FREELINE

Corporate Presentation

October 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

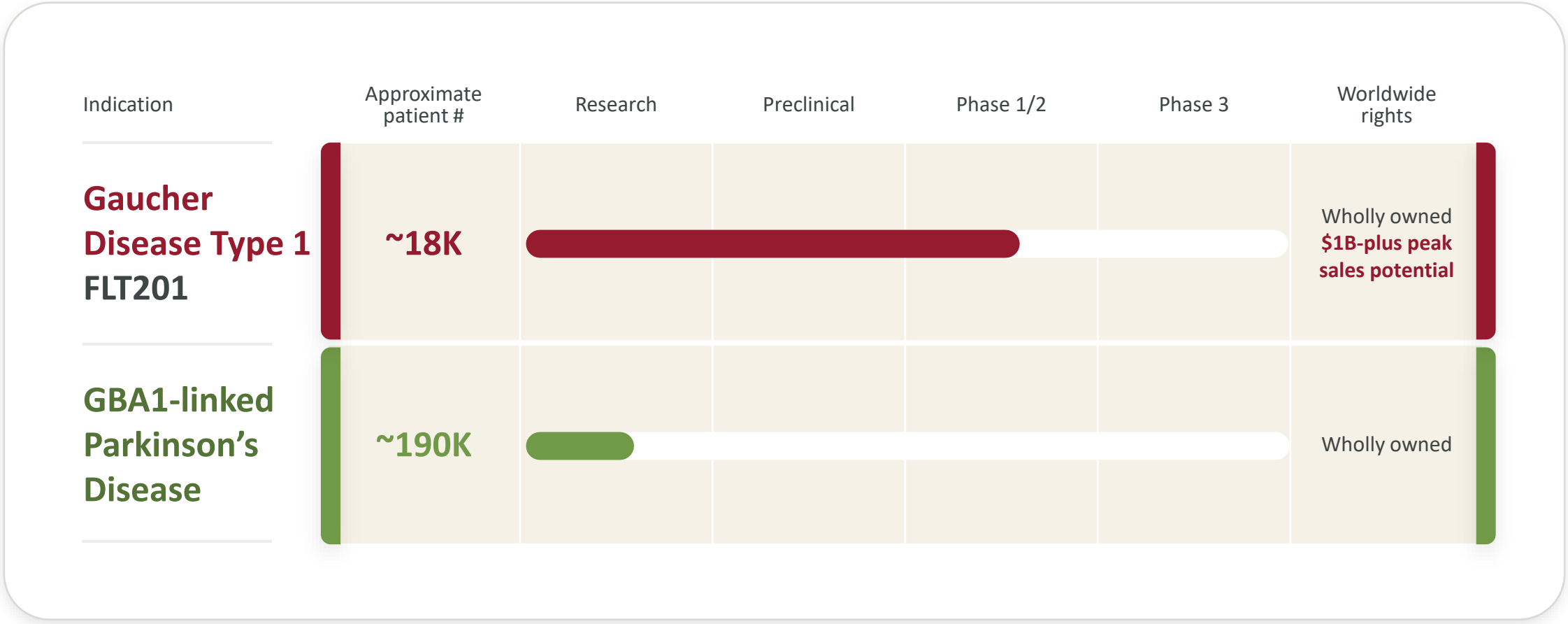
Lead research program leveraging our novel GCase variant for GBA1-linked Parkinson's disease

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

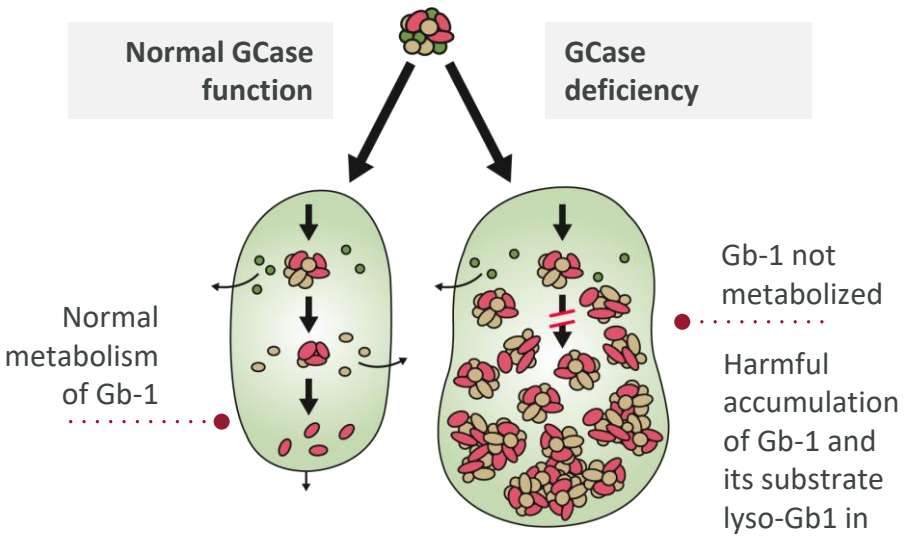


Estimated patient numbers for Gaucher disease Type 1 are for US, UK, EU4 and Israel (Hematology. 2017 Mar;22(2):65-73. doi: 10.1080/10245332.2016.1240391; this figure represents the total theoretical genetic prevalence of the indication. The seroprevalence of antibodies against the AAVS3 capsid renders 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.

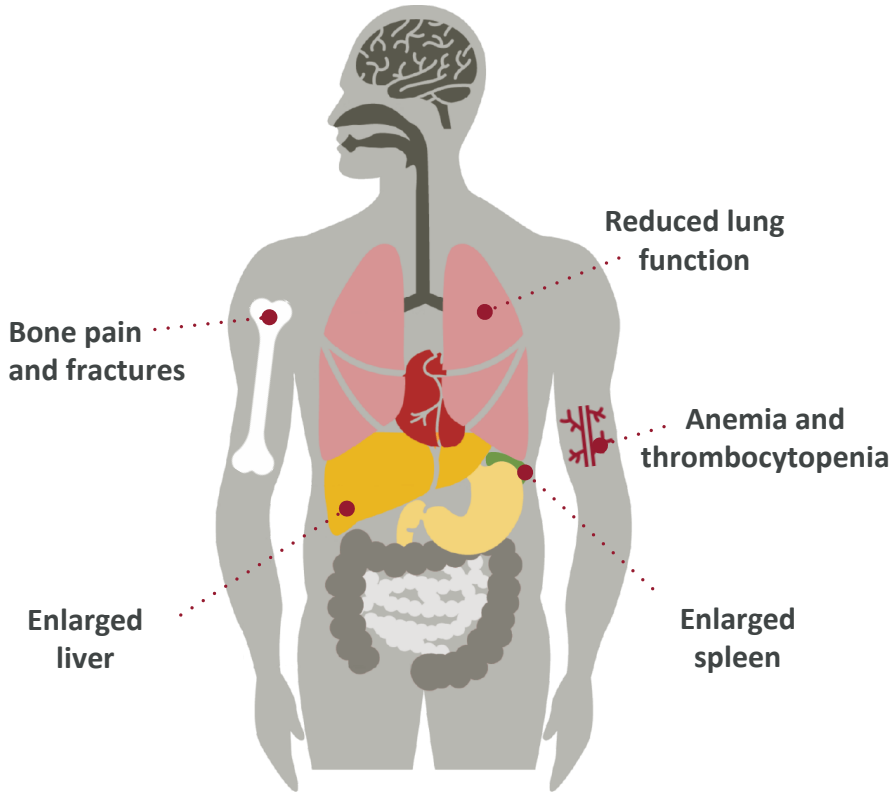
FLT201 in Gaucher Disease

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

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



Affects multiple organs, leading to wide range of symptoms and shortening life span[1]



