LONG-TERM SAFETY OF MIGALASTAT HCl IN PATIENTS WITH FABRY DISEASE

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BACKGROUND

Fabry disease (FD) results from an inborn X-linked error of glycosphingolipid metabolism in which deficiency of α-galactosidase A (α-Gal A) leads to accumulation of globotriaosylceramide (GL-3). Accumulation of GL-3 in the vascular endothelium and visceral tissues throughout the body leads to multiorgan dysfunction, including progressive kidney or heart disease, and/or stroke.

Migalastat HCl (AT1001/GR181413A) is an oral investigational pharmacologic chaperone that binds and stabilizes α-Gal A. Specific mutant forms of α-Gal A have been identified as amenable to migalastat HCl with a cell-based assay. Migalastat HCl is currently in Phase 3 development for Fabry disease in patients with α-Gal A mutations amenable to treatment.

Study FAB-CL-205 (NCT00526071/MGM116045) is an open label, long-term extension study for patients completing one of four preceding Phase 2 trials of migalastat HCl (FAB-CL-201, -202, -203, or -204). These four studies were all open-label, with an initial treatment period of 12 to 24 weeks and an optional extension period giving 48 to 96 weeks total duration of treatment. Enrollment included both patients with amenable and patients with non-amenable mutant forms of α-Gal A.

STUDY OBJECTIVES

Primary: The primary objective of this study was to evaluate the long-term safety and tolerability of oral migalastat HCl in patients with Fabry disease.

Secondary: The secondary objective was to gain information about the pharmacodynamics (PD) and pharmacokinetics (PK) of orally administered migalastat HCl in patients with Fabry disease.

Exploratory: An exploratory objective was to evaluate the effect of migalastat HCl on disease related outcomes, particularly renal function.

STUDY DESIGN

Initial patients (15/23) received migalastat HCl 150 mg every other day (QOD). Following a protocol amendment, all patients participated in a dose escalation period (DEP), in which they received 250 mg for 3 days on/4 days off (3on/4off) for 2 months before escalating to a dose of 500 mg for 3 days on/4 days off. Later, as the 500 mg 3on/4off dose regimen had no clear additional benefit in increasing α-Gal A activity or decreasing urine GL-3, the protocol was amended and the dose was returned to 150 mg QOD.

Data is presented up to an interim analysis date of April 2012; Last patient-last visit (LPLV) for this study occurred on 8 October 2012. Eligible subjects could then enroll in MGM116041 (NCT01458119), an open-label extension study for all migalastat HCl studies.

SAFETY & PD PARAMETERS

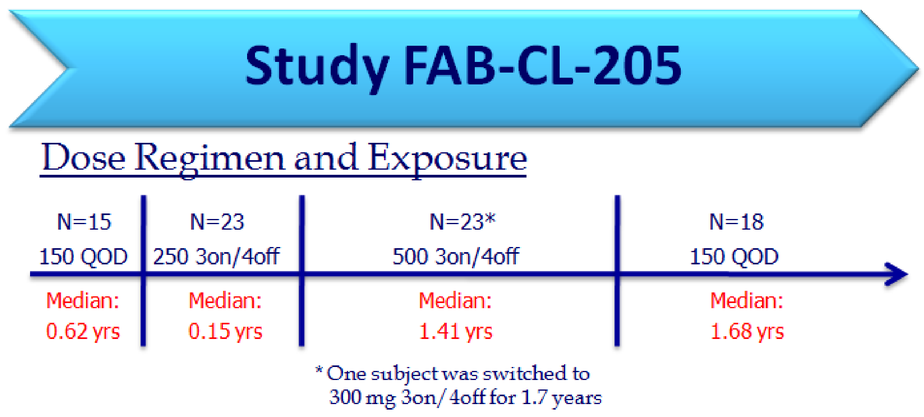
Safety parameters included adverse events (AEs), serious AEs (SAEs), vital signs (systolic and diastolic blood pressure, pulse, weight), clinical laboratory tests (hematology, serum chemistry, and urinalysis), electrocardiograms, physical examinations, and use of concomitant medications.

From the laboratory results, proteinuria and estimated glomerular filtration rate (eGFR) were also assessed. For eGFR, it was calculated with the CKD-EPI equation, using the visit-specific age for each subject.

