Durability of FLT201: An Investigational Gene Therapy for Gaucher Disease Type 1 Encoding an Engineered Variant of the GCase Enzyme

Rose Sheridan

ASGCT Abstract **174**

May 15, 2025 Time: 8:00 AM - 9:45 AM

Disclosure

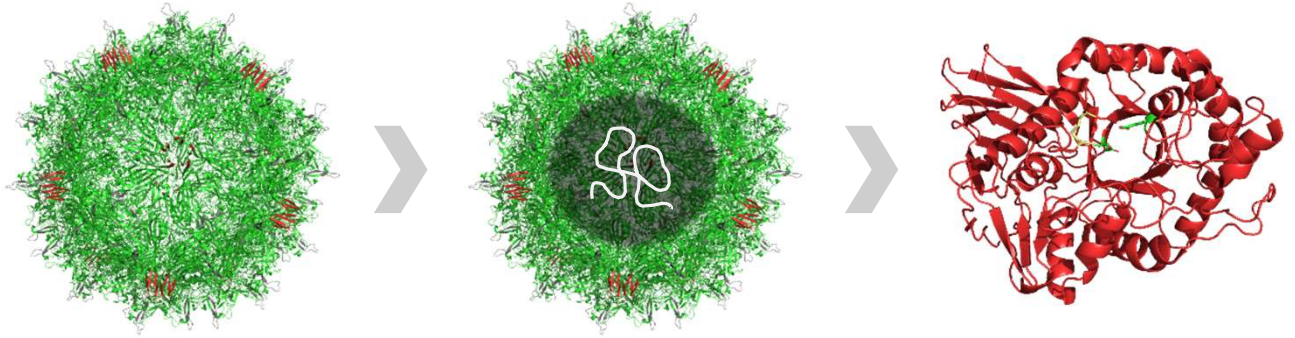
Rose Sheridan is full time employed at Spur Therapeutics Limited.

FLT201

Targeting Gaucher Type 1

- Efficient liver transduction
- Liver restricted expression
- Robust and sustained secretion of GCase into blood stream
- GCase variant 85 shows increased stability at lysosomal and physiological pH

Optimized liver-directed AAV gene therapy for Gaucher Type 1



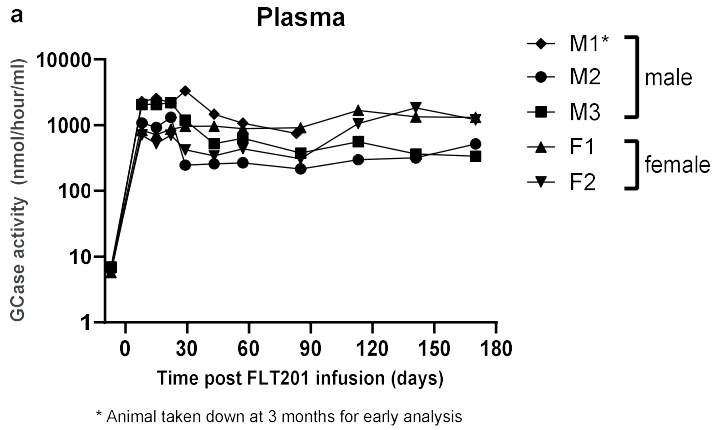
Liver Selective Capsid
AAVS3

Optimized Genome
through promoter design and codon optimization

Stable Engineered GCase
for optimized exposure and efficacy

FLT201 leads to durable GCase expression in non-human primates (NHP)

