MO034

A SUBGROUP ANALYSIS OF FEMALE PATIENTS IN A PHASE 3 OPEN-LABEL STUDY TO ASSESS THE SAFETY AND EFFICACY OF PEGUNIGALSIDASE ALFA IN PATIENTS WITH FABRY DISEASE PREVIOUSLY TREATED WITH AGALSIDASE ALFA

Derralynn Hughes[1], Gabriela Dostalova[2], Kathy Nicholls[3], Michael West[4], Camilla Tøndel[5], Ana Jovanovic[6], Pilar Giraldo Castellano[7], Bojan Vujkovac[8], Tarekegn Geberhiwot[9], Einat Almon[10], Sari Alon[10], Mali Szlaifer[10], Raul Chertkoff[10], Ales Linhart[11]

[1]University College London, [2]General University Hospital in Prague, First Faculty of Medicine, Charles University, 2nd Department of Internal Cardiovascular Medicine, Prague, Czech Republic, [3]Royal Melbourne Hospital, Australia, [4]Dalhousie University, Division of Nephrology , Department of Medicine, Canada, [5]University of Bergen, Department of Clinical Medicine, Bergen, Norway, [6]Salford Royal NHS Foundation Trust, Department of Endocrinology and Metabolic Medicine, Salford, United Kingdom, [7]Hospital Universitario Miguel Servet, Unidad de Investigación Traslacional - Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain, [8]General Hospital Slovenj Gradec, Fabry Center, Slovenj Gradec, Slovenia, [9]University of Birmingham, Institute of Metabolism and Systems Research, Birmingham, United Kingdom, [10]Protalix Biotherapeutics, Karmiel, Israel and [11]General University Hospital in Prague, Head of Clinic, Prague, Czech Republic

BACKGROUND AND AIMS: Females with Fabry disease (FD) often develop symptoms and disease complications later in life than males. However, they can experience significant health declines, including renal function impairment. Pegunigalsidase alfa is a novel PEGylated alpha-galactosidase A enzyme in development for the treatment of patients with FD with potential pharmacokinetic benefits. We previously reported that males with FD showed improvements in several parameters including median (minimum, maximum) estimated glomerular filtration rate (eGFR) slope from -4.6 (-20.5, 4.8) to -1.1 (-18.6, 14.2) mL/min/1.73m2/year after treatment with pegunigalsidase alfa.(Tondel et al. ASN 2020. PO0562. www.asn.scientificposters.com) Here we report a subgroup analysis of the safety and efficacy of pegunigalsidase alfa treatment in females with FD.

METHOD: BRIDGE (PB-102-F30; NCT03018730) is a phase 3, open-label, switch-over study designed to assess the safety and efficacy of pegunigalsidase alfa in adults with FD previously treated with agalsidase alfa for at least 2 years. Patients received intravenous pegunigalsidase alfa at 1 mg/kg every other week for 12 months.

RESULTS: Twenty-two patients were enrolled in the study; of the 20 patients who completed 12 months of study treatment, 7 were female. Females had a mean age of 46.7 years (range: 26–59 years), and had the following median (minimum, maximum) baseline measurements: residual enzymatic activity in leucocytes of 23.7% (16, 46) of the normal laboratory mean; plasma lyso-Gb3 of 12.9 (7.4, 23.2) nmol/L; eGFR of 87.7 (55.3, 109.2) mL/min/1.73m2; and an annualized eGFR slope of −3.7 (-11.2, 1.5) mL/min/1.73m2/year. After 12 months of pegunigalsidase alfa treatment, the annualized eGFR slope was 1.4 (-6.3, 4.1) mL/min/1.73m2/year, indicating an improvement from baseline of 5.9 mL/min/1.73m2/year. In addition, plasma lyso-Gb3 had a reduction of 23.3% (-45.7, -17.3). Although all females had baseline mean residual enzyme activity $>$ 5% and were previously treated with agalsidase alfa, only 2 had stable kidney disease (eGFR slope $\geq$ -3 mL/min/1.73m2/year), while 2 had moderately progressing kidney disease (eGFR slope between $\geq$-5 and $<$ -3 mL/min/1.73m2/year), and 3 had fast progressing kidney disease (eGFR slope $<$ -5 mL/min/1.73 m^2/year).(Wanner et al. 2018 Mol Genet Metab 124:189-203) After treatment all but 1 patient experienced categorical improvement or remained stable; this patient had a decline of $<$ 3 mL/min/1.73m2/year and remained in the fast progressing disease category. Mean left ventricular mass index in females increased from 66.9 g/m2 at baseline to 74.1 g/m2 at month 12, but remained within normal ranges(47–77 g/m2).(Kawel-Boehm et al. 2015 J Cardiovasc Magn Reson 17:29) All females had at least 1 treatment-emergent adverse event (TEAE), and all TEAEs were mild or moderate. The most common TEAEs reported in female were nasopharyngitis (n=2), oropharyngeal pain (n=2), and headache (n=2). None of these TEAEs were considered related to treatment. However, 2 females had injection site reactions and 2 developed transient, non-neutralizing anti-drug antibodies to pegunigalsidase alfa treatment.

CONCLUSION: The current study included females with symptoms of Fabry disease comparable to the disease presentation of males enrolled in this study. At baseline most females had eGFR decline characterizing progressive or rapidly progressive kidney disease. Most females showed improvements in disease status following 12 months of pegunigalsidase alfa treatment, as previously reported for males enrolled in this study. This long-term, controlled study suggests a potential benefit and a favorable safety profile for pegunigalsidase alfa on renal function in females with FD previously treated with agalsidase alfa. While this subgroup analysis should be interpreted with caution due to the small number of patients, these findings may provide valuable insight for future studies.