2ND SUMMIT
RARE
DISEASES
COPAC

A, B or C, a decision based on beliefs or clinical evidence? You will decide...

sanofi

Disclosures

- Consultant: Sanofi Genzyme, Freeline
- Speaker fees: Sanofi Genzyme, Shire, Amicus, Chiesi

FRASE DE SALVAMENTO

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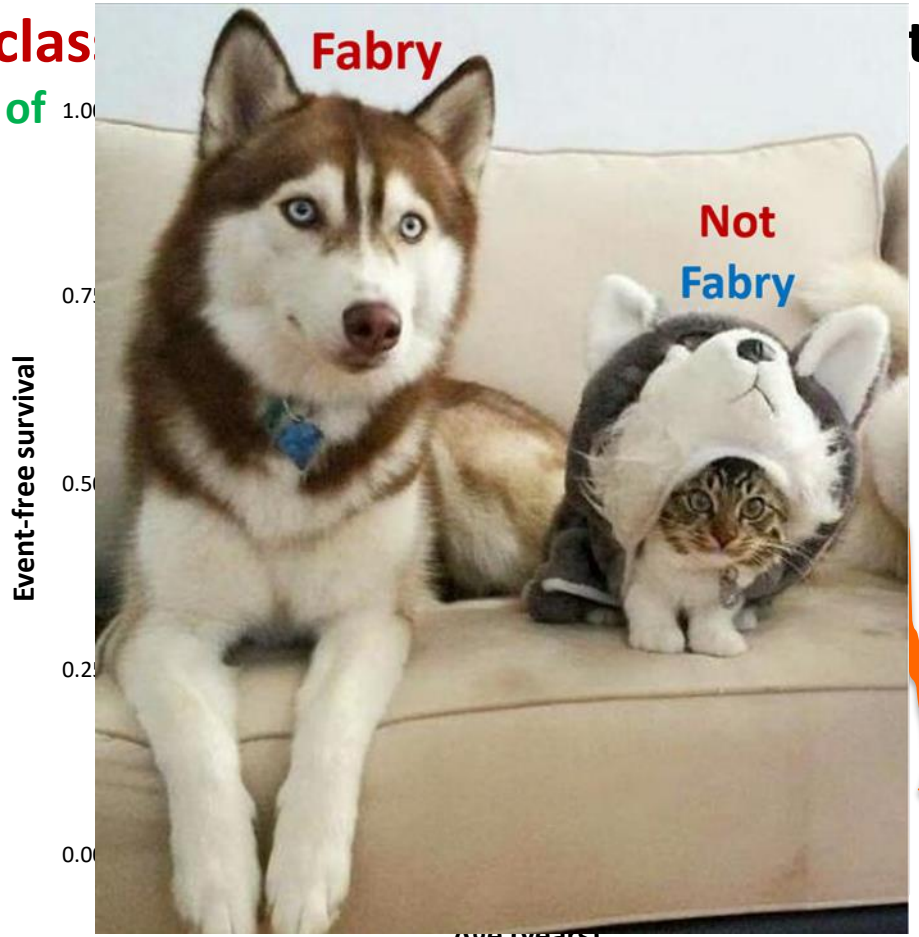
Natural history of severe event-free survival: clas ts

The importance of early therapy

Natural history



There are even "**non-Fabry**" "Fabry patients"!

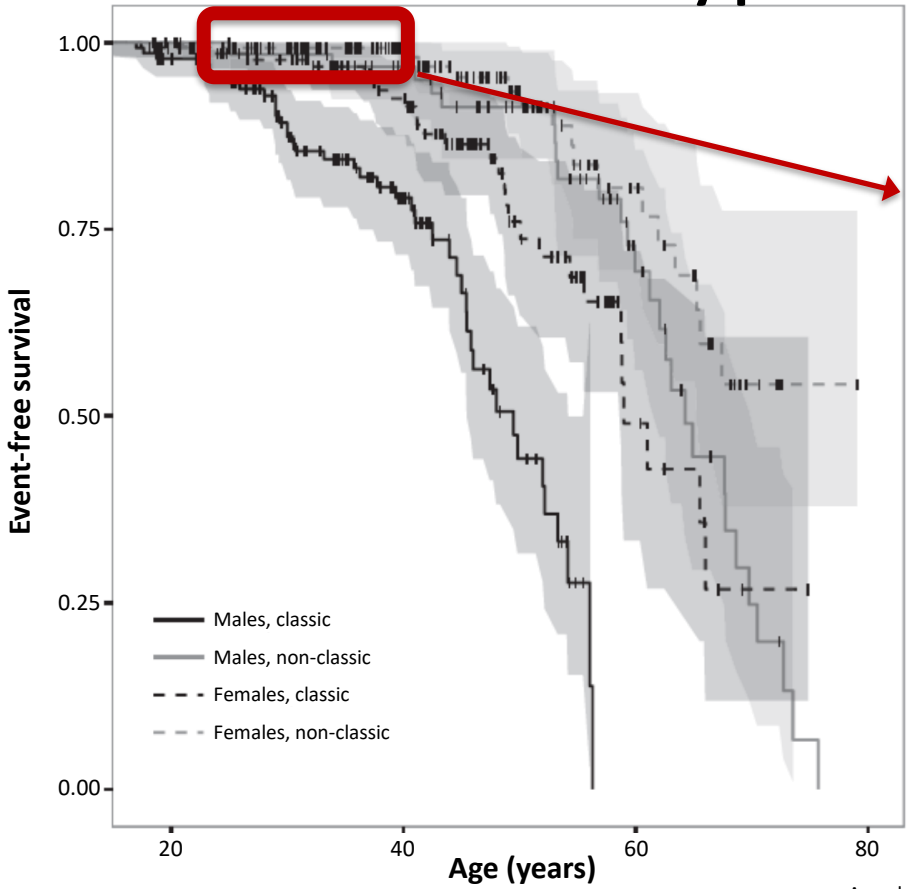
Retrospective assessment of event-free survival from birth to the first clinical visit (before ERT) in 499 adult patients (mean age 43 years; 41% men; 57% classic phenotype) from 3 international centers of excellence

ERT, enzyme replacement therapy.

Arends M, et al. J Am Soc Nephrol. 2017;28:1631-41.

Natural history of severe event-free survival: classic males vs other Fabry patients

Natural history



The so-far-so-good window

Retrospective assessment of event-free survival from birth to the first clinical visit (before ERT) in 499 adult patients (mean age 43 years; 41% men; 57% classic phenotype) from 3 international centers of excellence

ERT, enzyme replacement therapy.

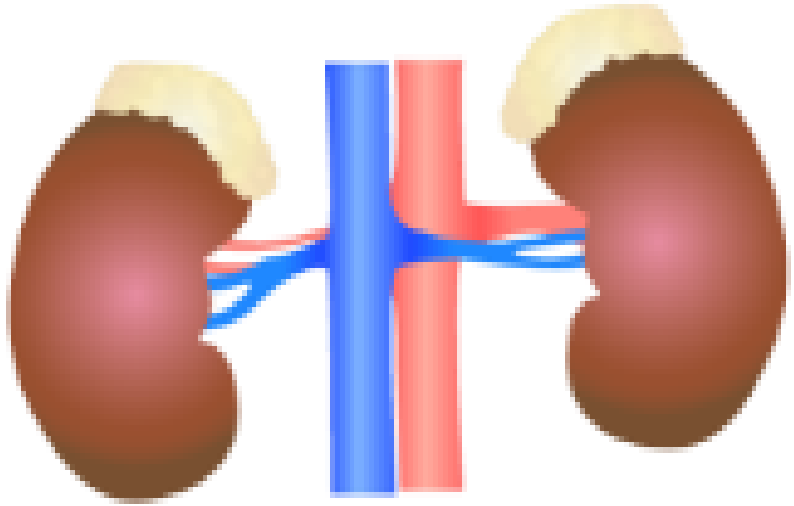
Arends M, et al. J Am Soc Nephrol. 2017;28:1631-41.

And all of them, from the more severe to the less severe to the "**non-Fabry**" "Fabry patients" are being reported **together** and **mixed up** in some publications……

… and in some cases, these new publications of this mixture of patients is compared with the early clinical trial of ERT which were performed **mostly in classic males**

eGFR **83** ml/min/1.73 m^2
at age **32 years**
Eng NEJM 2001

eGFR **>90** ml/min/1.73 m^2
at age almost **50 years**
Hughes DA. J Med Genet. 2017

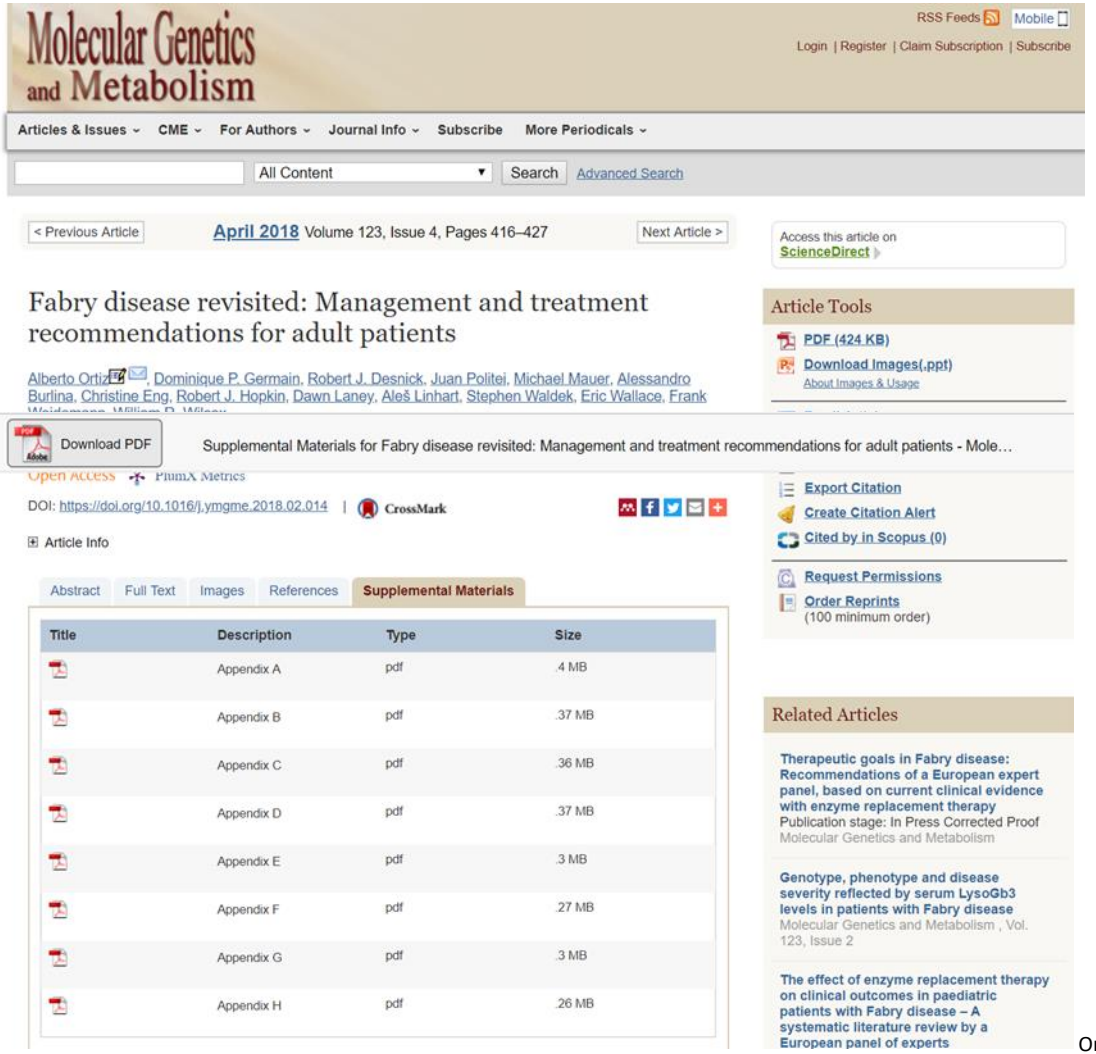


Mean age at **RRT**: **40** years (males and females), but approx. 20-fold less females
Ortiz A, et al. Nephrol Dial Transplant. 2010 Mar;25(3):769-75

Mean age at **cardiac** event **45** and **54** years, males and females, respectively
Patel MR, et al. J Am Coll Cardiol. 2011 Mar 1;57(9):1093-9

https://upload.wikimedia.org/wikipedia/commons/4/48/201405_kidney.png

How to treat?



Open access

Ortiz A, et al. Mol Genet Metab. 2018;123:416-27.

Treatment options for Fabry disease

Fabry disease specific therapy

- **Replace** the missing enzyme

Enzyme Replacement therapy (ERT) **For all** (some age limits for children)

A **Agalsidase alfa** (**0.2** mg/kg EOW **IV**) **Ex-US**

B **Agalsidase beta** (**1.0** mg/kg EOW **IV**) **US and others**

- **Upgrade** the defective enzyme

C **Chaperone**

Migalastat (**123** mg **EOD** **oral**) **US and others**

For some

Amenable *GLA* variants that cause Fabry disease

Relatively preserved kidney function (**eGFR >30 ml/min/1.73 m²**)

Older children than those that can receive ERT

Symptoms and tissue-protective therapy

Meds

Pain

Kidney protection

RAS blockers
SGLT2 inhibitors

Consequences of kidney dysfunction

CKD-MBD, anemia, metabolic acidosis

Arrhythmia

Devices

ICD: Implantable **C**ardioverter-**D**efibrillator

Organ transplantation

Kidney

Heart

Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416-427; https://www.ema.europa.eu/en/documents/product-information/galafold-epar-product-information_en.pdf

https://www.ema.europa.eu/en/documents/assessment-report/galafold-epar-public-assessment-report_en.pdf

The effect of increased enzyme activity was sustained for several days after removal of the drug from the test medium, with half-lives that varied depending on the specific mutation, ranging from 11 hours to >120 hours. To further investigate the effect of a wash-out period, Fabry fibroblasts with two specific mutations showed a **decrease in GL-3 levels when treated for 7 days with a 3 day wash-out period**. In contrast, **no decrease in GL-3 level was seen after 10 days continuous treatment**, indicating **an inhibitory effect of migalastat on enzyme function when it is bound to α-GAL A**.

