

FREELINE

# **FLT201: Initial Clinical Data**

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October 6, 2023

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# Creating better gene therapies for chronic debilitating diseases



## Potential first- and best-in-class lead program

Highly differentiated gene therapy candidate FLT201 for Gaucher disease type 1 in first-in-human clinical trial



## Compelling initial clinical data

Robust enzyme activity and favorable safety and tolerability in first two patients treated with FLT201



## Extending innovation into Parkinson's disease

Lead research program leveraging our novel GCase variant for GBA1-linked Parkinson's disease

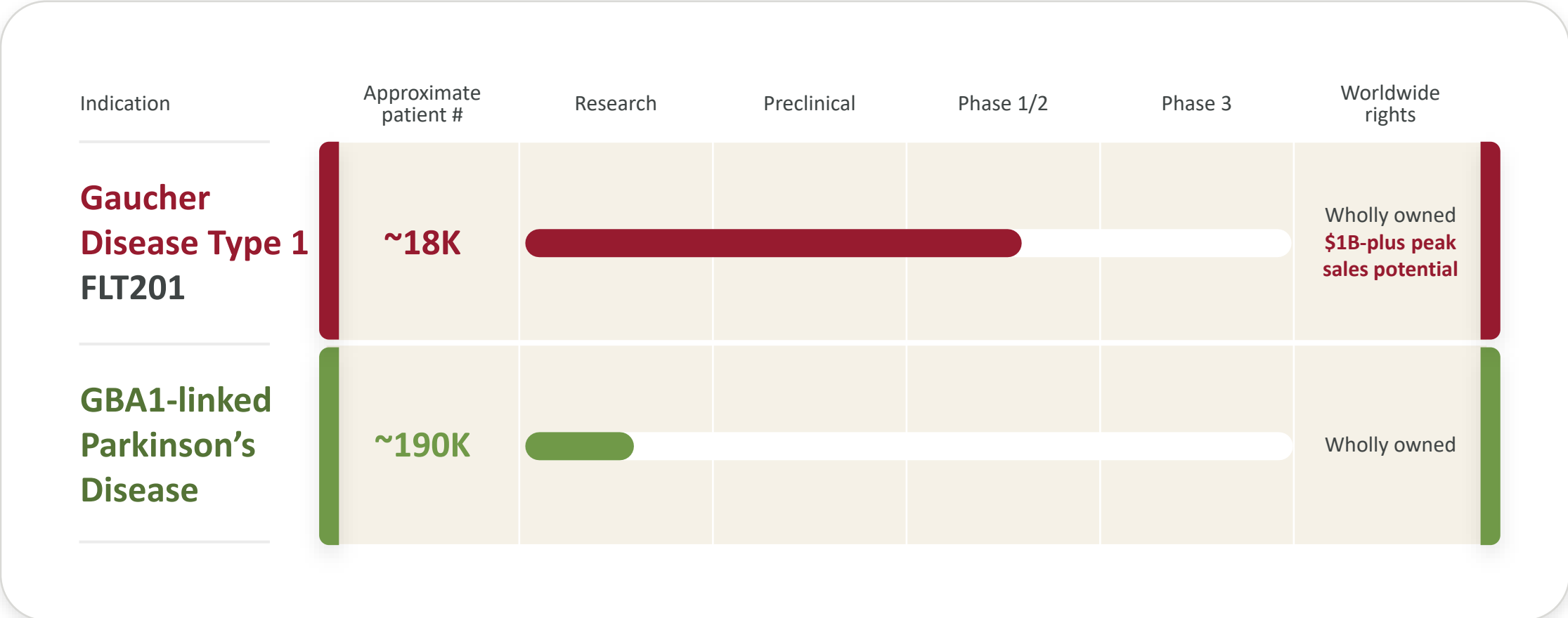


## Experienced management team

Seasoned leaders with the experience and expertise to drive progress and execution

**Our approach is to optimize all components of our product candidates to unlock the true potential of gene therapy**

# Lead clinical program with first- and best-in-class potential with research extending innovation into larger disease area



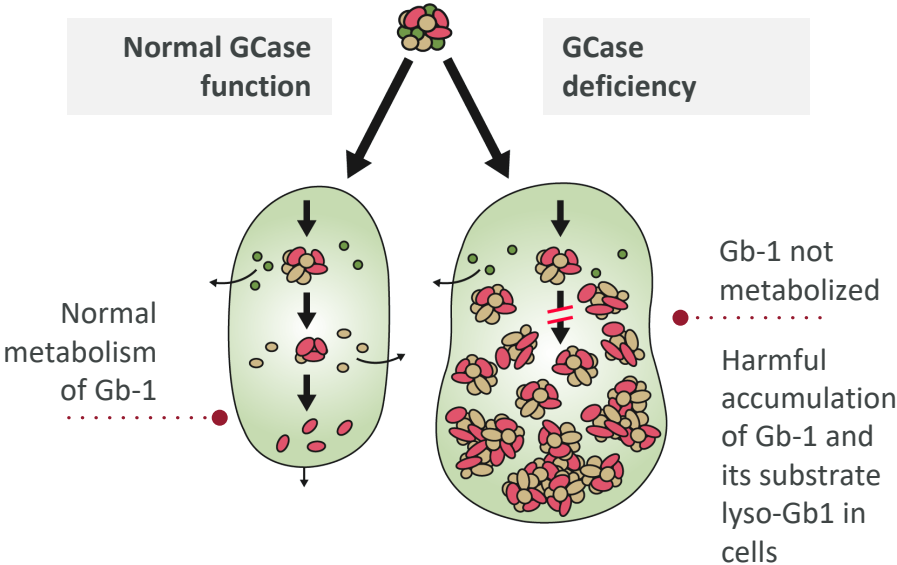
Estimated patient numbers for Gaucher disease Type 1 are for US, UK, EU4 and Israel (Hematology. 2017 Mar;22(2):65-73. doi: 10.1080/10245332.2016.1240391; this figure represents the total theoretical genetic prevalence of the indication. The seroprevalence of antibodies against the AAVS3 capsid renders some patients ineligible for AAV gene therapy. We estimate approximately 60% would be eligible for AAVS3 gene therapy. Company estimate of patient numbers for GBA1-linked PD are for US, UK and EU4.



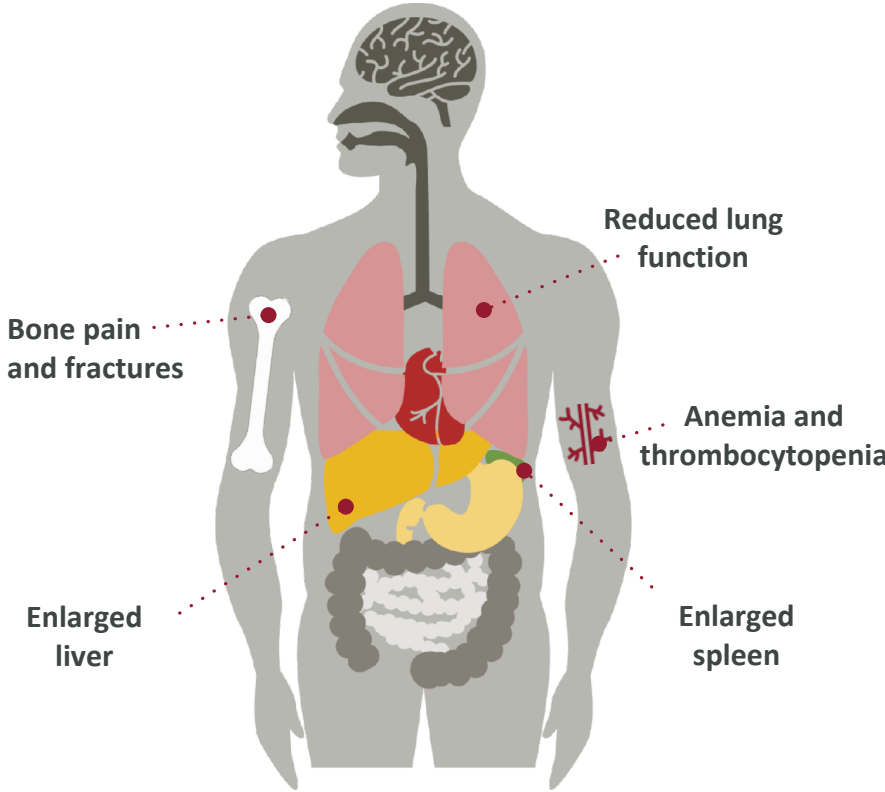
**FLT201  
in Gaucher  
Disease**

# Gaucher disease type 1 is a debilitating, chronic and progressive disorder with life-altering symptoms

Deficiency of GCCase enzyme needed to metabolize Gb-1 in the lysosome



Affects multiple organs, leading to wide range of symptoms and shortening life span<sup>1</sup>



<sup>1</sup>Weinreb, et al., 2008

GCCase = glucocerebrosidase. Gb-1 = glucosylceramide. Lyso-Gb-1 = glucosylsphingosine.

