Results from GALILEO-1, a first-in-human clinical trial of FLT201 gene therapy in patients with Gaucher disease Type 1

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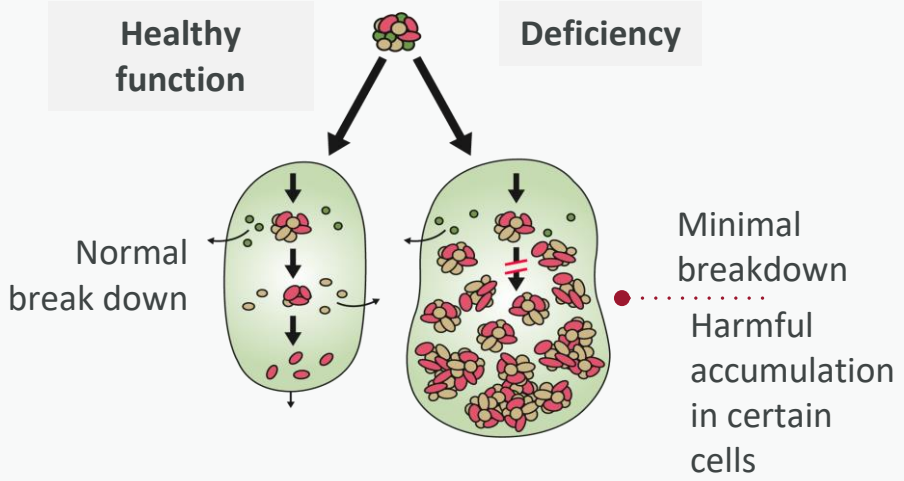
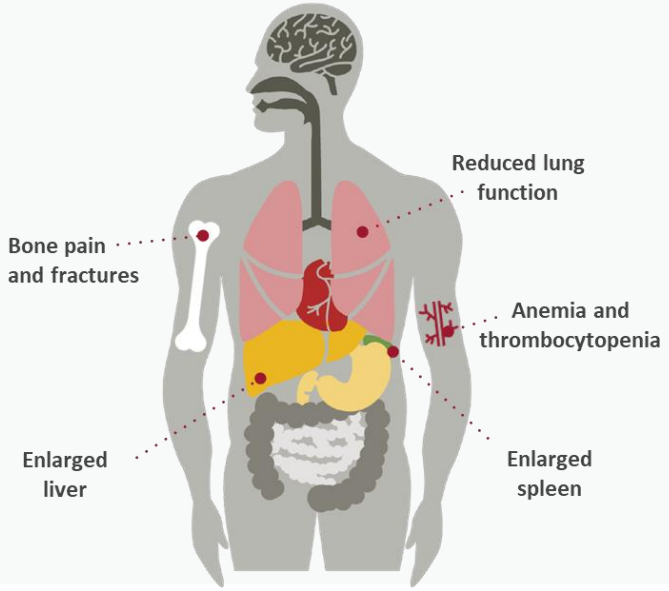
Conflicts of Interest

- Dr Goker-Alpan is an investigator on the Freeline FLT201 GALILEO-1 study and has received funding from Freeline for travel and sponsorship to attend this meeting.

Gaucher disease Type 1 is a progressive multisystem disorder

- Rare genetic LSD resulting from deficiency of glucocerebrosidase (GCase) due to mutations in *GBA1*
- GCase deficiency leads to accumulation of glucocerebroside throughout the body, including in macrophages and the reticuloendothelial system



