SYNCONA

# Syncona Investor Webinar: Freeline Therapeutics

Synconaltd.com

13 May 2024


# Overview of today's session

## Chris Hollowood, SIML CEO

- Market backdrop
- Syncona update including Freeline acquisition

## Michael Parini, Freeline CEO

- Overview of the business
- Strategy and pipeline

## Pamela Foulds, Freeline CMO

- Overview of the FLT201 Gaucher disease programme including commercial potential
- Recent data at ASGCT

SYNCONA

# Syncona: Company update


Synconaltd.com

Chris Hollowood,
SIML CEO

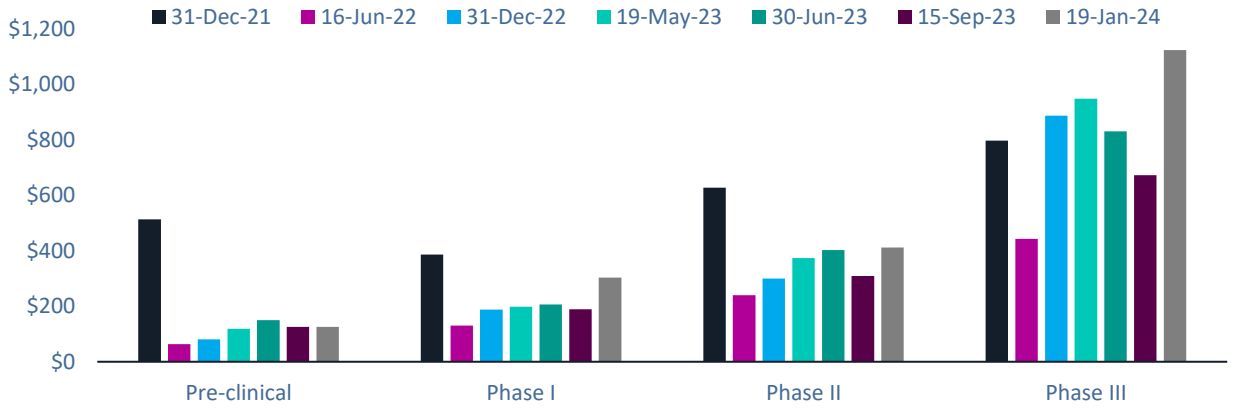
# Market activity beginning to normalise

## Value returning at late-stage

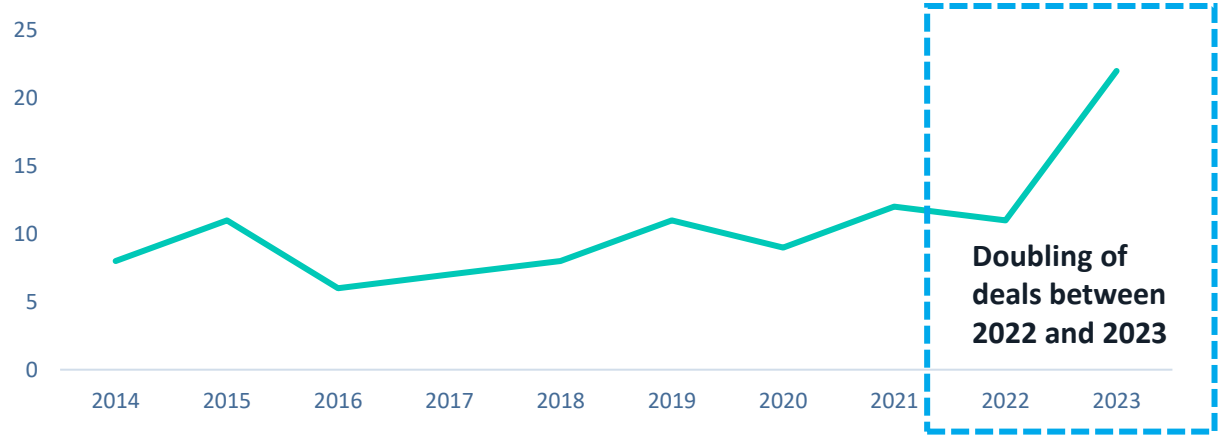
### Private and public financing environment remains challenging

- Valuations are recovering in companies developing late-stage assets in the public markets and moving beyond levels seen in last 18-24 months
- Financing challenges remain for clinical and pre-clinical companies – reflecting importance of focusing on commercial opportunity
- Long-term structural trends and recent market activity underline the key role played by biotech in drug development
  - Pharma continues to be reliant on biotech for product development, with +$200bn in US pharma revenue at risk of patent expiry in the second half of the decade
  - Number of recent late-stage deals where big pharma have acquired biotech companies at attractive multiples, with a significant recovery in deal flow in 2023 vs 2022

**Average Enterprise Value of a Biotech listed on US exchanges by stage of development[2]**




**Biopharma M&A activity – number of transactions valued +$1bn[2]**




1 – Stifel 2 – TD Cowen

# Working to maximise value

## Last 12 months have brought challenges to management teams across biotech

### Capital allocation focused on maximising value for shareholders

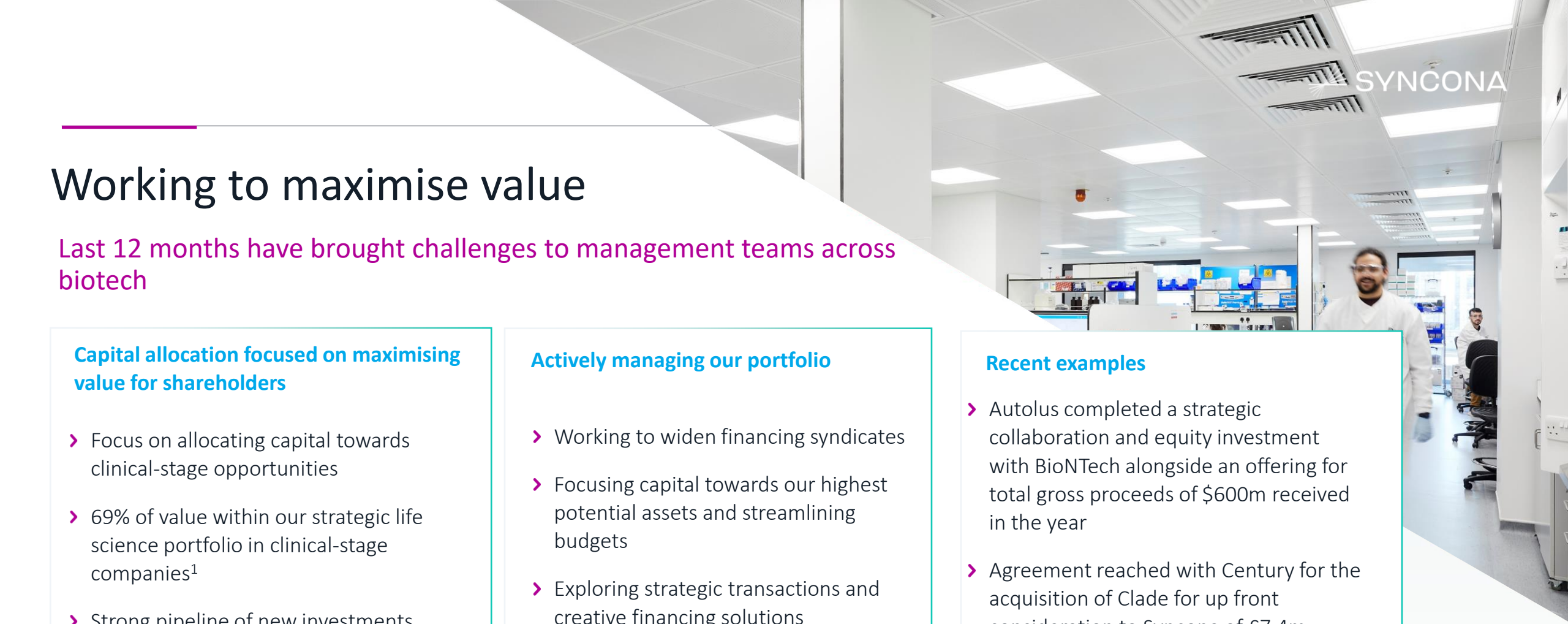
- Focus on allocating capital towards clinical-stage opportunities
- 69% of value within our strategic life science portfolio in clinical-stage companies[1]
- Strong pipeline of new investments includes focus on clinical-stage opportunities