# Existing therapies poorly address certain aspects of disease

LENGTHY INFUSION  
EVERY TWO WEEKS



**ERT**

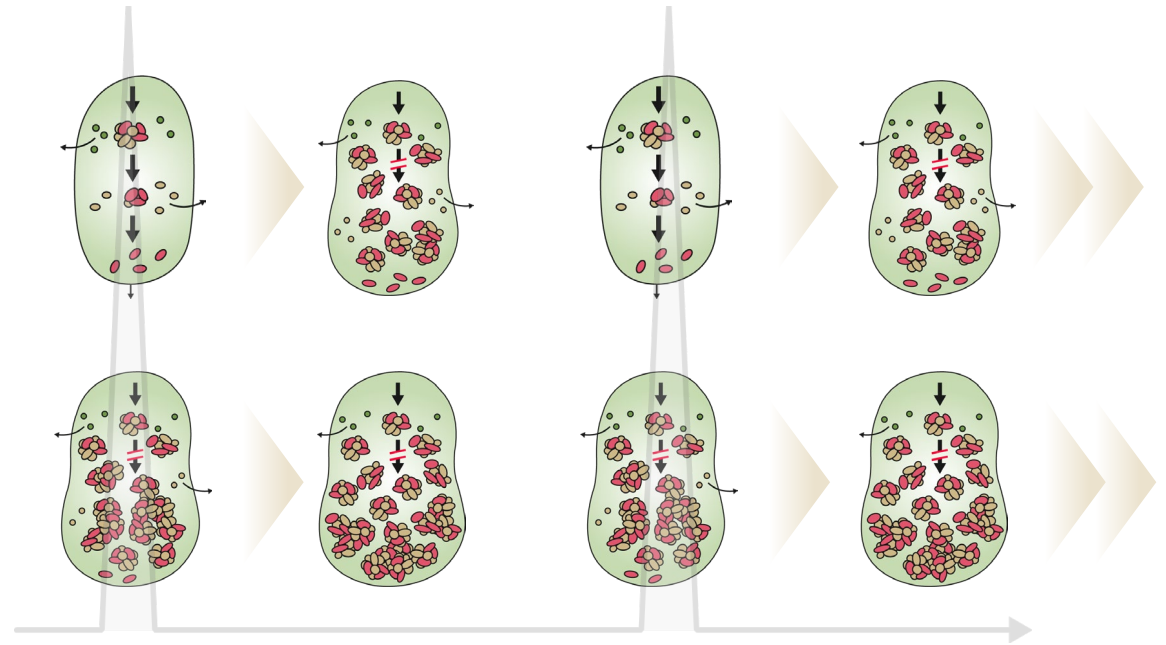
Enzyme replacement  
therapy current standard  
of care

PEAKS AND TROUGHS in enzyme levels between  
infusions allow harmful substrates to build back up

Easier to reach  
organs: liver, spleen



Harder to reach  
organs: bone, lung



**DOES NOT ADEQUATELY  
PENETRATE** deeper organs,  
including bone and lung

# Despite treatment with ERT, many patients continue to have disease progression and debilitating symptoms

After 10+ years on ERT up to **60%** still experience symptoms<sup>1</sup>



bone pain



enlarged liver



enlarged spleen



low blood counts

**43%**

still have bone pain<sup>†</sup>

**56%**

still have severely enlarged livers<sup>†</sup>

**61%**

still have severely enlarged spleens<sup>†</sup>

**43%**

still have severely low platelet counts<sup>†</sup>

**68%**

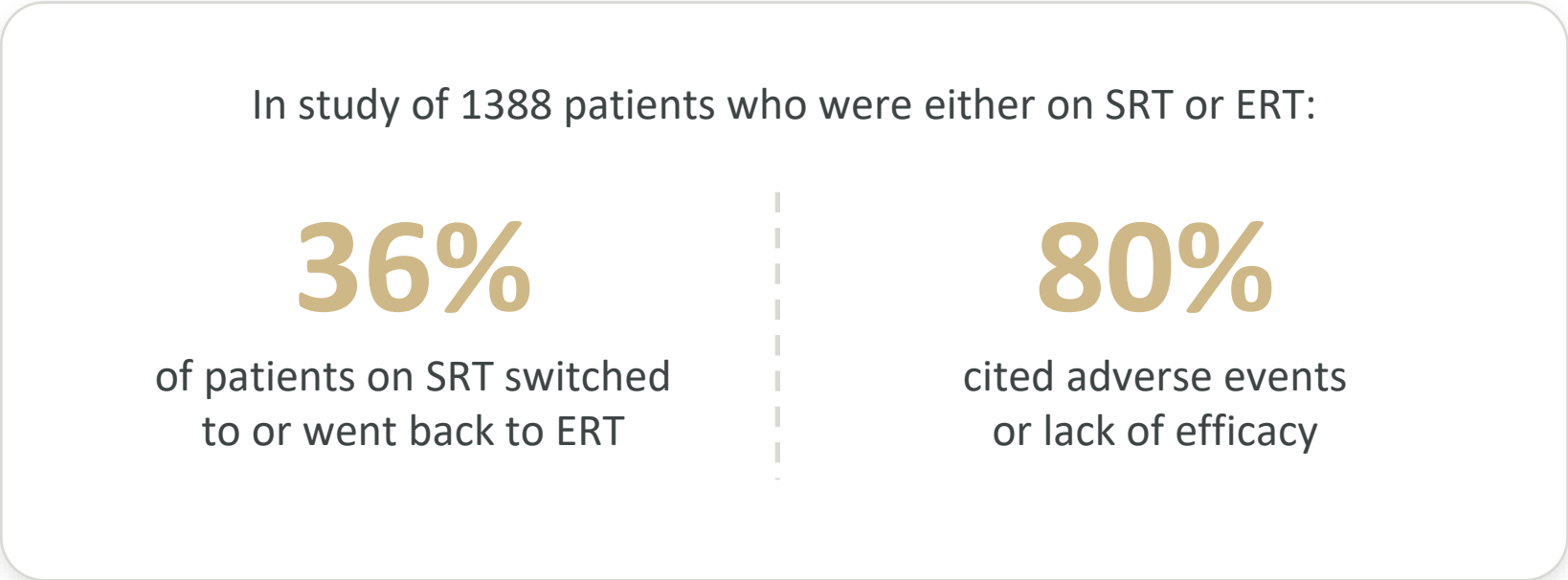
have pulmonary dysfunction at baseline with most likely not having any normalization with ERT<sup>2</sup>

<sup>1</sup> Weinreb et al., 2013; <sup>2</sup> Kerem, et al., 1996 and Goitein, et al 2001; <sup>†</sup> in those with these symptoms before ERT



