Safety and efficacy of FLT190 for the treatment of patients with Fabry disease: Results from the MARVEL-1 Phase 1/2 clinical trial

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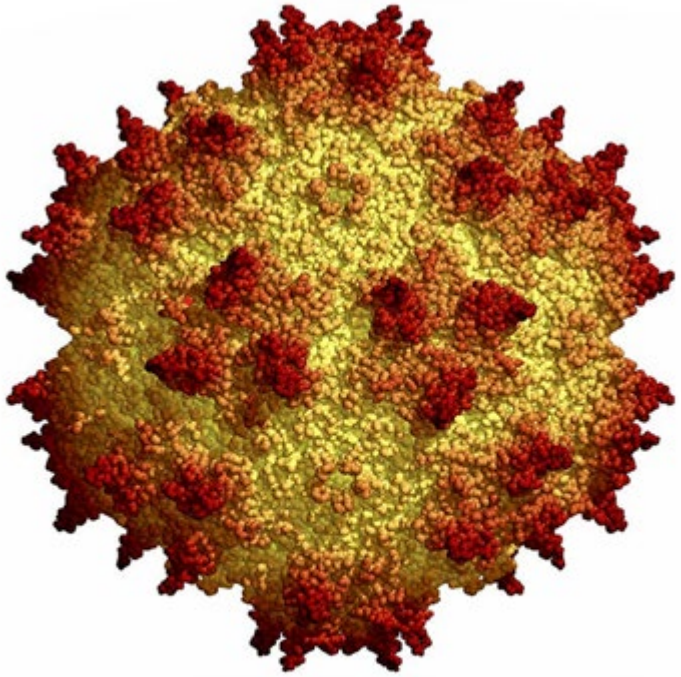
FLT190 is an adeno-associated virus (AAV) gene therapy in development for the treatment of patients with Fabry disease



FLT190 consists of a rationally designed capsid (AAVS3) containing an expression cassette with a codon-optimised human *GLA* cDNA under the control of a liver-specific promoter

- ITR Inverted terminal repeat
- FRE1 Liver-specific promoter
- SV40i SV40 intron
- BgpA Bovine growth hormone polyadenylation signal sequence
- *GLA*co Codon-optimised α-galactosidase A transgene

AAV *in vivo* gene therapy delivered via a one-time intravenous infusion

In vivo gene therapy offers the potential for sustained and durable increase in α-Gal A activity

- From a single intravenous administration
- Without pre-infusion conditioning
- Without stem cell harvest or *ex vivo* stem cell manipulation

Vector construct

Targeted functional gene

Simple virus – AAV Native genes removed

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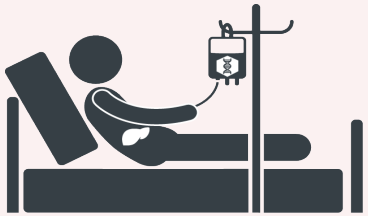
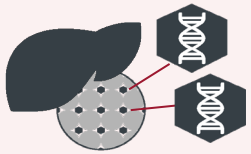
Gene encapsulated in AAV

Administration

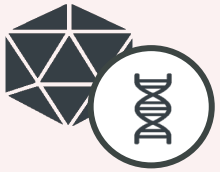


Patient receives infusion with capsid targeting liver

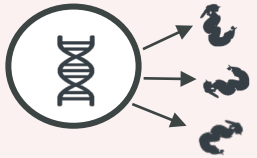


Liver hepatocytes transduced

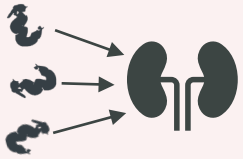
Enzyme production and uptake



α-Gal A produced in hepatocytes



Hepatocytes secreting functional α-Gal A



α-Gal A uptake from circulation into tissues

MARVEL-1: The first clinical trial of *in vivo* gene therapy in Fabry disease

Novel features of MARVEL-1

- Adaptive dosing design to facilitate dose finding
- Prophylactic immune management regimen to prevent vector-related transaminitis

Design

- Open-label, multicentre, ascending single-dose, Phase 1/2 clinical trial
- One dose of FLT190 administered intravenously over 1-2 hours

Duration

- 38 weeks for MARVEL-1
- 5 years for long-term follow-up study (MARVEL-2)

Key inclusion criteria	Key exclusion criteria
• Adult males (aged ≥18 years) • Classic Fabry disease	• Neutralising antibodies to AAVS3 • Liver disease

Endpoints

- Safety, as assessed by AEs
- Level of α-Gal A in plasma
- Clearance of Gb3 and LysoGb3 from plasma and urine

AEs = adverse events; α-Gal A = alpha-galactosidase A; Gb3 = globotriaosylceramide; LysoGb3 = globotriaosylsphingosine.

