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

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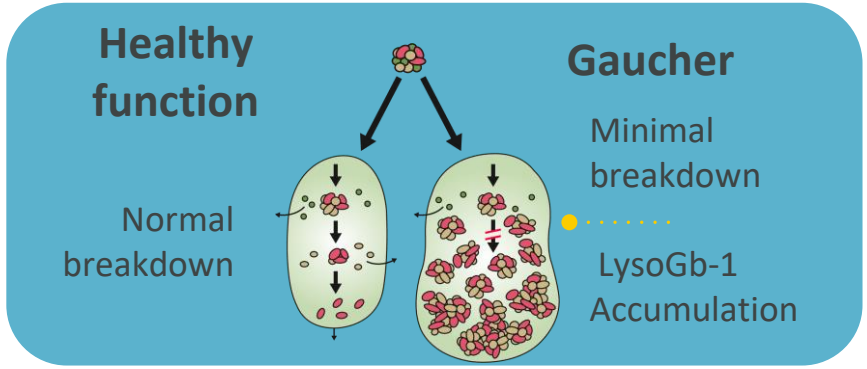
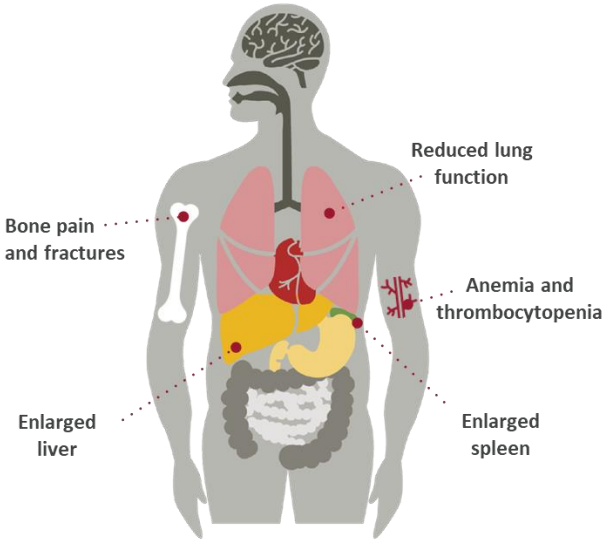
Disclosures

Francesca Ferrante is full time employed at Spur Therapeutics Limited

Gaucher disease Type 1 is a rare progressive disorder resulting from deficiency of glucocerebrosidase (GCase) due to mutations in *GBA1*

- GCase deficiency leads to accumulation of glucosylsphingosine (lysoGb-1)
  - A diagnostic and treatment predictor biomarker





- Anemia, thrombocytopenia
- Liver, spleen enlargement
- Bone pathology, pain
- Fatigue

Up to 60% of patients treated with ERT still experience symptoms, likely due to limited systemic distribution and short-lived retention in cells

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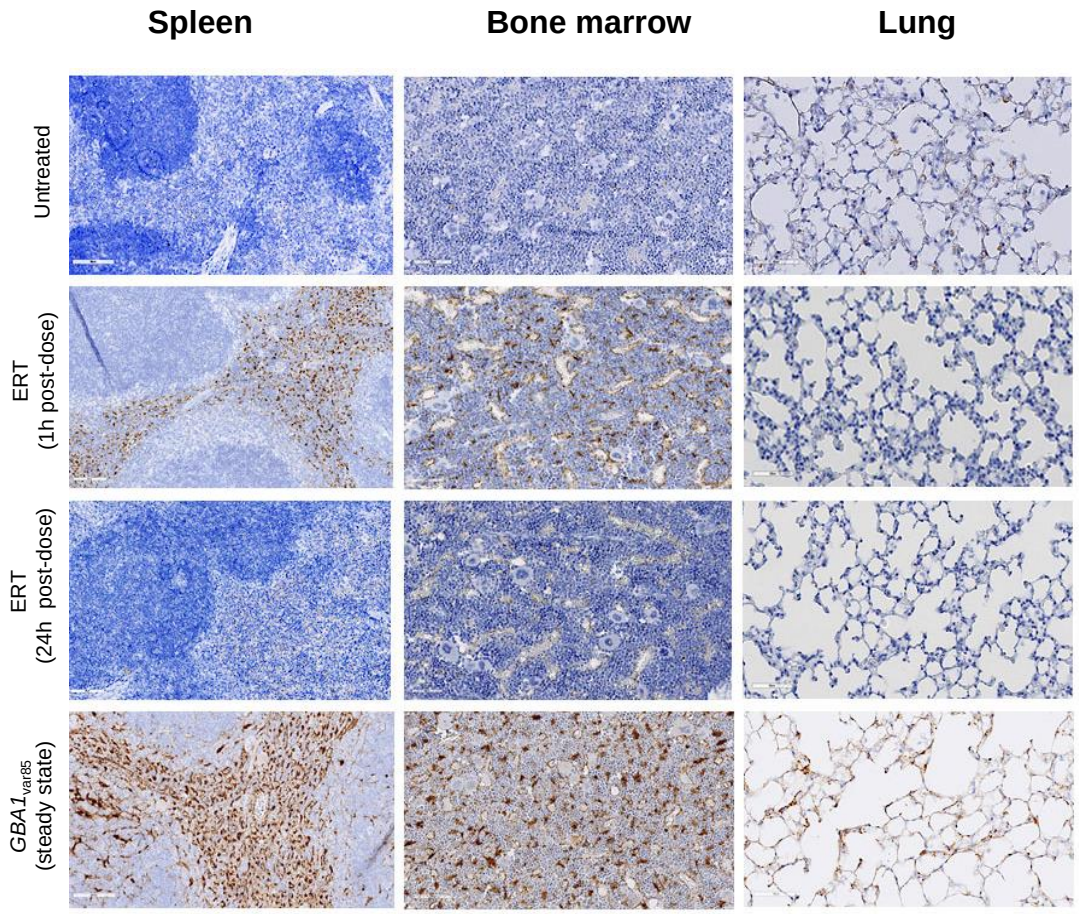
FLT201 is an AAV vector serotype S3 encoding a protein engineered human β-Glucocerebrosidase (GCase85)