Mouse model: human mutant α-GAL A transgene on a mouse Gla knockout background (hR301Q α-GAL A Tg/KO). This mouse model shows age-dependent accumulation of GL-3 in disease-relevant tissues.

After **4 weeks of continuous treatment**, **α-GAL A tissue levels were increased** in skin, heart and kidney, **dose-dependently up to 300** mg/kg/day. **However, GL-3 reductions were optimal at 30 mg/kg/day**.

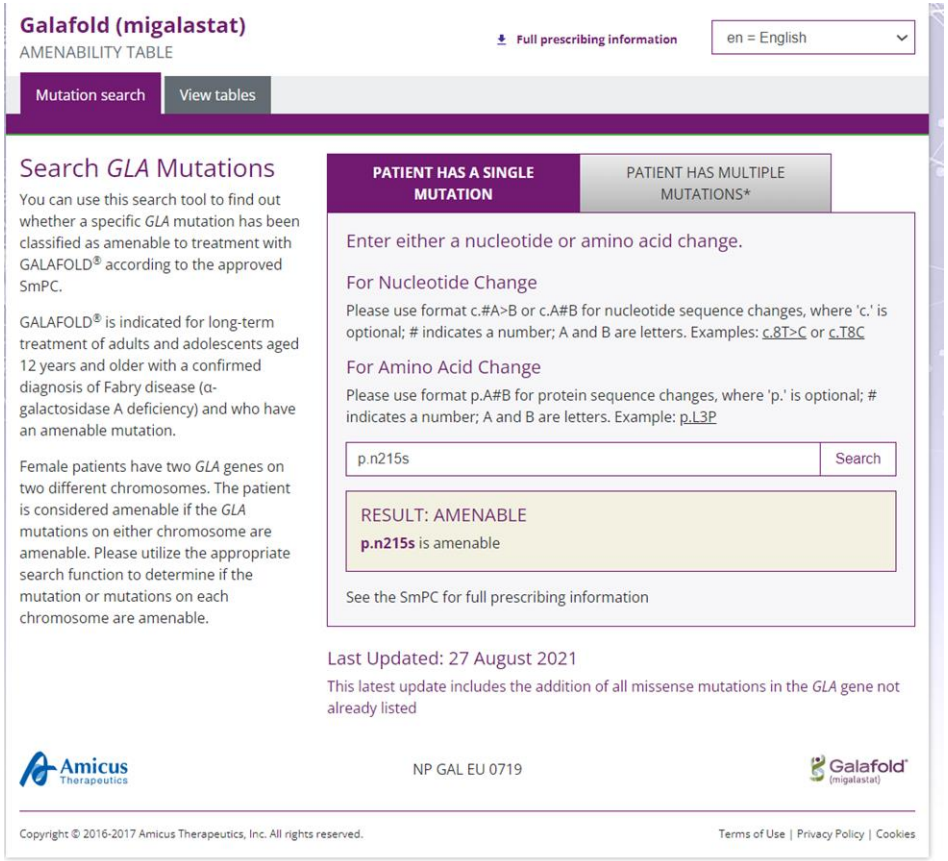
Different dosing regiments however, showed that **dosing for 4 days, followed by 3 days wash-out**, resulted in a greater reduction in tissue GL-3 than daily dosing at 300 mg/kg/day.

What is **amenable**?

A ***GLA* gene variant**
that encodes a protein product
whose enzymatic **activity is increased**
upon exposure to **migalastat**,
usually by protecting the protein
from quality control-induced degradation,
thus, allowing it to reach (and be functional) in lysosomes

Amenable, disease-causing

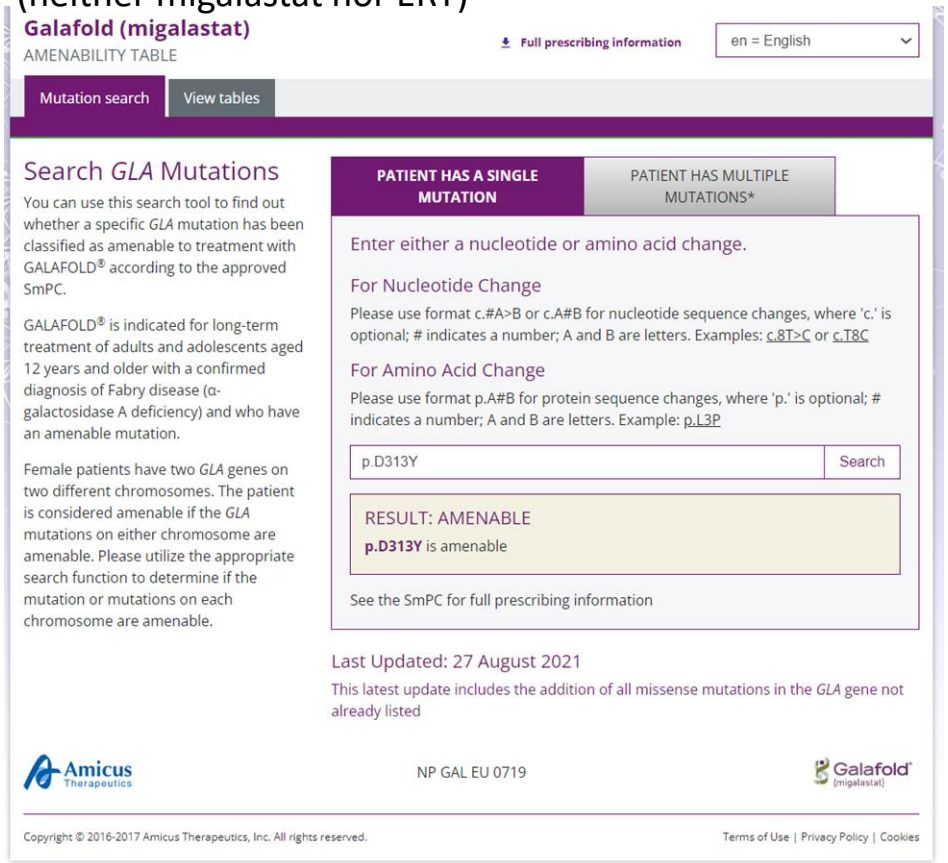
Fabry patient, candidate to treatment with **migalastat**



https://www.ema.europa.eu/en/documents/product-information/galafold-epar-product-information_en.pdf

Amenable, not disease-causing

Person has **not** Fabry disease, **not** candidate to treatment (neither migalastat nor ERT)

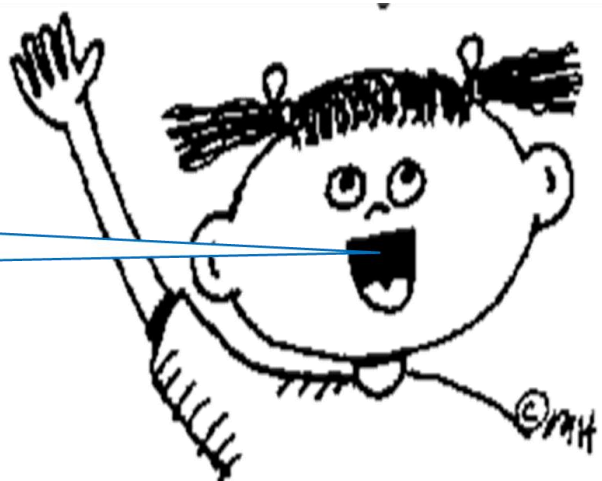


https://www.galafoldamenabilitytable.com/

Amenable

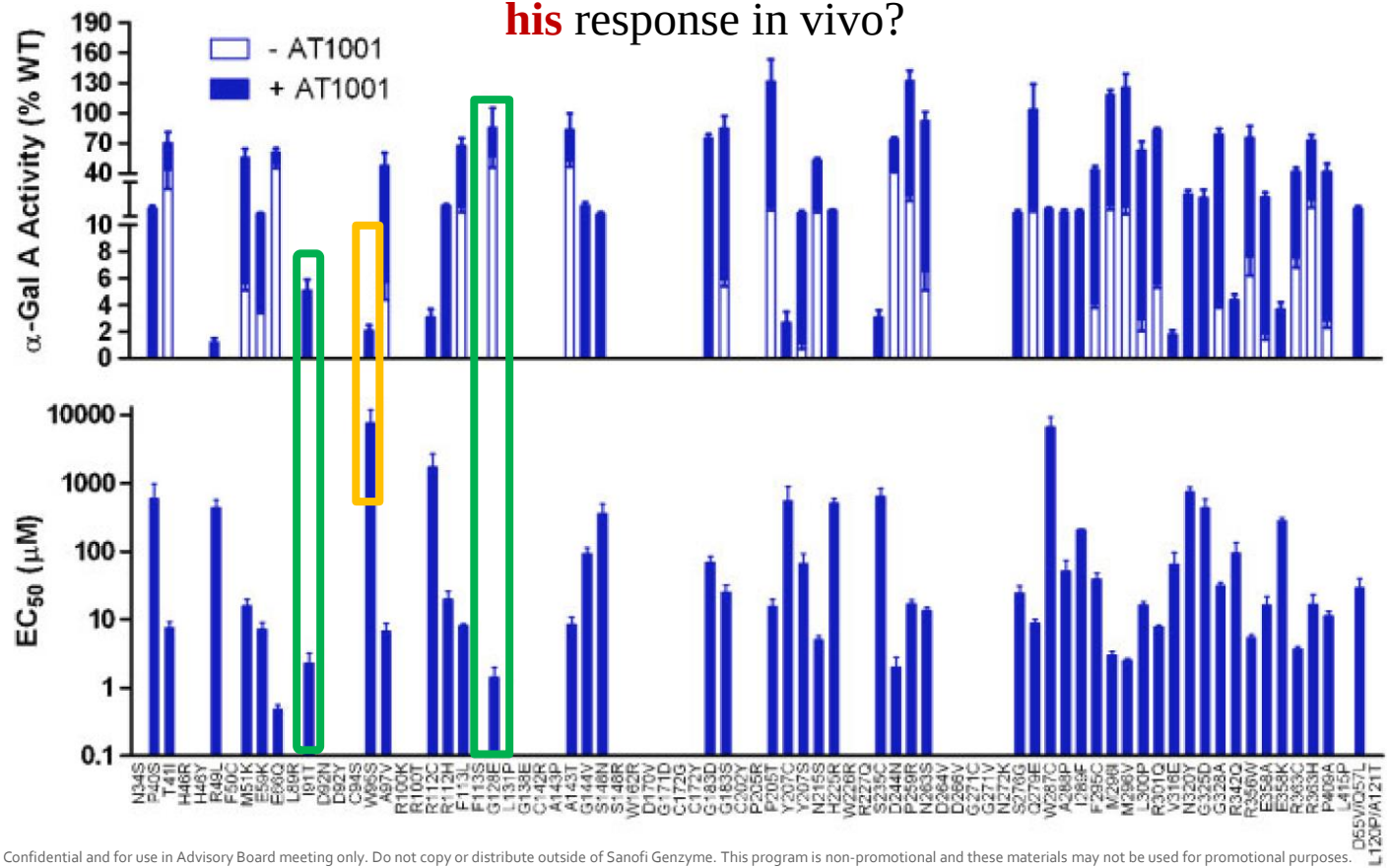
Not amenable

Teacher!
There must be a **problem!**
Does chaperone **increase activity** the same in all?



Migalastat: The issue in clinical practice

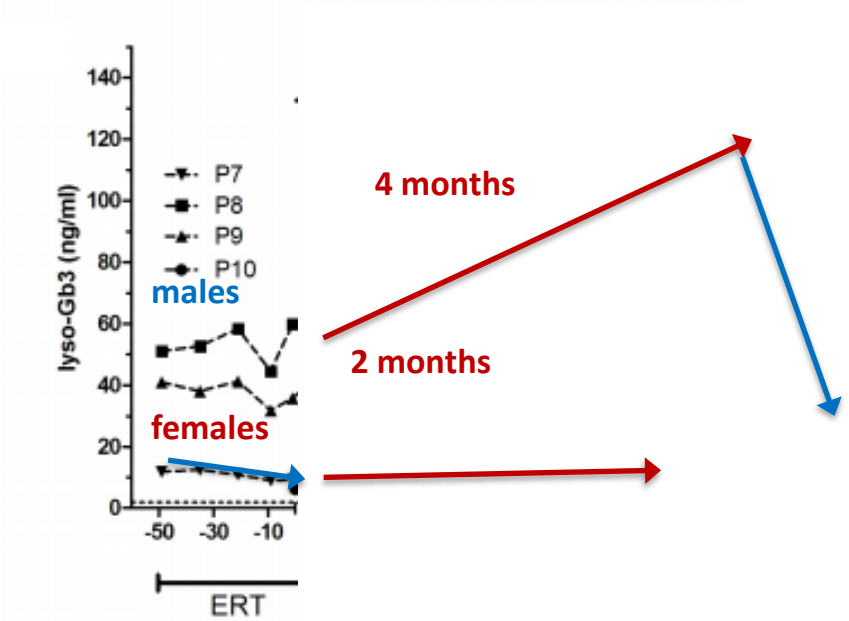
Who is our patient and what is **his** response in vivo?