### Actively managing our portfolio

- Working to widen financing syndicates
- Focusing capital towards our highest potential assets and streamlining budgets
- Exploring strategic transactions and creative financing solutions
- Exploring portfolio company consolidations and M&A

### Recent examples

- Autolus completed a strategic collaboration and equity investment with BioNTech alongside an offering for total gross proceeds of $600m received in the year
- Agreement reached with Century for the acquisition of Clade for up front consideration to Syncona of £7.4m, enabling redeployment of proceeds and resource in line with capital allocation focus
- Decision to take Freeline private




1 – As at 31 December 2023

# Freeline: an exciting opportunity for shareholders

## Aligns with Syncona model and capital allocation focus

**Exciting lead programme with platform potential**

- Strong data from Gaucher programme published to date in an area of high unmet need
- Opportunity to leverage technology to move into larger indications such as Parkinson's Disease

**Leading management team**

- Management team has led the company effectively through the recent challenging market environment
- Strong platform now exists to deliver for patients

**Differentiated opportunity to fully acquire a clinical-stage asset**

- Challenging market conditions provided a differentiated opportunity to take Freeline private
- Acquisition in an all-cash transaction which valued Freeline at c.$28.3 million

## Freeline provides an opportunity to drive strong risk-adjusted returns

FREELINE

# Advancing the next generation of gene therapies

Michael Parini,
Freeline CEO

# Freeline: A bold ambition to redefine gene therapy

**Our Purpose**

Unlock the true potential of gene therapy to change the lives of patients and their families

**Our Goal**

Develop next-generation gene therapies to set new standards of care for chronic, debilitating and life-threatening diseases

**Our Approach**

Optimize every component of our product candidates to provide one-time gene therapies specifically tailored to each disease

# Creating the next generation of gene therapies

**Targeting well-defined diseases**

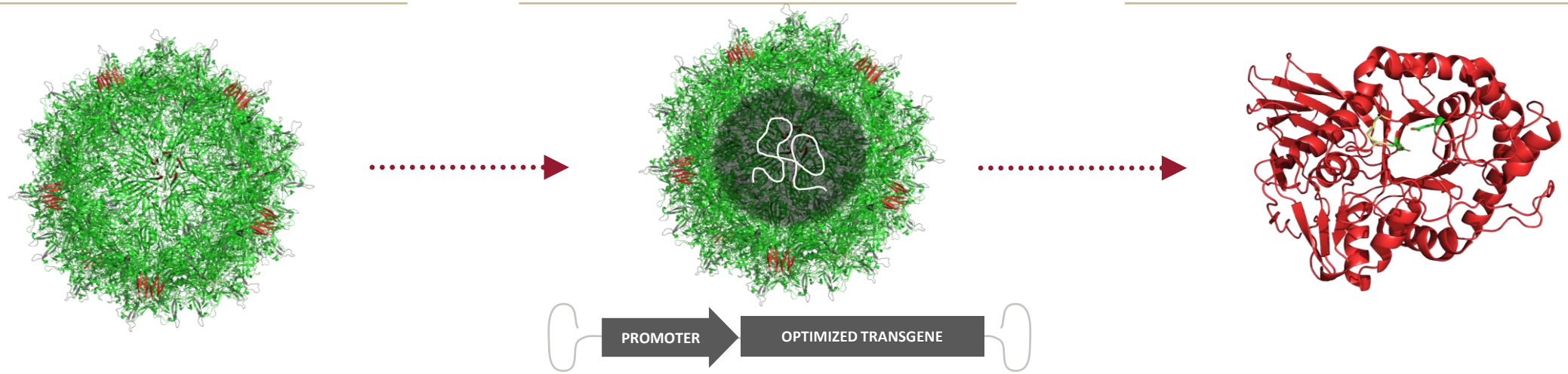
- Serious, chronic diseases
- High unmet need
- Right target with validated biology
- Consistent delivery of therapeutic protein highly likely to improve patient outcomes

## Optimizing every component of our product candidates

### Selective Capsid
directed at the right cells

### Optimized Genome
through promoter design and codon optimization

### Engineered Therapeutic
For optimized exposure and efficacy



# Growing pipeline of first- and best-in-class programs with potential to expand into larger disease areas

| DISEASE AREA | PROGRAM | APPROXIMATE PATIENT # | DISCOVERY / PRECLINICAL | PHASE 1/2 | PHASE 3 |
|---|---|---|---|---|---|
| LSDs | GAUCHER DISEASE TYPE 1<br>FLT201 | ~18K<br>US, UK, EU4, Israel | | | |
| CNS | GBA1 PARKINSON'S DISEASE | ~190K<br>US, UK, EU4 | | | |
| | LEWY BODY DEMENTIA | >1M<br>US | | | |
| Cardiovascular | SEVERE CHRONIC HEART FAILURE SUBSET | 10 – 20K<br>annually US, UK, Western Europe | | | |
| | ADDITIONAL CHRONIC HEART FAILURE POPULATIONS | Future | | | |

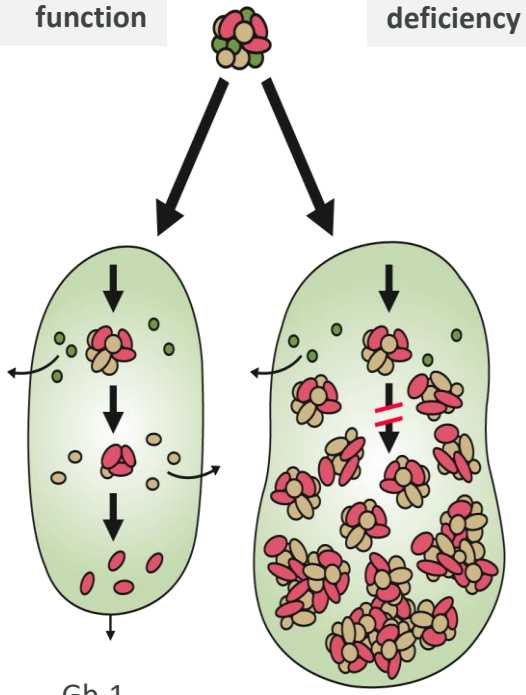
Indicates potential for expansion

Estimated patient numbers for Gaucher disease Type 1 represent 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. Estimated population affected by LBD. Estimated number of diagnosed GBA1-PD patients. Estimated number of treatable post-MI HFrEF patients annually.

