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SPUR THERAPEUTICS

Long-term durability of FLT201: an investigational gene therapy for Gaucher disease Type 1 encoding an engineered variant of the GCase enzyme

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Background

Gaucher Disease is a rare genetic lysosomal storage disorder caused by mutations in the *GBA1* gene, resulting in deficient glucocerebrosidase (GCase) and impaired breakdown of glycosphingolipids.[1]

- This deficiency leads to the accumulation of glucosylceramide and its toxic metabolite, glucosylsphingosine (lyso-Gb1), in multiple cell types.
- Gaucher disease Type 1 (GD1), the most common form, is characterized by hepatosplenomegaly, bone disease, anemia, thrombocytopenia, fatigue, pain, and pulmonary pathology.
- While enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are currently standard of care for the treatment of GD1 patients, significant unmet need remains.[2-6]
- Life-long requirements for treatment and variable or incomplete responses negatively impact patient outcomes and quality of life.

FLT201, an investigational gene therapy for the treatment of GD1, is designed to overcome the limitations of ERT/SRT.

- Novel, proprietary, liver-tropic capsid (AAVS3) with a unique GBA1-85 transgene encoding an engineered variant of β-glucocerebrosidase (GCase85).

GCase85 provides extended stability compared to wild type GCase both in serum and at lysosomal pH .

- Allows for significant uptake into multiple cells and tissues (liver, spleen, bone, lung, macrophage) and prevention of substrate accumulation across all tested tissues (in Gaucher mice)

	Human serum Half-life (hours)	Lysosomal pH Half-life (hours)
wt GCase	0.4	6.5
GCase85	2.4	>144
Fold increase	**6X**	**>21X**

Table 1: Stability of GCase85 versus wt GCase (velaglucerase alfa) in *in vitro* analyses

- No changes in immunogenicity compared to velaglucerase alfa
- This therapeutic approach provides continuous sustained GCase exposure beyond what is achievable with ERT, allowing for a low vector genome dose (4.5 x10^{11} vg/kg), a key component for a favourable safety profile.

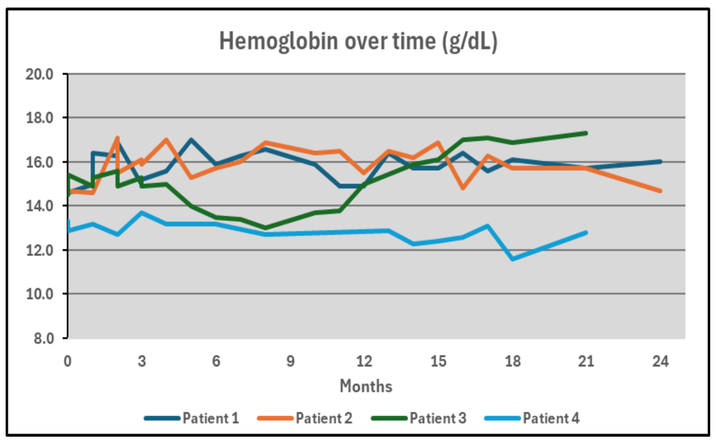
Patient demographics and disease characteristics at baseline

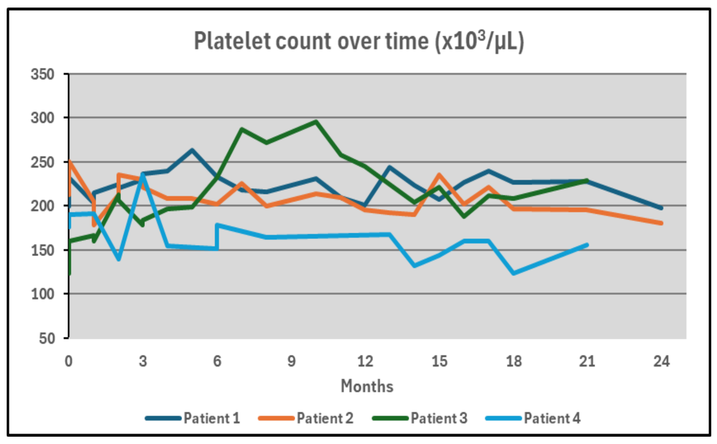
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age / Gender	35 / M	25 / M	24 / M	30 / F	24 / M	58 / F
Age at diagnosis	4	3	16	15	20	15
GBA1 Variant	p.Val433Leu; p.Asn409Ser	p.Asn409Ser; p.Leu483Pro	p.Gln112Valfs*32; p.Leu422fs; p.Leu483Pro; p.Ala495Pro	p.Asn409Ser; p.Leu483Pro	p.Asn409Ser; p.Leu29Alafs*18	p.Asn409Ser; p.Trp223Arg
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)	103	10	486#	73	257	53
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