[1]Weinreb, et al., 2008

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

Existing therapies poorly address certain aspects of disease

LENGTHY INFUSION EVERY TWO WEEKS

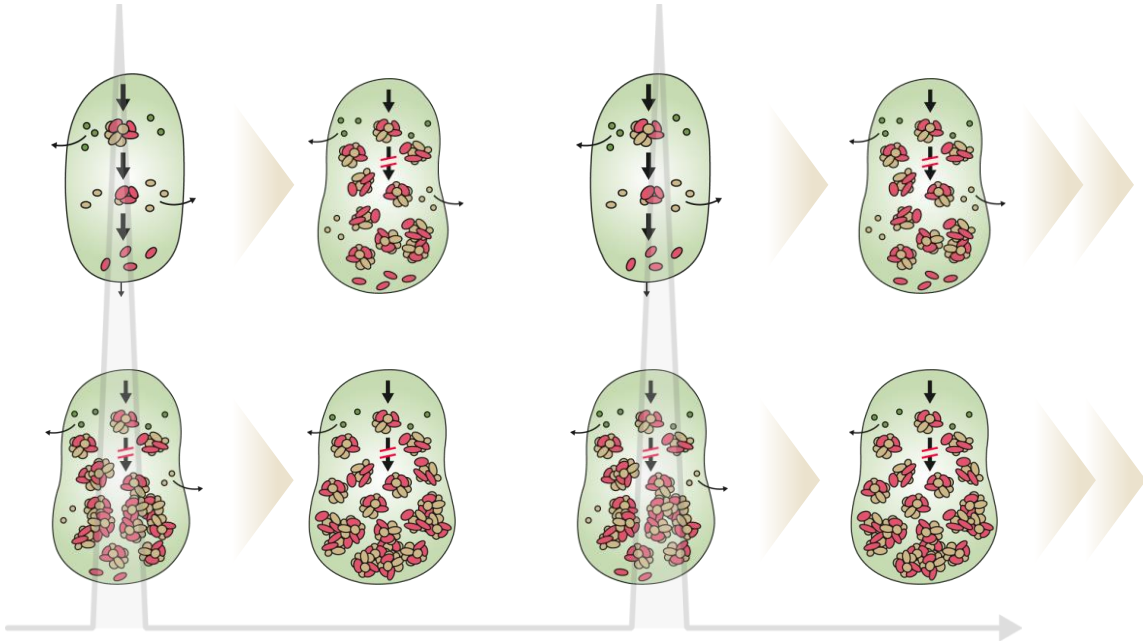
ERT

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[1]

bone pain

enlarged liver

enlarged spleen

low blood counts

43%
still have bone pain†

56%
still have severely enlarged livers †

61%
still have severely enlarged spleens †

43%
still have severely low platelet counts †

68%
have pulmonary dysfunction at baseline with most likely not having any normalization with ERT[2]

[1] Weinreb et al., 2013; 2 Kerem, et al., 1996 and Goitein, et al 2001; † 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

In study of 1388 patients who were either on SRT or ERT:

36%

of patients on SRT switched to or went back to ERT

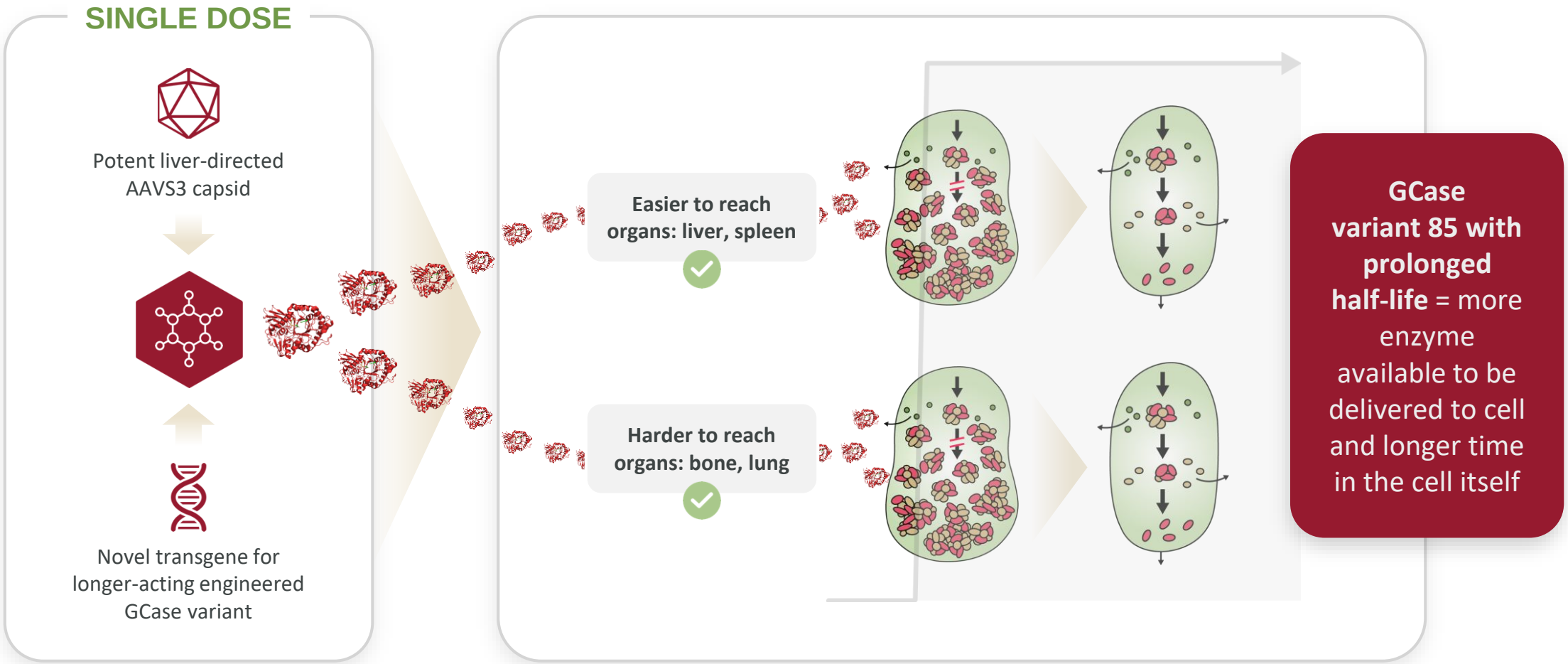
80%

cited adverse events or lack of efficacy

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

Hughes, et al J. Clin. Med. 2022, 11, 5158. https://doi.org/10.3390/jcm11175158;