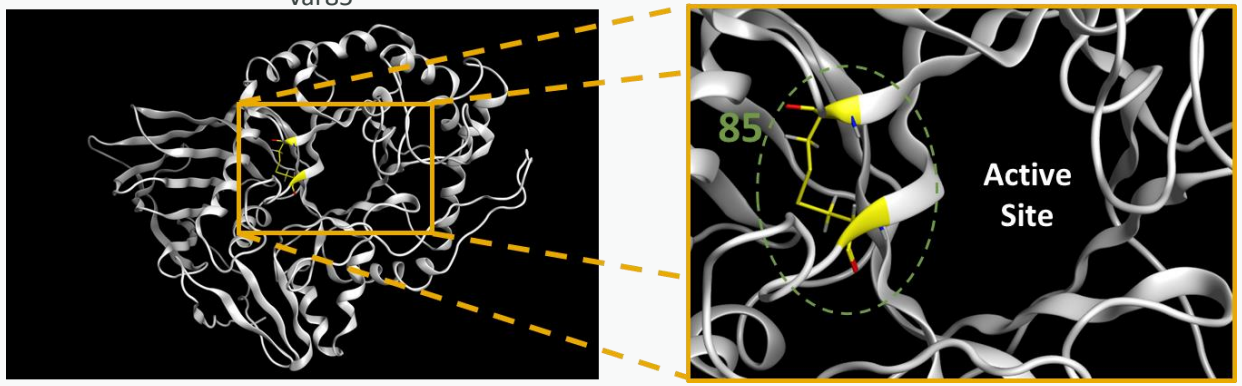


- GD Type 1 is characterized by hepatosplenomegaly, anaemia, thrombocytopenia, bone disease and pulmonary involvement without neurological involvement
- Approved therapies for GD Type 1 are enzyme replacement therapy (IV) and substrate reduction therapy (oral)

FLT201 is an adeno-associated virus (AAV) gene therapy in development for the treatment of patients with Gaucher disease Type 1

- A novel human liver-tropic AAV capsid (AAVS3)
- Encodes for a novel variant of glucocerebrosidase (GCase-variant 85)
- Produces robust and sustained secretion of GCase into the bloodstream
- Similar catalytic properties to wild-type GCase and velaglucerase alfa (ERT)
- No changes in predicted immunogenicity compared to velaglucerase alfa

Model of $GCase_{var85}$



GCase-variant 85 contains two novel amino acid substitutions to the mature human GCase, resulting in increased enzymatic stability

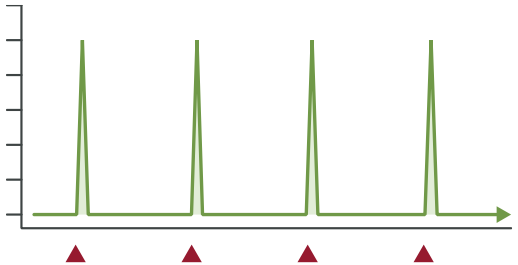
- **6-fold increase** in human serum
- **20-fold increase** in at lysosomal pH conditions

GBA = glucosylceramidase beta; LSP = liver-specific promoter; PolyA = polyadenylation signal sequence.

FLT201: continuous endogenous GCase production may address aspects of the disease that ERT cannot

ERT

Every 2 weeks



Transient elevations in plasma and cellular GCase lead to incomplete systemic distribution and short-lived presence in cells

After 10 years on ERT up to

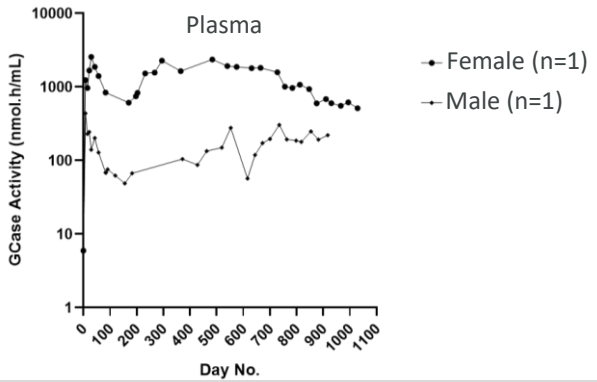
60%

still experience symptoms[1]

FLT201

Single dose

Steady, constant GCase expression in plasma and within all cell types tested[2]



Near complete prevention of substrate accumulation[2]

