PLACE 2026
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

MINICORSI
ROMA, 24 Giugno 2026

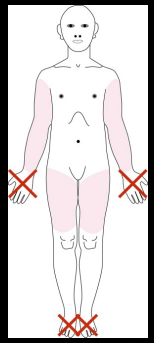
Malattiadi Anderson-Fabry

La terapia nella malattia di Anderson-Fabry

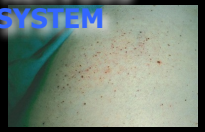
Sandro Feriozzi
Nefrologia
Università Campus Bio-Medico
Roma

DISCLOSURES

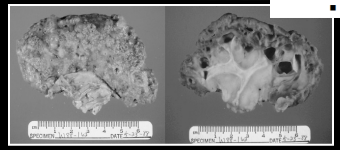
S. Feriozzi has received travel assistance and honoraria for lecturing and for participating in advisory boards from Sanofi/Takeda/Amicus/Medtronic/ Chiesi



PERIPHERAL NERVOUS SYSTEM

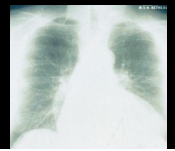


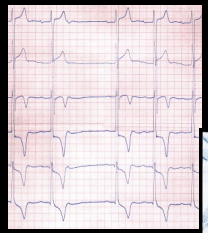
ANGIO

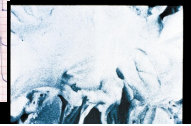


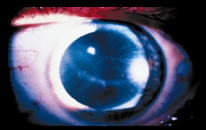
RENAL FAILURE

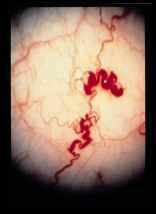
By cortesy R. Parini











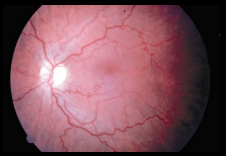
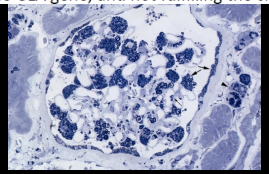


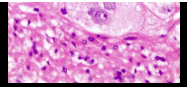
Table 3

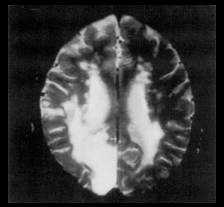
Criteria for phenotypic classification

Classical FD	
Men	Women
▪ A mutation in the GLA gene* ▪ ≥ 1 of the following characteristic Fabry disease symptoms: Fabry neuropathic pain, angiokeratoma and/or cornea verticillata ▪ Severely decreased or absent leukocyte AGAL activity (<5% of the normal mean)	▪ A mutation in the GLA gene ▪ ≥ 1 of the following characteristic Fabry disease symptoms: Fabry neuropathic pain angiokeratoma and/or cornea verticillata
Non-classical FD	
▪ A mutation in the GLA gene, and not fulfilling the criteria for classical FD	

Arends JASN 2016







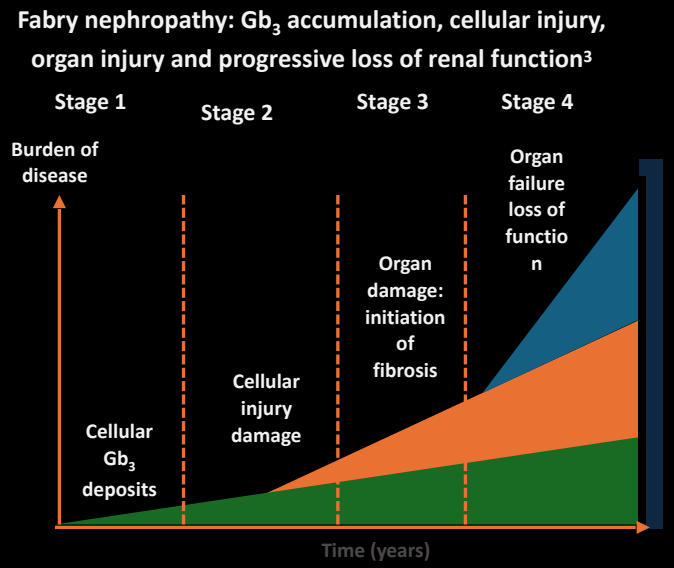
CENTRAL NERVOUS SYSTEM

PROGRESSION OF RENAL DISEASE IN FABRY DISEASE

- Renal involvement typically becomes apparent in patients in their mid-30s,although it can occur in childhood

- Renal **cellular injury and organ damage may occur before clinic**al signs of renal involvement become apparent
- Renal function often declines progressively over time and may lead to ESRD in nearly all male and some female patients

- **Proteinuria is an important risk factor for progression** of nephropathy: higher baseline proteinuria in patients with Fabry disease is associated with more rapid progression of renal disease and progression to ESRD



adapted from Schiffmann R, NDT 2009

Therapeutics

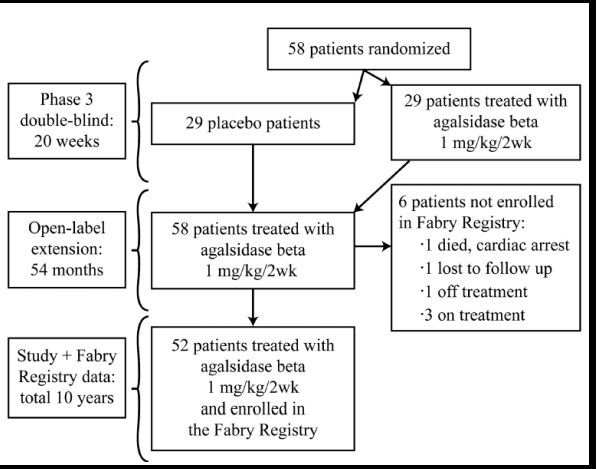
ORIGINAL ARTICLE

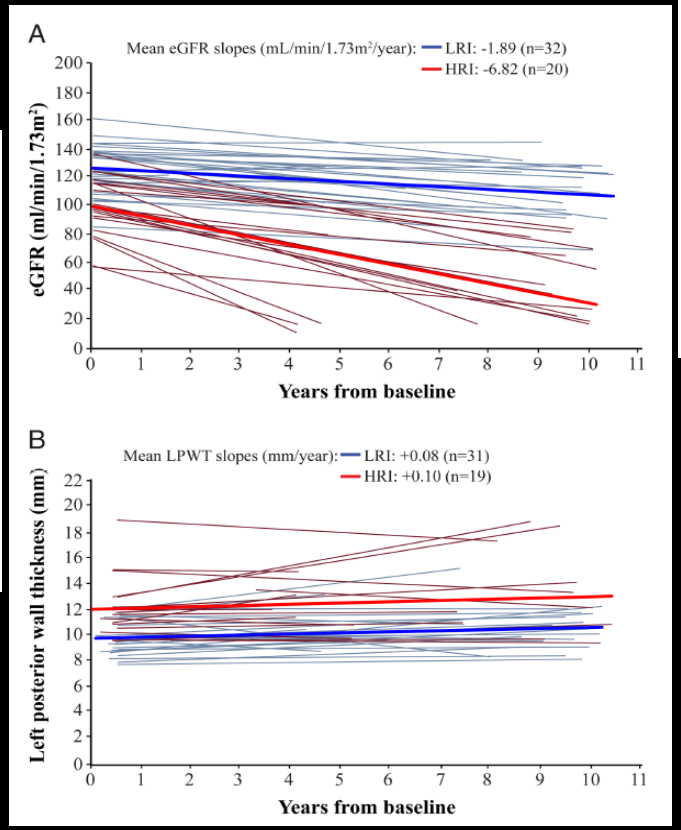
OPEN ACCESS

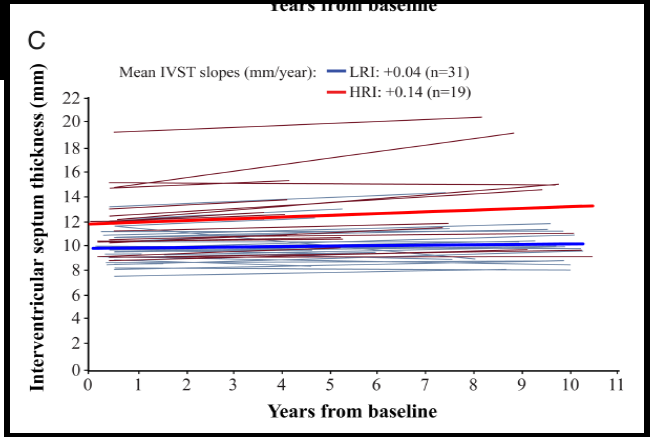
2015;52:353–358. doi:10.1136/jmedgenet-2014-102797

Ten-year outcome of enzy… with agalsidase beta in patients with Fabry disease

Dominique P Germain,[1] Joel Charrow,[2] Robert J Desnick,[3] Nathalie Guffon,[4] Judy Kempf,[5] Robin H Lachmann,[6] Roberta Lemay,[5] Gabor E Linthorst,[7] Seymour Packman,[8] C Ronald Scott,[9] Stephen Waldek,[10] David G Warnock,[11] Neal J Weinreb,[12] William R Wilcox[13]







Conclusions This 10-year study documents the effectiveness of agalsidase beta (1 mg/kg/2 weeks) in patients with Fabry disease. Most patients remained alive and event-free. Patients who initiated treatment at a younger age and with less kidney involvement benefited the most from therapy. Patients who initiated treatment at older ages and/or had advanced renal disease experienced disease progression.