# FLT201 in Gaucher Disease

Pamela Foulds,
Freeline CMO

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




## Gaucher disease

- Mutations in *GBA* gene cause deficiency of GCase enzyme needed to metabolize Gb-1 in the lysosome, resulting in accumulation of toxic substrate lyso-Gb1
- Affects multiple organs, leading to wide range of symptoms and shortening life span
- Type 1 most common form of disease, affecting ~94% of Gaucher patients

## High ongoing unmet need

- Many patients continue to experience debilitating symptoms despite treatment
- Approved therapies come with heavy life-long treatment burden
- Poses a significant burden and cost for patients as well as on healthcare system

## Significant market opportunity

**~18k**
Patients in US, UK, EU4 and Israel

**$2B**
Revenue forecast for Gaucher drugs in 2030

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.

GCase=glucocerebrosidase; Gb-1= glucosylceramide ; lyso-Gb1=glucosylsphingosine

# No substantial advances in treatment in last two decades

| | PRE-1991 | 1991-2002 | 2002-PRESENT |
|---|---|---|---|
| | **No disease-modifying therapies** | **ERT is only disease-modifying treatment** | **Despite emergence of SRT, ERT remains standard of care** |
| LIMITATIONS OF THERAPY | Life-threatening disease, with disabling symptoms<br><br>Only symptomatic treatments available<br><br>Splenectomies common intervention | Meaningful advance but not a cure<br><br>Requires frequent and lengthy infusions<br><br>GCase quickly eliminated, leading to lack of coverage between infusions<br><br>Does not fully address myriad of symptoms | SRT offers an oral treatment option but not a cure<br><br>Tolerability, compliance and lack of efficacy limit its use<br><br>Less than 20% of market<br>• 8 in 10 patients report side effects or lack of efficacy<br>• 1 in 3 switch to or return to ERT |

## FLT201

Potential one-time gene therapy with better efficacy and opportunity to set new standard-of-care

# Despite treatment with ERT, many patients continue to have debilitating symptoms and diminished quality of life

After 10+ years on ERT, up to

**60%**

still experience symptoms, including bone pain, lung dysfunction, enlarged organs, fatigue and low platelet counts

**1 in 3**

report increased stress, anxiety about the future and fear of missing infusions

**1 in 3**

report treatment restricts choices about education, work and leisure activities

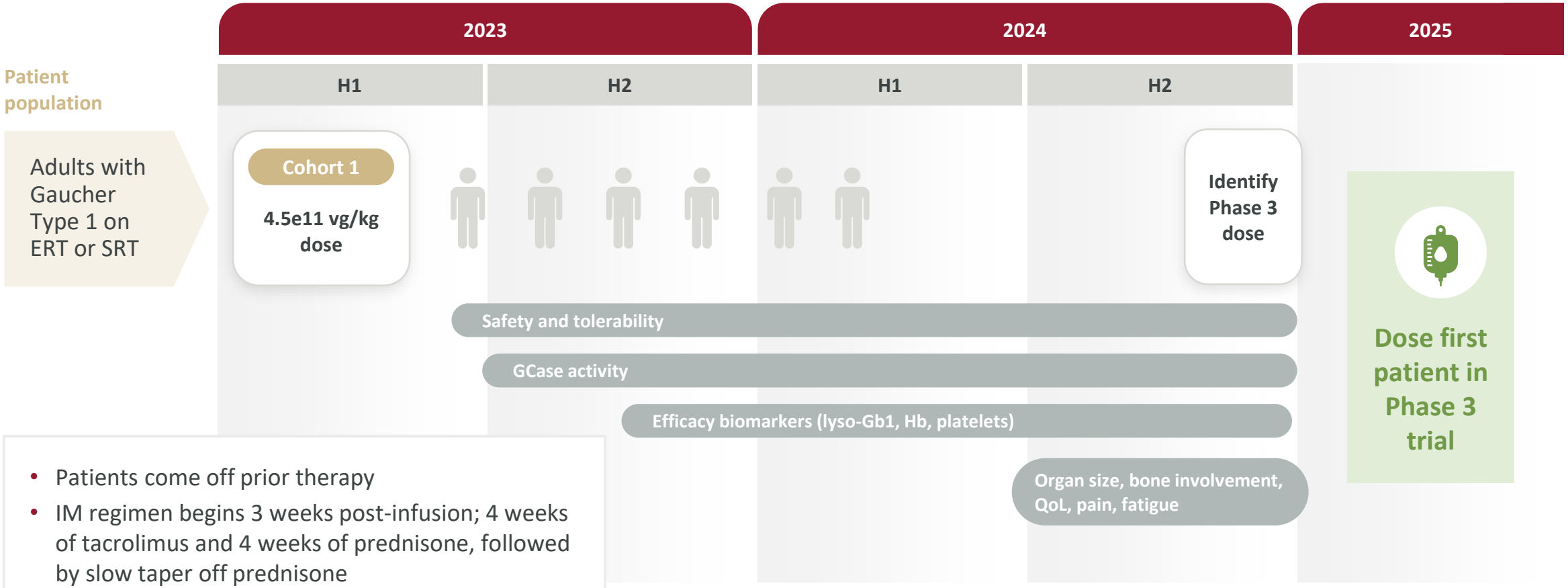
## Gaucher takes a toll on patients' overall well-being, including:

- Feelings of sadness, disappointment and frustration
- Fear of losing or changing jobs due to implications for healthcare insurance
- Aggravation caused by dealing with medical problems
- Effects on their ability to meet family obligations
- Guilt about the cost of the disease

1 Weinreb et al., 2013; 2 Kerem, et al., 1996 and Goitein, et al 2001; † in those with these symptoms before ERT
3 Elestein, 2022; Thirty patients had GD1; only three patients had GD3. 30 were receiving treatment (26 with GD1 and three with GD3) and four were treatment naïve
r Dinur et al. Orphanet J Rare Dis (2020) 15:284
Packman et al. American Journal of Medical Genetics 2010

# Ongoing GALILEO-1 Phase 1/2 dose-finding study

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




- Patients come off prior therapy
- IM regimen begins 3 weeks post-infusion; 4 weeks of tacrolimus and 4 weeks of prednisone, followed by slow taper off prednisone
- Patients roll into long-term follow-up study

