

A man in an orange t-shirt and black shorts is running on a paved path. He is wearing large white headphones and has a joyful expression. The background features a city skyline with several tall buildings, including the Empire State Building, across a body of water. The sun is low in the sky, creating a strong lens flare effect. A chain-link fence runs along the path.

FREELINE

# Corporate Presentation

---

10 May 2022

# Legal disclaimer

This presentation contains statements that constitute “forward looking statements” as that term is defined in the United States Private Securities Litigation Reform Act of 1995, including statements that express the opinions, expectations, beliefs, plans, objectives, assumptions or projections of Freeline Therapeutics Holdings plc (the “Company”) regarding future events or future results, in contrast with statements that reflect historical facts. Examples include statements regarding upcoming milestones in its Phase 1/2 B-LIEVE dose-confirmation and potential pivotal Phase 3 clinical trials of FLT180a, Phase 1/2 MARVEL-1 clinical trial of FLT190 and Phase 1/2 dose-finding clinical trial of FLT201, including trial design, dosing of patients and data readouts; that its product candidates have the potential to be best-in-class, first-in-class and/or functional cures and to deliver transformative therapies; that a dose of 7.7e11 vg/kg with the Company’s immune management regimen will result in consistent Factor IX (“FIX”) levels in the normal range; regarding planned regulatory filings; or regarding the Company’s expectations regarding its use of cash and cash runway; as well as any other discussion of the Company’s strategies, financing plans, business plans and prospects, capital allocation objectives and manufacturing, research, pipeline and clinical trial plans, including anticipated development milestones for the Company’s product candidates. In some cases, you can identify such forward-looking statements by terminology such as “anticipate,” “intend,” “believe,” “estimate,” “plan,” “seek,” “potential,” “project” or “expect,” “may,” “will,” “would,” “could” or “should,” the negative of these terms or similar expressions. Forward-looking statements are based on management’s current beliefs and assumptions and on information currently available to the Company, and you should not place undue reliance on such statements. Forward-looking statements are subject to many risks and uncertainties, including the Company’s recurring losses from operations; the uncertainties inherent in research and development of the Company’s product candidates, including statements regarding the timing of initiation, completion and the outcome of clinical studies or trials and related preparatory work and regulatory review, regulatory submission dates, regulatory approval dates and/or launch dates, as well as risks associated with preclinical and clinical data, including the possibility of unfavorable new preclinical, clinical or safety data and further analyses of existing preclinical, clinical or safety data; the Company’s ability to design and implement successful clinical trials for its product candidates; the recent departures of a number of executive officers of the Company, and the Company’s ability to fill open positions, implement an orderly transition process and retain key talent; whether the Company’s cash resources will be sufficient to fund the Company’s foreseeable and unforeseeable operating expenses and capital expenditure requirements for the Company’s expected timeline; the potential for a pandemic, epidemic or outbreak of infectious diseases in the United States, United Kingdom or European Union, including the COVID-19 pandemic, to disrupt and delay the Company’s clinical trial pipeline; the Company’s failure to demonstrate the safety and efficacy of its product candidates; the fact that results obtained in earlier stage clinical testing may not be indicative of results in future clinical trials; the Company’s ability to enroll patients in clinical trials for its product candidates; the possibility that one or more of the Company’s product candidates may cause serious adverse, undesirable or unacceptable side effects or have other properties that could delay or prevent their regulatory approval or limit their commercial potential; the Company’s ability to obtain and maintain regulatory approval of its product candidates; the Company’s limited manufacturing experience which could result in delays in the development, regulatory approval or commercialization of its product candidates; and the Company’s ability to identify or discover additional product candidates, or failure to capitalize on programs or product candidates. Such risks and uncertainties may cause the statements to be inaccurate and readers are cautioned not to place undue reliance on such statements. Many of these risks are outside of the Company’s control and could cause its actual results to differ materially from those it thought would occur. The forward-looking statements included in this presentation are made only as of the date hereof. The Company does not undertake, and specifically declines, any obligation to update any such statements or to publicly announce the results of any revisions to any such statements to reflect future events or developments, except as required by law.

For further information, please refer to the Company’s reports and documents filed with the U.S. Securities and Exchange Commission. You may obtain these documents by visiting EDGAR on the SEC website at [www.sec.gov](http://www.sec.gov).

Certain information contained in this presentation relates to, or is based on, studies, publications, surveys and other data obtained from third party sources and the Company’s internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, they have not been independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third party sources. In addition, all of the market data included in this presentation involve a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, although the Company believes its own internal research is reliable, such research has not been verified by any independent source.

Transforming the lives of patients with systemic debilitating diseases using AAV-mediated gene therapies

## Pioneering transformative gene therapies with best-in-class potential



**High protein expression at low doses in humans** enabled by proprietary capsid



**Developing novel, high-quality gene therapy product candidates at commercial scale** using proprietary protein engineering, analytics and CMC platform

Targeting diseases where high protein expression at low doses offers best-in-class potential and unlocks disease opportunities beyond the reach of first-generation AAV gene therapy

# Three clinical-stage programs with best-in-class and/or first-in-class potential

**FLT180a**

**For treatment of  
hemophilia B**

Demonstrated Factor IX activity levels in normal range enabling potential for functional cure<sup>1</sup>

**FLT190**

**For treatment of  
Fabry disease**

Data from lowest dose cohort show promising and durable efficacy upon which to build

**FLT201**

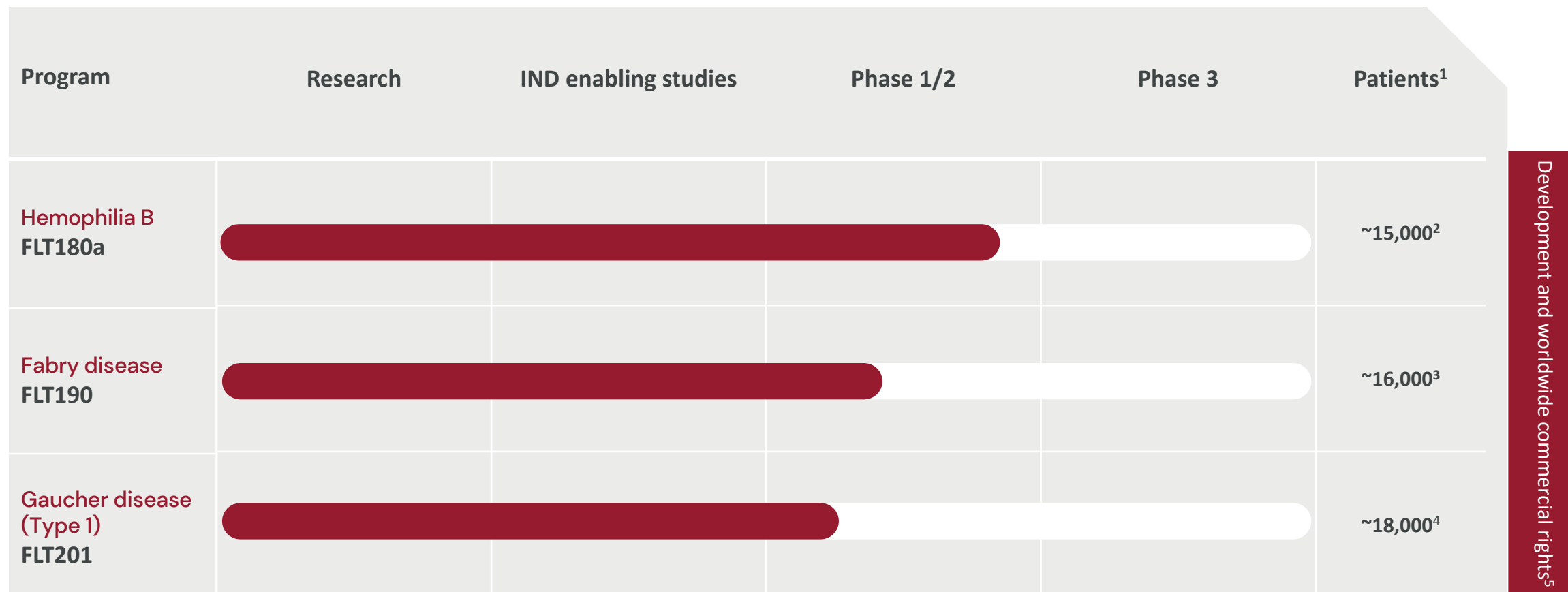
**For treatment of  
Gaucher disease<sup>2</sup>**

Novel protein engineered treatment shows promising pre-clinical data; first AAV gene therapy program for Gaucher

<sup>1</sup> Certain adult hemophilia B patients

<sup>2</sup> Gaucher disease Type 1

# Product Pipeline: Progressing three clinical-stage programs



<sup>1</sup> These figures represent the total approximate diagnosed population of Hemophilia B patients and the total theoretical genetic prevalence of the other indications. The seroprevalence of antibodies against the AAV capsid renders approximately 30-50% of patients currently not eligible for gene therapy.

<sup>2</sup> Hemophilia epidemiology: World Federation of Hemophilia 2020; Markets: EU4, UK, US, Japan, RoE.

<sup>3</sup> Ann Intern Med. 2003;138:338-346; Markets: EU4, UK, US, Japan.

<sup>4</sup> Hematology. 2017 Mar;22(2):65-73. doi: 10.1080/10245332.2016.1240391; Markets: EU4, UK, US, Israel.

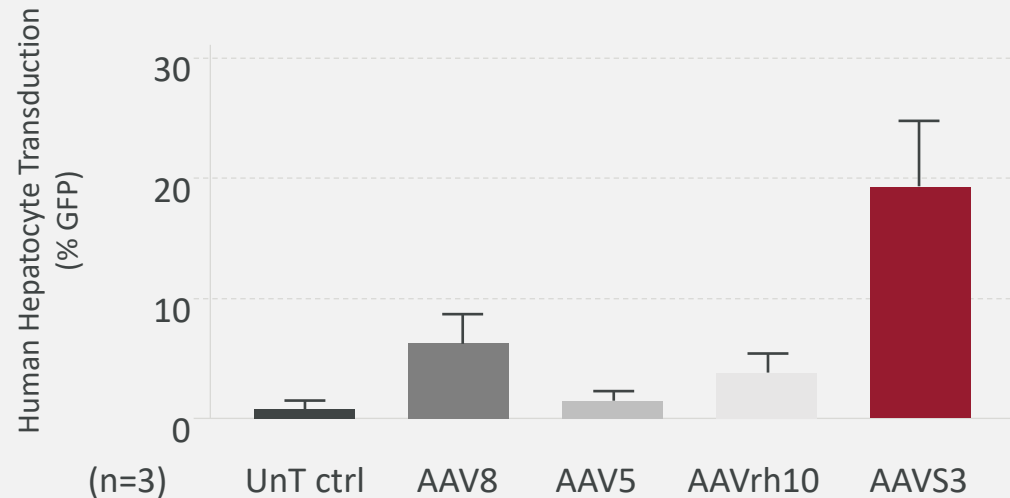
<sup>5</sup> Owned and in-licensed intellectual property rights.



# Platform Technology: AAVS3 capsid engineered to more efficiently transduce human hepatocytes

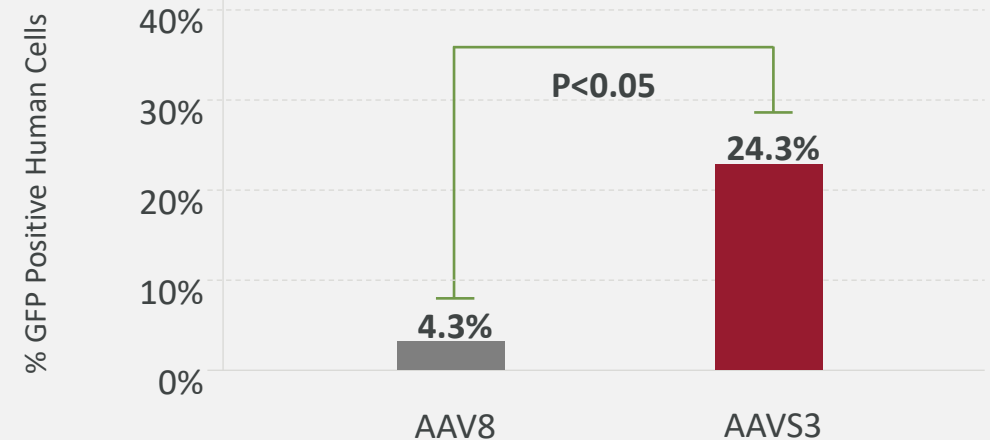
AAVS3 transduction significantly higher compared to other serotypes and untreated control

Transduction efficiency of AAVS3 in vitro compared with other vectors in primary human hepatocytes<sup>1</sup>



AAVS3 achieved nearly 6-fold higher transduction compared to AAV8

Transduction of human hepatocyte *in vivo* in AAV8 and AAVS3<sup>2</sup>



<sup>1</sup> Percentage of vectors containing GFP, green fluorescent protein, measured in primary human hepatocytes following transduction. AAVS3 pseudo typed vector used.