Molecular Genetics and Metabolism Reports 3 (2015) 21–27

Contents lists available at

Molecular Genetics and M

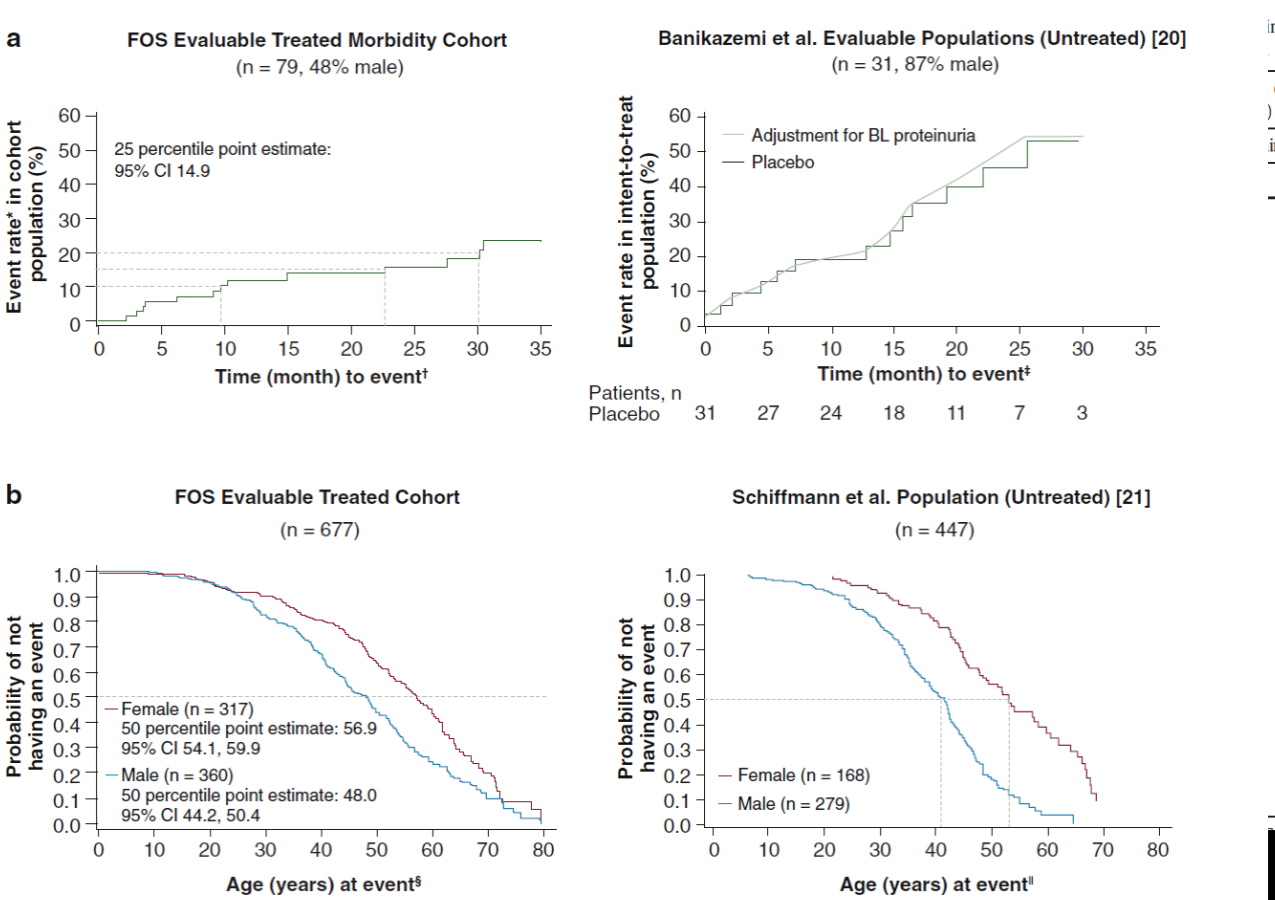
journal homepage: http://www.journals.els
metabolism-re

Long-term effectiveness of agalsidase alfa enzy disease: A Fabry Outcome Survey analysis

Michael Beck [a,*], Derralynn Hughes [b], Christoph Kampmann Guillem Pintos-Morell [d], Uma Ramaswami [b], Michael West the Fabry Outcome Survey Study Group

Table 5
Progression of cardiomyopathy, determined a and female patients stratified by the presenc

Baseline LVH status	n	FOS Evaluable Trea Cardiac cohort Mean annualized
Males		
Total	71	0.33 (0.1 [0.13, 0.5
LVH	29	0.19 (0.1 [−0.13, (
No LVH	42	0.47 (0.1 [0.22, 0.7
Females		
Total	93	0.48 (0.0 [0.30, 0.6
LVH	45	0.77 (0.1 [0.49, 1.0
No LVH	48	0.19 (0.1 [−0.03, (



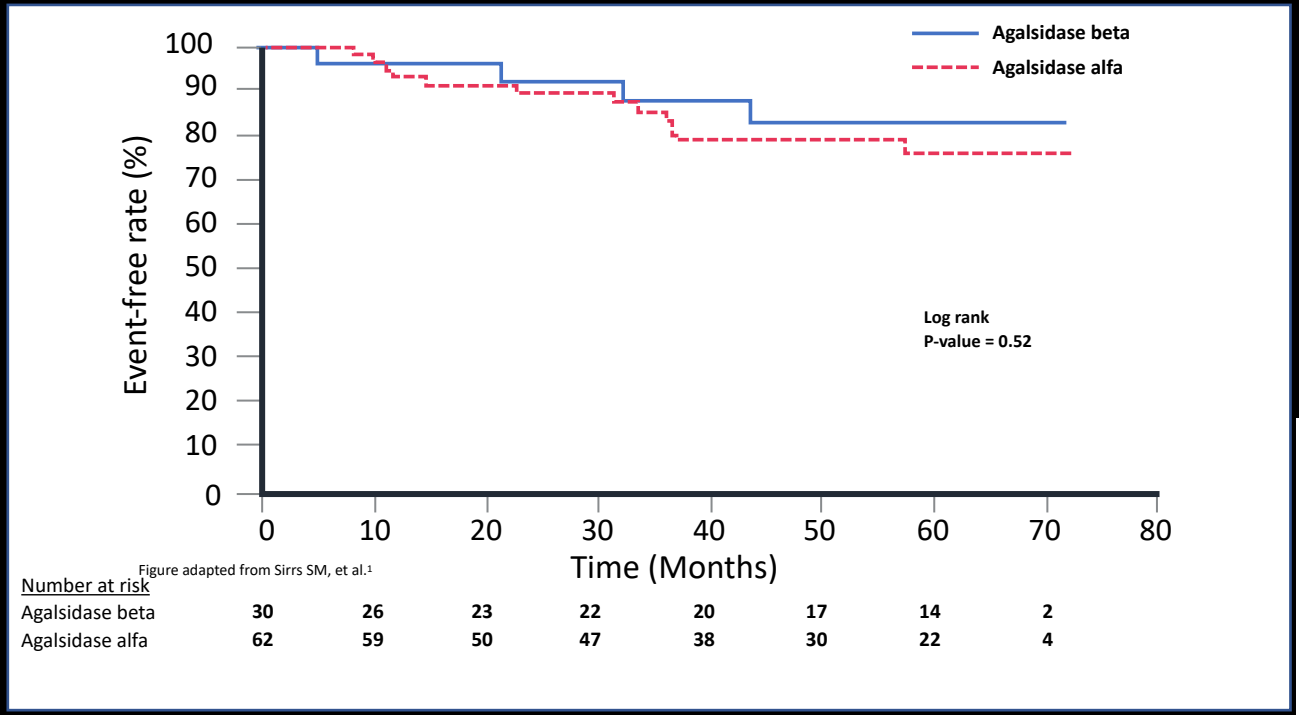
in eGFR in male

et al.
) [21]
in/1.73 m²/y

−3.0 (0.1)
−6.8 (1.5)
−0.9 (0.9)
−2.1 (1.6)
−6.9 (1.5)
−3.3 (1.8)
−1.6 (1.5)
−4.6 (2.3)
−2.2 (2.2)
−0.6 (2.6)

CANADIAN FABRY DISEASE INITIATIVE

Kaplan–Meier plot showing composite clinical endpoint for patients on algasidase alfa vs agalsidase beta (Cohort 1b)



For agalsidase alfa vs agalsidase beta

- Primary endpoint was met in 19.4% vs 13.3% of patients (*P*=0.57)
- Hazard ratio: 1.29 (*P*=0.67)

Cohort 1a Subjects receiving ERT prior to the start of the CFDI and are maintained on the ERT formulation (agalsidase alfa or agalsidase beta) at entry.