Are there greys?

Potential grey identified in Germany

Increase in lyso-Gb3 after switch from ERT to migalastat in mutations with disputed amenability (L294S)



Increasing UACR (from **220** to **508** and from **181** to **429** mg/g, respectively)

A2 to **A3** albuminuria

Lenders M, et al. J Med Genet. 2019;56:548-556.

The need for **real world** evidence related to **different GLA variants**

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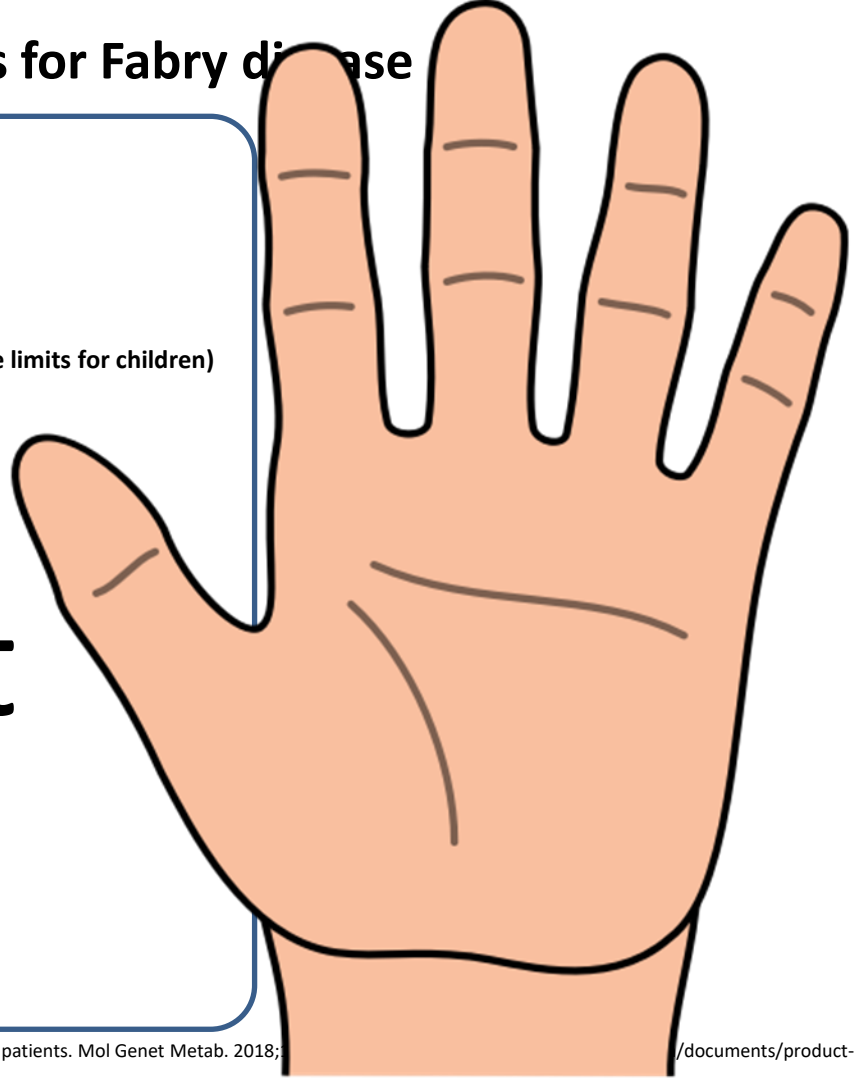
Enzyme Replacement therapy (ERT) **For all** **(some age limits for children)**

A **Agalsidase alfa** (**0.2** mg/kg EOW **IV**) **Ex-US**

B **Agalsidase beta** (**1.0** mg/kg EOW **IV**) **US and others**

5-fold different dose



Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018; /documents/product-information/galafold-epar-product-information_en.pdf

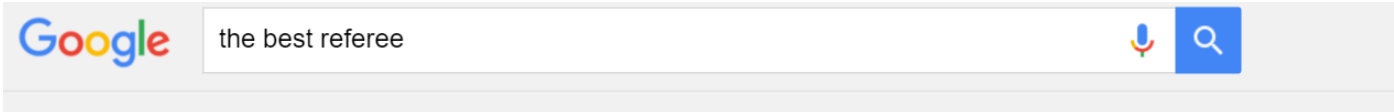
Dose of peginugalsidase?

Biosimilars?

Q2. Are the two enzymes equivalent in a mg per mg basis?

Independent referee!!

The very best independent referee!!

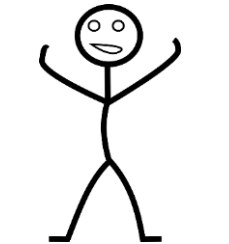


Pierluigi Collina

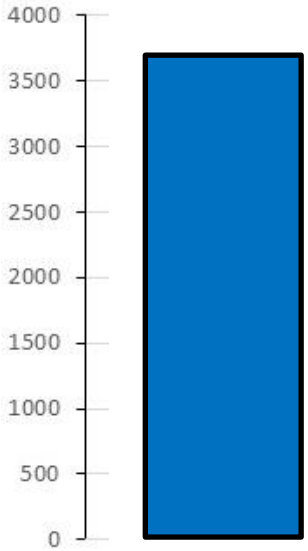
Migalastat studies

Intracellular leukocyte **enzyme activity in humans following iv ERT**

Area Under Curve α-Gal A activity exposure in leukocytes from blood samples at 0, 2, 4, 24,168, and 336 hours post-dose



hr[nmol/hr/mg]

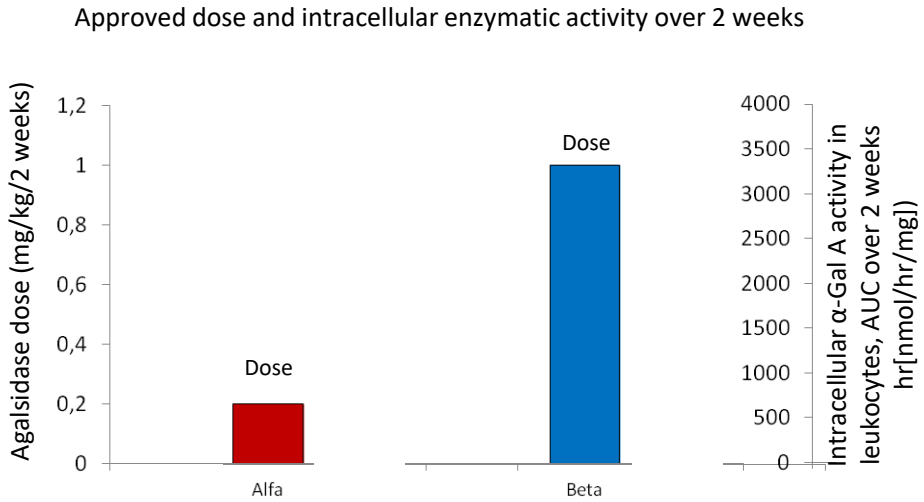


1.0 mg/kg agalsidase **beta**

0.2 mg/kg agalsidase **alfa**

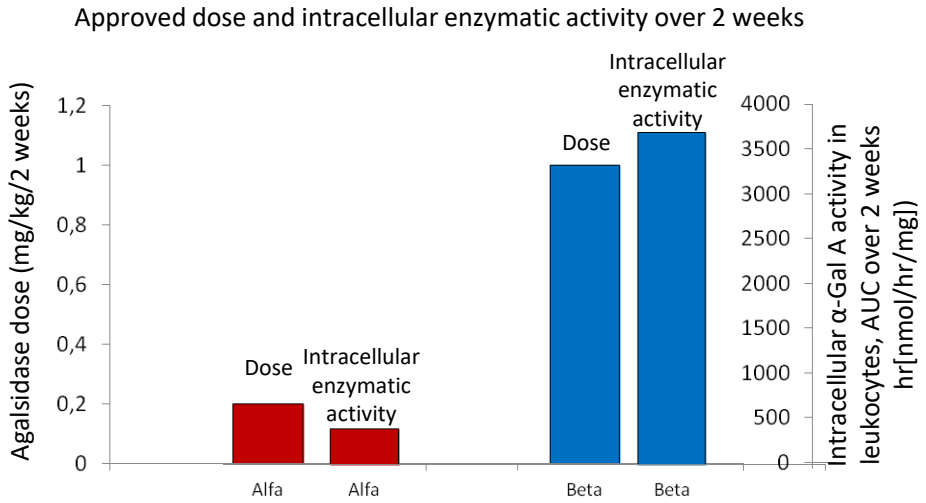
Johnson et al. Mol Genet Metab 117 (2016) S63 doi:10.1016/j.ymgme.2015.12.307

A 5-fold lower dose results in …..



Ortiz et al. Submitted. Elaborated with data from:
Johnson FK et al Mol Genet Metab 2016;117: S63

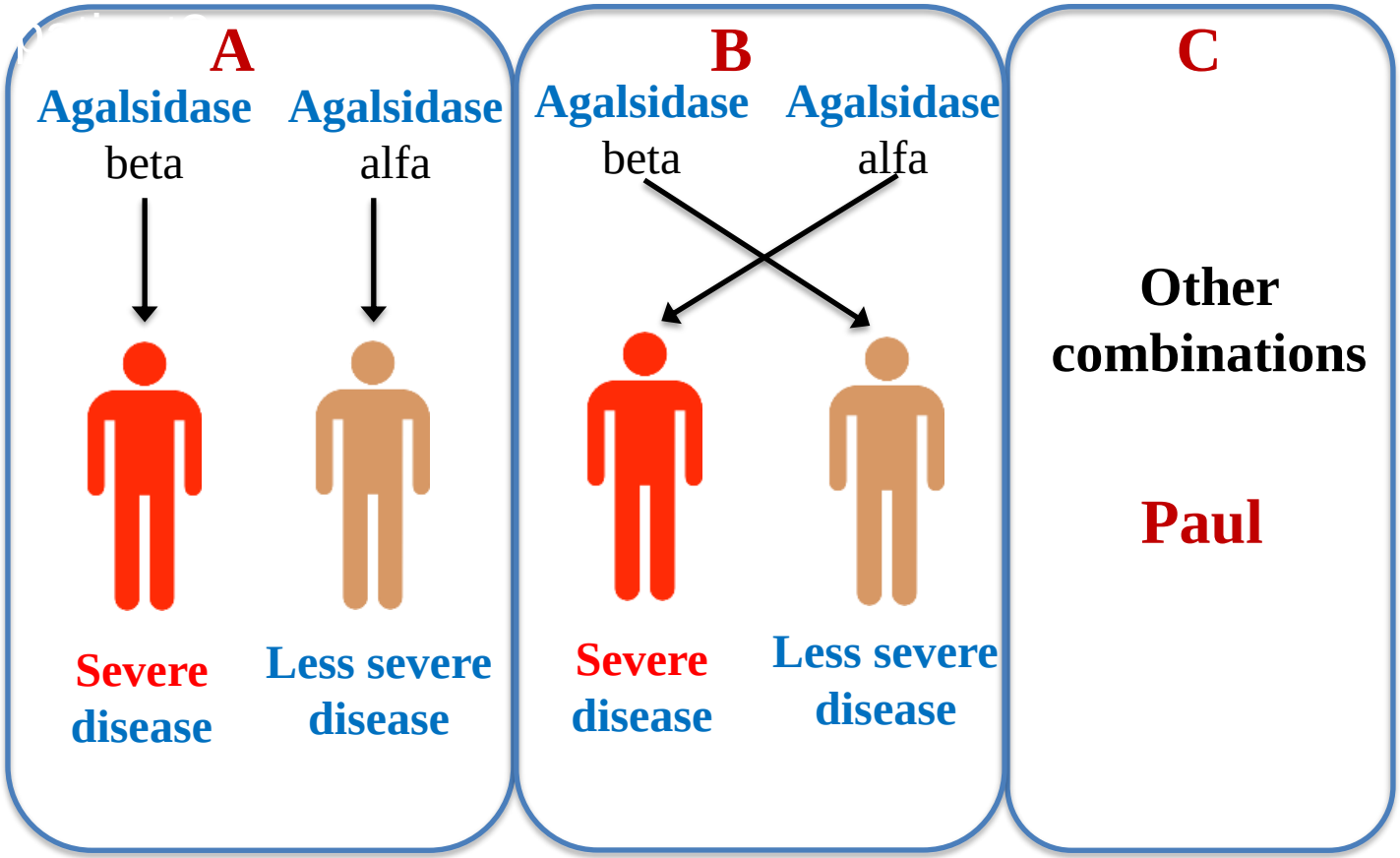
A 5-fold lower dose results in more than 5-fold lower intracellular enzymatic activity in Fabry patients



Ortiz et al. Submitted. Elaborated with data from:
Johnson FK et al Mol Genet Metab 2016;117: S63

How would you choose the agalsidase preparation for your patient (assuming you want to use both available enzymes)?

