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Pre-clinical proof of concept of an AAV5-GLA gene therapy for Fabry disease resulting in cross-correction in GLA KO mice and non-human primates in target organs

Abstract number OR19

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uniQure Forward Looking Statement and Disclosure

Forward Looking Statement

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as “anticipate,” “believe,” “could,” “estimate,” “expect,” “goal,” “intend,” “look forward to,” “may,” “plan,” “potential,” “predict,” “project,” “should,” "will,” “would” and similar expressions. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. These forward-looking statements include, but are not limited to, statements regarding the development of our gene therapies, the success of our collaborations, and the risk of cessation, delay or lack of success of any of our ongoing or planned clinical studies and/or development of our product candidates. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, risks associated with the COVID-19 pandemic, collaboration arrangements, our and our collaborators’ clinical development activities, regulatory oversight, development of product candidates, product commercialization and intellectual property claims, as well as the risks, uncertainties and other factors described under the heading "Risk Factors" in uniQure’s Annual Report on Form 10-K filed on March 1, 2021 and Quarterly Report on Form 10-Q filed July 26, 2021. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future.

Disclosure

Employee of uniQure biopharma BV

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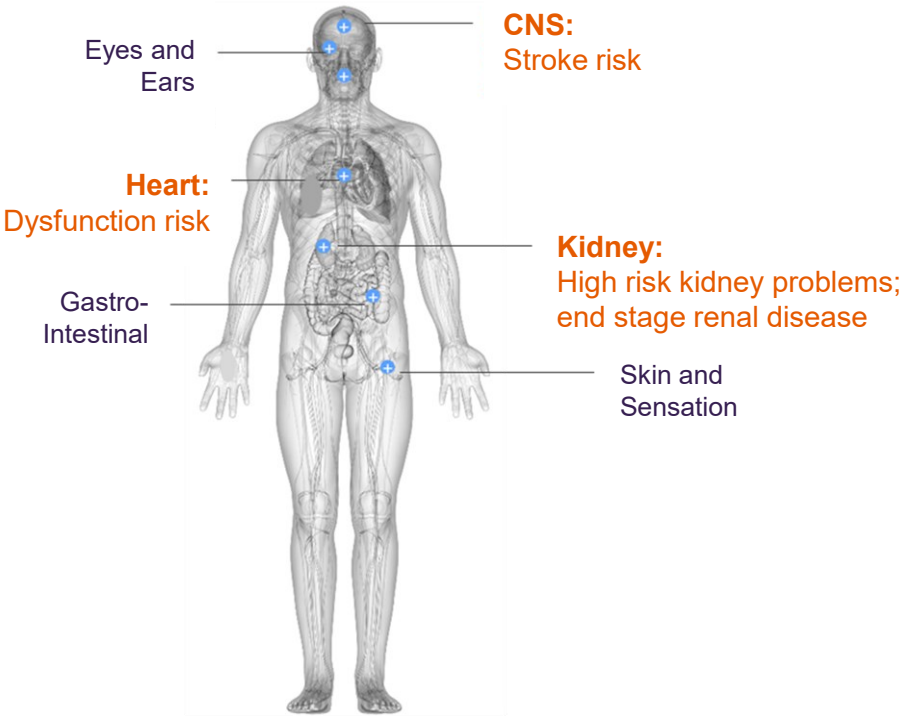
Fabry disease: a lysosomal storage disease

- X-linked genetic disorder
- Deficiency of α-galactosidase A (GLA)
- Prevalence: 1:3,700 – 80,000 live births *
- Population: ~15,000 in US and Europe

Symptoms:

- Fatigue and hearing loss
- Neuropathic pain
- Angiokeratomas
- Corneal opacity
- Cardiac disease
- Renal failure
- Stroke risk



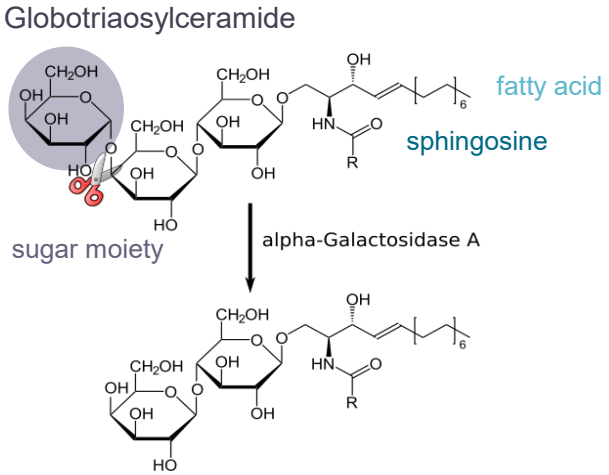
* Spada, et al, Am. J. Hum. Gent. 2006:79, 31-40