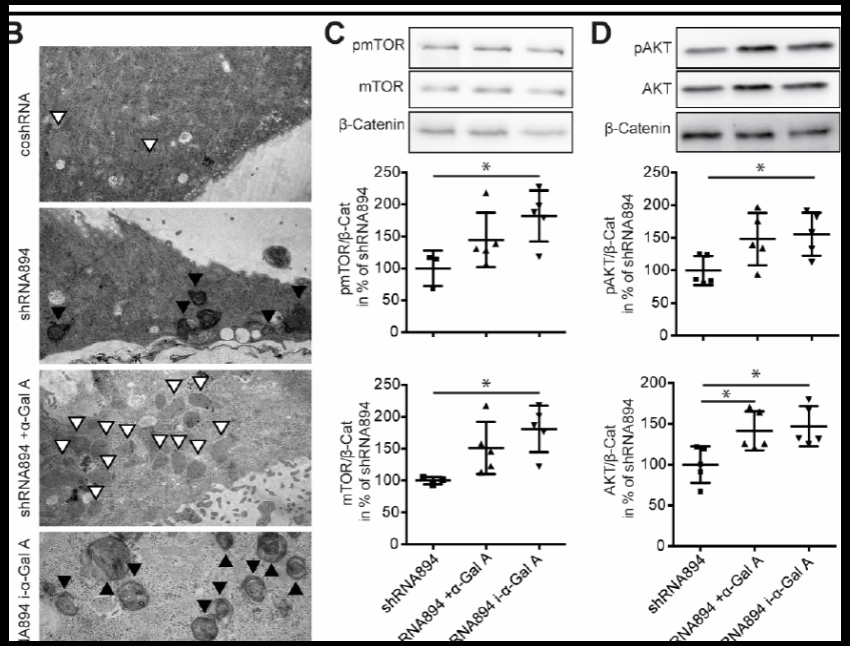
Cohort 1b Subjects naive to ERT who meet ERT criteria and undergo 1:1 randomization, stratified by gender, to either agalsidase alfa or agalsidase beta.

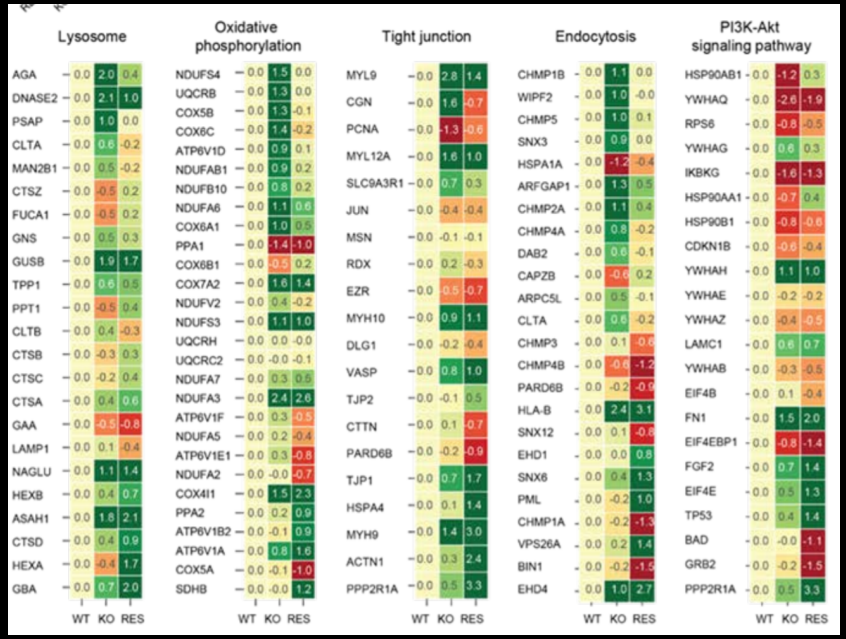
Cohort 1c Subjects naive to ERT who do not meet ERT criteria OR who do not consent to ERT. At any point, should a subject in Cohort 1c develop an indication for ERT, they are offered randomization into Cohort 1b.

ERT is given intravenously every other week using product monograph doses: agalsidase alfa 0.2 mg/kg and agalsidase beta 1 mg/kg.

Sirrs *et* al. *Mol Genet Metab* 2014;111:499–506

GB3 INDEPENDENT PATHWAYS





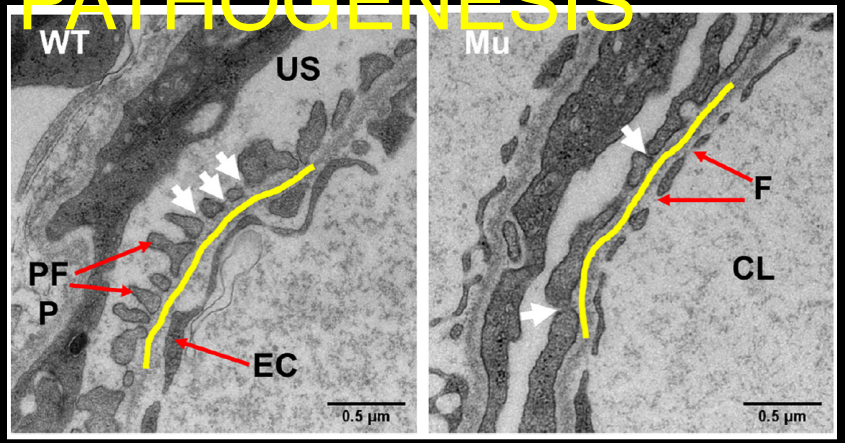
"Surprisingly, Gb3 removal failed to improve dysregulated autophagy and a profibrotic phenotype providing first molecular evidence for Gb3-independent disease mechanisms…"

Braun, Cell Physiol Biochem 2019

Rescues with inducible AGAL expression only have partially normalised protein expression. A loss of AGAL function results in profound changes in cellular pathways; therapies may not be sufficient to completely reverse all dysregulated pathways

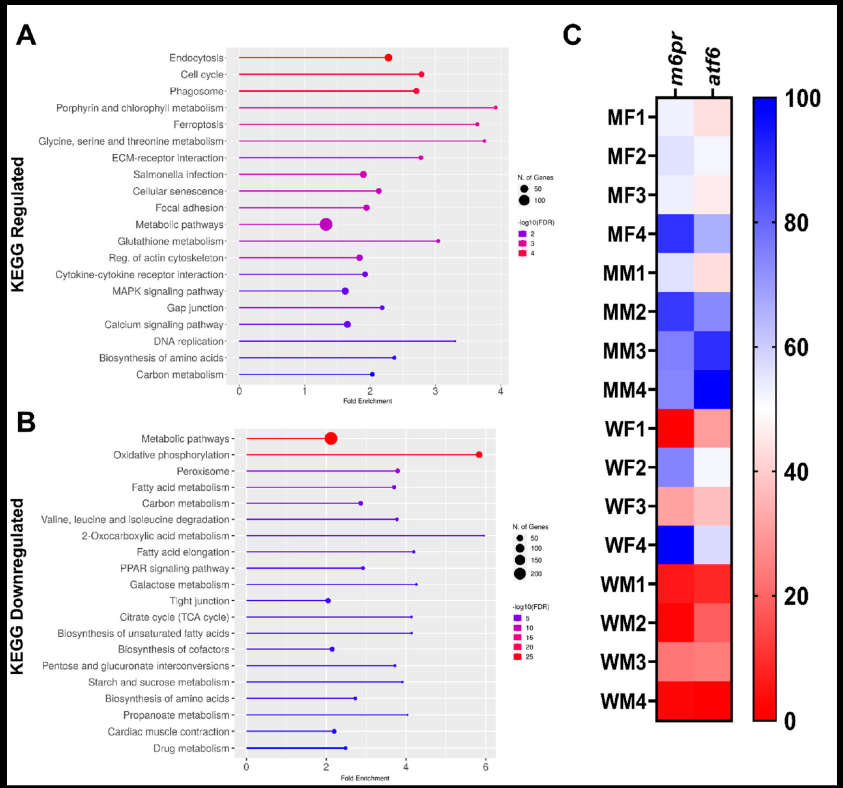
Jehn Int J Mol Sci 2021

ALTERNATIVE WAY TO THINK TO FABRY PATHOGENESIS



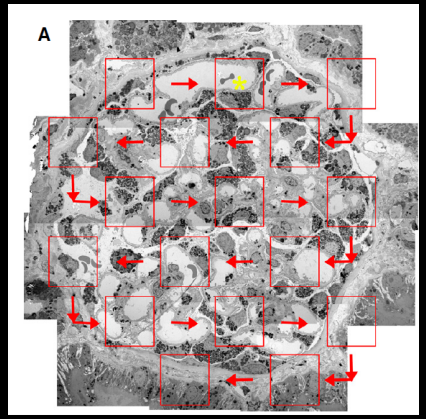
«Zebrafish lacks of Gb3 synthase:no Gb3 production zebrafish with decreased GLA gene expresion and the mutant animals had higher plasma creatinine and proteinuria»

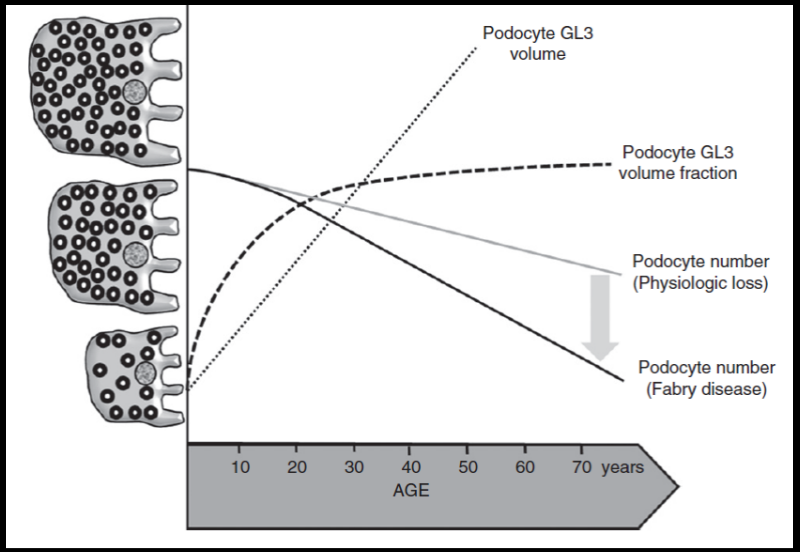
Elsaid MGM 2022

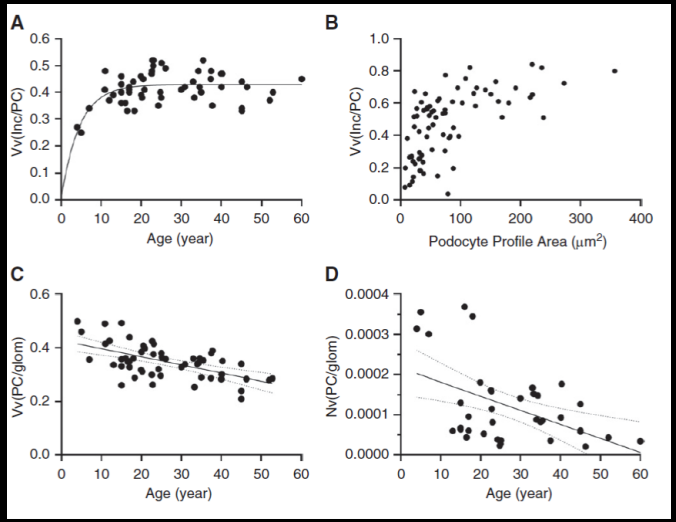


«indipendent of Gb3,calcium ion flux disruption and altered mitochondrial and lysosomial pathways can be estabilshed and maintened»