- Novel human AAV capsid (AAVS3) with high liver tropism
- Transgene encoding GCase85, a novel engineered glucocerebrosidase
- GCase85 has similar catalytic properties to human GCase with increased enzymatic stability
  - **6-fold increase** in human serum
  - **>20-fold increase** at lysosomal pH conditions
- Produces robust and sustained secretion of more stable GCase into the bloodstream
- No changes in predicted immunogenicity compared to velaglucerase alfa

Sustained GCase uptake across all key tissues compared to ERT

- Untreated tissue shows absence of GCase
- Variable presence of GCase 1 hour post-ERT in different tissues
- Rapid clearance of GCase 24 hours post-ERT
- Sustained uptake in spleen, bone marrow and lung 42 days post single IV dose of AAV8-FLT201

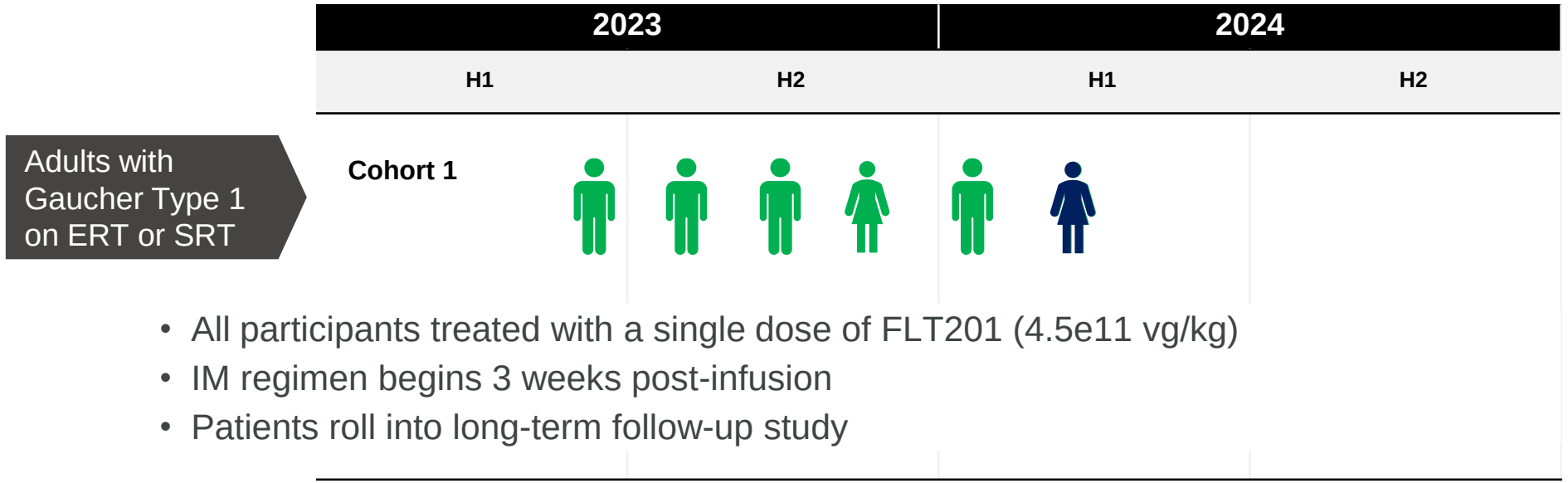


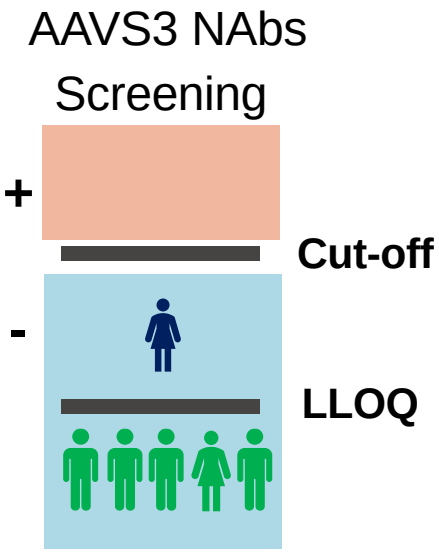
Anti-GCase – DAB, Haematoxylin counterstain, AAV8

