



**Company Presentation**  
**September 2020**

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A man with dark hair and glasses, wearing a grey sweater, a patterned scarf, and dark jeans, is walking from left to right. He is carrying a black bag over his shoulder. In the background, there are two large, stylized DNA double helix structures. One is pink and on the left, and the other is blue and on the right. The background is dark and textured.

# AVROBIO





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**Our mission: Giving people with genetic  
disease freedom for life**



# Multiple programs in the clinic











12 patients dosed to date across three indications

Investigational Gene Therapy		Proof-of-Concept	IND-Enabling	Phase 1/2	Commercial Rights
Fabry AVR-RD-01		Phase 2			AVROBIO
Gaucher AVR-RD-02		Phase 1/2			AVROBIO
Cystinosis AVR-RD-04		Phase 1/2			AVROBIO
Pompe AVR-RD-03		Preclinical			AVROBIO

# Addressing multi-billion dollar market opportunity



## CURRENT STANDARD OF CARE COSTS

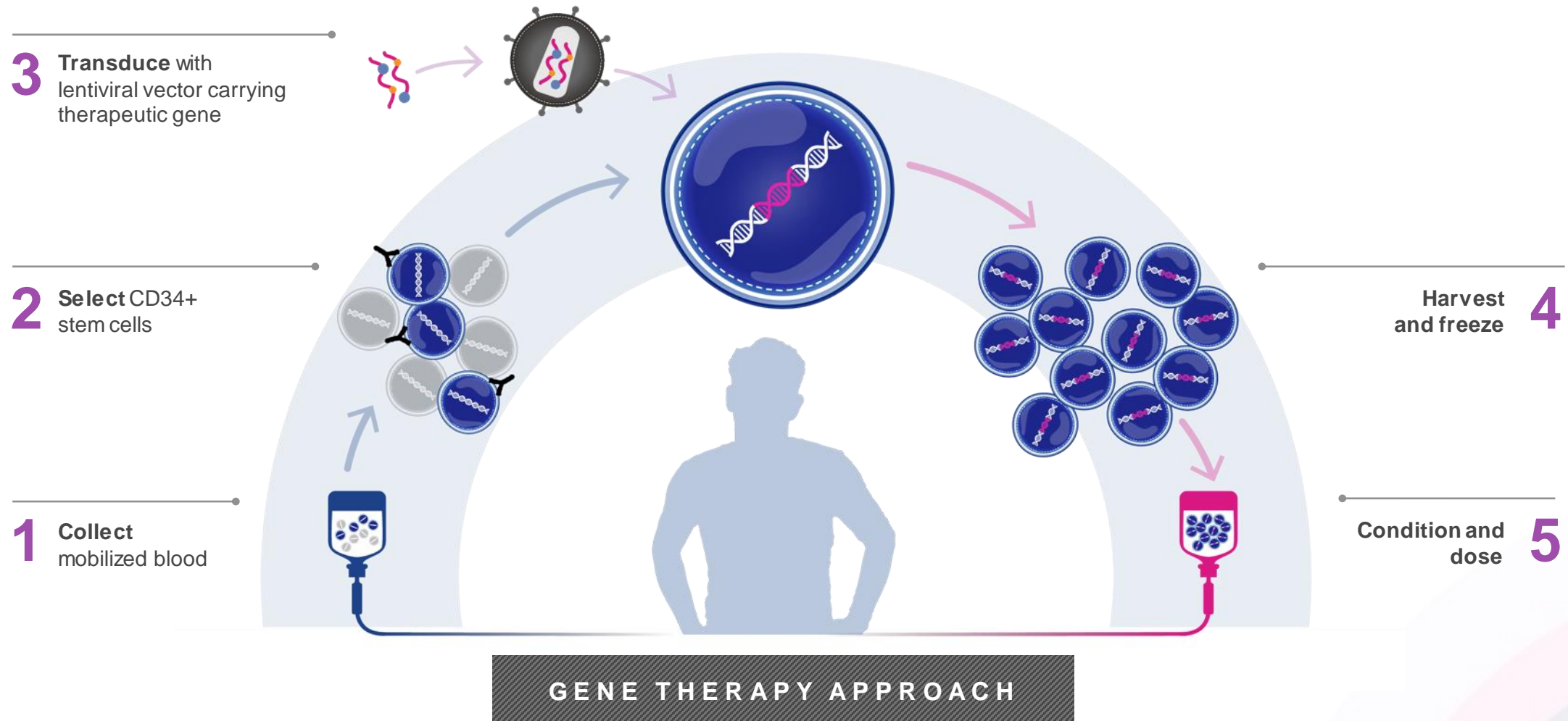
Disease	Est. Cost Per Patient Per Year	Approx. 2019 Net Sales	Selected Companies
<i>Fabry</i>	\$320k	\$1.4B	SANOFI GENZYME   
<i>Gaucher</i>	\$250k-400k	\$1.4B	SANOFI GENZYME   
<i>Pompe</i>	\$500k	\$1.0B	SANOFI GENZYME 
<i>Cystinosis</i>	\$625k-700k*	\$0.2B	  

Sources: Rombach S et al, Orphanet J Rare Dis, 2013; van Dussen L et al, Orphanet J Rare Dis, 2014; WAC pricing from Redbook; 2019 Net Sales from company annual and other reports

\* for Horizon's Procysbi oral therapy (delayed release cysteamine bitartrate)

Note: Shire acquired by Takeda in 2019

# Established *ex vivo* lentiviral approach







# Fabry Disease



AVR-RD-01



# Goals for gene therapy in Fabry disease

## UNMET NEEDS:



### Kidney function

**Unmet needs:** proteinuria, polyuria, kidney failure



### Cardiac function

**Unmet needs:** left ventricular hypertrophy, fibrosis, heart failure



### Neuropathic pain

**Unmet needs:** pain and burning sensations in hands and feet, pain crises



### CNS complications

**Unmet needs:** TIA/stroke, depression, impaired executive function, white matter hyperintensities



### Everyday burden of illness and life expectancy

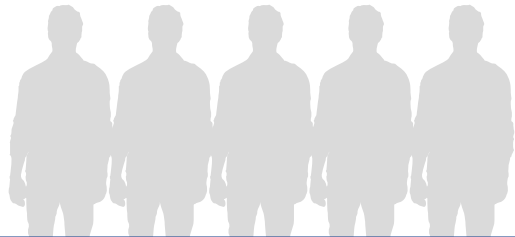
**Unmet needs:** fatigue, inability to sweat, joint pain, abdominal pain, diarrhea, vomiting, cloudy vision, hearing loss, tinnitus, rash, angiokeratomas, biweekly infusions, shortened lifespan