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



Our engineered GCase variant has substantially longer half-life than wildtype

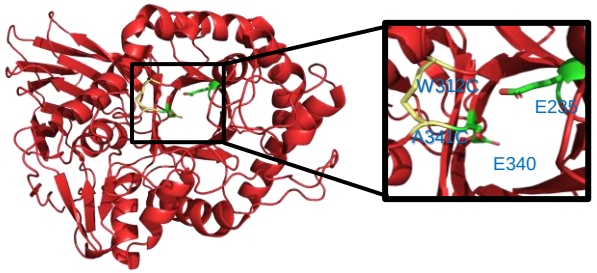
Key features of GCase variant

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

GCase variant 85 structure

Two internal amino acid substitutions

- Does not impinge on the active site
- Minimizes 3D structural change

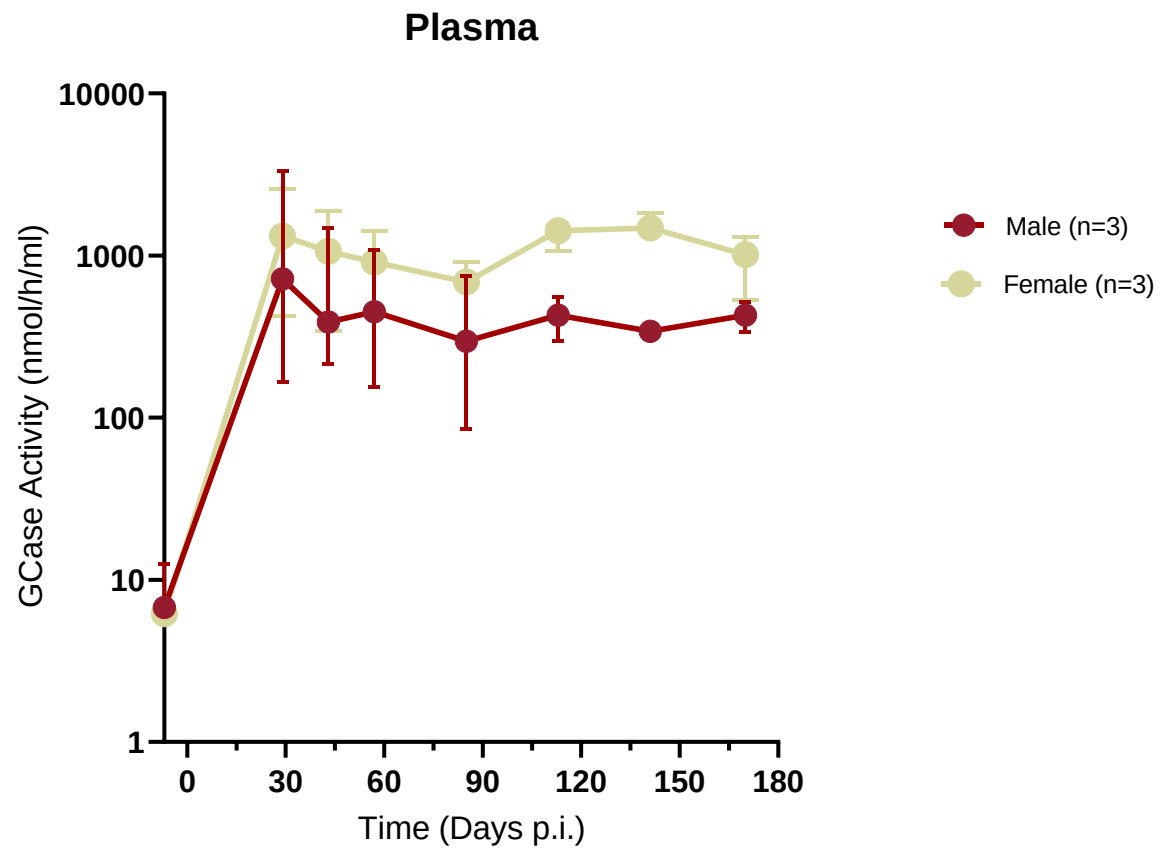


Biophysical properties of variant 85 and wildtype GCase

	Lysosomal pH	Human serum
	HALF-LIFE (MINUTES)	
WT GCase	388	24
Variant 85	>8,639	143
Improvement	**>21X**	**6X**

WORLD*Symposium* 2021: Fabrizio Comper et al. Generation of β-Glucocerebrosidase Variants with Increased Half-life in Human Plasma for Liver Directed AAV Gene Therapy Aimed at the Treatment of Type 1 Gaucher Disease

FLT201 shows high and durable GCase expression in non-human primates

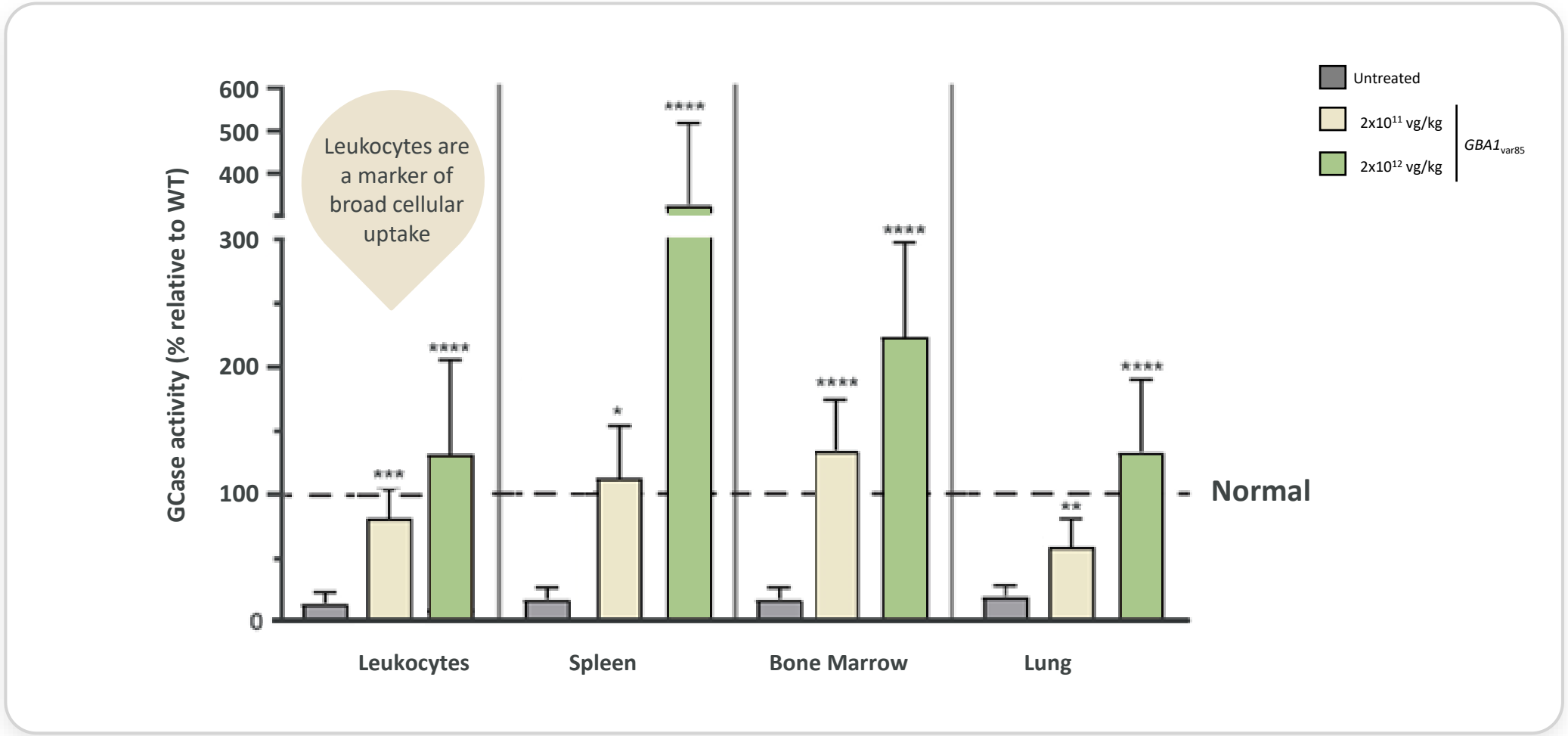


Achieved steady increases in GCase plasma levels

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

Dose: FLT201 $2x10^{12}$ vg/kg (long-term observational trial)