ELIGIBILITY CRITERIA

Each subject had completed the main treatment period of a preceding Phase 2 trial of migalastat HCl in Fabry disease with no major protocol violations. Subjects were excluded if they had undergone or were scheduled to undergo kidney transplantation, or were currently on dialysis; if they were or had been treated with another investigational drug (except migalastat HCl) within 30 days of study start; and/or if the subject had been treated with Fabrazyme (agalsidase beta), Replagal (agalsidase alfa), Glyset (miglitol) or Zavesca (miglustat) within 2 weeks prior to enrollment.

STUDY SCHEMATIC, EXPOSURE, & PATIENT DISPOSITION



Within FAB-CL-205, the overall median duration of exposure to migalastat HCl was 3.64 years (range 1.0 to 4.3 years) and reflects 75 patient-years of treatment.

Disposition	Amenable mutation n (%)	Non-amenable mutation n (%)	Total n (%)
Treated with Migalastat HCl	16 (100)	7 (100)	23 (100) Median Age: 42 14 males; 9 females
Completed as of April 2012	1 (6.3)	0	1 (4.3)
Ongoing as of April 2012	12 (75.0)	4 (57.1)	16 (69.6)
Primary Reason for Discontinuation			
Adverse event	1 (6.3)	0	1 (4.3)
Protocol violation	0	0	0
Withdrew consent	1 (6.3)	0	1 (4.3)
Lost to Follow-up	0	0	0
Other*	1 (6.3)	3 (42.9)	4 (17.4)

* In all instances, the "Other" reason for discontinuation reported was for male subjects being discontinued for lack of response.

ADVERSE EVENTS & LABORATORY RESULTS

- **Adverse Events**

Category of AE	n (Subjects)	n (AEs)	Additional Information
Any AEs	23	538	
Treatment Emergent AEs (TEAEs)	23	465	Most common (≥ 6 subjects): arthralgia, fatigue, back pain, and pain in extremity
Treatment Related TEAEs	12	35	Most common systems: gastrointestinal (GI), musculoskeletal, and nervous system
SAEs (Treatment Emergent)	7	22	No SAEs were treatment-related. The only SAE reported by more than one subject was atrial fibrillation (2 subjects).
Deaths	0	0	
AEs Leading to Discontinuation	1	2	SAE of ventricular fibrillation & stroke
AEs Leading to Dose Reduction (all from 500 mg 3on/4off)	2	7	Patient 1: muscle twitching; Patient 2: intention tremor, confusion, arthralgia, myalgia, dizziness

- **Laboratory Results**
  - **Clinical Laboratory Results:** Occasional potentially clinically significant (PCS) values were observed; all PCS values were not sustained or were consistent with the patient's underlying Fabry disease.
  - **Proteinuria:** 9 patients had a baseline 24-hour urine sample available and were evaluable for changes in proteinuria.
    - 8 patients with amenable mutations had decreases in proteinuria from baseline
      - For 6 patients at baseline, protein at baseline was less than 300 mg
        - 4 on ACE inhibitors and/or ARBs
      - For 2 patients at baseline, protein at baseline was greater than 300 mg
        - 1 on ARB declined from 616 mg to 462 mg
        - 1 on spironolactone, not on an ACE inhibitor or ARB, declined from 4,600 mg to 610 mg
    - 1 patient with a non-amenable mutation had an increase in proteinuria from baseline
      - Protein at baseline was less than 300 mg; on ACE inhibitor
  - **eGFR:** Overall, as calculated using the CKD-EPI formula, eGFR was generally stable with a median annualized eGFR slope less than 1mL/min/1.73 m^2/year. For selected subgroups, the median annualized rate of change in eGFR is presented below.

Demography	Category	n	Median Annualized Change in eGFR	Minimum	Maximum
ALL	ALL	23	-0.09	-3.8	3.2
	Baseline eGFR below 90	6	-0.16	-3.7	3.2
Male	ALL	14	-0.73	-3.8	1.6
	Amenable	11	-1.20	-3.8	1.1
	Non-Amenable	3	0.78	0.5	1.6
Female	ALL	9	0.31	-3.7	3.2
	Amenable	5	0.31	-1.1	2.2
	Non-Amenable	4	0.31	-3.7	3.2

CONCLUSIONS

- Migalastat HCl doses of 150 mg every other day (QOD) and 250 mg 3 days on/4 days off were generally well tolerated.
- eGFR was generally stable.