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Study Title: Multi-center, Open-label Study of the Safety and Efficacy of Control of Proteinuria with ACE Inhibitors and ARBS in Patients with Fabry Disease Who Are receiving Farazyme : Tha Farazyme + Arbs + ACE inhibitors Treatments (FAACET) Study: The FAACET Study
Chief Investigator: Dr Stephen Waldek
SRCTN: Not Applicable
EudraCT Number: 2007-007482-21
UK Sponsor Details: Salford Royal NHS Foundation Trust

This study was registered on the Sponsor's database 05 August 2008, but failed to proceed any further. Sponsor records show that the study was listed as abandoned on 10 June 2009, before any regulatory approvals were in place and therefore the study did not commence and there is no analysis to report on.

- Brief Synopsis of the FAACET Study (taken from Protocol 2.1, February 6, 2007

TITLE: FABRAZYME® + ARBS + ACE INHIBITOR TREATMENT (FAACET) STUDY Multi-center, Open-label Study of the Safety and Efficacy of Control of Proteinuria with Angiotensin Receptors Blockers (ARBs) and Angiotensin Converting Enzyme Inhibitors (ACEIs) in Patients with Fabry Disease Who Are Receiving Fabrazyme®.
PROTOCOL NO. UAB NEPHROLOGY 001-2006
SPONSOR: University of Alabama at Birmingham, Birmingham, AL 35294
NAME OF FINISHED PRODUCTS: Angiotensin Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, Fabrazyme®
INVESTIGATOR/STUDY CENTERS: Fourteen (14) study sites worldwide
PRIMARY OBJECTIVE To determine whether decline of GFR can be slowed by titrating ACEI/ARB anti-proteinuric therapy to target urine protein/creatinine ratio of ≤ 0.5, or 50% reduction from baseline, in Fabry patients with significant kidney involvement ($20 \leq eGFR_{MDRD} \leq 60$ ml/min/1.73 m²), and baseline urine protein/creatinine ratio > 0.5 (based on the last value obtained before initiating ACEI/ARB therapy or obtained at screening before the first Evaluation Visit of the FAACET Study), who are receiving standard of care treatment for Chronic Kidney Disease (CKD), and Fabry disease. **SECONDARY OBJECTIVES** a. To determine whether urine protein/creatinine ratio ≤ 0.5, or $\geq 50\%$ reduction from baseline, can safely be achieved in Fabry patients with ACEI/ARB therapy. b. To determine whether urine protein/creatinine ratio ≤ 0.5, or $\geq 50\%$ reduction from baseline, result in a slower rate of GFR decline compared to patients who cannot achieve this target. c. To determine if GFR decline can be slowed by titrating ACEI/ARB therapy to target urine protein/creatinine ratio ≤ 0.5, or 50% reduction from baseline, in Fabry patients with definite kidney

involvement ($125 \geq eGFR_{MDRD} \geq 60$ ml/min/1.73 m²), and baseline urine protein/creatinine ratio > 1.0 (based on the last value obtained before initiating ACEI/ARB therapy or obtained at screening before the first Evaluation Visit of the FAACET Study) who are receiving standard of care treatment for Chronic Kidney Disease (CKD), and Fabry disease.

METHODOLOGY

This will be a multi-center, multinational, open-label study to confirm the safety and the effectiveness of ACE inhibitors and ARBs against proteinuria in patients with advanced Fabry disease who are receiving Fabrazyme® at 1 mg/kg every other week. Following an initial 3-month Evaluation Period, during which ACEI/ARB therapy will be titrated to reduce urinary protein/creatinine ratio to a target of 0.5, or 50% of baseline level, the patients will be followed for 24 months in an Observation Period with continued monitoring of their $eGFR_{MDRD}$ and protein excretion every 3 monthly for 24 months. ACEI/ARB therapy will continue to be titrated to maintain the proteinuria target in the Observation Period. The baseline urine protein/creatinine ratio is defined as the last value obtained in the individual patient before they began any ACEI/ARB therapy.

STUDY SITES: 40 patients will be enrolled in the FAACET Study at 14 Study Sites.

INCLUSION CRITERIA:

The patient must provide written, informed consent, and be ≥ 19 yrs of age.

The patient is already receiving Fabrazyme® at 1 mg/kg every two weeks at the time of enrollment.

Patient has confirmed Fabry disease (plasma αGAL activity of < 1.5 nmol/hr/mL, or leukocyte αGAL activity of < 4 nmol/hr/mg), or a known mutation compatible with Fabry disease.

Patients with either:

(a) $eGFR_{MDRD} \geq 20$ and ≤ 60 ml/min/1.73 m^2, and documented baseline urine protein/creatinine ratio > 0.5, based on the last value obtained before initiating ACEI/ARB therapy or obtained at screening before the first Evaluation Visit of the FAACET Study; or

(b) $eGFR_{MDRD} \leq 125$ ml/min/1.73 m^2 and > 60 ml/min/1.73 m^2 with documented baseline urine protein/creatinine ratio > 1, based on the last value obtained before initiating ACEI/ARB therapy or obtained at screening before the first Evaluation Visit of the FAACET Study.