# Two AVR-RD-01 Fabry clinical trials

9 patients dosed across Phases 1 and 2



## PHASE 1

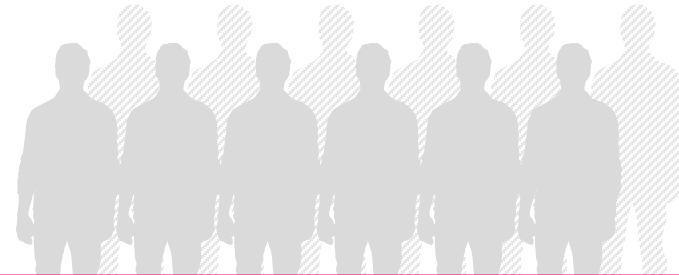
Investigator-Sponsored Trial\*

### Patients

n = 5 (fully enrolled)  
On ERT > 6 months prior to enrollment  
18 - 50 year-old males

### Key Objective

Safety and preliminary efficacy



## PHASE 2

AVRO – FAB-201 Trial

### Patients

n = 8-12 (4 patients dosed to-date)  
Treatment-naïve  
16 - 50 year-old males

### Key Objectives

Safety and efficacy

FAB-201 = AVRO-RD-01-201 Study

\* Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada

ERT: Enzyme Replacement Therapy



# Fabry FAB-201 Patient Characteristics

Treatment-naïve  
Fabry patients

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Age of symptom onset / diagnosis	10 / 19 years	36 / 37 years	13 / 13 years	9 / 9 years
Age dosed with AVR-RD-01	21 years	46 years	40 years	26 years
Mutation	c.1021G>A (p.E341K)	c.644A>G (p.N215S)	c.639+1G>T	c.833dupA
Primary disease signs and symptoms	<ul style="list-style-type: none"><li>• Kidney disease</li><li>• Chronic pain</li><li>• GI symptoms</li><li>• Decreased cold sensation</li></ul>	<ul style="list-style-type: none"><li>• Cardiac disease</li><li>• Peripheral neuropathy</li><li>• Chronic pain</li><li>• Increased tiredness</li><li>• GI symptoms</li><li>• Intermittent tinnitus</li><li>• Mild high frequency hearing loss</li><li>• Raynaud's syndrome</li></ul>	<ul style="list-style-type: none"><li>• Kidney disease</li><li>• GI symptoms</li><li>• Peripheral neuropathy</li><li>• Bilateral deafness</li><li>• Tinnitus</li><li>• Peripheral edema</li><li>• Decreased cold sensation</li></ul>	<ul style="list-style-type: none"><li>• Chronic pain</li><li>• Peripheral neuropathy</li><li>• Neuropathic shuffling gait</li><li>• Lethargy</li><li>• Temperature intolerance</li><li>• Tinnitus</li><li>• Hearing loss</li><li>• GI symptoms</li></ul>
Leukocyte AGA enzyme activity at baseline (nmol/hr/mg protein)	0.10*	2.38**	0.58**	0.46**
Plasma lyso-Gb3 at baseline (nM)	202***	8***	147***	92***
Comment	IgA deposits in kidney biopsy	Cardiac variant, not a classic Fabry male		

\* Mayo Lab, ref range  $\geq 23.1$  nmol/hr/mg protein

\*\* Rupa Lab, ref range 24-56 nmol/hr/mg protein

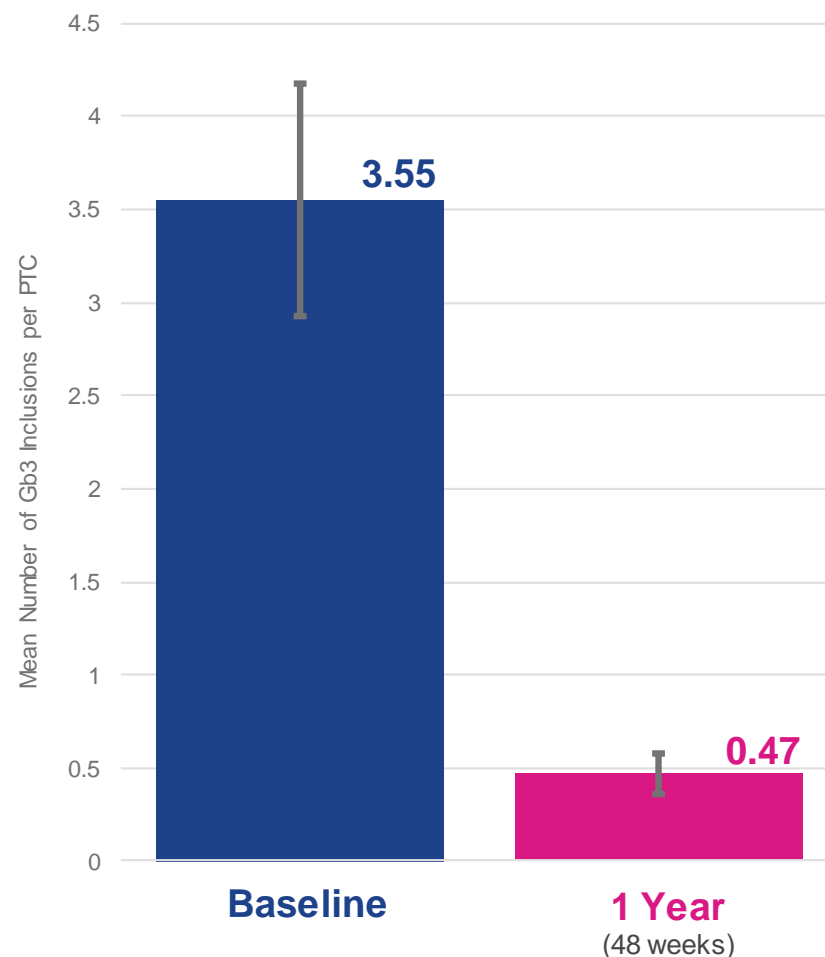
\*\*\* Reference value  $\leq 2.4$  nM

AGA:  $\alpha$ -galactosidase A; Lyso-Gb3: Globotriaosylsphingosine; GI: Gastrointestinal; IgA: Immunoglobulin-A