PODOCYTES ACCUMULATION OF Gb3







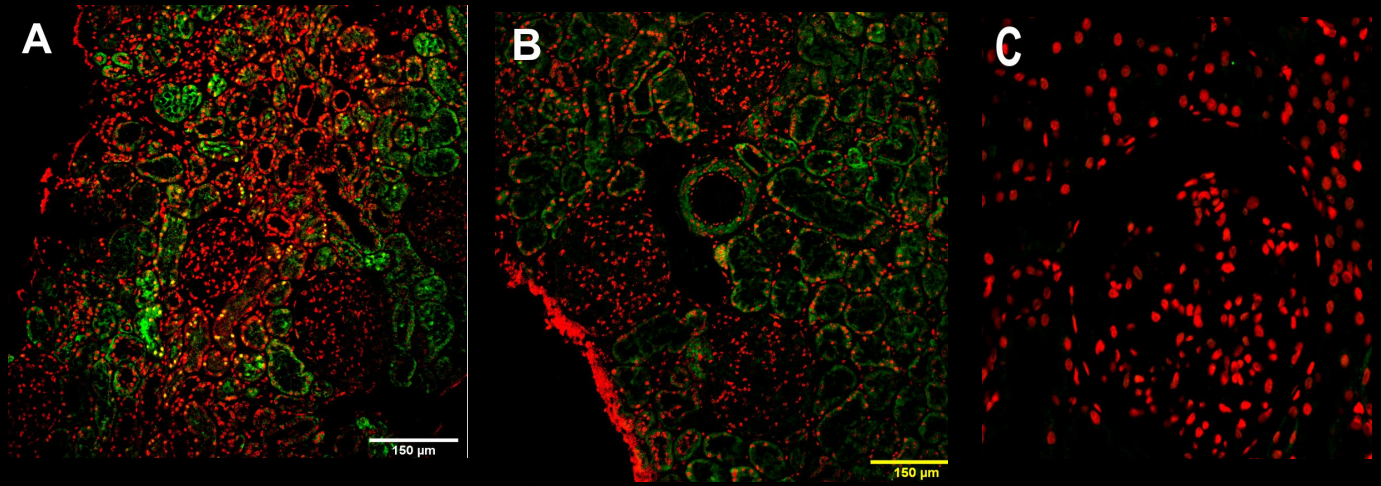
The fraction of the podocyte cytoplasm occupied by Gb3 increases with age, reaching a plateau at 27 y

Voume continues to increases for podocyte stress and podocyturia occurs

Behzad Najafian et al. Accumulation of Globotriaosylceramide in Podocytes in Fabry Nephropathy Is Associated with Progressive Podocyte Loss. J Am Soc Nephrol 2020, 31 (4) 865-875

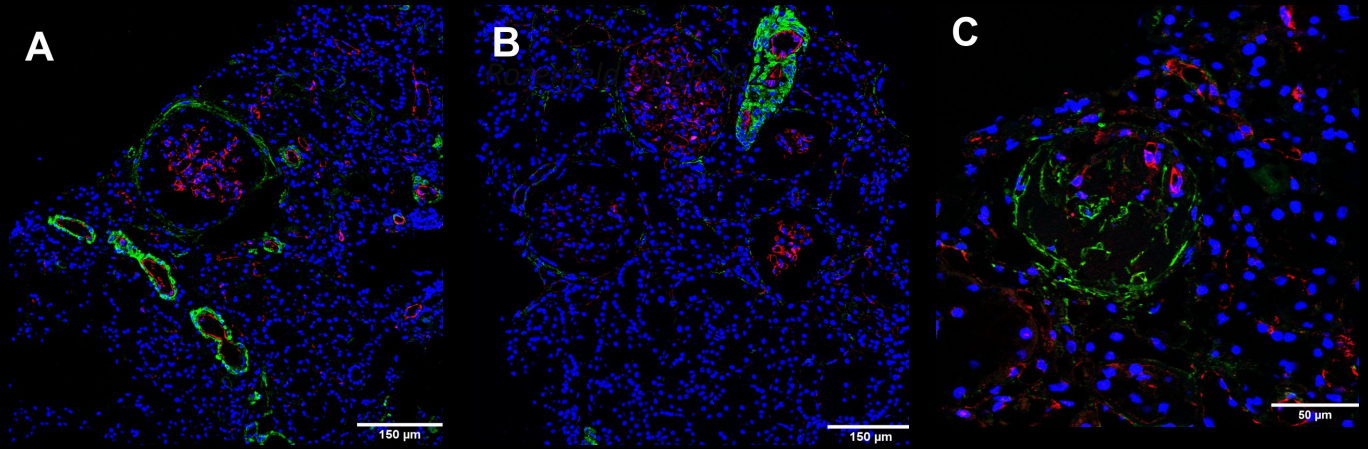
FN: THE PATHWAYS LEADING TO FIBROSIS

TGF-β green



α-SMA green

CD31 red



Rozenfeld, et al MGM 2019

A-GAL A AND ENDOPLASMIC STRESS AND UNFOLDED PROTEIN REACTION

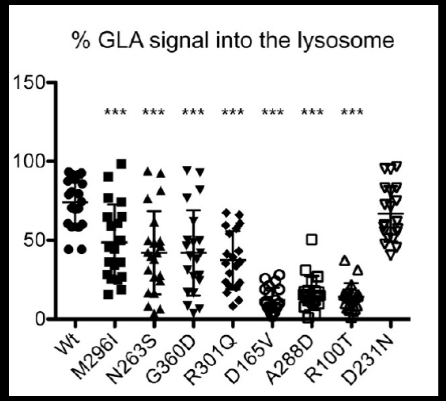
Contents lists available at ScienceDirect

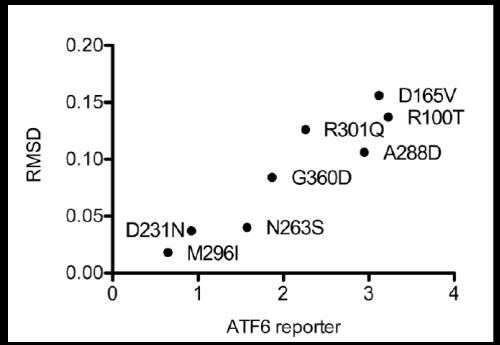
Molecular Genetics and Metabolism Reports

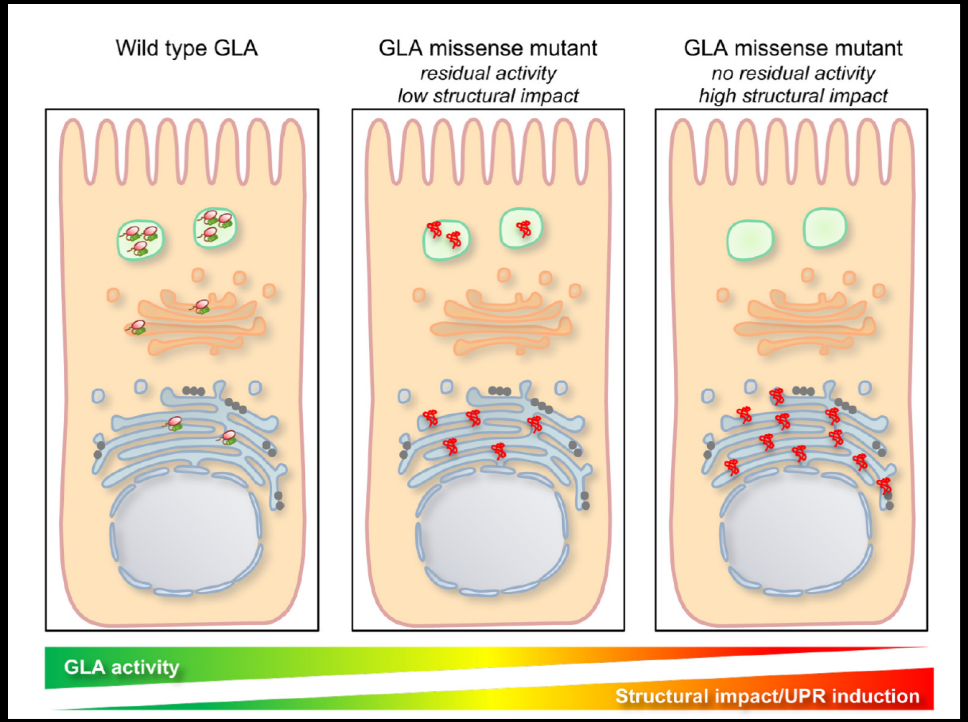
journal homepage: www.elsevier.com/locate/ymgmr

