Lucerastat, an Investigational Oral Substrate Reduction Therapy in Fabry Disease: Kidney Biopsy Results from the MODIFY Open-Label Extension Study

Dominique P. Germain[1,2], Peter Blattmann[3], Markus Cybulla[4], Aline Frey[3], Kolbeinn Gudmundsson[3], Ana Jovanovic[5], Michael Meinel[3], Vanessa Moreno[6], Peter Nordbeck[7,8], David B. Thomas[9], Laura Barisoni[10,11]

[1]Referral Centre for Fabry Disease and Lysosomal Storage Disorders, MetabERN European Reference Network, Paris Saclay University Paris, France; [2]Division of Medical Genetics, University of Versailles, Montigny, France; [3]Idorsia Pharmaceuticals Ltd., Allschwil, Switzerland; [4]Center of Internal Medicine, Department of Nephrology and Rheumatology, Nephrologicum Markgräflerland MVZ, Müllheim, Germany; [5]Mark Holland Metabolic Unit, Northern Care Alliance NHS Foundation Trust, Salford, UK; [6]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, North Carolina, USA [7]Department of Internal Medicine I, University Hospital Würzburg, Würzburg, Germany; [8]Fabry Center for Interdisciplinary Therapy (FAZiT), University Hospital Würzburg, Würzburg, Germany; [9]IYM Health Financial Services, PLLC, Durham, North Carolina, USA; [10]Department of Pathology, Division of AI and Computational Pathology, Duke University, Durham, North Carolina, USA; [11]Department of Medicine, Division of Nephrology, Mayo Clinic, Rochester, Minnesota, USA.

Rationale

- Lucerastat, an oral glucosylceramide synthase (GCS) inhibitor, reduces the synthesis of glucosylceramide (Gb1), preventing accumulation of globotriaosylceramide (Gb3) and related glycosphingolipid substrates in patients with Fabry disease (FD), a rare , X-linked, lysosomal disorder.[1]
- Reduction in renal Gb3 accumulation in peritubular capillary (PTCs) is an FDA-recognized surrogate marker of clinical benefit in FD.[2] This sub-study was designed to evaluate the level of kidney Gb3 inclusions in adult males with classic FD after at least 2 years of exposure to lucerastat monotherapy.
- Males with classic FD were selected because they have consistently higher baseline Gb3 burdens in kidney tissues, show more severe and faster-progressing disease, [2,3] and therefore, provide a clearer, more sensitive measure of treatment effect.
- The results of this kidney biopsy sub-study of the open label extension (OLE) of the MODIFY study[6] (NCT03737214) are reported in this poster.

Objectives

The main objective was to assess kidney Gb3 inclusions using a quantitative scoring system in adult male participants with classic FD, after at least 2 years of treatment with lucerastat monotherapy.

Methods

- The sub-study* enrolled six male adult patients with classic FD who had received lucerastat monotherapy (250–1000 mg b.i.d. eGFR adjusted) for ≥2 years to undergo a single post-baseline kidney biopsy.
- All biopsies were centrally processed.
- Gb3 inclusions in approximately 300 peritubular capillaries (PTCs) were quantified by a panel of 3 renal pathologists using established quantitative (Barisoni Lipid Inclusion Scoring System (BLISS)[4]) and semi-quantitative (Fabrazyme Scoring System (FSS)[5]) methods.

Study Limitations

- Small number of participants (N = 6).
- No baseline biopsies were performed.

Results

- The mean age of the participants at baseline was 36 years (range: 22 to 53 years).
- At enrollment in MODIFY, 4 participants were enzyme replacement therapy (ERT) naïve or pseudo-naïve and 2 switched**.
- Baseline Gb3 plasma levels were between 2050 - 3480 ng/ml.
- Median exposure to lucerastat was 56 months.

Baseline† demographics and disease characteristics

	Total Lucerastat (N=6)
Age, years, mean (SD)	35.7 (10.2)
Race , n (%)	
White	6 (100)
Time since initial FD diagnosis (years), Mean (SD)	11.57 (11.23)
Time since first known FD symptoms (years), Mean (SD)	24.33 (11.84)
Plasma Gb3 (ng/ml) , Mean (SD)	2616.67 (583.15)
Plasma LysoGb3 (ng/ml), Mean (SD)	67.87 (44.01)
ADA Status [n(%)]‡	4
ADA+	2 (50.0)
ADA-	2 (50.0)
Historical eGFR slope within-participant linear regression (mL/min/1.73m2 per year), Mean (SD)	-5.94 (11.05)
eGFR (mL/min/1.73m2), Mean (SD)	106.7 (22.9)
UACR (mg/g) , Mean (SD)	61.48 (72.59)

ADA: Anti-drug antibody; eGFR: Estimated glomerular filtration rate; UACR: urine albumin-creatine ratio.