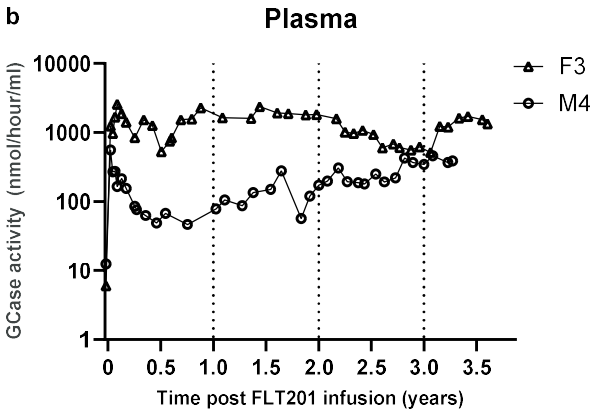
Safety analysis for FLT201 dosed at $2x10^{12}$ vg/kg (n=7, 4M/3F)
FLT201 was well tolerated in NHPs
No deaths or adverse treatment-related effects
Minimal or mild infiltrates observed in the DRG (4/5 animals) and kidneys (2/5 animals)
Infiltrates were not considered adverse and unlikely to be related to the administration of FLT201



* Animal taken down at 3 months for early analysis

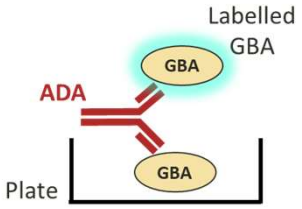
Two animals continue on study to 5 years

Animal	Age (yr)	Weight (kg)	Total Dose (vg)
F3	3.5 yr	4.4	8.8e12
M4	1 yr	2.5	5e12



a: GRC 2023: Sheridan et al. Development of a Novel Liver-Directed AAV Gene Therapy Candidate for Gaucher Disease Type I

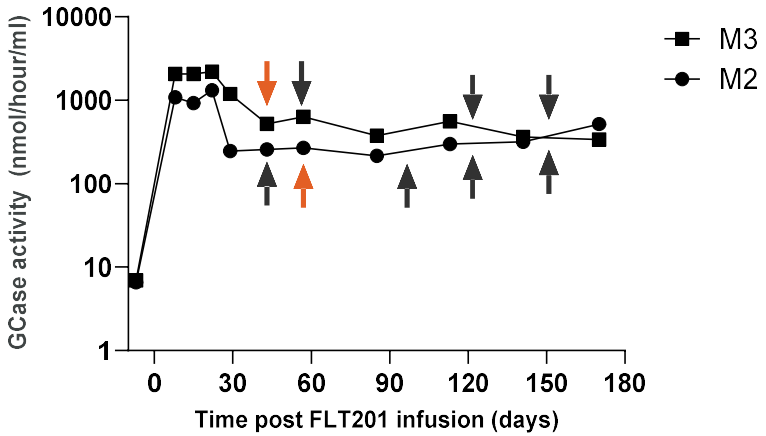
Total antibodies to GCase were transient with no long-term impact



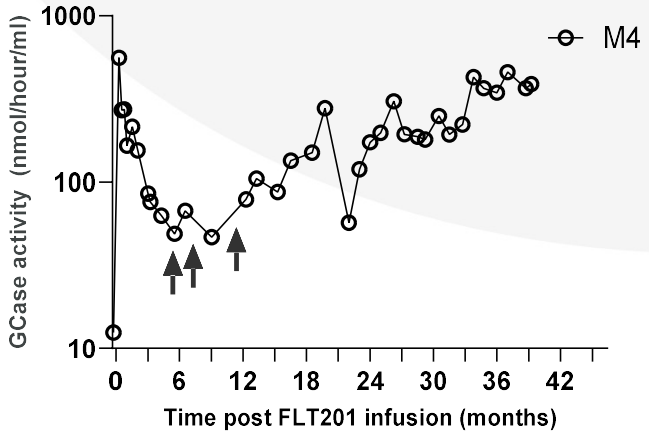
Total antibodies µg/mL plasma (min-max)	
M3	2.1-8.3
M2	2-20.1
M4	1.7-1.9