α-Gal A missense variants associated with Fabry disease can lead to ER stress and induction of the unfolded protein response

Francesco Consolato [a,1], Maurizio De Fusco [a,1], Céline Schaeffer [a], Federico Pieruzzi [b], Francesco Scolari [c], Maurizio Gallieni [d], Chiara Lanzani [e], Sandro Feriozzi [f], Luca Rampoldi [a,g,*]

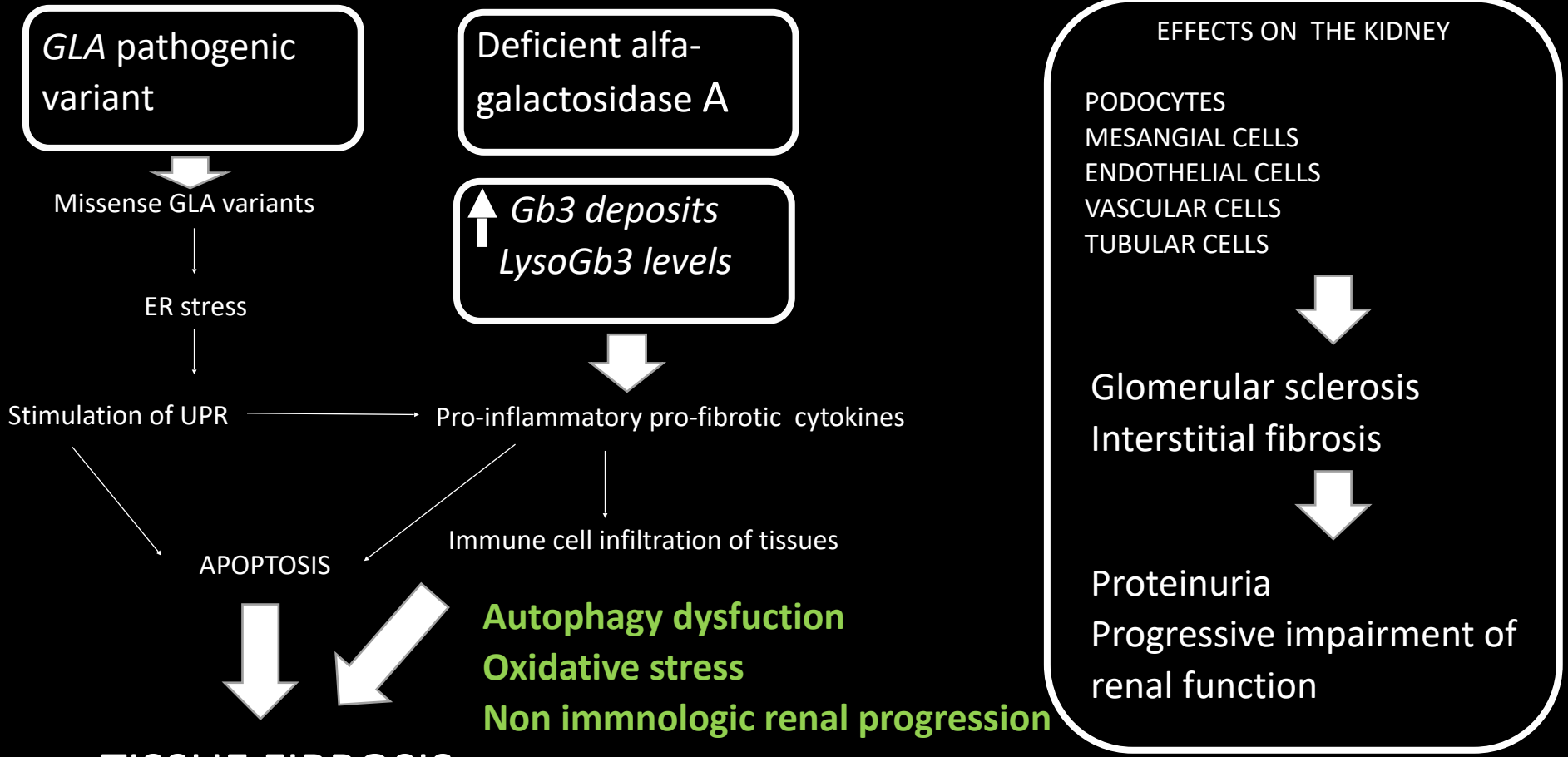






«α GAL mutants with residual activity are partially retained inducing ER stress and UPR mutants no residual activity have a structural impact and a robust stress with UPR»

THE INFLAMMATORY PATHOGENETIC PATHWAYS OF FN



Feriozzi & Rozenfeld RDODJ 2024

Clinical Kidney Journal

Reduction in kidney function decline and risk of severe clinical events in agalsidase beta-treated Fabry disease patients: a matched analysis from the Fabry Registry

Clinical trials of agalsidase beta may not be generalizable to all Fabry patients and do not address long-term outcomes. This analysis investigates long-term eGFR changes and risk of clinical events with agalsidase beta treatment in real-world populations.

Methods

Patients:
Agalsidase beta-treated (Fabry Registry) and untreated patients (Natural History Study) aged ≥16 years

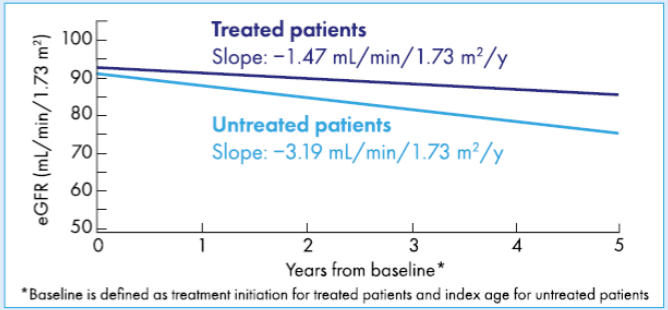
Outcomes:
- eGFR slope: change in eGFR over time
- Risk of composite clinical event: cardiovascular, cerebrovascular or renal event, or death

Analysis:
1:1 matching: untreated patients matched to similar treated patients to compare eGFR slopes and clinical events

Results

Estimated GFR slopes

53.9% reduction in rate of eGFR decline with agalsidase beta

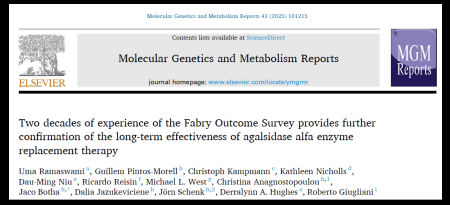


Composite clinical event

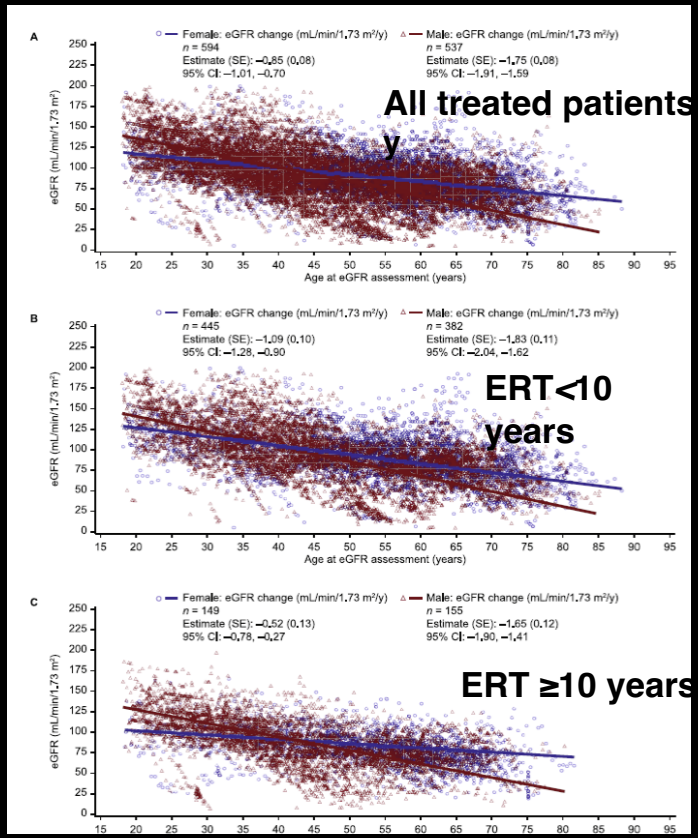
59% lower risk of composite clinical event with agalsidase beta

Conclusion: This real-world study provides evidence that long-term agalsidase beta treatment preserves kidney function and delays progression to severe clinical events among patients aged ≥ 16 years.