<sup>2</sup> Number of human hepatocytes expressing GFP following transduction. Measured in a human xenograft mouse model.

# Clinical data demonstrates greater potency of AAVS3 relative to competitors

The FLT180a dose listed, 3.84e11 vg/kg, is equivalent to 4.5e11 vg/kg under the previous equivalent dosing nomenclature.

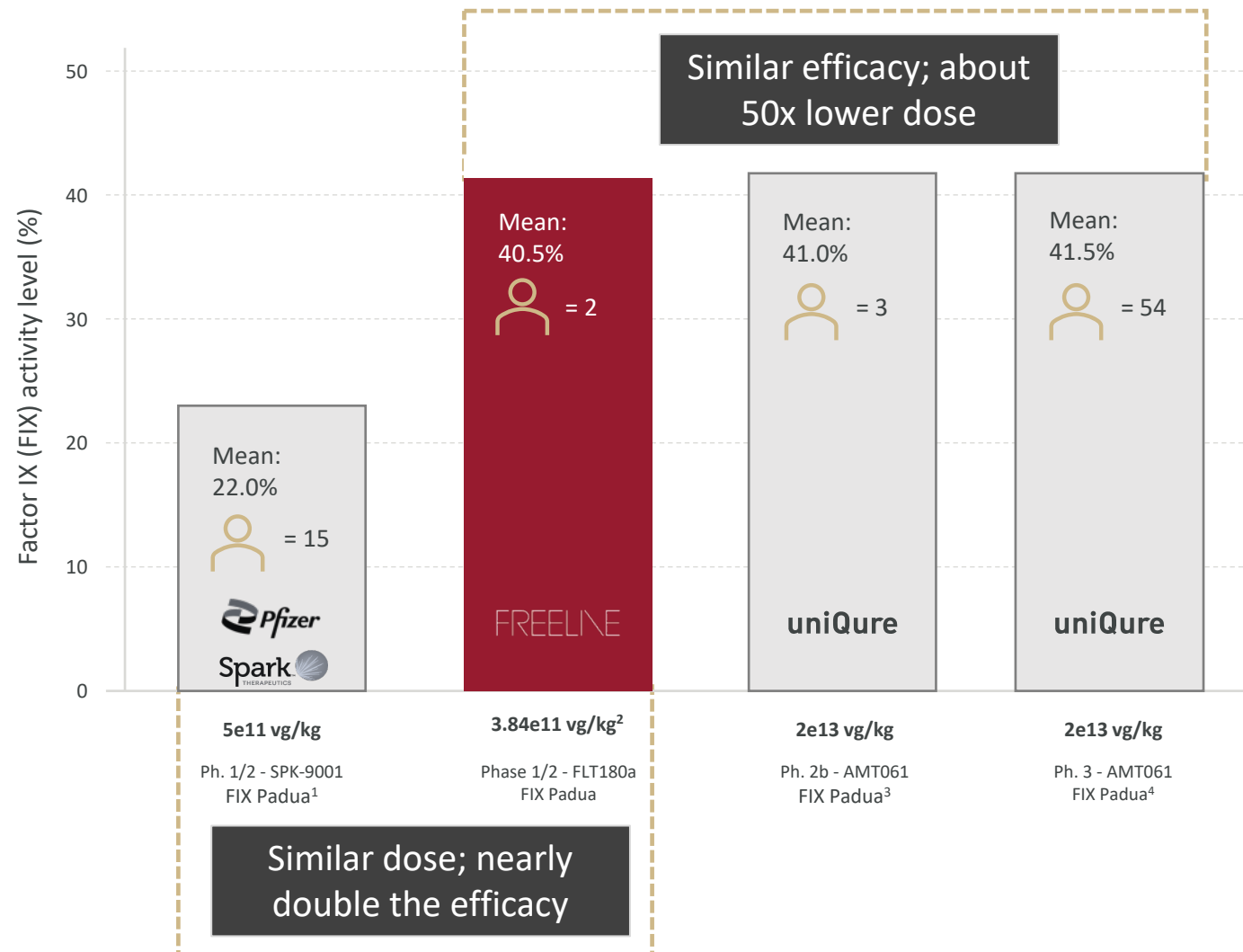
<sup>1</sup> Pfizer R&D Day Sep 2020 – up to four-year follow-up data in 15 patients from Phase 1/2 trial.

<sup>2</sup> As of the data cut-off date of September 20, 2021 measured using one-stage assay, central laboratory measurement. Two patients dosed at this dose level, with mean value calculated based on following Week 52 FIX activity levels: Patient 1, 45%, Patient 2, 36%.

<sup>3</sup> Miesback et al; Blood 2018 131:1022-1031.

<sup>4</sup> uniQure R&D day June 22, 2021 – 12-month follow-up data in 54 patients from the HOPE-B Phase 3 trial. Uncontaminated central laboratory data.

Mean 52-week Factor IX Activity Level



# Company Strategy: Pioneering innovations that transform the lives of patients

1

**Leverage highly potent capsid and platform capabilities** to deliver best-in-class and first-in-class treatments

Clinical programs with potential to deliver transformative therapies

2

**Execute clinical programs** to generate data demonstrating the value of Freeline's products and technology

Data anticipated across all clinical programs throughout 2022

3

**Invest in future innovations** by leveraging Freeline's unique scientific capabilities in new disease areas

Next generation capsid design and development; novel protein variants engineered with enhanced therapeutic properties; CMC innovation



# Lean organization with core gene therapy discovery and development capabilities



Executive Team with deep experience in leading and running life science organizations



Leading industry experts in clinical development



Optimally-sized organization of ~190 FTEs



Cash runway into H2 2023



Deep experience in gene therapy manufacturing



Distinct in-house research capabilities and CMC technology

**Operational efficiency enhances financial flexibility for future growth and platform investments**



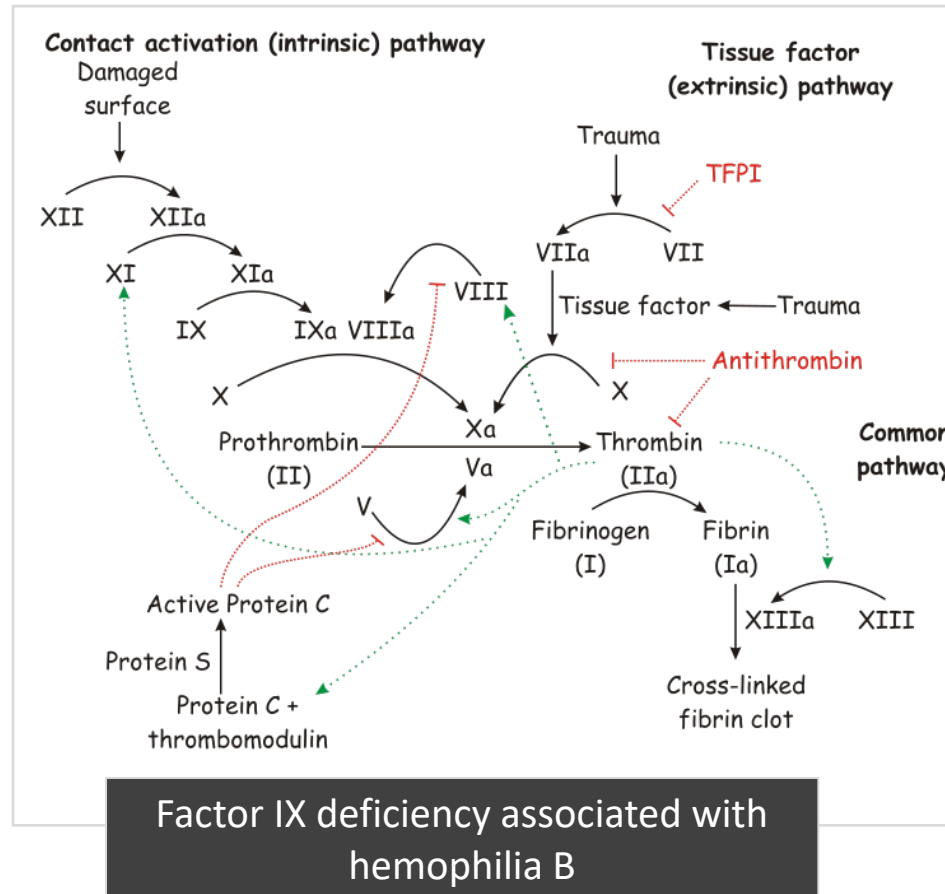
# Hemophilia B

# Hemophilia B Overview

## Disease Characteristics:

- Rare, X-linked, congenital bleeding disorder caused by deficiency of coagulation Factor IX (FIX)
- Depending on the severity of the disease, symptoms can range from frequent, spontaneous bleeding into joints and muscles to abnormal bleeding from minor injuries
- The majority of patients are male given that hemophilia is an X-linked disorder

## Blood Coagulation Cascade

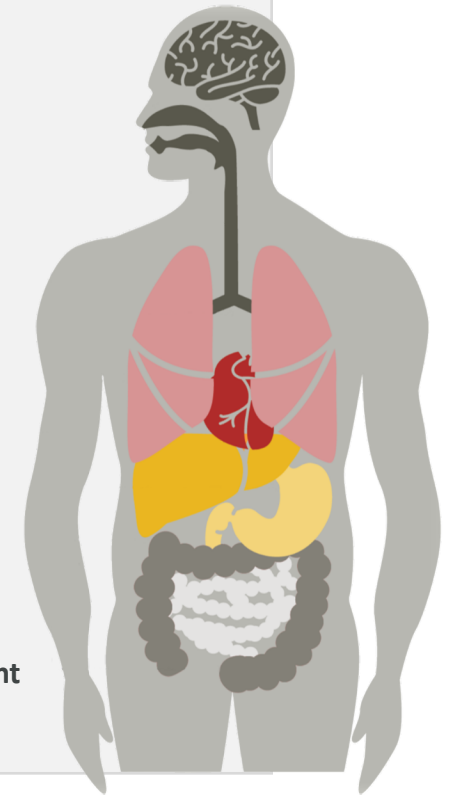


## Clinical Manifestations

Frequent, spontaneous bleeding

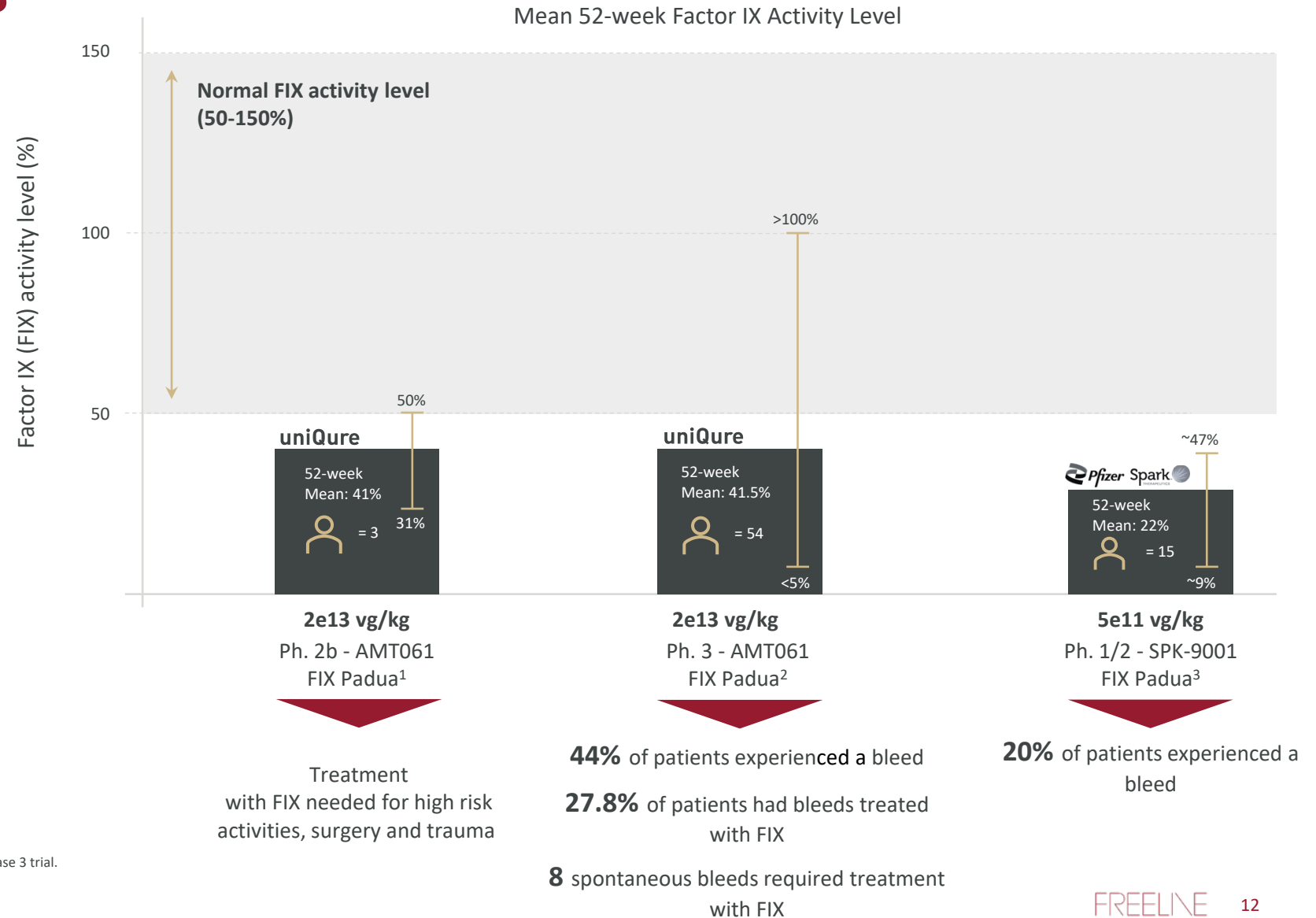
Abnormal bleeding from minor injuries

Risk of joint bleed which may result in permanent joint damage



# Challenge: First generation capsids do not adequately protect patients from bleeds

FIX activity levels achieved using first generation capsids are in the mild range with large variability



<sup>1</sup> Miesback et al; Blood 2018 131:1022-1031.