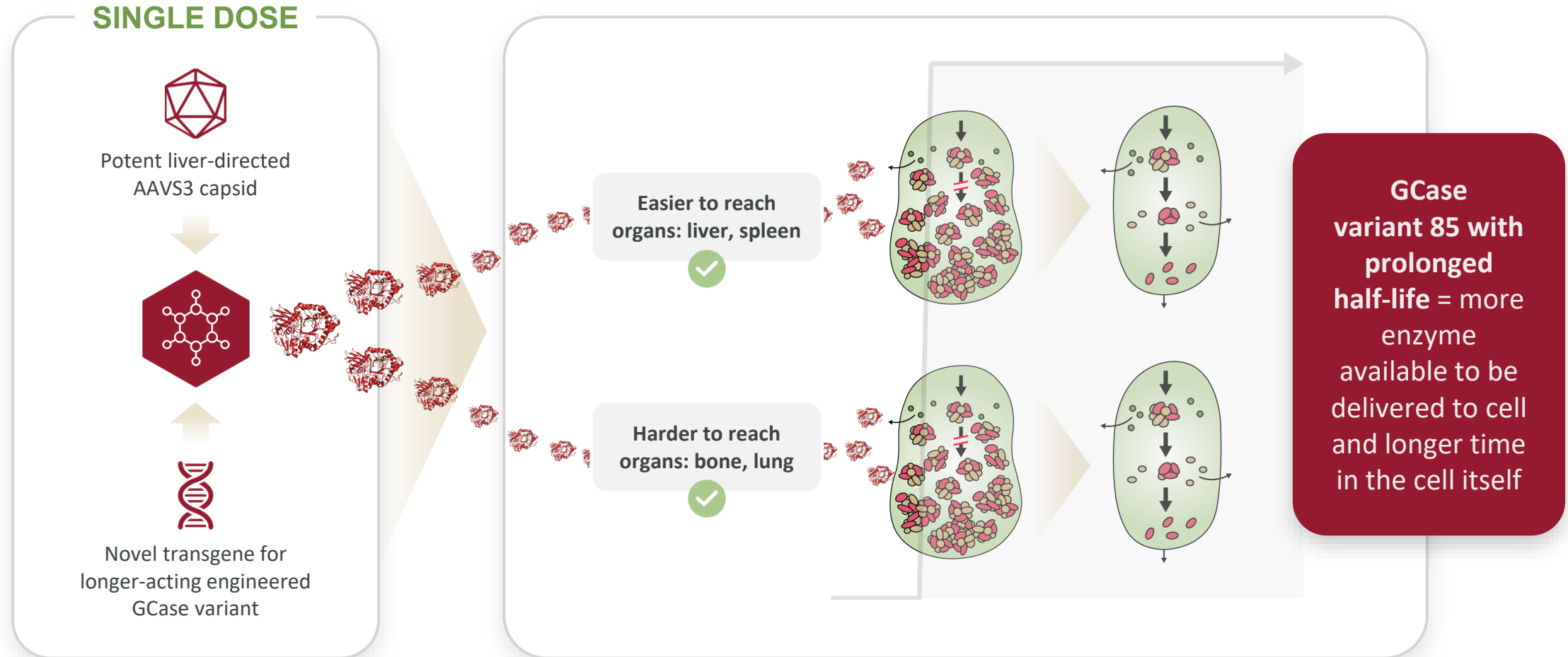
# SRT offers an oral treatment option, but tolerability, compliance and perceived lack of efficacy limit its use

Substrate reduction therapy (SRT) represents less than **20%** of the market in Gaucher disease



**Physicians report compliance with 2-3x/day SRT is worse than for ERT**

# FLT201 has potential to deliver continuous level of enzyme and penetrate deeper tissues that existing therapies do not reach



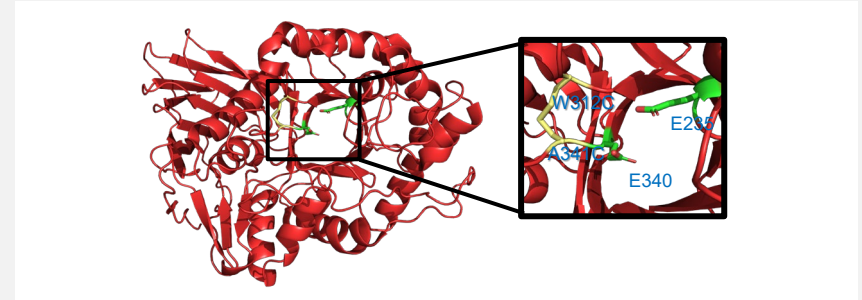
# Our engineered GCCase variant has substantially longer half-life than wildtype

## Key features of GCCase variant

- ✓ 20-fold increase in half-life in lysosomal pH compared with wildtype (wt)
- ✓ Specific activity unchanged compared to wt GCCase
- ✓ 6-10 fold increase in half-life compared to wt, enabling increased steady-state plasma levels *in vivo*

## GCCase variant 85 structure

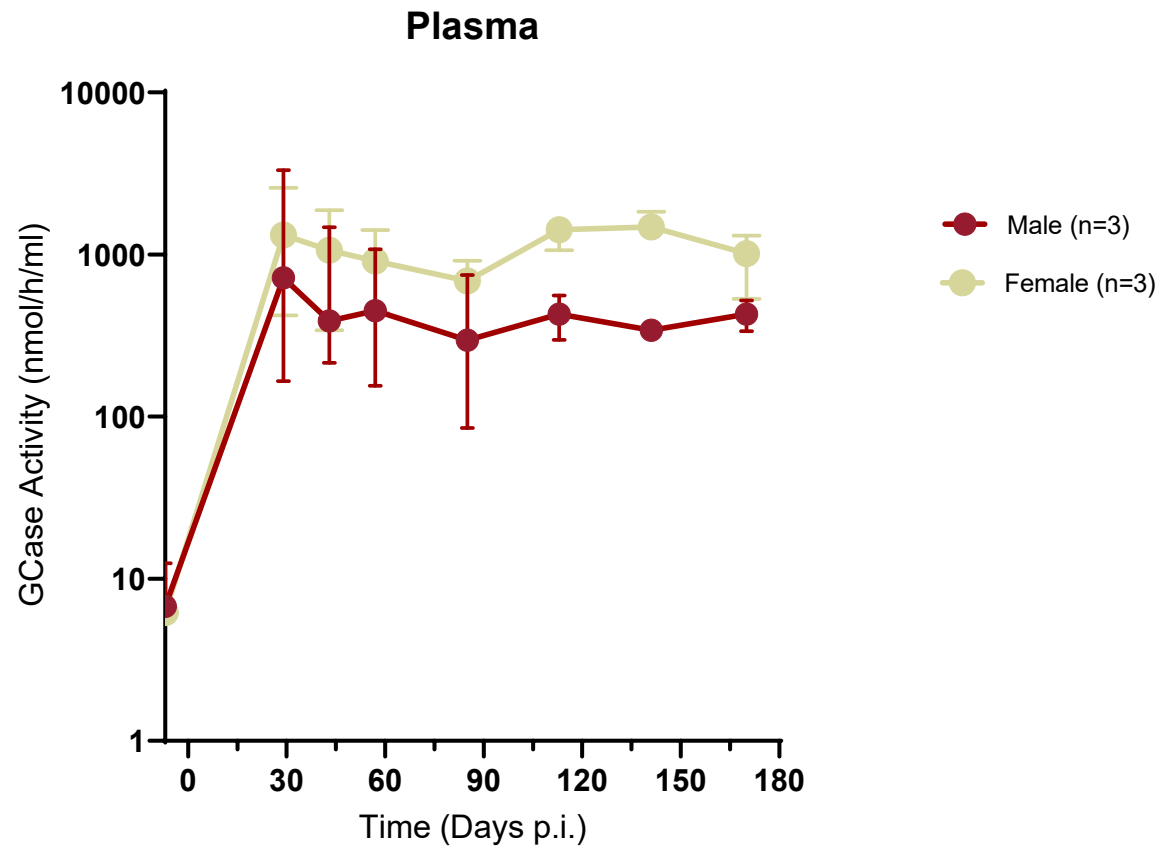
- Two internal amino acid substitutions
- Does not impinge on the active site
  - Minimizes 3D structural change



## Biophysical properties of variant 85 and wildtype GCCase

	Lysosomal pH	Human serum
	..... HALF-LIFE (MINUTES) .....	
WT GCCase	388	24
Variant 85	>8,639	143
<b>Improvement</b>	<b>&gt;21X</b>	<b>6X</b>