Batista, J. L.
Clinical Kidney Journal (2024)
Julie.Batista@sanofi.com
@CKJsocial



ANNUALISED eGFR CHANGE IN THE TREATED PATIENTS



All treated patients

y

Slope/

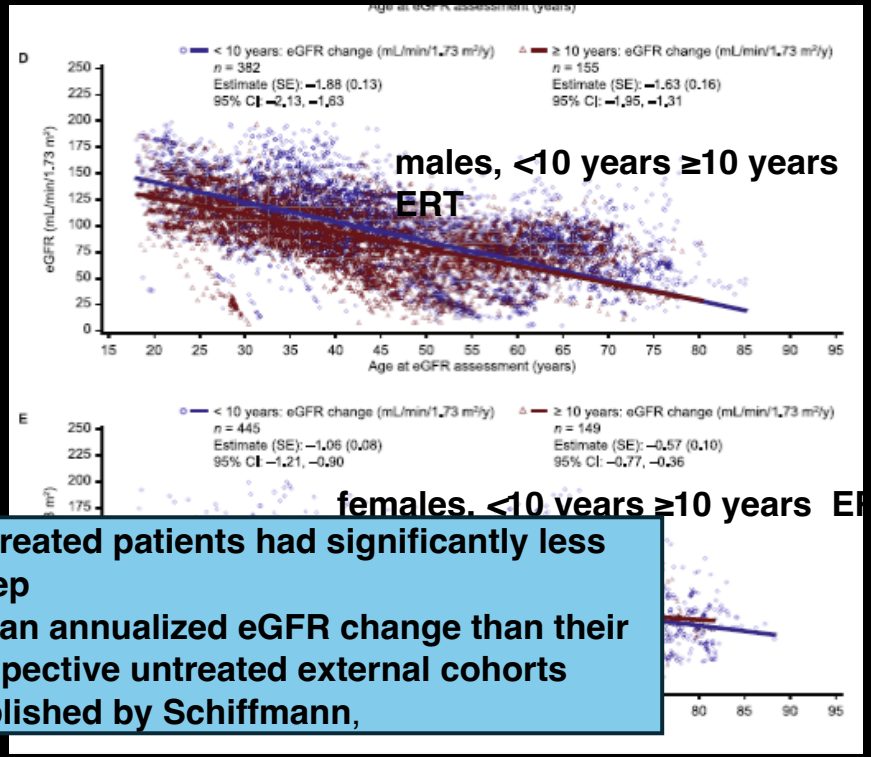
y

-0.85 f

-1.76

ERT<10 years

ERT ≥10 years

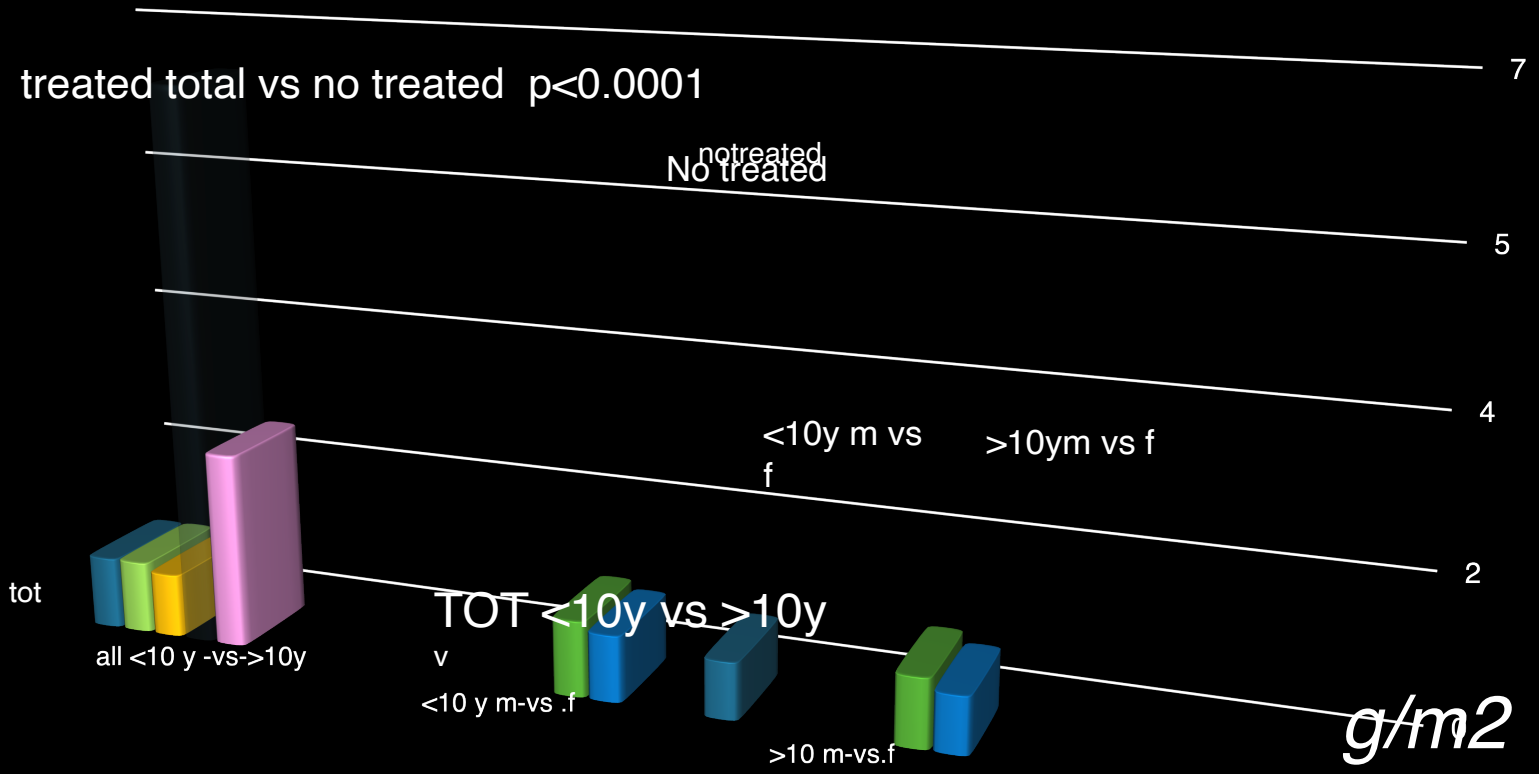


males, <10 years ≥10 years ERT

females, <10 years ≥10 years ER

all treated patients had significantly less steep
mean annualized eGFR change than their respective untreated external cohorts published by Schiffmann,


Molecular Genetics and Metabolism Reports
Two decades of experience of the Fabry Outcome Survey provides further confirmation of the long-term effectiveness of agalsidase alfa enzyme replacement therapy


treated total vs no treated p<0.0001
notreated
No treated
7
5
4
2
<10y m vs f
>10ym vs f
tot
all <10 y -vs->10y
TOT <10y vs >10y
v
<10 y m-vs .f
>10 m-vs.f
g/m2

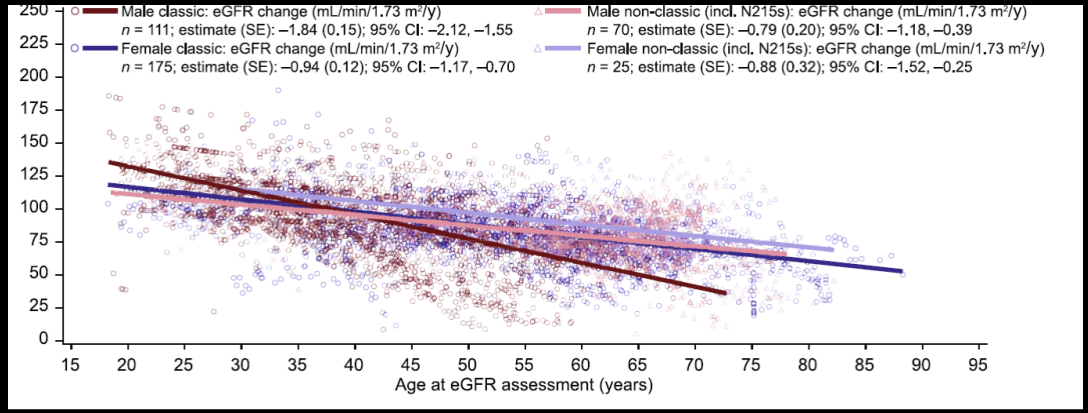
OUTCOMES ACCORDING TO MUTATION: classical vs non

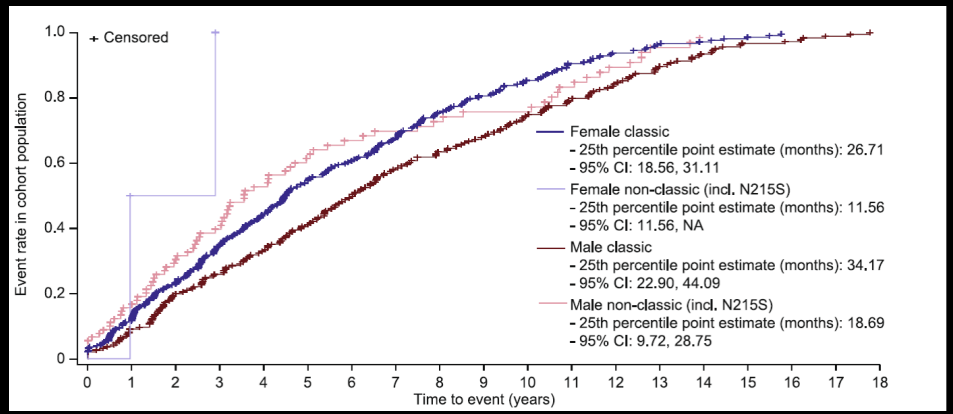
A) Classical males

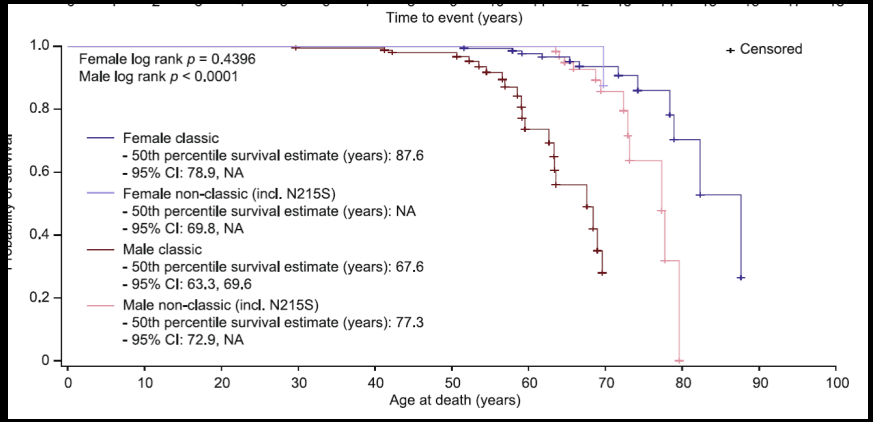
B) No-classical males and classical females