<sup>2</sup> uniQure R&D day June 22, 2021 – 12 month follow-up data in 54 patients from the HOPE-B Phase 3 trial. Uncontaminated central laboratory data.

<sup>3</sup> Pfizer R&D Day Sep 2020 – up to four year follow-up data in 15 patients from Phase 1/2 trial.

# Opportunity: Best-in-class therapy that achieves durable FIX activity levels in the normal range protecting patients from bleeds

## Urgent need in the market<sup>1</sup>



### Patients

Will wait for a gene therapy that delivers durable FIX activity levels in the normal range



### Physicians

Eliminating bleeds is an important consideration in selecting gene therapy



### Payers

Consider the curative and cost-saving potential of gene therapy attractive

## Hemophilia B target product profile



Predictably provide FIX activity levels in the normal range (50-150%)



Provide stable, durable FIX activity levels



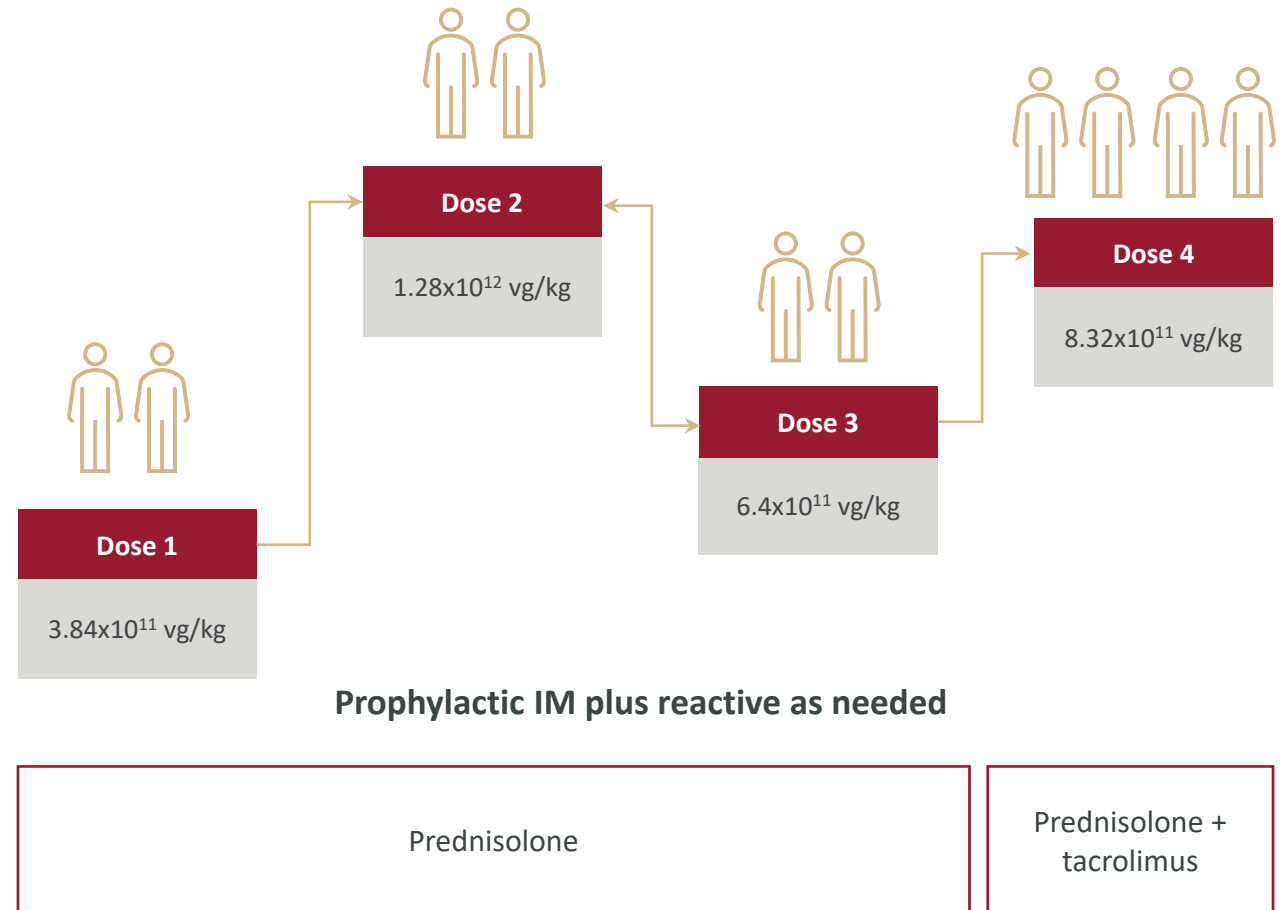
Significantly reduce or eliminate the occurrence of spontaneous bleeds

<sup>1</sup> Market research: Interviews, survey and analysis



# B-AMAZE Phase 1/2 dose-finding trial design

Novel features of B-AMAZE	
<ul style="list-style-type: none"> <li>Targeting normal range of FIX (50–150%)</li> <li>Adaptive dosing design to facilitate dose finding</li> <li>Prophylactic immune management plus reactive as needed for vector-related transaminitis</li> </ul>	
Duration	
<ul style="list-style-type: none"> <li>26 weeks for B-AMAZE</li> </ul>	<ul style="list-style-type: none"> <li>15 years for the LTFU trial</li> </ul>
Key inclusion	Key exclusion
<ul style="list-style-type: none"> <li>Adults (aged <math>\geq 18</math> years)</li> <li>FIX levels <math>\leq 2\%</math></li> </ul>	<ul style="list-style-type: none"> <li>Neutralizing antibodies to AAVS3</li> <li>Liver disease</li> <li>FIX inhibitors</li> </ul>
B-AMAZE Week 26 endpoints	
<ul style="list-style-type: none"> <li>Safety, as assessed by AEs</li> </ul>	<ul style="list-style-type: none"> <li>FIX activity</li> </ul>



FLT180a (verbrinacogene setparvovec) uses the potent, rationally designed AAVS3 capsid carrying a FIX-R338L 'Padua' variant transgene to enable high FIX expression with relatively low vector doses.

ClinicalTrials.gov identifiers: NCT03369444 for B-AMAZE and NCT03641703 for the LTFU trial.

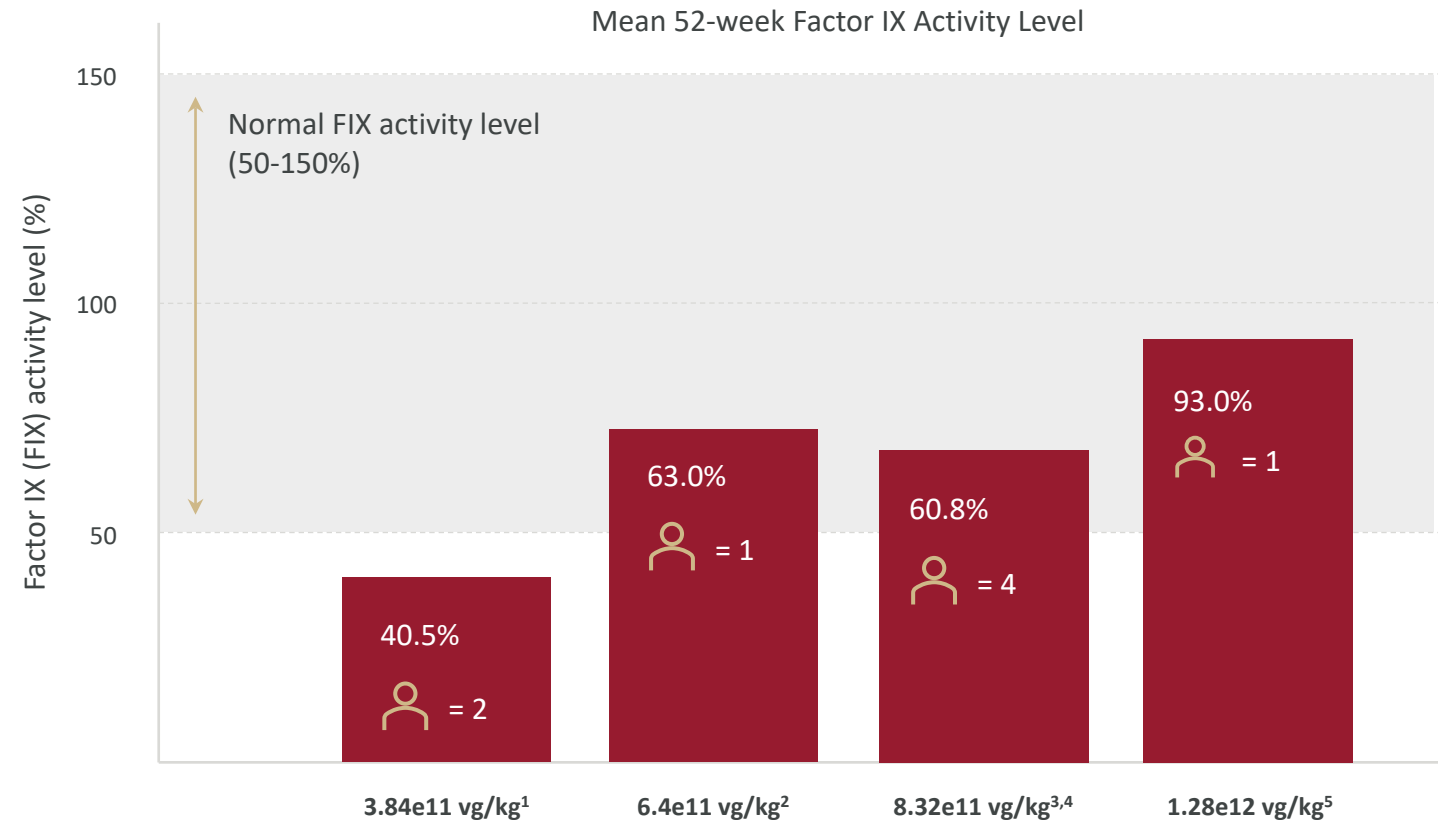
AAV, adeno-associated virus; AE, adverse event; FIX, Factor IX; IM, immune management; LTFU, long-term follow-up; vg, vector genomes.



# FLT180a achieved FIX activity in the normal range and significantly reduced bleeds

## Phase 1/2 B-AMAZE trial 52-week FIX activity level

As of September 20, 2021, measured using one-stage assay, central laboratory measurement



<sup>1</sup> 3.84e11 vg/kg dose: Two patients dosed at this level, with mean value calculated based on following Week 52 FIX activity levels: Patient 1, 45%, Patient 2, 36%.

<sup>2</sup> 6.4e11 vg/kg dose: Two patients dosed at this level. Patient 4 experienced loss of expression due to transaminitis and is not represented on this chart. At Week 52, Patient 4 FIX activity level was 1.5%, which would result in a mean FIX activity level of 32.2% for this dose cohort. Patient 5 missing measurement Week 52 measurement. Was imputed with a later measurement made at Month 13. Month 13 FIX activity levels, 63%.