↓ Total antibodies detected ↓ Max

a Transient Antibodies 2/5 NHP to 6 months



b Transient Antibodies 1/2 NHP to 3.5 years

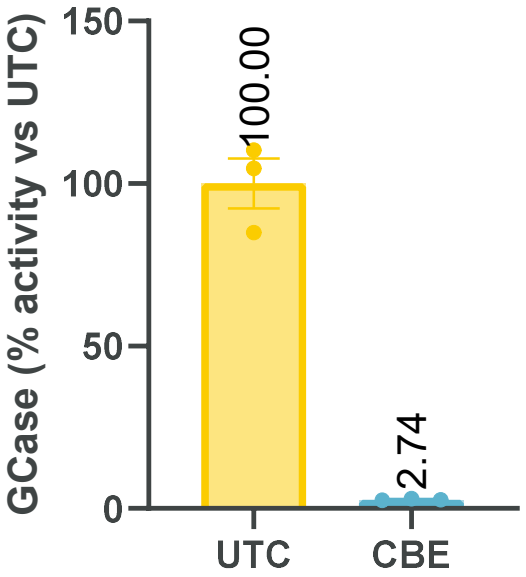


Total antibodies to expressed GCase may be responsible for a drop in peak activity
Antibodies are transient, GCase expression recovers

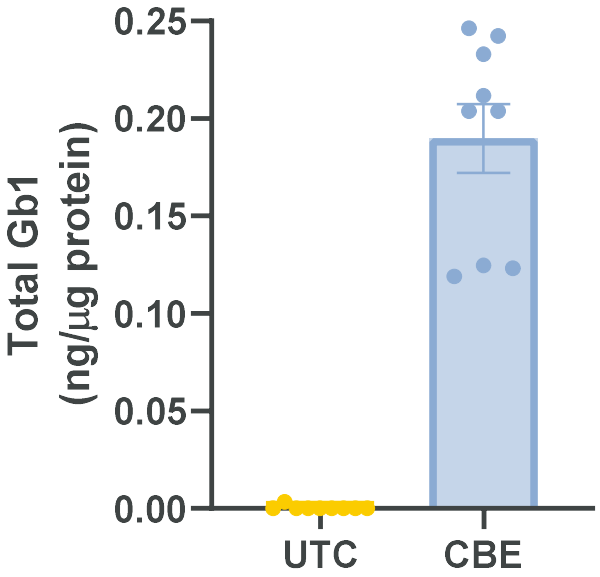
1% rhesus plasma average + 1.645*SD used as Limit of Blank (LoB); MRD (100) applied to all samples

Conduritol-β-epoxide (CBE), an irreversible inhibitor of GCase, provides an *in vitro* macrophage model of GCase deficiency

GCase activity is inhibited in CBE treated MØ



Substrate Gb1 accumulates in CBE treated MØ



MØ: macrophage

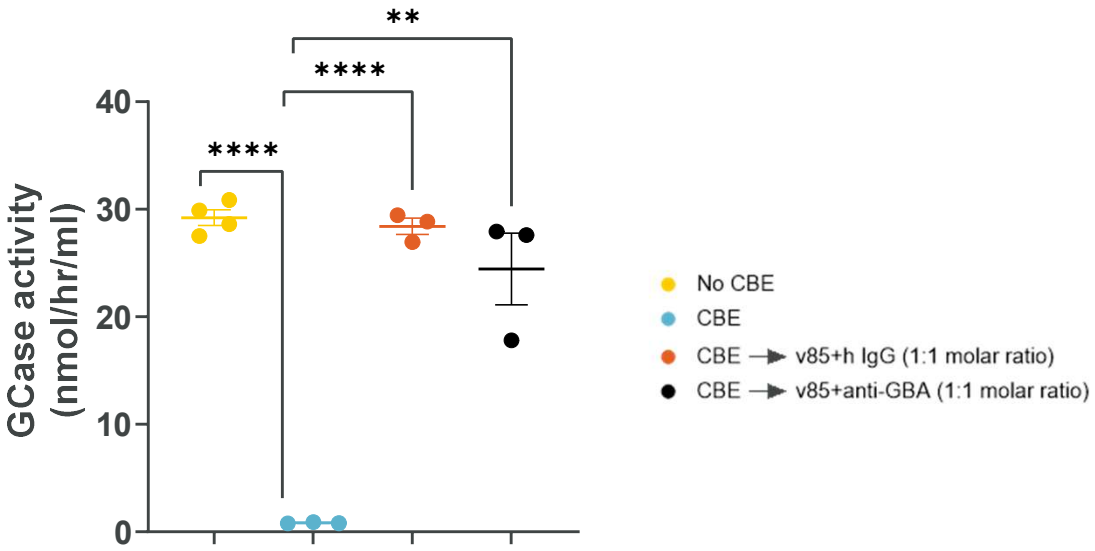
CBE: conduritol-β-epoxide, 10 days pre-treatment