# Patient 1: 87% substrate reduction in kidney biopsy at 1 year

Average  
number of **Gb3**  
inclusions  
per peritubular  
capillary (PTC)



- Unpaired t-test for difference between  $n=55$  PTCs at baseline vs.  $n=101$  PTCs at 1 year;  $p < 0.0001$
- Error bar represents the standard deviation

Baseline: The last available, non-missing observation prior to AVR-RD-01 infusion

Note: With respect to Fabry disease, Gb3 inclusions per PTC is interchangeable with GL-3 inclusions per KIC

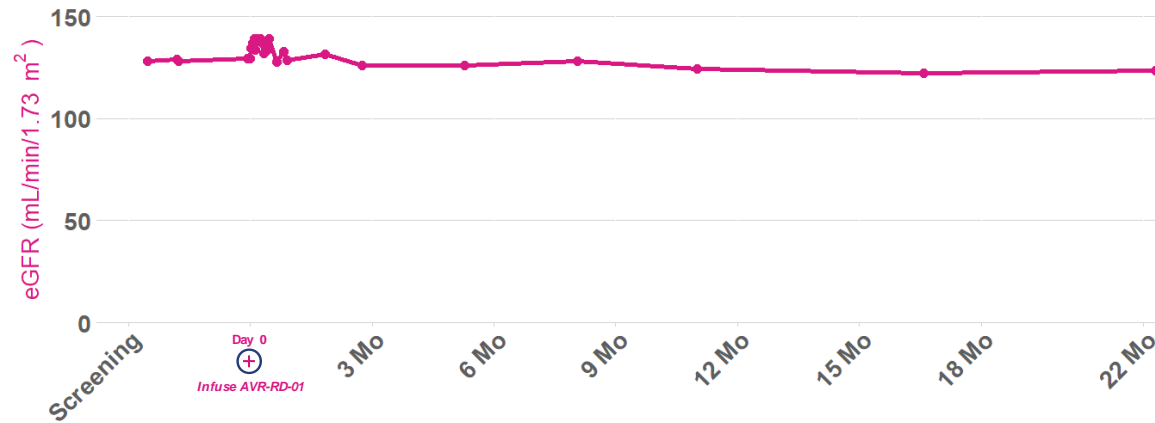
FAB-201-1: First patient in FAB-201 clinical trial

PTC: Peritubular Capillary; Gb3: Globotriaosylceramide; GL-3: Globotriaosylceramide; KIC: Kidney Interstitial Capillary



# Patient 1: Sustained response across multiple measures up to 22 months

Estimated Glomerular Filtration Rate

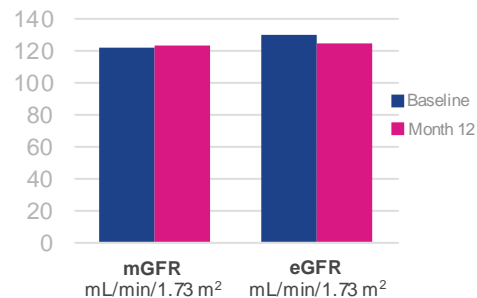


eGFR: Estimated Glomerular Filtration Rate



## KIDNEY FUNCTION

remains within normal range at 12 mos.



Normal Range mGFR/eGFR: Average 116\* mL/min/1.73 m<sup>2</sup> Male (20–39 years)

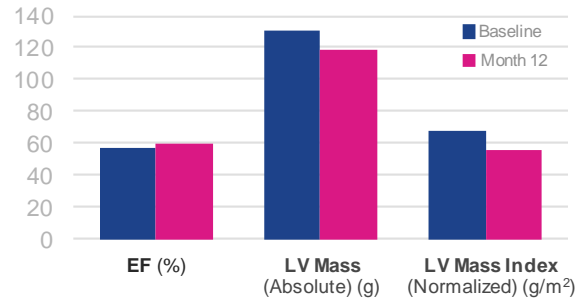
\*Source: <https://www.kidney.org/atoz/content/gfr>

mGFR: Measured Glomerular Filtration Rate; eGFR: Estimated Glomerular Filtration Rate



## CARDIAC FUNCTION

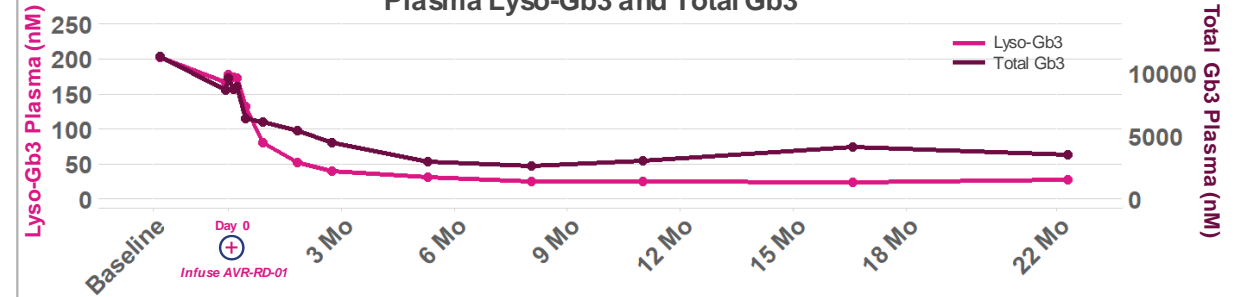
remains within normal range at 12 mos.