Fabry disease: unmet need with current enzyme replacement therapy (ERT)

- α-galactosidase A (GLA) degrades:
  - Globotriaosylceramide (Gb3)
  - Lyso-Gb3
- Systemic accumulation of substrate in lysosomes of endothelial cells in the kidney, heart and brain

The standard of care is bi-weekly enzyme replacement therapy (ERT)

- ERT has limited tissue penetration and biodistribution
- Results in poor substrate clearance in the heart and kidney
- Disease progresses despite ERT



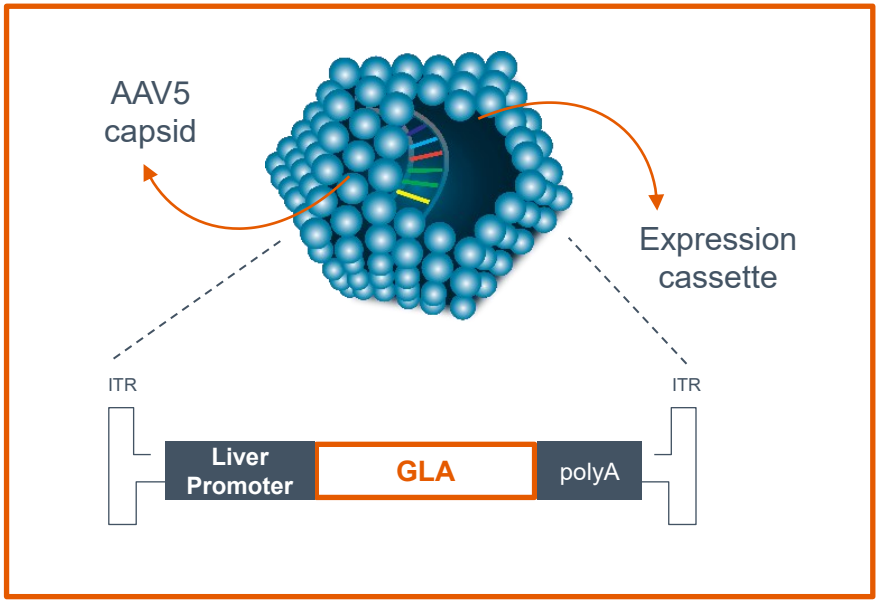
Desnick and Schuchman Annu. Rev. Genomics Hum. Gent. 2012; 13:307-35

AMT-191: a one-time treatment for Fabry Disease

AMT-191 AAV5-GLA

AAV5 encoding an α-galactosidase A (GLA) transgene

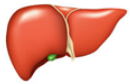
- **AAV5-vector**
  - Low immunogenicity *
  - Excellent liver distribution
- **Liver specific promoter**
  - Potent and specific proprietary promoter



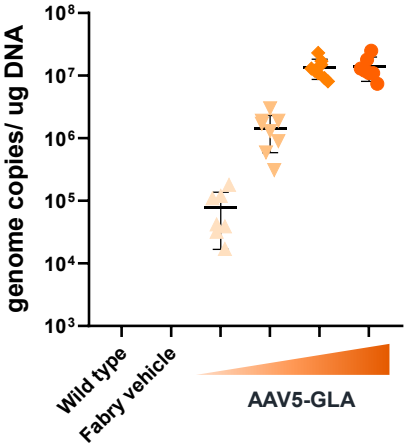
* Majowicz A. et al. Haemophilia 2020; 26:20-20