AAV8-FLT201 = AAV8 pseudo-typed FLT201 genome
Dose: 2 x 10^{12} vg/kg

American Society of Gene & Cell Therapy 2021 Annual Meeting: Romuald Corbau et al. FLT201, a Novel Investigational AAV-Mediated Gene Therapy Candidate for Gaucher Disease Type 1 WORLD*Symposium* 2021: Romuald Corbau et al. FLT201: An AAV-Mediated Gene Therapy for Type 1 Gaucher Disease Designed to Target Difficult to Reach Tissues

Positive proof-of-concept results from GALILEO-1
A first-in-human, open-label, multicenter study of FLT201

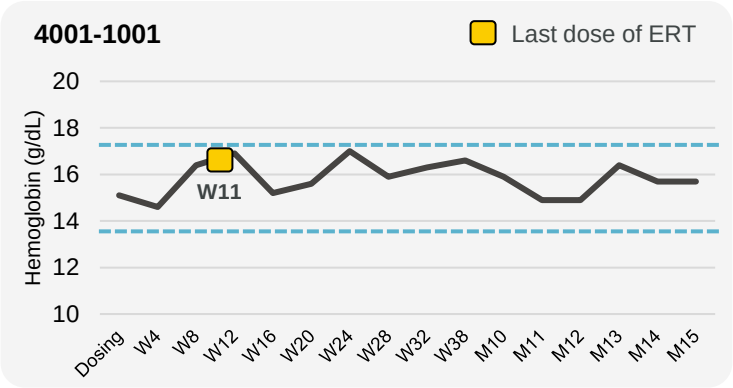


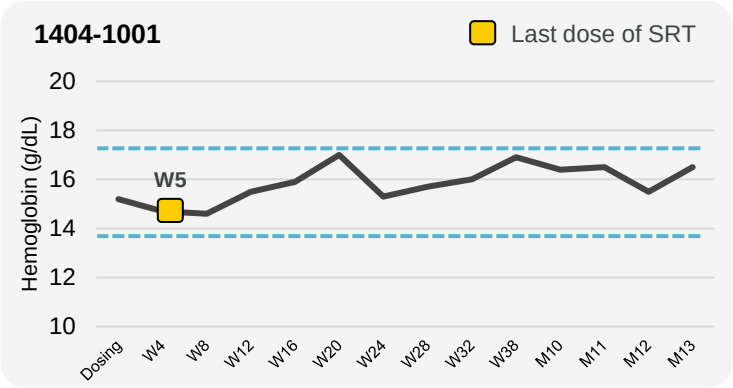


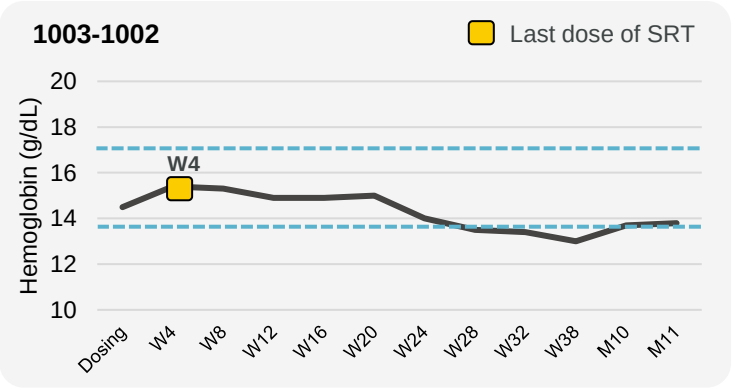
- No infusion-related reactions or dose limiting toxicities
- Treatment-related adverse events have been mild to moderate
- Mild ALT elevations managed with immune therapy, with no impact on efficacy
- Anti-GCase antibodies in 2 patients: 1 transient and 1 declining