<sup>3</sup> 8.32e11 vg/kg dose: Four patients dosed at this level, with mean value calculated based on following Week 52 FIX activity levels: Patient 7, 48%, Patient 8, 117%, Patient 9, 43%, Patient 10, 35%.

<sup>4</sup> One patient in the 8.32e11 vg/kg dose cohort, Patient 8, received exogenous FIX for treatment of a traumatic bleed; at the time, this patient's FIX activity level was and remains in the low end of the normal range.

<sup>5</sup> Includes data from one patient, Patient 3. Data from patient with supranormal levels of FIX (Patient 6) not available for this timepoint due to pandemic-induced constraints, and was not imputed with a later measurement.

**No spontaneous bleeds that required treatment with supplemental FIX**

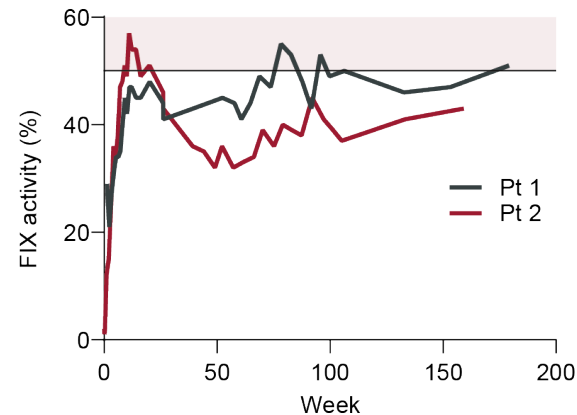
# FLT180a has sustained expression up to 3.5 years

**FIX expression has been sustained in 9 of 10 B-AMAZE patients.**

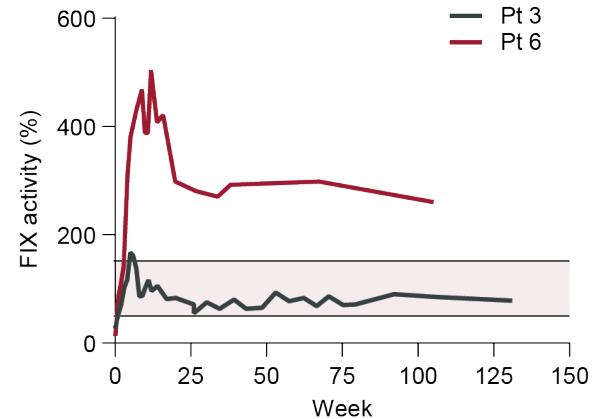
Data as of September 20, 2021. FIX levels for each patient by dose are shown in panels a–d. The normal range of FIX (50–150%) is indicated in each panel in pink. Patient 4 resumed prophylaxis and is indicated with a dashed line. FIX was measured at a central laboratory with a one-stage assay.

FIX, Factor IX; Pt, Patient; vg, vector genomes.

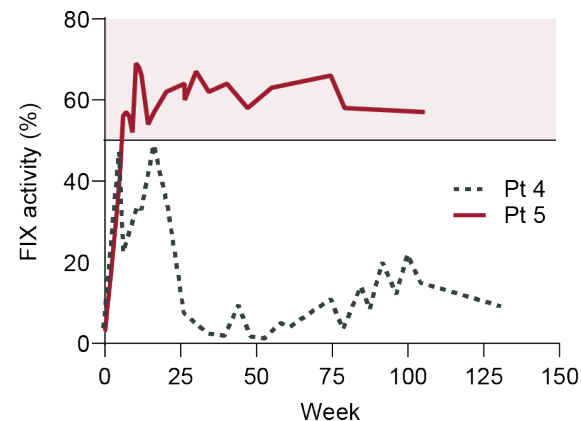
a. Dose level 1:  $3.84 \times 10^{11}$  vg/kg



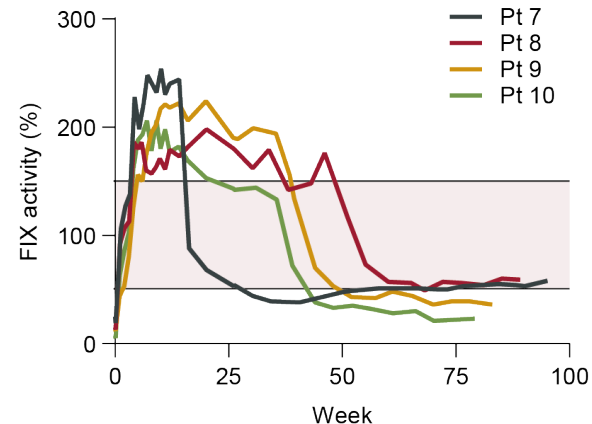
b. Dose level 2:  $1.28 \times 10^{12}$  vg/kg



c. Dose level 3:  $6.4 \times 10^{11}$  vg/kg



d. Dose level 4:  $8.32 \times 10^{11}$  vg/kg



9 of 10 patients did not receive FIX prophylaxis after FLT180a treatment:

- One patient lost FIX expression after transaminitis

Across 9 patients with sustained expression:

- One traumatic bleed was treated with FIX replacement
- No spontaneous bleeds required FIX replacement

# Safety: FLT180a was generally well tolerated

- No infusion reactions or allergic reactions, and no evidence of FIX inhibitors
- Transient transaminitis with or without an associated decline in FIX was the most common FLT180a-related AE
  - Late reductions in FIX were observed in patients in the
- $8.32 \times 10^{11}$  vg/kg dosing group who received prolonged courses of prophylactic tacrolimus beyond the taper of corticosteroids
- One patient in the high-dose group with FIX expression above the normal range had an SAE of arteriovenous fistula thrombosis

# FLT180a has potential to provide a functional cure by normalizing FIX activity levels

Key learnings from the Phase 1/2 B-AMAZE dose-finding clinical trial

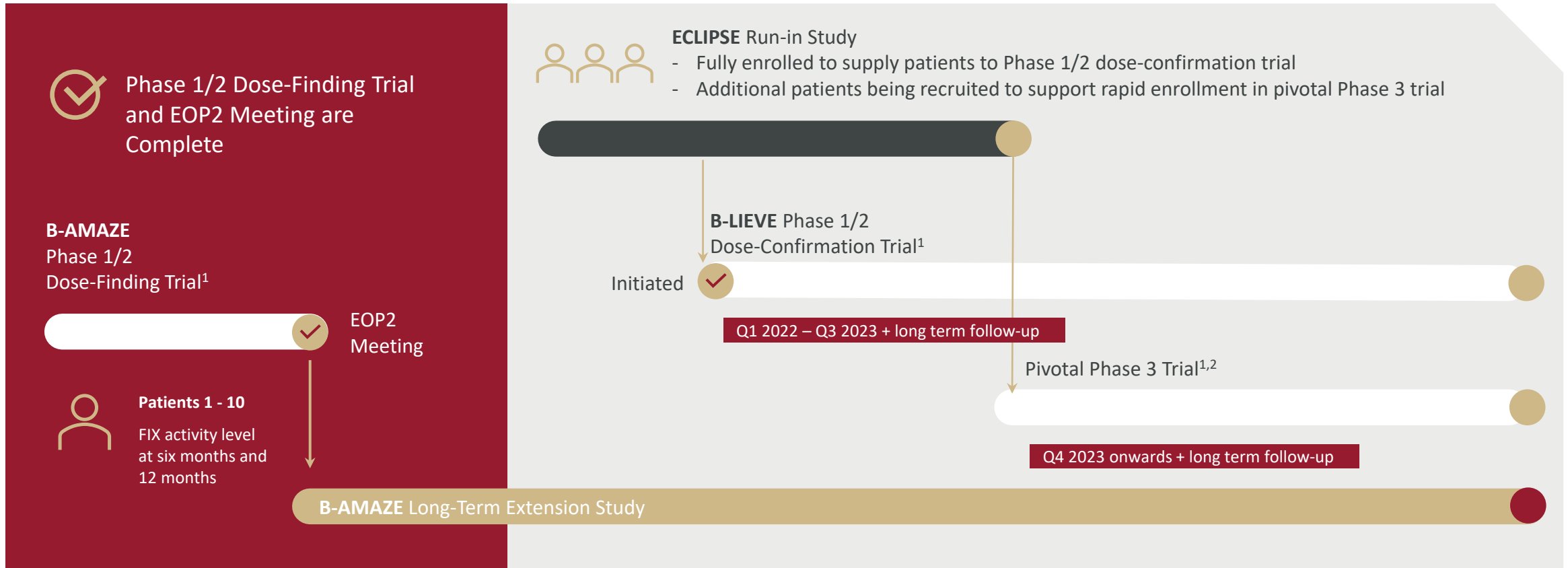
- ✓ Demonstrated efficacy with FIX activity in the normal range achieved with relatively low vector doses
- ✓ Stable and durable response up to 3.5 years post-treatment to date
- ✓ No spontaneous bleeds that required treatment with supplemental FIX<sup>1</sup>
- ✓ Favorable safety profile
- ✓ Proactive immune management approach expected to preserve FIX activity levels in the normal range
- ✓ Learnings from immune management regimen applied to other programs

**A dose of 7.7e11 vg/kg with updated immune management regimen is expected to result in consistent FIX levels in the normal range and is being evaluated in the ongoing dose-confirmation trial (B-LIEVE)**

<sup>1</sup> One patient in the 6.4e11 vg/kg dose cohort (7.5e11 vg/kg under the previous equivalent dosing nomenclature) lost expression due to transaminitis and resumed FIX prophylaxis.

# FLT180a clinical development plan

- B-LIEVE: Phase 1/2 trial to confirm the dose and immune management regimen for use in a pivotal Phase 3 trial
- Plan to file using Phase 3 Annualized Bleeding Rate (ABR) and FIX activity levels at 52 weeks after gene expression



<sup>1</sup> To measure safety, efficacy and durability.

<sup>2</sup> Pending discussion with regulators, the Company intends to conduct a Phase 3 trial with the aim to file based on Annualized Bleeding Rate and FIX expression

# Anticipated FLT180a milestones

**FLT180a – Hemophilia B** Phase 1/2 B-LIEVE dose-confirmation trial

2022		2023	
H1	H2	H1	H2
Completed dosing of the first cohort	Complete dosing of the second cohort or additional patients in the first cohort (if necessary) by end of Q3	Report updated safety and biomarker data	
Report safety and biomarker data from the first cohort		Phase 3 pivotal trial start-up activities	
	Report updated safety and biomarker data		





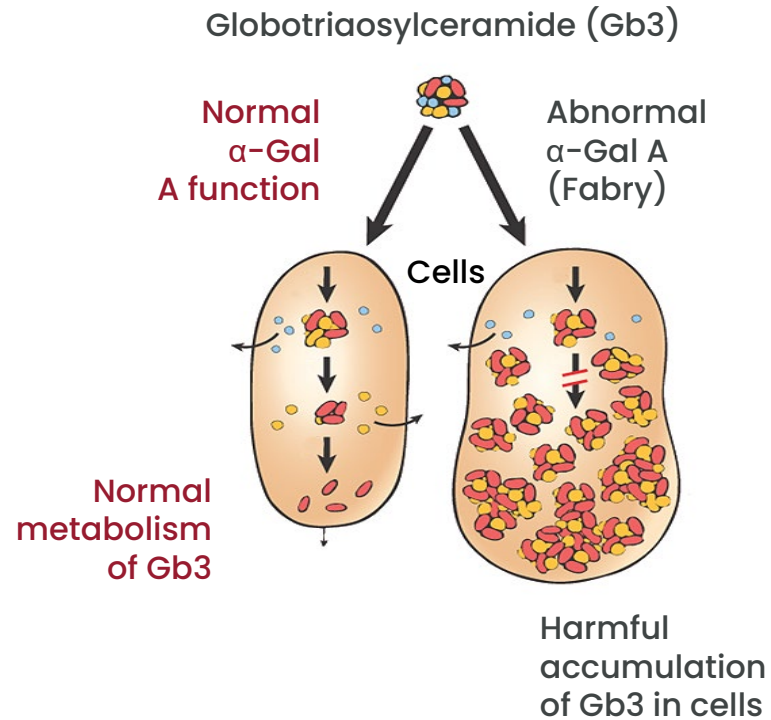
## Fabry Disease

# Fabry Disease Overview

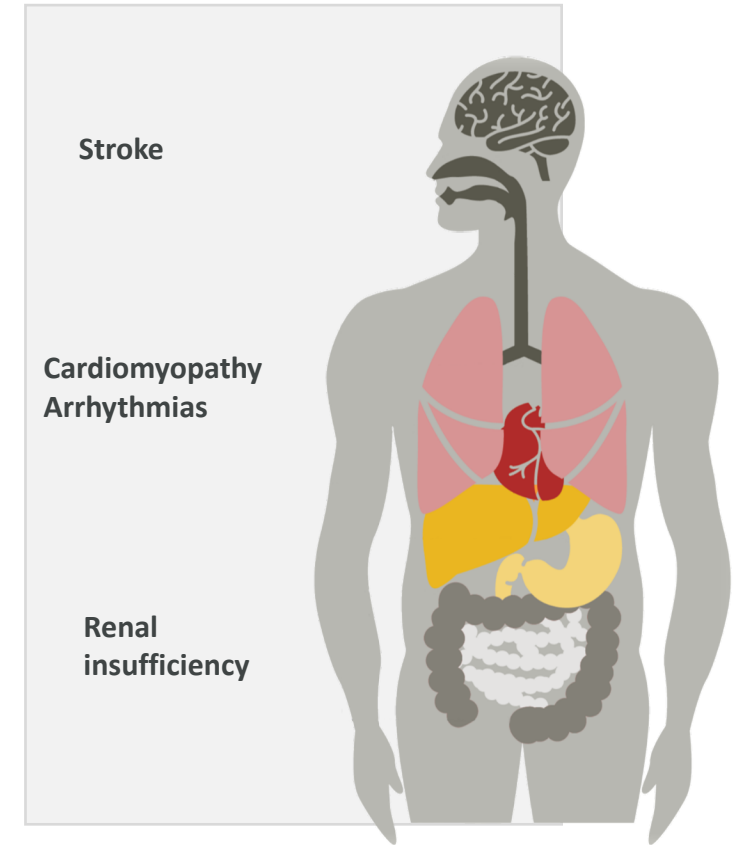
## Disease Characteristics:

- Rare X-linked lysosomal storage disorder (LSD) resulting from deficient activity, or absence, of  $\alpha$  Galactosidase A ( $\alpha$ -Gal A)
- Deficiency of  $\alpha$ -Gal A levels result in accumulation of substrates such as Gb3 and lyso-Gb3
- Characterized by progressive multi-systemic damage including the kidney, heart and vasculature

## Fabry Disease Mechanism



## Clinical Manifestations



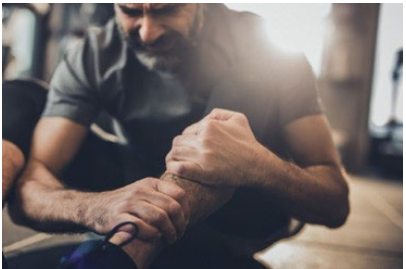
# Challenge: No curative therapy exists and high unmet medical need remains for Fabry disease patients receiving ERT

## Fabry disease patient perspectives<sup>1</sup>



### ERT treatment burden

“Travelling to and from the hospital, the time spent for infusions, and trying to keep my spirit up and adjusting to treatment is a significant challenge.”



### Need for greater efficacy

“My son who is 35 was having bi-weekly infusions with not much positive results.”



### Exhaustion

“The pain doesn't just affect me but so does the fatigue. Sometimes the pain literally wipes me out.”

## Limitations of ERT

- Lifelong, intravenous infusions every 2 weeks placing significant burden on patients and healthcare systems
- Despite treatment with ERT, patients continue to experience debilitating symptoms and disease progression resulting in a shortened lifespan

Average life expectancy <sup>2</sup>	General population	Fabry disease population
US Males	74.7 years	58.2 years

- ERT is seen as expensive and burdensome by physicians

ERT= Enzyme Replacement Therapy

<sup>1</sup> Market research - interviews, survey and analysis

<sup>2</sup> Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med. 2009 Nov;11(11):790-6.



# Opportunity: Patients need a therapy that delivers sustained levels of $\alpha$ -Gal A eliminating the need for ERT

## Competitor landscape

- Short half-life ERT therapies do not deliver sustained protein levels and patients continue to experience debilitating symptoms and disease progression

## Urgent need in the market<sup>1</sup>



### Patients

Attracted to freedom from bi-weekly infusions provided by gene therapy



### Physicians

Will prescribe gene therapy with long-lasting efficacy results that are comparable to or better than ERT



### Payers

Recognize potential for cost savings compared to chronic lifelong ERT

## Fabry disease target product profile



Durable increased  $\alpha$ -Gal A activity levels in or above the normal range



Sustained reduction in Gb3



Significantly reduce or eliminate the need for ERT

<sup>1</sup> Market research - interviews, survey and analysis

# FLT190 treatment for Fabry disease: Potential efficacy demonstrated in Fabry mouse model

WORLD symposia 2019: Jey Jeyakumar et al. Liver-directed gene therapy corrects Fabry disease in mice.

FLT190 vector genome pseudo-typed with AAV8 in GLA knockout ("GLA KO") mice; Dose: 2e12 vg/kg. Error bars: mean  $\pm$  SD.

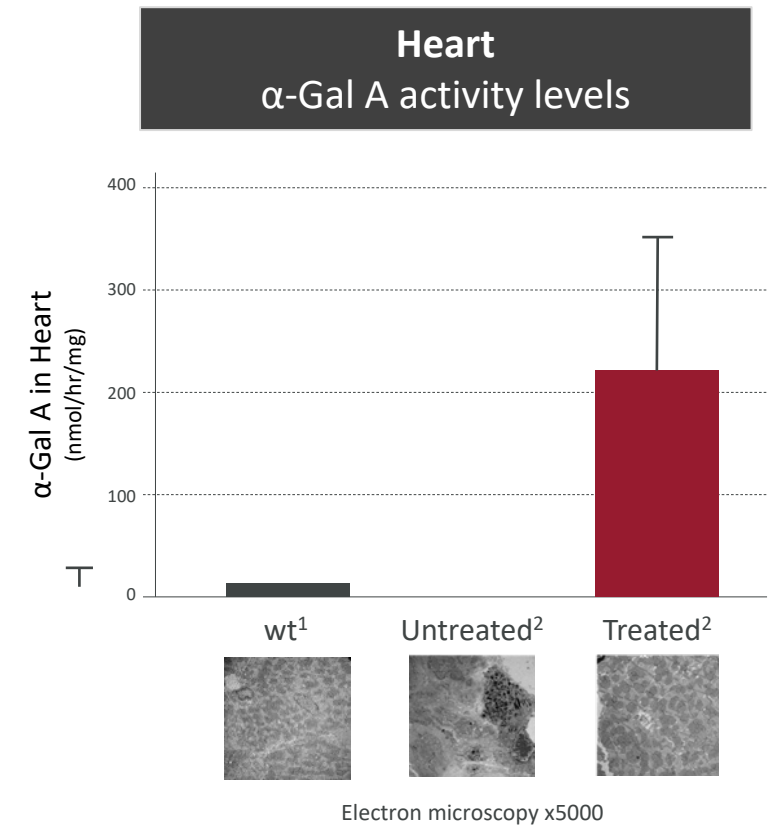
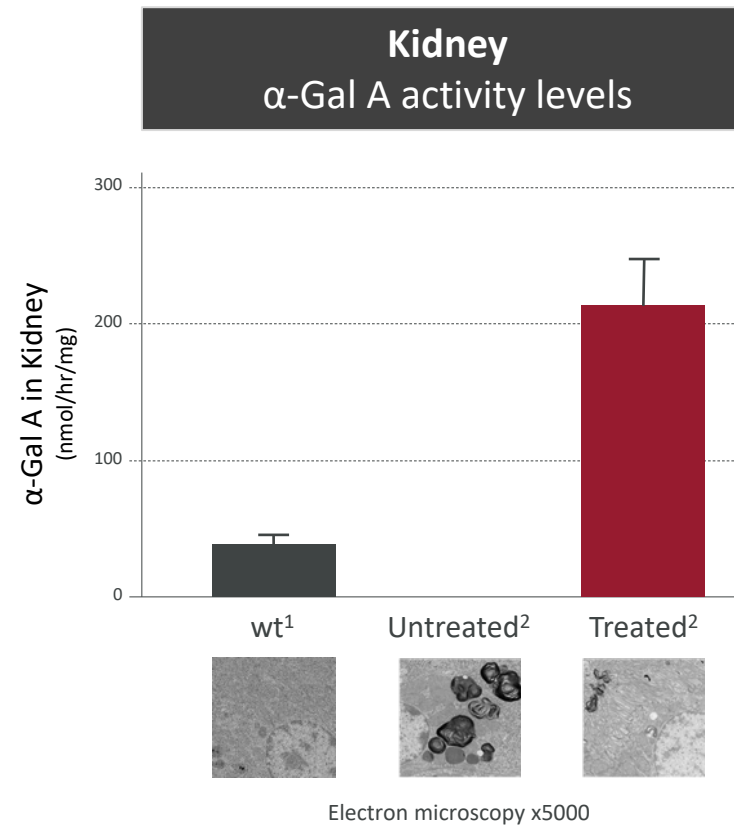
Time point: 16-week disease development prior to treatment; analysis 14 weeks post-treatment. Gb3/Lyso-Gb3 data (n=4, 2 males and 2 females).

<sup>1</sup> Untreated wild-type (non-GLA KO) mice.

<sup>2</sup> GLA KO mice.

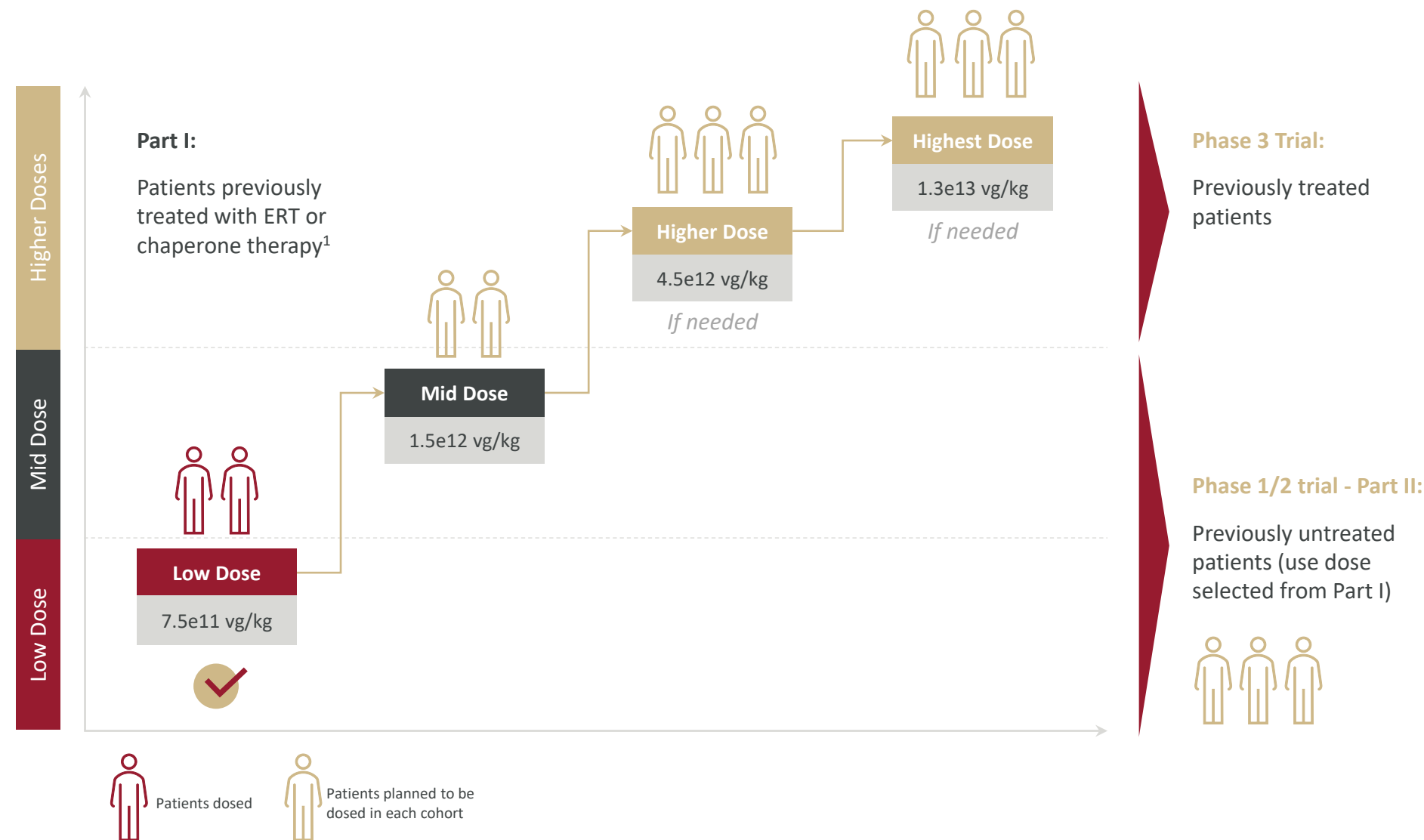
Fabry mouse model: Ohshima T, Murray GJ, Swaim WD, Longenecker G, Quirk JM, Cardarelli CO, Sugimoto Y, Pastan I, Gottesman MM, Brady RO, Kulkarni AB. (1997). alpha-Galactosidase A deficient mice: a model of Fabry disease. PNAS: 18;94(6):2540-4.