Reference Range Mean Values ± SD: EF (%) 64.3 ± 4.2%; LV Mass (Absolute) (g) 138.9 ± 24.5 g Male (20–39 years); LV Mass Index (Normalized) (g/m<sup>2</sup>) 67.8 ± 10.7 g/m<sup>2</sup>

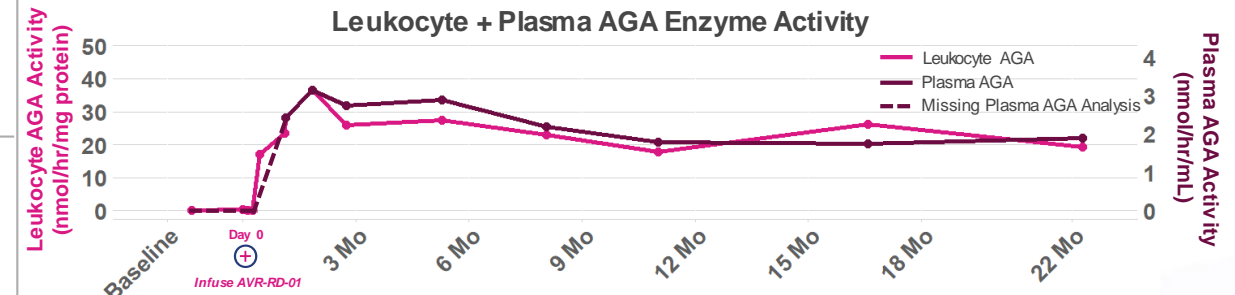
Source: Alifakh K et al, J Magn Reson Imaging, 2003  
EF: Ejection Fraction; LV: Left Ventricular

Plasma Lyso-Gb3 and Total Gb3



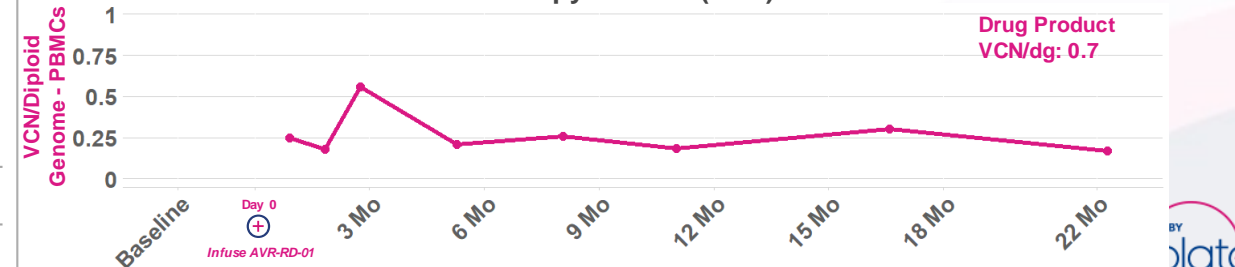
Lyso-Gb3 Plasma Reference Value: 2.4 nM; Total Gb3 Plasma Reference Value: 4961 nM; 6012 nM before August 2018 (until Day 28 for Patient 1)  
Lyso-Gb3: Globotriaosylsphingosine; Gb3: Globotriaosylceramide

Leukocyte + Plasma AGA Enzyme Activity



Lab A: Mayo Clinic Laboratories; Lab B: Rupa Laboratory; Lab A Leukocyte AGA Activity Reference Range: >23.1 nmol/hr/mg protein; Lab B Reference Range: 24–56 nmol/hr/mg protein; Plasma AGA Activity Reference Range: 5.1–9.2 nmol/hr/mL; AGA: α-galactosidase A

Vector Copy Number (VCN)



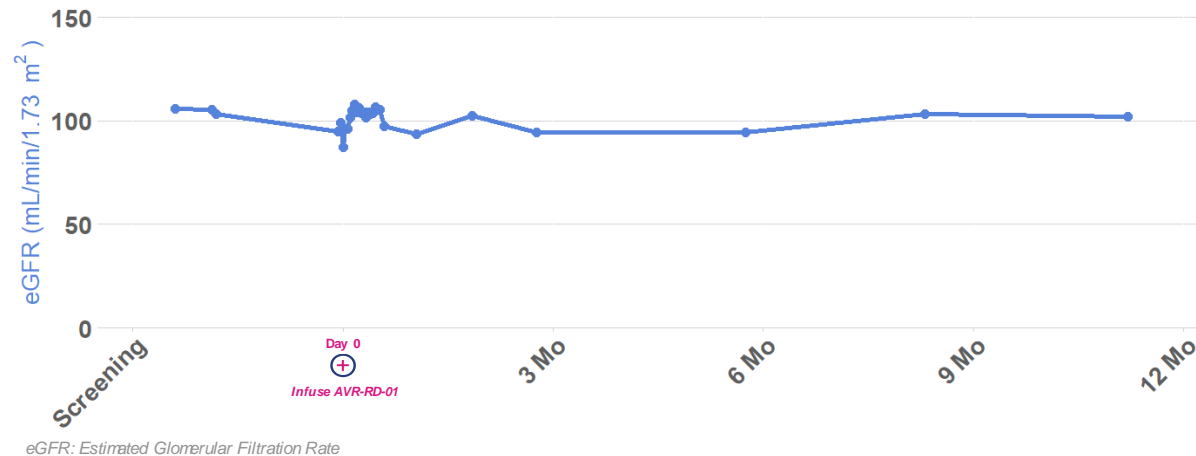
VCN: Vector Copy Number; PBMCs: Peripheral Blood Mononuclear Cells