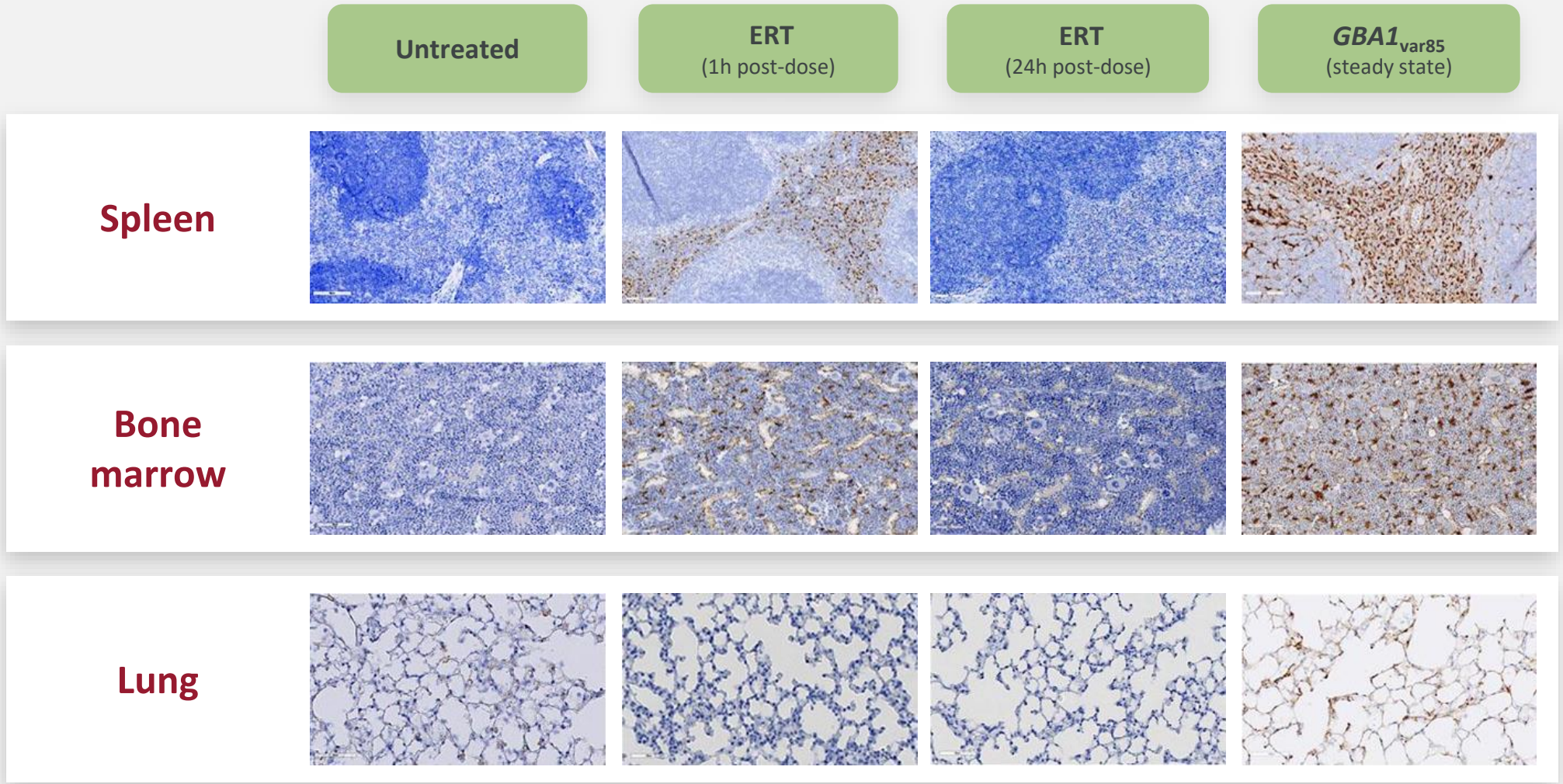
FLT201 demonstrated uptake in key tissues in Gaucher mice



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
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

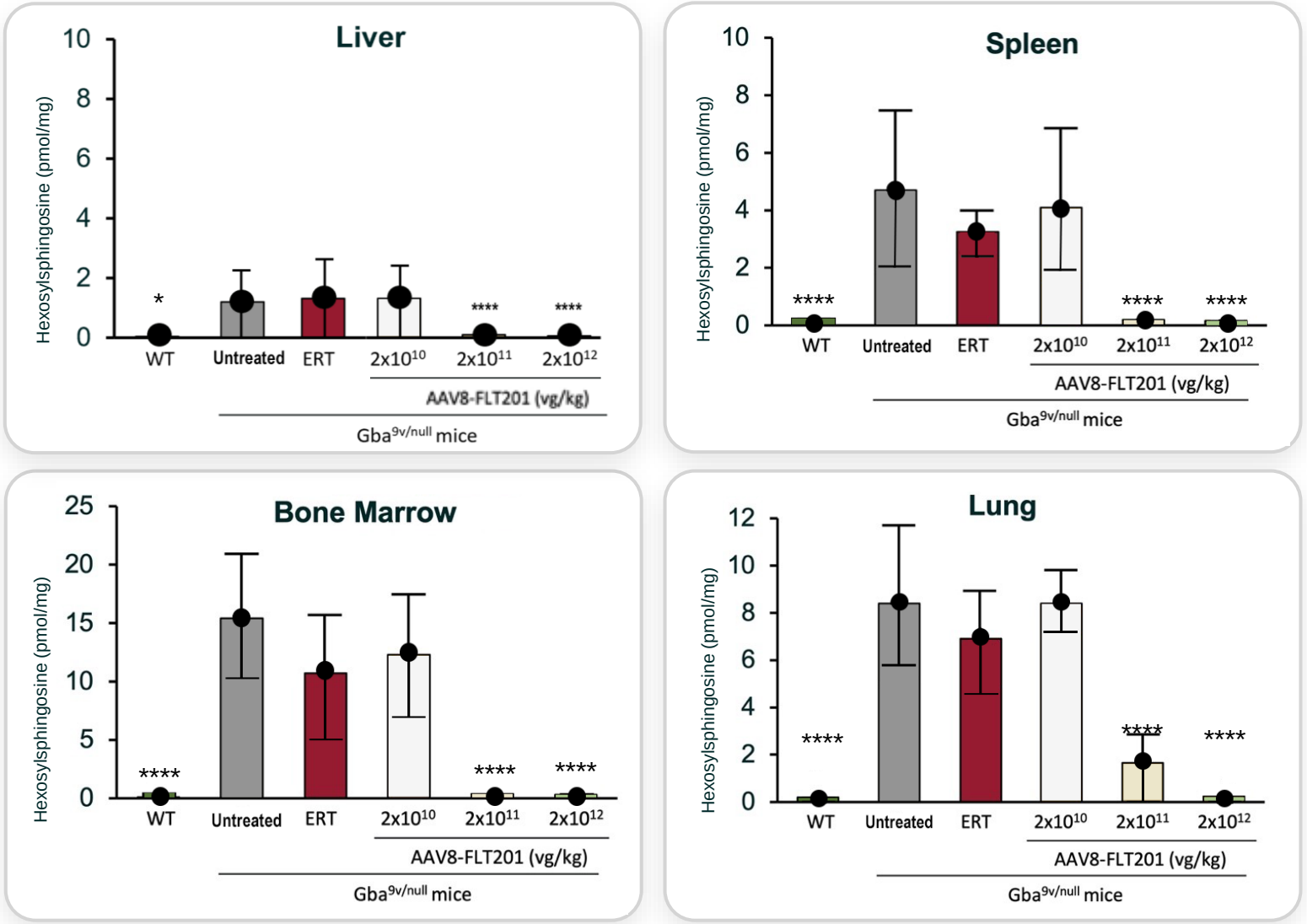
FLT201 demonstrates persistent coverage, while ERT is rapidly eliminated



Anti-GCase – DAB, Haematoxylin counterstain, AAV8

ERT=Velaglucerase alfa

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



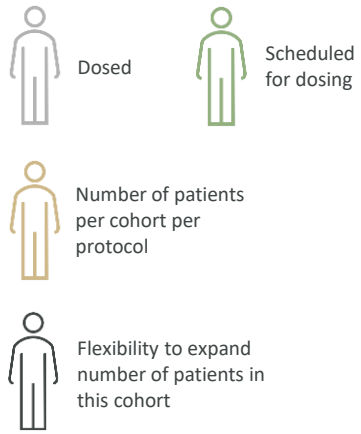
WORLD*Symposium* 2021: Romuald Corbau et al. FLT201: An AAV-Mediated Gene Therapy for Type 1 Gaucher Disease Designed to Target Difficult to Reach Tissues
AAV8-FLT201 = AAV8 pseudo-typed FLT201 genome. WT = wild-type mice. Evaluated 12 weeks post-injection. *p<0.05 ****p < 0.0001 versus untreated.

