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

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# **BACKGROUND**

**Gaucher disease (GD)** is one of the most common lysosomal storage disorders. Pathogenic variants in the *GBA1* gene attenuate or abrogate the activity of the lysosomal acting enzyme glucocerebrosidase (GCase)<sup>1</sup>.

While enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are currently standard of care for the treatment of type 1 GD (GD1) patients, significant unmet need remains. Life-long requirements for treatment and variable or incomplete responses negatively impact patient outcomes and quality of life<sup>2-6</sup>.

**FLT201**, an investigational gene therapy for the treatment of GD1, is a novel, proprietary, livertropic capsid (AAVS3) with a unique GBA1 transgene encoding an engineered variant of  $\beta$ -glucocerebrosidase (GCase85) that provides extended stability in serum and at lysosomal pH compared to wild type GCase, allowing for greater residence time and availability for use by tissues.

#### **AIMS**

To assess safety and tolerability of FLT201 and to investigate the effects on disease-relevant clinical parameters.

# **METHODOLOGY**

# **GALILEO-1 Study**

- A first-in-human, open-label, dose-finding study of a single intravenous infusion of FLT201 at a dose of 4.5 × 10<sup>11</sup> vector genomes per kilogram (vg/kg) of body weight.
- Eligible patients have GD1, are 18 years or older, on stable ERT or SRT for ≥2 years and have a negative AAVS3 neutralizing antibody test.
- Immune management regimen began 3 weeks post-infusion [prednisone only (n=4), prednisone + tacrolimus (n=2)].
- Discontinuation of background ERT or SRT occurred at the discretion of the investigator once GCase levels were recorded as increased.
- Participants were monitored for 38 weeks after the infusion before entering long-term follow-up.

#### Table 2: 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 (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 <sup>3</sup> /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

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)		

# **Exposure and Safety**

All patients 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 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 (Figure 1). Both resolved, one spontaneously and one after tapering off prednisone.

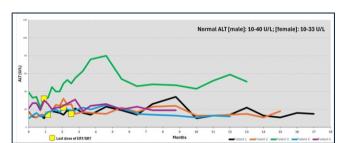


Figure 1: ALT over time (central lab)

At data cut off, patients have been exposed to the lowest dose of FLT201 (4.5e11vg/kg) for 9-17 months. All patients who came off their prior SoC therapy (between weeks 4-11) remain off (10-14 months). One patient (patient 6), who had a low but detectable anti-AAVS3 titer at baseline, has not had detectable GCase expression and remains on SoC (not included in the efficacy data set).

Two participants developed transient anti-GCase antibodies with no impact on safety. Neither patient experienced loss of clinical benefit during this period although both demonstrated a reduced GCase expression to varying degrees (data not shown), with one (patient 4) rebounding fully to pre-antibody levels once antibody negative. A resulting rebound in GCase measurement in the other patient (patient 5) has not yet occurred.

# Efficacy (n=5)

All patients experienced maintenance or improvement in outcomes after receiving FLT201. All but one patient came off their longtime SoC (ERT/SRT) within 4-11 weeks after receiving FLT201 (patient 5 remains on SRT). DBS lyso-Gb1 levels improved rapidly in those with elevated levels at baseline (Baseline mean [range]: 185.8 ng/mL [10.3-486.4 ng/mL]; Week 38 mean/range: 49.8 ng/mL [12.0-172.0 ng/mL], a 73% reduction). Hemoglobin and platelet levels improved or remained in the normal range (Figures 2 and 3). One patient experienced a drop in hemoglobin due to a diagnosed iron deficiency. Once iron supplements were initiated, the hemoglobin levels returned to normal. Liver and spleen volumes improved or remained stable (Figures 4 and 5). One patient had an enlarged spleen at study entry. By Week 38, this patient had a reduced spleen volume, now into the target goal.

# **RESULTS**

So far, six participants previously treated with TRE or TRS have received FLT201, with a follow-up period ranging from 6 to 15 months.

# Safety (n=6)

Six patients were dosed with FLT201 at 4.5e11vg/kg. **Table 1** details the baseline demographics and disease status for all enrolled patients. All patients demonstrated continued disease activity at study entry.

# CONCLUSION

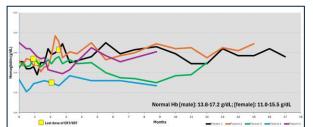


Figure 2: Hemoglobin over time

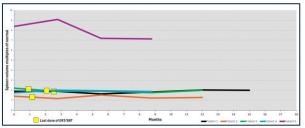


Figure 4: Spleen volume over time (multiples of normal)

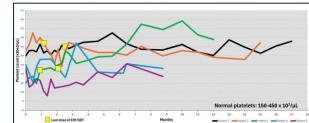


Figure 3: Platelets over time

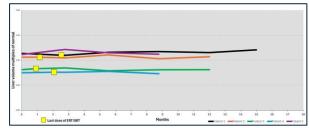


Figure 5: : Liver volume over time (multiples of normal)

- GALILEO-1 trial shows a favorable safety and tolerability profile with a single low dose of 4.5e11 vg/kg.
- Clinical parameters and key biomarkers showed sustained improvement or maintenance up to 14 months after withdrawal of ERT/SRT.
- 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 existing standard of care with a single infusion.

# REFERENCES

1. Stirnemann J, Belmatoug N, Camou F, et al. Int J Mol Sci. 2017;18(2):441. 2. Gary SE, Ryan E, Steward AM, Sidransky E.Expert Rev Endocrinol Metab. 2018;13:107–118. 3. ShaymanJA. Advances in Gaucher disease: basic and clinical perspectives. Future Medicine Ltd, Grabowski: London; 2013; 240–256.4. Weinreb NJ, et al. J Inherit Metab Dis. 2013;36: 543–553. 5.Wyatt K, et al. Health Technol Assess. 2012;16:1-543. 6. Revel-VilkS, et al. Br J Haematol. 2018;182:467-480.