Dosed

# Robust and continuous expression in plasma GCase and clear evidence of cellular uptake

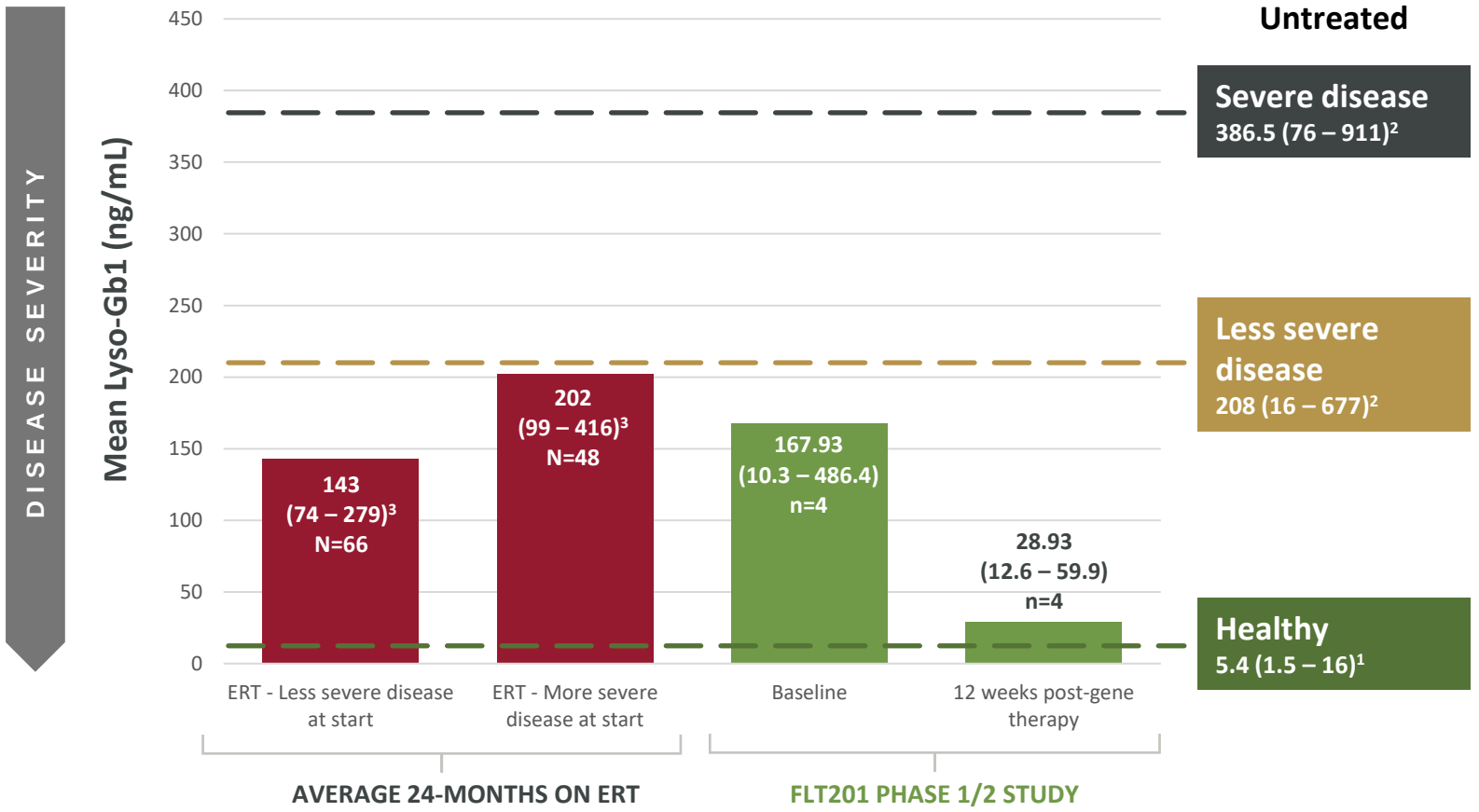
**Significant increases in plasma GCase in patients up to 38 weeks.**

GCase activity remained at supraphysiological levels post-immune management regimen.

**Increases in leukocyte GCase activity demonstrates cellular uptake of GCase85 from plasma.**

Leukocytes are a broad marker of cellular uptake.

# FLT201 reduces lyso-Gb1 to near-normal levels within three months of single infusion




## FLT201 drives lyso-Gb1 lower relative to ERT

Lyso-Gb1 an established biomarker of disease and treatment response.

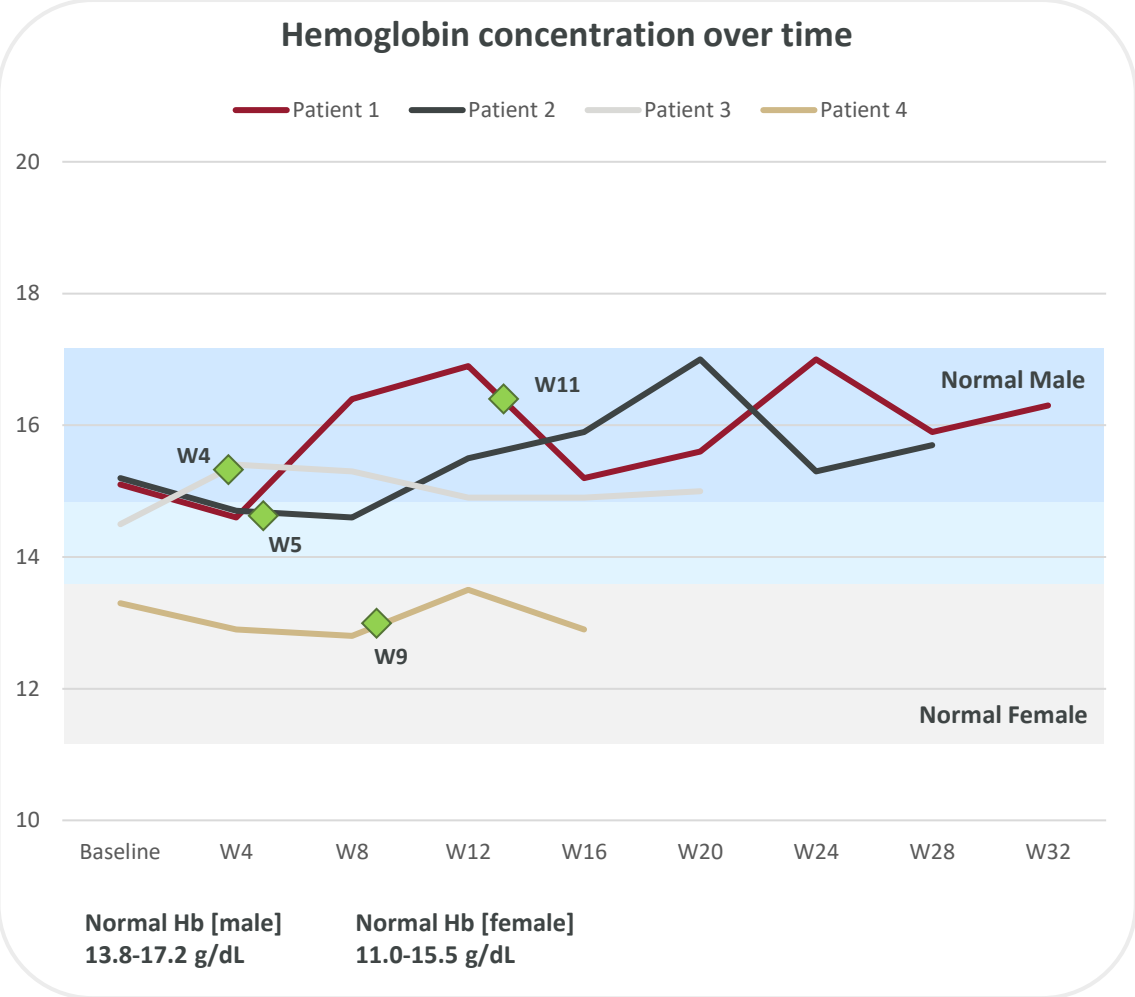
Substantially reduced levels of lyso-Gb1 observed in patients with persistently high lyso-Gb1 levels, despite years on prior treatment with ERT or SRT.