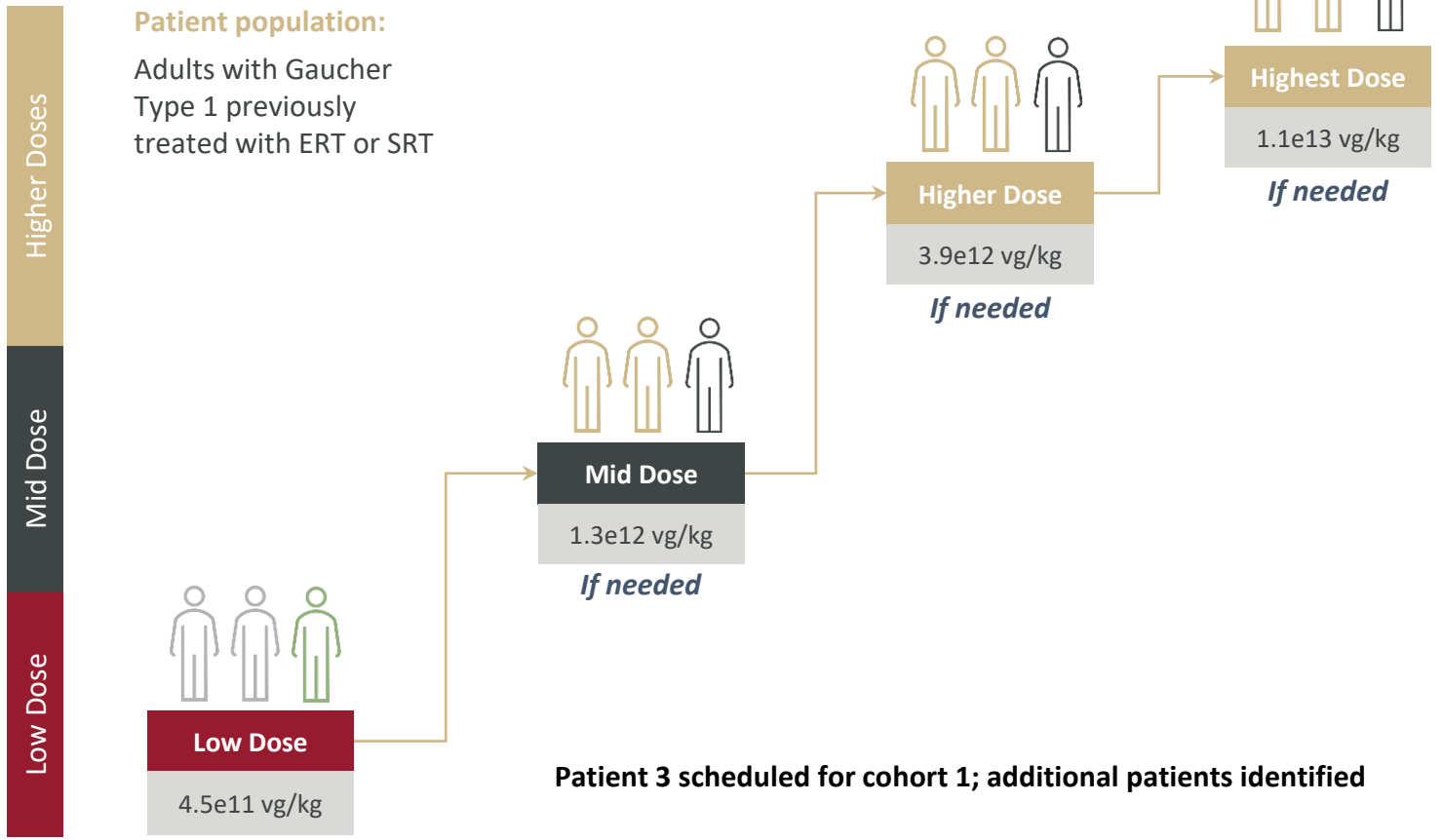
Initial Clinical Data for FLT201

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





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

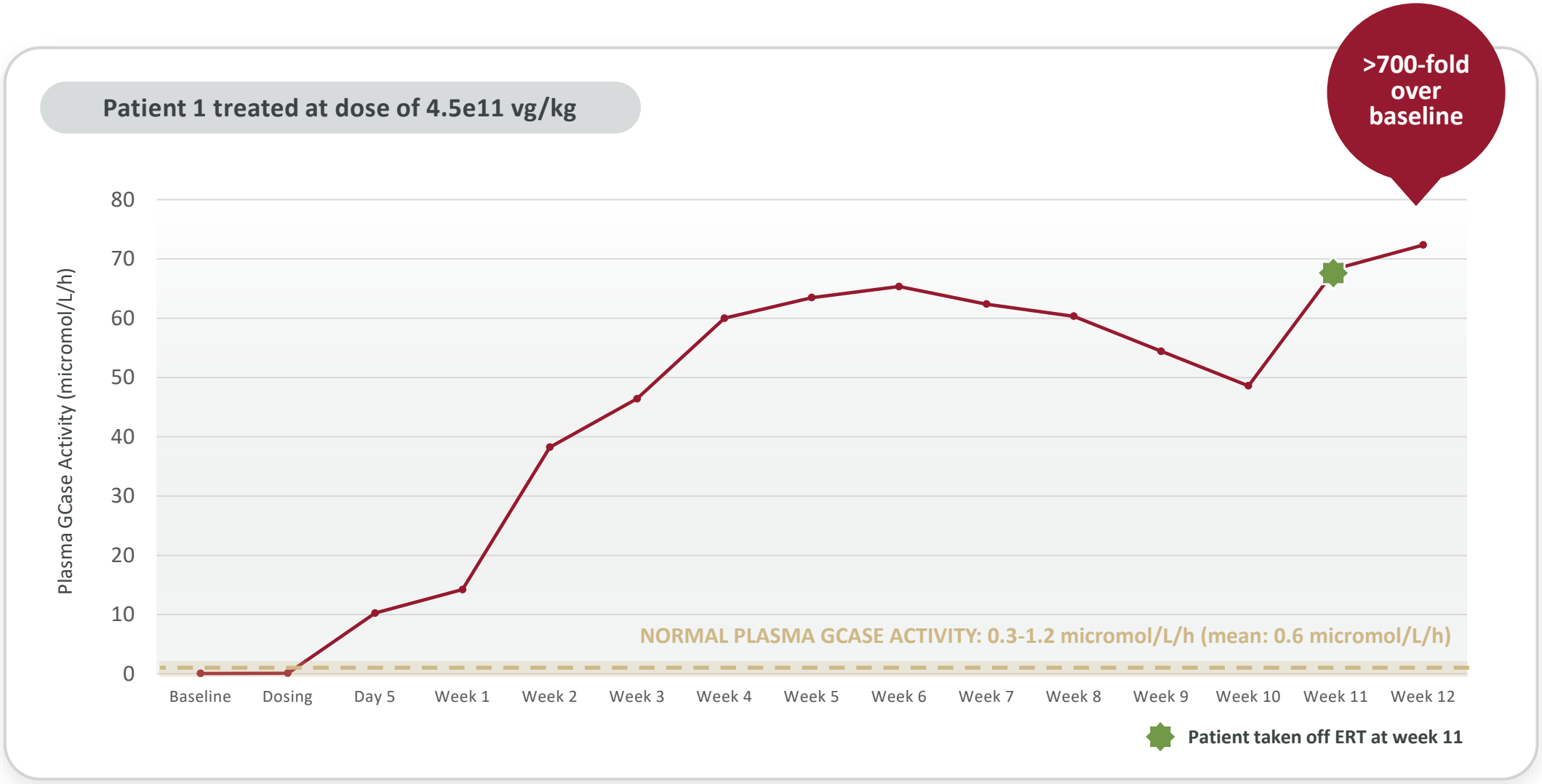
	PATIENT 1	PATIENT 2
Dose (vg/kg) Absolute dose (vg)	4.5×10^{11} 2.835×10^{13}	4.5×10^{11} 2.84×10^{13}
Gaucher therapy at baseline	ERT	SRT
Age	35	25
Gender	Male	Male
Body weight	63kg	63.1kg
Plasma GCase activity (μmol/L/h)	0.07	0.014
DBS GCase activity (μmol/L/h)	0.3	0.3
Leukocyte GCase activity (nmol/h/mg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

