focuses on male Fabry patients with the aim to explain variations in lysoGb3. The lysoGb3 value seems to stabilize at a level above normal even during treatment. The value varies among individual male patients. It appears that the mutation plays a part, but it does not explain everything. Chaperone therapy seems to increase the level of lysoGb3 a lot in one male patient. Antibody formation appears to influence a rise in lysoGb3. Our male patients with kidney transplants have lower levels of lysoGb3. We have also compared the development of lysoGb3 in treated versus non treated brothers. The result is a clear drop in lysoGb3 in both treated brothers. It also seems like age of treatment start matters, but antibody formation rises the level of lysoGb3 again, but not as high as before treatment start.

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A comparison of the gut microbiome in children affected by Fabry disease and their unaffected siblings: A pilot project

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Fabry disease (FD) is an X-linked genetic deficiency of a lysosomal enzyme, alpha-galactosidase, that causes accumulation of globotriaosylsphingosine (lyso-Gb3). Most patients with FD report gastrointestinal (GI) symptoms including diarrhea, vomiting, abdominal pain and early satiety. These symptoms can be severe and negatively impact quality of life. The mechanisms of GI symptoms in FD are unclear, but there is increasing suspicion that the microbiome plays a role. An altered gut microbiome has been associated with similar symptoms in other populations. Recently, high levels of lyso-Gb3 were shown to significantly alter gut bacteria composition and function in vitro. In this small pilot study, we aimed to compare the gut microbiomes of FD-affected children with unaffected siblings. Six FD-affected children and five unaffected siblings provided a stool sample for analysis. Participants also completed ROME IV questionnaires to measure irritable bowel syndrome-like symptom severity. Microbiome composition was characterized via next- generation sequencing (Illumina) of the V4-V5 variable regions of the 16S rRNA gene. Bacterial diversity and relative abundance of the operational taxonomic units were evaluated using QIIME2 and compared by ANOVA and Welch's *t*-tests. Compared to unaffected siblings, children with FD exhibited increased proportions of Christensenellaceae R-7 group ($p = .012$), unclassified genera in Ruminococcaceae ($p = .013$), Negativibacillus ($p = .014$), Methanobrevibacter ($p = .043$) and Ruminococcaceae UCG-005 ($p = .045$), and decreased proportions of Burkholderiaceae ($p = .05$). Functional abundance was predicted using PICRUSt2 and differences in functional pathways were investigated. These intriguing trends may implicate the microbiome in FD symptoms. While these results did not achieve significance after correction for multiple testing, further investigation is warranted. A larger cohort of pediatric and adult FD patients is likely to better resolve microbiome differences that may contribute to GI symptoms in FD. This could lead to new insights into the pathophysiology and treatment of this disease.

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Intracerebroventricular cerliponase alfa for CLN2 disease: Clinical practice considerations from US clinics

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CLN2 disease, a rare, autosomal recessive, neurodegenerative lysosomal disorder caused by TPP1 deficiency, is characterized by language delay, epilepsy, progressive motor and cognitive decline, blindness, and early death. Intracerebroventricular (ICV)-administered cerliponase alfa, a recombinant human TPP1 enzyme, is an approved treatment for CLN2 disease in the United States and European Union. ICV infusion represents a novel delivery method for enzyme replacement therapy. Here, key practice considerations are presented to facilitate safe administration of cerliponase alfa. 15 healthcare professionals (neurosurgeons, neurologists, hospitalists, registered and advanced practice nurses) from 9 institutions in the US met to share current practices in administering ICV-delivered cerliponase alfa, and preventing and managing associated complications. Common practices among the participants that were deemed essential to achieving successful infusions include developing an institutional protocol for infusions, high sterility standards, and a multidisciplinary infusion team with a designated staff member to coordinate care. The use of multiple different cleansing agents as part of aseptic technique is common. Considerable variations in practice exist, based on experience, regarding CSF sampling frequency for infection monitoring and actions taken with a positive culture, infusion setting, and post-infusion procedures, such as length of stay and monitoring. Clear communication across departments and with families throughout the process is critical. The sharing of practices among institutions familiar with cerliponase alfa has identified similar as well as differing practices which new institutions may adapt in developing their policies. Continued sharing of experiences is essential for developing standards and guidelines for patient care.

