Results from GALILEO-1, a first-in-human clinical trial of FLT201 AAV- gene therapy in adult patients with type 1 Gaucher Disease

Reena Sharma, MD
Salford Royal Hospital, UK
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Incomplete therapeutic responses are common for people with Gaucher disease, despite years on conventional therapy

- **60% failed** to achieve at least one of 6 therapeutic goals after 4+ years of ERT[1]
- Many continue to exhibit **bone pain, organomegaly, and cytopenia** after 10 years of ERT[2]
- **25% have physical limitations** after 2 years of ERT, primarily due to bone disease[3]
- 80% of individuals with severe bone marrow burden (BMB) showed **no meaningful improvement after 8 years on ERT**[4]
- **65% report fatigue** despite treatment with ERT/SRT[5]

Prospective registry of 757 GD1 patients on ERT after 10 years[2]

Persistence after 10 years ERT	Non-splenectomized Patients	Splenectomised Patients
Bone pain	43%	63%
Splenomegaly	38%	N/A
Thrombocytopenia	23%	1%
Hepatomegaly	14%	19%
Anemia	12%	9%
Bone crisis	7%	17%

Although ERT/SRT are effective in reversing many aspects of the disease, there are still medical needs that remain

1. Weinreb N, et al. *Am J Hematol.* 2008. 2. Weinreb N, et al. *J Inherit Metab Dis.* 2013. 3. Giraldo P, et al. *Qual Life Res.* 2005. 4. De Fost M, et al. *Blood.* 2006; Low ERT dose cohort. 5. Wagner V, et al, *J Genet Counsel*. 2018.

FLT201 is an AAV vector serotype S3 encoding a protein engineered human β-Glucocerebrosidase (GCase85)

- Novel human liver-tropic AAV capsid (AAVS3)
- Transgene encoding GCase85, a novel engineered variant of glucocerebrosidase
- GCase85 has similar catalytic properties to human GCase with *increased enzymatic stability*
  - **6-fold increase** in human serum
  - **20-fold increase** at lysosomal pH conditions
- Produces robust and sustained secretion of GCase into the bloodstream
- No changes in predicted immunogenicity compared to velaglucerase alfa

Preclinical studies demonstrate[1]:

- High and durable expression with favorable tolerability out past 3.5 years
- Uptake in all disease-affected tissues
- Greater residence time in disease-affected tissues and organs compared to ERT
- Greater reduction of lyso-Gb1, a disease-causing substrate and biomarker, versus ERT in all disease-affected tissues

1. Comper et al, 2024, manuscript submitted for publication (Dec); AAV=adeno associated virus; LSP=liver specific promoter; ERT=enzyme replacement therapy; Lyso-Gb1=glucosylsphingosine

GALILEO-1: A first-in-human, open-label, multicenter study of FLT201

Adults with Gaucher Type 1 on ERT or SRT

Cohort 1
4.5e11
vg/kg dose

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age / Gender	35 / M	25 / M	24 / M	30 / F	24 / M	58 / F
Age at diagnosis	4	3	16	15	20	15
GBA1 Variant	p.Val433Leu; p.Asn409Ser (c.1297G>T; c.1226A>G)	p.Asn409Ser; p.Leu483Pro (c.1226A>G; c.1448T>C)	c.334_338del (p.(Gln112Valfs*32)) / c.1265_1319del55; 1448T>C; 1483G>C;1497G>X	p.Asn409Ser; p.Leu483Pro (c.1226A>G; c.1448T>C)	p.Asn409Ser; p.Leu483Pro (c.1226A>G; c.1448T>C)	p.Asn409Ser; p.Trp223Arg c.1226A>G; c.667T>C
Duration of SoC	4 years	22 years	9 years	14 years	4 years	24 years
Therapy at entry	ERT	SRT	SRT	ERT	SRT	SRT
Plasma GCase activity (µmol/L/h)	0.1	0.09	0.04	<0.1*	0.5	<0.1*
DBS Lyso-Gb1 (ng/mL)	102.85	10.29	486.41#	72.6	257	52.6
Hemoglobin (g/dL)	15.1	15.2	14.5	13.3	17.0	12.6
Platelet count (x10^3/mL)	200	213	124	176	167	113
Spleen volume (MN)	1.88	1.39	2.20	1.73	8.39	5.65
Liver volume (MN)	1.14	1.06	0.81	0.75	1.11	0.88

