



**Freedom from a lifetime of disease**

**March 13, 2019**

**Cowen and Company 39<sup>th</sup> Annual Healthcare Conference**

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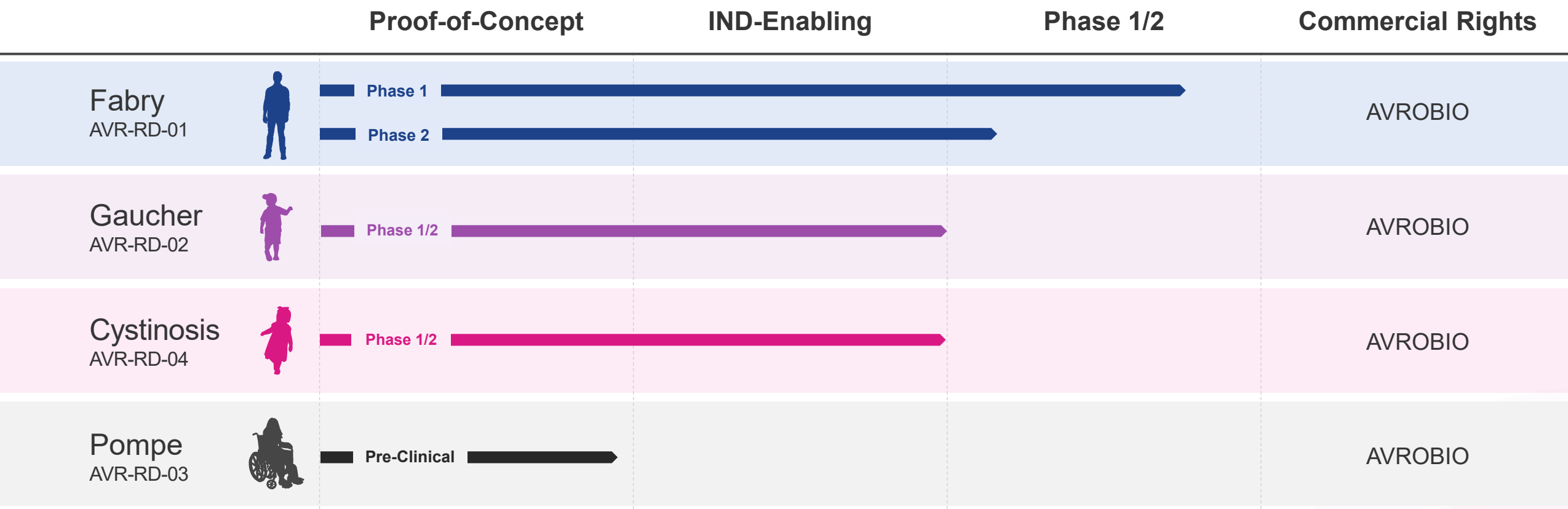
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# Steady stream of clinical programs

Worldwide rights across portfolio



# Cell, gene and rare disease industry leaders



## AVROBIO expands and strengthens team

### MANAGEMENT TEAM



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President and CEO



**Birgitte Volck, PhD, MD**  
President of Research and Development



**Kim Warren, PhD**  
Head of Operations



**Erik Ostrowski**  
Chief Financial Officer



**Chris Mason, MD,**  
PhD, FRCS  
Chief Science Officer



**Steven Avruch, JD**  
General Counsel



**Deanna Petersen, MBA**  
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**Josie Yang, PhD**  
Head of Regulatory Affairs



**Kathryn McNaughton, PhD**  
SVP Portfolio & Program Management



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# Patient focus groups December 2018

## Significant unmet need and continued disease progression on ERT

*"I feel awful and there [are] so many, so many things that don't show up on tests."*

*"I have severe pain, severe exhaustion."*

*"My reason for doing ERT is not so like I'll feel better. I wish it was. It would be great if it lessened my pain or something. It is longevity of life, period."*

*"The GI issues and pain, the infusions don't really help with that."*

*"[ERT] is not going to help a stroke."*

*"My mother has Parkinson's. My brother is 34 and 2 weeks ago because of his Gaucher's, he just had a double hip replacement."*

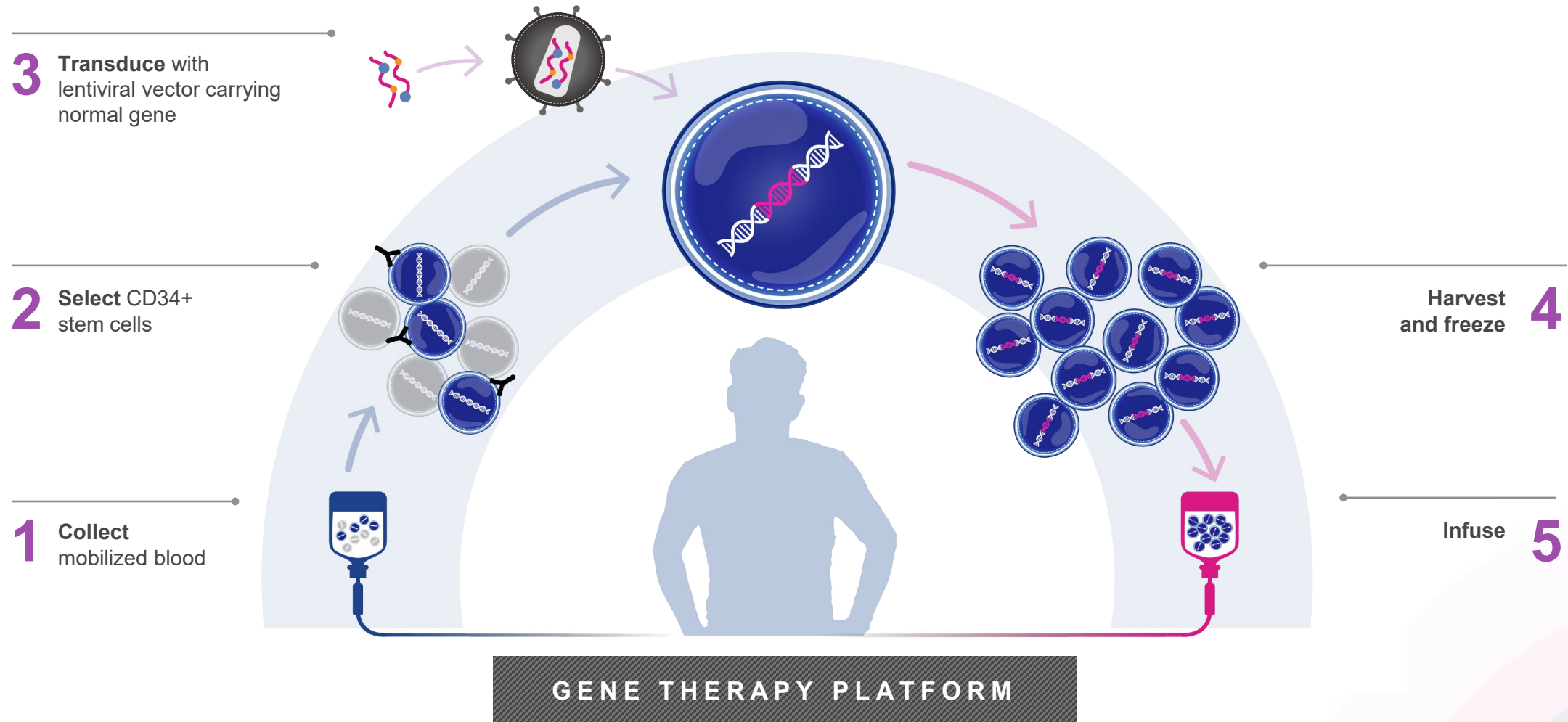
*"I have avascular necrosis in both my hips."*

*"A day or two before I have my treatment, I don't notice as much. My partner notices. You look white as a ghost. I'm exhausted. I'm snappy and I clearly had 8 hours of sleep, but no part of me feels that way."*

