMB, which will make decisions regarding unblinding. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

### 8.6.1 Independent Data and Safety Monitoring Board

Data Safety Monitoring Board (DSMB) will be headed by a biochemical geneticist from an outside hospital. Other members include a neurologist and biochemical geneticist at SCH, and a member of the UW ITHS. Our study biostatistician will provide statistical support when needed. The DSMB will review data mainly relating to safety. There will be a pre-study review and interim reviews every year conducted by the DSMB for the purpose of monitoring study conduct and assessing individual safety. All eligible individuals who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

# 9 Data Handling and Record Keeping

## 9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

## 9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## 9.3 Case Report Forms

The electronic study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. Reasons for missed visits should be collected when possible and documented. Within REDCap, a CRF should not be marked as "Complete" until all fields are completed or are intentionally left blank (e.g., due to a procedure or questionnaire not being completed during the acceptable time window).

### Data Management

Data collection is the responsibility of the study staff at the site under the supervision of the site Primary Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

The DMCC will develop, test, and maintain the data capture system using a web-based data collection system, REDCap, as the primary source of data entry and storage. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data developed by Vanderbilt University, with collaboration from a consortium of institutional partners including the University of Cincinnati Academic Health Center. The REDCap system provides a secure, web-based application that is flexible and provides: 1) an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry; 2) HIPAA-compliant and 21 CFR Part 11-ready audit trails for tracking page views, data manipulation and export procedures; 3) record locking and electronic signature functions; 4) fine grained control of user rights to view and manipulate data, and tool to sequester data access for multiple sites; 5) a report builder for reporting, monitoring and querying patient records; and 6) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Study data will be entered into REDCap, supported by the DMCC. The REDCap system complies with all applicable guidelines to ensure patient confidentiality, data integrity, and reliability. All data management best practices including quality controls and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. A data management plan will be developed which will describe the data collection process, database development, quality control processes and reporting.

**Data Processing**

Data will be entered into the eCRF by single entry at each participating site by the study coordinator or investigator within 3 business days of data collection.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

**Data Security and Confidentiality**

All subjects enrolled into this study will be assigned a unique numerical identifier. The code linking this study number to the identifiable patient will be kept secure behind the Mayo Clinic firewall on password protected drives only accessible by essential study staff. The linking will also be maintained securely at each local site. All other records will also be kept in this fashion. Hard copy records will be maintained in binders housed in staff only areas and will be locked behind doors and/or desks as able.

We will use a system of coded identifiers to protect subject confidentiality and safety. Each subject enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the enrolling site will have access to the linkage between this number and the personal identifier of the subject. When the subject is enrolled in the study, a web-based system will be used to

generate another subject ID number (e.g. Globally Unique Identifier or GUID). Thus, each subject will have two codes: the local one that can be used by the enrolling site to obtain personal identifiers and a second code assigned by the web-based system. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. Using this methodology, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a subject for data entry since the numbers should match to properly identify the subject.

**Data Quality Assurance**

The initial data entry will take place by a single member of the study team. An additional study team member may verify that this data matches the medical record and/or CRFs.

**Data Clarification Process**

After data have been entered into the study database, a system of computerized data validation checks will use normative data ranges for first line queries. These automatic queries can be corrected by the study coordinator at the time of data entry. The DMCC will issue additional queries which should be addressed by the study team within 10 days before a second query is generated. All queries will be tracked and resolved through the EDC system.

### 9.4 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

Subject names and other identifiable information will not be included on any reports, publications, or other disclosures of clinical study outcomes.

The investigator will retain the specified records and reports for;

1. Until 2 years after shipment and delivery of the drug for investigational use is discontinued OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"[redacted]

whichever is longer.

## 10 Study Monitoring, Auditing, and Inspecting

### 10.1 Study Monitoring Plan

The investigator at each local site will allocate adequate time for such monitoring activities. The Investigator at each local site will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities

(e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

### 10.1.1 Study synopsis

A synopsis of the study is provided in the Study Summary and is greater than minimal risk. The proposed participating clinical sites in which recruitment, consent, and study procedures will occur will be Seattle Children's Hospital, Mayo Clinic in Minnesota, and Children's Hospital of Philadelphia.