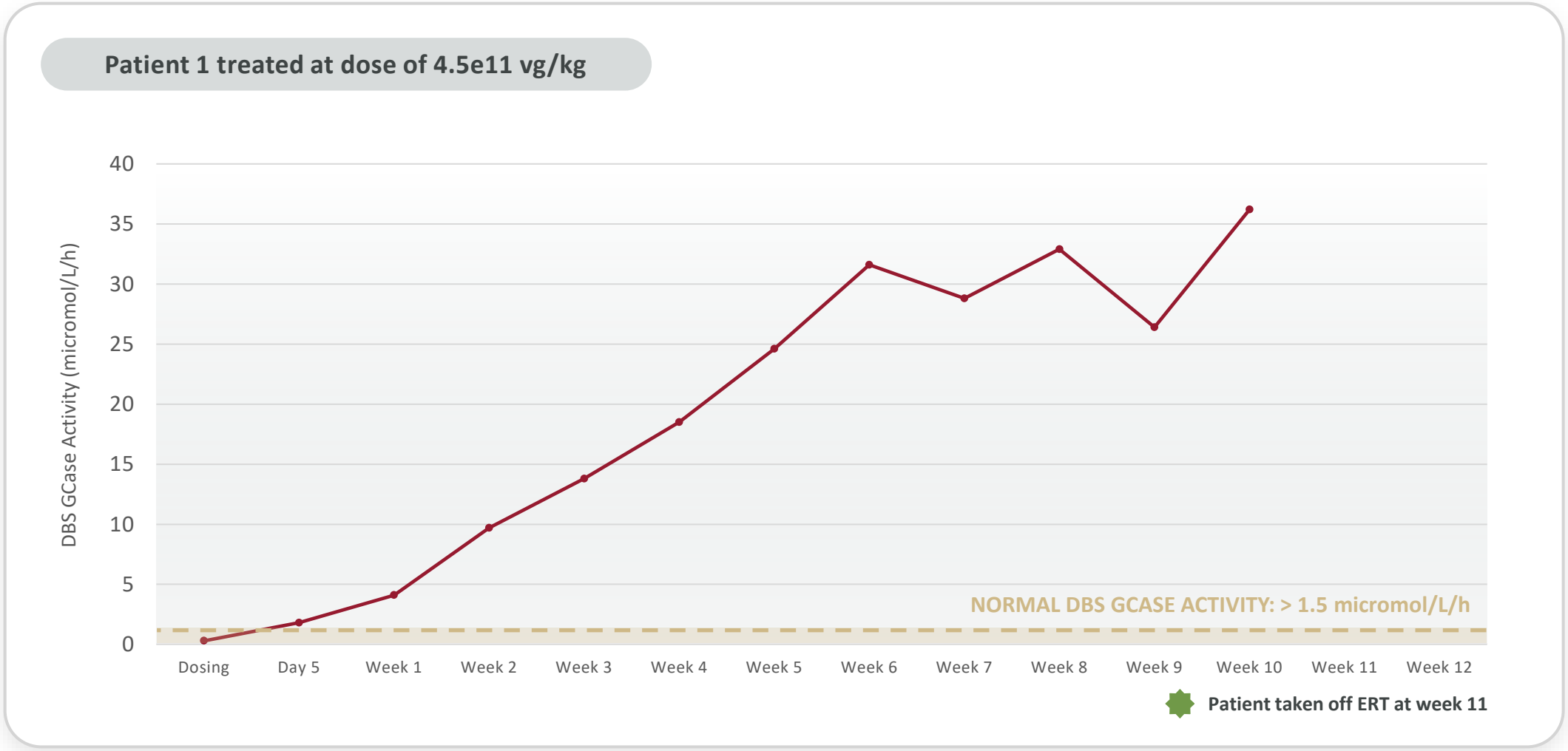
As of Sept. 27, 2023 data cutoff.

Patient 1: Robust increases in plasma GCase activity



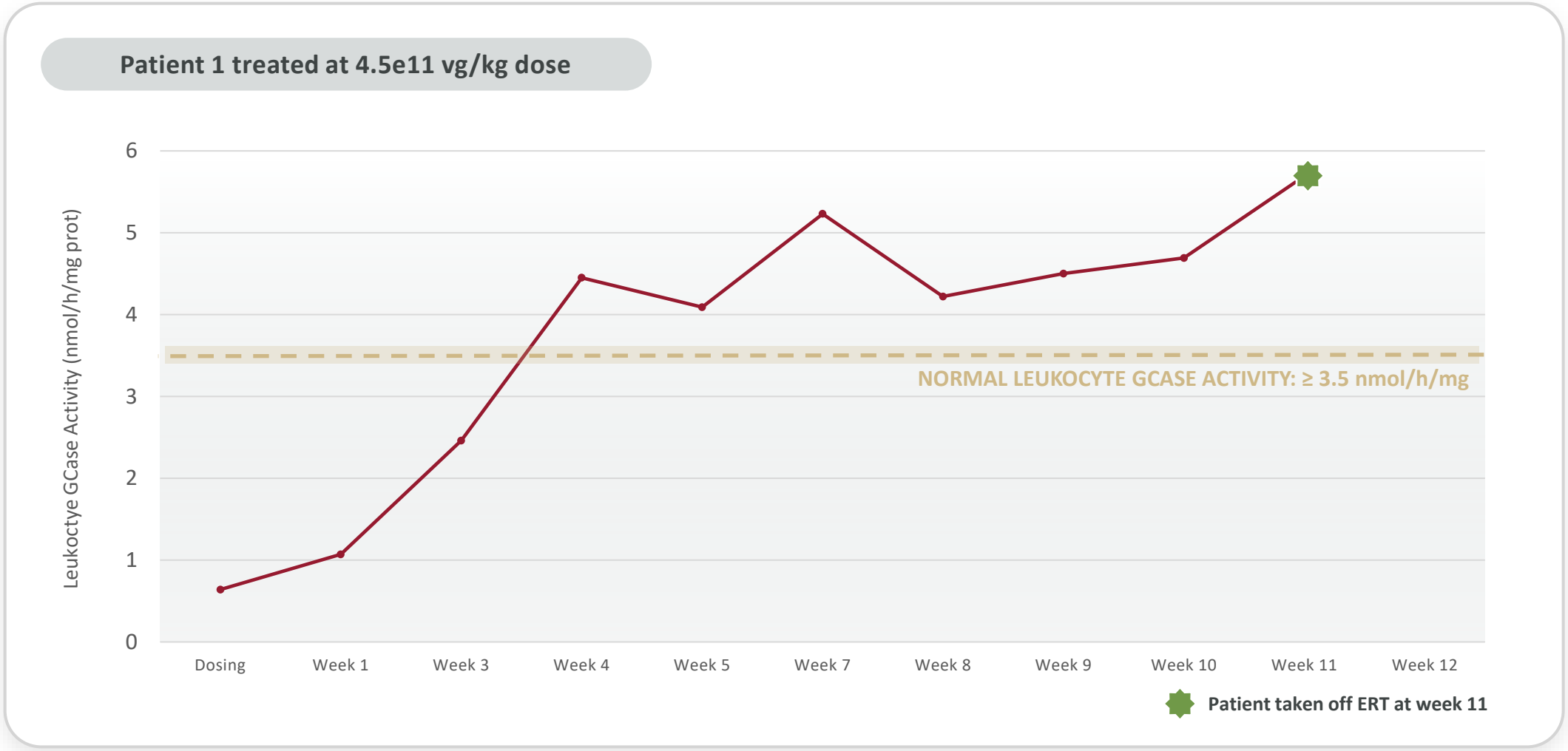
As of Sept. 27, 2023 data cutoff. Enzyme activity measured at 5 and 13 days post-ERT administration when there is no GCase from ERT remaining in the system.