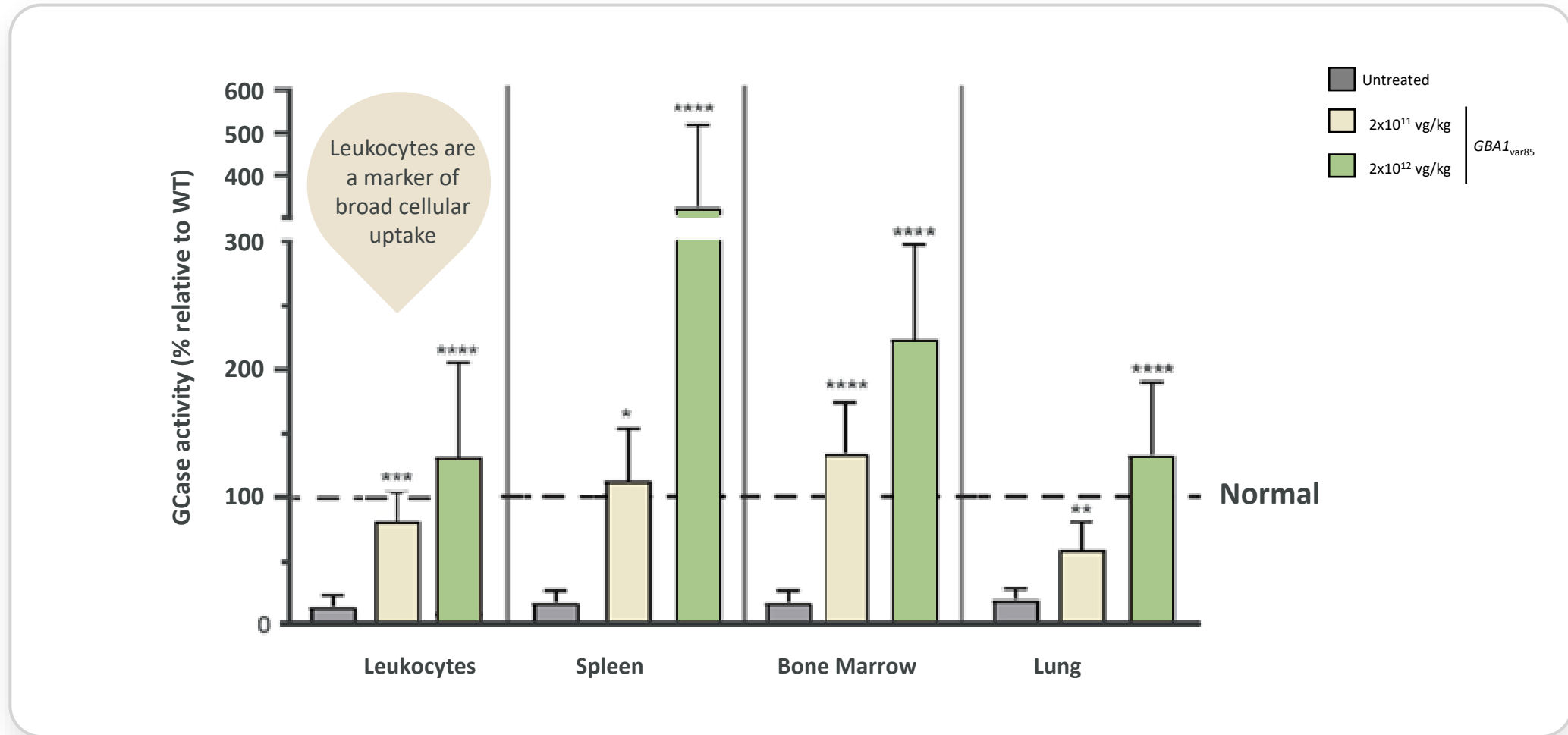
# FLT201 shows high and durable GCa6 expression in non-human primates



## Achieved steady increases in GCa6 plasma levels

- A single injection of FLT201 was well tolerated
- Additional data from this study shows durable expression up to 3 years

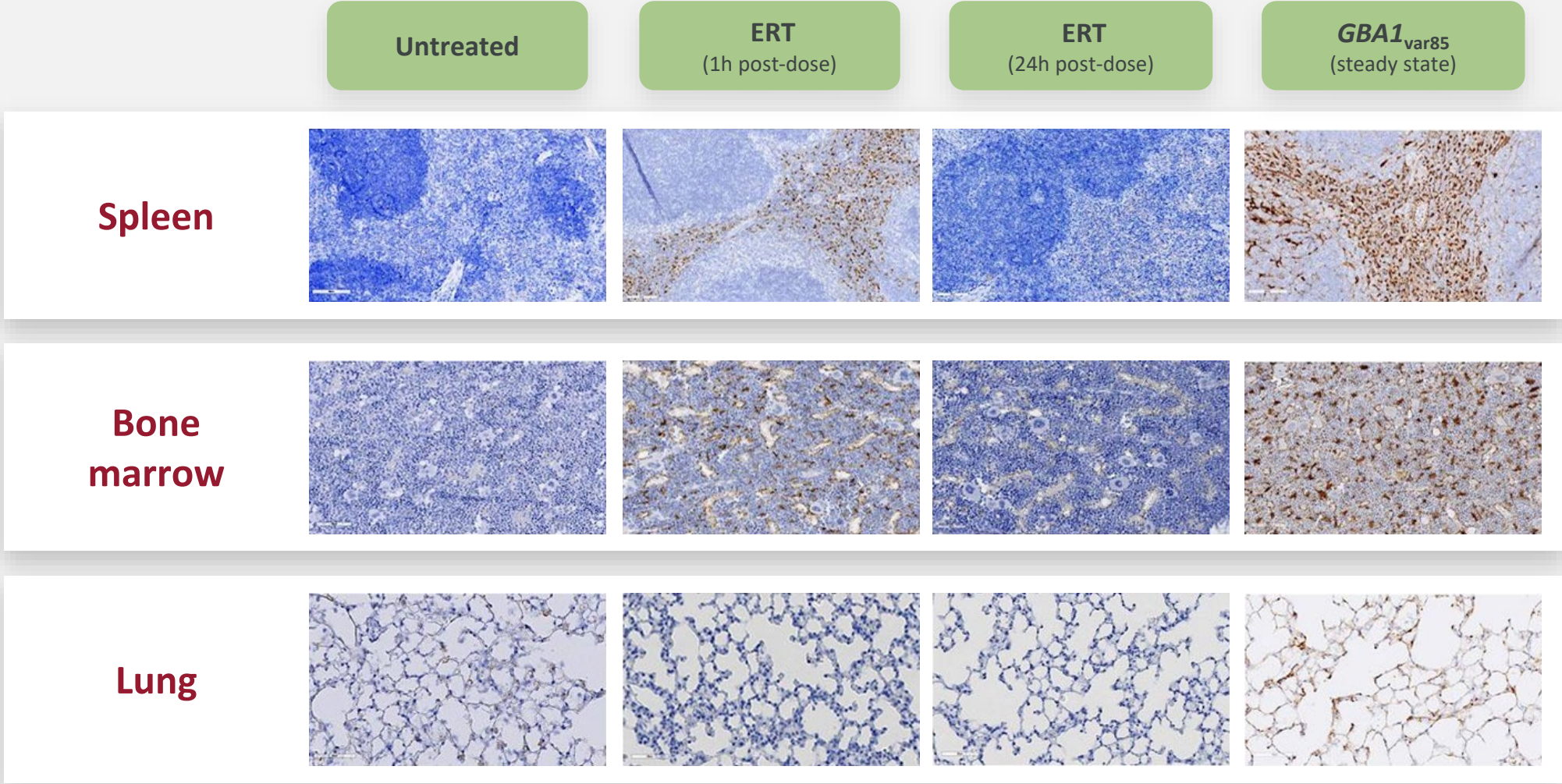
# FLT201 demonstrated uptake in key tissues in Gaucher mice