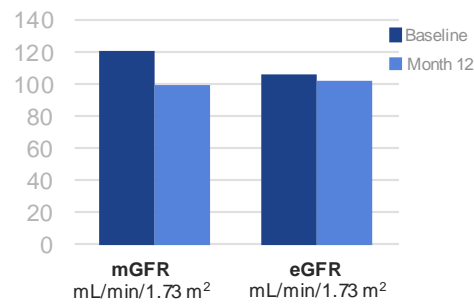


# Patient 2: Sustained response across multiple measures up to 18 months

Estimated Glomerular Filtration Rate



## KIDNEY FUNCTION remains within normal range

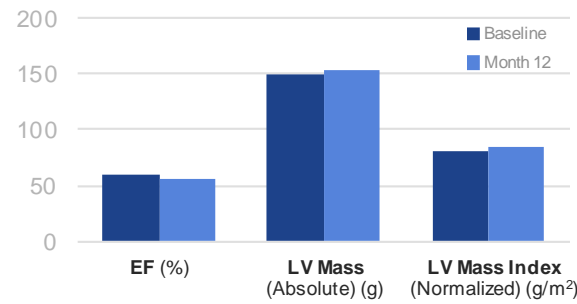


Source: <https://www.kidney.org/atoz/content/gfr>

mGFR: Measured Glomerular Filtration Rate; eGFR: Estimated Glomerular Filtration Rate

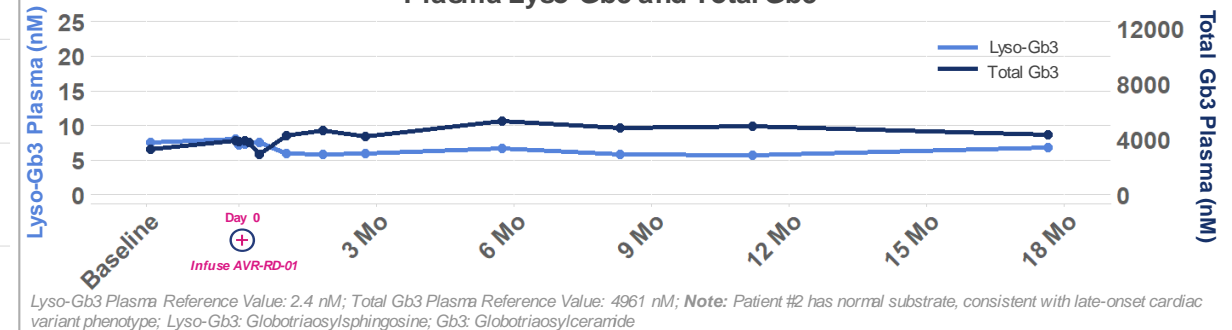
\*1-year/ "Month 12" = 48 weeks per protocol

## CARDIAC FUNCTION remains within normal range

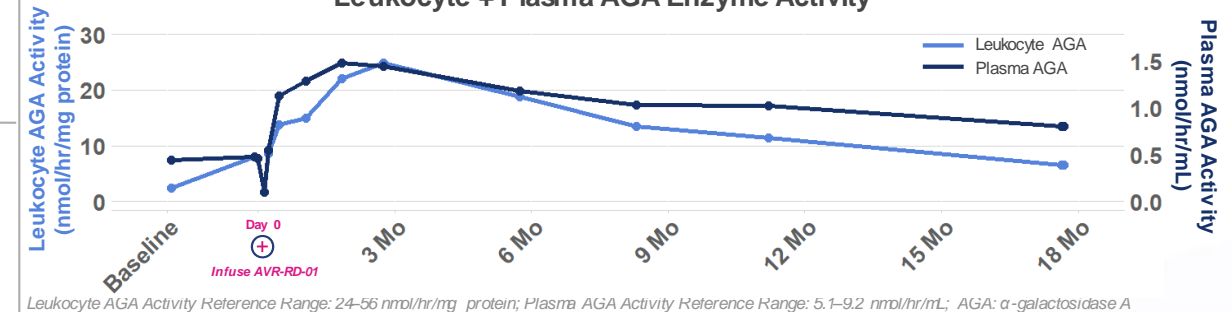


Source: Maceira AM et al, J of Cardiovascular Magnetic Resonance, 2006  
EF: Ejection Fraction; LV: Left Ventricular