### 10.1.2 Roles and Responsibilities

The investigators including the lead principal investigator, site principal investigators, and co-investigators are responsible for monitoring the safety of the trial. All investigators are qualified providers with expertise in managing genetic conditions. The DSMB will also aid in determination of safety and if the trial needs to be paused or discontinued, or if the trial can resume (see section 8.6.1).

### 10.1.3 Trial Safety

See section 8 for description of any specific events that would preclude a subject from continuing the intervention and managing any medication related issues. See section 1.5 for potential risks and measures in place to protect subjects against foreseeable risks. Consent and assent procedures are described in section 11 below. Individuals will be consented or assented in person face to face. Subject privacy will be protected by the following measures - interviews will take place in a private room, testing data will be shared with subject's legally authorized representative, privacy for minors, communication between investigators and subject will be performed via secure means including via secure telephone, web portal, telehealth software. Trial stopping rules are described in section 8.5. Incidental findings will be reported to the subject and their parent/legal guardian, or legally authorized representative as well as their clinical provider. Decisions regarding management of these incidental findings will be deferred to the subject's clinical provider and family. Any conflicts of interest will be disclosed as per section 12.2. As a multi-center study, compliance with the monitoring plan will be ensured by the site PI, and data will be reported across study sites electronically. Additionally, all study related data will be collected in a centralized database as per section 9. Data security measures to protect the confidentiality of the data are also described in section 9.

### 10.1.4 Reportable Events

The process and timeline for reporting AEs, SAEs, and UPIRSO are described in section 8.3.

### 10.1.5 Data Management, Analysis, and Quality Assurance

Data sources include PROMIS questionnaire (paper or electronic, Appendix C), mini-ICARS scores – Appendix B and video recordings, medical records, and medication adherence questionnaire – Appendix E. These data sources will be stored in electronic records that will be password protected behind institutional firewalls labeled only with the subject ID and study ID. Physical data sources (i.e., paper questionnaires or records) will be stored in a secure area that is locked from the public that only the study team will be able to access. The DMCC will intermittently review the data of the demographics of subjects and randomization to ensure that

subject recruitment and enrollment are on target for the validity and integrity of the data. They will provide the investigators a report electronically (e-mail) regarding recruitment status once every 3 months. The trial will be performed, and the data will be generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP).

### 10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

Self-monitoring of participant sites will be coordinated by the Mayo program coordinator. Self-monitor forms will be sent to all participating sites on an annual basis. Each site will be responsible for reviewing study documentation, completing the forms, and returning them to the Mayo program coordinator, who will then review the forms, clarify any questions or concerns, and send a self-monitor acknowledgment letter to site PI and coordinator. Each site, as well as the IND sponsor, will retain self-monitor documentation and letters in their regulatory binders.

## 11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects with a developmental and actual age of ≥18 years will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

The PI or a designee will determine whether adult subjects are able to provide consent using both previous results from formal assessments of intellectual capacity (such as neuropsychological testing results) and/or determinations made based on conversations with the impaired adult at and before the time of consent. Some adult patients might not be able to give informed consent due to developmental disabilities. If patients' developmental functioning level is less than 18

years of age, the patient will be classified as “unable to consent for self.” To assess an adult patient’s capacity to consent, we will use both previous formal assessments of intellectual capacity (such as neuropsychological testing results) as well as determinations made based on conversations with the impaired adult at and before the time of consent. We will obtain informed consent for intellectually impaired adults using their appointed surrogate decision-maker or another legally authorized representative (LAR), such as a person who has a legal guardian or for whom a durable power of attorney (DPA) has been granted. An appropriate LAR is one who at least: 1) understands that the protocol involves research; 2) understands the risks, potential benefits (if any), and alternatives to the study; and 3) has sufficient reason to believe participation in the study is consistent with the subject's preferences and values. When subjects are judged to have mental competence above that of a 7-year-old, the team will use the assent process (when possible and appropriate) in addition to obtaining informed consent via a LAR.