Meaningful increase in  $\alpha$ -Gal A expression leading to reduction in pathologic substrate in key tissues



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

**Adaptive trial:**  
To establish a dose of FLT190 that delivers sustained increased  $\alpha$ -Gal A activity to levels that reduce substrate accumulation



ERT= Enzyme Replacement Therapy.  
✓ Marks cohort with patients dosed



# Durable $\alpha$ -Gal A activity over 2 years in Patient 1 and near-normal levels in Patient 2

**~40% increase in total dose with ~400% increase in activity<sup>1</sup>**

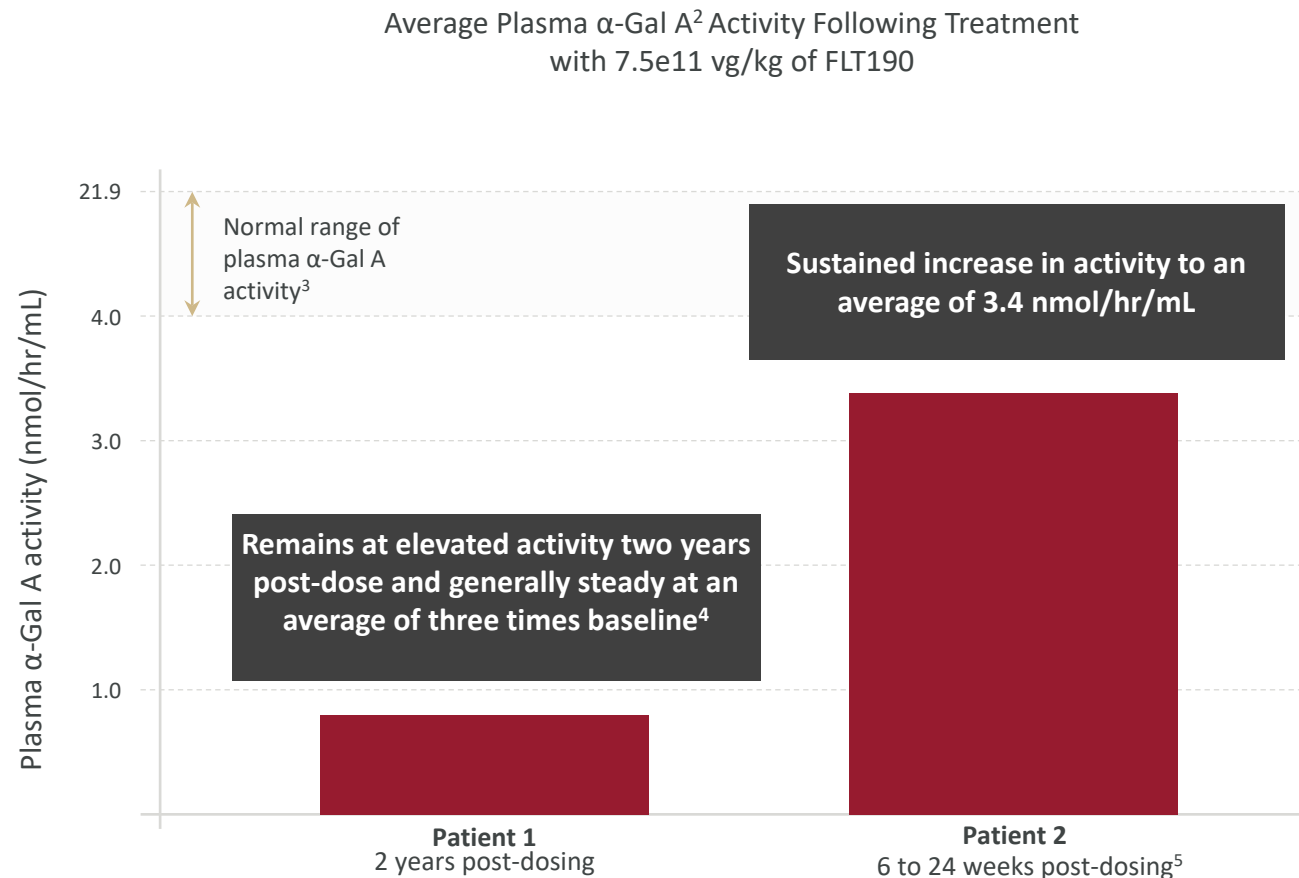
<sup>1</sup> As of the data cut-off date of Dec 22, 2021.

<sup>2</sup>  $\alpha$ -Gal A: Plasma  $\alpha$ -galactosidase A, the missing enzyme in Fabry disease.

<sup>3</sup> Current assay normal range: 4.0-21.9 nmol/hr/mL.

<sup>4</sup> Patient 1 had a subtherapeutic response with mean trough plasma  $\alpha$ -Gal A of 0.8 nmol/hr/mL.

<sup>5</sup> The total vector genome (vg) dose Patient 2 received was approximately 40% higher than Patient 1 due to differences in their weights



## Patient 2

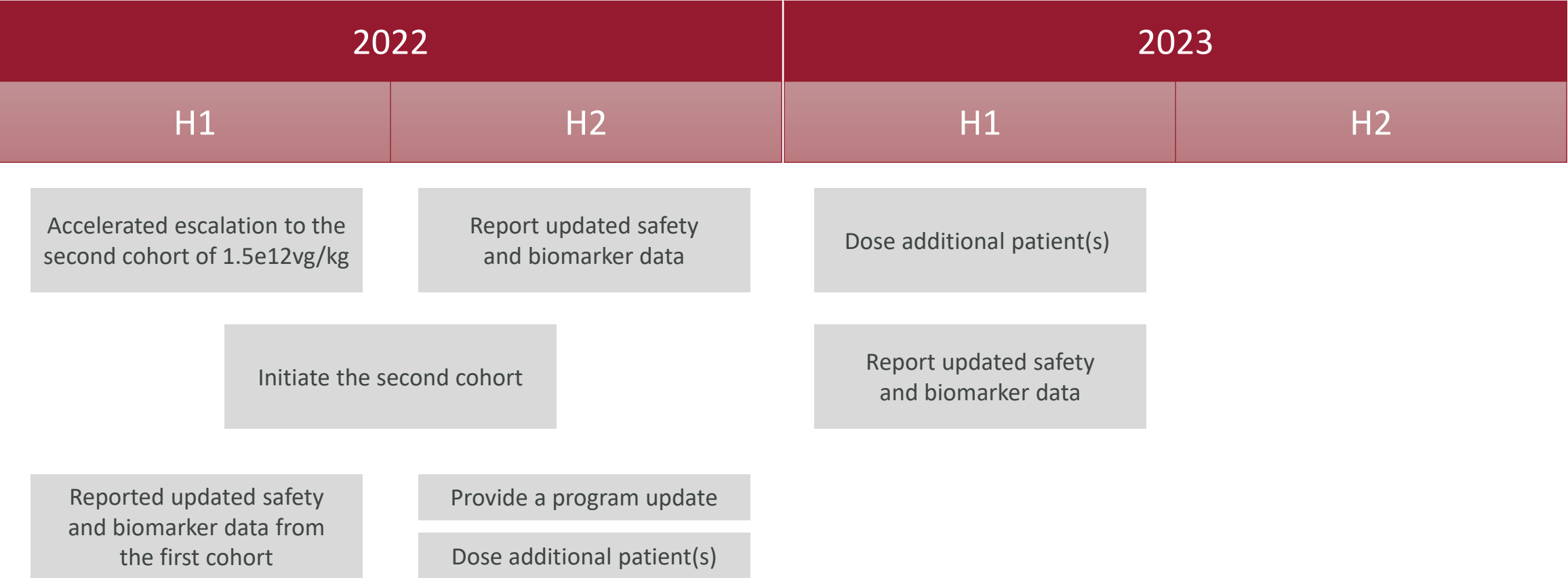
- No rise in ALT/AST levels; received optimized immune management regimen
- Treatment well-tolerated with no SAEs
- Transient troponin-T elevation has returned to baseline consistent with mild myocarditis

## Patient 1

- Experienced no enduring clinical sequelae of the mild transient myocarditis episode previously reported in 2019

# Anticipated FLT190 milestones

FLT190 – Fabry disease Phase 1/2 MARVEL-1 dose-finding trial





## Gaucher Disease (Type 1)

---

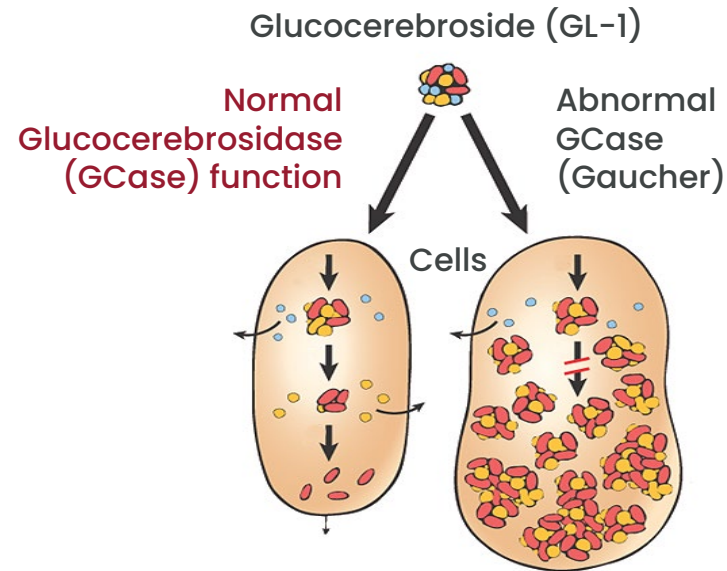


# Gaucher disease (Type 1) Overview

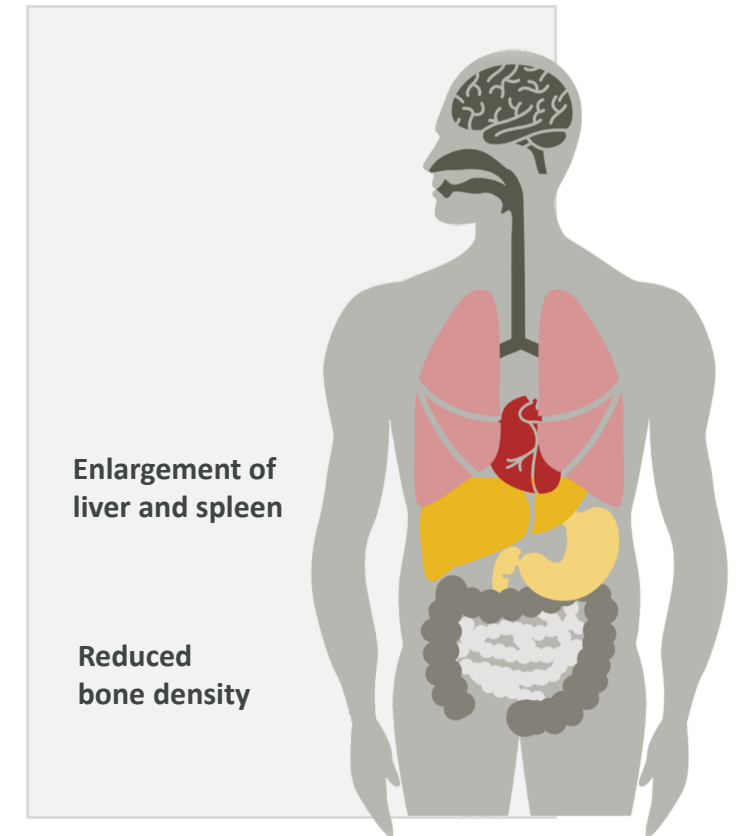
## Disease Characteristics:

- Rare genetic LSD resulting from deficiency of glucocerebrosidase (GCase)
- Leads to accumulation of glucocerebroside (GL-1)
- Characterized by bone disease, hepatosplenomegaly, anaemia and thrombocytopenia with absence of primary CNS disease

## Gaucher Disease Mechanism



## Clinical Manifestations



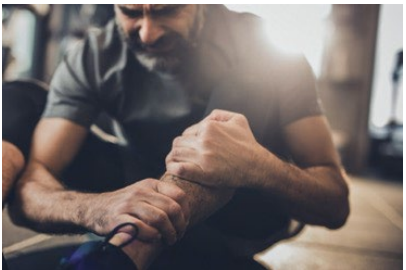
# Challenge: No curative therapy exists for Gaucher disease (Type 1) patients receiving lifelong ERT or SRT

## Gaucher disease patient perspectives<sup>1</sup>



### ERT treatment burden

“... It would be a lot easier if I didn’t have to do the infusions every two weeks...it takes two or three hours...”