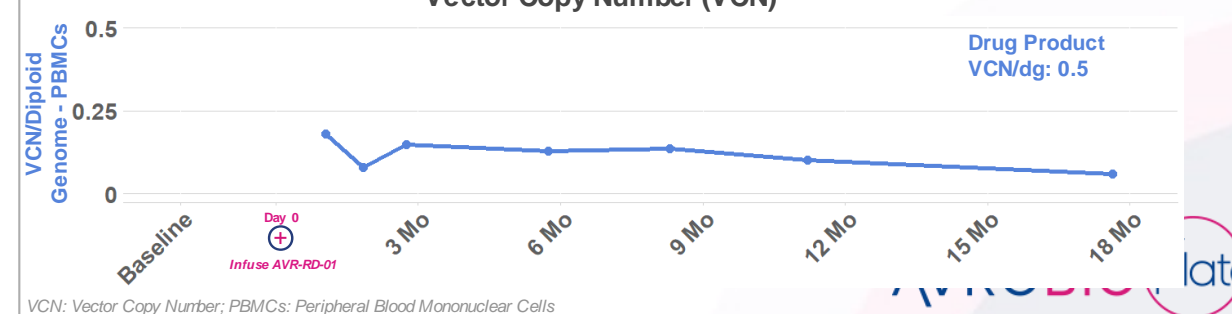
Plasma Lyso-Gb3 and Total Gb3



Leukocyte + Plasma AGA Enzyme Activity

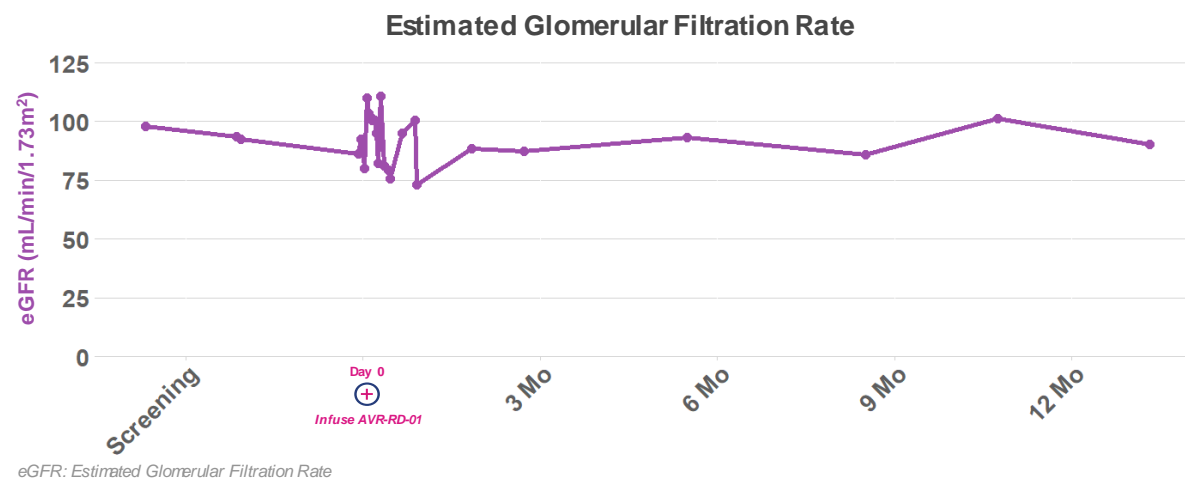


Vector Copy Number (VCN)

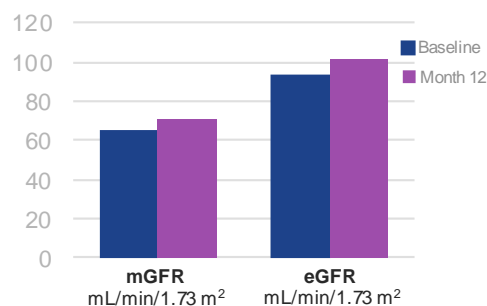




# Patient 3: Sustained response across multiple measures up to 1 year\*



**KIDNEY FUNCTION**  
remains within normal range

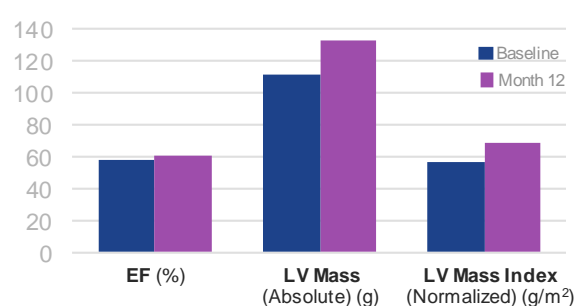


Normal Range mGFR/eGFR Average 99 mL/min/1.73 m<sup>2</sup> Male (40-49 years)

Source: <https://www.kidney.org/atoz/content/gfr>

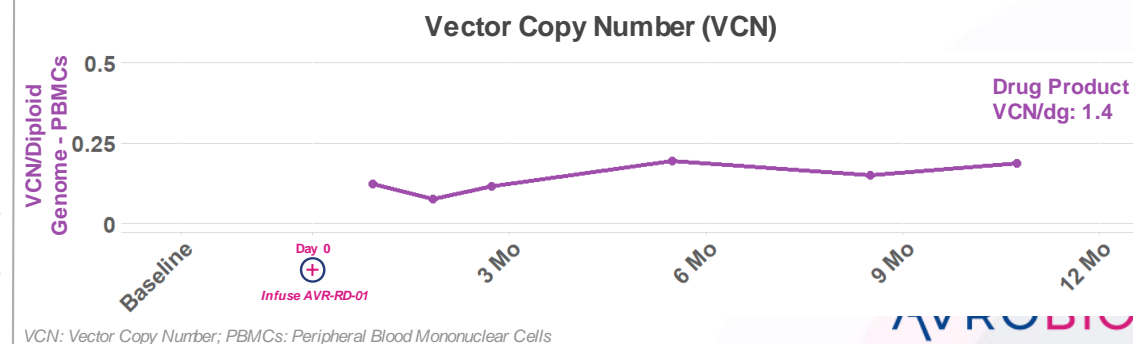
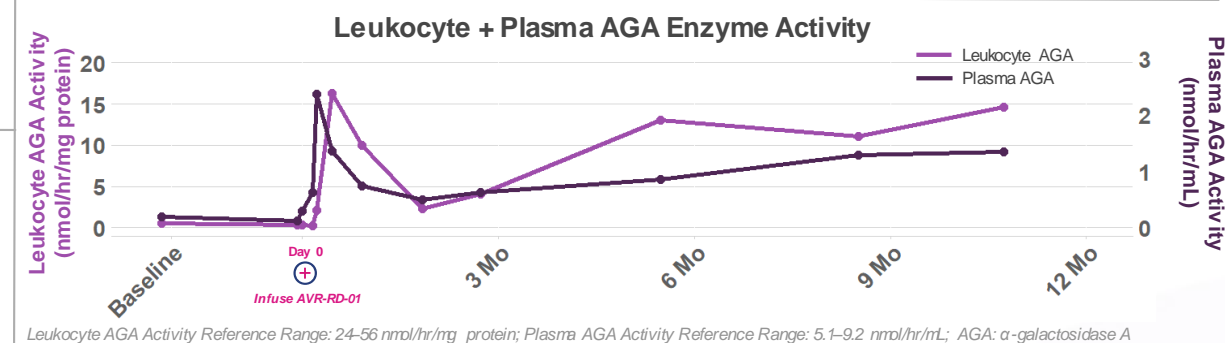
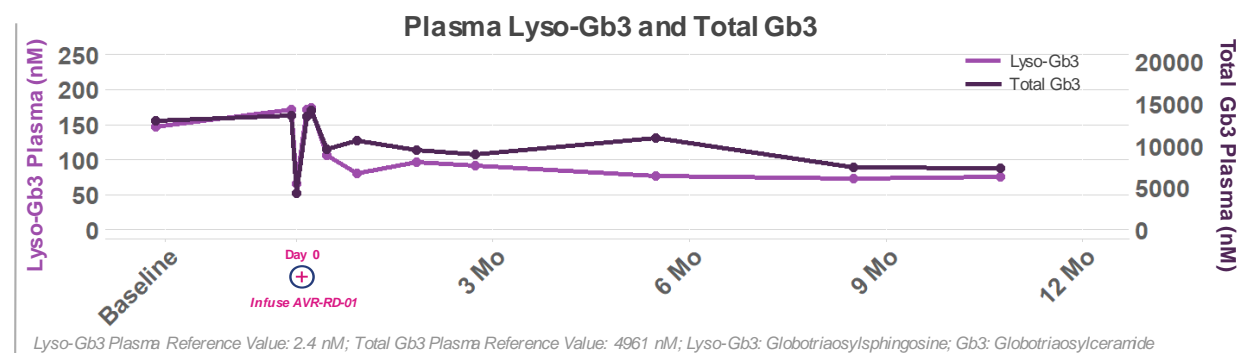
mGFR: Measured Glomerular Filtration Rate; eGFR: Estimated Glomerular Filtration Rate