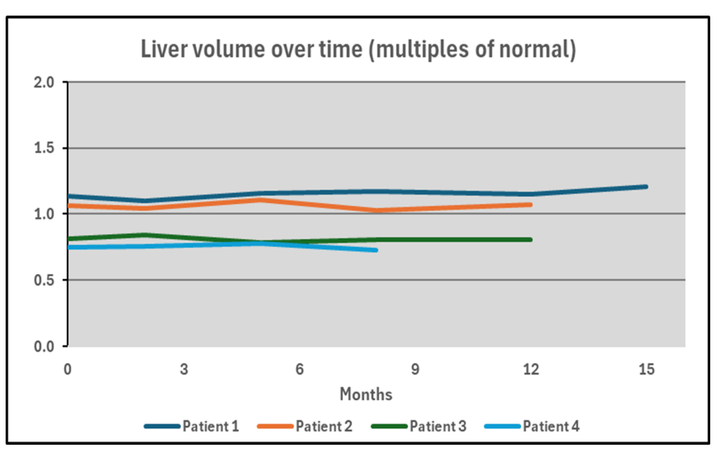
average of two baseline values

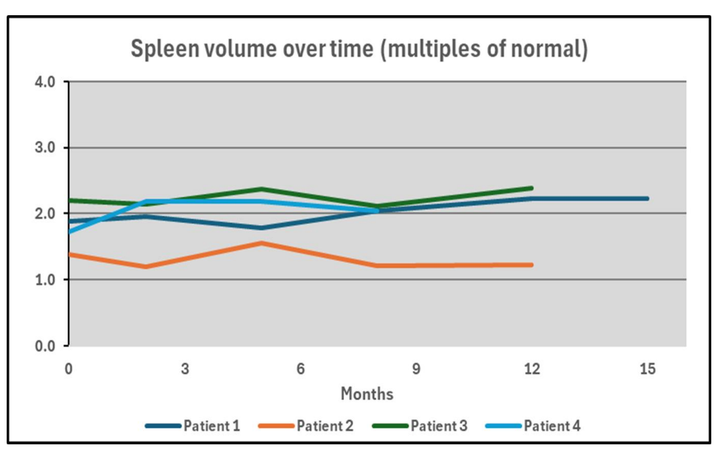
GALILEO-1 / GALILEO-2 overview

- GALILEO-1 was a first-in-human clinical trial of adult patients with GD1 who had been on a stable background therapy of ERT or SRT for at least 2 years.
- Study objectives are to assess safety and tolerability of FLT201 and to investigate the effects on disease-relevant clinical parameters.
- Six participants have received FLT201 at a low dose of 4.5 x 10^{11} vg/kg.
- At the discretion of the investigators, four participants discontinued ERT/SRT following FLT201 administration and remain off their background therapy.
- Two participants remain on SoC: Patient 5 and Patient 6, neither of these participants are included in the FLT201 efficacy analysis presented here. Additional commentary on these two participants is available in the safety section below.
- All participants have enrolled in GALILEO-2, the long-term follow up study.
- Follow-up duration ranges from 17 to 26 months.