“... The main reason for considering a gene therapy would be to be free of the infusions. It would be brilliant, absolutely brilliant...”

### Limitations of ERT and SRT

- Lifelong intravenous infusions every two weeks placing significant burden on patients and healthcare systems
- Daily oral administration for SRT makes it difficult for patients to adhere to treatment
- SRT and ERT are viewed as expensive by physicians
- No curative therapy exists; patients continue to experience disease progression

# Opportunity: Freeline has most advanced AAV gene therapy program for Gaucher disease (Type 1)

## Competitor landscape

- Limited competition in the Gaucher gene therapy market
- Short-half life therapies do not deliver sustained protein levels. Gene therapy offers the potential of chronically sustained normal GCase levels
- *Ex vivo* lentiviral gene therapy is more burdensome and invasive for the patient compared to AAV approaches. Manufacturing scale-up is also highly complex

## Urgent need in the market<sup>1</sup>



### Patients

Attracted to freedom from bi-weekly infusions provided by gene therapy



### Physicians

Will prescribe durable gene therapy with efficacy comparable to or better than ERT



### Payers

Are attracted to the potential cost savings associated with the displacement of chronic ERT

## Gaucher disease target product profile



Durable increased GCase activity levels



Sustained reduction in GL-1



Significantly reduce or eliminate the need for ERT / SRT

<sup>1</sup> Market research - interviews, survey and analysis

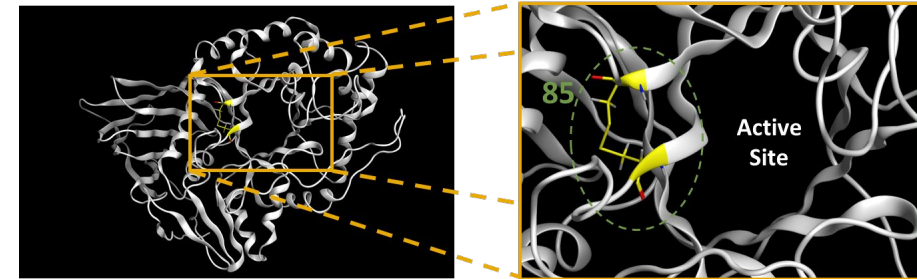


# FLT201 produces a more stable GCase variant that achieves higher expression levels

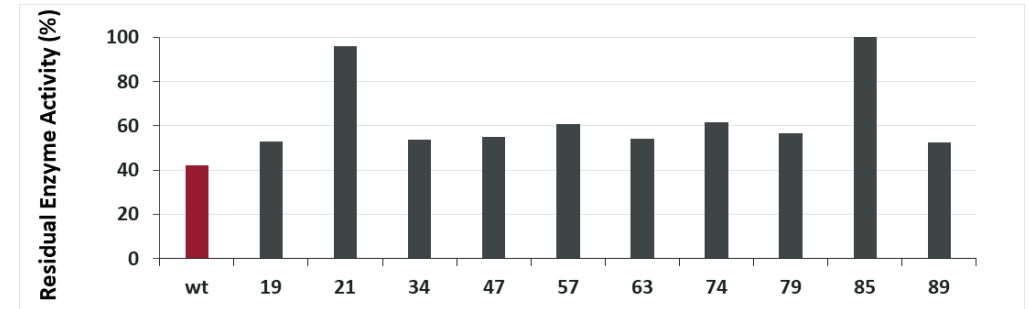
## Key features of GCase variant

- ✓ > 20-fold increase in half-life in lysosomal pH compared with wild type (wt)
- ✓ Compared to wt, 6-10 fold increase in half-life in serum, resulting in a 20-fold increase in potency of the vector
- ✓ Unchanged kinetics or the anticipated antibody response

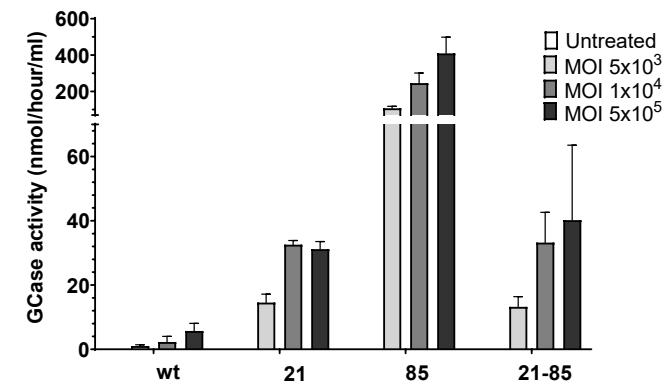
Structure of GCase variant:  
GCase variant 85



*In vitro* stability: 10 of 86 GCase protein variants showed improved stability compared with wt



Variant 85 showed the highest level of GCase activity when transduced using AAVS3 in Huh7 cells: >80-fold increase in activity vs. wt GCase



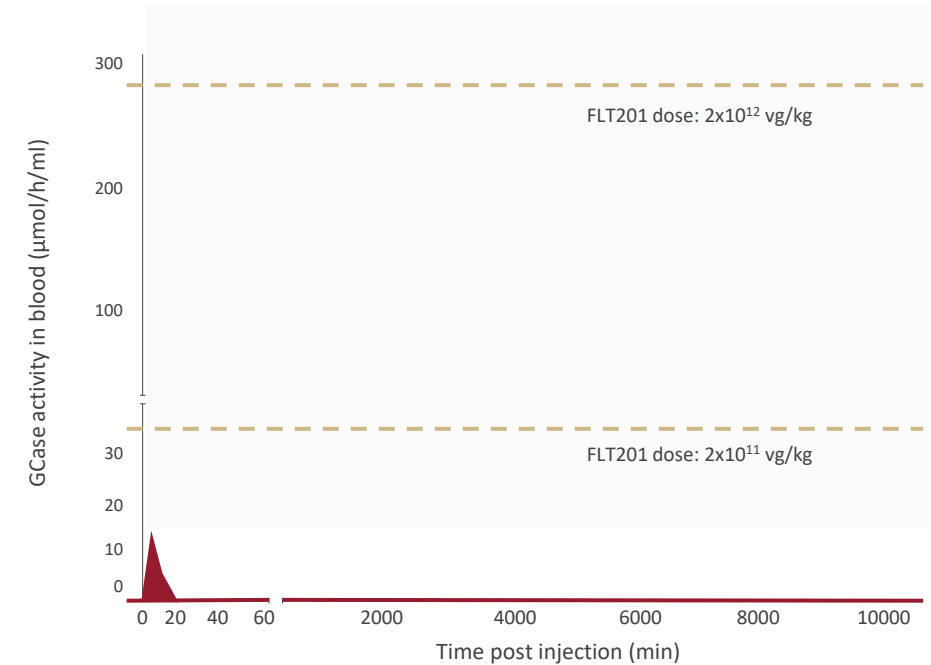
# FLT201 produces more stable protein; higher uptake in Gaucher mice

## Higher GCase expression at low doses and increased uptake in key tissues

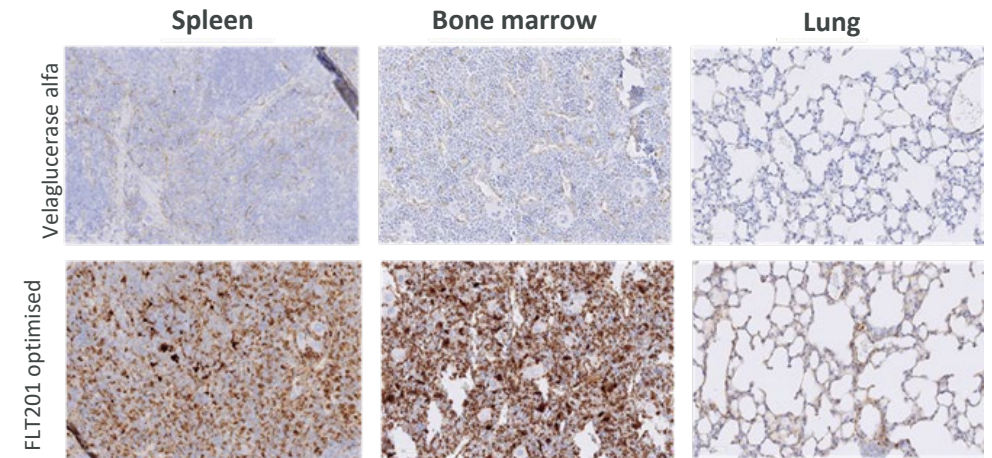
- Novel GCase variant produced by FLT201 is more stable in plasma than wild-type protein
- Greater than 20-fold increase in potency vs. vector expressing wild-type protein and better uptake in key tissues in Gaucher mice
- Enhanced potential for substrate clearance in key tissues in Gaucher mice

Increased protein stability sustains higher GCase levels compared with velaglucerase alpha<sup>1</sup>

ERT (60 U/kg) ———  
AAV-GBA (FLT201)<sup>2</sup> - - -



Enhanced and sustained GCase uptake observed in key tissues as compared with velaglucerase alpha



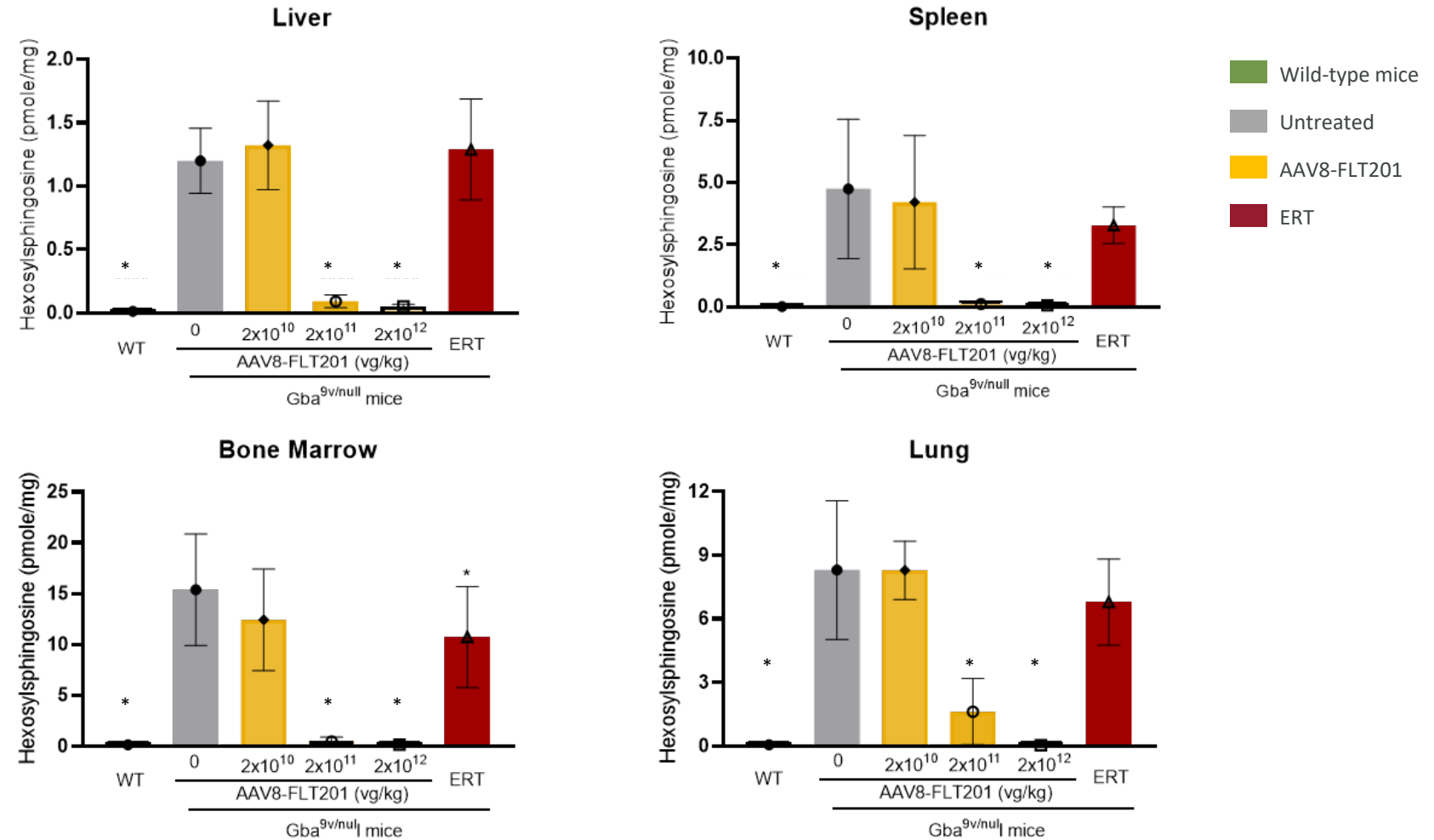
<sup>1</sup> Velaglucerase alpha is an Enzyme Replacement Therapy (ERT) for Gaucher disease.