MARVEL-1 is a Phase 1/2 dose-finding trial assessing the safety and efficacy of FLT190 in adult Fabry patients

Adaptive study design* to establish a dose of FLT190 that delivers sustained increases in α-Gal A activity to levels that reduce substrate accumulation

α-Gal A = alpha-galactosidase A; ERT = enzyme replacement therapy; DMC = Data Monitoring Committee.

Patients dosed

Patients planned to be dosed in each cohort

Safety results for Cohort 1 – 7.5 x 10^{11} vg/kg

- FLT190 was generally well tolerated
- No infusion reactions or allergic reactions
- Transient transaminitis observed in Patient 1, but not Patient 2
  - Transaminitis in Patient 1 was observed at Week 8 and was treated with methylprednisolone + tacrolimus
  - A new prophylactic immune management regimen was implemented (per protocol amendment) at Week 3 for Patient 2
- Increases in troponin-T levels consistent with mild transient myocarditis occurred in both patients assessed as possibly related to FLT190
  - No evidence of myocarditis on cardiac MRI at time of event
  - Events did not require intervention
  - No enduring clinical sequelae noted on cardiac MRI and left ventricular ejection fraction remained normal throughout
  - No significant arrhythmias have been detected in either patient

MRI = magnetic resonance imaging.

Review of elevated troponin-T levels

Patient 1 (29-year-old male, dosed August 2019)

Immune regimen

- Started corticosteroids at Week 4

Clinical event

- Chest pain and troponin-T elevation (18 pg/mL) at Week 8 visit
  - Peak troponin-T of 161 pg/mL 3 days later
  - ECG – ST elevation in V1
  - Cardiac MRI – No evidence of myocarditis

Follow-up

- Troponin-T and ECG settled within 4 days
- Chest pain dissipated within 3 weeks
- Cardiac MRI stable at 2 years

Clinical impression – mild transient myocarditis

Protocol changes

- Exclude patients with history of myocarditis
- Added routine troponin and ECG monitoring
- New prophylactic immune management regimen (tapering dose of corticosteroids with a short course of tacrolimus)

Patient 2 (45-year-old male, dosed June 2021)

Immune regimen

- Started corticosteroids with a short course of tacrolimus at Week 3

Clinical event

- Incidental finding of asymptomatic cardiac biomarker abnormality on routine per protocol monitoring
  - Peak troponin-T elevation (94.6 pg/mL) at Week 7
  - ECG - T-wave inversion
  - Cardiac MRI – No evidence of myocarditis
  - Holter – No significant arrhythmias

Follow-up

- Remains asymptomatic.
- Troponin-T remains at baseline
- Further cardiac MRI planned per protocol

Clinical impression – mild transient myocarditis

ECG = electrocardiogram; MRI = magnetic resonance imaging.

Evaluation and impressions of elevated troponin-T levels in MARVEL-1

Comprehensive review by independent cardiologists and study Data Monitoring Committee

Natural history of Fabry disease

- Cardiac manifestation typically by 40s in classic males
  - Left ventricular hypertrophy, conduction abnormalities, tachyarrhythmias, heart failure
- Substrate accumulation, hypertrophy, inflammation and fibrosis are believed to be part of disease progression and trajectory in Fabry cardiomyopathy

Two cases of mild transient myocarditis in Fabry patients

- Patient 1 presented in setting of chest pain and transaminitis at Week 8
- Patient 2 presented incidentally on routine follow-up and identified due to routine per protocol monitoring