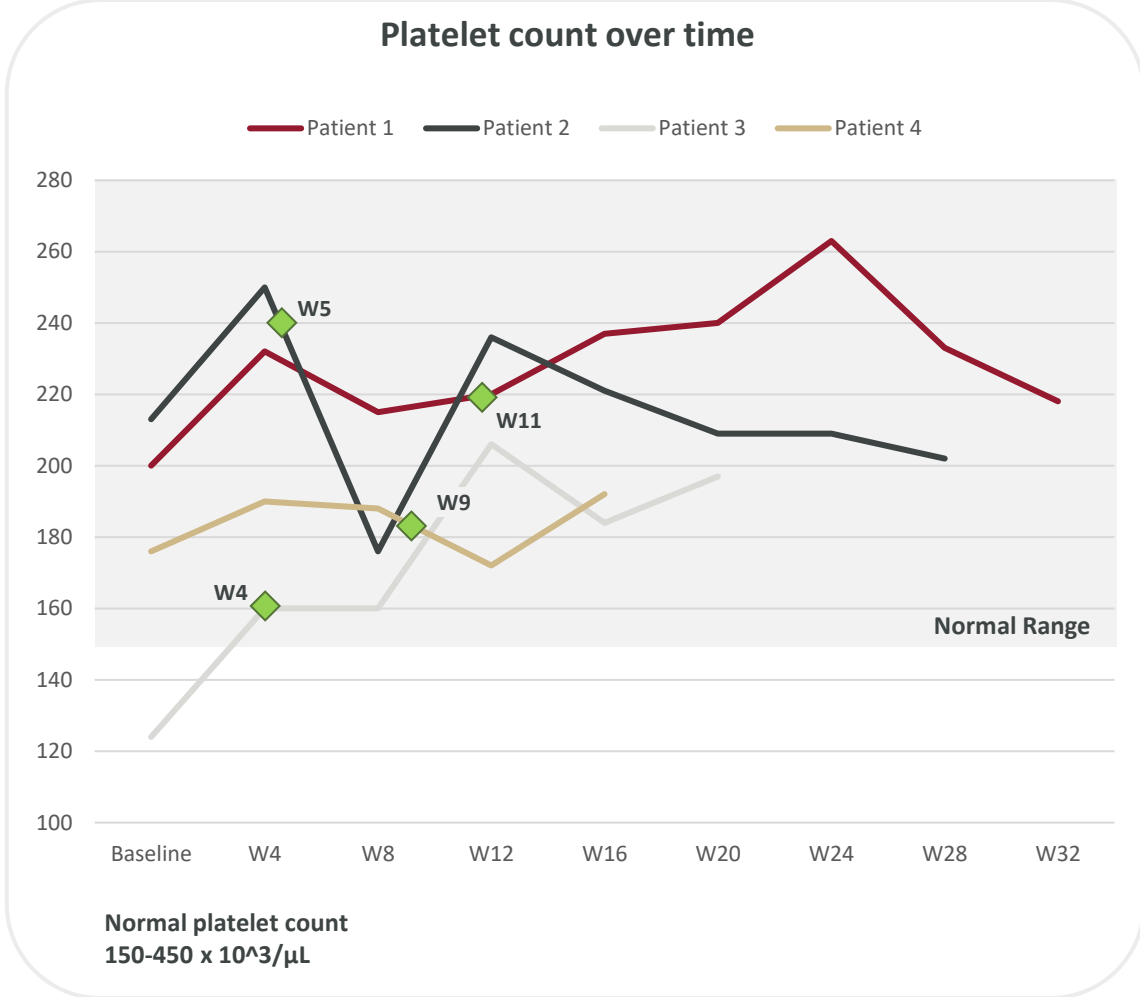
**Mean DBS lyso-Gb1 concentration (range); measured in different populations at different timepoints**