Patients with Fabry disease

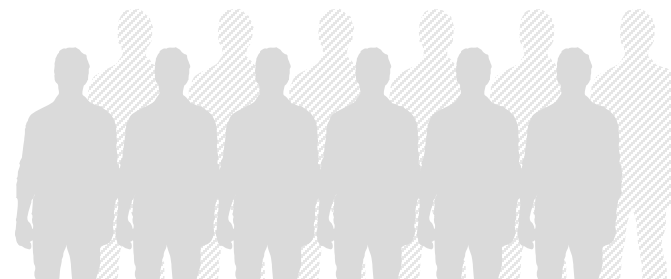
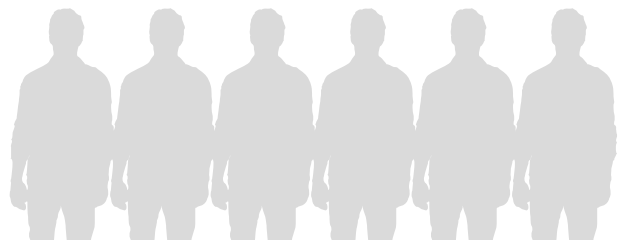
Patients with Gaucher disease

# One platform applied across our portfolio



# AVR-RD-01 Fabry clinical trials

6 patients dosed across Phases 1 and 2



## PHASE 1

Investigator-Sponsored Trial\*

### Patients

n = up to 6

On ERT > 6 months prior to enrollment  
18-50 year-old males

### Key Objective

Safety

## PHASE 2

AVRO – FAB-201 Trial

### Patients

n = 8-12

ERT-naïve  
≥ 16 year-old males

### Key Objectives

Safety and efficacy

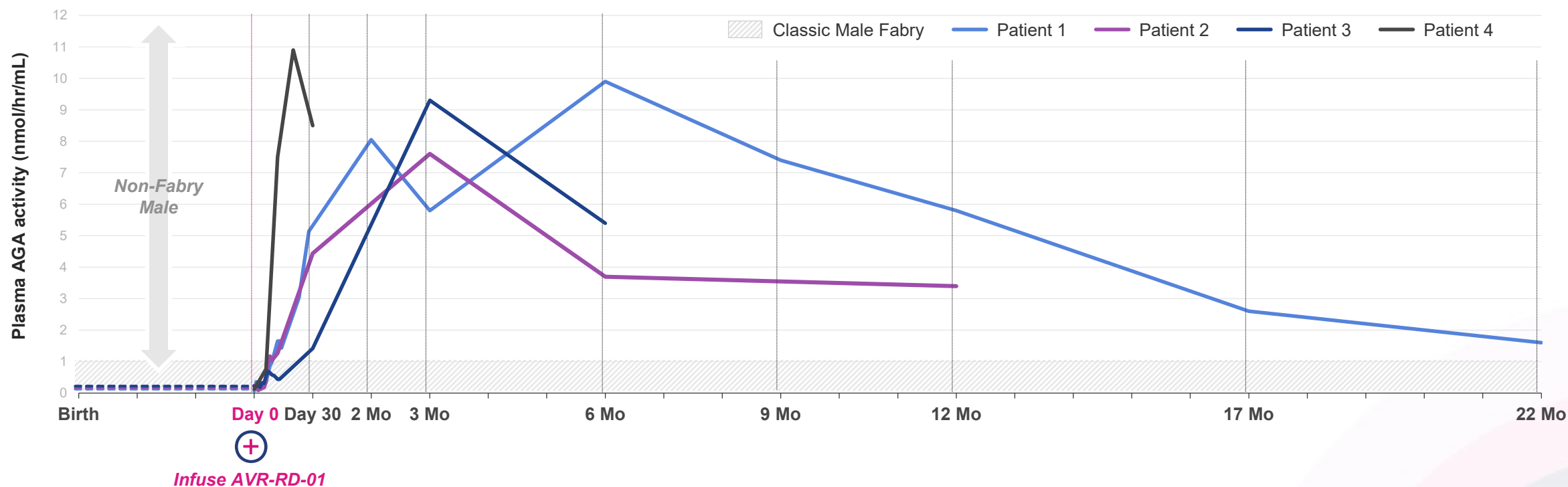
\* Sponsored by FACTS team (Fabry disease Clinical research and Therapeutics) in Canada

# Phase 1: Substantial enzyme activity elevation

Sustained at 22 months



*Level of AGA enzyme activity rose from nearly undetectable levels to levels above the range for males with classic Fabry disease*