Liver, spleen, bone marrow, lung

in non-clinical studies at doses of $2x10^{11}$ and $2x10^{12}$ vg/kg

1 Weinreb et al., 2013; 2 Internal Freeline data from non-clinical Gaucher models

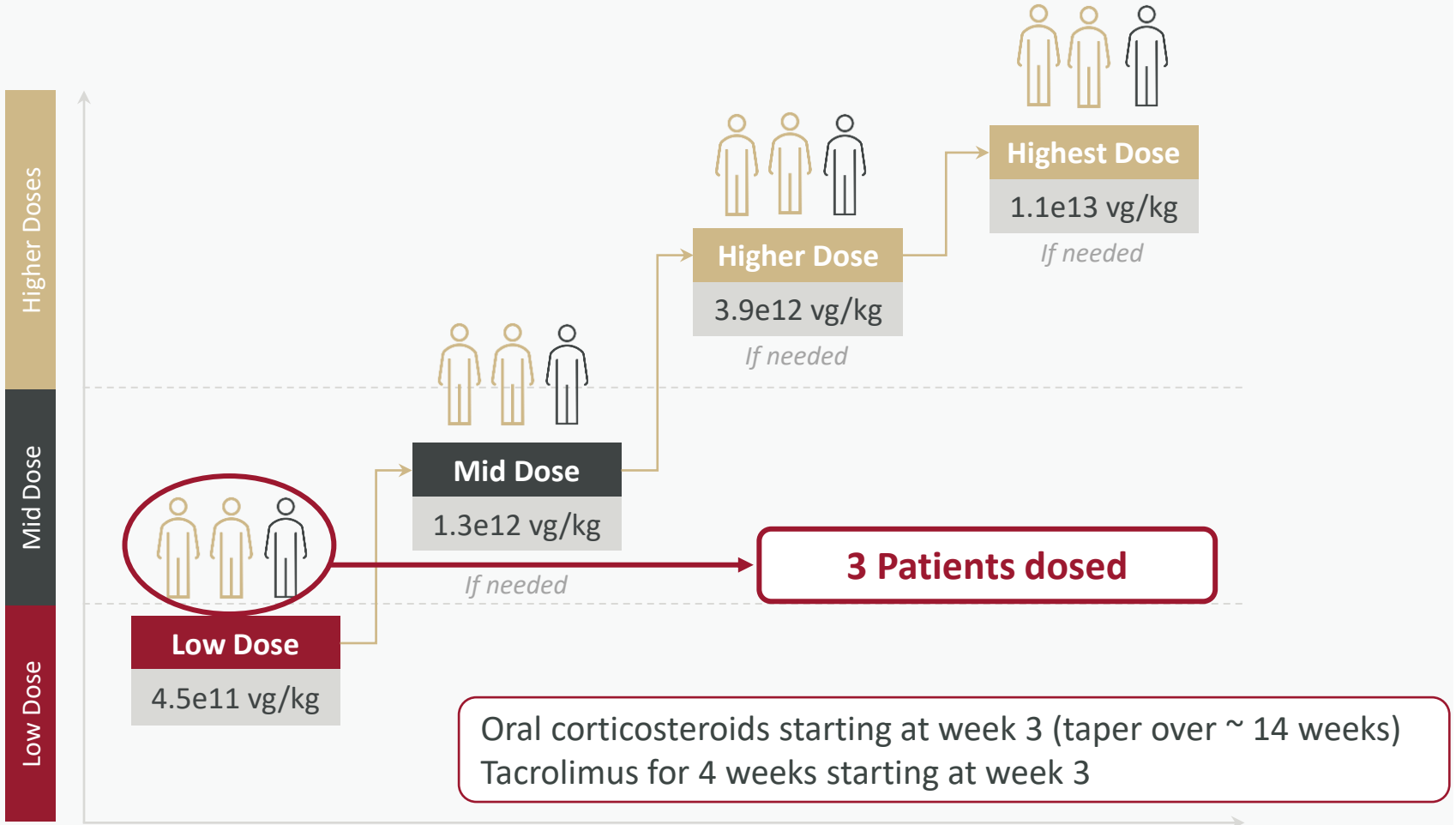
GALILEO-1 dose-finding trial is enrolling

First-in-human, open-label study of FLT201 in adults with GD Type 1 receiving ERT or SRT