<sup>2</sup> FLT201 vector genome pseudo-typed with AAV8 in Gaucher mice

# FLT201 clears substrate in key tissues in Gaucher mice

GCase tissue penetration and enzymatic activity leads to substrate level reduction across key tissues

- Dose-dependent reductions of lyso-GB1 observed in all tissues analyzed, including bone marrow and lung



Data from trial conducted in collaboration with Professor Ying Sun (Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA) and presented at the 17th Annual WORLD Symposium.  
Velaglucerase alpha - an ERT used for Gaucher disease.  
AAV8-FLT201 = AAV8 pseudo-typed FLT201 genome.  
ERT = Velaglucerase alfa 60 U/kg biweekly (equivalent of the standard of care in humans).

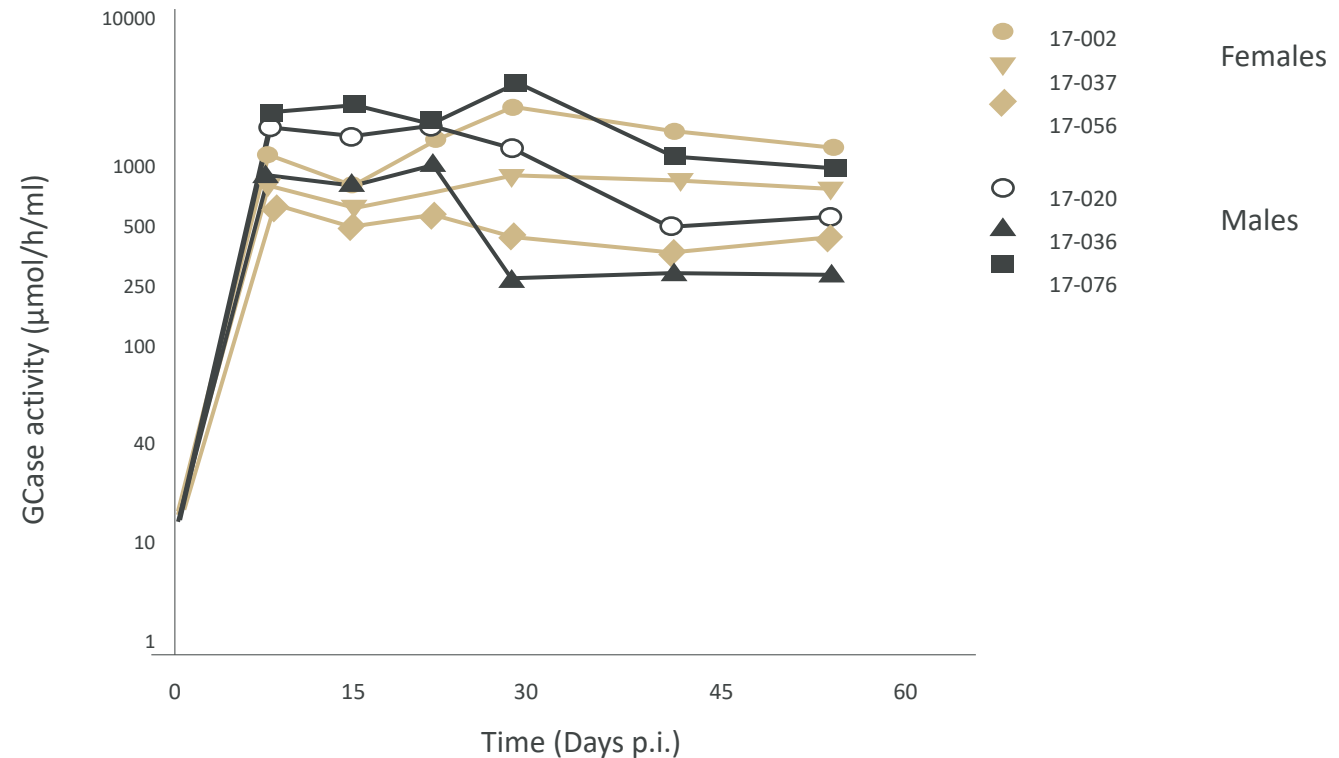
WT = wild-type mice.  
Evaluated 12 weeks post-injection.  
<sup>1</sup> Lack of GCase enzyme in humans leads to the accumulation of lyso-GB1 and Gaucher disease.  
\*p ≤ 0.0001.

# FLT201 demonstrates high levels of GCase expression in non-human primates

## Achieves steady increases in GCase plasma levels

- A single injection of FLT201 was well tolerated
- Resulted in a rapid increase of GCase in plasma that was sustained for at least two months (trial ongoing)

Plasma

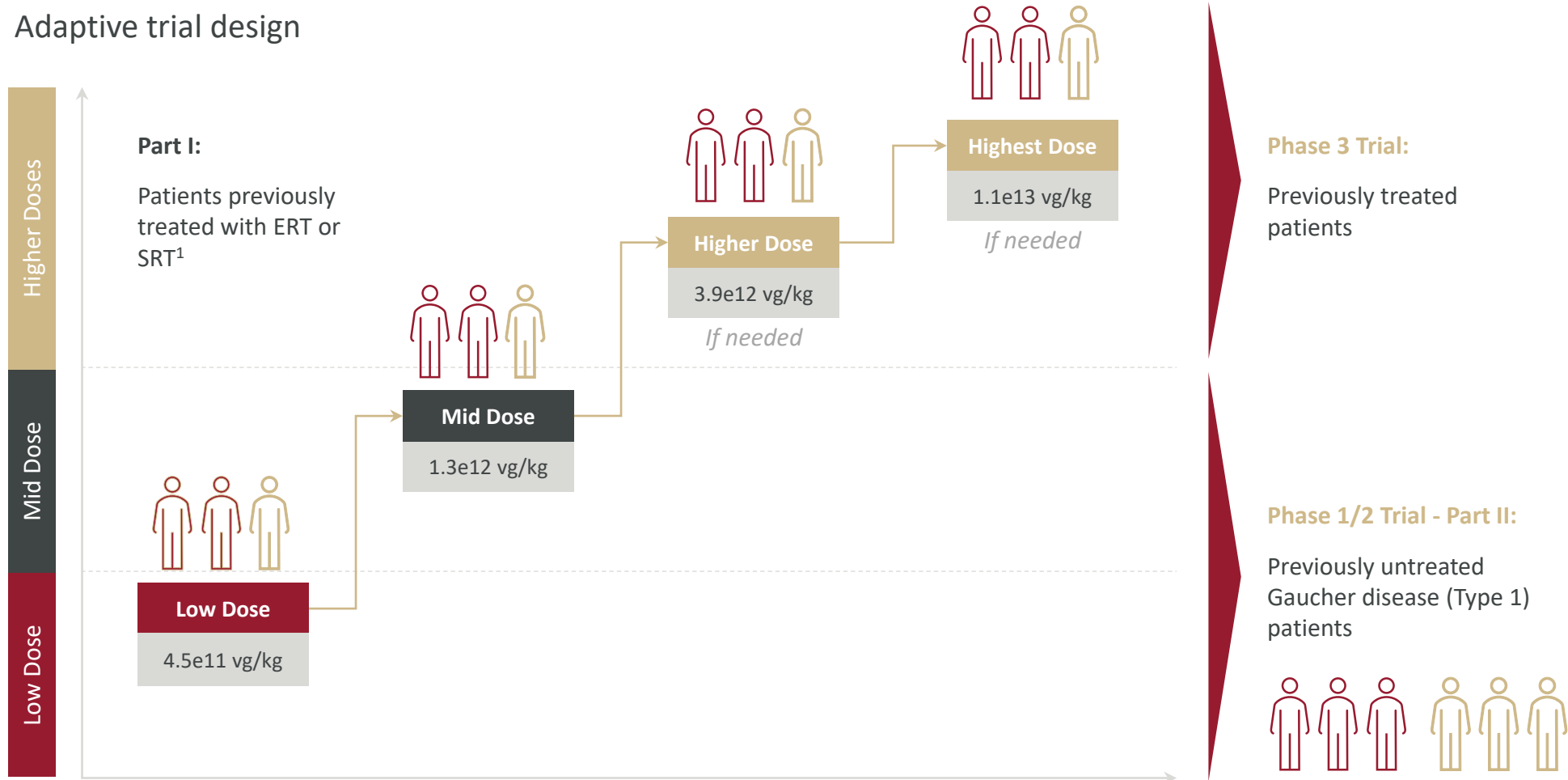


Dose: FLT201 2x10<sup>12</sup> vg/kg (long-term observational trial)

# Phase 1/2 dose-finding trial design

Trial to evaluate safety and tolerability of FLT201 and establish a dose that delivers sustained increased GCase to levels that reduce substrate accumulation and improve clinical parameters

## Adaptive trial design



GCase = glucocerebrosidase

The trial protocol allows for testing up to four doses in Part I of the clinical trial. However, depending on dose response in the initial cohorts, we may not ultimately need to escalate to the later doses.

The Data Monitoring Committee (DMC) 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.

<sup>1</sup> ERT = Enzyme Replacement Therapy; SRT = Substrate Reduction Therapy



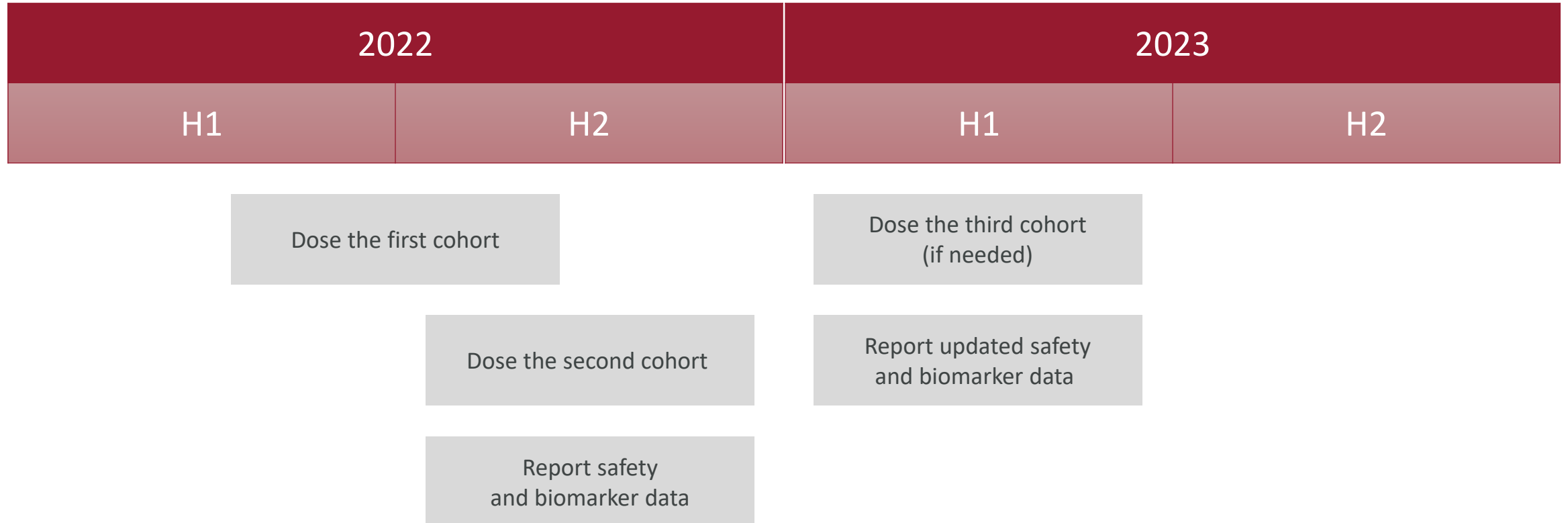
This symbol equates to one patient planned for dosing.



If appropriate, we may decide to expand the number patients dosed in a given cohort. This symbol represents an additional potential patient for dosing.

# Anticipated FLT201 milestones

FLT201 – Gaucher disease (Type 1) Phase 1/2 dose-finding trial







FREELINE

**Thank you**

---

10 May 2022