Two-year follow up of avigbagene parvec (FLT201) investigational AAV gene therapy in adults with Gaucher disease type 1: Results from GALILEO-1 and GALILEO-2

I Schwartz[1], O Goker-Alpan[2], R Sharma[3], P Giraldo[4], P Foulds[5], S Flynn[5]

1. Hospital de Clinicas de Porto Alegre, Brazil; 2. Lysosomal and Rare Disorders Treatment Center, Virginia, USA; 3. Salford Royal Hospital, UK; 4. Hospital Universitario Quironsalud, Zaragoza, Spain; 5. Spur Therapeutics, Stevenage, UK

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]
- ERT requires intravenous (IV) infusions every 2 weeks for life, however due to its short half-life GCase levels become undetectable in target cells within 1–2 days leading to substrate reaccumulation.
- SRT is an alternative oral option for some patients that inhibits glucosylceramide synthesis but requires chronic daily dosing.

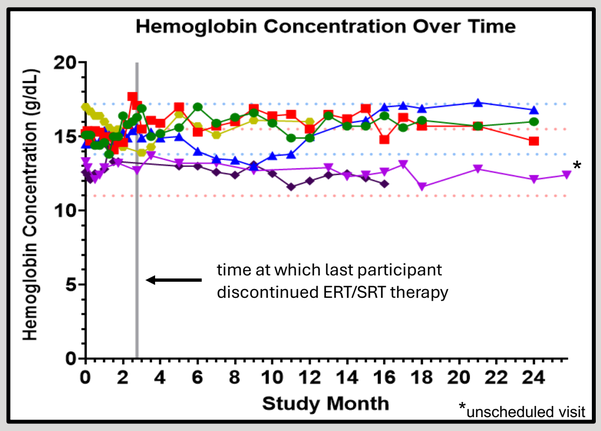
Avigbagene parvec (FLT201) an investigational gene therapy for the treatment of GD1, is designed to overcome the limitations of ERT/SRT.

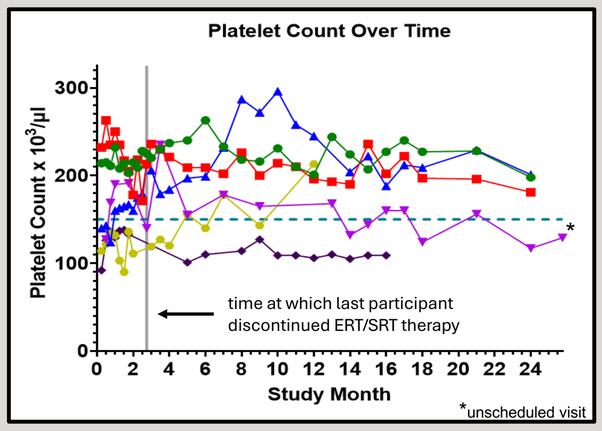
- Novel, proprietary, liver-tropic capsid (AAVS3) with a unique GBA1-85 transgene encoding an engineered variant of β-glucocerebrosidase (GCase85).
- GCase85 provides extended stability compared to wild-type GCase both in serum and at lysosomal pH.
- Allows for significant uptake into multiple cells and tissues (liver, spleen, bone, lung, macrophage) and prevention of substrate accumulation across all tested tissues (in Gaucher mice).[7]

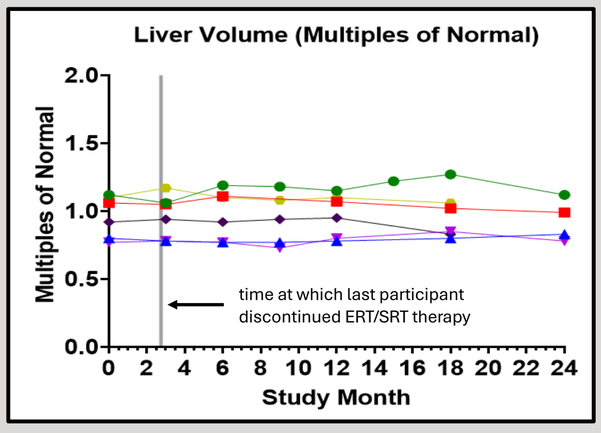
	Human serum Half-life (hours)	Lysosomal pH Half-life (hours)
wt GCase	0.4	6.5
GCase85	2.4	>144
Fold increase	**6X**	**>21X**

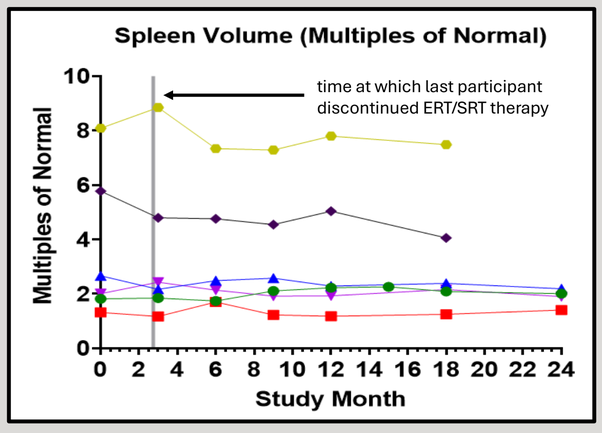
Table 1: Stability of GCase85 versus wt GCase (velaglucerase alfa) in *in vitro* analyses

- No difference in predicted 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 favorable safety profile.