Source of reference bar: Tsukimura T et al, Mol Genet Metab, 2014

Note: Enzyme measurements are taken at ERT troughs

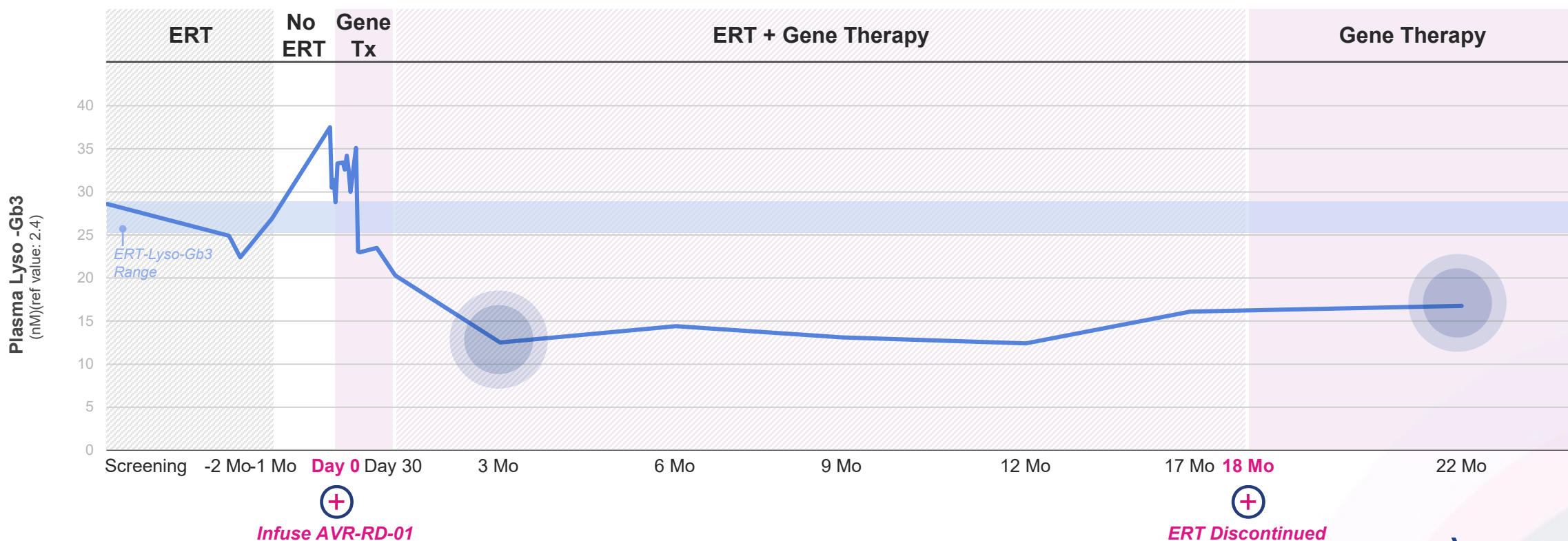
Note: Dotted line illustrative only



# Phase 1: Plasma Lyso-Gb3 reduction sustained after discontinuation of ERT



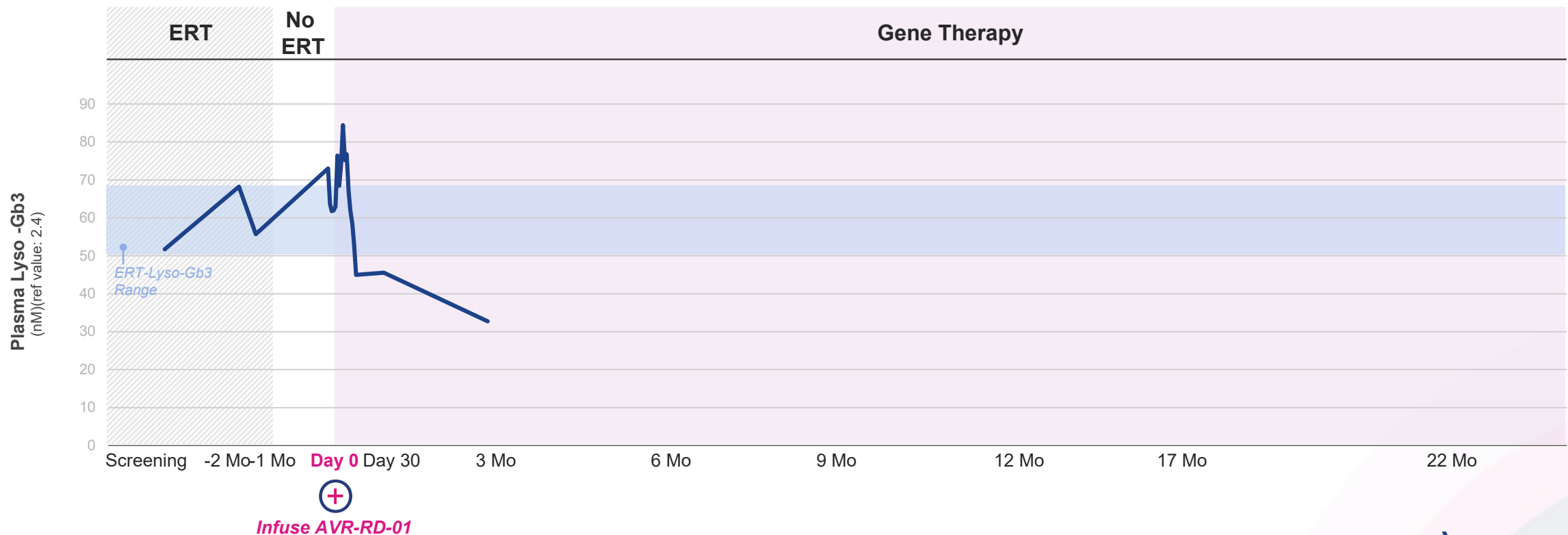
*PATIENT #1: Plasma Lyso-Gb3 remains below ERT levels with AVR-RD-01 gene therapy alone*



# Phase 1: Plasma Lyso-Gb3 declines below levels on ERT with **gene therapy alone**



*PATIENT #3: Did not resume ERT treatment following AVR-RD-01 dosing*



# Phase 1: Vector Copy Number (VCN)



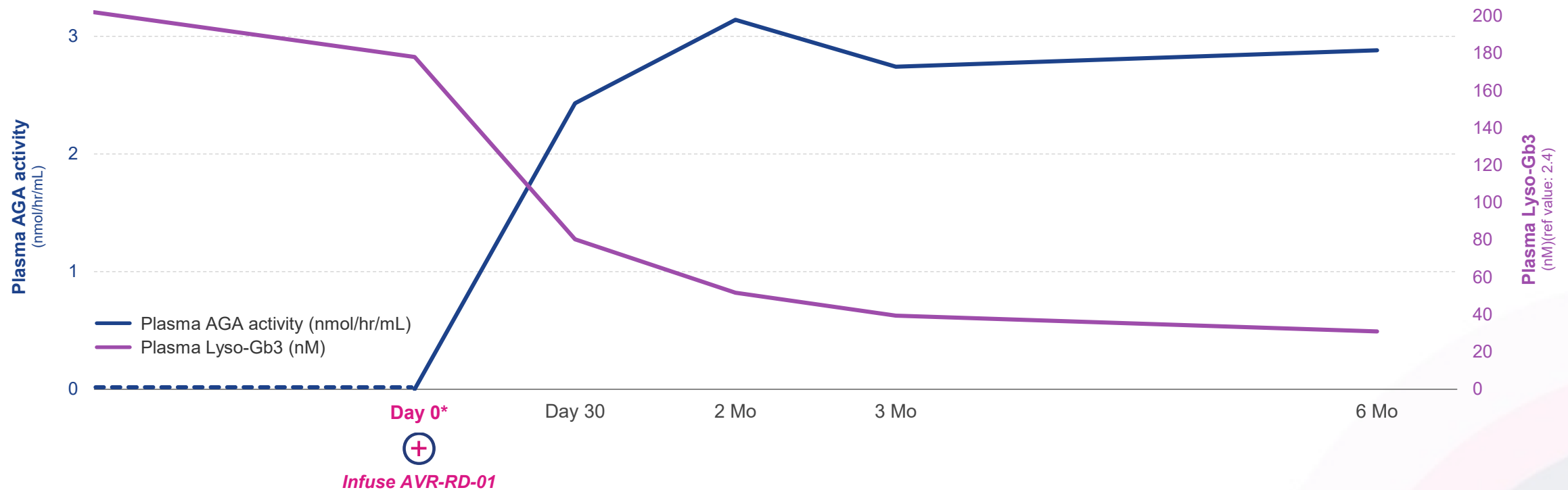
Drug Product VCN		Peripheral Blood VCN	Patient 1	Patient 2	Patient 3
Patient 1	0.7	1 Month	0.4	0.8	0.2
		3 Months	0.6	1.1	0.8
Patient 2	1.4	6 Months	0.4	0.4	0.5
		9 Months	0.3	-	
Patient 3	0.8	12 Months	0.2	0.4	
		17 Months	0.1		
Patient 4	1.4	22 Months	0.1		

*PATIENT #1: At 14 months, 13% of bone marrow mononuclear cells were vector positive*