Dr Ortiz personal observation

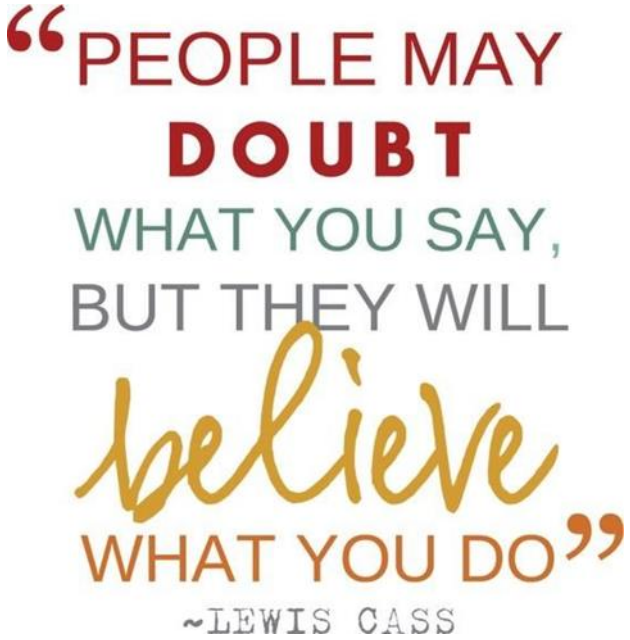


Note that these are different molecules and differ by more than just dose.

Paul

https://elarchipielagogadzooks.wordpress.com/octopus-420x0/

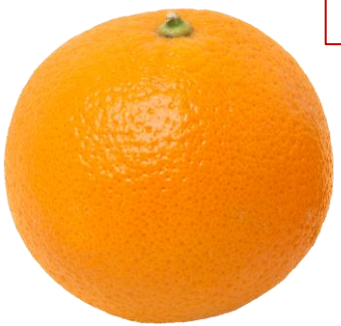
Expert opinion?

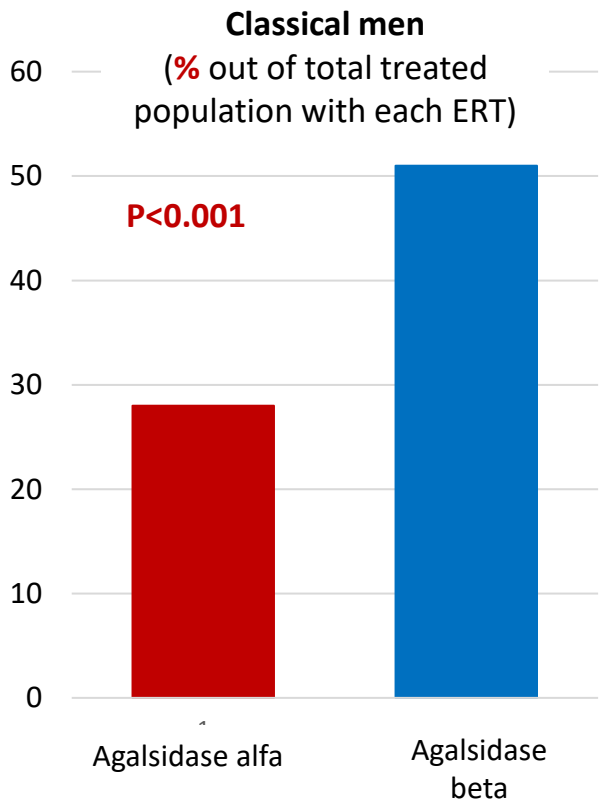


How were patients distributed between Agalsidase-alfa 0.2 mg/kg/2weeks and Agalsidase-beta 1.0 mg/kg/2 weeks in a recent multicenter observational study?

- Academic Medical Center (AMC), The Netherlands;
- Royal Free London NHS Foundation Trust, UK
- University Hospital Wuerzburg, Germany
- Cohort 1b, CFDI, Canada

The correct response is **A**





Arends M et al. J Med Genet Published Online First: 07 February 2018. doi: 10.1136/jmedgenet-201

There appears to be a **systematic bias** in observational studies in the literature regarding the severity of disease of patients on alfa and on beta

Arends M et al. J Med Genet Published Online First: 07 February 2018. doi: 10.1136/jmedgenet-2017-104863

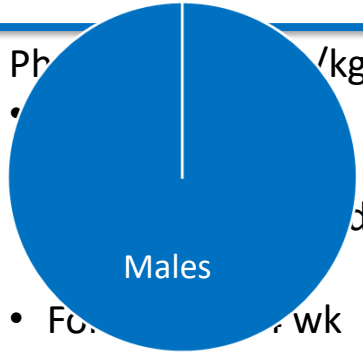
Fabry disease natural history is measured in **decades**

What is the **available evidence** from **RCT** on **long-term efficacy** for Fabry disease?

Agalsidase alfa

Dose finding:
Up to **0.1** mg/kg tested

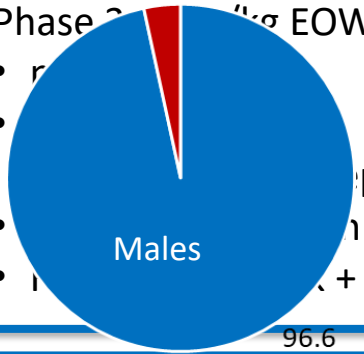
Ph /kg EOW
•
pain
dothelial
• Fo wk



Agalsidase beta

Dose finding:
Up to **3.0** mg/kg tested

3.4
Phase 2 /kg EOW
•
•
posits
n
+ 6 mo

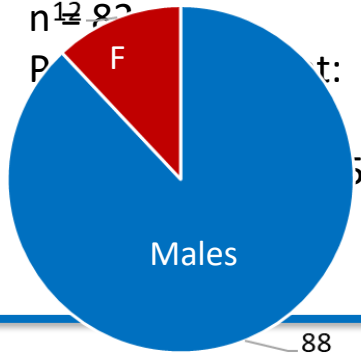


96.6

5-year extension
- Biopsies
- Stable eGFR

10-year follow-up
- Events
- eGFR slope
- LVH

Phase 4: **1**mg/kg EOW
- n 12 83
- P t:
- 5 mo



88

CFDI head-to-head comparison
Primary endpoint: events
Follow-up: up to 10 years

LVH, left ventricular hypertrophy.

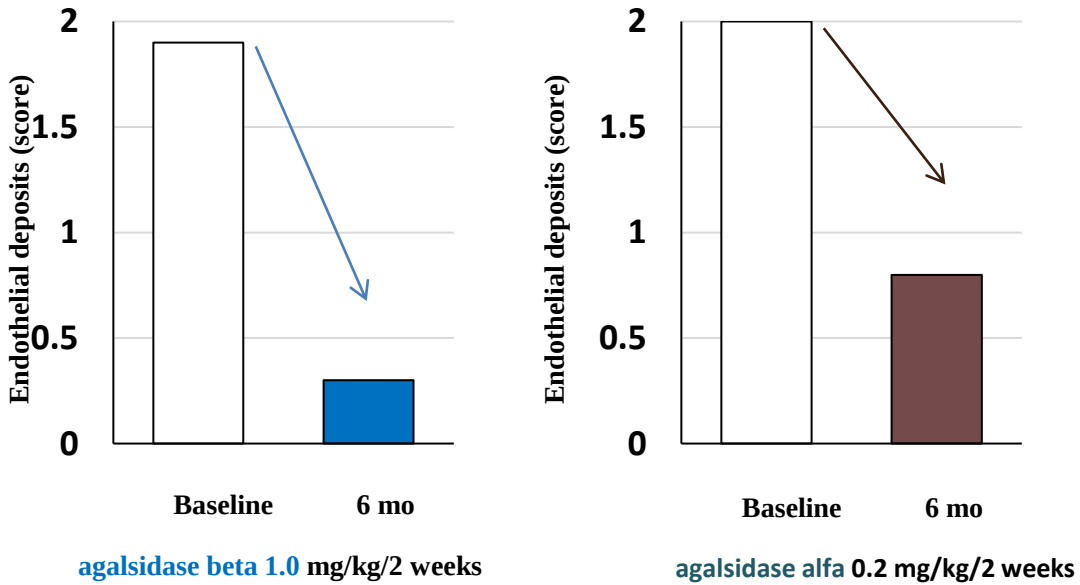
Banikazemi M, et al. Ann Intern Med. 2007;146:77-86. Eng CM, et al. N Engl J Med. 2001;345:9-16. Germain DP, et al. J Am Soc Nephrol. 2007;18:1547-57. Germain DP, et al. J Med Genet. 2015;52:353-8. Schiffmann R, et al. JAMA. 2001;285:2743-9.

What did we learn from?

1. RCT

Endothelial findings may not apply to podocytes

Endothelial deposits in placebo-controlled phase II/III RCT

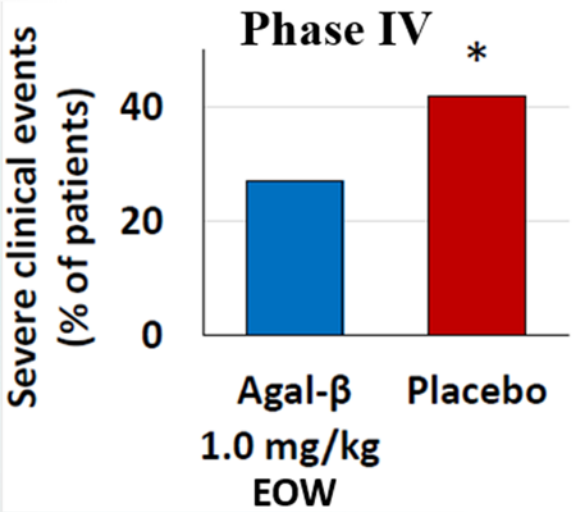


RCT, randomised controlled trial

Eng, Christine M et al. *N Eng J Med* 2001:9–16; Schiffmann, Raphael et al. *JAMA* 2001:2743–9; Ortiz et al. Med Clin Med Clin 2017:132–8

Agalsidase-beta 1mg/kg/EOW and Severe Clinical events in a Randomized Clinical Trial

Agalsidase-beta 1.0 mg/kg/2 Weeks SUBSTANTIALLY LOWERS THE RISK OF MAJOR CLINICAL EVENTS



*HR 0.47; p=0.06

treatment-related hazard ratio associated with agalsidase beta with adjustment for baseline proteinuria

- Multicenter, randomized, double-blind, placebo-controlled study (N=82)
- Risk reduction in the intent-to-treat population was 53% (P=0.06).
- In a secondary analysis, in protocol-adherent patients who were adjusted for baseline proteinuria, Fabrazyme treatment resulted in a 61% reduction in the risk of major clinical events (P=0.034).
  - Eight patients were excluded from the per-protocol population due to major protocol violations: 5 patients missed infusions, 1 patient did not meet the required clinical inclusion criteria, and 2 patients received wrong treatments.

Most treatment related adverse events were mild-moderate infusion associated reactions (55% agalsidase beta patients, 23% placebo pts)

Banikazemi M, Bultas J, Waldek S, et al; Fabry Disease Clinical Trial Study Group. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007;146(2):77-86

What did we learn about ERT and long-term kidney outcomes from RCTs?

Canadian
Fabry
Disease
Initiative

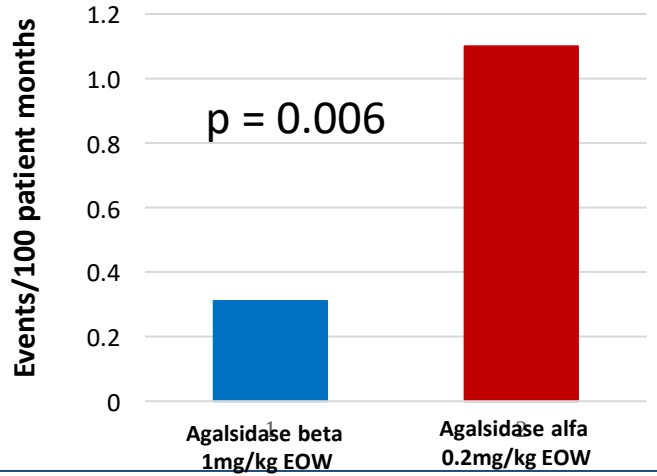
- Agalsidase **alfa 0.2**mg/kg EOW
  vs
  Agalsidase **beta 1**mg/kg EOW
- **RCT**
- Primary endpoints: cardiac, neurological, or renal events or death

RCT, randomized controlled trial.

CFDI: the Canadian Fabry Disease Initiative

10-year outcomes of an RCT of ERT[1]

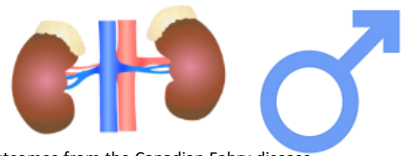
Events: (renal replacement therapy, doubling of serum creatinine, proteinuria > 3.5 g/day)



More renal events in males receiving agalsidase alfa than in males receiving agalsidase beta
(1.1 vs 0.31 events/100 patient months **IRR 0.24** p = 0.006)

Estimated sample size: **600**
Enrolled: **132** patients
n = 56 agalsidase beta 1mg/kg/EOW
n = 76 agalsidase alfa 0.2mg/kg/EOW
Median follow-up: 99 mos
(range 5–123)

- **Rates of cardiac or neurological events or death did not differ**
- **No difference in renal events, or in the rate of decline in eGFR in females**



Statistical test, Safety outcomes were not reported in this abstract

IRR, incidence rate ratio.

Sirrs SM, et al. Differential effects of agalsidase alfa and beta in Faby outcomes: 10 year outcomes from the Canadian Fabry disease initiative. J Inherit Metab Dis. 2018;41(Suppl 1):abstract P-373.
Image available from:
https://upload.wikimedia.org/wikipedia/commons/4/48/201405_kidney.png.