Our study will involve greater than minimal risk on children as a study drug is being administered. However, the risk is justified by the prospect of direct benefit to the individual subject, the relation of the anticipated benefit to the risk is favorable to the subject as compared to the lack of available alternative therapeutic approaches in PMM2-CDG; and adequate provisions will be made for soliciting the permission of their parents or legal guardians or legally authorized representative. A legal guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to (a) general medical care when general medical care includes participation in research; or (b) to participate in research [DHHS 45 CFR §46.402(e); FDA 21 CFR 50.3(s)]. A legally authorized representative is an individual, judicial, or other body authorized under applicable law (e.g., a person appointed as a health agent, a court-appointed legal guardian of the person, as well as next-of-kin) to consent or otherwise provide permission on behalf of a subject, either prospectively or during the course of research, to the subject's participation in the procedure(s) involved in the research. [DHHS 45 CFR §46.102(c); FDA 21 CFR §50.3(l)].

An assent form will be used in children that are capable of providing assent. This same assent form will also be used for selected intellectually impaired adults with sufficient comprehension. Consent for children will be obtained from a parent/legal guardian.

Minors will be asked to complete an adult research consent form when they reach 18 years of age if not developmentally disabled as noted above. If they do not complete the adult research consent form, they will be classified as a partial withdrawal. The research team/registry will keep their specimens, and scientists will have access to their specimens and study data (e.g. answers to health surveys), however, we will not recontact them and their name and contact information will not be released to researchers for recruitment into follow-up studies.

Subjects will be free to voluntarily withdraw from participation at any time. To minimize drop-out or loss to follow up, subjects will be contacted at least once a year by the study coordinator. At that time contact information will be verified and major changes in disease evolution or treatment will be noted, along with significant health issues.

# 12 Study Finances

## 12.1 Funding Source

This study is funded by the FCDGC (Frontiers of Congenital Disorders of Glycosylation Consortium). The FCDGC is funded through a U54 NIH Grant. External funding through institution-based organizations may also be sought prospectively.

## 12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study investigator prior to participation in this study.

# 13 Publication Plan

The principal investigator and site principal investigators and co-investigators will be responsible for the publication of the results of this study. Approval from the principal investigator must be obtained before any information can be used or passed on to a third party. The study will be registered to ClinicalTrials.gov (https://register.clinicaltrials.gov/) prior to subject recruitment and enrollment, and results will be posted to ClinicalTrials.gov within 12 months of final data collection for the primary outcome.

# 14 References

Acetazolamide. (2020). In *Physicians' Desk Reference*. Retrieved from https://www.pdr.net/drug-summary/Acetazolamide-Tablets-acetazolamide-667.

Bain PG, O'Brien MD, Keevil SF, et al. Familial periodic cerebellar ataxia: a problem of cerebellar intracellular pH homeostasis. *Ann Neurol* 1992;31:147–154.

Barone R, Fiumara A, Jaeken J. Congenital disorders of glycosylation with emphasis on cerebellar involvement. *Semin Neurol* 2014;34:357–366.

Barone R, Carrozzi M, Parini R, et al. A nationwide survey of PMM2-CDG in Italy: high frequency of a mild neurological variant associated with the L32R mutation. *J Neurol* 2015;262:154–164.

De Diego V, Martínez-Monseny AF, Muchart J, et al. Longitudinal volumetric and 2D assessment of cerebellar atrophy in a large cohort of children with phosphomannomutase deficiency (PMM2-CDG). *J Inherit Metab Dis* 2017;40:709–713.

Distelmaier F, Sengler U, Messing-Juenger M, et al. Pseudotumor cerebri as an important differential diagnosis of papilledema in children. Brain and Development. 2006;28:190-195. [PubMed 16368210]

Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurology of inherited glycosylation disorders. *Lancet Neurol* 2012;11:453–466.

Grünewald S, Matthijs G, Jaeken J. Congenital disorders of glycosylation: a review. *Pediatr Res* 2002;52:618–624.

Grünewald S. The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia). *Biochim Biophys Acta* 2009;9:827-34.