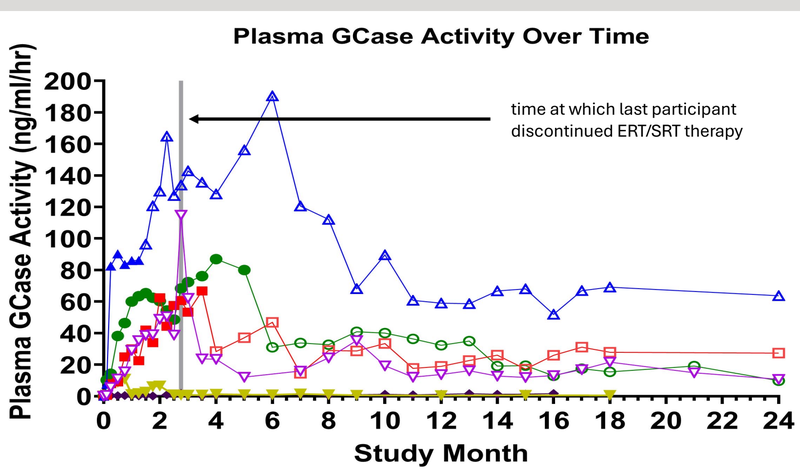




Normal values indicated by dashed line on charts above:
- Normal Hb [male] 13.8-17.2 g/dL
- Normal Hb [female] 11.0-15.5 g/dL
- Normal platelet count 150-450 x 10^3/µL

Legend for all graphs

Patient 1 — Patient 2 — Patient 3 — Patient 4 — Patient 5 — Patient 6



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 a single low dose of FLT201: 4.5 x 10^{11} vg/kg.
- Immune management regimen began 3 weeks post-infusion and consisted of oral steroids (prednisolone/prednisone) and/or oral tacrolimus.
- All participants have enrolled in GALILEO-2, the long-term follow up study.
- Patient follow-up ranges between 20 to 29 months after FLT201 dosing.

	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]; [Asn409Ser]	p.[Asn409Ser]; [Leu483Pro]	p.[Gln112ValfsTer32]; [Leu422ProfsTer4; Leu483Pro; Ala495Pro]	p.[Asn409Ser]; [Leu483Pro]	p.[Asn409Ser]; [Leu29AlafsTer18]	p.[Asn409Ser]; [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)	102.9	10.3	383.3	72.2	257.0	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)	1.82	1.32	2.67	2.01	8.09	5.78
Liver volume (MN)	1.12	1.06	0.80	0.77	1.10	0.92
Total BMB Score	7	7	11	11	13	7

Table 3: Patient demographics and baseline characteristics

[#] Below lower limit of quantification

Efficacy

Four participants have discontinued their longtime SoC therapy (ERT/SRT).
- SoC was discontinued between 4-11 weeks post FLT201 infusion, all remain off ERT/SRT.
- Duration since stopping ERT/SRT ranges between 22-26 months to data cut.

These four participants have experienced maintenance or an improvement in outcomes:
- Hemoglobin and platelet levels have improved or remained in the normal range.
- Liver and spleen volumes have remained stable.
- GCase activity shows a substantial increase from baseline.
- Lyso-Gb1 levels were maintained or reduced.

Two participants remain on their SoC.
- Patient 5 – No durable enzyme expression or sustained improvements in lyso-Gb1; likely attributable to a heightened and less regulated immune response due to a confluence of contributing factors impacting transgene expression.
- Patient 6 – No apparent GCase expression, detectable pre-existing AAVS3 NAbs at a titer below exclusion cut-off.

Safety

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.
- Two patients had an ALT elevation above the normal range (≤2xULN) and considered related to therapy. Both resolved, one spontaneously and one after tapering off prednisone.

Immunogenicity
- Two participants developed transient anti-GCase antibodies.
  Patient 4 demonstrated no impact on efficacy during this short time and remains off ERT/SRT.
  Patient 5 had early GCase expression and reduction in lyso-Gb1 levels, which was subsequently lost starting at Week 3. At that time, the patient was negative for anti-GCase antibodies.
  Transient anti-GCase antibodies were detected, starting at week 12 thru to week 24 following FLT201 administration. This patient remains on SoC.
- Patient 6 who had a low but detectable anti-AAVS3 titer at baseline, has not had detectable GCase expression and remains on SoC.

GALILEO-3 (Phase 3) will focus on patients with no detectable AAVS3 Nabs.

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

- **GALILEO-1 / GALILEO-2 show a favorable safety and tolerability profile for FLT201 with a single infusion at a low dose of 4.5 x 10^{11} vg/kg.**
- **Clinical parameters and key biomarkers show sustained improvement or maintenance up to 26 months to date after withdrawal of ERT/SRT.**
- **The continuous expression of GCase85, which is more stable than recombinant human GCase, ensures constant exposure to enzyme.**
- **FLT201 shows potential for meaningful improvements in clinical outcomes over the existing SoC (ERT/SRT) with a single infusion.**

Acknowledgements

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References

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Abbreviations: ADR: Adverse drug reaction; AE: adverse event; BMB: bone marrow burden; DBS: dried blood spot; Hb: Hemoglobin; IM: Immune management; lyso-Gb1: glucosylsphingosine; MN: Multiples of normal; NAbs: neutralizing antibodies; SoC: Standard of care; WT: Wild type.

Data cut off as of November 20, 2025

GALILEO-1 / GALILEO-2 / GALILEO-3 studies are sponsored by Spur Therapeutics

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