# FAB-201: Substantial increase in AGA enzyme activity with associated reduction in Plasma Lyso-Gb3



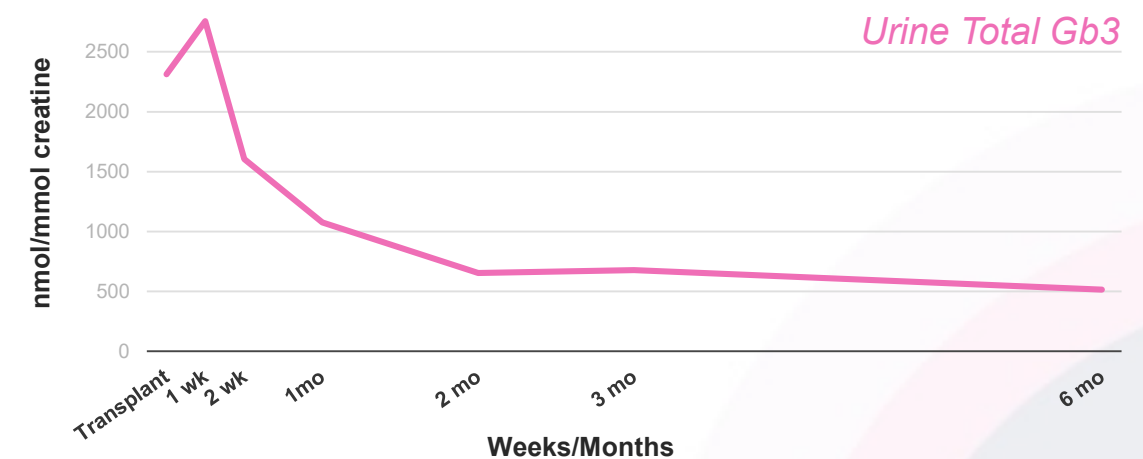
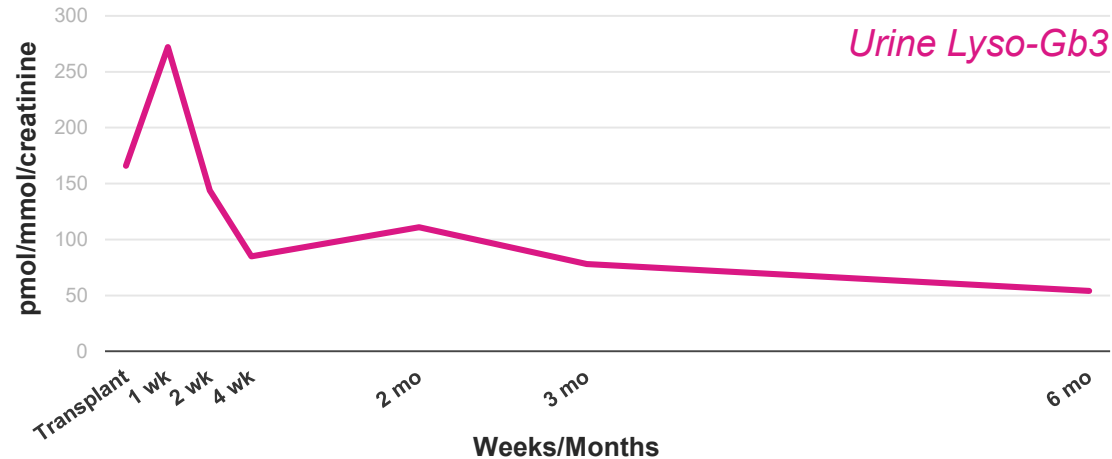
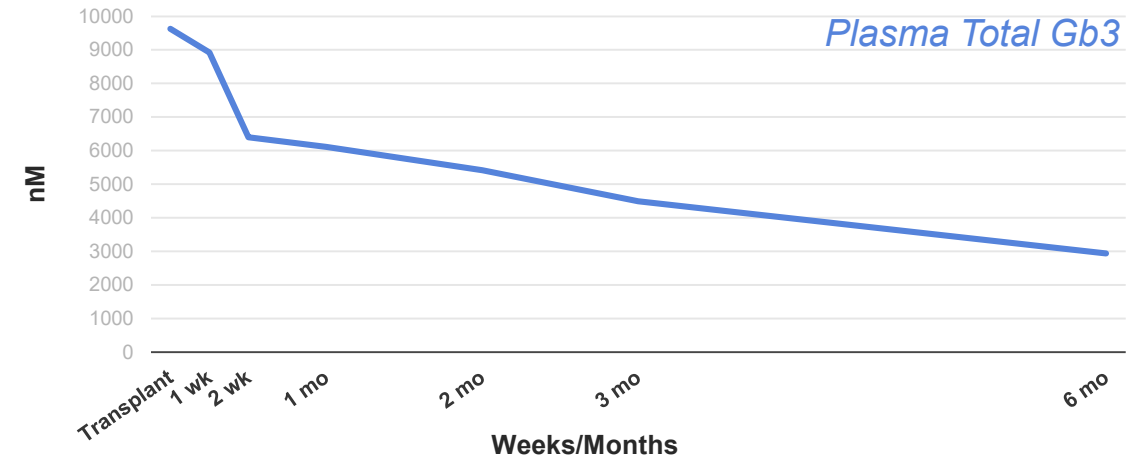
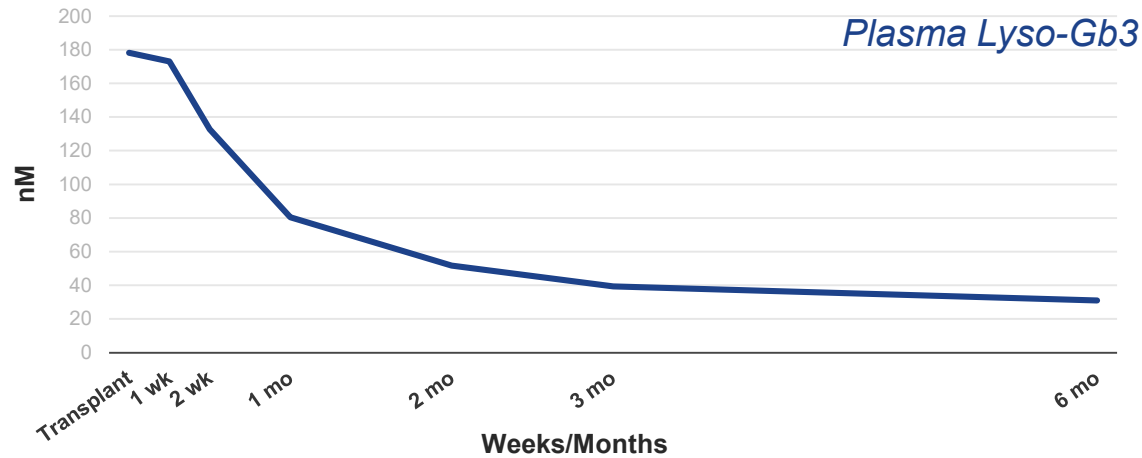
*Patient #1: 85% reduction in plasma lyso-Gb3 levels observed within 6 months*



\* Dotted line represents AGA activity measured in serum

# FAB-201: Patient #1 – Decline in multiple substrate/metabolite levels following gene therapy

## Gb3 and lyso-Gb3



# FAB-201: Vector Copy Number (VCN)



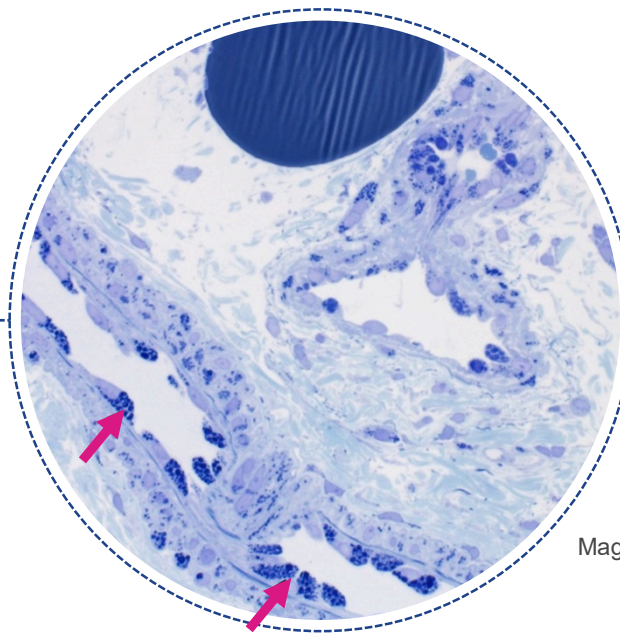
Drug Product VCN		Peripheral Blood Average VCN	Patient FAB-201-1
Patient FAB-201-1	0.7	1 Month	0.2
		2 Months	0.2
		3 Months	0.5
		6 Months	0.2

# FAB-201: Reduction in substrate inclusions in skin endothelial cells



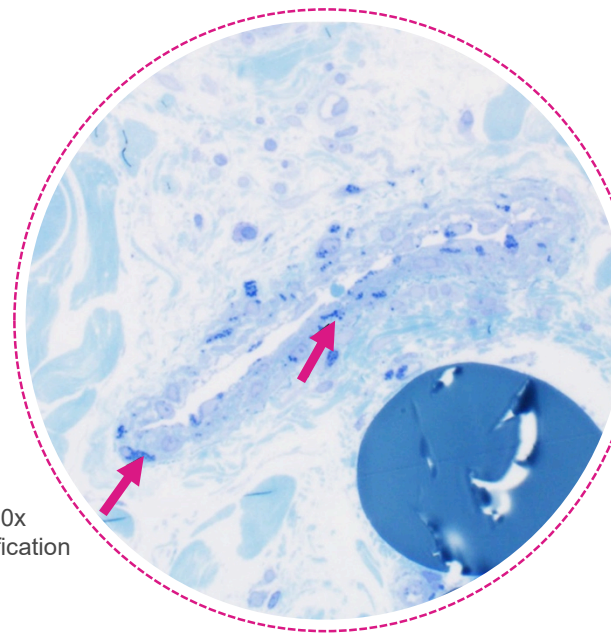
*Patient #1 achieved reduction in skin biopsy score from 3 to 2 within 6 months*