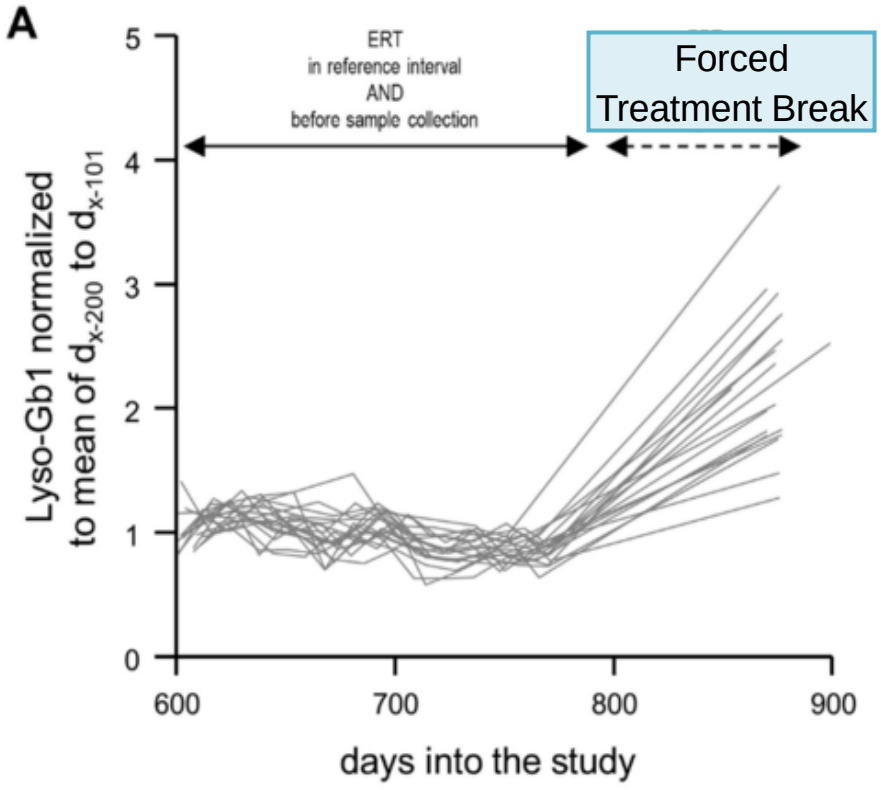
* Below lower limit of quantification; # average of two baseline values

DBS: dried blood spot; ERT: enzyme replacement therapy; GBA1: glucosylceramidase beta 1; GCase: Glucocerebrosidase; lyso-Gb1: Glucosylsphingosine; MN: Multiples of normal; SoC: standard of care; SRT: substrate reduction therapy

- All participants treated with a single dose of FLT201 (4.5e11 vg/kg)
- Immune management regimen begins 3 weeks post-infusion
- Post FLT201 follow up between 9 and 17 months
- Withdrawal of Standard of Care treatment (ERT or SRT) 4-11 weeks post FLT201