ERT/SRT is stopped once blood levels of GCase are above normal

Planned to be dosed in each cohort

Flexibility to expand number of patients dosed



Immune management may be adapted based on patient response and investigator input in discussion with Freeline medical.
Trial protocol allows for testing up to four doses. The Data Monitoring Committee (DMC) provides recommendation on dosing based on emerging safety/tolerability, PK, PD and efficacy data.
ERT: enzyme replacement therapy; SRT: substrate reduction therapy

GALILEO-1 trial for patients with Gaucher Disease Type 1
Baseline characteristics

	Participant 1	Participant 2	Participant 3
Dose (vg/kg) **Absolute dose (vg)**	4.5×10^{11} 2.8×10^{13}	4.5×10^{11} 2.8×10^{13}	4.5×10^{11} 3.3×10^{13}
Age / gender / Body weight	35 / M / 63kg	25 / M / 63.1kg	24 / M / 73.7kg
GBA1 variant(s)	p.Val433Leu, p.Asn409Ser (c.1297G>T, c.1226A>G)	p.Asn409Ser, p.Leu483Pro (c.1226A>G, c.1448T>C)	Not known (result pending)
Gaucher therapy	ERT	SRT	SRT
Plasma GCase activity (μmol/L/h) [*Normal 0.3 – 1.2, mean 0.6* μmol/L/h]	0.07	0.014	0.05
DBS GCase activity (μmol/L/h) [*Normal > 1.5* μmol/L/h]	0.3	0.3	0.1
Leukocyte GCase activity (nmol/h/mg prot) [*Normal ≥ 3.53, median 5.18* nmol/h/mg prot]	0.64	0.82	0.01
Haemoglobin (g/dL)	15.1	15.2	14.5
Platelet count ($x10^3/\mu L$)	200	213	124
DBS lyso-Gb1 (ng/mL)	102.85	10.29	589.53

Data cut-off 13 October 2023

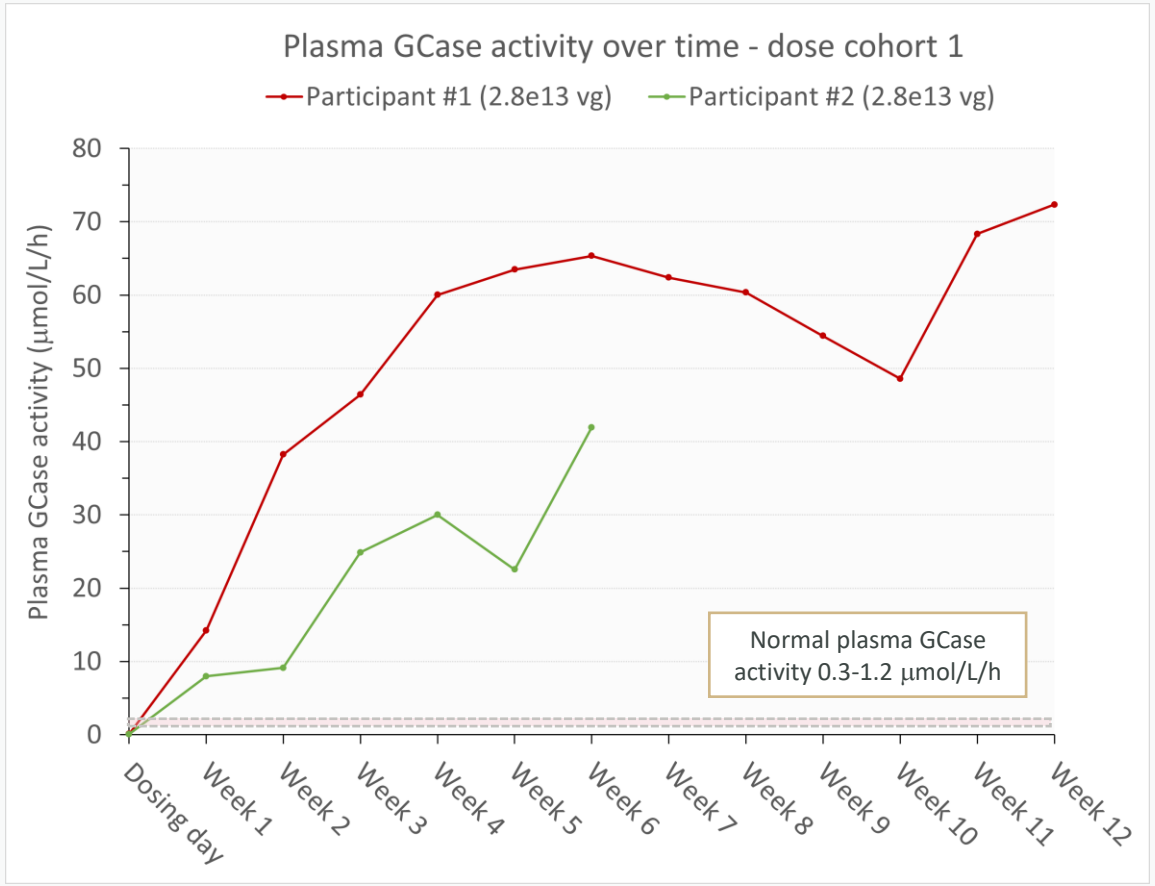
Favourable safety profile in the first 3 patients up to 16 weeks after dosing

