Lucerastat Effect on Kidney Function in Patients with Fabry Disease: 4-Year Results from the Ongoing Open-Label Extension (OLE) of the Phase 3 Clinical Program

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Background

- Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, which encodes the α-galactosidase A (α-Gal A) enzyme.[1]
- Deficient α-Gal A activity causes progressive and toxic accumulation of glycosphingolipids, including globotriaosylceramide (Gb3), in lysosomes, leading to organ dysfunction and decreased quality of life.[1-3] Kidney involvement is one of the hallmark consequences of FD, with progressive Gb3 accumulation leading to proteinuria, declining eGFR and kidney damage.[1]
- Lucerastat, an oral glucosylceramide synthase (GCS) inhibitor, provides substrate reduction therapy by lowering Gb3 synthesis and limiting its lysosomal accumulation in multiple cell types in FD. We present 48-month interim findings from the ongoing global Phase 3 MODIFY open-label extension (OLE) study.[4,5]

Objectives

The objective of this analysis was to evaluate the long-term effect of lucerastat on the renal function of subjects with FD and on the biomarkers of FD.

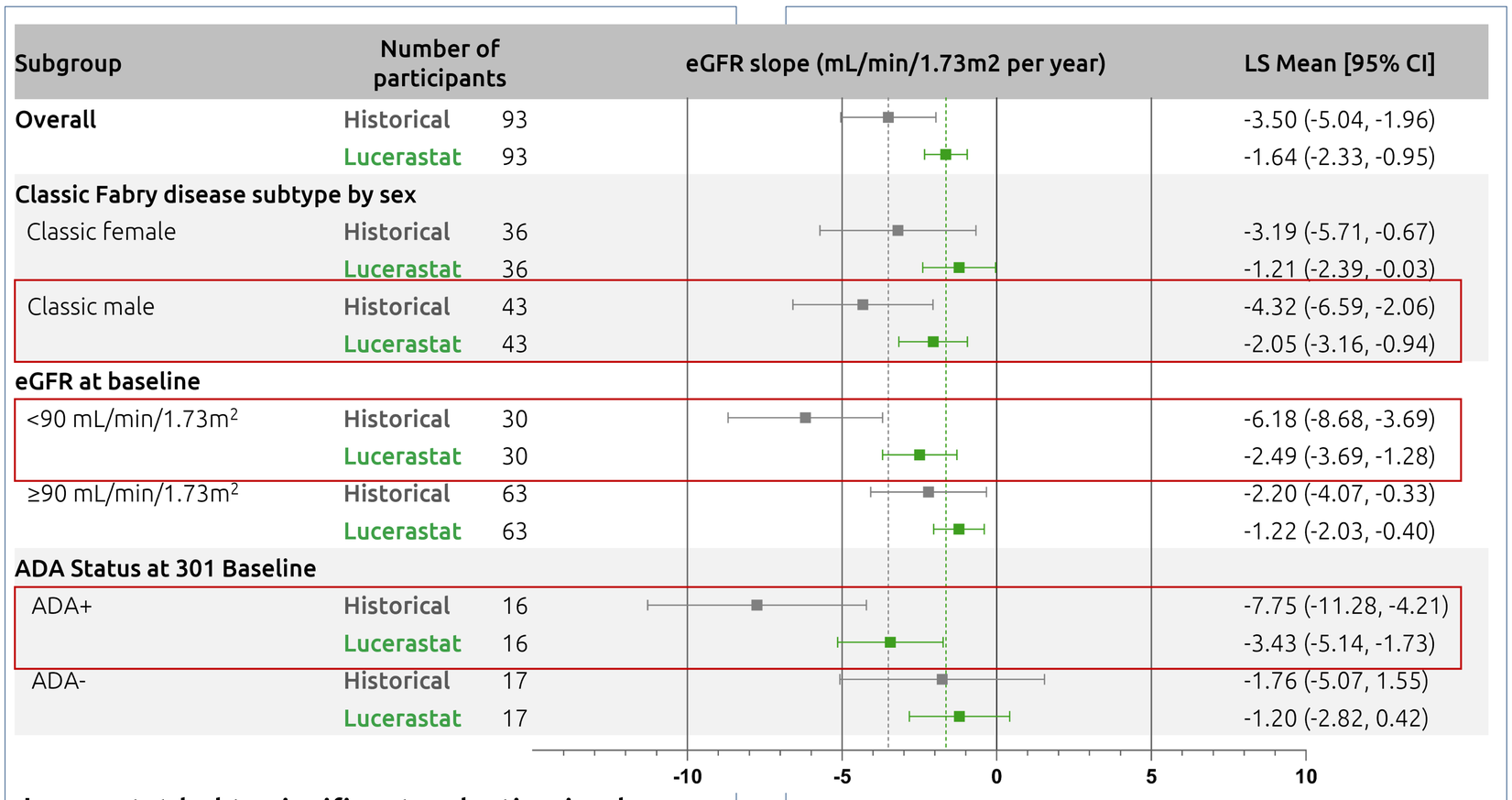
Methods

- MODIFY[4] (NCT03425539) randomized adult patients with FD 2:1 to lucerastat 1000 mg b.i.d. orally (dose adjusted by eGFR) or placebo for 6 months. Participants who completed MODIFY were eligible to enter the OLE (NCT03737214) for up to 96 months, during which all received lucerastat.
- Prespecified efficacy endpoints included change from baseline in plasma Gb3 and annualized eGFR slope (mL/min/1.73m² per year) in the OLE. Analyses included participants with ≥2 pre-randomization creatinine values to derive a historical eGFR slope for comparison with the on-treatment slope.