**Baseline  
Biopsy Score: 3**  
*Severe accumulation*



400x  
Magnification

**6-Month  
Biopsy Score: 2**  
*Moderate accumulation*



## **Skin Biopsy Scoring:**

3 = Large accumulations of inclusions, with some clusters at the juxtanuclear region and around cytoplasmic borders, and bulging of the vessel lumens

2 = Multiple vessels with multiple sites of single or multiple inclusions

1 = Majority of vessels with a single endothelial inclusion

0 = None or only trace microvascular endothelial deposits of GL-3 (normal or nearly normal)

Source: Thurberg B et al, J Investigative Dermatology, 2004

# Significant advances in Fabry clinical program

## Growing body of clinical data in Fabry

- + 6 patients dosed across 2 active clinical trials
- + All patient data to-date demonstrated **AGA enzyme activity** above the diagnostic range
- + **Substantial reduction in substrate and metabolites** observed in both ERT-treated and ERT-naïve patients
- + AVR-RD-01 observed to be **generally well tolerated**





# Introducing plato™

AVROBIO's foundation for worldwide commercialization



A **vector system** and cell **manufacturing solution** designed to support commercialization

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**Automated, closed manufacturing system** for CD34+ gene therapy

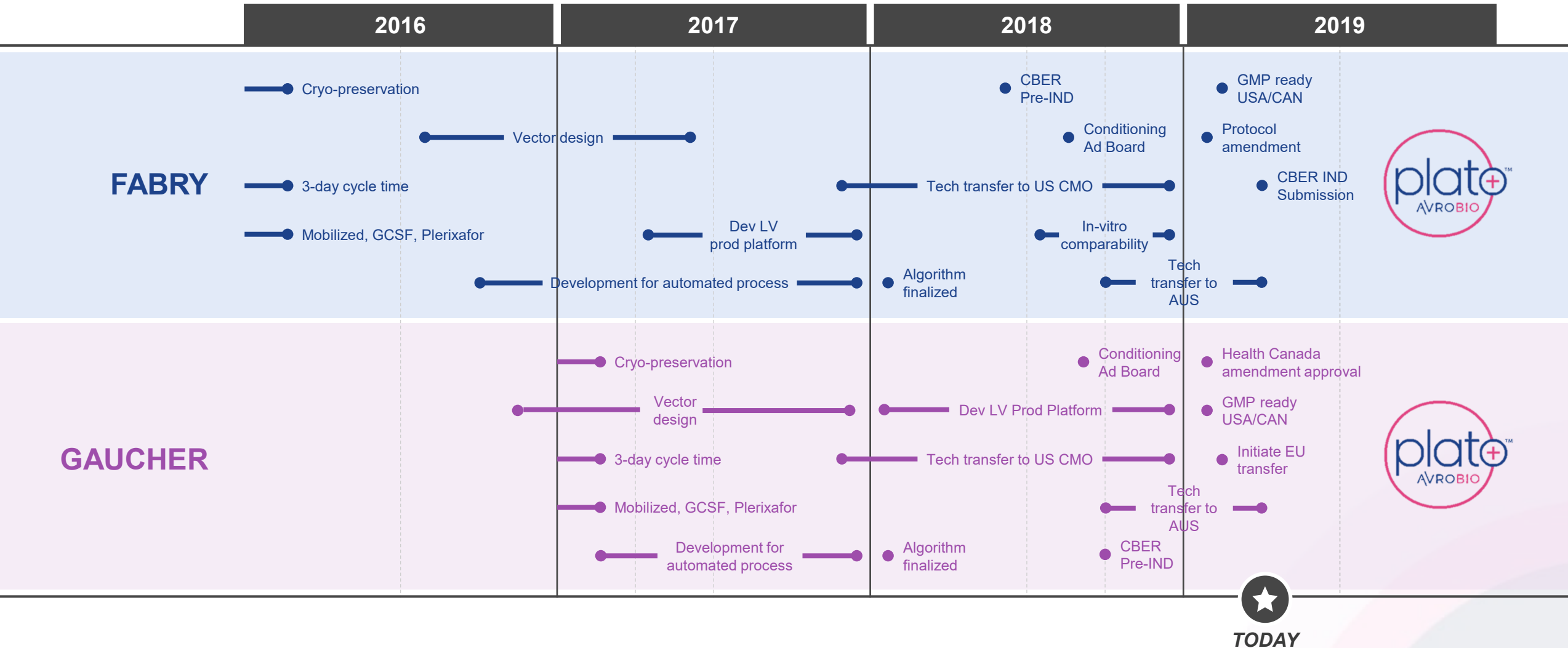
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Designed to safely deliver **long-term efficacy** and **durability**

# plato™: Commercial platform over 3 years in the making

Clinical trials H2 2019, regulatory milestone obtained



# plato™ overcomes historical bottlenecks to enable commercialization



## Expanded Scale

Potential to reach thousands of patients per year



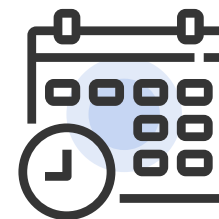
## Broader Reach

Portable platform for flexible global production using low grade clean rooms



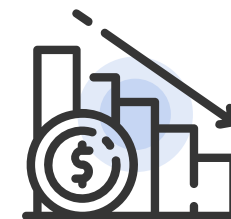
## High Quality

Automated, closed system designed to improve quality and consistency



## Longer Shelf-Life

Cryopreservation simplifies logistics and patient scheduling












## Lower Costs

Efficiencies in vector design / scalable cell and vector production

# plato™: Three 2019 upgrades designed to optimize **potency, safety, and durability**



 UPGRADES	Increased enzyme activity	Increased transduction efficiency	Increased VCN	Increased marrow space / engraftment	Increased consistency and safety
			 *		 **
					
					
<i>Upgrades designed to increase Vector Copy Number (VCN), chimerism and durability</i>					

\* Average VCN per cell  
\*\* TDM (therapeutic drug monitoring)

**CONDITIONING UPGRADE:****plato™ transitions to busulfan TDM for anticipated advances in safety and efficacy**

**WHAT** Switch from 100mg/m<sup>2</sup> melphalan to **busulfan** with **Therapeutic Drug Monitoring (TDM)**

**WHY**

Busulfan **used successfully** in many gene therapy indications

TDM intended to **elevate safety profile** while permitting higher intensity

Potential to **impact CNS manifestations** which affect many LSD patients

**SAFETY TRACK RECORD**

Busulfan in **non-malignant** conditions

- Literature shows >700 patients with **NO reports** of t-MDS / t-AML
- **Isolated case** of t-MDS in a sickle cell patient in bluebird bio's gene therapy trial