AMT-191:
leads to efficient expression of GLA in Fabry mice

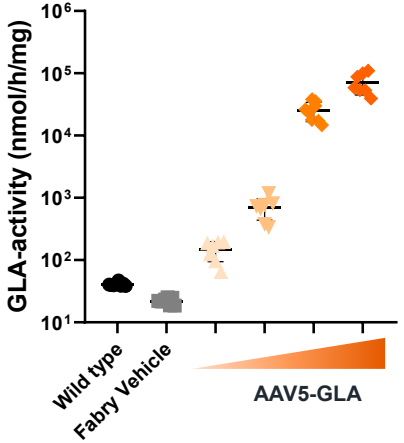
GLA KO mice
12 wks post-IV
AAV5-GLA



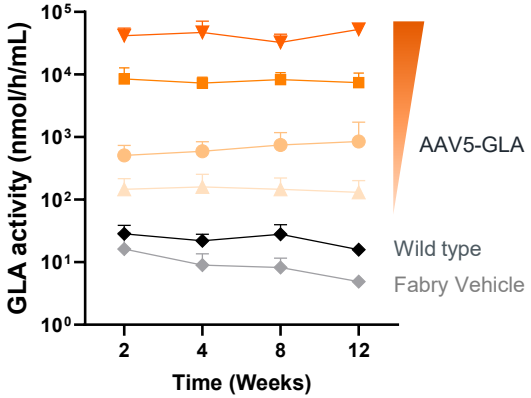
Liver vector DNA



Liver GLA activity



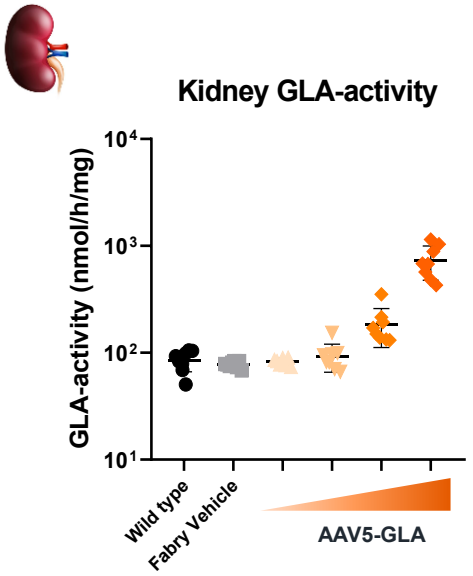
Plasma GLA-activity

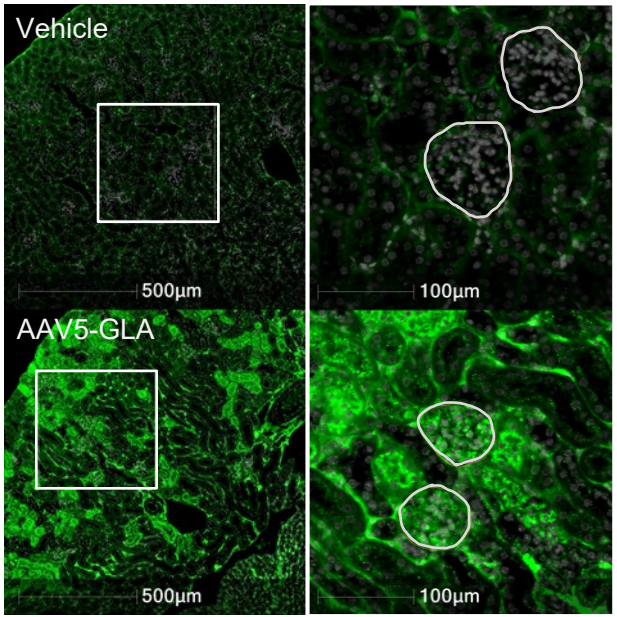


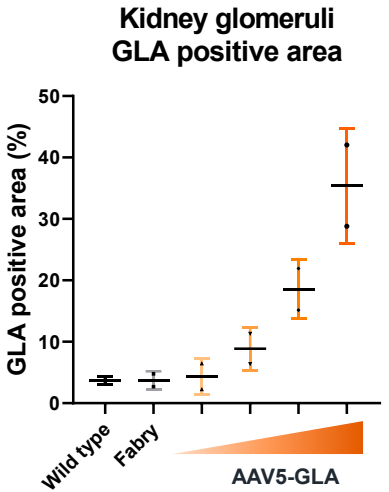
Conclusions:

- Dose dependent increase of GLA activity in liver and plasma in the Fabry disease mouse model