UTC: Untreated control

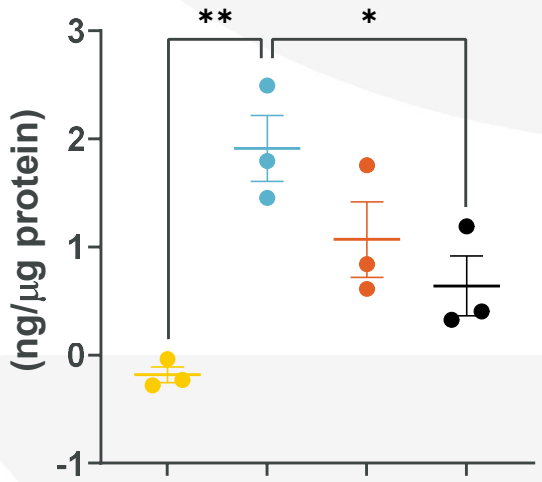
Continued GCase uptake despite the presence of antibodies may account for durable outcomes

Rescue of CBE treated human macrophages

†Anti-GCase antibody does not appear to impair GCase uptake



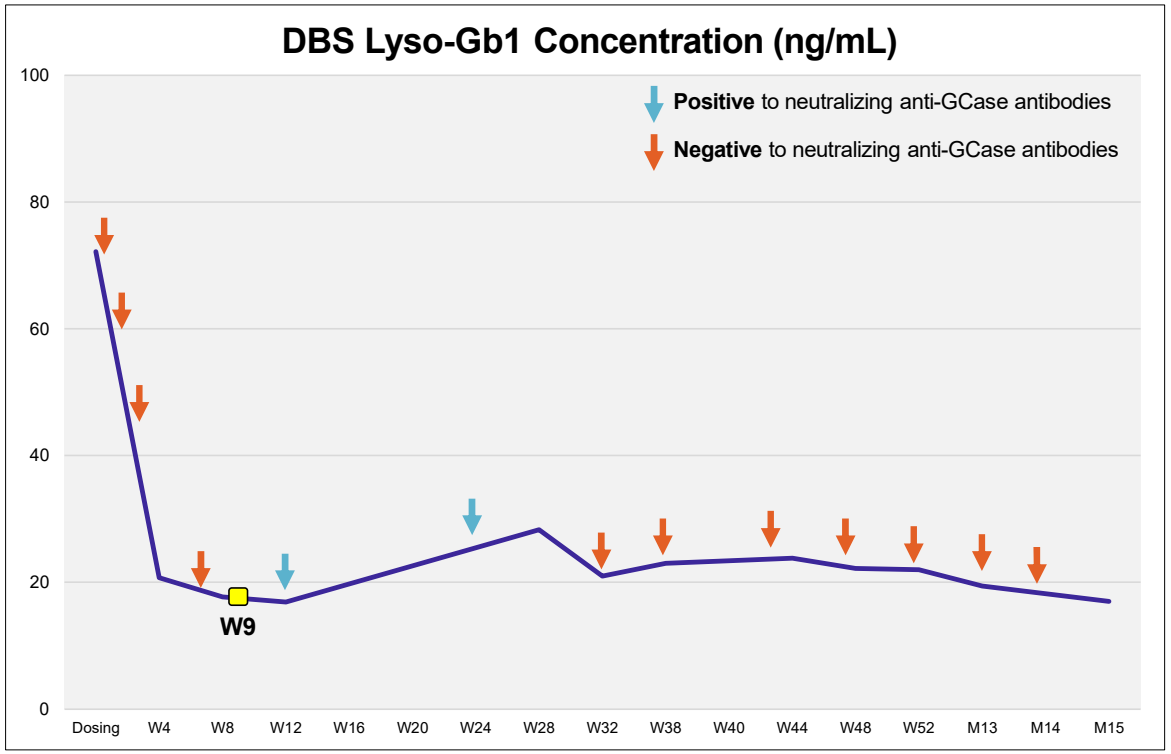
†Anti-GCase antibody does not appear to impair substrate reduction