Impact of treatment interruption: Benchmark for treatment switch evaluation

Worsening of Lyso-Gb1



Lyso-Gb1 values as normalized to the 100-day reference interval: n=19

Worsening of hemoglobin and platelets

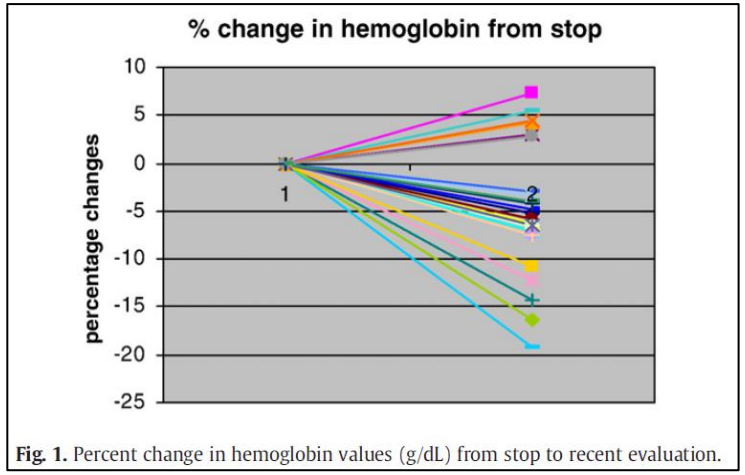
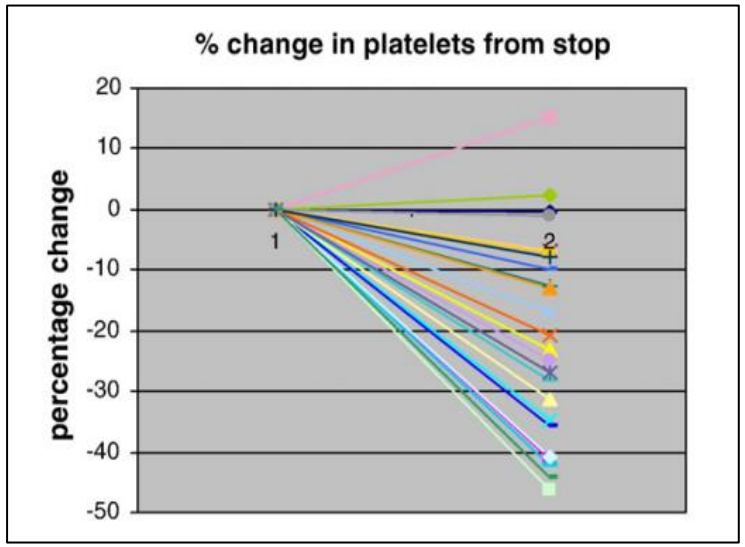


Fig. 1. Percent change in hemoglobin values (g/dL) from stop to recent evaluation.



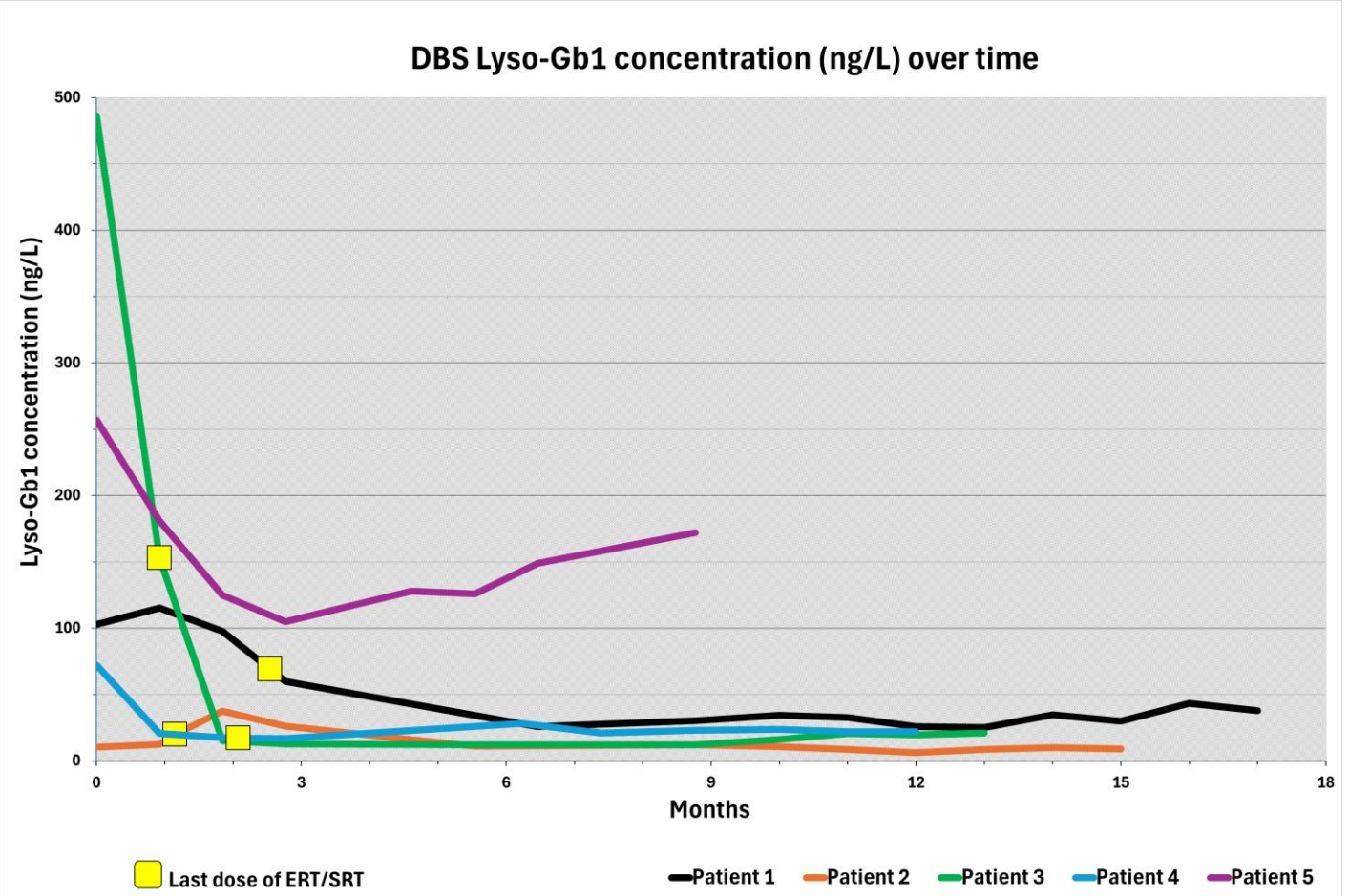
N=26; mean duration from interruption: 6.9 months
(all patients ≤12 months from interruption)