Is there a **biological plausibility** for the impact of ERT **dose** on renal function?

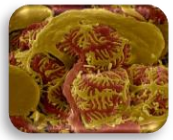
Yes!

- Impact of podocyte glycolipid deposits
- Impact on lyso-Gb3

Goker-Alpan O, et al. JIMD Rep. 2016;25:95-106
Skrunes R, et al. Clin J Am Soc Nephrol. 2017;12:1470-9.
.

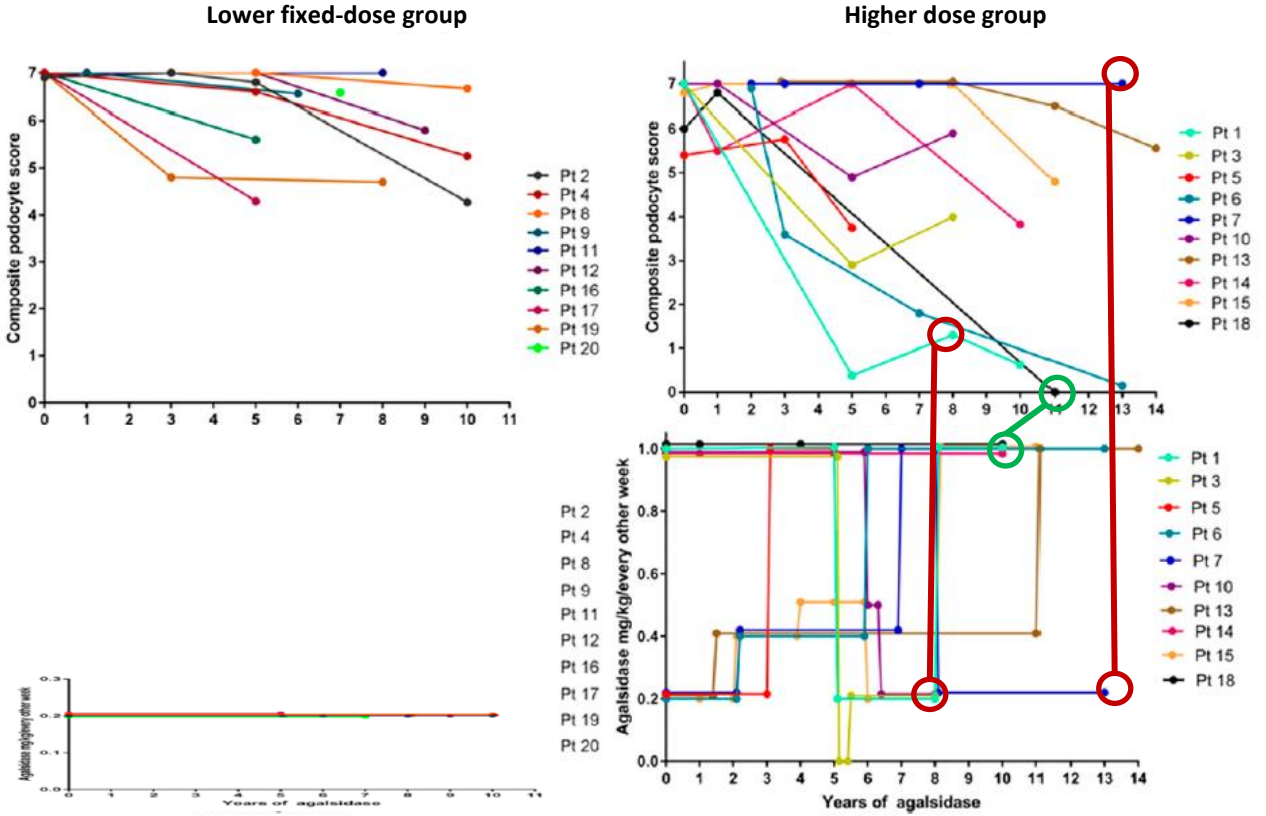
Observational: Long-term dose-dependent agalsidase effects on kidney histology in Fabry disease

- Reduction of **podocyte Gb3** correlated with **cumulative dose**



- Residual plasma **lyso-Gb3** correlated with **cumulative dose** in men

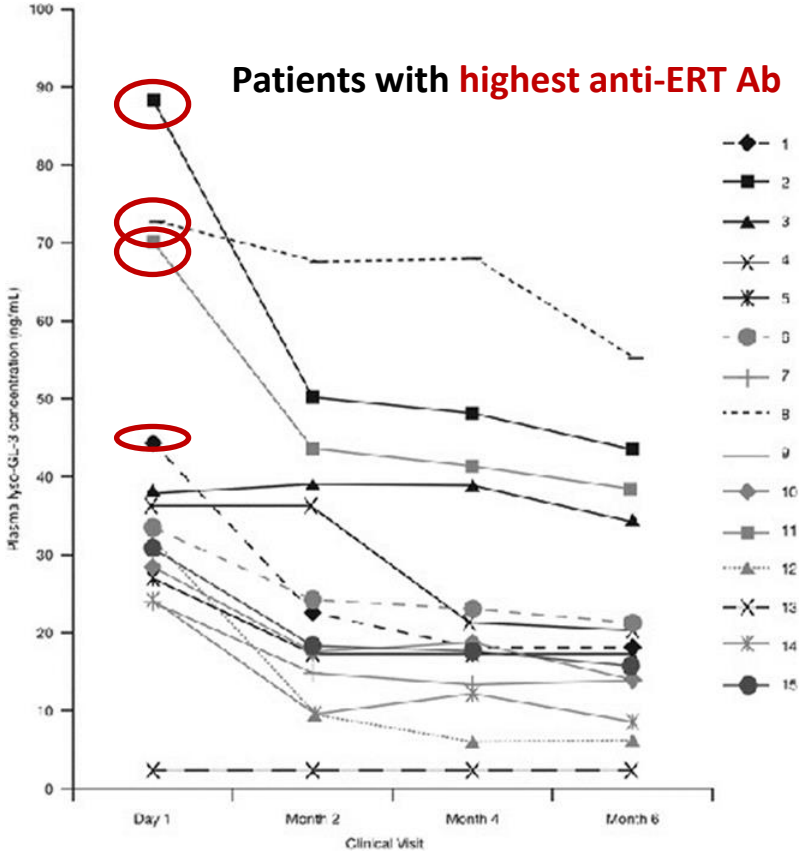
Endothelium cleared in all

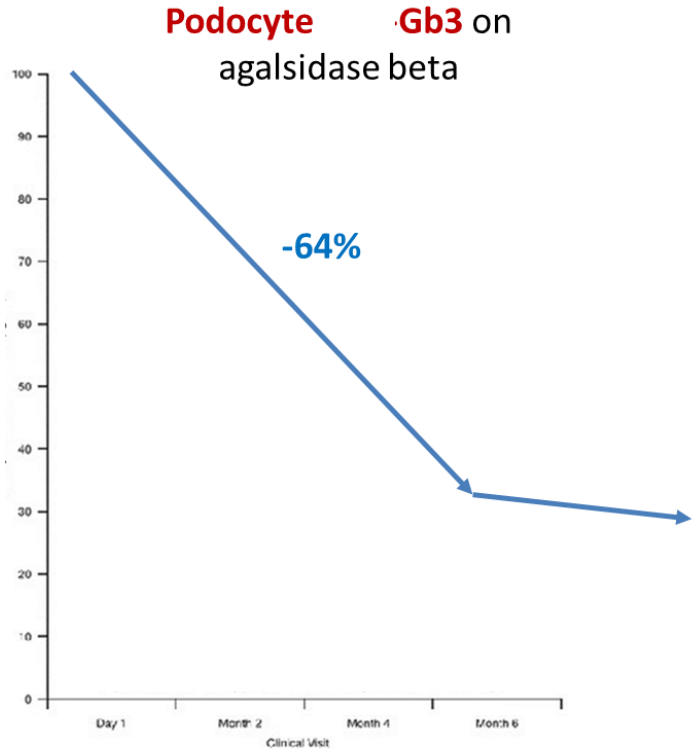


Gb3, globotriaosylceramide.

Skrunes R, et al. Clin J Am Soc Nephrol. 2017;12:1470-9.

Plasma lyso-Gb3 decreased when ERT switched from agalsidase alfa 0.2mg/kg EOW to agalsidase beta 1mg/kg EOW





Najafian et al. Molecular Genetics and Metabolism. Vol 132, Issue 2, Pages S13-S116 (February 2021)

Ab, antibody.

Goker-Alpan O, et al. JIMD Rep. 2016;25:95-106.

What did we learn from?

1. RCT

2. **Registry data**

ERT at 1mg/kg/2 weeks with agalsidase beta and incidence of severe clinical events*

Fabry registry data: 1044 patients

Median age at start ERT: 40 years = late!!

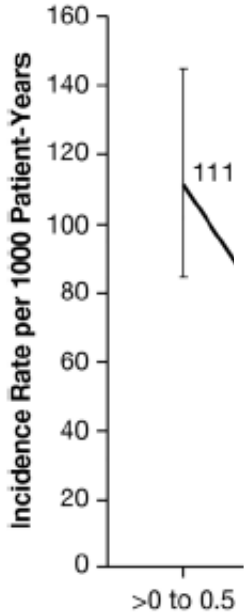
Late-onset variants
excluded from the analysis

* severe clinical events were defined as: death , renal, cardiac event or stroke.

Ortiz at al for the Fabry Registry, J Med Genet 2016; Jul;53(7):495-502

ERT (1 mg/kg/2 weeks agalsidase beta) and incidence of severe clinical events*

Fabry registry data: 1044 patients



Median age at start ERT: 40 years = late!!

Incidence rate within the first 6 months of ERT

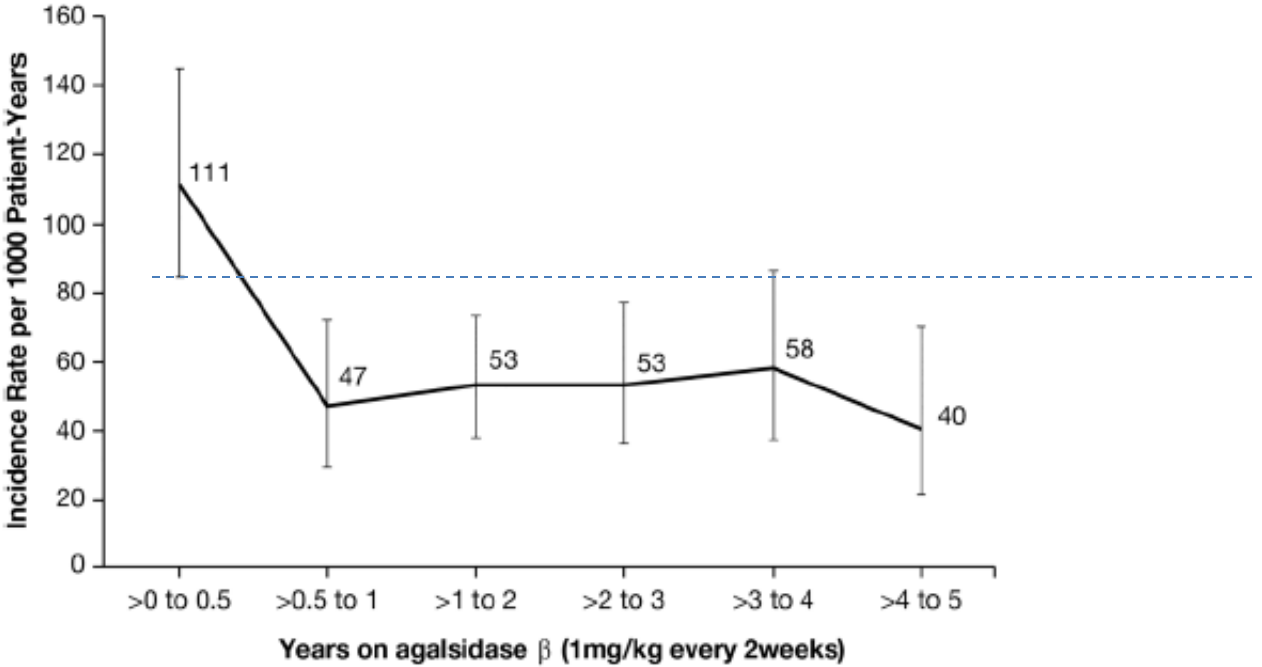
* severe clinical events were defined as: death , renal, cardiac event or stroke.

Ortiz at al for the Fabry Registry, J Med Genet 2016; Jul;53(7):495-502

ERT (1mg/kg/2 weeks agalsidase beta) was associated with a decreased incidence of severe clinical events* AFTER 6 mo

Fabry registry data: 1044 patients

Median age at start ERT: 40 years = late!!



* severe clinical events were defined as: death , renal, cardiac event or stroke.

Ortiz at al for the Fabry Registry, J Med Genet 2016; Jul;53(7):495-502

What did we learn from?