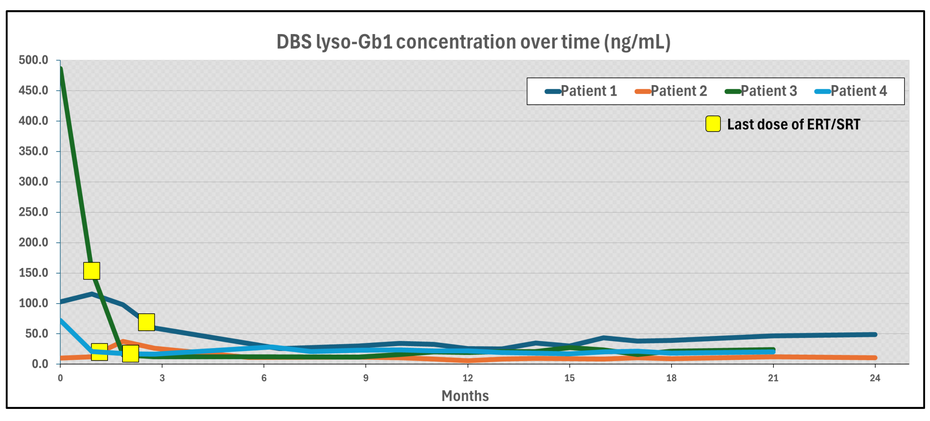
Efficacy (n=4, participants who discontinued SoC)

Four participants discontinued longtime SoC therapy (ERT/SRT) within 4-11 weeks after receiving FLT201. These four participants experienced maintenance or an improvement in outcomes, and all remain off background SoC for a duration of between 19-23 months to date.

Hemoglobin and platelet levels have improved or remained in the normal range. One participant experienced a transient drop in hemoglobin due to a newly diagnosed iron deficiency. Once iron supplements were initiated, hemoglobin levels returned to normal.

Liver and spleen volumes have remained stable.

DBS lyso-Gb1 levels were reduced or maintained. (Baseline mean [range]: 167.9 ng/mL [10.3-486.4 ng/mL]; Month 21 mean/range: 26.0 ng/mL [12.5-46.8 ng/mL], an 84.5% reduction). A similar picture was also seen in plasma lyso-Gb1.



Safety (n=6, all participants)

All participants experienced at least one ADR. ADRs occurring more than once are listed in **Table 2**. The most common ADRs associated with FLT201 were ALT increase and fatigue. ALT elevations even within the normal range were considered AEs of special interest as per protocol and therefore included as an ADR. Only two patients had an ALT elevation above the normal range and considered related to therapy**.** Both resolved, one spontaneously and one after tapering off prednisone.

Two participants developed transient anti-GCase antibodies. Patient 4 demonstrated no impact on efficacy during this short time. Patient 5 had early GCase expression and lyso-Gb1 reduction, which was subsequently lost, potentially due to anti-GCase antibodies and COVID infection in the month prior to receiving FLT201, which may have led to a heightened immune response impacting transgene expression. This patient remains on SoC.

One participant (patient 6), who had a low but detectable anti-AAVS3 titer at baseline, has not had detectable GCase expression and remains on SoC.

Table 2: Adverse Drug Reactions with 2 or more reports

Summary of ADRs (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)

Conclusions

- **The GALILEO-1 trial shows a favorable safety and tolerability profile with a single low dose of 4.5 x 10^{11} vg/kg.**
- **Continuous expression of GCase85, which is more stable than recombinant human GCase, ensures constant exposure to enzyme.**
- **Clinical parameters and key biomarkers show sustained improvement or maintenance up to 24 months to date after withdrawal of ERT/SRT in some patients.**
- **FLT201 shows potential for meaningful improvements in clinical outcomes over existing standard of care with a single infusion.**

Acknowledgements

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References

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Data cut off as of August 25, 2025

Abbreviations: ADR: Adverse drug reaction; DBS: dried blood spot; Hb: Hemoglobin; IM: Immune management; lyso-Gb1: Glucosylsphingosine; MN: Multiples of normal; SoC: Standard of care; WT: Wild type