EXCLUSION CRITERIA:

The patient has undergone kidney transplantation or is currently on dialysis, or is planning on receiving a kidney transplant during the first year of the study.

The patient has diabetic nephropathy or the presence of another, confounding kidney disease unless there is kidney biopsy confirmation that the patient does not have diabetic nephropathy or another, confounding kidney disease.

The patient has a clinically significant organic disease, or other condition that in the opinion of the investigator would preclude participation in the full extent of the trial.

The patient is unwilling to comply with the requirements of the protocol, including continuing on Fabrazyme® at 1 mg/kg body weight every two weeks.

Patients who have documented allergies to ACE inhibitors and to ARBs are not eligible to participate in the FAACET Study.

The patient is pregnant or intends to become pregnant during the course of the study.

TREATMENT REGIMEN

During the Evaluation Period, the patients will be titrated with ACEI/ARBs to reduce their morning urine protein/creatinine ratio to ≤ 0.5, or 50% of the baseline level. During the Observation Period, the ACEI/ARB therapy will be dose-adjusted, as tolerated, to maintain their urine protein/creatinine ratio at target level. Patients will continue to receive Fabrazyme® intravenously every 2 weeks throughout the study**.** Unless there is a compelling clinical indication, patients in the FAACET study should avoid all potentially nephrotoxic agents (e.g., NSAIDs, aminoglycoside antibiotics, X-ray contrast agents, etc.)

STUDY DURATION: 3 month Evaluation Period, followed by 24-month Observation Period.

CRITERIA FOR EVALUATION

Efficacy: Change in renal function will be assessed with the $eGFR_{MDRD}$ for the FAACET

patients, and compared to the Phase IV patient population (AGAL008 and AGAL025) to assess the additional impact of ACEI/ARB therapy on the decline in $eGFR_{MDRD}$ in patients receiving Fabrazyme® therapy. Patients who every received Fabrazyme for at least 12 months in AGAL008/AGAL025 or Phase III/extension study will be included in the Control Cohorts: a). if $eGFR_{MDRD} \leq 60$ ml/min/1.73 m^2 and urine protein/creatinine ratio > 0.5 at Baseline before initiating treatment with Fabrazyme®, OR b). Baseline $eGFR_{MDRD} \leq 125$ and ≥ 60 ml/min/1.73 m^2, and urine protein/creatinine ratio > 1.0 at Baseline before initiating treatment with Fabrazyme®. These patients will be used in analyses for comparison to the FAACET Study patients based on their characteristics before initiating Fabrazyme®.

Safety: Safety will be monitored in terms of adverse experiences, vital sign parameters, physical examinations, laboratory safety parameters, concomitant medications and antibody formation.

DSMP and DSMB: A Data Safety Monitoring Plan has been developed for the FAACET Study, and the Steering Committee will assume the responsibilities usually attributed to a Data Safety Monitoring Board. A summary log will be kept of all adverse events reported to the UAB IRB.

STATISTICAL METHODS

Efficacy: The primary efficacy analysis will be the change in renal function assessed as $eGFR_{MDRD}$ for the patient group that reaches and maintains their urine protein/creatinine ratio ≤ 0.5, or ≤ 50% of their baseline, to assess the impact of ACEI/ARB therapy on decline of $eGFR_{MDRD}$ in patients receiving Fabrazyme® therapy. A secondary efficacy analysis will be carried out on the change in $eGFR_{MDRD}$ for the patient group that cannot maintain their urine protein/creatinine ratio ≤ 0.5, or less than 50% of their baseline. The Phase III/Phase III extension and Phase IV/Phase IV extension patients, who met the Criteria for evaluation listed above, will serve as the Control Cohorts for comparison to the FAACET patients in the various analyses.

The Control Cohort will be defined *a priori* before FAACET enrollment begins. The age, gender, baseline $eGFR_{MDRD}$, systolic blood pressure, and baseline proteinuria, as well as duration of Fabrazyme® therapy versus the appropriate mixed models with random slopes for individual patients. The mixed model analyses will be adjusted as needed for the covariates assumed to be most important in determining the rate of decline in kidney function (i.e. age, gender, baseline $eGFR_{MDRD}$, systolic blood pressure, baseline proteinuria, and duration of Fabrazyme® therapy).

Safety: Adverse events and serious adverse events will be summarized by body system and preferred term using a standardized coding dictionary (MedDRA). The severity and relationship of treatment to adverse events will be summarized. Clinically significant laboratory values, and physical exam findings will be summarized. Overall antibody status, including seroconversion rates, and titer levels will be summarized. Concomitant medications will be detailed at each study visit.

Report prepared on behalf of Sponsor by Beverley Greenhalgh, Sponsorship Support & Compliance Manager. 09 October 2019