Myocarditis not observed in haemophilia B program using the same AAVS3 capsid

Hypothesis

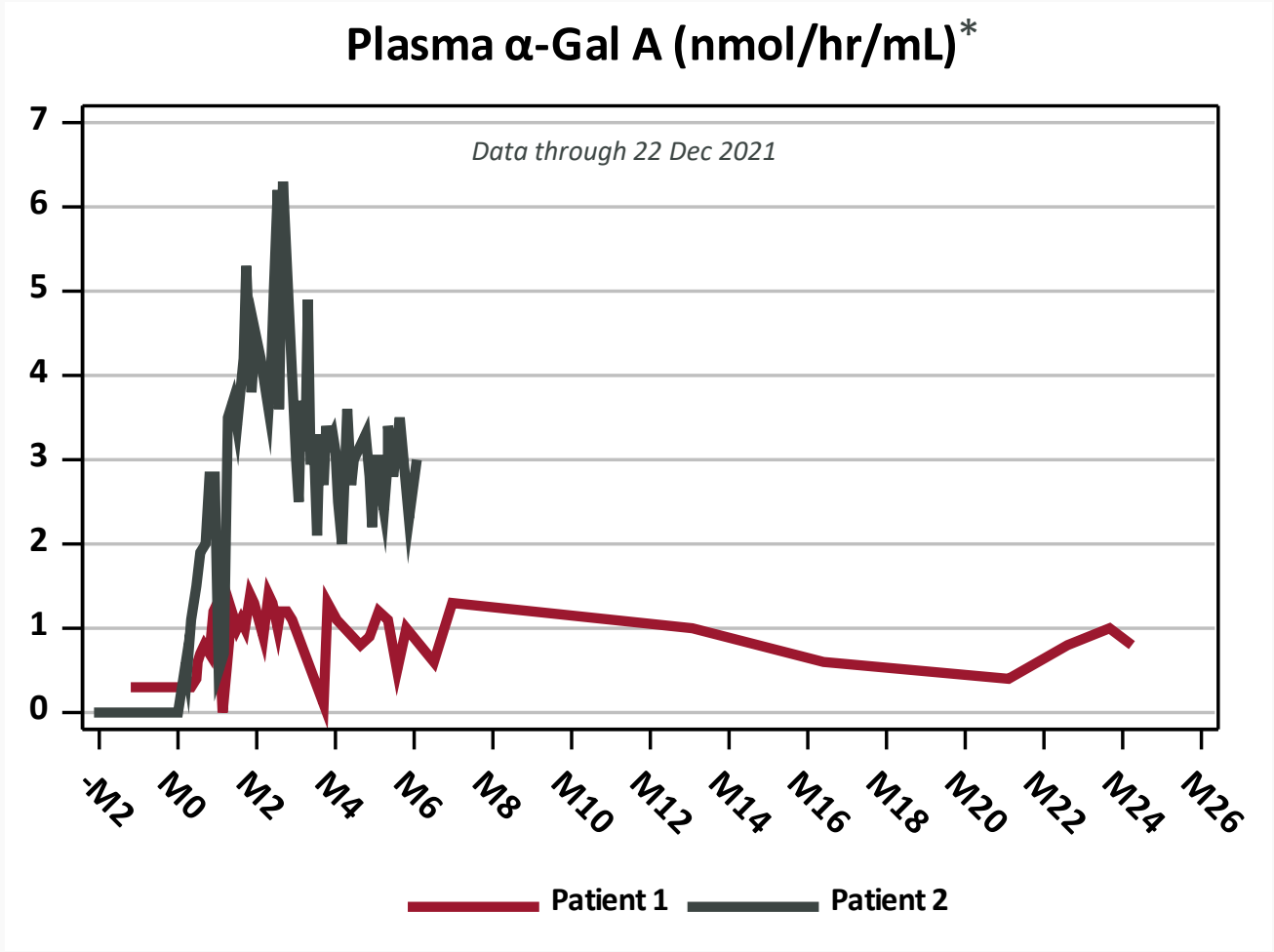
- Inflammation following substrate accumulation is seen in Fabry cardiomyopathy. Potential for transient immune reaction following therapy.

DMC recommendations

- Recommended to proceed with dosing a third patient at the same $7.5x10^{11}$ vg/kg dose level with cardiac monitoring and subsequent review by the DMC

DMC = Data Monitoring Committee.

Results from Cohort 1 suggest a dose-dependent increase in plasma α-Gal A levels



Patient 1 (>2 years of follow-up)

- FLT190 absolute total dose: 4.125 x 10^{13} vg
- Subtherapeutic response
- Restarted ERT at Week 6
- Trough α-Gal A of 0.8 nmol/hr/mL (~3x baseline) at 2 years

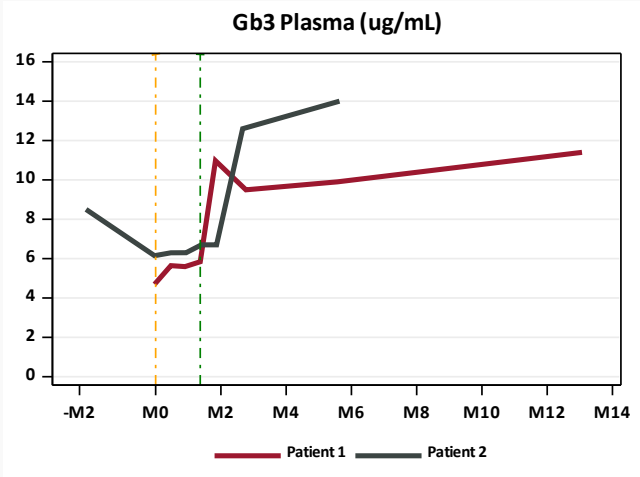
Patient 2 (24 weeks of follow-up)