*t-MDS = Treatment-related myelodysplastic syndrome*

*T-AML = Treatment-related acute myeloid leukemia*

*References available upon request*

*bluebird bio is a registered trademark of Bluebird Bio, Inc.*

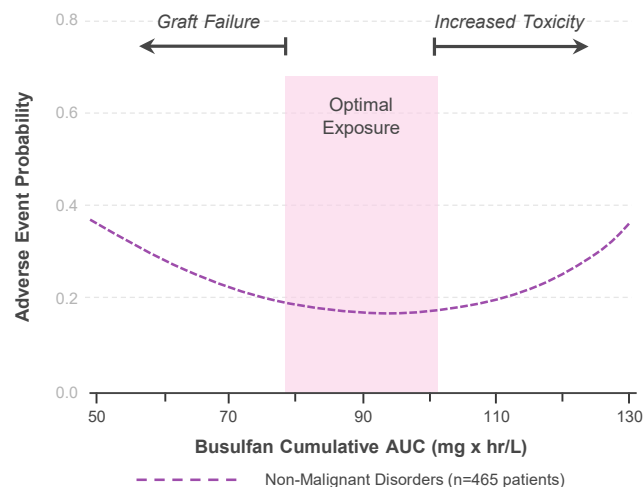


## CONDITIONING UPGRADE:

# Busulfan intended to balance engraftment with enhanced safety

### Optimized Dosing

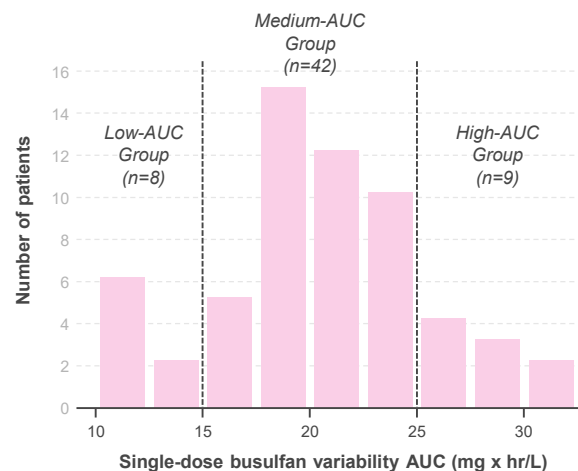
Designed to Enhance Tolerability



Lowest rate of complications in the Bu90 range

### Optimized Monitoring

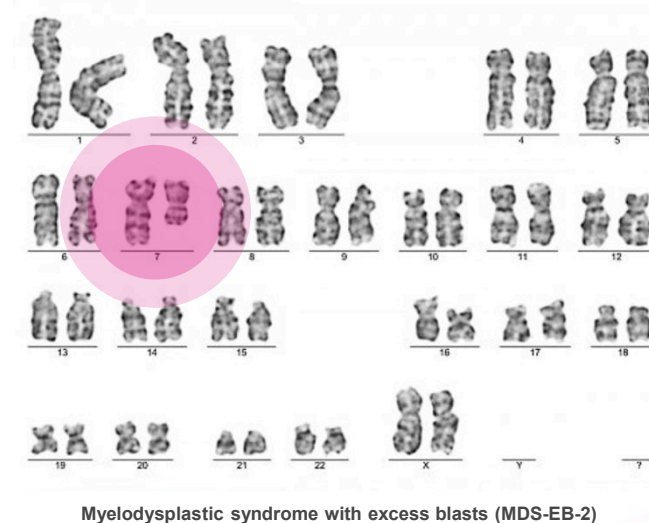
Designed to Enhance Safety



TDM via area under the curve (AUC) intended to eliminate out-of-bounds toxicity

### Optimize Screening

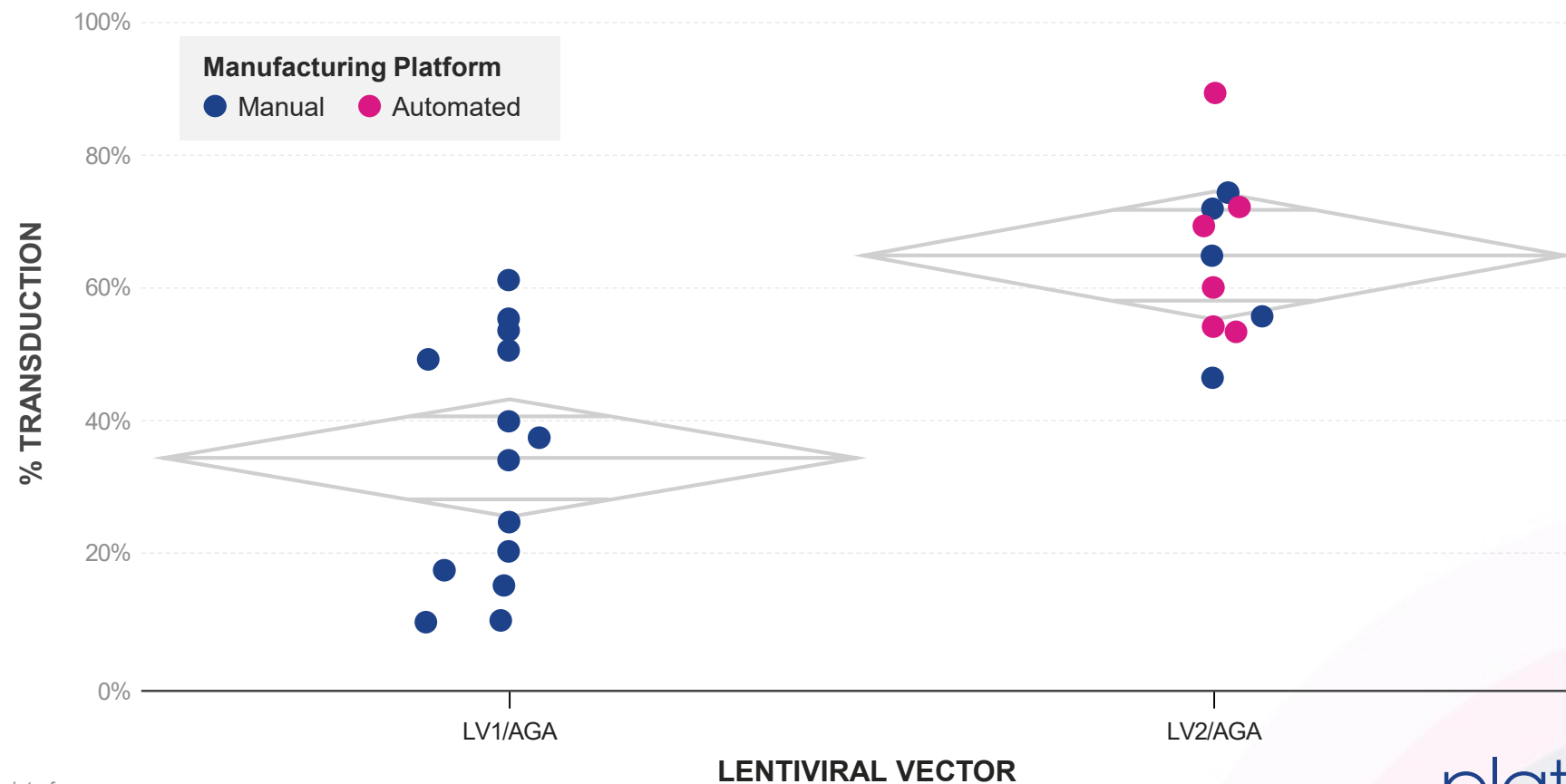
Designed to Reduce Patient Risk



Pre-screening for molecular and cytogenetic abnormalities has potential to further reduce risk