1. RCT

2. Registry data

3. **Meta-analyses**

CLINICAL KIDNEY JOURNAL

ckj

OXFORD

era edta
LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2020, 1–11

doi: 10.1093/ckj/sfaa065
Original article

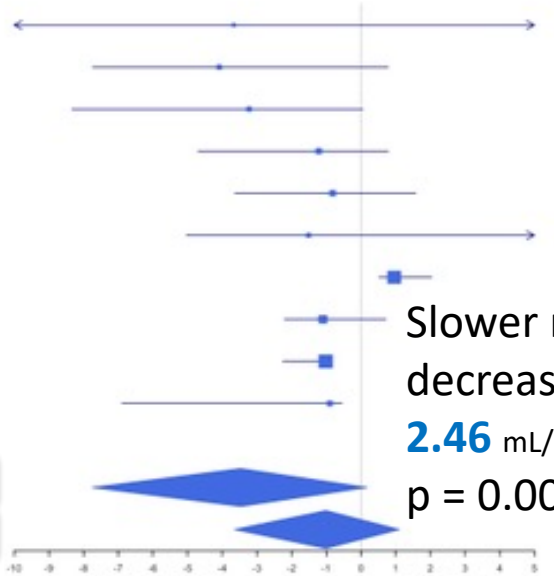
ORIGINAL ARTICLE

Agalsidase beta treatment slows estimated glomerular filtration rate loss in classic Fabry disease patients: results from an individual patient data meta-analysis

Alberto Ortiz[1], Steve Kanters[2], Alaa Hamed[3], Pronabesh DasMahapatra[3], Eugene Poggio[4], Manish Maski[5], Mario Aguiar[5], Elvira Ponce[5], Jeroen P. Jansen[6], Dieter Ayers[2], Rachel Goldgrub[2] and Robert J. Desnick[7]

Individual level meta-analysis:
agalsidase beta preserves renal function in Classic phenotype when compared to untreated patients

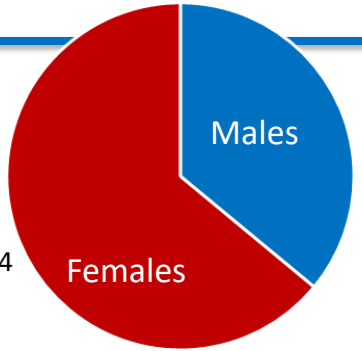
Study	Treatment	Sample size	Median Slope (IQR)
Phase III	Untreated	29	-3.67 (-20.44, 9.34)
Phase IV	Untreated	30	-4.09 (-7.74, 0.78)
Natural History Study	Untreated	123	-3.23 (-8.33, 0.05)
Phase III	Treated	57	-1.22 (-4.69, 0.78)
Phase IV	Treated	49	-0.82 (-3.64, 1.57)
Breunig 2006	Treated	17	-1.51 (-5.03, 6.61)
Politei 2014	Treated	6	0.96 (0.52, 2.03)
Kim 2016	Treated	15	-1.1 (-2.21, 0.71)
Pisani 2013	Treated	10	-1.02 (-2.25, -0.83)
Tahir 2007	Treated	6	-0.9 (-6.89, -0.55)
Overall untreated		**182**	**-3.4 (-7.74 0.17)**
Overall treated		**133**	**-1.01 (-3.64, 1.10)**



Slower median eGFR decrease:
2.46 mL/min/1.73 m^2/year
p = 0.0087

Forest plot comparing the adjusted median eGFR slopes in agalsidase beta-treated vs -untreated patients

Ortiz et al. Clin Kidney J 2020, doi: 10.1093/ckj/sfaa065

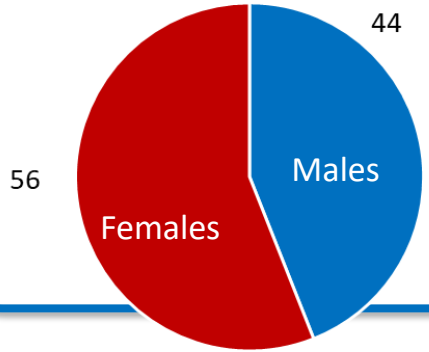


Migalastat

Phase 3 placebo-controlled
- n = 67
- Primary endpoint: kidney endothelial deposits
- Follow-up: 12 mo + extension

No published 5–10 year follow-up

No phase 4 with primary endpoint: events



Phase 3 ATTRACT
- n = 57
- Primary endpoint: GFR
- Comparator ERT
- Follow-up: 18 mo

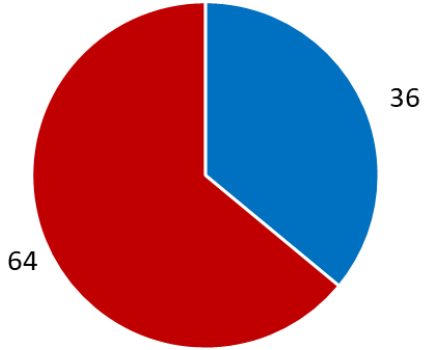
No long-term (up to 10 years) comparison with agalsidase beta

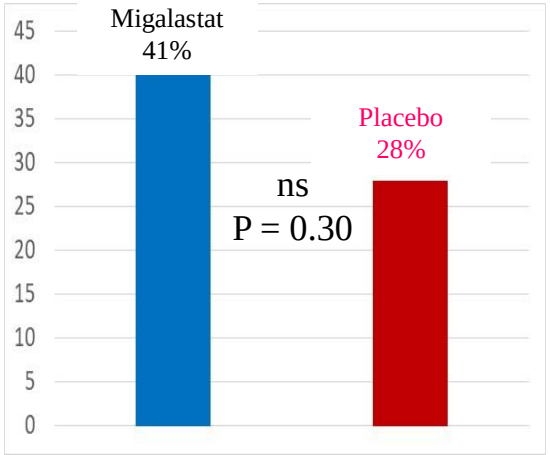
Germain DP, et al. N Engl J Med. 2016;375:545-55. Hughes DA, et al. J Med Genet. 2017;54:288-96.

The **difficulty** of doing **trials** with a large **female** population

Phase 3 AT1001-011: The FACETS Trial

- Patients randomised to receive either oral migalastat or matching placebo.
- **Primary endpoint: % of patients** who had a response (≥50% reduction in the number of Gb3 **inclusions** per kidney interstitial **capillary**) at 6 months





Key Result:

- The **primary** end-point ITT analysis, involving patients with mutant α-galactosidase forms that were **suitable or not suitable** for migalastat therapy, did not show a significant treatment effect
- n=32 per group=64

Germain et al. N Engl J Med 2016;375:545-55
*http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004059/WC500208434.pdf

Phase 3 AT1001-011: The FACETS Trial

45 patients with suitable mutant α-galactosidase
post hoc analysis (6 months) and pre-specified (12 months)

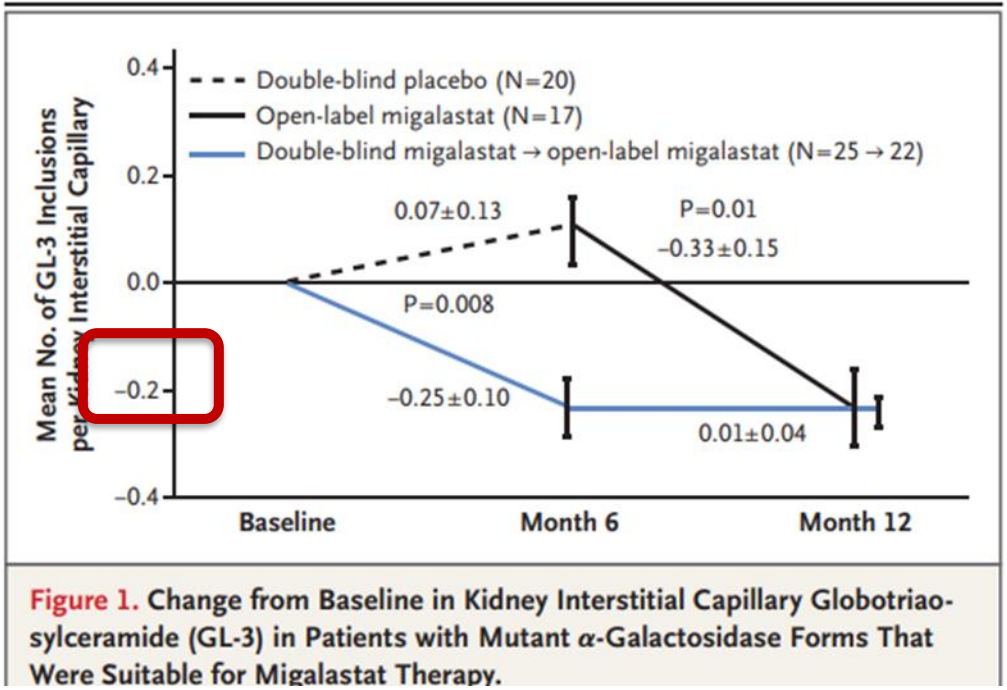
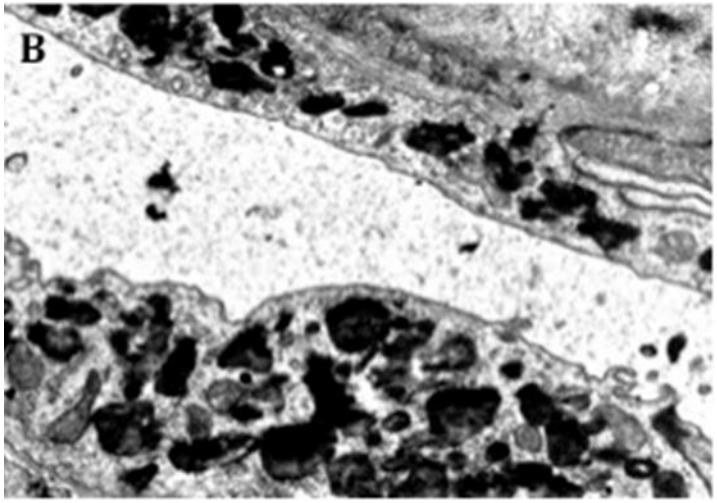


Figure 1. Change from Baseline in Kidney Interstitial Capillary Globotriaosylceramide (GL-3) in Patients with Mutant α-Galactosidase Forms That Were Suitable for Migalastat Therapy.



Germain et al. N Engl J Med 2016;375:545-55

Desnick RJ. https://www.dermatologyadvisor.com/home/decision-support-in-medicine/dermatology/fabry-disease-anderson-fabry-disease-alpha-galactosidase-a-deficiency-angiokeratoma-corporis-diffusum-ceramide-trihexosidase-deficiency-fabrys-disease-gla-deficiency-hereditary-dystopic-l/

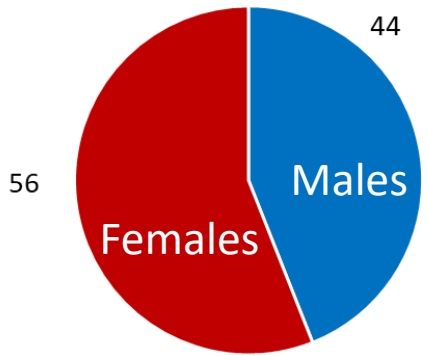
Phase 3 AT1001-012: the ATTRACT trial

Active-controlled, 18 month open-label **randomized-stop** study comparing migalastat and ERT, in which patients were switched from ERT to migalastat without a period of being untreated, followed by a 12-month open-label extension with migalastat

- ERT > 12 months before baseline
- GFR ≥ 30 mL/min/1.73 m^2

- **Migalastat** n = 36
  - 32 amenable per GLP assay
    - 24 previously on agalsidase alfa 0.2mg/kg EOW
    - 8 previously on agalsidase beta 1mg/kg EOW
- **ERT** n = 21 (18 amenable per GLP assay)

- **Primary co-endpoints (annualized change)**
  - **Change in eGFR$_{CKD\text{-}EPI}$ at 18 months**
  - **Change in mGFR$_{iohexol}$ at 18 months**



49 years old

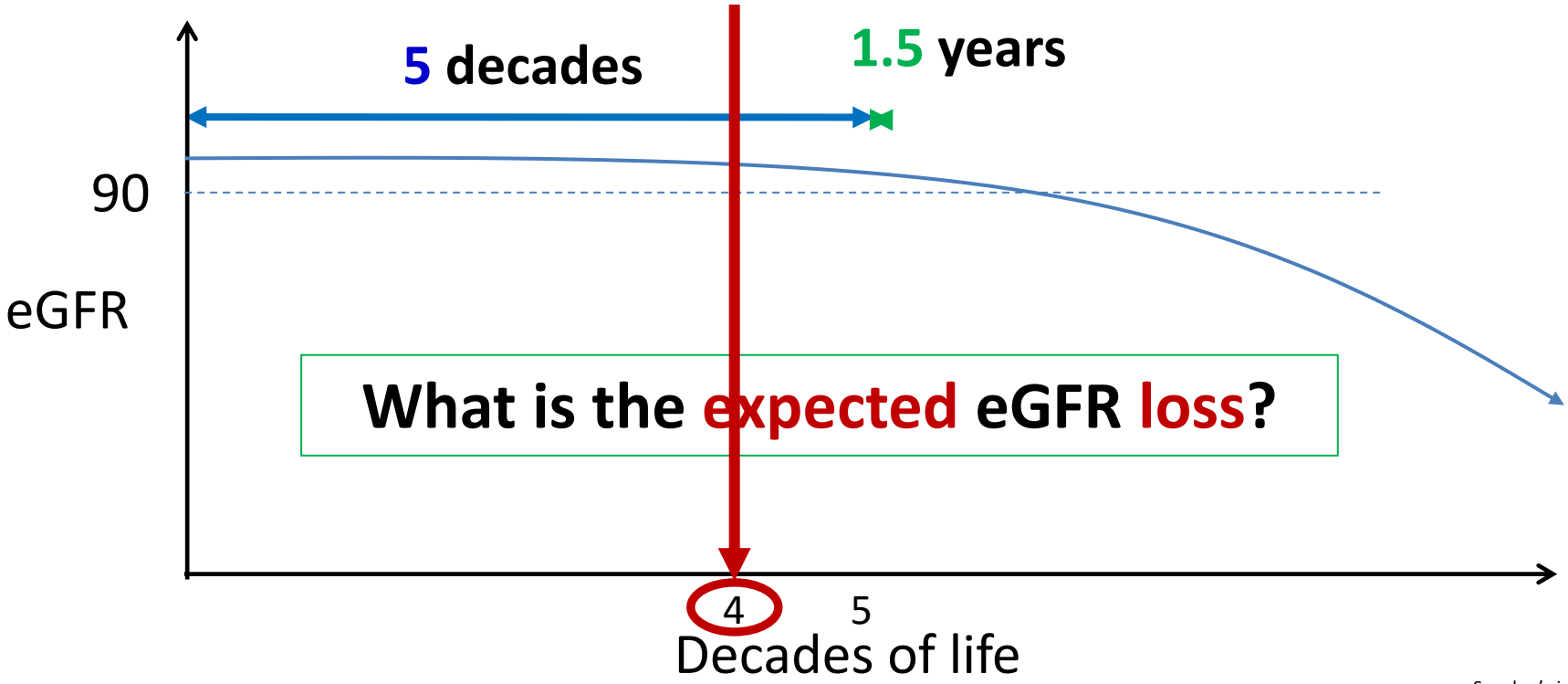
Baseline characteristics of the safety population

- eGFR **92** mL/min/1.73 m^2
- Proteinuria 0.3 g/day
- 65% agalsidase alfa

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; mGFR, measured glomerular filtration rate.