[1] Median value and range (Dinur 2022); [2] Curado 2023; 3 Dinur 2021

Data cut off 19 Feb 2024

# Maintenance of hemoglobin and improvement in platelets observed post withdrawal of ERT and SRT



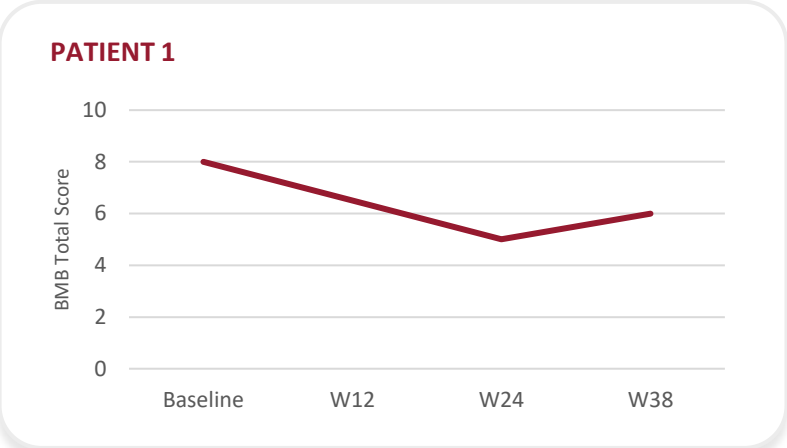



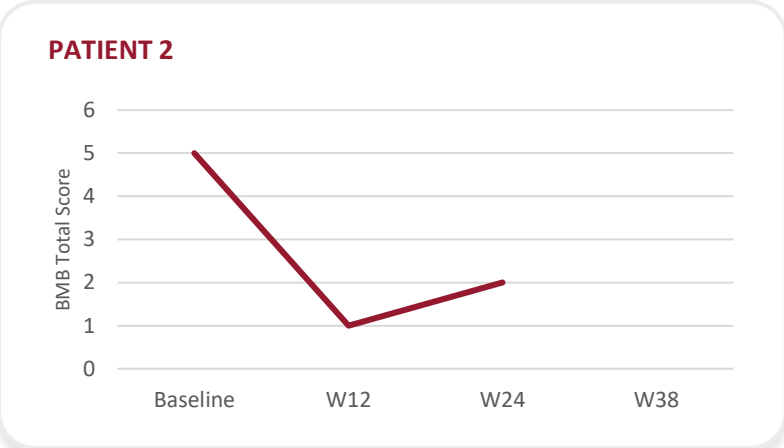

Data cut off Feb. 19, 2024.
Data presented at ASGCT 2024

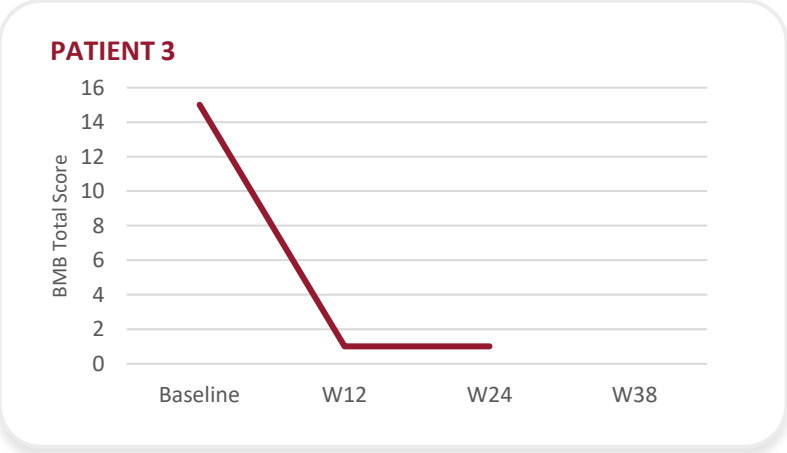
◆ Removal of prior treatment

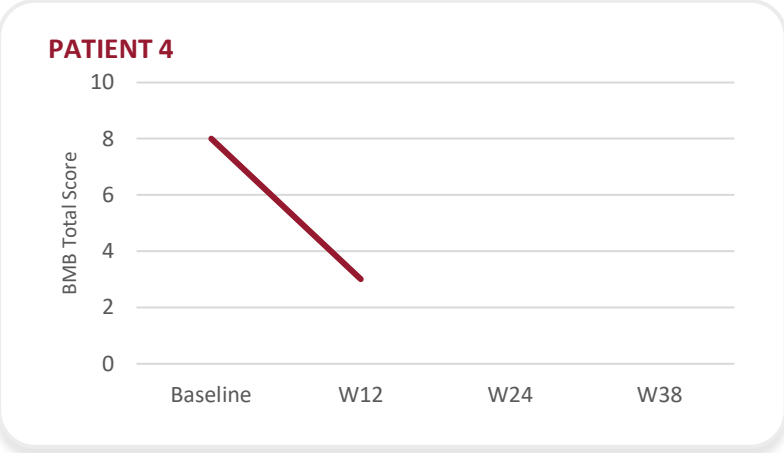
# Emerging data demonstrate beneficial effect on Bone Marrow Burden (BMB)

## BMB score by MRI over time




## Improvements even in patients with severe BMB*

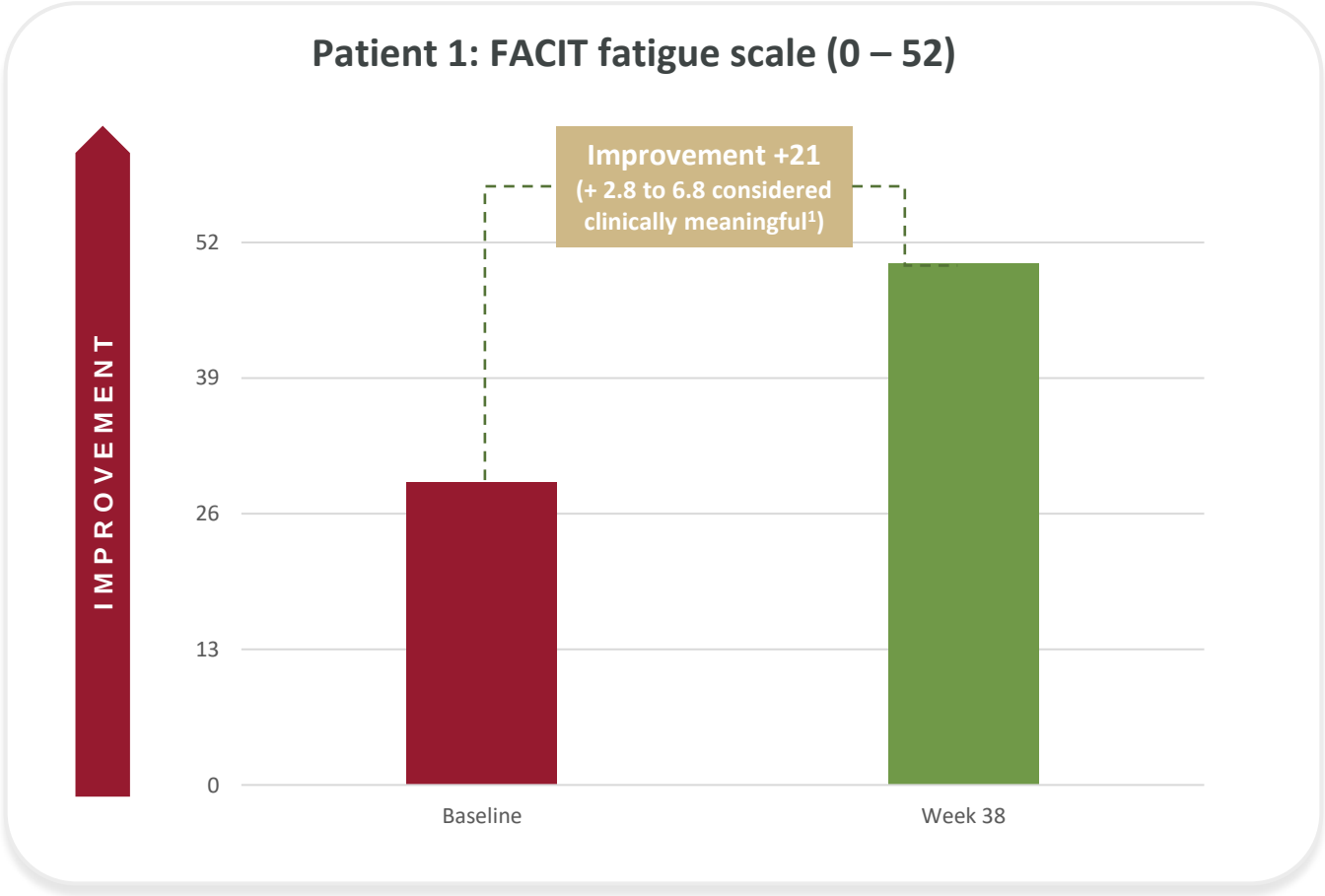
Early signs of clinical improvement observed in BMB as of 12 to 38 weeks post-dosing.

Indicates clearance of substrate from the bone marrow and reappearance of healthy, fatty marrow.

Bone involvement a prevailing unmet need for patients, as tissue difficult to reach for current standard of care.

Data cut off April 8, 2024; Presented at ASGCT May 9, 2024
*De Fost 2006; score of 6 or higher defined as severe BMB

# Clinically meaningful improvement in fatigue




**FACIT = Functional Assessment of Chronic Illness Therapy**

## Patient reported significant improvements in fatigue and ability to perform daily activities

- Has energy
- Able to do usual activities
- No longer feels tired, washed out or weak all over
- No longer has trouble starting or finishing things due to tiredness
- No longer frustrated by being too tired to do the things they want to do
- No longer has to limit social activity due to tiredness

Data cut off April 8, 2024: patients with available W38 data. Presented at ASGCT on May 9, 2024.