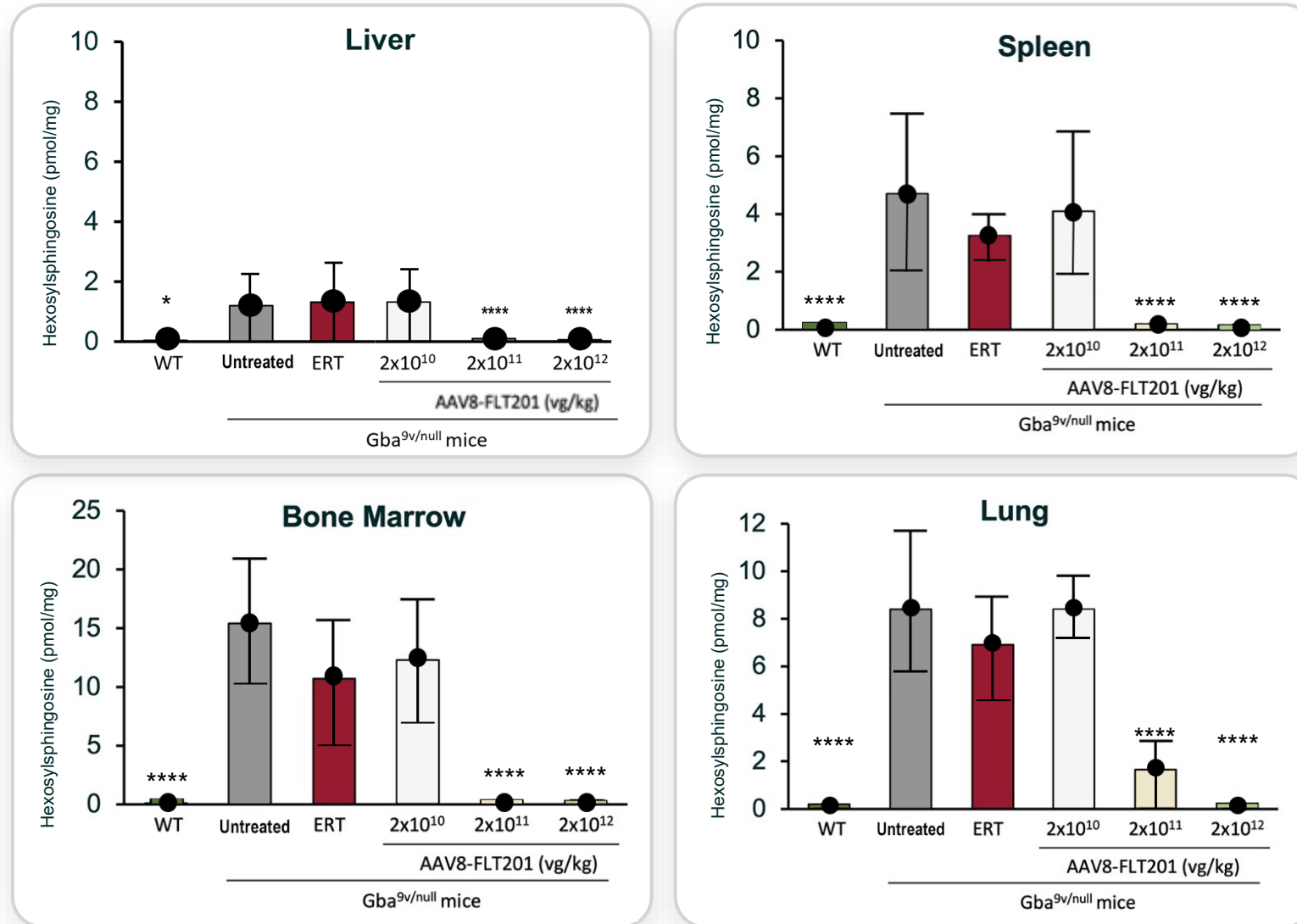
Data represented as mean ± SD. n= 9 to 16 per treatment group. \* P≤0.05, \*\* P≤0.001, P≤0.001, \*\*\*\* P ≤ 0.0001 vs. untreated, one-way ANOVA.

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  
 WORLDSymposium 2021: Romuald Corbau et al. FLT201: An AAV-Mediated Gene Therapy for Type 1 Gaucher Disease Designed to Target Difficult to Reach Tissues

# FLT201 demonstrates persistent coverage, while ERT is rapidly eliminated



# FLT201 demonstrates superior substrate elimination vs. ERT in all key tissues in Gaucher mice





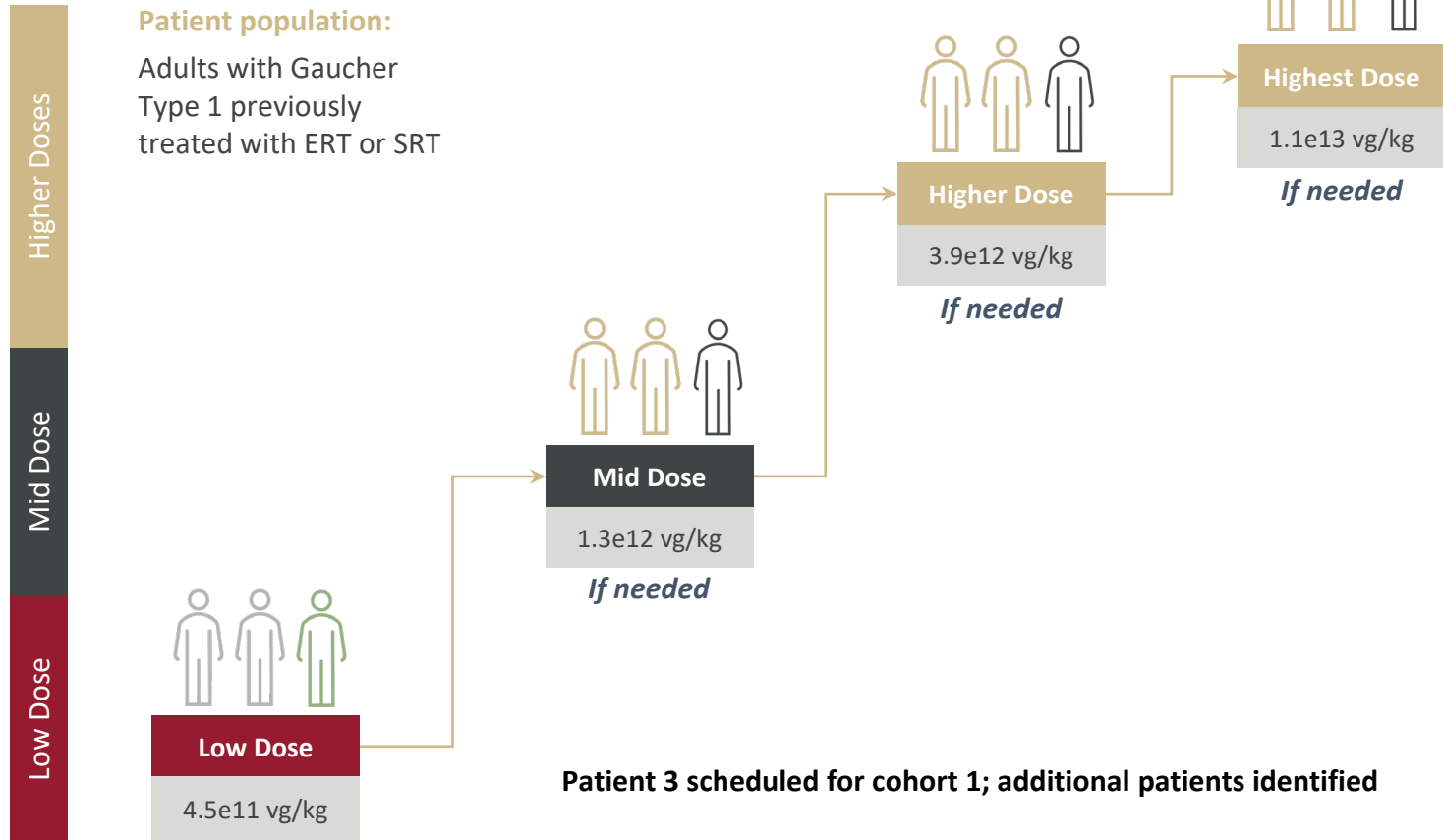
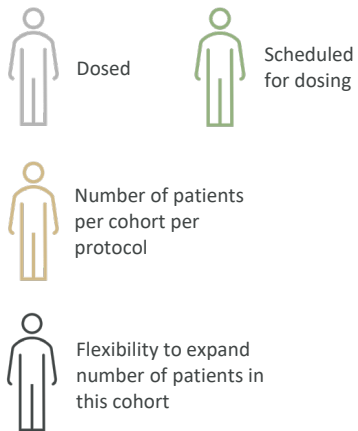
**Patient 1 and  
Patient 2 Data**



# GALILEO-1 Phase 1/2 dose-finding trial design

*First-in-human, open-label, multicenter study*

Establish a dose that delivers sustained increases in GCase activity to reduce substrate accumulation and improve clinical parameters



**Phase 3 Trial:**  
Previously treated patients

Trial protocol allows for testing up to four doses. Depending on dose response in the initial cohorts, we may not ultimately need to escalate to the later doses. The Data Monitoring Committee may recommend the next dose level at the next planned dose level, at same, higher or lower dose level based on emerging safety/tolerability, PK, PD and efficacy data. A 4-week stagger between patients is built into the protocol, with the exception of the US where there is an 8-week stagger prior to dosing a subsequent patient.