**CARDIAC FUNCTION**  
remains within normal range



Reference Range Mean Values Male (40-49 years) 58-75% 108 - 185 g 58-91 g/m<sup>2</sup>

Source: Maceira AM et al, J of Cardiovascular Magnetic Resonance, 2006  
EF: Ejection Fraction; LV: Left Ventricular



\*1-year/ "Month 12" = 48 weeks per protocol



# Patients 1-4: Leukocyte and plasma enzyme activity sustained up to 22 months

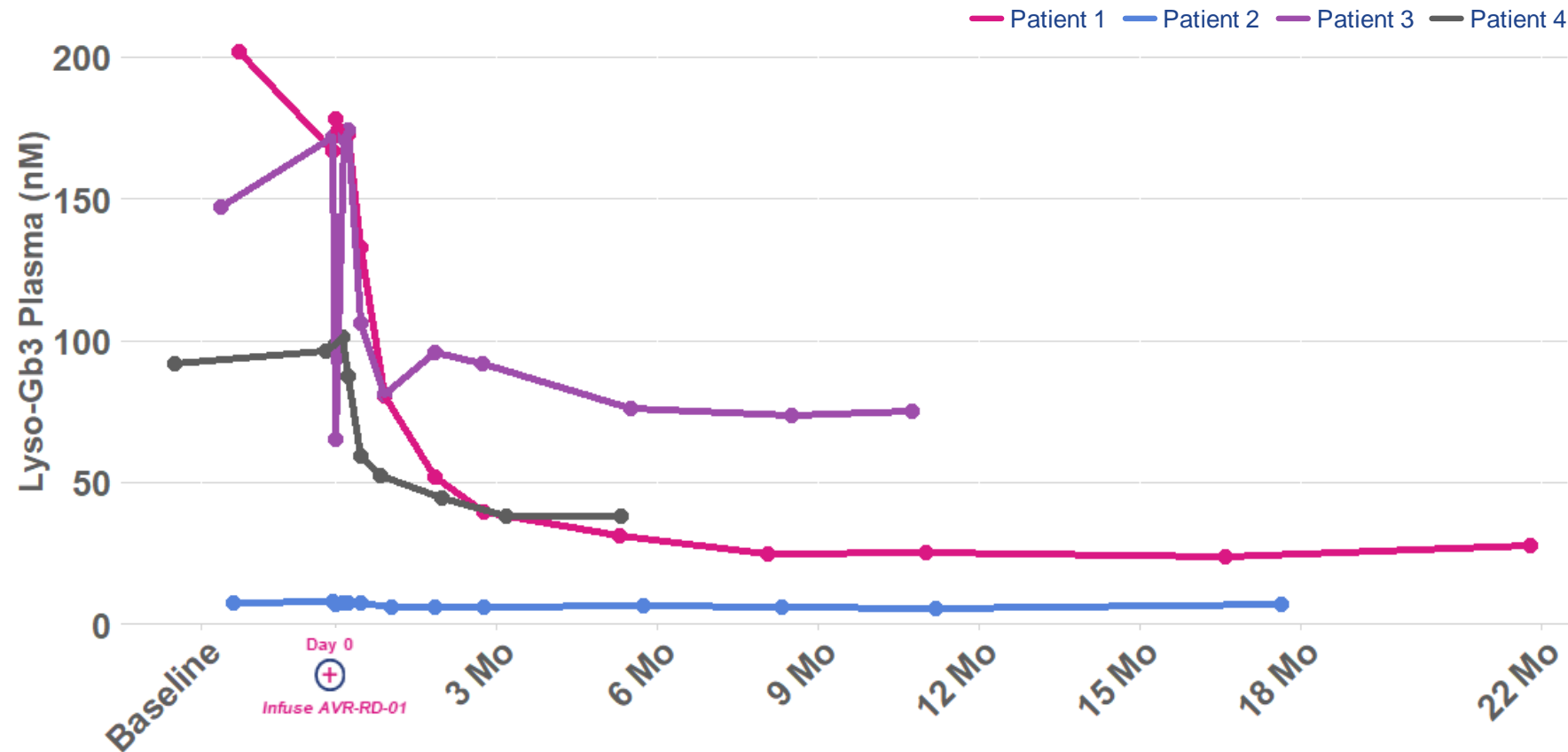
Patient #4 dosed using plato<sup>®</sup>



Leukocyte AGA Activity Reference Range: 24–56 nmol/hr/mg protein; Plasma AGA Activity Reference Range: 5.1–9.2 nmol/hr/mL; AGA:  $\alpha$ -galactosidase A