[1] Greenbaum 2020; clinically meaningful in cancer, lupus, HUS, RA

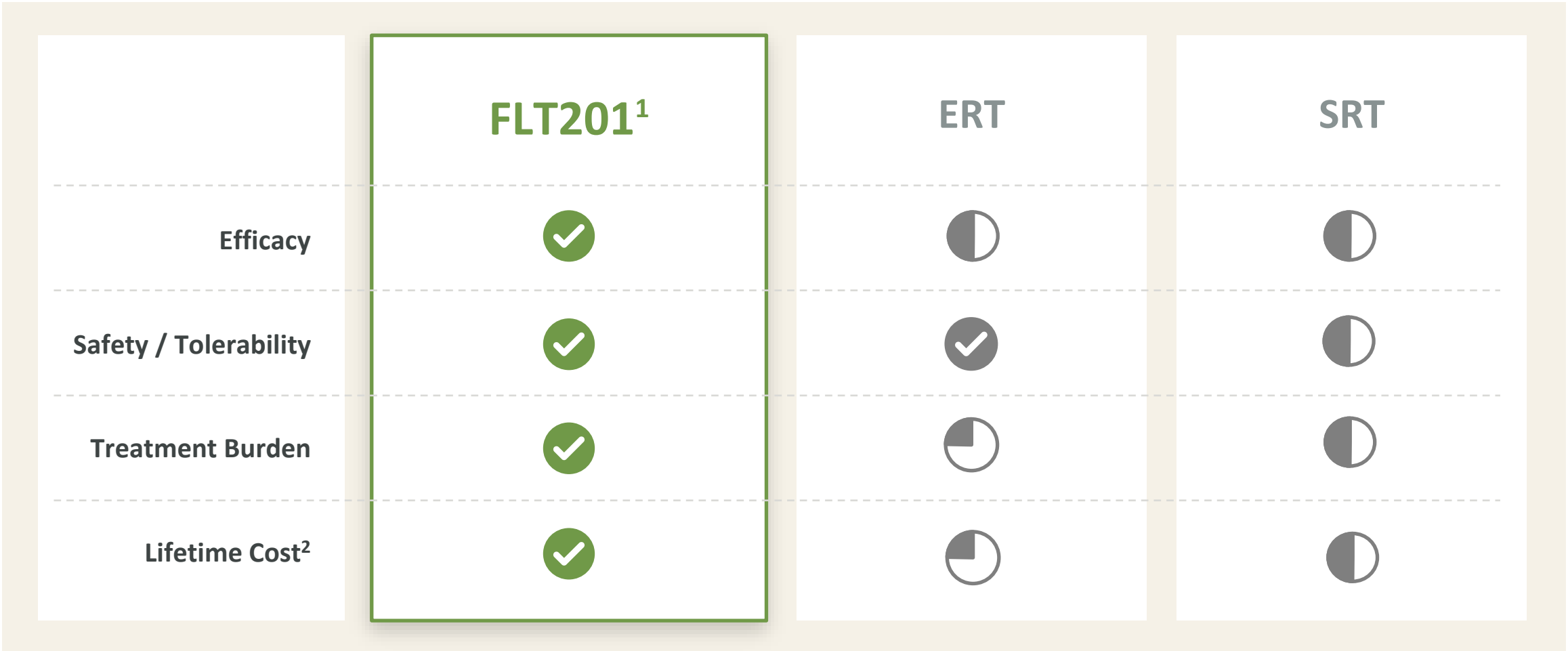
# FLT201 has been well-tolerated with clean safety profile to date

## Safety

- Infusions well tolerated; no reactions
- No serious adverse events
- No severe adverse events or dose-limiting toxicities
- Any modest ALT elevations managed with immune therapy with no impact on efficacy
- Non-serious adverse events all mild or moderate in severity
- AEs related to immune management consistent with known profile of prednisone and tacrolimus

Data cut off Feb. 19, 2024
Presented at ASGCT 2024

# FLT201: Differentiated profile with opportunity to set new SoC



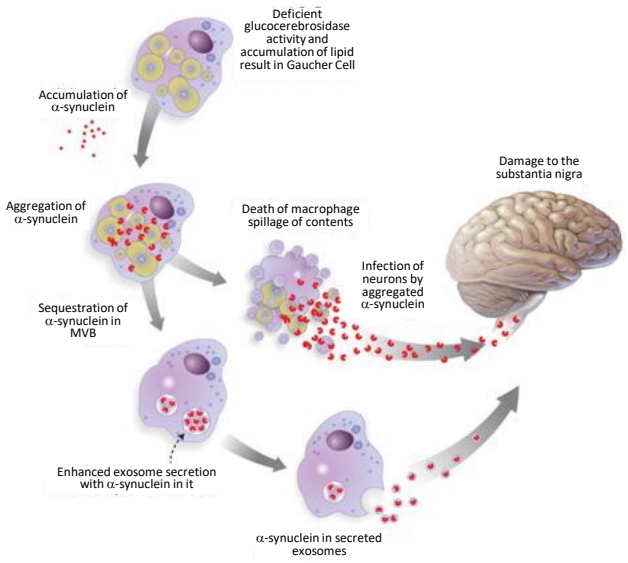

[1]FLT201 target product profile; [2]ERT and SRT have annual costs per patient of c.$615k and c.$390k in the U.S., respectively.

# GBA1 Parkinson's Disease

Pamela Foulds,
Freeline CMO

# Our longer-acting GCase85 provides opportunity for best-in-class gene therapy for GBA1 Parkinson's disease

GCase deficiency leads to formation of Lewy bodies (alpha-synuclein aggregates) and death of dopaminergic neurons via multiple mechanisms




## GBA1 Parkinson's disease

- *GBA* mutations are most common genetic risk factor for PD
- Associated with earlier onset and more severe disease
- Evidence of reduced GCase activity even in patients without a known *GBA* mutation

## High ongoing unmet need

- No disease-modifying therapies exist for PD
- Symptomatic treatments become less effective over time

**Substantial, well-defined patient population**

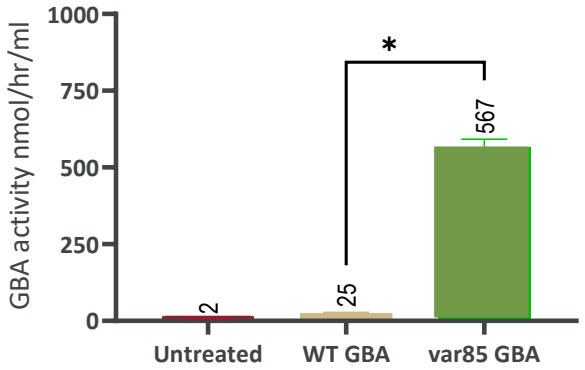
**5-15%**
of people with PD have *GBA1* mutations†

**~190k**
GBA1 PD patients in US, UK and EU4

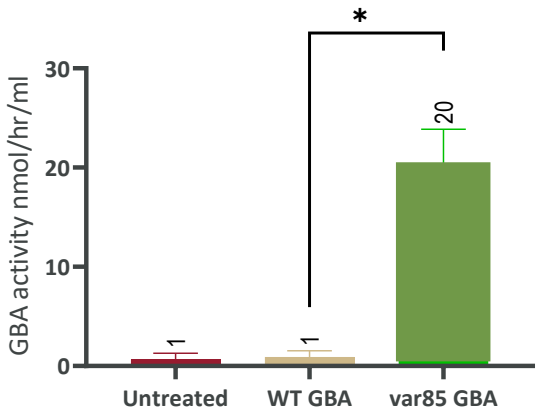
†Cells 2022, 11(8), 1261; https://doi.org/10.3390/cells11081261