# VECTOR & AUTOMATION UPGRADES: plato™ designed to enhance potency and long-term durability

Increased  
% Transduction

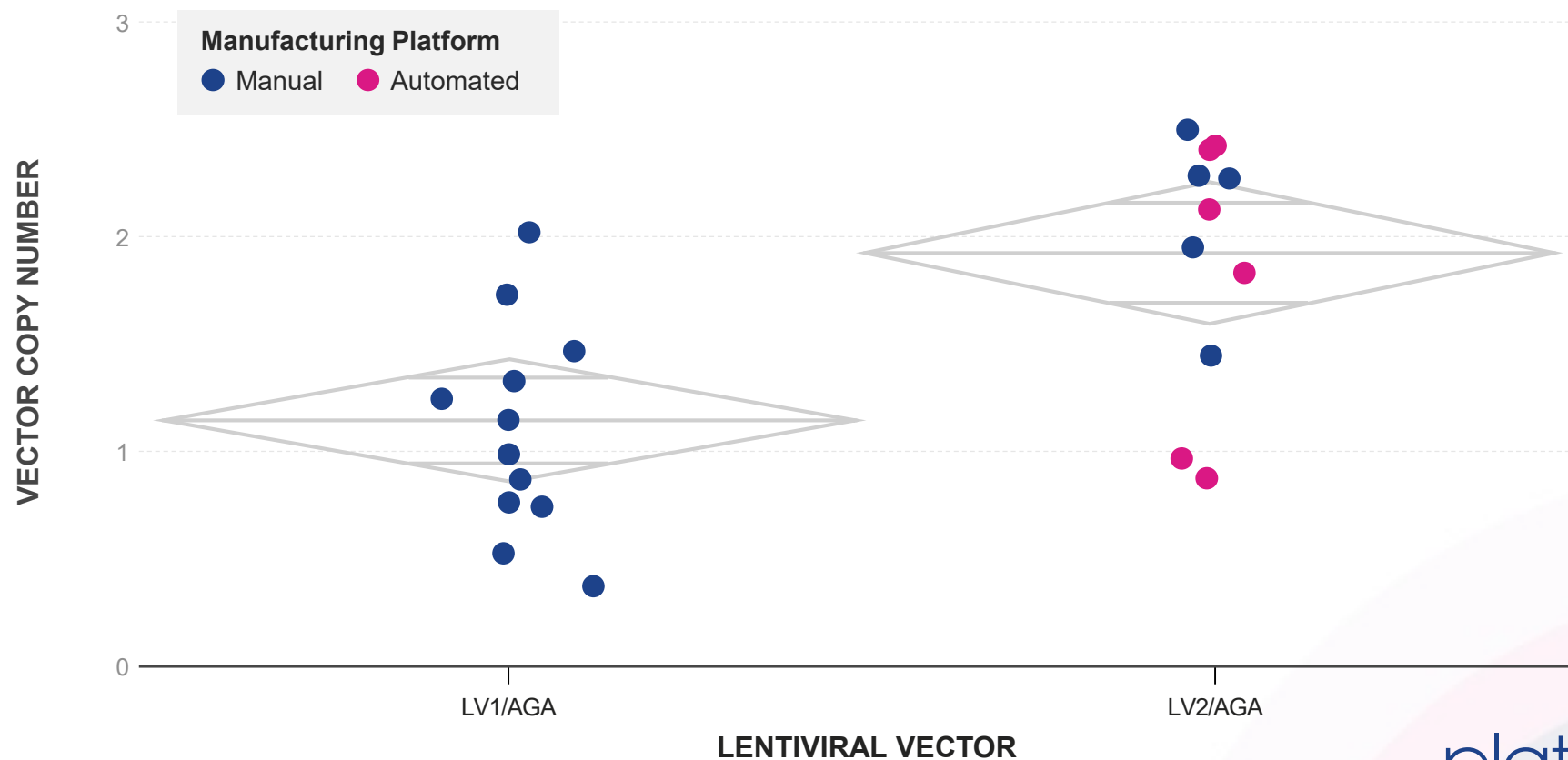


*Note: Data from all development runs using normal donor cells and data from four Fabry patients Drug Products are included, as of Oct 2018*

# VECTOR & AUTOMATION UPGRADES: plato™ designed to enhance potency and long-term durability



—  
*Increased  
Vector Copy  
Number (VCN)*  
—



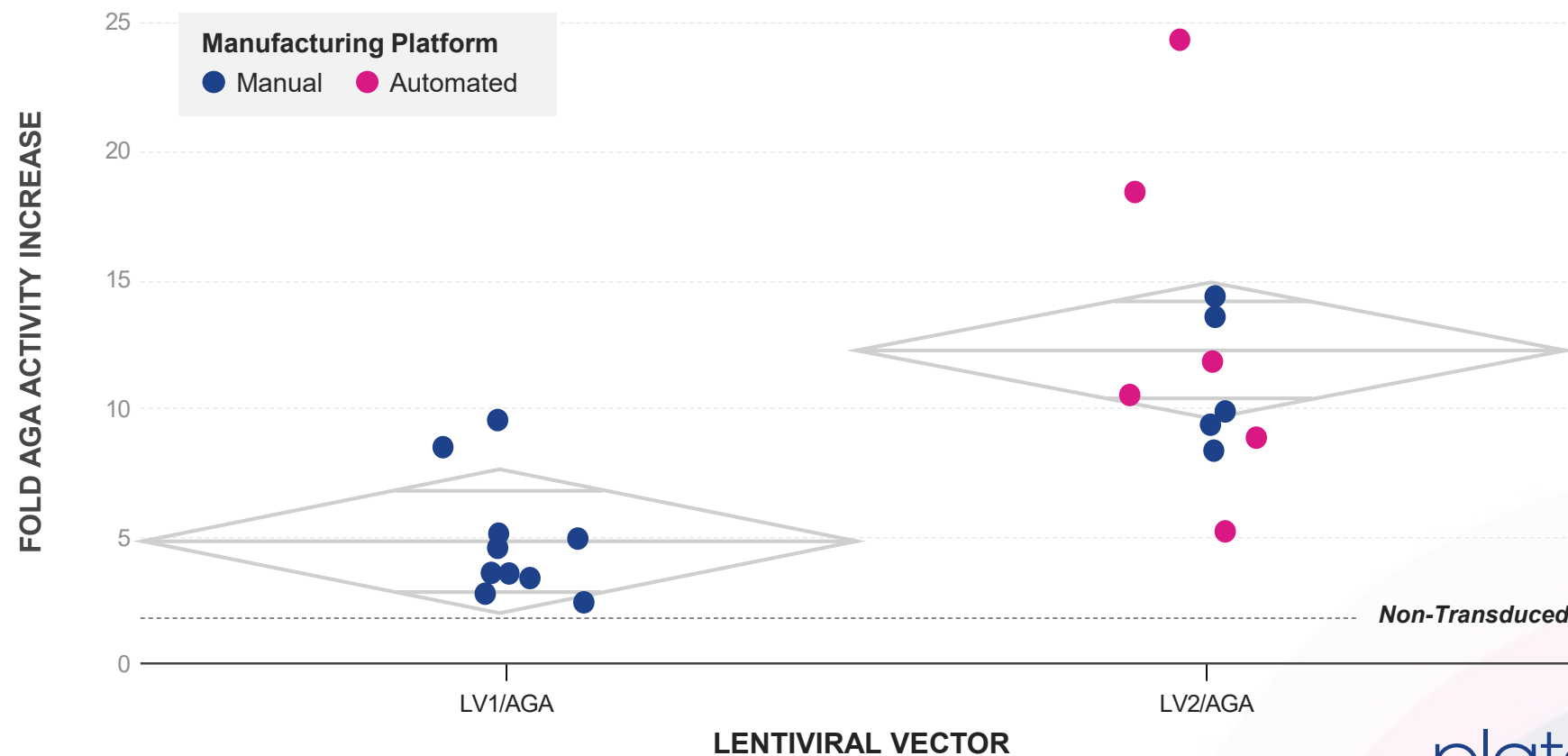
*Note: Data from all development runs using normal donor cells and data from four Fabry patients' Drug Products are included, as of Oct 2018*



# VECTOR & AUTOMATION UPGRADES: plato™ designed to enhance potency and long-term durability



—  
*Increased  
AGA Enzyme  
Activity*  
—

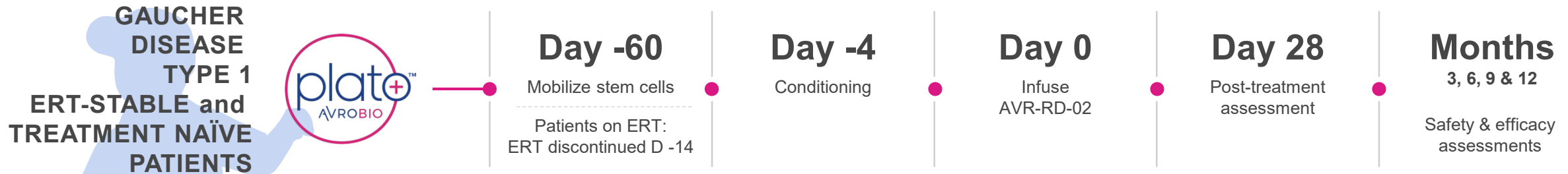


*Note: Data from all development runs using normal donor cells,  
as of Oct 2018*



