Trial in Progress: GALILEO-3, a Phase 3 Registrational Trial of avigbagene parvec (FLT201) Gene Therapy Candidate in Patients with Gaucher disease type 1

R Sharma[1], S Revel-Vilk[2,3], O Goker-Alpan[4], I Schwartz[5], P Giraldo[6], P Foulds[7], S Flynn[7], D Hughes[8,9]

1. Salford Royal Hospital, UK 2. Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel; 3. Faculty of Medicine, Hebrew University, Jerusalem, Israel; 4. Lysosomal and Rare Disorders Treatment Center, Virginia, USA; 5. Hospital de Clinicas de Porto Alegre, Brazil; 6. Hospital Quironsalud de Zaragoza, Spain; 7. Spur Therapeutics, Stevenage, UK; 8. Royal Free Hospital, London, UK; 9. University College London, 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; 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.

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 were to assess safety and tolerability of FLT201 and to investigate the effects on disease-relevant clinical parameters.
- Six participants received a single low dose of FLT201: 4.5 x 10^{11} vg/kg.
- All participants have enrolled in GALILEO-2, the long-term follow up study.
- Clinical parameters and key biomarkers show sustained improvement or maintenance in patients who discontinued ERT/SRT.
- GALILEO-1 / GALILEO-2 show a favorable safety and tolerability profile for FLT201.

GALILIEO-3 will assess the safety and efficacy of FLT201

Measure stability:

- Hemoglobin
- Platelets
- Liver volume
- Spleen volume

Monitor:

- Adverse events
- Immune responses
- Clearing of vector

Measure changes:

Gaucher disease activity

- GCase activity
- Lyso-Gb1 levels
- Bone marrow burden
- Bone mineral density
- GD-DS3 score

Patient-reported outcomes

- QoL (SF-36 score)
- FACIT-Fatigue score
- GD1-PROM

Key Inclusion Criteria*

- Adult ≥18 years at time of screening
- Diagnosis of Gaucher disease type 1
- Stable hemoglobin concentration
- Stable platelet count
- Receiving ERT or SRT without interruption for at least 2 years

Key Exclusion Criteria*

- Diagnosed or suspected Gaucher disease type 2 or type 3
- Positive for AAVS3 neutralizing antibodies
- History of total splenectomy
- Abnormal lab values, conditions or diseases that would make the participant unsuitable for the study
- Positive pregnancy test or lactating
- History of hematopoietic stem cell transplant (HSCT)/bone marrow transplant or any solid organ transplant
- History of receiving any gene therapy or cell therapy

* Additional protocol defined criteria apply

Avigbagene parvec (FLT201)

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.

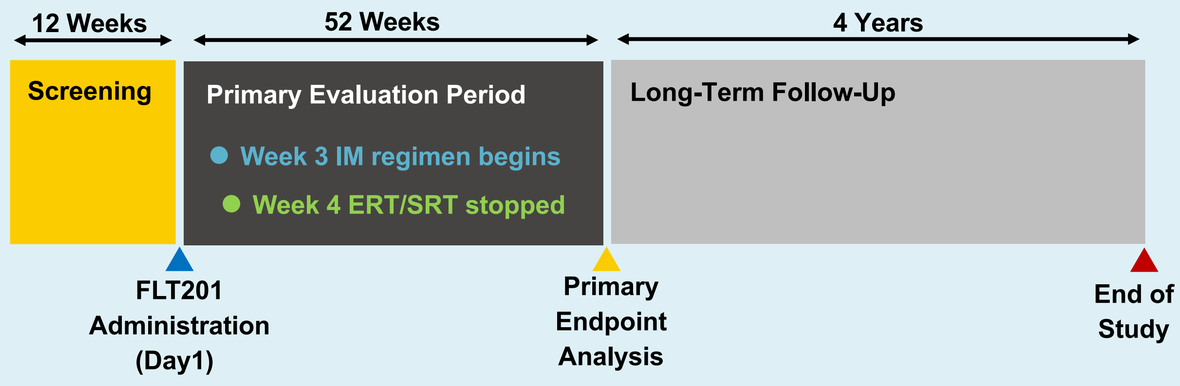
- Allows for significant uptake into multiple cells and tissues (liver, spleen, bone, lung, macrophage) and prevention of substrate accumulation across all tested tissues (in Gaucher mice).[7]

	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 wild-type 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.

GALILIEO-3 Study schema



GALILEO-3 trial design

GALILEO-3 (NCT07223944) is an open label, non-randomized, global, multicenter, phase 3 study designed to evaluate the safety and efficacy of FLT201 in adults with GD1.

- The study will enroll approximately 45 adults with GD1 who have been on stable treatment with ERT or SRT for at least 2 years.
- Participants who provide informed consent will be screened for trial eligibility over a period of up to 12 weeks during which time baseline assessments will be collected.
- Participants will receive a single IV infusion of FLT201 at a low dose of 4.5 x 10^{11} vg/kg.
- Following administration of FLT201, participants will receive a prophylactic regimen of immunosuppressants. Immunosuppressants may also be administered during the trial in a reactive regimen to treat any immune-mediated event e.g. ALT elevation.
- Participants will maintain their current ERT/SRT treatment regimen until Week 4 after which ERT/SRT will be stopped.
- Participants will be followed for 5 years during which time safety, efficacy, and durability of transgene expression will be assessed.
- A primary analysis will occur at Week 52 with the option for an interim analysis to occur at Week 24 and a final analysis at the end of study.
- The primary endpoint for the study is the proportion of participants with stable hemoglobin concentration at Week 52.
- Key secondary efficacy endpoints include the proportion of participants with stable platelet count, spleen volume, and liver volume at Week 52.
- Other secondary endpoints will evaluate the safety of FLT201, FLT201 driven expression of GCase, changes from baseline in additional measures of GD activity including lyso-Gb1 levels, BMB, BMD, GD-DS3, various patient reported outcome measures to assess quality of life and fatigue.

Conclusions

- GALILEO-3 is a pivotal phase 3 switch study that is designed to evaluate the safety and efficacy of FLT201 in adult GD1 participants on stable ERT/SRT therapy.
- This study is intended to support the registration of FLT201 in the adult GD1 population.

References

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Abbreviations: BMB: bone marrow burden; BMD: bone mineral density; GD-DS3: Gaucher disease severity scoring system; GD1-PROM: Gaucher disease type 1-specific patient reported outcomes measures; IM: Immune management; QoL: quality of life; SF-36: short-form health survey.

SPUR THERAPEUTICS

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