# GCase85 demonstrated up to 20-fold greater activity levels compared to wildtype in preclinical studies

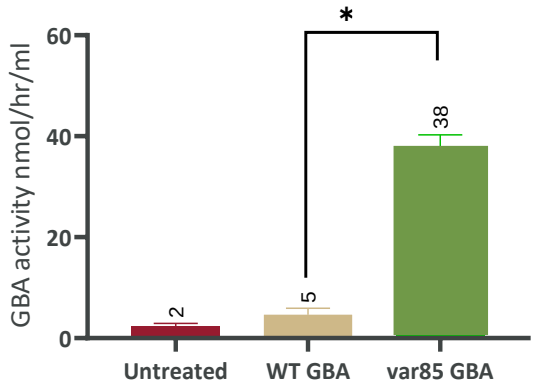
**Brain epithelial cell line (H4)**




**Neuroblastoma cell line (NB1643)**



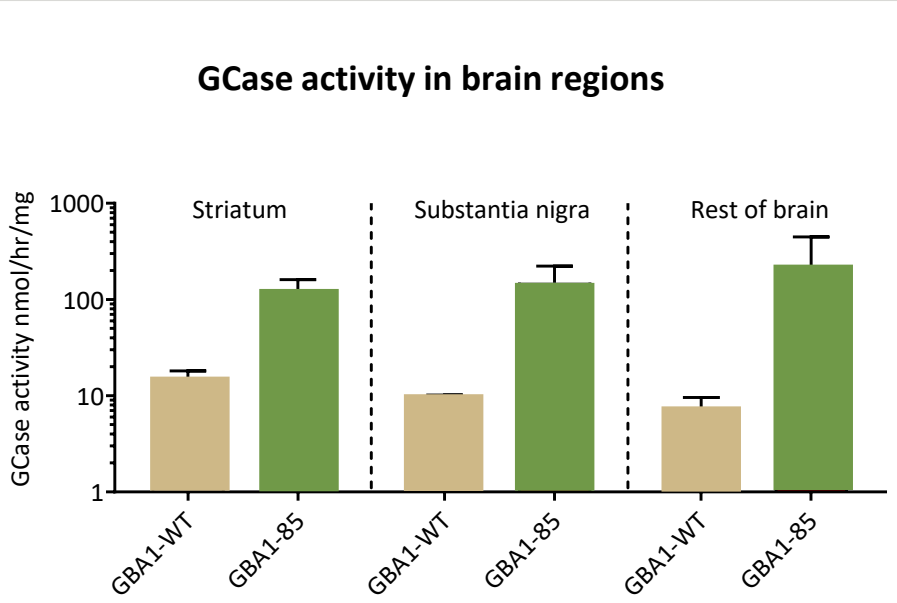

**Neuronal cell line (SH-SY5Y)**




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

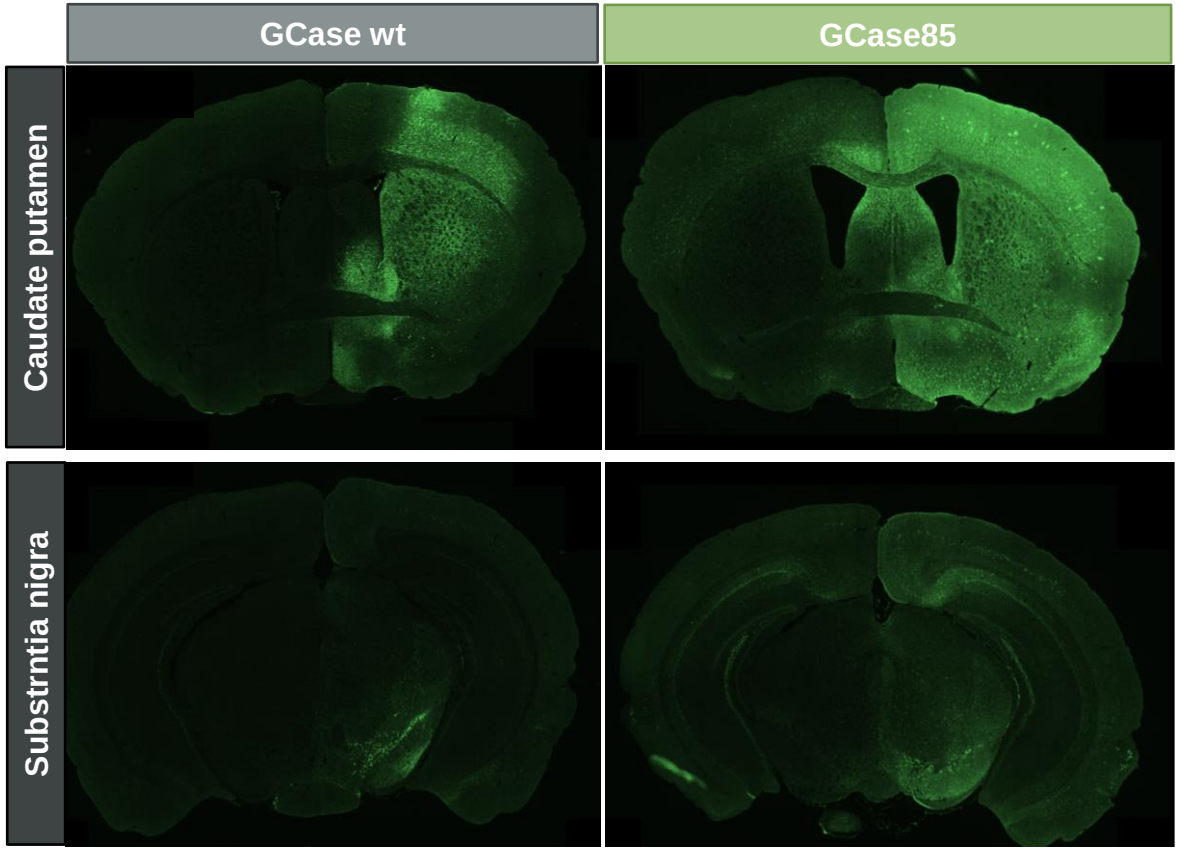
Presented at ASGCT May 9, 2024

# GCase85 shows greater brain distribution and higher enzyme levels than wildtype GCase *in vivo*




Injected with indicated AAVs, samples dissected from striatum, substantia nigra or the rest of the brain. The GCase activity is normalised for VG, n=3, data denoted as mean ± SD.

**GCase distribution in the brain**




Representative coronal sections of animals injected with either AAV9-GBA1-WT or AAV9-GBA1-85 labelled for GCase, n=4. Dosed AAV9 at 1.3e10 vg per mouse by unilateral injection of to right hemisphere striatum.

Data presented at ASGCT 2024

# Summary

Michael Parini,
Freeline CEO

# Anticipated upcoming milestones

## GAUCHER DISEASE

FLT201

- Complete dosing in Phase 1/2 GALILEO-1 trial in Q2 2024
- Report additional data from Phase 1/2 GALILEO-1 trial in H2 2024
- Initiate Phase 3 trial in 2025

## GBA1-PD

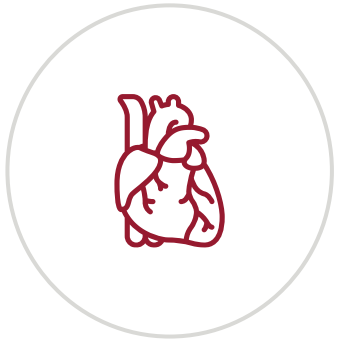
Leveraging GCase85

- Select development candidate in H2 2024

# Advancing the next generation of gene therapies

FLT201: A potential first-and best-in-class gene therapy for Gaucher disease backed by compelling clinical data

Extending the impact of our longer-acting GCase85 into GBA1 Parkinson's disease



Ambitious research strategy to move gene therapy into larger patient populations

# Thank you.

FREELINE