Galafold SmPC. Available from: www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/004059/WC500208434.pdf.
Hughes DA, et al. J Med Genet. 2017;54:288-96.

40 years old: mean age at start of dialysis in classic Fabry males and females



Speaker's image and data.

Phase 3 ATTRACT (AT1001-012)
Efficacy – renal function at 18 months

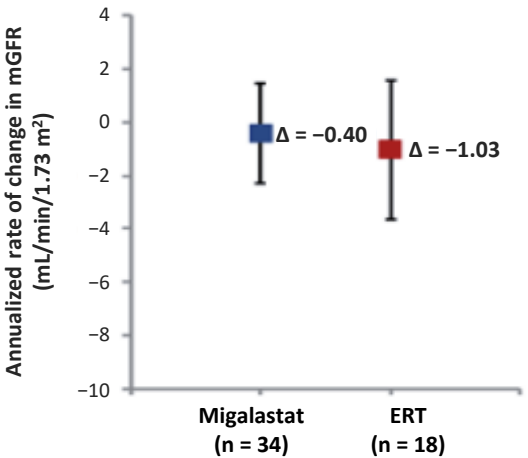
Pre-specified criteria for comparability between migalastat and ERT

Difference between the means for annualized change in GFR for migalastat and ERT within 2.2 mL/min/1.73 m^2/year

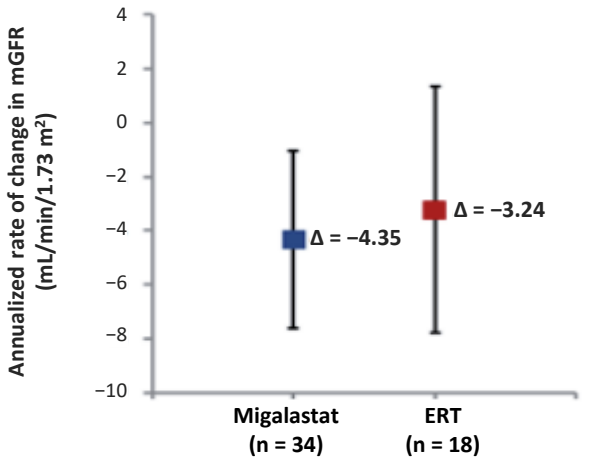
and

> 50% overlap of the 95% CI between migalastat and ERT

Primary endpoint at 18 months



eGFR using CKD-EPI formula



eGFR measured by iohexol clearance

- **Co-primary endpoints showing comparability of kidney function in patients switched from ERT to migalastat at 18 months were met**

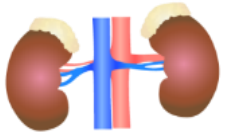
CI, confidence interval.

Hughes DA, et al. J Med Genet. 2017;54:288-96.

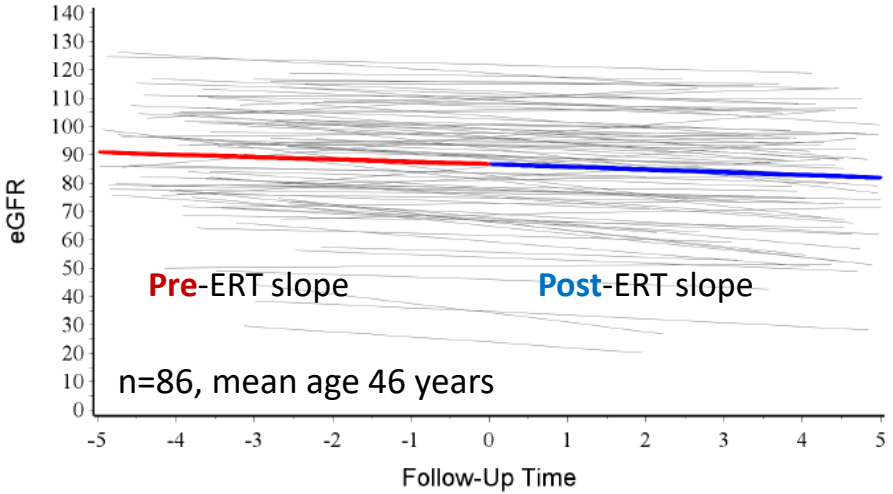
…most of Fabry women do not lose renal function faster than expected for age

Impact of Agalsidase beta 1.0 mg/kg EOW on kidney and heart in adult females (late-onset excluded) in Fabry Registry

Agalsidase beta 1 mg/kg EOW ≥2 years, having ≥2 pre- and ≥2 post -records within -5/+5 years of ERT initiation, excluding those with baseline ESRD Fabry-database.org: 53.5% classic or others (unclassified or unreported).



Overall slope **–1.0** ml/min/1.73m^2/year
Slope difference 0.13, P= 0.80



Wanner C et al Mol Gent Metab 2019;126(2):S17–S156 doi:10.1016/j.ymgme.2018.12.388

The need for **real world** evidence related to **different GLA variants**


Fabry
Not
Fabry

TABLE 3 Characteristics of common controversial *GLA* variants according to genetic databases and in silico prediction softwares

	c.427G>A; p.(Ala143Thr) / p.(A143T) / Thr143	c.937G>T; p.(Asp313Tyr) / p.(D313Y) / Tyr313	c.196G>C; p.(Glu66Gln) / p.(E66Q) / Gln66	c.352C>T; p.(Arg118Cys) / p.(R118C) / Cys118	c.376A>G; p.(Ser126Gly) / p.(S126G) / Gly126
GnomAD v2.1.1	**A143T**	**D313Y**	**E66Q**	**R118C**	**S126G**
AF (%) in exomes, genomes (total)	0.055, 0.018 (0.051)	0.30, 0.31 (0.30)	0.012, 0.0045 (0.011)	0.022, 0.032 (0.023)	0.033, 0.063 (0.036)
Highest AF (%) by population	0.095 in European (non-Finnish)	0.69 in Ashkenazi Jewish 0.45 in European (non-Finnish)	0.15 in East Asian	0.044 in European (non-Finnish)	0.074 in European (non-Finnish)
Pathogenicity according to FD-specific databases					
dbFGP	Benign	Benign	Benign	Benign	Likely benign
The Japanese Fabry Database	LO [5]; classic [4]; B [3]; VUS [1]; np [8]	Classic [5]; B [2]; LO [1]; np [9]	B [5]; classic [5]; LO [3]; np [3]	LO [2]; np [5]	LO [1]; np [6]
Pathogenicity according to general databases					
ClinVar	VUS [10]; LP [4]; P [2]	LB [13]; VUS [3]; B [2]	VUS [4]; LB [2]	VUS [12]; LP [2]; LB [1]	LB [6]; VUS [4]; B [1]
LOVD	LB [2]; VUS [1]	LB [3]; B [2]; VUS [1]	np	VUS [3]; P [1]	2 LB [2]; VUS [1]
OMIM	FD	VUS (recently reclassified)	Functional polymorphism and not disease causing	not provided	not provided
ACMG classification according to VarSome (date of query)	**LP** (2019-12-05) **VUS** because highest ethnic frequency = 0.10% (2020/01/20) **P** because a user has reported this variant is classified LP in one article (Spada et al.[5]) and that is confirmed by a functional study (2020-08-03)	**VUS** (2019-12-05) **B** because highest ethnic frequency = 0.69% (2020-01-20) **LP** because alternative variant (Asp313Asn) is classified P by UniProt Variants (and confirmed using ACMG) (2020-08-04)	**VUS** (2019-12-05) **B** because highest ethnic frequency = 0.15% (2020-01-20) **LP** because highest ethnic frequency no longer takes into account again (2020-08-04)	**LB** (2019-12-05) **B** (2020-01-20) **LB** (2020-08-04)	**VUS** (2019-12-05) **B** because highest ethnic frequency = 0.074% (2020-01-20) **VUS** because highest ethnic frequency no longer taken into account (2020-08-04)
Polyphen-2	Probably damaging (1)	Probably damaging (0.996)	Probably damaging (0.996)	Probably damaging (0.993)	Benign (0.043)
Provean	Deleterious (−3.119)	Deleterious (−3.183)	Deleterious (−2.754)	Deleterious (−4.667)	Deleterious (−2.823)
SIFT	Damaging (0.004)	Damaging (0.001)	Damaging (0.002)	Damaging (0.001)	Tolerated (0.060)
Mutation taster	Disease causing	Polymorphism	Disease causing	Polymorphism	Disease causing

Note: Last accessed 2020-08-04. [ ]: The number of times referenced.

Abbreviations: AF, allele frequency; B, benign; dbFGP, International Fabry Disease Genotype–Phenotype Database; FD, Fabry disease; gnomAD, Genome Aggregation Database; LB, likely benign; LOVD, Leiden Open (source) Variation Database; LP, likely pathogenic; np, not provided; P, pathogenic; VUS, variant of unknown significance.

In the case of FD, where a "pharmacogenetic" specific treatment exists, it should be noted that "**amenability**" of a given GLA variant **does not necessarily imply pathogenicity**, since the available amenability table includes proven non-pathogenic variants such as p.(Arg118Cys), p.(Ala143Thr) and p.(Asp313Tyr)

R118C **A143T** **D313Y**

(www.galafoldamenabilitytable.com,last accessed on November 24th, 2021).

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy
doi:10.1093/ehjcvp/pvab025

ORIGINAL ARTICLE

Treatment of Fabry Disease management with migalastat—outcome from a prospective 24 months observational multicenter study (FAMOUS)

Malte Lenders [1], Peter Nordbeck [2], Christine Kurschat[3], Maria Eveslage[4], Nesrin Karabul[5], Jessica Kaufeld[6], Julia B. Hennermann[7], Monica Patten[8], Markus Cybulla[9], Jonas Müntze[2], Nurcan Üçeyler[10], Dan Liu[2], Anibh M. Das[11], Claudia Sommer[10], Christian Pogoda[12], Stefanie Reiermann[1], Thomas Duning[13], Jens Gaedeke[14], Katharina von Cossel[15], Daniela Blaschke[16], Stefan-Martin Brand[17], W. Alexander Mann[5], Christoph Kampmann[7], Nicole Muschol[15], Sima Canaan-Kühl[14], and Eva Brand[1]*

Germain DP, Levade T, Hachulla E, et a... 30-402.