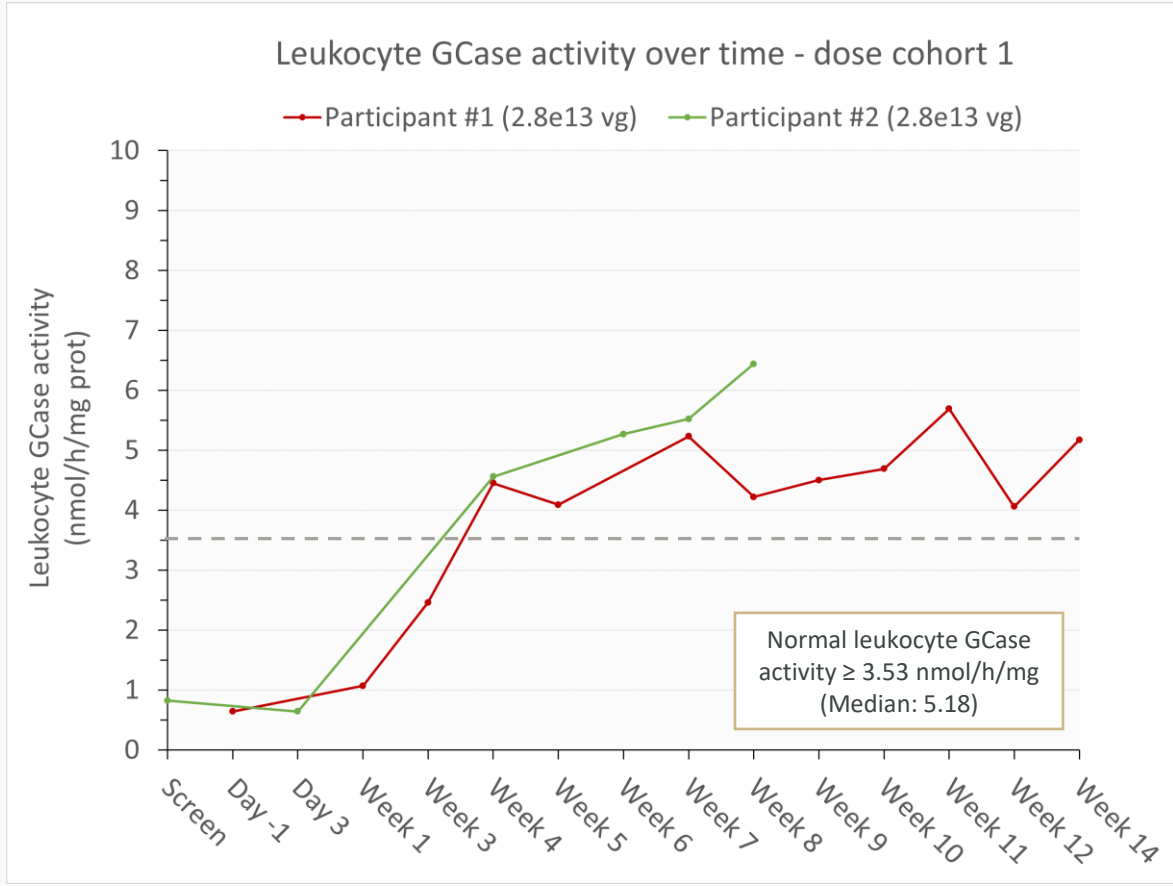
- **Three participants dosed in cohort 1 (4.5e11 vg/kg)**
  - Weeks 1, 9 and 16 after dosing*