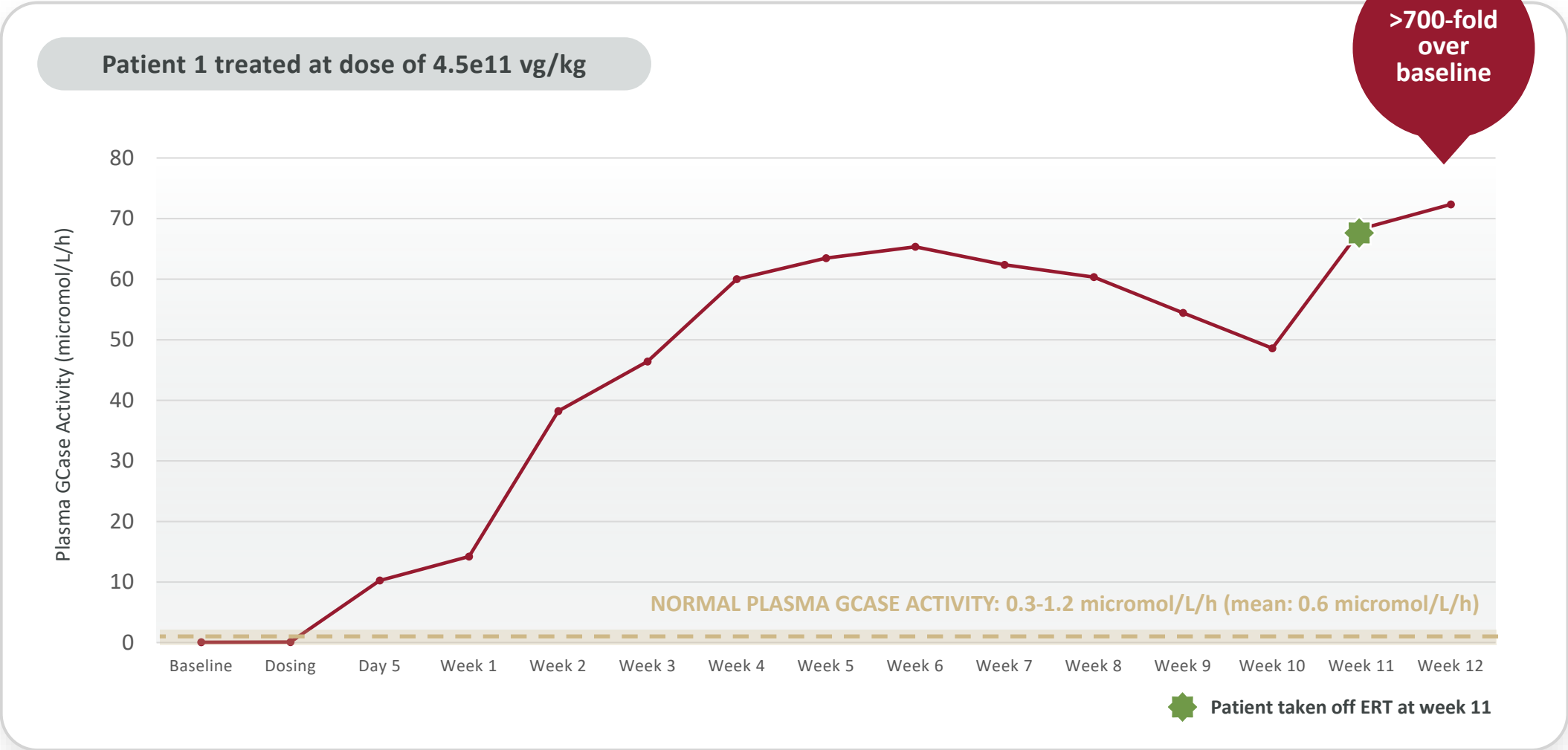
# Baseline patient characteristics

	PATIENT 1	PATIENT 2
Dose (vg/kg)	4.5 x 10 <sup>11</sup>	4.5 x 10 <sup>11</sup>
Absolute dose (vg)	2.835 x 10 <sup>13</sup>	2.84 x 10 <sup>13</sup>
Gaucher therapy at baseline	ERT	SRT
Age	35	25
Gender	Male	Male
Body weight	63kg	63.1kg
Plasma GCase activity (μmol/L/h)	0.07	0.014
DBS GCase activity (μmol/L/h)	0.3	0.3
Leukocyte GCase activity (nmol/h/mg prot)	0.64	0.82
Lyso-Gb1 (ng/mL)	102.85	10.29
Hemoglobin (g/dL)	15.1	15.2
Platelet count (x10 <sup>3</sup> /μL)	200	213

# FLT201 has been well-tolerated with clean safety profile to date

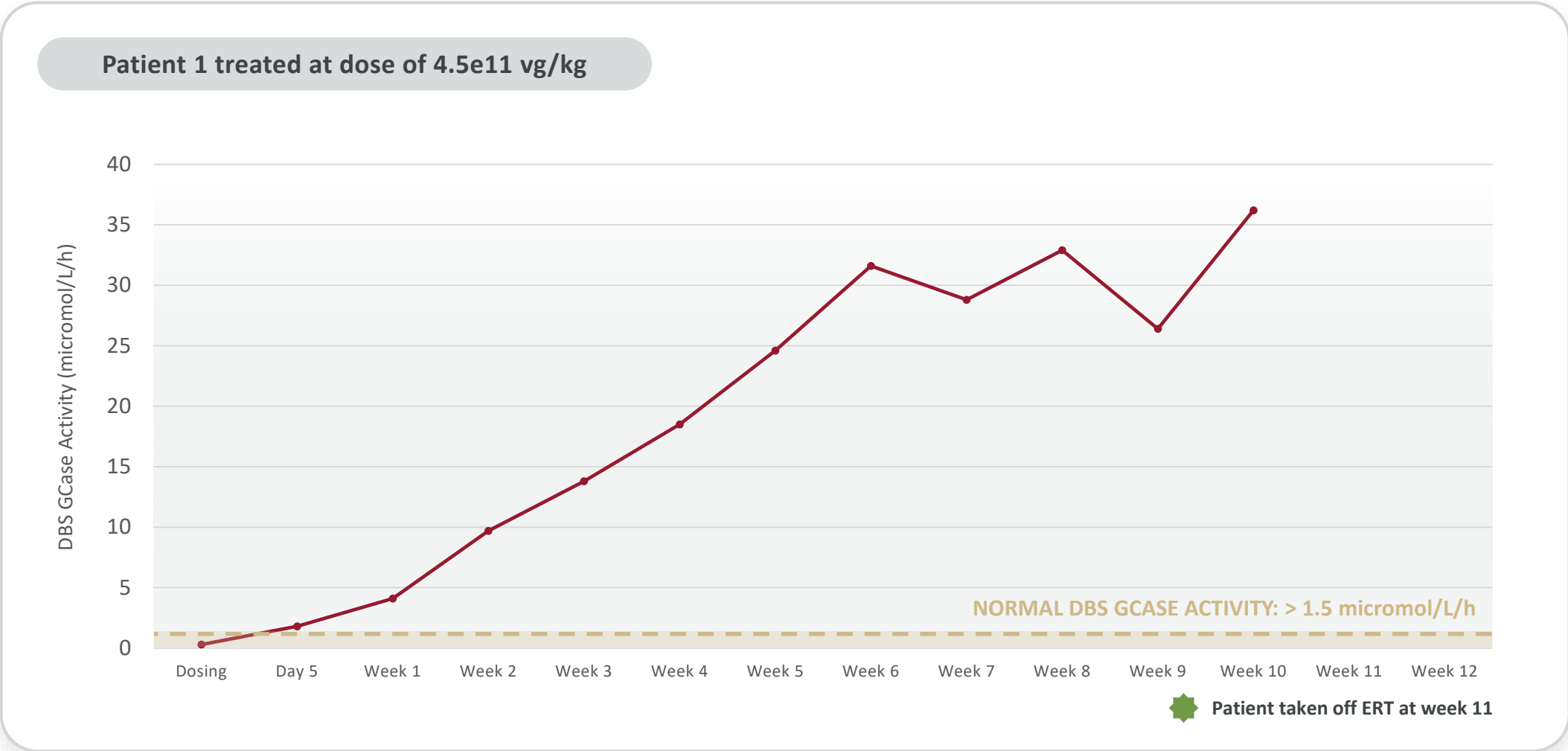
- Infusion well tolerated
- No SAEs
- All treatment-related AEs were Grade 1 and resolved without intervention
- No ALT and AST elevations
  - Patient 1 through 13 weeks
  - Patient 2 through 6 weeks

