LB-30

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

Derralynn A. Hughes,[1,2] Sima Canaan-Kühl,[3] Sharon Barton,[4] Richard Collis,[4] Nicole Sherry[4]

1. Lysosomal Storage Disorders Unit, Royal Free London NHS Foundation Trust, London, United Kingdom; 2. University College London, London, United Kingdom; 3. Department of Medicine, Division of Nephrology, Charité, Universitätsmedizin Campus Mitte, Berlin, Germany; 4. Freeline Therapeutics, Stevenage, United Kingdom

# Disclosure information

**Derralynn A. Hughes**

I have the following financial relationships to disclose:

Advisory Board: Freeline, Sanofi, Takeda, Amicus, Idorsia

Consulting Fees: Freeline, Sanofi, Takeda, Amicus, Idorsia, Protalix, Sangamo

Honoraria: Freeline, Sanofi, Takeda, Amicus, Idorsia

I will discuss the following investigational use in my presentation: investigational use of FLT190 for the treatment of patients with Fabry disease

MARVEL-1 study sponsor: Freeline Therapeutics

# 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**

## 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

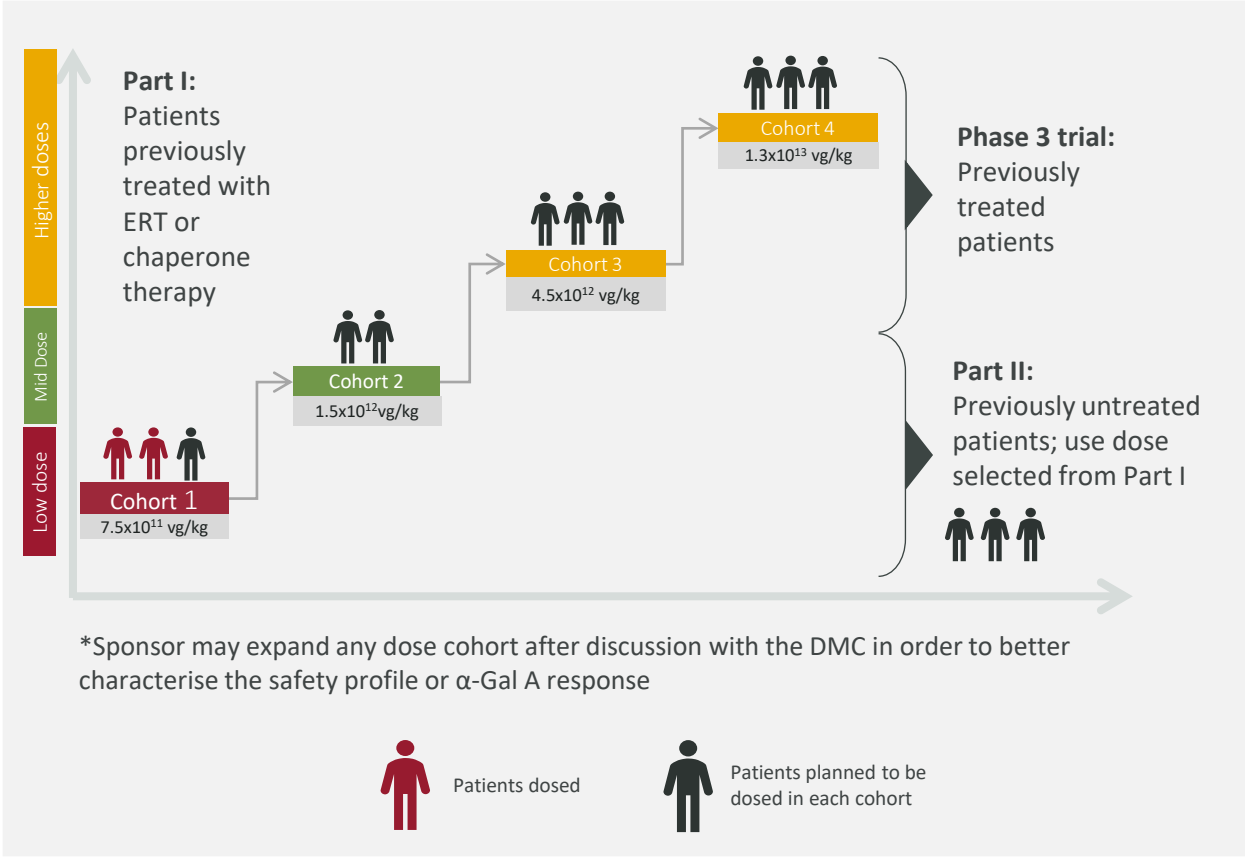
## Duration

- 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)<br>• Classic Fabry disease | • Neutralising antibodies to AAVS3<br>• Liver disease |

## Endpoints

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



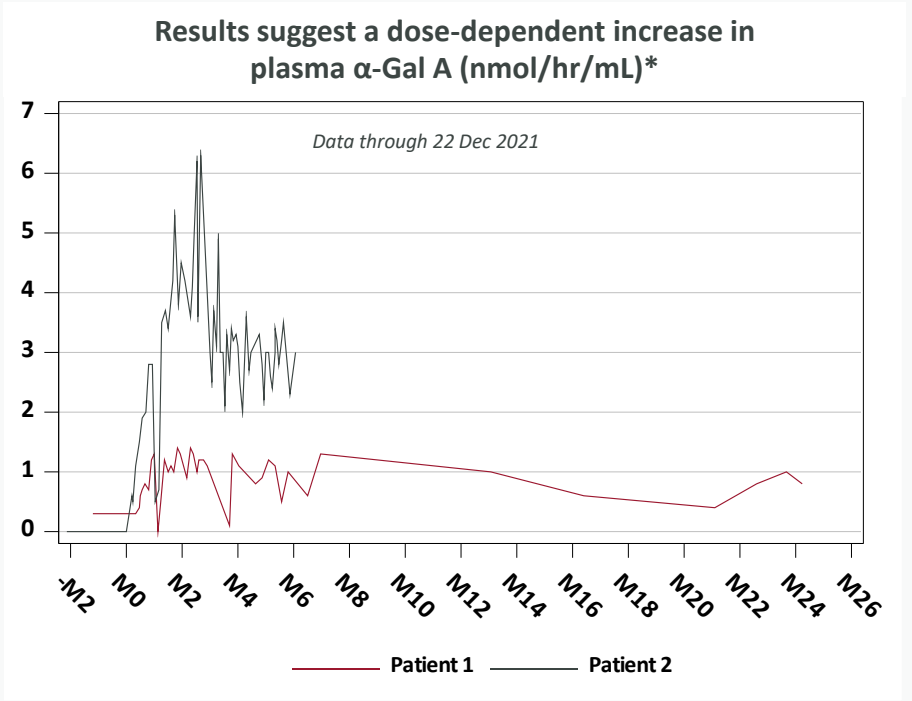

α-Gal A = alpha-galactosidase A; AEs = adverse events; DMC = Data Monitoring Committee; ERT = enzyme replacement therapy; Gb3 = globotriaosylceramide; LysoGb3 = globotriaosylsphingosine.

# Results for Cohort 1 – 7.5 x $10^{11}$ vg/kg

## Safety

- FLT190 was generally well tolerated
- No infusion reactions or allergic reactions
- Transient transaminitis observed in Patient 1, but not in Patient 2
  - Transaminitis in Patient 1 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

## Efficacy




**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; no transaminitis
- Increase in α-Gal A to 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; MRI = magnetic resonance imaging.

# 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 ($7.5 \times 10^{11}$ 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 $7.5 \times 10^{11}$ 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