# AVR-RD-02: AVROBIO Phase 1/2 study in Gaucher Type 1 patients

CTA NOL 2018; plato™ NOLs Jan. and Feb. 2019; First patient planned H2 2019



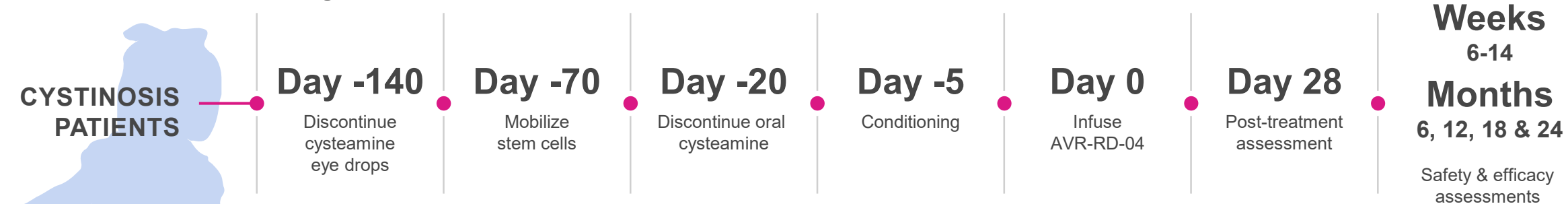
*An adaptive, open-label, multinational phase 1/2 study of the safety and efficacy of ex vivo, lentiviral vector mediated gene therapy AVR-RD-02 for subjects with Type 1 Gaucher disease*

OBJECTIVES	PATIENTS	ASSESS
<ul style="list-style-type: none"><li>• Safety</li><li>• Engraftment</li><li>• Efficacy (functional endpoints and biomarkers)</li></ul>	<ul style="list-style-type: none"><li>• 8-16 patients</li><li>• 16-35 year old males and females</li><li>• Two arms<ul style="list-style-type: none"><li>– Treatment naïve</li><li>– Stable receiving ERT</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Vector Copy Number (VCN)</li><li>• Chimerism</li><li>• GCase activity, including in CSF</li><li>• Efficacy<ul style="list-style-type: none"><li>– Hematologic values</li><li>– End-organ volumes and BMD</li><li>– Biomarkers and QoL</li></ul></li><li>• Safety</li></ul>



# AVR-RD-04: Investigator-sponsored\* Phase 1/2 study in Cystinosis patients

IND approved by FDA Dec. 2018; First patient planned H2 2019



*A Phase 1/2 study to determine the safety and efficacy of transplantation with autologous human CD34+ Hematopoietic Stem Cells (HSC) from Mobilized Peripheral Blood Stem Cells (PBSC) of patients with Cystinosis modified by ex vivo transduction using the pCCL-CTNS lentiviral vector*

OBJECTIVES	PATIENTS	ASSESS
<ul style="list-style-type: none"><li>• Safety</li><li>• Efficacy</li></ul>	<ul style="list-style-type: none"><li>• 6 patients</li><li>• adults and potentially adolescents 14–17 years old</li><li>• Using oral and ophthalmic cysteamine</li></ul>	<ul style="list-style-type: none"><li>• Cystine levels in granulocytes</li><li>• Vector Copy Number (VCN)</li><li>• Chimerism</li><li>• Renal, respiratory and endocrine function, ophthalmologic findings, muscle strength, growth, bone density, neurologic and psychometric measures</li><li>• Safety</li></ul>

\* Sponsored by UCSD  
AVROBIO



# Pompe is a serious rare genetic disease

## Integrated 3-part solution advancing

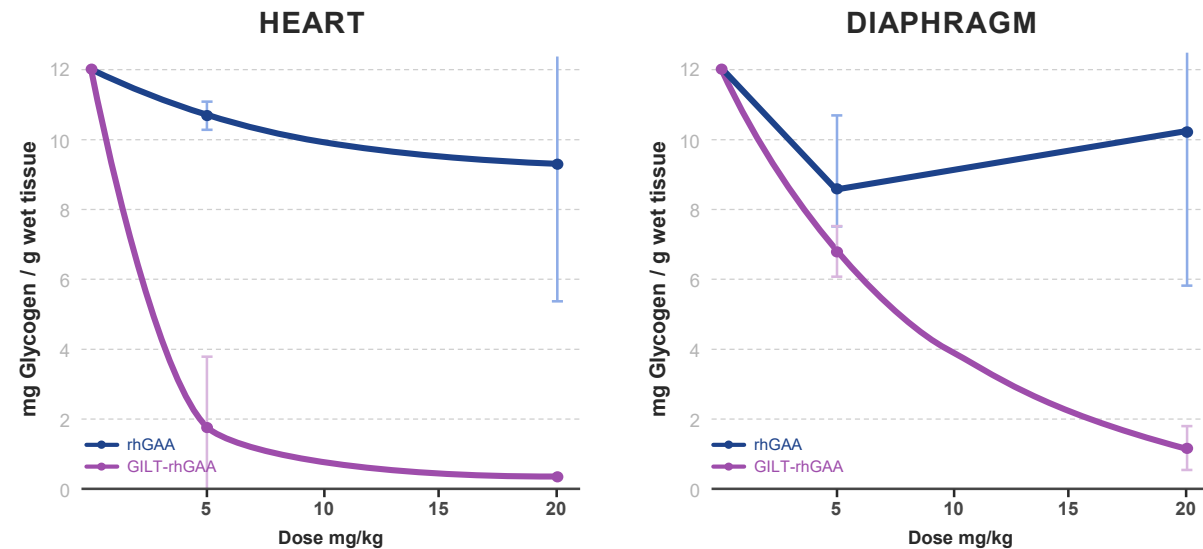
### THE CHALLENGE

- Pompe requires **20x more ERT** than Fabry or Gaucher
- Requires GAA activity restored to **muscle and CNS**

### AVROBIO's SOLUTION

- Potent transgene promoter
- GILT uptake tag
- plato™ for CNS impact

**Gilt-tagged** recombinant human (rh)GAA impacts levels of stored glycogen compared to non GILT-tagged recombinant human (rh)GAA in a Pompe mouse model



### DISEASE

- Mutations in the acid alpha-glucosidase (GAA) gene resulting in deficient enzyme activity
- Leads to accumulation of glycogen in tissues and organs, especially in muscles

### IMPACT

- Premature mortality
- Proximal myopathy (eventually wheelchair bound), respiratory insufficiency (often requiring ventilation), chronic respiratory infections, sleep apnea, fatigue

### STANDARD OF CARE – ERT

- Not curative, relentless progression of disease continues
- Burdensome and expensive

### POPULATION ESTIMATES

- 1:58,000 live births, detection projected to increase to 1:22,000 due to newborn screening

Sources: Burton B et al, J Pediatr, 2017; Aulsems M et al, Eur J Hum Genet, 1999; Gungor D et al, Orphanet J Rare Dis, 2011; Maga JA et al, J of Bio Chem 2013

Foundation for  
growth and future  
commercialization

## Substantial progress on all fronts

- + Compelling Fabry data across 2 clinical trials
- + Gaucher program expected in clinic 2019
- + Cystinosis program expected in clinic 2019
- + **plato**<sup>™</sup> expected in clinic 2019
- + Pompe preclinical program advancing
- + Strengthened leadership team

# Multiple 2019 milestones anticipated



## FABRY

- Phase 1 recruitment set to complete H1 2019
- FAB-201 Phase 2 trial continues recruitment
- **plato™** to be incorporated in FAB-201 H2 2019
- Additional trial sites to open in Canada and USA
- Additional readouts throughout the year



## GAUCHER

- First patient dosed in AVR-RD-02 Phase 1/2 trial H2 2019
- **plato™** to be incorporated in AVR-RD-02 H2 2019



## CYSTINOSIS

- First patient dosed in AVR-RD-04 Phase 1/2 trial H2 2019



## POMPE

- Preclinical program advances



## Momentum in 2019

- **Compelling Fabry data** across 2 clinical trials
- Substantial **platform and pipeline advances**