† **anti-GBA** Partially neutralizing monoclonal antibody 25% inhibition, tested at ~1 µM in 5% normal human serum; **v85**: rGCase85 4h treatment, 2 µg/mL -/+ IgG or Ab- 1:1 molar ratio; **h IgG**: Human IgG isotype control

Clinical benefit continues after transient anti-GCase antibodies detected in GALILEO-1

In a patient that successfully discontinued ERT*, continued stability of clinical parameters continue



Patient 4 Response to FLT201:

- Single **low dose** of FLT201 (4.5e11 vg/kg)
- Rapid and sustained reduction of **lyso-Gb1 levels** enabling ERT discontinuation
- Transient **anti-GCase antibodies** corresponded with transient increases in lyso-Gb1 and decreases in GCase activity.
- **Plasma GCase** expression consistently greater than thresholds for healthy individuals (data not shown).
- **No safety** concerns or **clinical deterioration** observed (hemoglobin, platelets, liver or spleen volume) through 15 months.

** Note: Transient anti-GCase antibodies were also observed in a second participant with low transduction efficiency that remains on SRT*

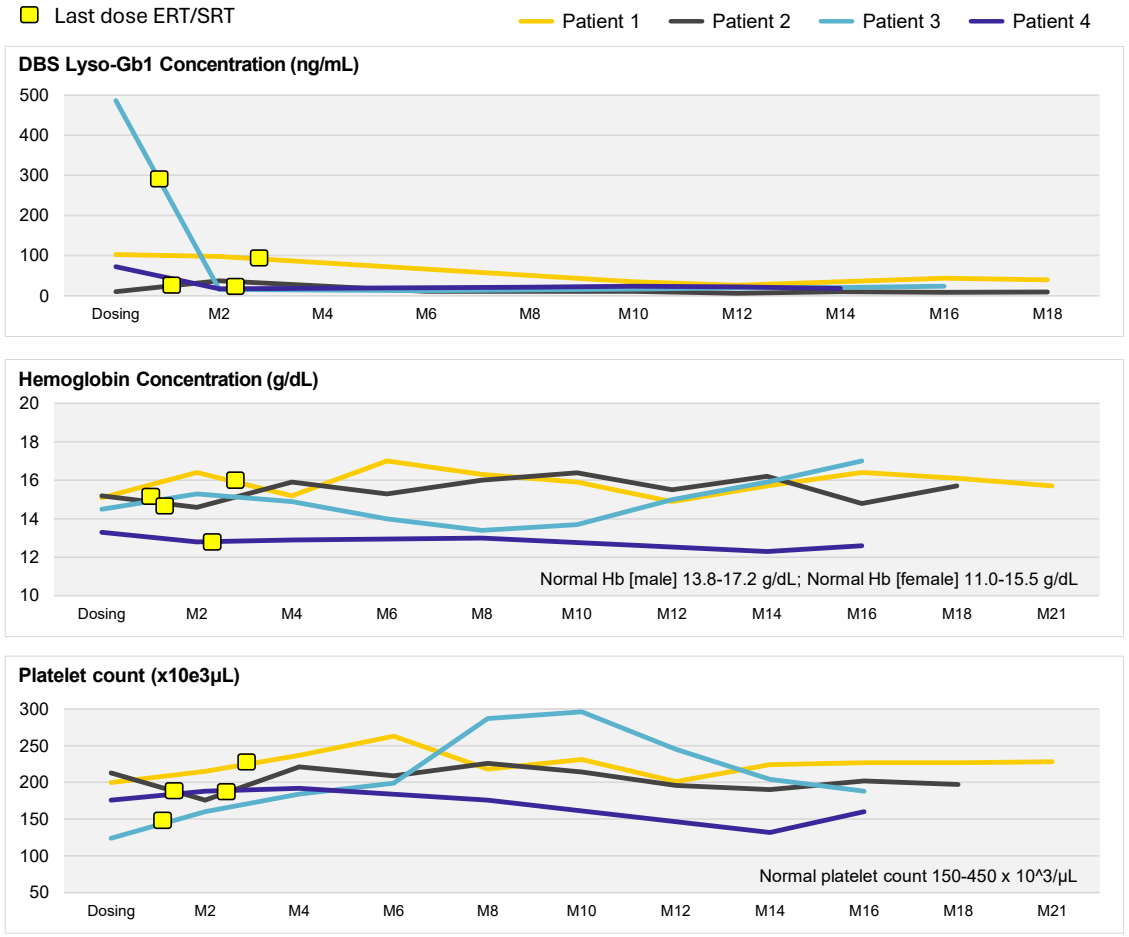
Durable clinical benefit observed for FLT201 treated Gaucher disease Type 1 patients