Cozma 2020, Zimran 2011

Substantial and durable reductions of Lyso-Gb1 in patients with persistently high levels despite years of prior treatment

Lyso-Gb1 is a reliable and validated biomarker for GD[1] and highly correlated to disease severity[2] and treatment response[3]

- Reductions in Lyso-GB1 seen as early as 1 month and sustained after SoC discontinuation (out to 14 months)
- 4/5 patients had elevated levels at baseline despite 4-24 years of SoC
- Low levels maintained in patient who entered trial with well-controlled lyso-Gb1

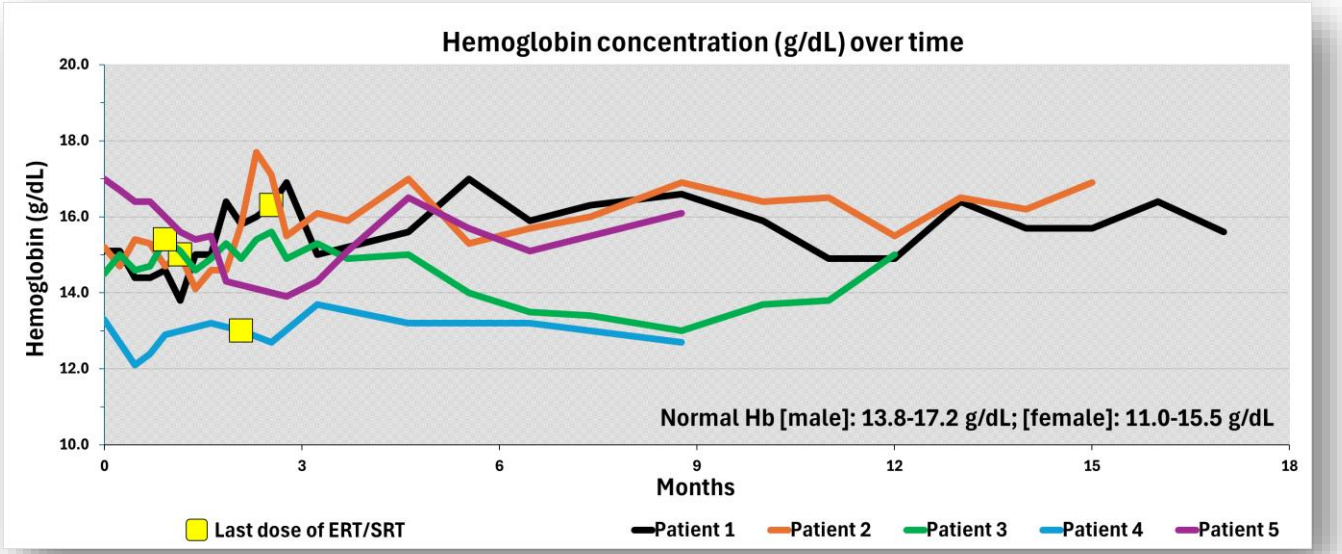


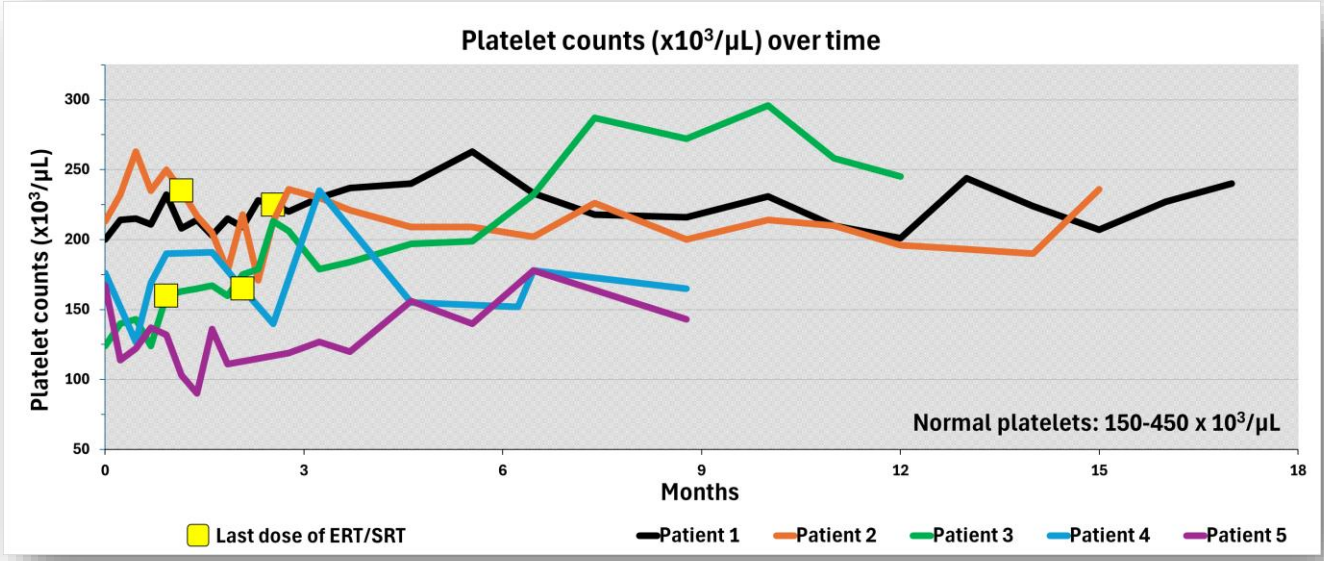
Data cut off as of 06 December 2024

DBS: Dried blood spot; Lyso-Gb1: Glucosylsphingosine

1. Rolfs A., et al, *PlosOne,* 2013, 2.Revel-Vilk S., *Int J. Mol Sci* 2020, 3. Peterschmitt et al. 2023

FLT201: Sustained improvement or maintenance of hemoglobin and platelets





Data cut off as of 06 December 2024

FLT201: well tolerated, with a favorable safety profile

- Infusions well tolerated; no infusion-related reactions
- ADRs were mild to moderate
- No dose-limiting toxicities
- 2 cases of ALT elevations above normal range (≤2 X ULN*) deemed related to therapy
  - Spontaneously resolved or managed with immune therapy
- Transient Anti-GCase antibodies in 2 patients