Sustained hemoglobin maintenance observed after withdrawal of ERT or SRT

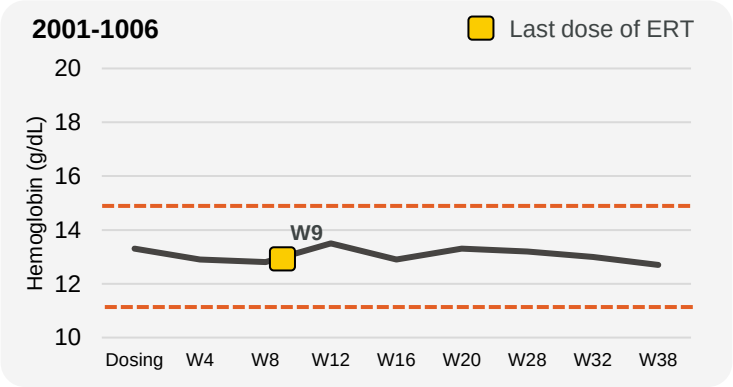
Hemoglobin concentration over time

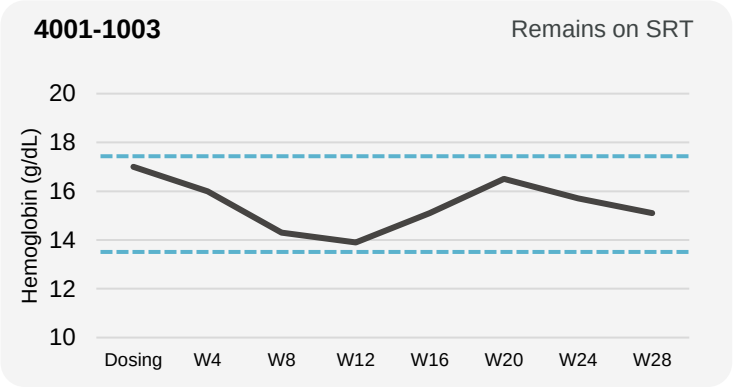






Patient recently diagnosed with iron deficiency unrelated to FLT201





Normal Hb [male] 13.8-17.2 g/dL

Normal Hb [female] 11.0-15.5 g/dL

Data cut off Sep. 27th, 2024

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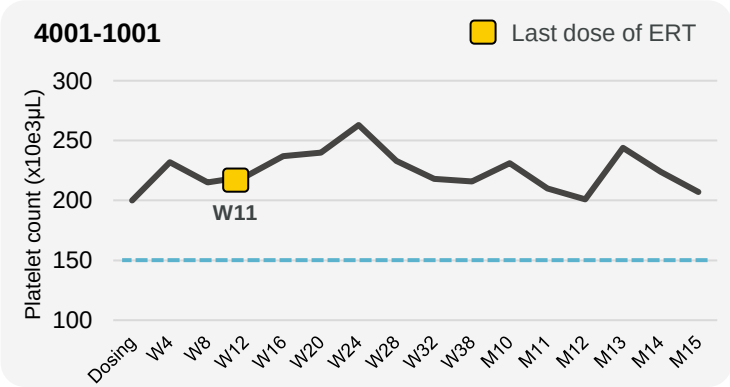
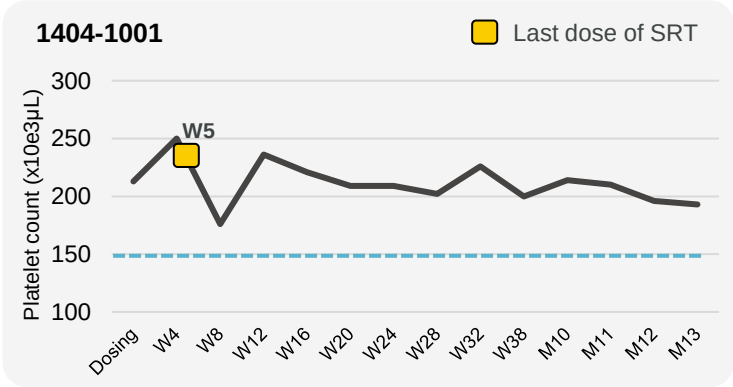
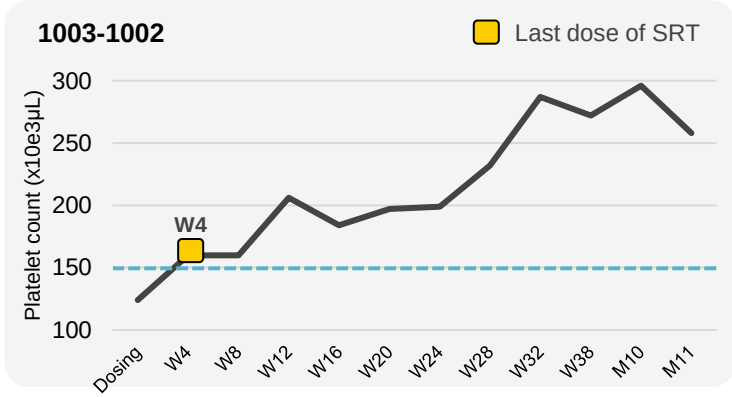
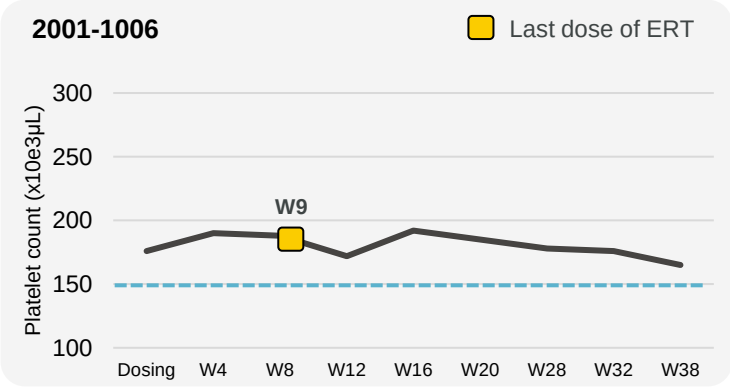
Sustained improvement or maintenance of platelets observed after withdrawal of ERT and SRT