A) No-classical females

M. Langeveld 8th update Fabry Disease, Hamburg 1-4 June 2024







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journal homepage: www.elsevier.com/locate/ymgmr

Effectiveness and tolerability of migalastat in adult Fabry disease: A single regional centre experience

Eamon P. McCarron [a,b,c], Rajkumar Chinnadurai [d,e], Karolina M. Stepien [a,e], John Bassett [a], Jonathan Meyer [a], Reena Sharma [a], Peter Woolfson [f], Ana Jovanovic [a,b,c]

Conclusion: Migalastat was well tolerated and maintained stable renal and cardiac parameters with plasma lyso-Gb3 improvement. However, a subset of patients showed progression or intolerance, underscoring that variant amenability alone may not predict clinical benefit.

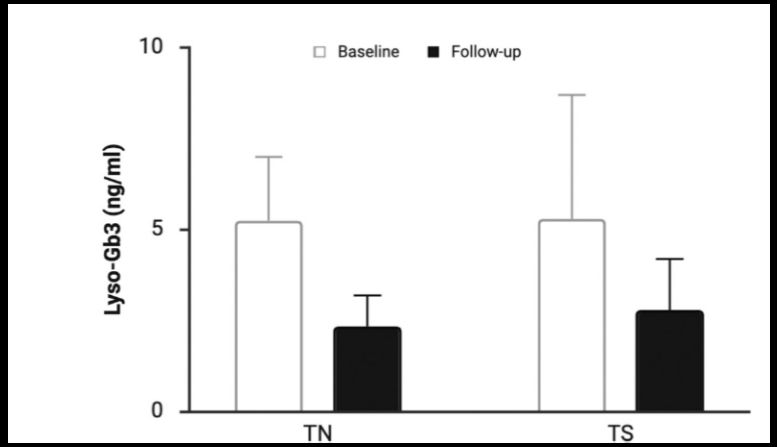

Table 3
Renal and cardiovascular parameters at baseline and follow-up in treatment-naïve and treatment-switch patients receiving migalastat.

	Treatment naïve ($N = 48$)			Treatment switch ($N = 39$)		
Variables	Baseline	Follow-up	p-Value	Baseline	Follow-up	p-Value
Biochemical						
eGFR >90, ml/min/1.73m^2	24/48 (50%)	14/48 (29%)	**0.037**	33/39 (84.6%)	12/39 (30.8%)	**<0.001**
eGFR >60, ml/min/1.73m^2	40/48 (83.3%)	34/48 (70.8%)	0.145	39/39 (100%)	35/39 (89.7%)	0.157
uPCR, mg/mmol	12 (7–21)	13 (8–30)	1.000	9 (7–16)	11 (5–19)	0.175
uACR, mg/mmol	3.7 (1.3–13.5)	4.55 (1.29–12.4)	0.343	1.8 (1–4.3)	2.15 (0.6–16)	0.564
Cardiovascular						
PR interval (ms)	158 (146–176)	169 (146–192)	0.067	156 (133–176)	163 (142.5–180.5)	0.063
QTc interval (ms)	435 (408–454.5)	444 (411–466.5)	0.319	418 (397.5–434)	442.5 (422–469)	**<0.001**
Systolic BP, mm Hg	133 (120–148)	132 (119–152)	0.257	133 (126–145)	129 (119–140)	0.060
Diastolic BP, mm Hg	80 (74–89)	82 (71–90)	0.301	80 (74–87)	82 (76–90)	0.340
Intraventricular septum at end-diastole (IVSd) (cm)	1.3 (1–1.7)	1.3 (1.2–1.65)	0.308	1.3 (0.96–1.6)	1.4 (1.2–1.7)	0.214
LVM (g)	224.6 (176.6–328.6)	237.1 (173.45–299.4)	0.739	233.5 (175.8–303.4)	219.1 (176.5–257.6)	0.110
LVMI (g/m^2)	110.9 (93.1–154.6)	113.8 (93–161.8)	0.736	121.7 (96.1–138.7)	105.3 (90.8–136.3)	0.088

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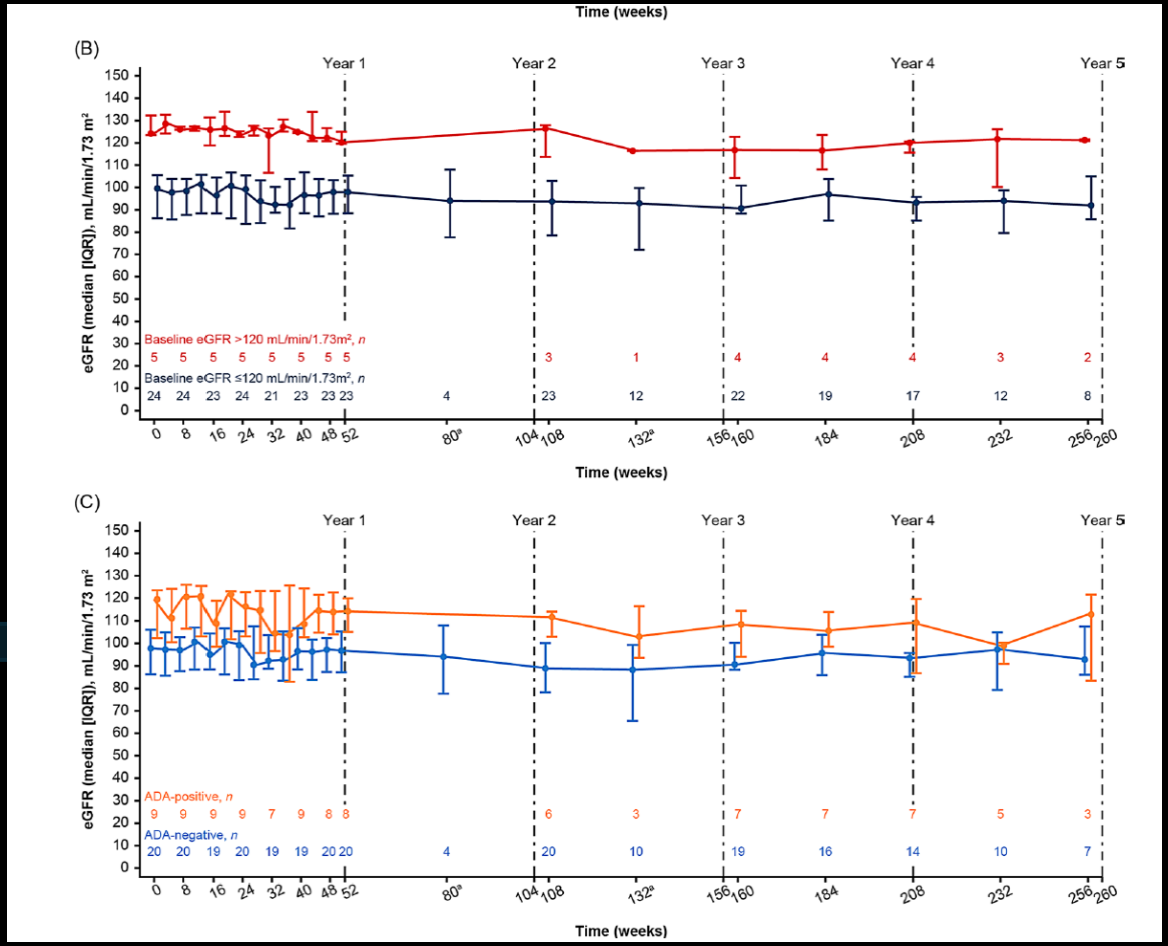
Orphanet Journal of Rare Diseases

RESEARCH Open Access

Long-term efficacy and safety of pegunigalsidase alfa administered every 4 weeks in adults with Fabry disease: results from up to 5 years of the BRIGHT F51 phase III, open-label extension study

Myrl Holida[1], Aleš Linhart[2], Nicola Longo[3], Eric Wallace[4], Camilla Tøndel[5], Derralynn Hughes[6], David G. Warnock[4], Antonio Pisani[7], François Eyskens[8], Patrick Deegan[9], Ulla Feldt-Rasmussen[10], Özlem Goker-Alpan[11], Ankit Mehta[12], Giovanni Piotti[13], Vito Fichera[13], Meng Wang[13], Raul Chertkoff[14], Stephen Waldek[15], William R. Wilcox[16] and John A. Bernat[1*]

Long-term treatment with pegunigalsidase alfa 2 mg/kg E4W was well-tolerated and Maintained disease stability, especially in females and ADA-negative males; more data are needed to better understand outcomesin ADA-positive males.