- ADRs related to immune management consistent with known profile

Summary of Adverse Drug Reactions for FLT201 and Immune Management (n≥2)	
Adverse Drug Reactions (ADR)	**# events (# patients)**
FLT201	
Elevated Alanine aminotransferase (ALT)	7 (6)
Fatigue	4 (3)
Activated partial thromboplastin time prolonged	2 (2)
Anti-GCase neutralizing antibodies	2 (2)
Prednisone	
Hyperglycemia	3 (3)
Weight increase	2 (2)
Panic attack	2 (1)
Tacrolimus	
Diarrhea	4 (4)

* Central lab values

Data cut off as of 06 December 2024

A single, low dose infusion of FLT201 shows positive outcomes up to 14 months after withdrawal of ERT/SRT

Safety	• FLT201 showed a favorable safety profile • Transient anti-GCase antibodies developed in two patients without impact on clinical parameters
Efficacy	• A single low dose of FLT201, with its increased enzymatic stability in the blood stream and cells, allows for constant availability of GCase to diseased tissues • Clinical parameters and key biomarkers showed sustained improvement or maintenance up to 14 months after SoC interruption
Conclusion	• Data from GALILEO-1 supports further development of FLT201 as a potential therapy to address unmet needs for type 1 GD • Phase 3 planning is underway with initiation expected in mid-2025

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