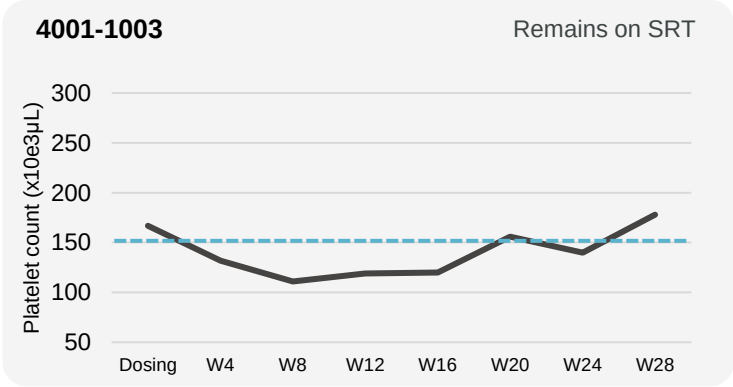
Platelet count over time











Normal platelet count 150-450 x 10^3/µL

Data cut off Sep. 27th, 2024

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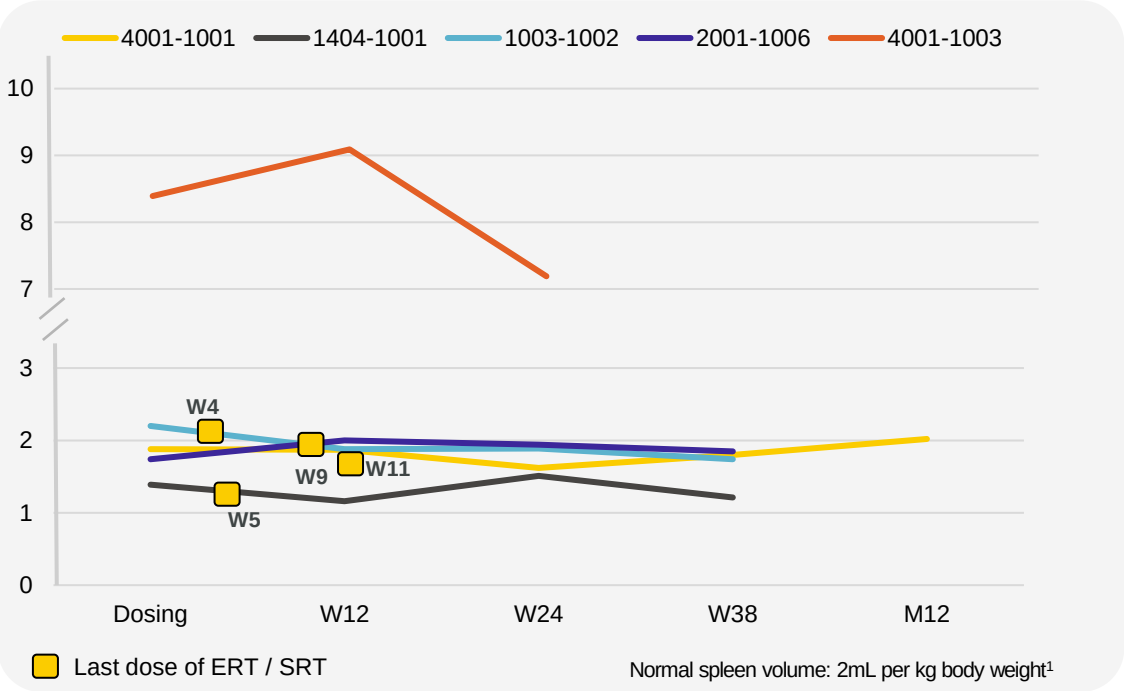
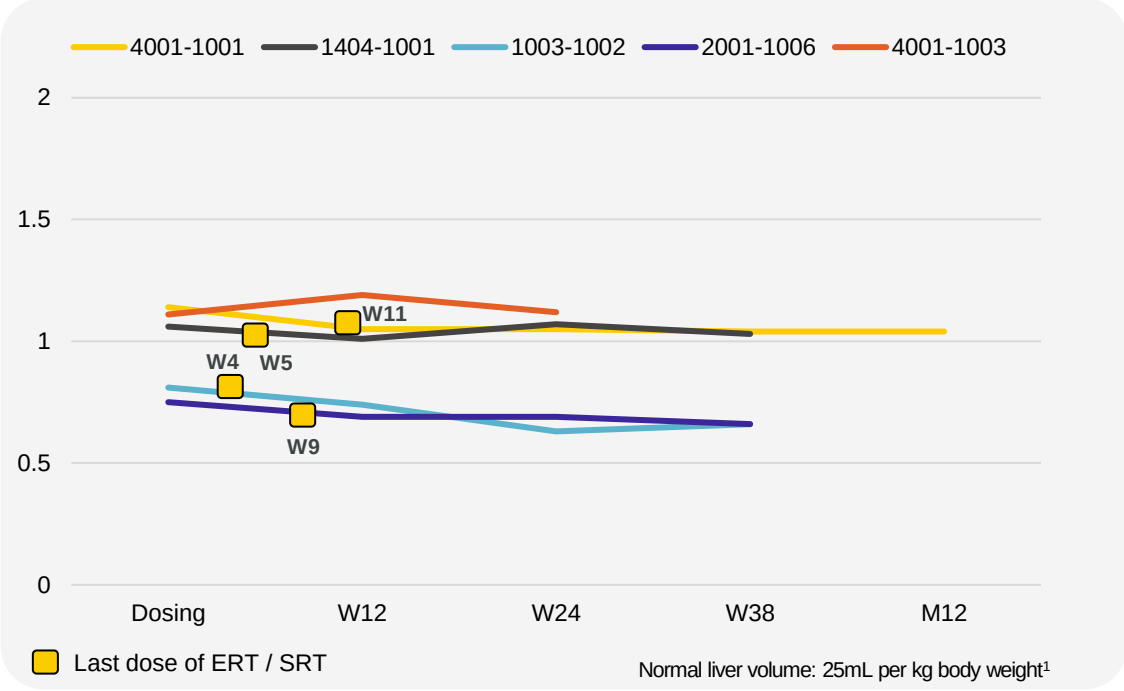
Spleen and liver volume maintenance or improvement observed after withdrawal of ERT and SRT