Hacifazlioglu N, Yilmaz Y. Pseudotumour cerebri in children: etiological, clinical features and treatment modalities. European Journal of Paediatric Neurology. 2012;12:349-355. [PubMed 22050895]

Izquierdo-Serra M, Martínez-Monseny AF, López L, et al. Strokelike episodes and cerebellar syndrome in phosphomannomutase deficiency (PMM2-CDG): evidence for hypoglycosylation-driven channelopathy. *Int J Mol Sci* 2018;19. pii: E619.

Jaeken J, Vanderschueren-Lodeweyckx M, Casaer P et al. Familial psychomotor retardation with markedly fluctuating serum proteins, FSH and GH levels, partial TBG-deficiency, increased serum arylsulphatase A and increased CSF protein: a new syndrome? *Pediatr Res* 1980;14:179.

Jaeken J, Lefeber D, Matthjs G. Clinical utility gene card for: phosphomannomutase 2 deficiency. *Eur J Hum Genet* Epub 2014; do i: 10.1038/ejhg. 2013.298.

Ko MW,Liu GT. Pediatric idiopathic intracranial hypertension (Pseudotumor cerebri). Horm Res Paediatr. 2010;74:381-389. [PubMed 20962512]

Martínez-Monseny AF, Bolasell M, Callejón-Póo L, et al. AZATAX: Acetazolamide safety and efficacy in cerebellar syndrome in PMM2 congenital disorder of glycosylation (PMM2-CDG). *Ann Neurol* 2019;85(5):740-751.

Moffett BS, Moffett TI, Dickerson HA. Acetazolamide therapy for hypochloremic metabolic alkalosis in pediatric patients with heart disease. Am J Ther. 2007;14(4):331-335. [PubMed 17667206 ]

Park, MK. Park's Pediatric Cardiology for Practitioners. 6th ed. Philadelphia, PA: Elsevier Health Sciences; 2014.

Per H, Canpolat M, Gumus H, et al. Clinical spectrum of the pseudotumor cerebri in children: etiological, clinical features, treatment and prognosis. Brain Dev. 2013;35:561-568. [PubMed 22981259]

Rangwala LM, Liu GT. Pediatric idiopathic intracranial hypertension. Survey of Ophthalmology. 2007;52(6):597-617. [PubMed 18029269]

Reiss WG and Oles KS, “Acetazolamide in the Treatment of Seizures,” Ann Pharmacother, 1996, 30(5):514-9. [PubMed 8740334]

Sappey-Marinier D, Vighetto A, Peyron R, et al. Phosphorus and proton magnetic resonance spectroscopy in episodic ataxia type 2. *Ann Neurol* 1999;46:256–259.

Serrano M, de Diego V, Muchart J, et al. Phosphomannomutase deficiency (PMM2-CDG): ataxia and cerebellar assessment. *Orphanet J Rare Dis* 2015;10:138.

Serrano NL, de Diego V, Cuadras D, et al. A quantitative assessment of the evolution of cerebellar syndrome in children with phosphomannomutase-deficiency (PMM2-CDG).*Orphanet J Rare Dis* 2017;12:155.

Soler D, Cox T, Bullock P, et al. Diagnosis and management of benign intracranial hypertension. Arch Dis Child. 1998;78:89-94. [PubMed 9534686]

Spennato P, Ruggiero C, Parlato RS, et al. Pseudotumor cerebri. Childs Nerv Syst. 2011;27:215-235. [PubMed 20721668]

Standridge S. Idiopathic intracranial hypertension in children: a review and algorithm. Pediatric Neurology. 2010;43(6): 377-390. [PubMed 21093727]

## 15 Attachments

Please see attached appendices.
Appendix A: Nijmegen Pediatric CDG Rating Scale (NPCRS)
Appendix B: mini-International Cooperative Ataxia Rating Scale (mini-ICARS)
Appendix C: Patient-Reported Outcome Measurement Information System (PROMIS)
Appendix D: Common Terminology Criteria for Adverse Events version 5 (CTCAE v5)
Appendix E: Medication adherence questionnaire