# Patient 1: Robust increases in plasma GCCase activity

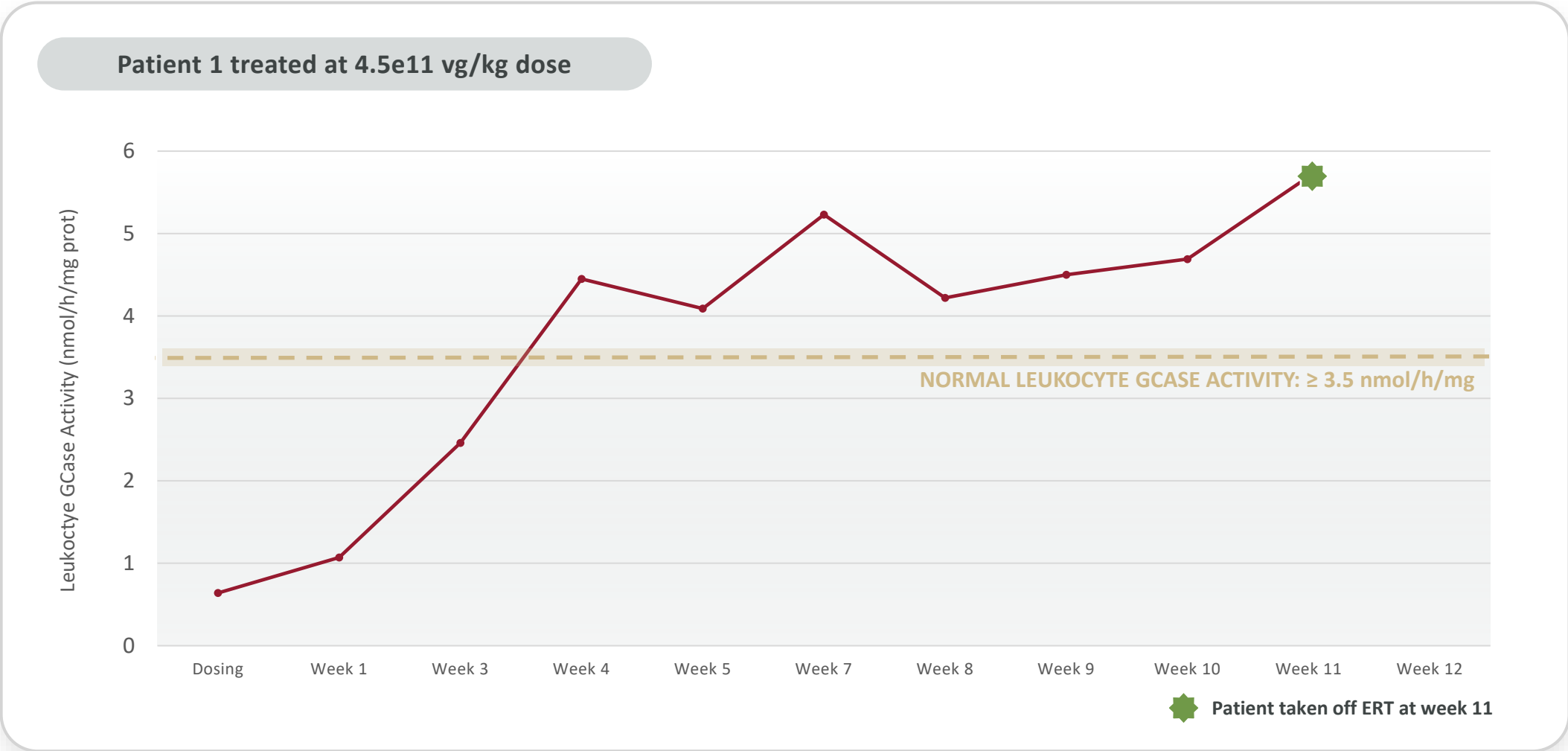


As of Sept. 27, 2023 data cutoff. Enzyme activity measured at 5 and 13 days post-ERT administration when there is no GCCase from ERT remaining in the system.