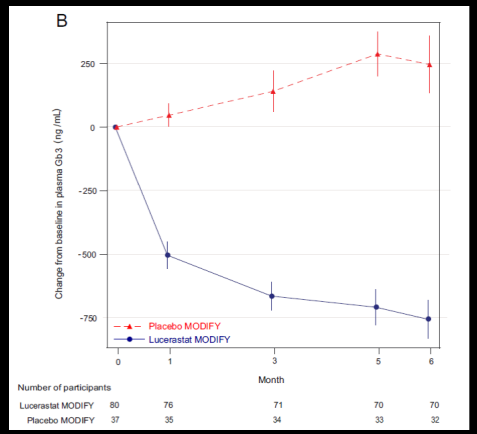


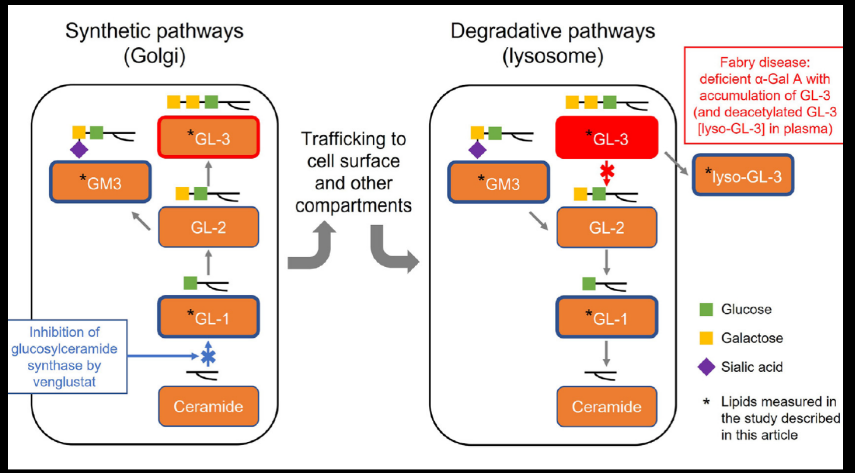
nature communications

Article

https://doi.org/10.1038/s41467-025-68256-5

Lucerastat, an oral therapy for Fabry disease: results from a pivotal randomized phase 3 study and its open-label extension





pre- and post-randomisation eGFR data was –3.50) and –1.48

Table 2 | Shift in eGFR slope category from pre-randomization to lucerastat treatment in MODIFY + OLE

Pre-randomization eGFR slope, category	eGFR slope (category) on lucerastat treatment, *n* (%)			
	Stable	Deteriorating	Fast deteriorating	Total
Stable	40 (43%)	5 (5%)	5 (5%)	50 (54%)
Deteriorating	16 (17%)	4 (4%)	2 (2%)	22 (24%)
Fast deteriorating	14 (15%)	4 (4%)	3 (3%)	21 (23%)
Total	70 (75%)	13 (14%)	10 (11%)	93 (100%)

eGFR estimated glomerular filtration rate.
Stable defined as eGFR slope >−3 mL/min/1.73 m^2 per year; deteriorating defined as eGFR slope ≥−5 and ≤−3 mL/min/1.73 m^2 per year; fast deteriorating defined as eGFR slope <−5 mL/min/1.73 m^2 per year.

STAAR, a Phase 1/2 study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease

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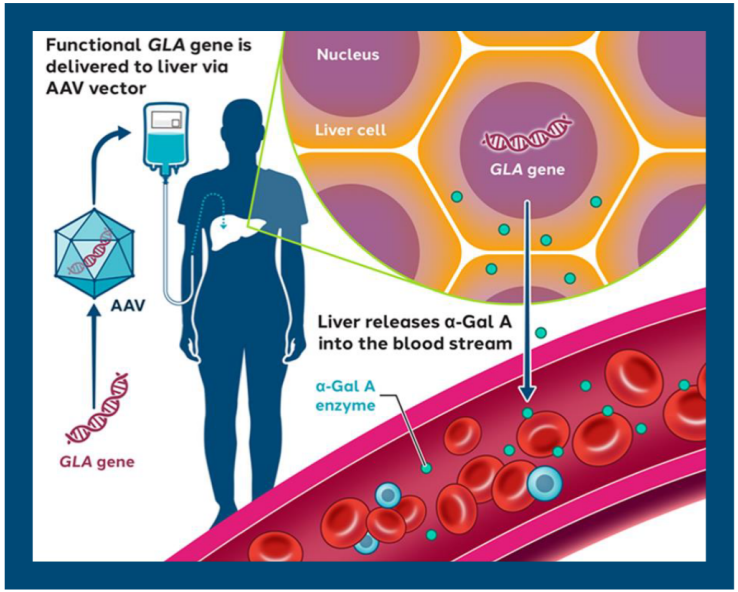
[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Isaralgagene civaparvovec (ST-920) for Fabry Disease Trea



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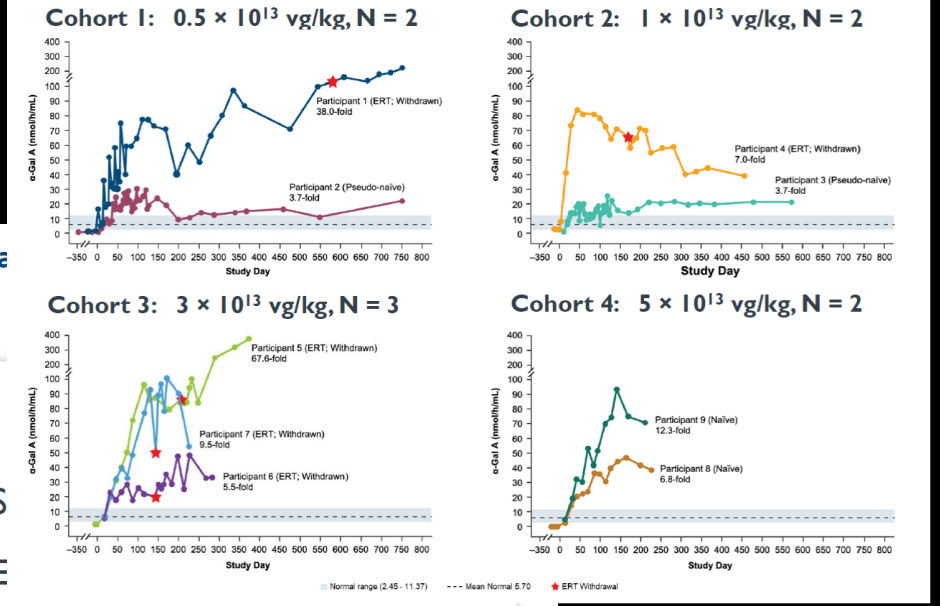

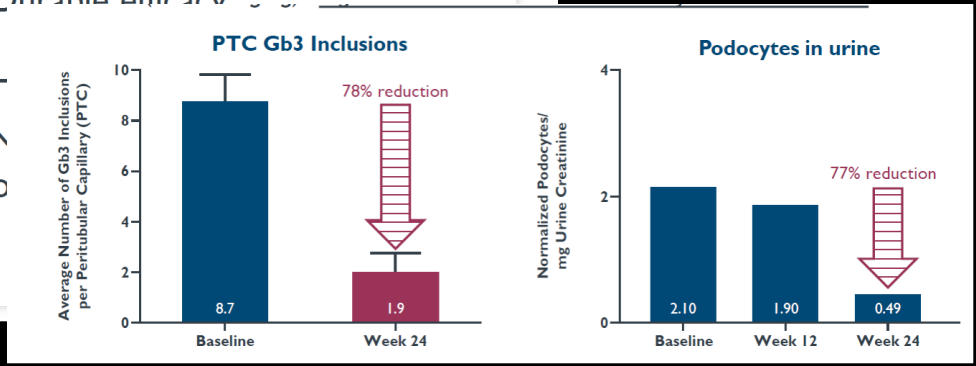

Journal of Clinical Medicine

Systematic Review

Clinical Efficacy and Real-World Effectiveness of Fabry Disease Treatments: A Systematic Literature Review

Ana Jovanovic [1], Eve Miller-Hodges [2], Felicia Castriota [3], Obaro Evuarherhe [4], Olulade Ayodele [3], Derralynn Hughes [5], Guillem Pintos-Morell [6], Roberto Giugliani [7], Sandro Feriozzi [8] and Csaba Siffel [3,9,*]

	Agalsidase alfa	Agalsidase beta	Mixed studies	Switch studies	Migalastat	Pegunsidase alfa
Number studies 187	23 (37)				0	11
Follow-up	26 weeks-				months-7 years	3-72 months
Short-med term >5<10 years	Stabilizat		alfa-beta:-0.85, p=0,2 No statistical difference		GFR >60 -1.0 — 5.9 mL/min/1.73 m2 GFR>60 :–0.4 — 3.5 mL/min/1.73 m	–2.39 mL/min/1.73 m2
Long term >1 years						
Comments			classical FD was more pronounced in those treated with agalsidase beta (βalfa-beta: –18.06 nmol/L, 95% CI –25.81 to –10.03, P<0.001)	randomized; therefore, treatment groups were not homogeneous.		Possibility of 2mg/kg every 4 weeks (E4W) Supposed low incidence of ADA Ab anti-PEG

stable renal function and cardiac structure. **Conclusions:** Overall, current treatments slow the progression of renal and cardiac decline in patients with Fabry disease. Large cohort studies with long-term follow-up and baseline stratification based on clinical phenotype are needed to address evidence gaps and provide clinicians with robust data to inform treatment decisions.

CONCLUSION

- The therapy has changed the Fabry outcome
- The enzyme replacement therapy with galactosidase alpha and beta has a longer collection of data, 20 years
- The Migalastat is only for amenable mutations
- The Pegunigalsidase has likely a less immunological impact, but its introduction in real life has been for a short time
- The key point in therapy is an early start to prevent the pathogenetic pathways that lead to progressive organ damage.