Patient 1: Similarly robust increases in DBS GCase activity



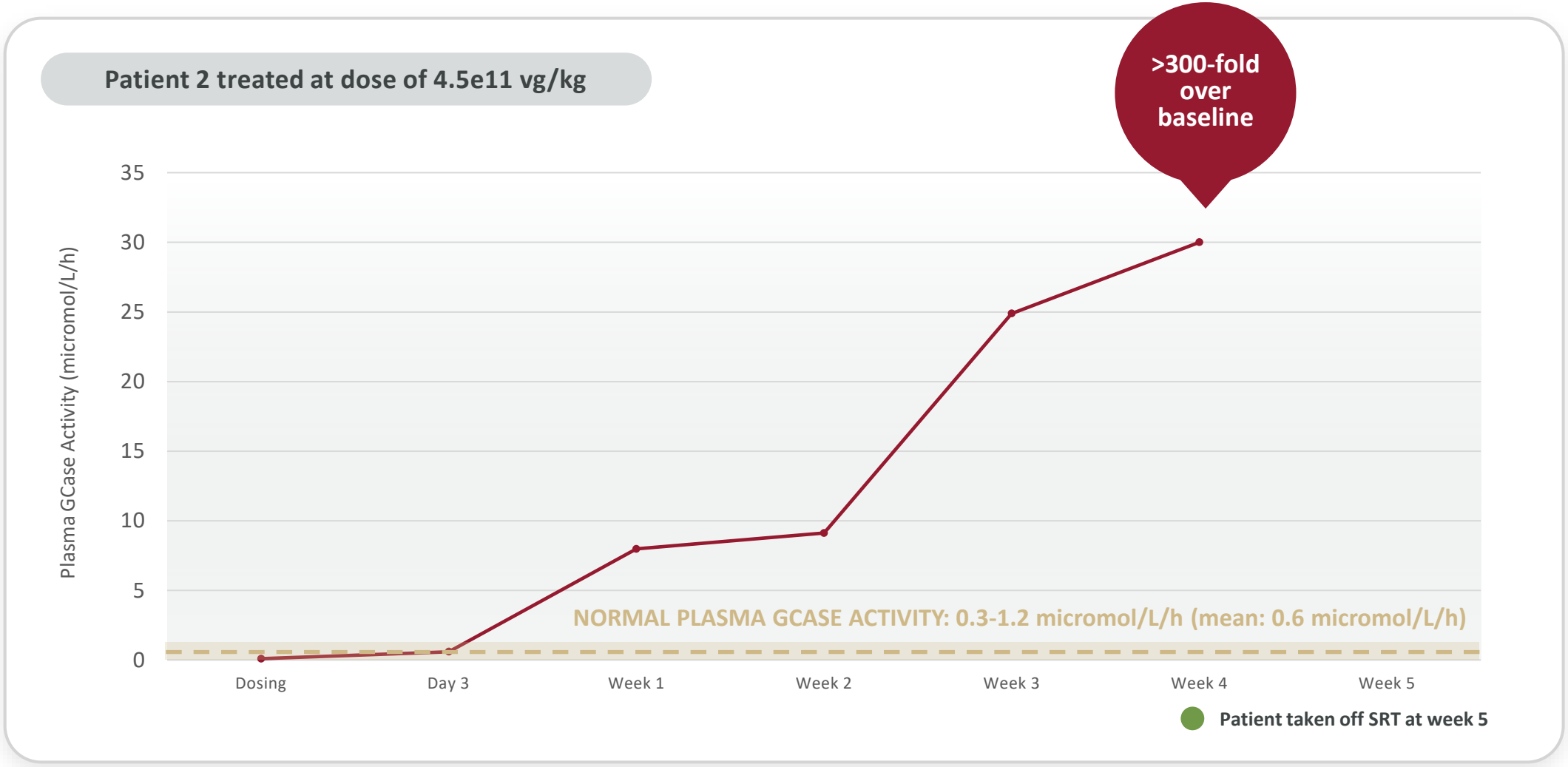
As of Sept. 27, 2023 data cutoff. Enzyme activity measured at 5 and 13 days post-ERT administration when there is no GCase from ERT remaining in the system. DBS = dry blood spot.

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



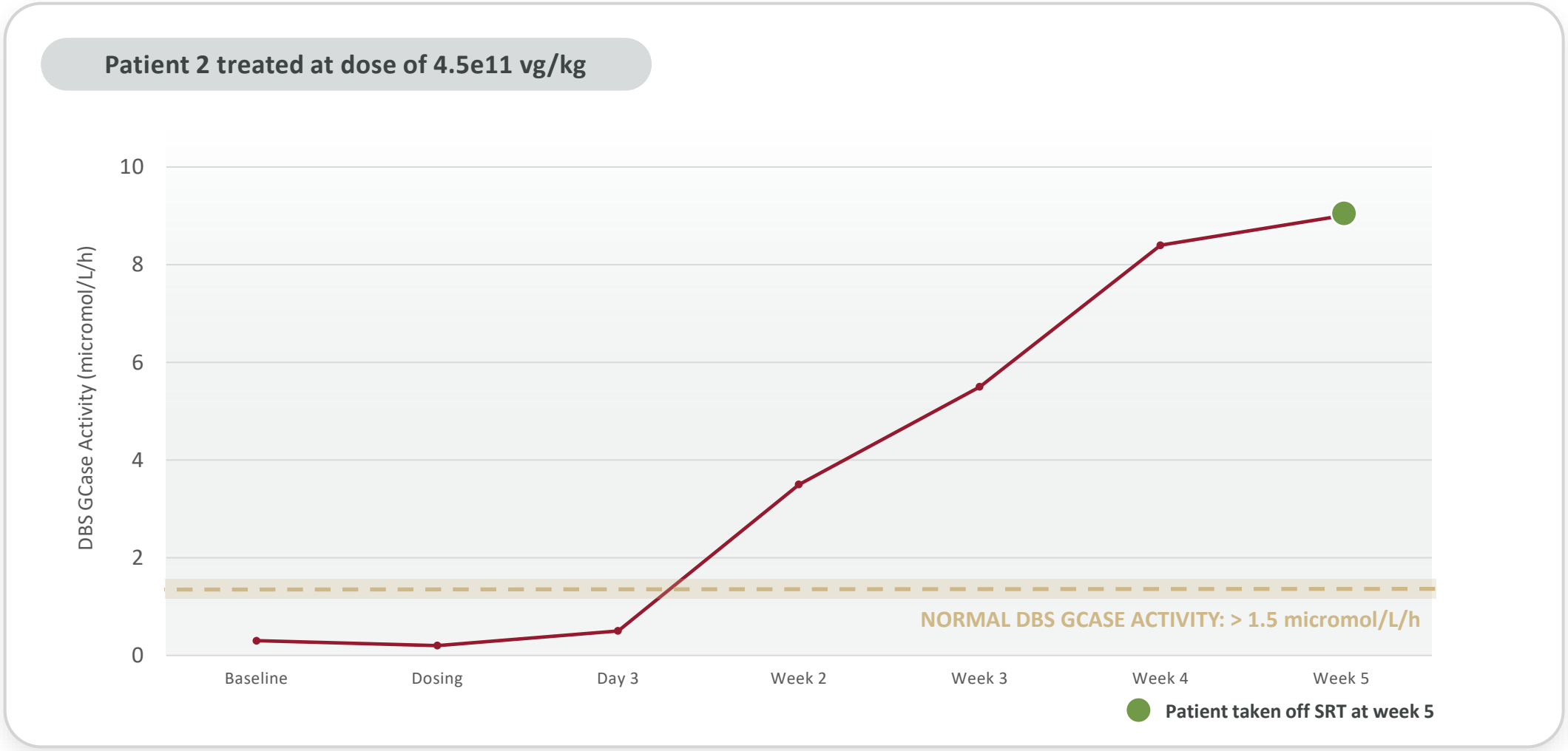
As of Sept. 27, 2023 data cutoff. Enzyme activity measured at 5 and 13 days post-ERT administration when there is no GCase from ERT remaining in the system.