Results

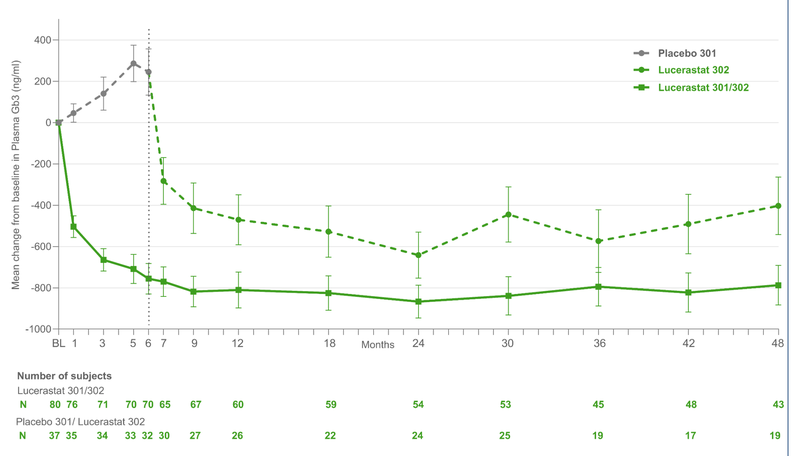
Lucerastat slowed the decline of kidney function

- At Month-48, the lucerastat group exhibited reduced decline in the kidney function compared to historical controls in the overall population (eGFR slope, historical: -3.50; Lucerastat: -1.64). Efficacy was independent of gene variants.
- This effect was also seen in all subgroups analyzed, with the most prominent effects in subgroups with severe disease course, such as:
  - classic males (historical: -4.32; Lucerastat: -2.05),
  - patients with impaired renal function at baseline (historical: -6.18; Lucerastat: -2.49),
  - Anti-Drug Antibody (ADA+) positive patients (historical: -7.75; Lucerastat: -3.43)

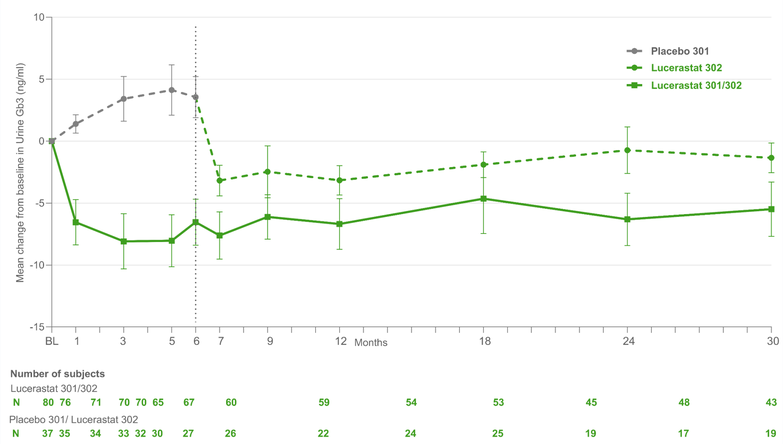


Lucerastat led to significant reduction in plasma and urine Gb3 levels

Lucerastat led to a sustained 58% decrease in plasma Gb3 levels by Month 48.



Lucerastat led to a sustained 51% decrease in urine Gb3 levels† by Month 30 (urine biomarkers were only measured up to Month 30).



Baseline* demographics and disease characteristics

- Of 118 participants randomized, 117 received study treatment (80 lucerastat, 37 prior placebo) in MODIFY.
- 107 (91%) participants were enrolled in the OLE, and 55 (47%) ongoing at Month-48 OLE interim analysis.
- Participants' demographic and baseline characteristics were similar across initial treatment groups.

	Total Lucerastat (N=118)
Age at screening, years, mean (SD)	39.3 (14.1)
Male, n (%)	55 (47%)
Race , n (%)	
White	113 (96%)
Asian	3 (3%)
Plasma Gb3 (ng/ml) , Mean (SD)	1702 (991)
Plasma LysoGb3 (ng/ml), Mean (SD)	32 (41)
Normalized urine Gb3 (µmol Gb3/mol creatinine), mean (SD)	9.9 (17.0)
ADA Status [n(%)]	
ADA+	18 (48.6)
ADA-	19 (51.4)
Missing	77
eGFR (mL/min/1.73m2), Mean (SD)	98.2 (25.2)
eGFR, ml/min/1.73m² , n (%)	
≥90	77 (65%)
<90	41 (34%)
UACR (mg/g) , median (Q1, Q3)	23.0 (12.0, 114.8)
UACR, n (%)	
≥30	48 (42.1)
<30	66 (57.9)

Safety

Lucerastat was generally well-tolerated. No new safety signals were identified during the OLE as compared to MODIFY.

Conclusions

Long term exposure to lucerastat was associated with reduced plasma and urine Gb3 levels and slower decline in kidney function compared to pre-randomization, suggesting a renal protective effect, a major therapeutic goal in patients with Fabry disease.

References

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Baseline is the last non-missing value up to and including the date of Study 301 randomization.
†*Urine Gb3 levels were normalized by creatinine (µmol Gb3/mol creatinine).*