Spleen volume by MRI as a multiple of normal



Liver volume by MRI as a multiple of normal



[1]Pastores et al Blood Cells, Molecules and Diseases 2014;53: 253–260
Data cut off Sep. 27th, 2024

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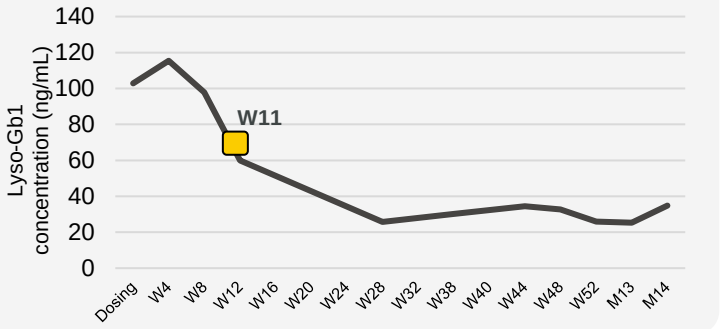
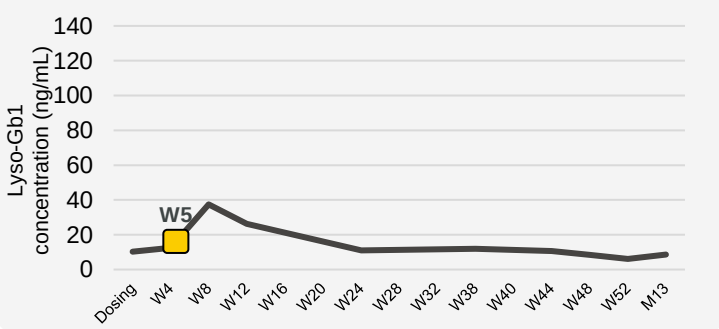
Substantial and durable reductions of toxic substrate in patients with persistently high levels despite prior treatment