Lenders M, Nordbeck P, Kurschat C, et al. Treatment et al. *Eur Heart J Cardiovasc Pharmacother*. 2021;pvab025. doi:10.1093/ehjcvp/pvab025

FAMOUS

Supplemental Table 1: Overview of included *α-galactosidase A* mutations.

sex	mutation (n)	sum (%)
females	p.N34S (1), p.A37T (1), p.R118C (2), p.S126G (5), p.A135V (3), p.W162G (1), p.K213M (1), p.N215S (4), p.G325S (2), p.M267T (1), p. G271D (1), p.L294S (2), p.R301Q (1), p.N320I (3)	28 (47.5)
males	p.S126G (1), p.N139S (1), p.W162G (1), p.P205T (1), p.N215S (13), p.K240N (1), p.I242V (1), p.P259R (1), p.M267T (2), p.T282I (1), p.M290L (1), p.L294S (2), p.M296V (1), p.N320I (1), p.G325S (2), p.T385A (1)	31 (52.5)

Therapeutics

OPEN ACCESS

ORIGINAL ARTICLE

Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study

Derralynn A Hughes,[1] Kathleen Nicholls,[2] Suma P Shankar,[3] Gere Sunder-Plassmann,[4] David Koeller,[5] Khan Nedd,[6] Gerard Vockley,[7] Takashi Hamazaki,[6,8] Robin Lachmann,[9] Toya Ohashi,[10] Iacopo Olivotto,[11] Norio Sakai,[12] Patrick Deegan,[13] David Dimmock,[14] François Eyskens,[15] Dominique P Germain,[16] Ozlem Goker-Alpan,[17] Eric Hachulla,[18] Ana Jovanovic,[19] Charles M Lourenco,[20] Ichiei Narita,[21] Mark Thomas,[22] William R Wilcox,[23] Daniel G Bichet,[24] Raphael Schiffmann,[25] Elizabeth Ludington,[26] Christopher Viereck,[27] John Kirk,[27] Julie Yu,[27] Franklin Johnson,[27] Pol Boudes,[28] Elfrida R Benjamin,[27] David J Lockhart,[29] Carrolee Barlow,[30] Nina Skuban,[27] Jeffrey P Castelli,[27] Jay Barth,[27] Ulla Feldt-Rasmussen[31]

Table 2 Amenable mutations of enrolled and treated patients and the corresponding clinical phenotype **ATTRACT**

Amino acid change (number of patients with the mutation)	Literature phenotype	Amino acid change	Literature phenotype
p.M96I	Non-classic	p.G260A	Classic
p.L32P (n=3)	Unknown	p.Q279E	Non-classic
p.G35R	Non-classic	p.M284T	Classic
p.D55V/Q57L	Unknown*	p.M296I	Non-classic
p.G85D (n=4)	Unknown*	p.R301P (n=3)	Classic
p.A97V	Non-classic	p.R301Q	Both
p.R112G	Unknown*	p.G328A	Classic
p.R112H	Non-classic	p.Q312R	Non-classic
p.A143T (n=3)	Non-classic	p.D322E (n=4)	Classic
p.A156T (n=6)	Classic	p.R356Q	Non-classic
p.P205T	Classic	p.R363H	Both
p.N215S (n=10)	Non-classic	p.L403S	Classic
p.Y216C	Classic	p.P409T	Unknown*
p.I253S	Unknown*		

Number of patients with each mutation is 1 unless indicated otherwise.
To date, 269 *GLA* mutations have been categorised as amenable to migalastat based on the Good Laboratory Practice human embryonic kidney assay. The supportive references for the literature phenotypes are provided in the online supplementary table S2

Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study [published correction appears in J Med Genet. 2018 Apr 16;:]. *J Med Genet*. 2017;54(4):288-296.

Lenders M, Nordbeck P, Kurschat C, et al. Treatment et al. *Eur Heart J Cardiovasc Pharmacother*. 2021;pvab025. doi:10.1093/ehjcvp/pvab025

Supplemental Table 4: Outcomes for males (n=28).

Measure	n	baseline			p-value	n	24 month follow-up	p-value
AGAL activity, µmol/L/h	11	2.8 [0.6 to 28.0]			0.8438	18	6.9 [2.8 to 100.0]	0.8125
BMI, kg/m²	26	26 [22 to 37]			0.0539	25	27 [22 to 35]	0.3417
BP systolic, mmHg	27	130 [106 to 175]			0.8475	24	135 [100 to 156]	0.1239
BP diastolic, mmHg	27	80 [50 to 100]			0.1730	24	80 [60 to 100]	0.6870
BP systolic above target, n	27	8 (29.6)			0.7237	24	14 (58.3)	**0.0433**
plasma lyso-Gb3, ng/ml	25	8.1 [0.9 to 59.8]			0.5184	27	4.8 [0.7 to 93.4]	0.5952
plasma lyso-Gb3 within the reference, n	25	4 (16.0)			0.9999	27	8 (26.6)	0.3293
creatinine, mg/dl	27	0.90 [0.64 to 1.25]	28	0.95 [0.68 to 1.27]	**0.0012**	28	0.98 [0.65 to 1.53]	**0.0028**
$eGFR_{creat}$, ml/min/1.73 m²	27	99.8±22.6	28	96.6±23.0	**0.0011**	28	92.4±24.0	**0.0028**
$eGFR_{cystC}$, ml/min/1.73 m²	24	89.6±22.2	26	86.7±23.2	**0.0005**	26	81.1±23.9	**0.0007**
$eGFR_{creat-cystC}$, ml/min/1.73 m²	24	93.6±21.5	26	91.3±22.1	**0.0003**	26	84.9±22.7	**0.0004**
ACR, mg/g	20	54 [6 to 3092]	21	62 [3 to 1756]	0.5619	24	89 [3 to 1924]	0.3955
Albuminuria, n	20	13 (65.0)	21	13 (61.9)	0.9999	24	15 (62.5)	0.9999
LVMi, g/m²	24	129.8±55.4	24	118.0±46.2	**0.0210**	24	119.9±44.2	0.0699
IVSd, mm	24	13.8±4.5	26	13.1±3.8	0.0907	21	12.9±3.1	0.5485
NT-ProBNP, ng/l	22	278 [30 to 2321]	25	176 [6 to 2121]	0.4374	27	114 [21 to 7430]	0.8878
FD-associated pain, n	28	14 (50.0)	27	14 (51.8)	0.9999	28	17 (60.7)	0.5913
MSSI total score	27	20.6±9.1	27	19.4±9.7	0.1685	27	19.9±10.0	0.4540
MSSI general score	27	3.5±2.3	27	2.6±1.4	**0.0035**	26	3.3±1.8	0.5126
MSSI cardiovascular score	27	10.7±6.8	27	9.8±7.4	0.0556	27	10.0±7.0	0.1783
MSSI neurological score	27	3.6±3.9	26	4.4±3.8	0.2753	27	4.1±3.4	0.9999
MSSI renal score	27	2.4±3.2	27	3.1±3.5	0.0571	27	2.6±2.9	0.7873
DS3 total score	16	19.3±8.0	17	17.8±9.0	0.6632	19	20.7±14.3	0.6399
DS3 PNS domain	26	1.3±1.2	24	1.0±0.9	**0.0434**	26	1.1±1.1	0.3695
DS3 CNS domain	22	1.1±2.1	24	0.7±1.4	0.1074	27	0.5±0.9	0.1819
DS3 cardiac domain	27	2.6±2.2	28	2.7±2.5	0.9999	28	2.9±2.5	0.6302
DS3 renal domain	21	1.3±1.3	21	1.8±1.7	0.3146	22	2.4±2.3	0.0731
DS3 patient domain	23	2.2±0.9	21	1.9±0.9	**0.0020**	21	1.9±1.0	**0.0419**

Values are given as median [range] or mean±SD for continuous data or n (%) for categorical data. Albuminuria is defined as an albumin-creatinine-ratio ≥30 mg/g. Target systolic BP for adult <65 years: 120 to <130 mmHg and age ≥65 years: 130 to <140 mmHg. Reference values for normal α-Gal A activity are >32 nmol/mg or >15.3 µmol/l/h. ACR: albumin-creatinine-ratio, AGAL: alpha-galactosidase A, BMI: body mass index, BP: blood pressure, DS3: Disease Severity Scoring System, eGFR: estimated glomerular filtration rate, FD: Fabry disease, LVH: left ventricular hypertrophy (>11.5 mm septum thickness), LVMi: left ventricular mass index (reference for males 49-115 g/m²), lyso-Gb_3: globotriaosylsphingosine, MSSI: Mainz Severity Score Index, NT-ProBNP: N-terminal pro-B-type natriuretic peptide.

Reference values for **normal α-Gal A** **>15.3** µmol/l/h

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Supplemental Table 3: Outcomes for females (n=26).

Measure	n	baseline	n	12 month follow-up	p-value	n	24 month follow-up	p-value
AGAL activity, µmol/L/h	10	20.8 [6.9 to 192.0]	16	27.0 [2.8 to 59.4]	0.9999	18	21.8 [2.8 to 37.0]	0.4609
BMI, kg/m²	26	26 [20 to 51]	26	26 [21 to 52]	0.3168	26	26 [19 to 48]	0.8921
BP systolic, mmHg	26	126 [103 to 160]	24	124 [100 to 170]	0.9731	26	125 [105 to 154]	0.7604
BP diastolic, mmHg	26	76 [64 to 95]	24	77 [65 to 92]	0.7349	26	80 [58 to 90]	0.8350
BP systolic above target, n	26	8 (30.8)	24	6 (25.0)	0.9999	26	12 (46.2)	0.3428
plasma lyso-Gb_3, ng/ml	23	2.5 [0.7 to 21.7]	22	2.3 [0.8 to 15.2]	0.4590	26	2.7 [0.9 to 16.2]	0.3753
plasma lyso-Gb3 within the reference, n	23	10 (43.5)	22	10 (45.4)	0.4034	26	10 (38.5)	0.7767
creatinine, mg/dl	25	0.70 [0.48 to 0.90]	23	0.73 [0.50 to 1.08]	**0.0075**	23	0.77 [0.49 to 1.09]	0.0950
$eGFR_{creat}$, ml/min/1.73 m²	25	98.6±15.2	23	92.9±19.4	**0.0059**	23	90.4±14.7	**0.0317**
$eGFR_{cystC}$, ml/min/1.73 m²	21	91.0±20.0	24	86.8±24.4	0.1464	25	85.8±22.7	**0.0017**
$eGFR_{creat-cystC}$, ml/min/1.73 m²	21	95.3±17.9	22	87.4±20.8	**0.0261**	23	85.0±15.2	**0.0007**
ACR, mg/g	16	36 [6 to 442]	15	26 [4 to 222]	0.7646	16	19 [5 to 229]	0.3013
Albuminuria, n	16	10 (62.5)	15	6 (40.0)	0.2890	16	7 (43.7)	0.4795
LVMi, g/m²	21	86.2±18.3	21	77.4±19.7	**0.0042**	21	81.6±21.3	0.0554
IVSd, mm	25	10.3±2.2	24	10.1±1.8	0.0574	22	10.2±1.9	0.2162
NT-ProBNP, ng/l	20	121 [15 to 937]	21	123 [21 to 1040]	0.1419	22	127 [43 to 1836]	**0.0159**
FD-associated pain, n	26	20 (76.9)	26	20 (76.9)	0.9999	26	20 (76.9)	0.9999
MSSI total score	26	14.9±8.3	26	17.1±9.0	**0.0282**	26	16.3±8.7	0.2701
MSSI general score	26	3.7±2.2	26	4.0±2.6	0.2122	26	3.5±2.3	0.6210
MSSI cardiovascular score	26	3.6±3.9	26	4.4±3.8	**0.0453**	26	5.1±4.4	**0.0155**
MSSI neurological score	26	6.4±3.8	26	6.6±3.9	0.4963	26	6.2±3.2	0.7541
MSSI renal score	26	1.2±2.2	26	2.0±2.8	0.0961	26	1.4±2.5	0.7876
DS3 total score	15	15.9±7.6	12	17.4±11.6	0.3079	14	16.6±9.1	0.6455
DS3 PNS domain	25	1.7±1.5	25	1.7±1.5	0.9999	25	1.8±1.4	0.9516
DS3 CNS domain	23	1.2±1.4	24	0.9±1.3	0.4254	24	0.9±1.3	0.3096
DS3 cardiac domain	26	1.2±1.6	25	1.1±1.6	0.9253	24	1.3±1.7	0.6321
DS3 renal domain	16	1.1±1.2	14	1.8±1.9	**0.0392**	21	1.7±1.7	0.1630
DS3 patient domain	23	1.9±1.0	21	1.8±1.0	0.6663	16	1.5±1.0	0.4973

Values are given as median [range] or mean±SD for continuous data or n (%) for categorical data. Albuminuria is defined as an albumin-creatinine-ratio ≥30 mg/g. Target systolic BP for adult <65 years: 120 to <130 mmHg and age ≥65 years: 130 to <140 mmHg. Reference values for normal α-Gal A activity are >32 nmol/mg or >15.3 µmol/l/h. ACR: albumin-creatinine-ratio, AGAL: alpha-galactosidase A, BMI: body mass index, BP: blood pressure, DS3: Disease Severity Scoring System, eGFR: estimated glomerular filtration rate, FD: Fabry disease, LVH: left ventricular hypertrophy (>11.5 mm

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Wrapping up

Amsterdam UMC
Universitair Medische Centra

Sphinx
Amsterdam
Lysosome Center

Protocol

Diagnosis, evaluation and treatment of Fabry disease in the Netherlands

Version 6, April 2020

Updated by:
M. Langeveld, C.E. Hollak, S. Klein van Loon, S. van der Veen, M. el Sayed, E. Eskes

https://www.medischcontact.nl/opinie/blogs-columns/bloggers-columnisten/bloggercolumnist/carla-hollak.htm

https://www.amc.nl/web/research-75/spinx/fabry-disease.htm

Initiation of treatment with agalsidase alfa or beta can be considered when treatment criteria are met, which have been published in an international guideline for the initiation and cessation of enzyme replacement therapy in Fabry disease[13]

Choice of drug is up to the treating physician and the patient.
Given a

- more robust reduction of the biomarker plasma lysoGb3 and a
- potential better effect on cardiac hypertrophy and complication rate in agalsidase-beta versus agalsidase-alfa treated patients[14,15],

in most patients agalsidase-beta will be prescribed.

In **individual** cases agalsidase-alfa may be preferred, given the shorter infusion time and a lower rate of infusion related reactions and formation of anti-drug antibodies (which may be dose related). [14,16,17]

Chaperone therapy (Migalastat, Galafold®) is EMA approved, but the Dutch ministry of health has decided **against reimbursement** given the **lack of robust evidence** on its therapeutic effectiveness[19]

Take-home message

- Observational studies suggest an impact of ERT **dose** on **podocyte** clearance
- It takes **years** to show efficacy in **renal** endpoints
  - Best marker to date is **lyso-Gb3** level: less invasive than **repeat** renal **biopsy**
- CFDI RCT supports the efficacy of **Fabrazyme** 1mg/kg EOW to decrease the number of **kidney** events in **males**
- This observation is in line with results from the phase 4, placebo-controlled, **agalsidase beta (Fabrazyme)** trial that had **severe** events as primary endpoint

ESRD, end-stage renal disease.