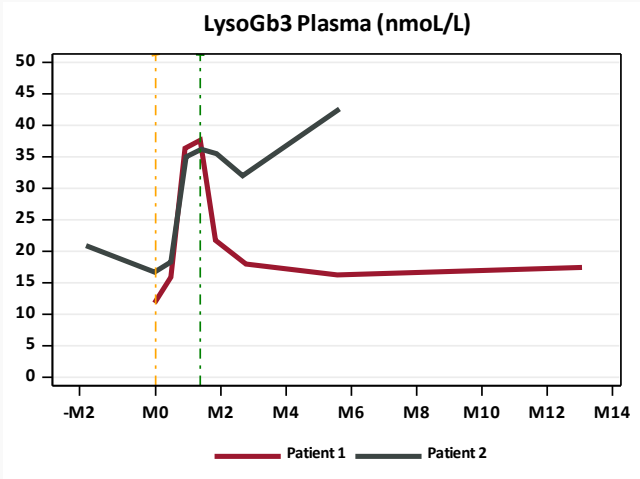
- FLT190 absolute total dose: 6.0375 x 10^{13} vg
- 46% higher absolute total dose than Patient 1 and did not show transaminitis
- Increase in α-Gal A from 0.0 at BL to near normal levels; mean of 3.4 nmol/hr/mL (Weeks 6-24)
- Remains off ERT

*Assay normal range 4-21.9 nmol/hr/mL
α-Gal A = alpha-galactosidase A; ERT = enzyme replacement therapy; BL = baseline.

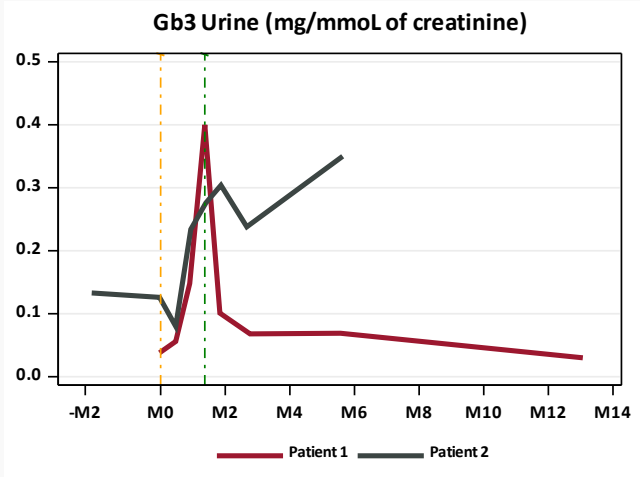
Gb3 and LysoGb3 biomarkers

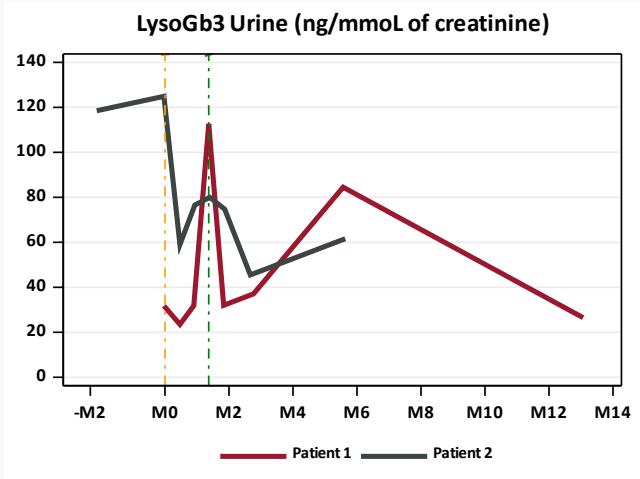
Plasma





Urine





ERT stopped

ERT restarted in Patient 1 at Week 6

Data through 22 Dec 2021

ERT = enzyme replacement therapy; Gb3 = globotriaosylceramide; LysoGb3 = globotriaosylsphingosine.

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Conclusions

- FLT190 has been well tolerated
- Novel prophylactic immune management regimen may have prevented development of vector-related transaminitis in Patient 2
- Mild myocarditis not associated with enduring clinical sequelae on cardiac MRI
  - Cardiac monitoring should be standard in gene therapy clinical trials for conditions like Fabry disease where underlying cardiac complications may contribute to treatment outcomes
- Results from lowest-dose (7.5×10^{11} vg/kg) cohort demonstrate promising efficacy
  - Suggest a dose-dependent increase in plasma α-Gal A levels
  - Durable α-Gal A levels sustained for up to 2 years in Patient 1
  - Patient 2 remains off ERT as of December 22, 2021
- Third patient to be dosed with FLT190 in 7.5×10^{11} vg/kg cohort by end of first quarter 2022
- As the dose of FLT190 is escalated in future cohorts, a similar dose-response effect is expected, with subsequent reduction in substrate and clearance from the tissues

Acknowledgements

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