AMT-191: high GLA-activity levels in the kidney of Fabry mice





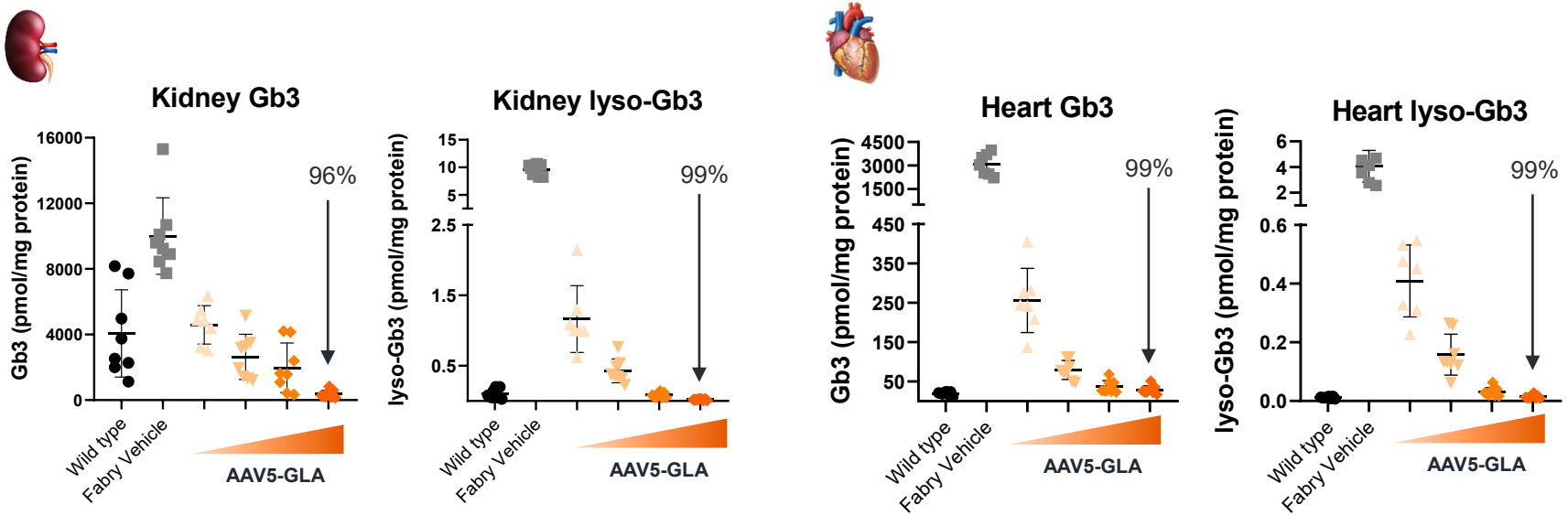


Conclusions:

- Dose dependent GLA-activity in the kidney of the Fabry disease mouse model
- Kidney glomeruli are positive for GLA-protein

AMT-191:
cross corrects in kidney and heart of Fabry mice

Collaboration Prof. Dr. Aerts

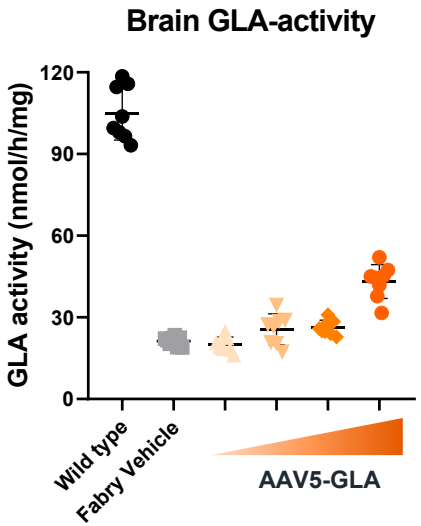


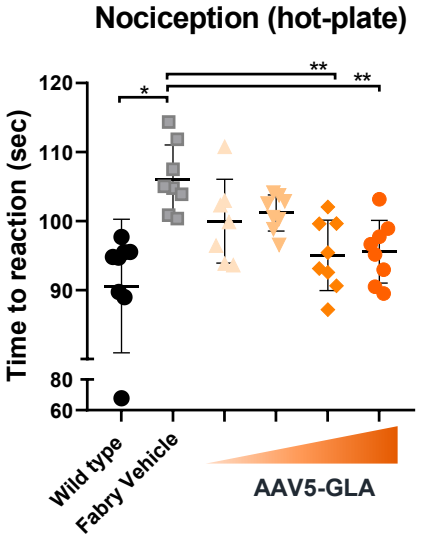
Conclusions:

- Up to 99% substrate reduction of both Gb3 and lysosomal localized lyso-Gb3
- Functional cross correction of kidney and heart

AMT-191:
improves phenotype of Fabry mice

Collaboration Prof. Dr. de Vries





Conclusions:

- Increased GLA-activity levels in the brain of Fabry mice
- Phenotype improvement of nociception after AAV5-GLA injection