Dried blood spot lyso-Gb1 concentration over time

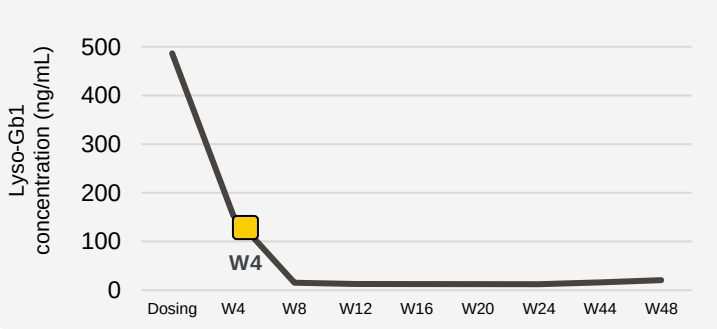
4001-1001 — **66% reduction**



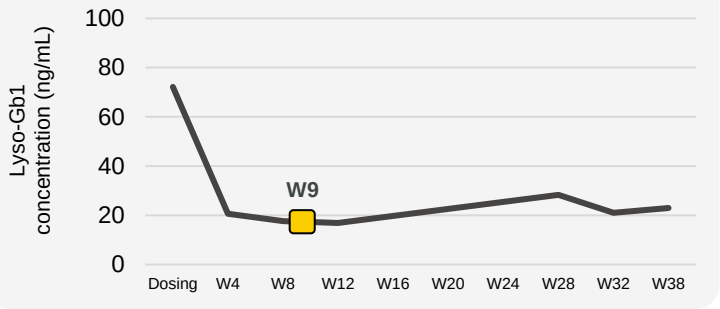
1404-1001 — **17% reduction**



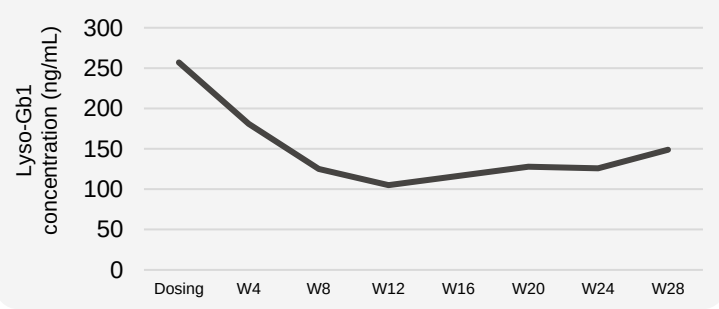
1003-1002 — **96% reduction**



2001-1006 — **68% reduction**



4001-1003 — **42% reduction**



Lyso-Gb1 is one of best predictors of disease severity and clinical response

- Highly correlated with outcomes in hemoglobin, platelets, spleen and bone
- Gaucher-specific, highly sensitive

Last dose of ERT/SRT

Data cut off Sep. 27th, 2024

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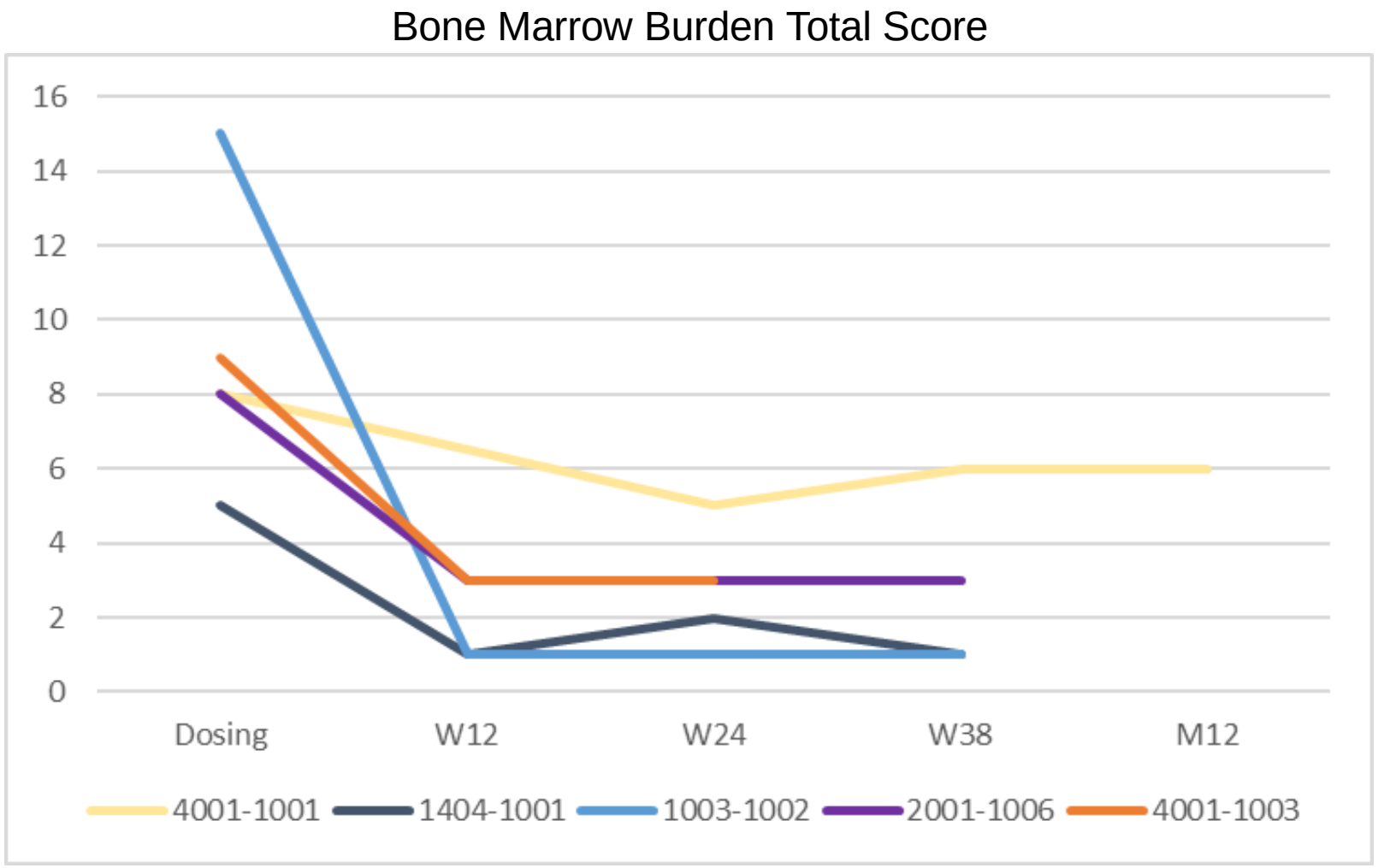
Substantial and durable reductions of bone disease