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



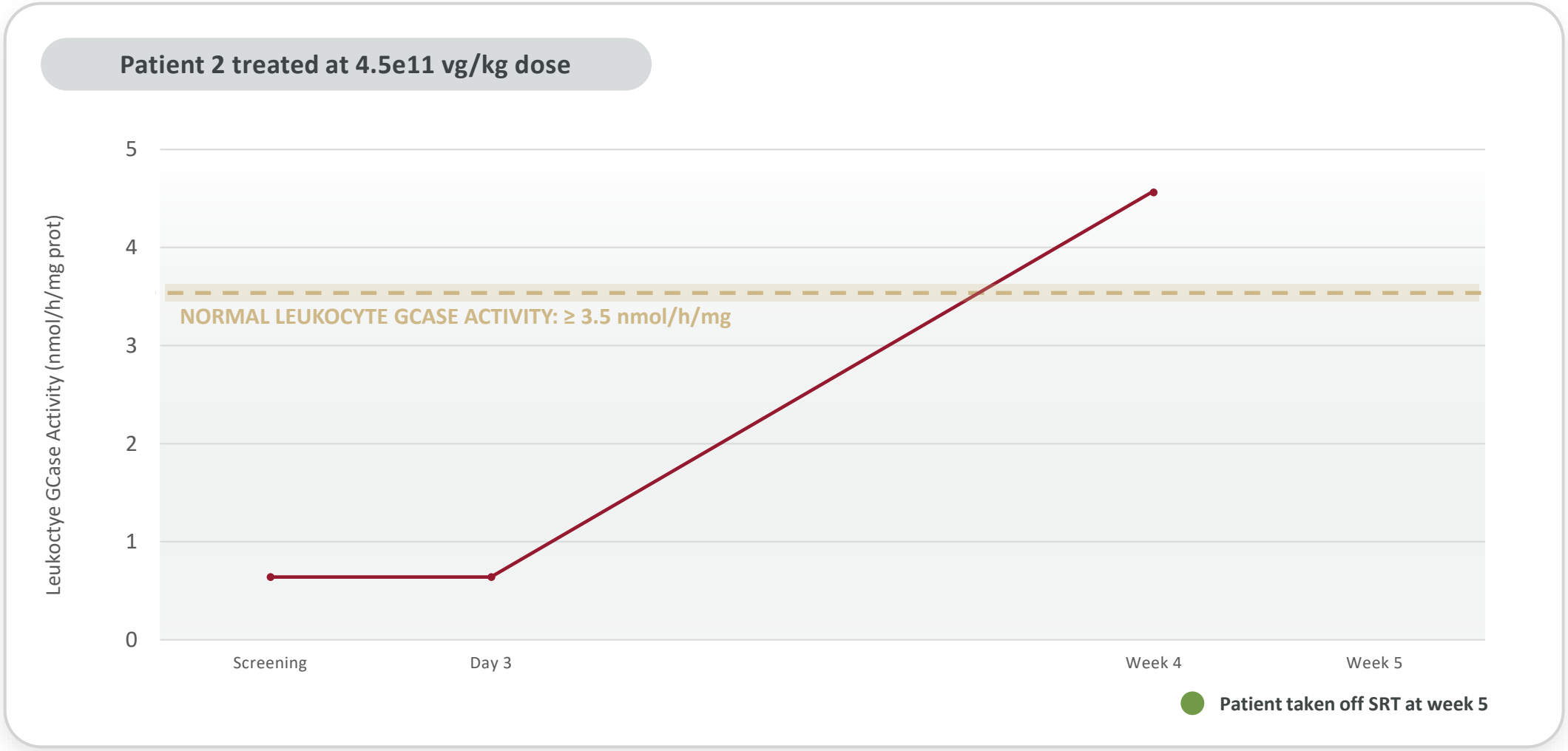
As of Sept. 27, 2023 data cutoff.

Patient 2: Similarly robust increases in DBS GCase 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.

Expeditiously advancing development of FLT201

- Dosing Patient 3 in cohort 1 given compelling enzyme activity and favorable safety
- Three additional patients identified and in scheduling; more patients in screening
- Awarded ILAP designation in UK, providing enhanced regulatory interactions
- Plan to apply for RMAT and PRIME designations to gain expanded access to regulators in US and EU
- Sharing further details on these initial clinical data in oral presentation at ESGCT

GBA1-linked Parkinson's Disease

Our longer-acting GCase variant may provide opportunity for best-in-class gene therapy for GBA1-linked PD

EXTEND OUR INNOVATION

- Leverages engineered longer-acting GCase variant with aim of achieving better brain distribution and coverage than wildtype
- Builds on our gene therapy expertise to optimize construct and delivery

HIGH UNMET NEED

- No disease-modifying therapies exist for PD
- GBA1-linked PD associated with earlier onset and more severe disease
- ~5-15% of PD patients have GBA1 mutations; most common genetic risk factor

EARLY DATA SUPPORT MOVE INTO PD

- Demonstrated superior in vitro activity and expression levels of our longer-acting GCase variant compared to wildtype

PD is a severe and progressive neurodegenerative disease with no approved disease-modifying therapies

Characterized by build-up of alpha-synuclein aggregates (Lewy bodies) and death of dopaminergic neurons

Symptoms worsen and treatment becomes less effective over time

No approved disease-modifying therapies

GBA1 mutations are most common genetic risk factor in Parkinson's disease

5-30x

greater risk of developing PD in people with GBA1 mutations[1]

- Associated with earlier onset and more severe disease
- Contributes to formation of Lewy bodies and death of dopaminergic neurons via multiple mechanisms
- Evidence of reduced GCase activity even in patients without a known GBA mutation

[1]Cells 2022, 11(8), 1261; https://doi.org/10.3390/cells11081261

GBA1-linked PD is a substantial and well-defined patient subset

PD is second most common neurodegenerative disease

~1.9M

diagnosed PD patients in US, UK and EU4*

5-15%

have GBA1 mutations†

~190,000

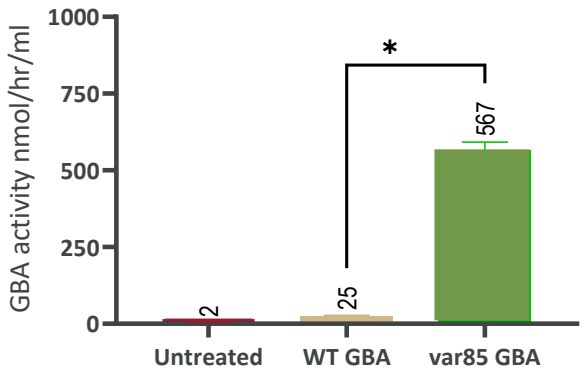
estimated GBA1-linked PD population

* Source: GlobalData; (Benito-León et al., 2003; Bergareche et al., 2004; Wickremaratchi et al., 2009; Blin et al., 2015; Pupillo et al., 2016; Uda et al., 2016; Heinzel et al., 2018; Mantri et al., 2019; United States Census Bureau, 2019)

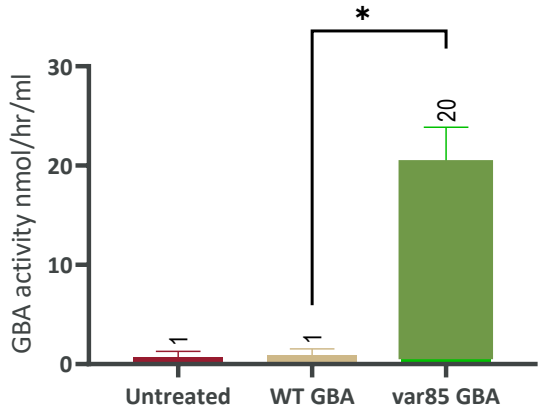
† Cells 2022, 11(8), 1261; https://doi.org/10.3390/cells11081261

Our GCase variant has demonstrated up to 20-fold greater activity levels compared to wildtype in preclinical studies

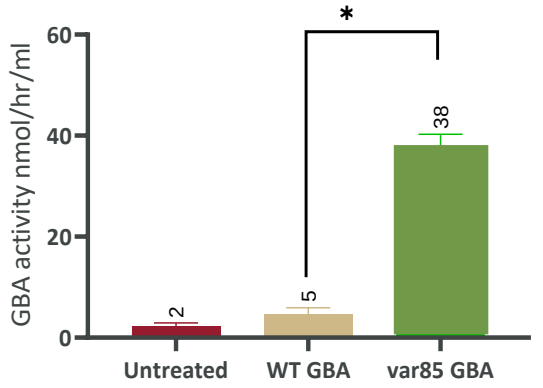
Brain epithelial cell line
(H4)



Neuroblastoma cell line
(NB1643)



Neuronal cell line
(SH-SY5Y)



AAV9 *in vitro* transduction & activity in supernatants; N=3; + SEM, t-test vs. Var85 , *P≤0.05

Freeline: Pioneering gene therapy

FLT201 is a potential first-and best-in-class gene therapy for Gaucher disease

Initial clinical data demonstrate robust enzyme activity and clean safety and tolerability

Extending impact of our innovation into GBA1-linked Parkinson's disease

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Thank you