AMT-191:
is well expressed in the liver of NHPs

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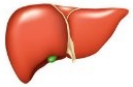
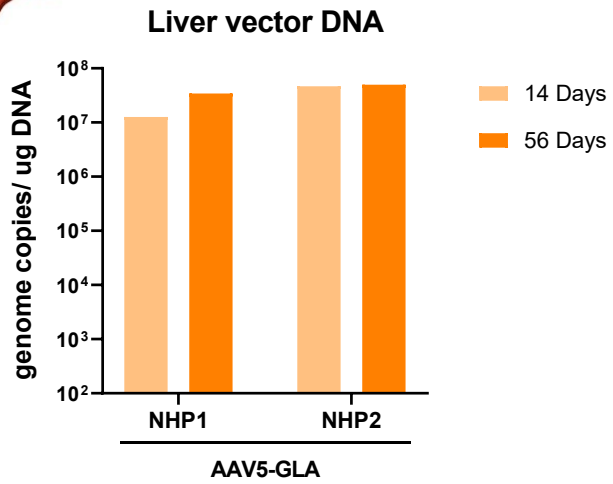
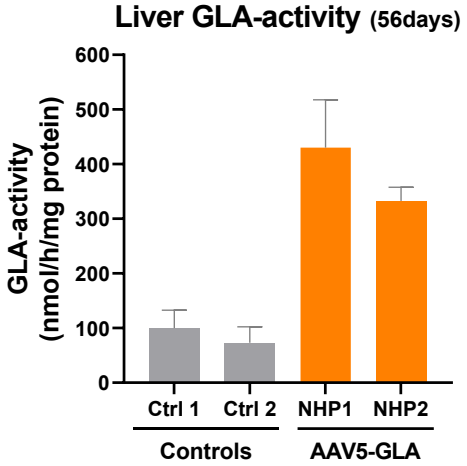
Wild type cynomolgus monkey
8 wks post-IV AAV5-GLA





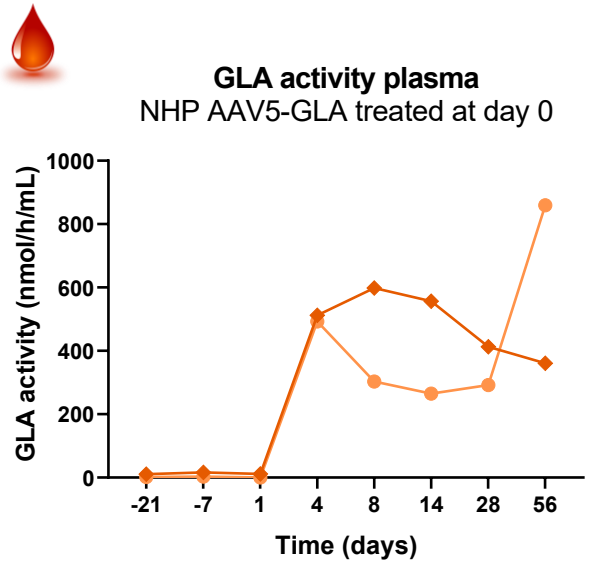


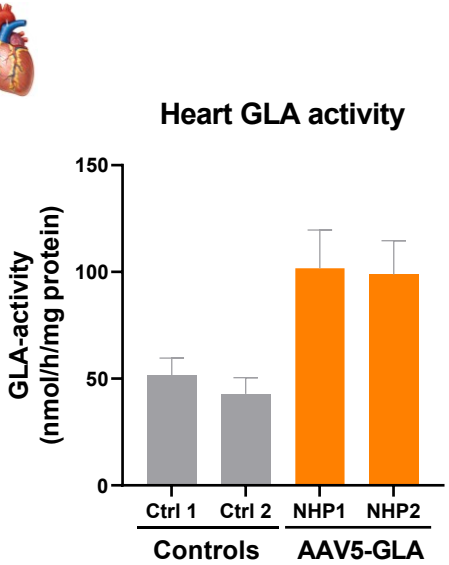
Conclusions:

- Sustained vector DNA levels in the liver
- High levels of GLA-activity in the liver, without anti-GLA IgG development

AMT-191:
Increases GLA-activity level in plasma and heart of NHP

Wild type cynomolgus monkey
8 wks post-IV AAV5-GLA





Conclusions:

- High and sustained plasma GLA activity levels
- Increased GLA-activity in heart indicate the cross-correction ability of AAV5-GLA

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Conclusions – AMT-191 AAV5-GLA

- Supraphysiological plasma GLA activity levels in Fabry mouse model and NHP
- Cross correction in afflicted organs (kidney, heart and brain) of Fabry disease mice
- Increased GLA activity in liver and heart in NHP, warranting further development

Acknowledgements

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