# Patient 1: Similarly robust increases in DBS GCCase activity

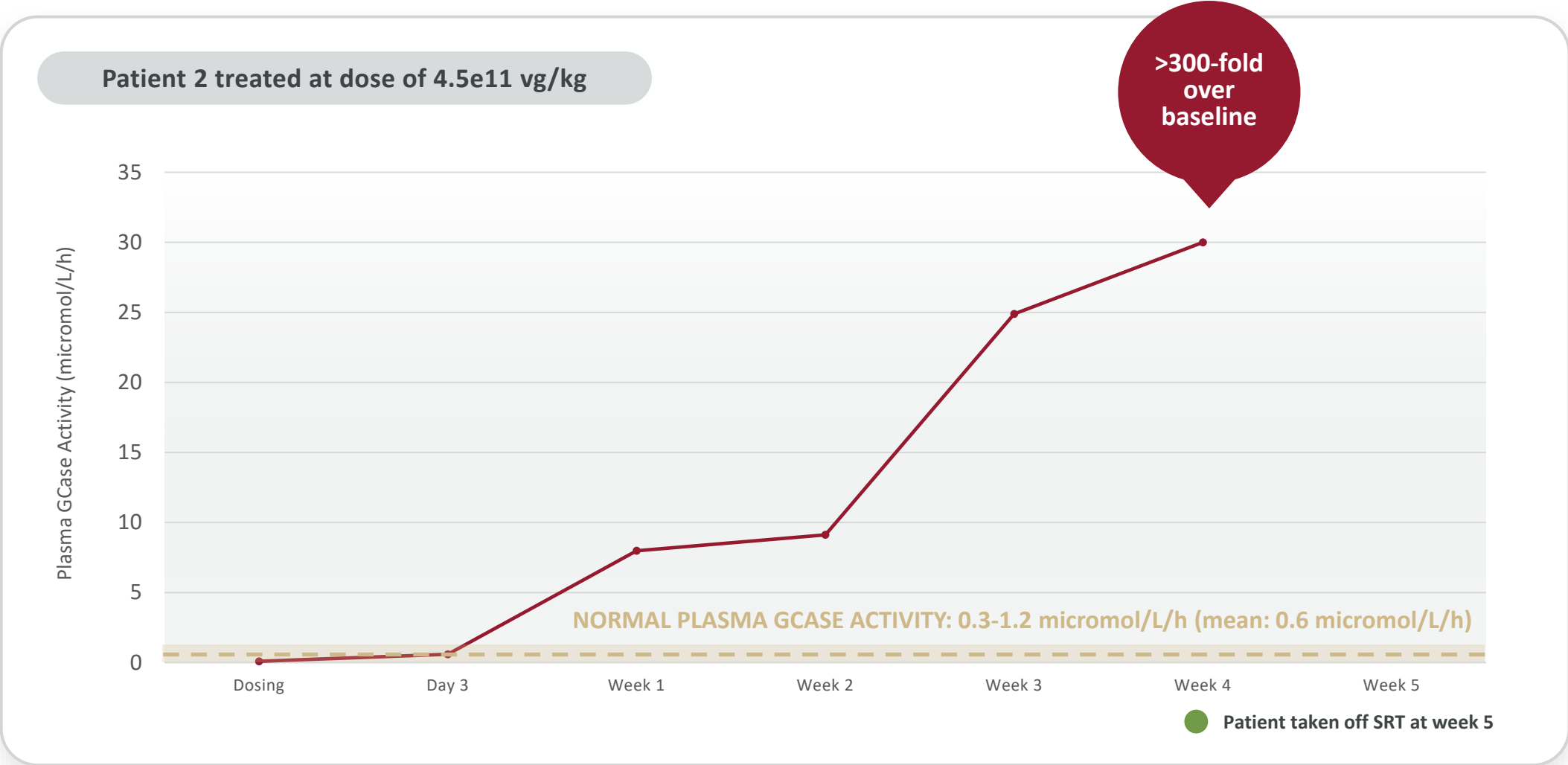


# Patient 1: Normalization of leukocyte GCCase activity demonstrates cellular uptake from plasma



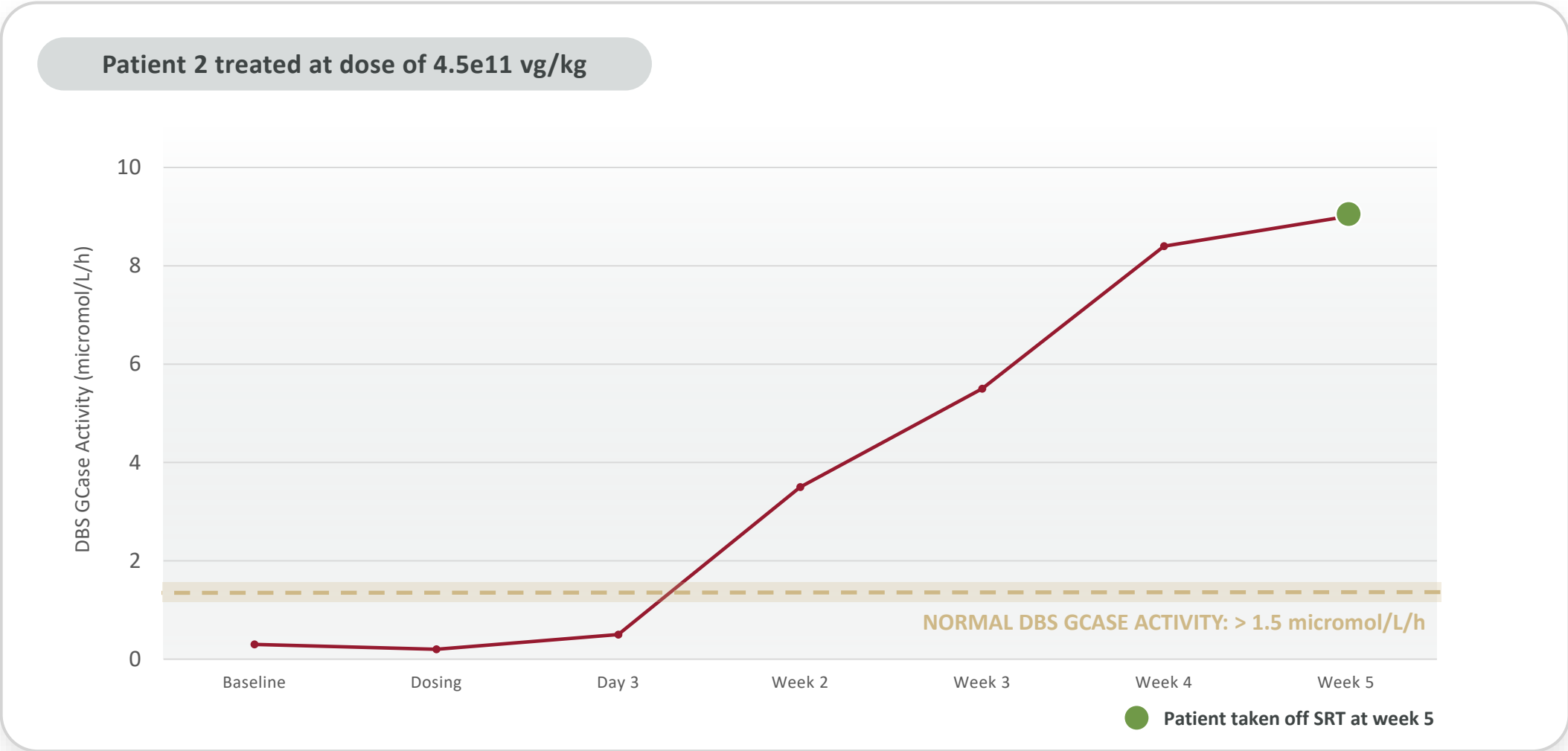
As of Sept. 27, 2023 data cutoff. Enzyme activity measured at 5 and 13 days post-ERT administration when there is no GCCase from ERT remaining in the system.

# Patient 2 replicates increases in plasma GCase activity seen in patient 1



As of Sept. 27, 2023 data cutoff.

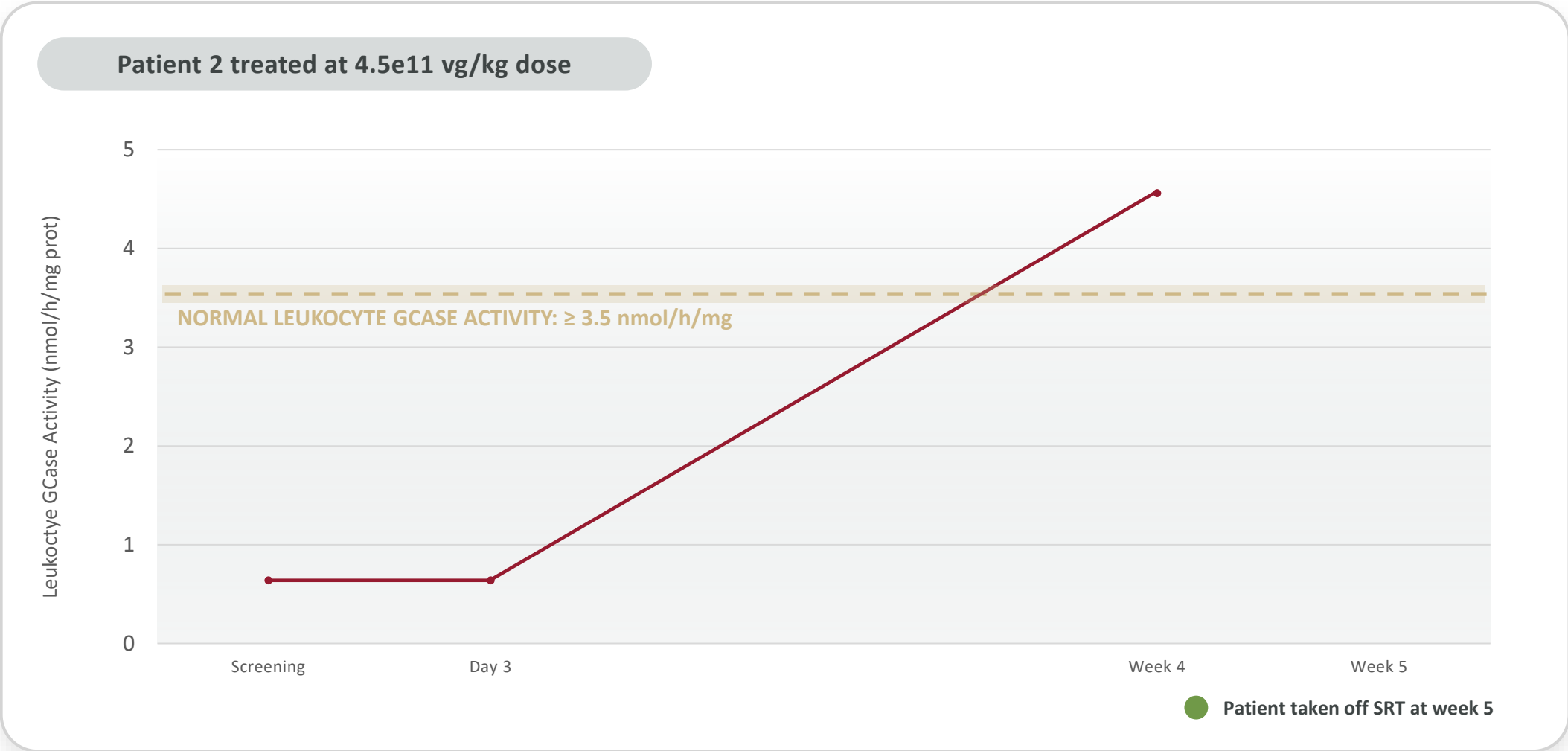
# Patient 2: Similarly robust increases in DBS GCCase activity



As of Sept. 27, 2023 data cutoff. DBS = dry blood spot.



# Patient 2: Normalization of leukocyte GCase activity demonstrates cellular uptake, consistent with patient 1



As of Sept. 27, 2023 data cutoff.

# Expediently advancing development of FLT201



Dosing Patient 3 in cohort 1 given compelling enzyme activity and favorable safety

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Three additional patients identified and in scheduling; more patients in screening

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Awarded ILAP designation in UK, providing enhanced regulatory interactions

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Plan to apply for RMAT and PRIME designations to gain expanded access to regulators in US and EU

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Sharing further details on these initial clinical data in oral presentation at ESGCT

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## Key takeaways

- ✔ Initial first-in-human clinical data demonstrate several hundred-fold increase in plasma GCase activity
- ✔ Normalization of leukocyte GCase provides evidence of cellular uptake
- ✔ Favorable safety and tolerability profile
- ✔ Strong patient and investigator interest in ongoing GALILEO-1 trial
- ✔ Advancing FLT201 expeditiously in clinical development

FLT201 is a potential first-and best-in-class gene therapy for Gaucher disease, with \$1B-plus peak sales potential

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**Thank you**