GALILEO-1/2 First-In-Human Trial of FLT201

- **Single, low dose (4.5e11 vg/kg):** Favorable safety and efficacy

Four participants that discontinued ERT/SRT prior to week 12 showed:

- **Durable GCase expression**: plasma GCase levels consistently greater than thresholds for healthy individuals (data not shown)
- **Sustained efficacy**: Improvement or maintenance of clinical endpoints up to 21 months



Data cut off as of 28 March 2025

Conclusions

FLT201 is a liver-directed AAV gene therapy delivering the GCase85 transgene designed for efficient liver transduction, stable systemic GCase secretion, and enhanced enzyme durability

- **FLT201 GCase expression is durable in both preclinical and clinical studies**
  - FLT201 showed durable GCase expression for up to 3.5 years in rhesus macaques, with no significant safety findings.
  - FLT201 shows durable clinical expression out to 21 months to date.

- **Durable GCase expression with FLT201 appears to translate into clinical benefit**
  - In humans, FLT201 led to rapid and sustained reductions in lyso-Gb1 and discontinuation of enzyme replacement therapy.

- **Anti-GCase antibodies appear to be transient in nature**
  - Transient anti-GCase antibodies were observed in some NHP animals and in some humans.
  - No clear detrimental impact on clinical benefit has been identified.

Acknowledgements

Spur Therapeutics

J Khinder

T Dodev

R Nunez-Toldra

A Dimokov

Dr. P Foulds

Dr. P Yin

CJ Miranda

JM Jeyakumar

KM Alawi

R Corbau

M Buono

Royal Free Hospital, UCL

Dr. and Prof. AC Nathwani

GALILEO-1 Study Investigators

USA – Dr. O Goker-Alpan, Dr. D Vats, Dr. G Maegawa

Spain – Dr. P Giraldo, Dr J Villarubia, Dr. M Camprodon, Dr. X Solanich Moreno

UK – Dr. R Sharma, Prof. D Hughes

Brazil – Dr. and Prof. I Schwartz

Israel –Prof. H Baris-Feldman, Prof. S Revel-Vilk, Dr. N Ruhrman Shahar

Paraguay – Dr. D Gonzalez

Germany – Dr. N Muschol, Dr. E Mengel

We thank all the patients who participated in the GALILEO-1 study and their families as well as those who support the Gaucher community.