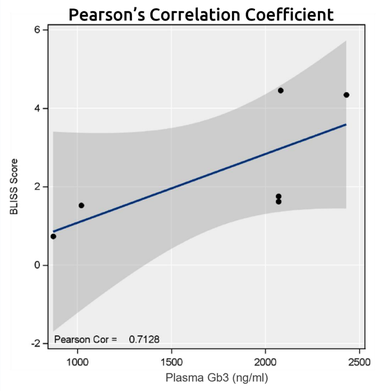
Safety

No significant adverse events (AEs) were reported. Two participants reported mild, non-serious, procedure-related AEs.

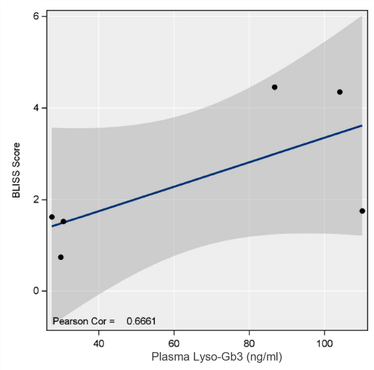
BLISS and FSS Outcomes: Low Gb3 Burden in Most Participants

- Median kidney Gb3 BLISS score (i.e. average number of Gb3 inclusions per PTC) was 1.7 (range: 0.7–4.5; mean (SD): 2.41 (1.59)).
- 1 of the 6 sub-study participants had a BLISS score < 1.0. A further 3 patients had scores between 1 and 2.
- The mean FSS scores were 0, indicative of “no or trace” accumulation, in 5 out of 6 participants and 1, indicative of mild accumulation, in 1 out of the 6 participants.
- Of note, the 2 patients who switched from ERT had BLISS scores of 1.6-1.8 and a FSS score of 0.

The highest correlation§ was observed between BLISS score and plasma Gb3 (Pearson r = 0.71) and plasma lysoGb3 (Pearson r = 0.67).

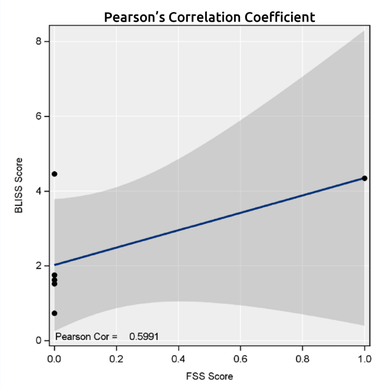


Plasma Gb3 (ng/mL)	
n	6
Mean (SD)	1756.83 (645.19)
Median (min., max.)	2070.00 (871.00, 2430.00)
Correlation of BLISS score with plasma Gb3	
Pearson's correlation coefficient	0.71
Spearman's rank correlation coefficient	0.93



Plasma lysoGb3 (ng/mL)	
n	6
Mean (SD)	64.78 (39.59)
Median (min., max.)	58.70 (27.50, 110.00)
Correlation of BLISS score with plasma Gb3	
Pearson's correlation coefficient	0.67
Spearman's rank correlation coefficient	0.60

Correlation between BLISS and FSS was moderate (Pearson r = 0.60).



Conclusions

Long term exposure to lucerastat monotherapy was associated with low-to-no levels of kidney Gb3 inclusions. The results of the sub-study support clinical benefit and renal protective effect of lucerastat.

Treatment group	ERT status **at baseline**	Duration of lucerastat exposure (months)	**Age at baseline** (years)	eGFR slope on lucerastat (mL/min/1.73 m²)	BLISS (represents Gb3 burden in kidneys)	**FSS**
Lucerastat 301/302	naïve	54.4	32	-2.01	**1.52**	0
Lucerastat 302 (Ex-placebo)	naïve	68.9	22	-2.32	**4.35**	1
Lucerastat 301/302	pseudo-naïve (>7 y)#	73.0	37	-1.10	**4.46**	0
Lucerastat 301/302	pseudo-naïve (>4.5 y)#	49.0	53	-2.41	**0.74**	0
Lucerastat 302 (Ex-placebo)	switch	43.0	32	-0.66	**1.62**	0
Lucerastat 301/302	switch	58.3	38	-1.82	**1.75**	0

Patients in the lucerastat 301/302 treatment group received lucerastat during the 301 and 302 studies. Patients in the lucerastat 302 treatment group only received lucerastat during study 302.

References

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**As this sub-study was descriptive in nature, no power calculations were performed. ** naïve (never treated with ERT), pseudo-naïve (stopped ERT ≥ 6 months prior to screening), and switch (stopped ERT at screening visit). † Baseline is the last non-missing value up to and including the date of Study 301 randomization. ‡ADA status was only assessed in ERT switch and pseudo naive participants (i.e. 4/6 patients). #Refers to time between stopping ERT and kidney biopsy. §Correlations based on low n-numbers might not be accurate.*