- **Safety**
  - Infusions well tolerated
  - No serious adverse events (SAE)
  - No ALT or AST elevations above upper limit of normal
  - Two mild (CTCAE grade 1) adverse reactions, both spontaneously resolved
  - Mild-moderate, non-serious AEs related to corticosteroids and tacrolimus (expected based on known profile of these medication)

*Data cut-off 13 October 2023

FLT201 induces expression of GCase in plasma, followed by normalization of intracellular GCase levels





ERT stopped at week 11 for participant 1; SRT stopped at week 5 for participant 2

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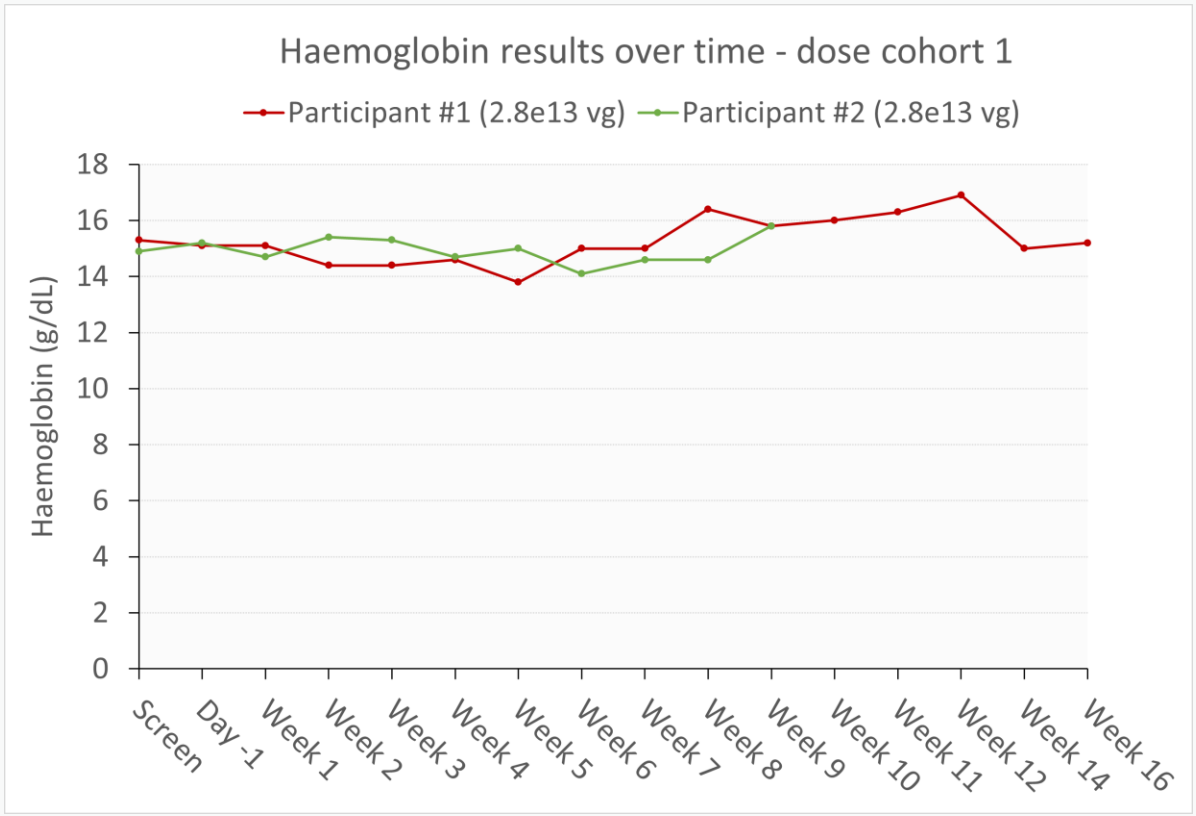
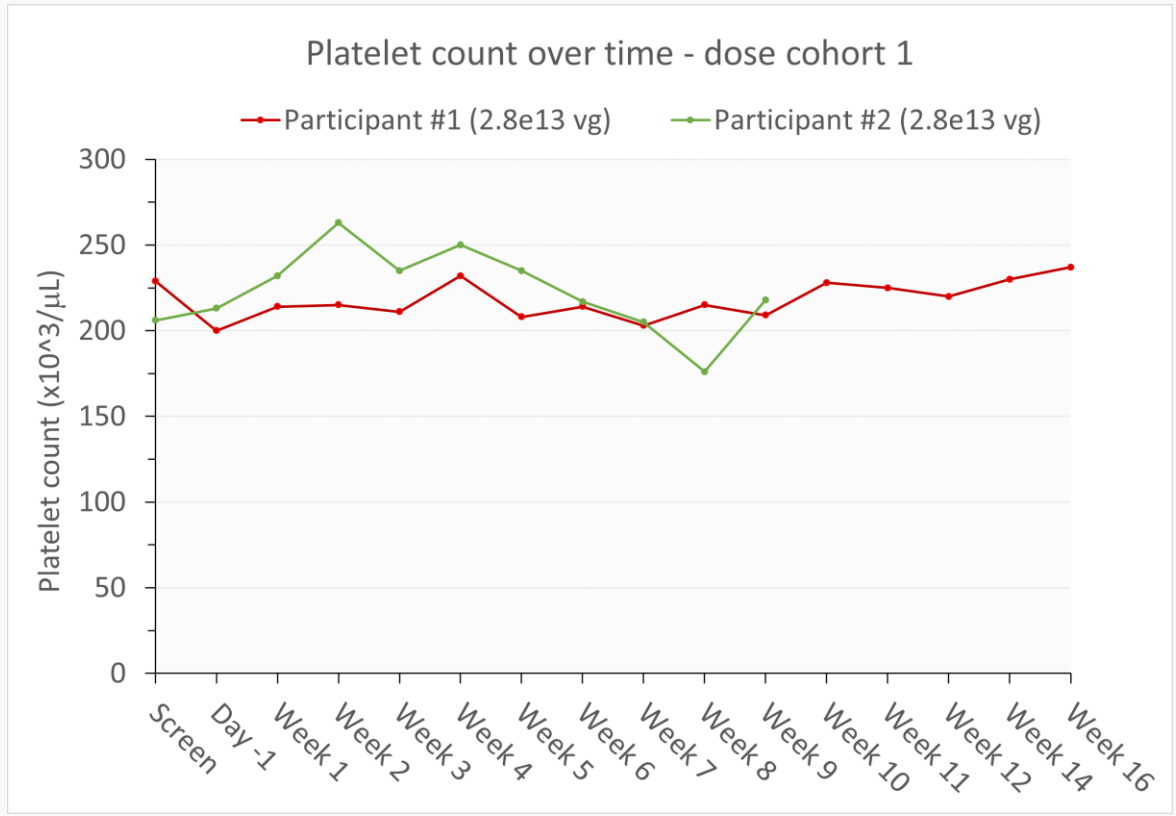
Stable haemoglobin and platelet count in both participants