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Long-term safety and efficacy of vestronidase alfa, rhGUS enzyme replacement therapy, in subjects with mucopolysaccharidosis type VII

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Vestronidase alfa (recombinant human beta-glucuronidase) is an enzyme replacement therapy for mucopolysaccharidosis type VII (MPS VII), a highly heterogeneous, ultra-rare disease. Twelve subjects, ages 8–25 years, completed a Phase 3, randomized, placebo-controlled, blind-start, single crossover study (UX003-CL301; NCT02230566), receiving 24–48 weeks of vestronidase alfa 4 mg/kg IV. All 12 subjects completed the blind-start study, which showed significantly reduced urinary glycosaminoglycans (uGAG) and clinical improvement in a multi-domain responder index, and enrolled in a long-term, open-label, extension study (UX003-CL202; NCT02432144). Here, we report the final results of the extension study, up to an additional 144 weeks after completion of the blind-start study. Three subjects (25%) completed all 144 weeks of study, eight subjects (67%) ended study participation before Week 144 to switch to commercially available vestronidase alfa, and one subject discontinued due to non-compliance after receiving one infusion of vestronidase alfa in the extension study. The safety profile of vestronidase alfa in the extension study was consistent with observations in the preceding blind-start study, with most adverse events mild to moderate in severity. There were no treatment or study discontinuations due to AEs and no noteworthy changes in a standard safety chemistry panel. There was no association between antibody formation and infusion associated reactions. Subjects receiving continuous vestronidase alfa treatment showed a sustained uGAG reduction and clinical response evaluated using a multi-domain responder index that includes assessments in pulmonary function, motor function, range of motion, mobility, and visual acuity. Reductions in fatigue were also maintained in the overall population. Results from this study show the long-term safety and durability of clinical efficacy in subjects with MPS VII with long-term vestronidase alfa treatment.

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Rationale and design of the MODIFY study: A phase 3 multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult subjects with Fabry disease

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Current Fabry disease (FD) treatments (enzyme replacement therapy [ERT] and chaperone therapy) show limited symptom improvement, particularly neuropathic pain (NeP). Their use may be restricted by mode of administration, immunogenicity, or type of *GLA*-gene mutation. Lucerastat, an iminosugar in clinical development as substrate reduction therapy to reduce the net globotriaosylceramide (Gb3) load in tissues, has the potential to alleviate FD symptoms with the goal to delay disease progression. The MODIFY study (ClinicalTrials.gov: NCT03425539) aims to determine the clinical efficacy of oral lucerastat monotherapy and evaluate its safety in subjects with FD. Eligible adults with genetically confirmed FD diagnosis and Fabry-specific neuropathic pain (FD-NeP) will enter screening (~6–7 weeks duration). Subjects with moderate/severe NeP who complete the daily eDiary during screening will be randomized (2:1) to receive either twice daily oral lucerastat or placebo. Lucerastat is renally excreted; starting doses will be adjusted based on individual estimated glomerular filtration rate. Treatment allocation will be stratified by sex and previous ERT (no ERT at screening [treatment-naïve subjects who never received ERT and pseudo-naïve subjects who stopped ERT ≥6 months prior to screening] vs. 'switch' subjects who stopped ERT at screening). At the end of the 6-month double-blind treatment period, subjects may enter an open-label extension study, to further assess safety and efficacy parameters. Symptoms will be assessed via a validated patient reported outcome instrument using an eDiary. Primary endpoint: response to treatment on FD-NeP (reduction from baseline to month 6 of ≥30% in the 'modified' Brief Pain Inventory Short Form Question 3 score, measured daily). Secondary endpoints include change from baseline to month 6 in plasma Gb3, and, for subjects with gastrointestinal symptoms at baseline, average daily score of abdominal pain (Numeric Rating Scale-11) and number of days with ≥1 stool of Bristol Stool Scale consistency type 6/7.

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Pegunigalsidase alfa, a novel PEGylated ERT, evaluated in Fabry disease patients with progressing kidney disease, RCT study design

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Fabry disease (FD) is an X-linked multisystem lysosomal disorder, affecting males and females caused by the deficient of α-galactosidase-A (α-Gal-A) activity. Long-term disease manifestations include progressive renal failure, hypertrophic cardiomyopathy, cardiac rhythm disturbances, stroke and death. Two enzyme replacement therapies (ERT) and an oral chaperon therapy are commercially available. The clinical benefit of available treatments may not be as robust as anticipated, especially in the subset of males with 'classic' Fabry disease. In the context of ERT, a combination of factors including dose, dosing interval, presence of anti-drug antibodies, estimated glomerular filtration rate (eGFR), age at the time of ERT initiation and proteinuria could explain the less than optimal responses achieved by the currently available ERT (Schiffmann et al. 2017). Pegunigalsidase alfa is a novel PEGylated homo-dimer ERT which is more stable, has a favorable safety profile, potential less development of anti-drug antibodies, and enhanced pharmacokinetic profile (~80 h half-life and higher AUC) compared to other available ERT. Adult FD patients (males and females) deteriorating in kidney function with annualized eGFR ≤ − 2 mL/min/1·73 m^2/year while on agalsidase beta have been enrolled into BALANCE, a phase-III double-blind active control study (NCT02795676), and were randomized (2:1 ratio) to pegunigalsidase alfa or continue agalsidase beta for 2