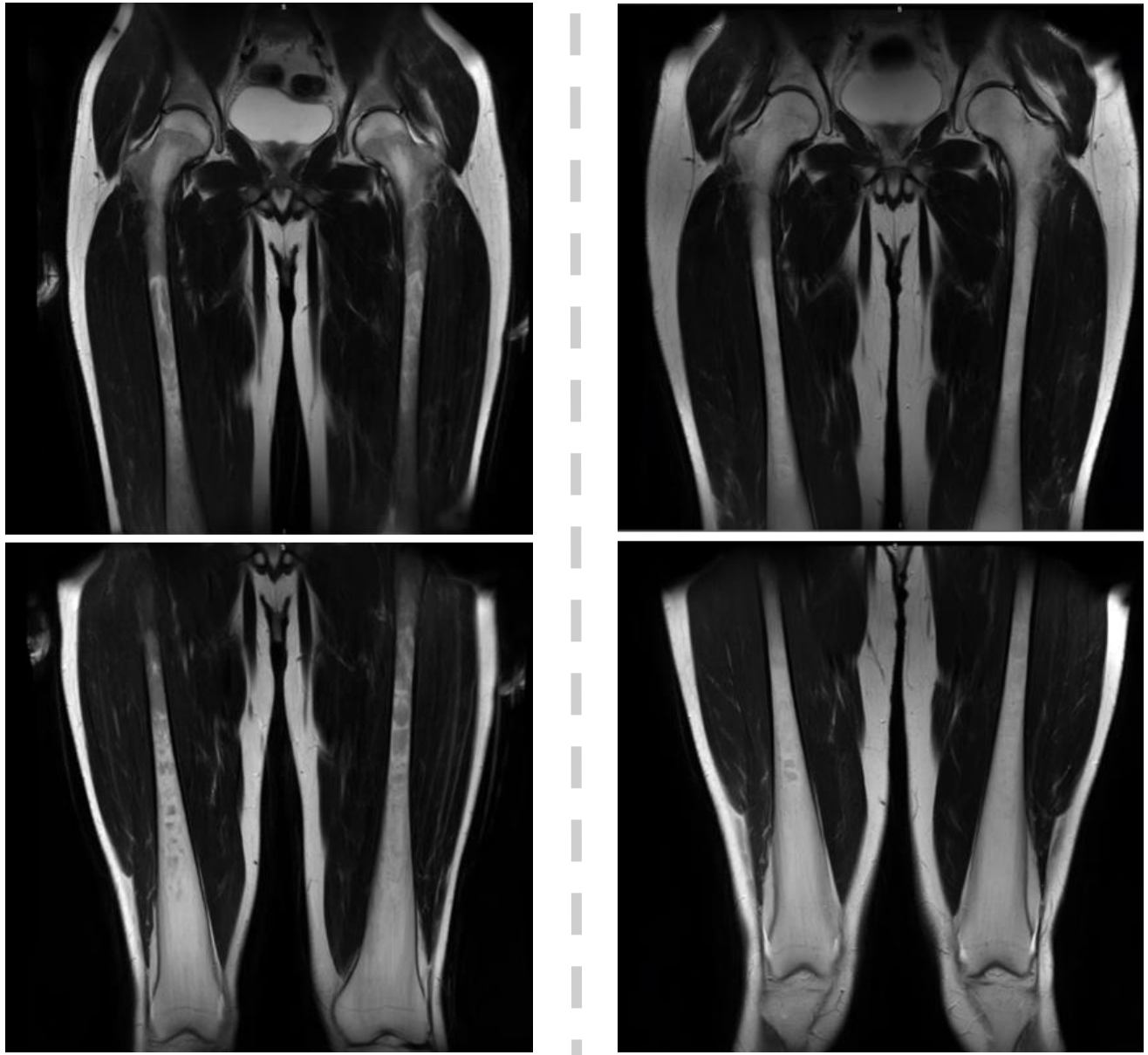


- Improvements even in patients with severe bone involvement
- BMB correlates with bone cell death, fractures, bone pain and joint replacements
- Associated reduction in pain and fatigue

De Fost 2006; score of 6 or higher defined as severe BMB

Substantial and durable reductions of bone disease

Baseline: BMB=15



38 weeks: BMB=1

Subject 1003-0112 BMB Total score – T2 weighed No contrast MRI

Promising initial data on FLT201 gene therapy for patients with Gaucher disease Type 1

- First-in-human trial shows a favorable safety profile
- In general, clinical parameters up to nearly 12 months after discontinuation of ERT/SRT maintained or improved
- Continuous presence of GCase85, which is more stable than recombinant human GCase, ensures constant access to the needed enzyme even in difficult to reach tissues
- FLT201 shows potential for meaningful improvements in clinical outcomes over existing standard of care with a single infusion

Acknowledgements

The Gaucher disease community

- Patients, families and friends
- Gaucher Community Alliance
- International Gaucher Alliance
- Gaucher Association UK

Study investigators

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