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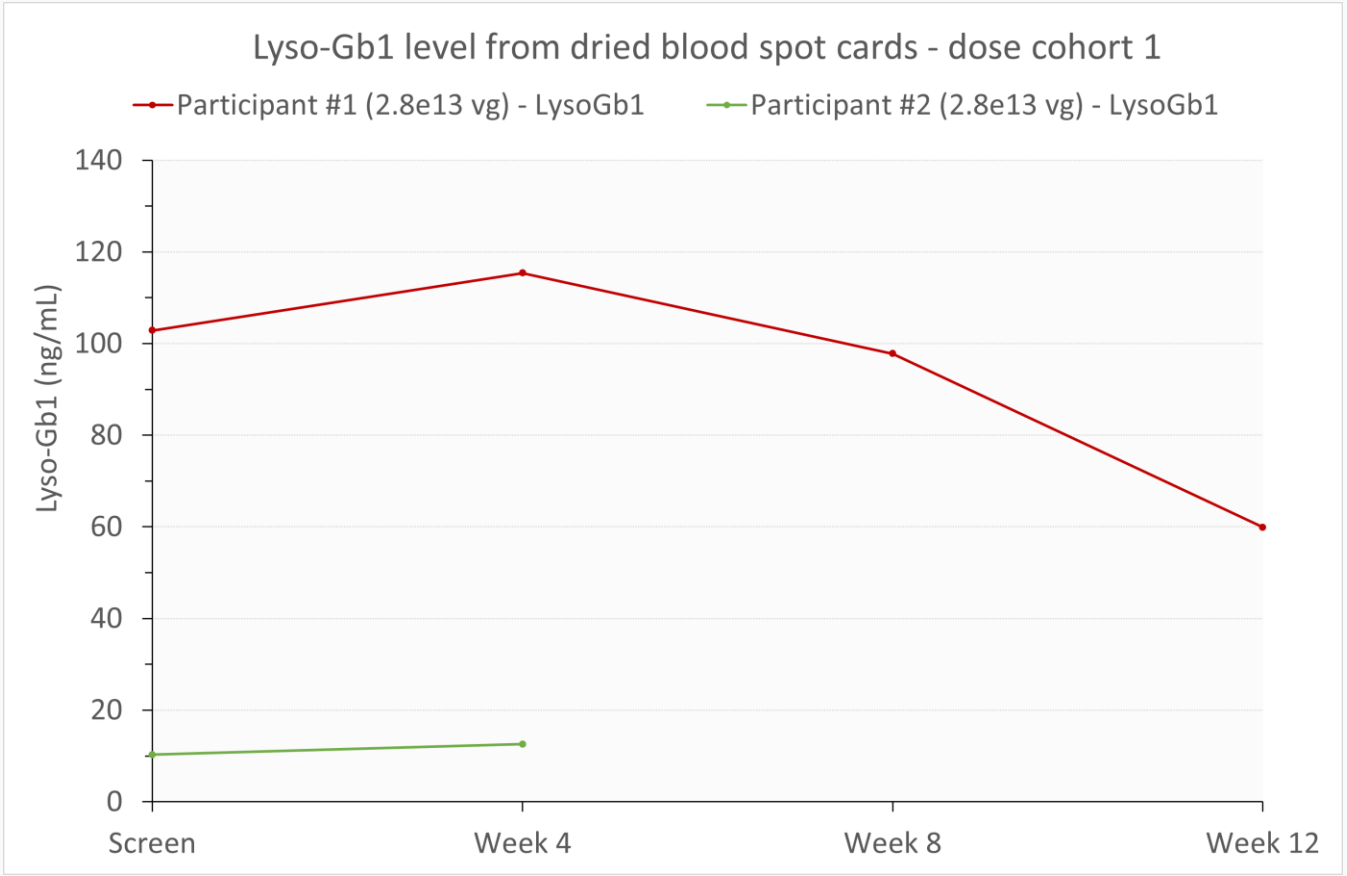
Initial effect on LysoGb1 substrate



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Data cut-off 13 October 2023
Lyso-Gb1: glucosylsphingosine

Promising initial data from GALILEO-1 on FLT201 gene therapy for patients with Gaucher disease Type 1

- FLT201 is an investigational AAV gene therapy being studied in adults with Gaucher disease Type 1
- GCase-variant 85, produced by FLT201, is more stable than recombinant human GCase providing continuous tissue access to the needed enzyme
- Early clinical data shows a favourable safety profile with robust GCase expression in plasma and normalization of levels within the cell
- Early lyso-Gb1 data suggests potential for meaningful improvements in outcomes

Acknowledgements

The Gaucher disease community

- Patients, families and friends
- Gaucher Community Alliance
- International Gaucher Alliance
- Gaucher Association UK

Study sites & investigators

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