# Patients 1-4: Plasma lyso-Gb3 reduction sustained up to 22 months



## Reduction from Baseline to Last Observation

Patient 1 86%

Patient 2 NA

Patient 3 49%

Patient 4 59%

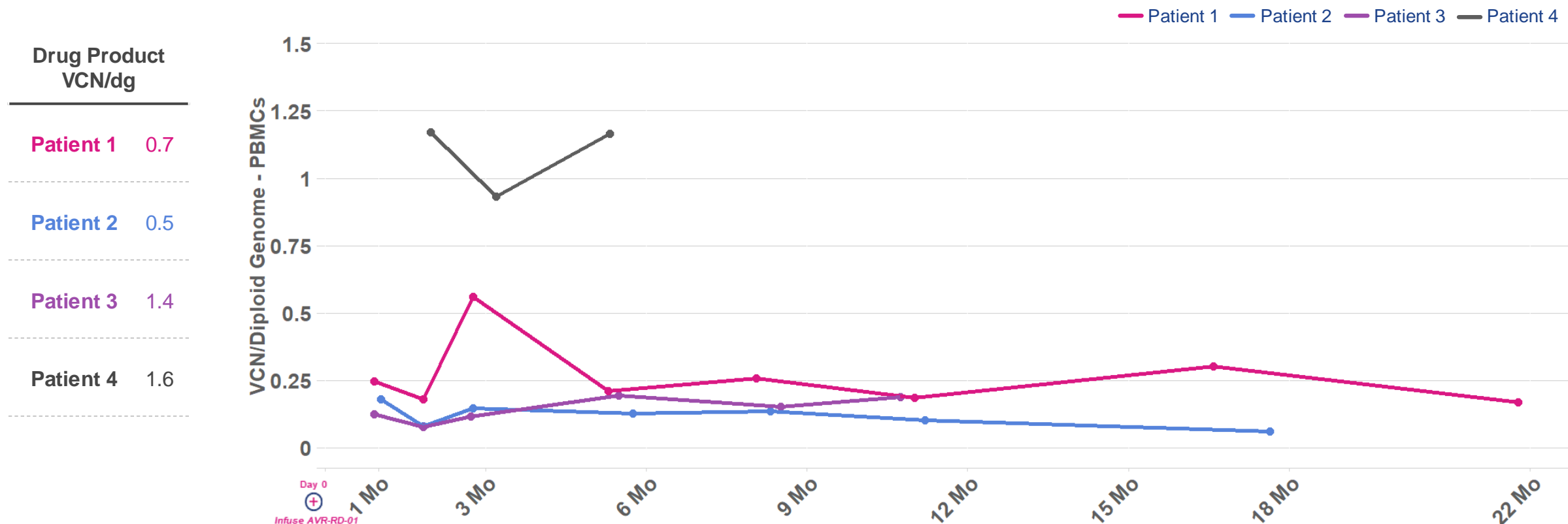
- Lyso-Gb3 Plasma Reference Value: 2.4 nM; Lyso-Gb3: Globotriaosylsphingosine
- Note: Patient #2 has normal substrate, consistent with late-onset cardiac variant phenotype





# Patients 1-4: VCN stable up to 22 months

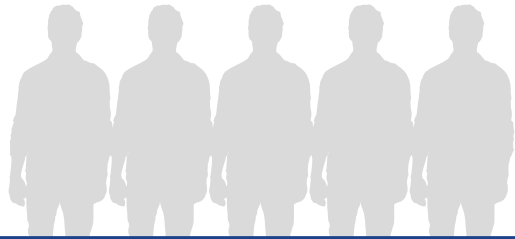
Patient #4 dosed using plato<sup>®</sup>





# Two AVR-RD-01 Fabry clinical trials

9 patients dosed across Phases 1 and 2



## PHASE 1

Investigator-Sponsored Trial\*

### Patients

n = 5 (fully enrolled)  
On ERT > 6 months prior to enrollment  
18 - 50 year-old males

### Key Objectives

Safety and preliminary efficacy



## PHASE 2

AVRO – FAB-201 Trial

### Patients

n = 8-12 (4 patients dosed to-date}  
Treatment-naïve  
16 - 50 year-old males



### Key Objectives

Safety and efficacy

FAB-201 = AVRO-RD-01-201 Study

\* Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada

ERT: Enzyme Replacement Therapy



# Fabry Phase 1 Patient Characteristics

## ERT-Treated Fabry Patients

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Age of symptom onset / diagnosis	18 / 37 years	9 / 29 years	10 / 0 years	7 / 4 years	10 / 14 years
Years on ERT	11 years	6 years	4 years	11 years	2 years
Age dosed with AVR-RD-01	48 years	39 years	40 years	37 years	30 years
Mutation	c.962A>G (p.Q321R)	c.1033T>C (p.S345P)	c.427G>C (p.A143P)	c.427G>C (p.A143P)	(p.Y134S)
Primary disease signs and symptoms	<ul style="list-style-type: none"><li>• Kidney disease</li><li>• Cardiac disease</li><li>• GI pain</li><li>• GI diarrhea</li><li>• Angiokeratoma</li><li>• Insomnia</li></ul>	<ul style="list-style-type: none"><li>• Kidney disease</li><li>• Cardiomyopathy</li><li>• Hypohidrosis</li><li>• Corneal verticillata</li><li>• Peripheral neuropathy</li><li>• GI symptoms</li><li>• Angiokeratoma</li><li>• Lymphedema</li><li>• Acroparesthesia</li></ul>	<ul style="list-style-type: none"><li>• Cardiac Disease</li><li>• Tinnitus</li><li>• Headaches</li><li>• Dizziness</li><li>• Acroparesthesia</li></ul>	<ul style="list-style-type: none"><li>• Cardiac Disease</li><li>• Hypohidrosis</li><li>• Tinnitus</li><li>• Corneal verticillata</li><li>• Angiokeratoma</li><li>• GI symptoms</li></ul>	<ul style="list-style-type: none"><li>• Kidney disease</li><li>• Hypertension</li><li>• Hypohidrosis</li><li>• Tinnitus</li><li>• Migraines</li><li>• Impaired hearing</li><li>• Angiokeratoma</li><li>• Sleep apnea</li><li>• Asthma</li><li>• Depression</li></ul>
Leukocyte AGA activity at baseline (nmol/hr/mg protein)	2.1*	1.1*	0.6*	2.2*	1.0*
Plasma lyso-Gb3 at baseline (nM)	25**	26**	59**	29**	16**
ERT discontinuation status	18 months after gene therapy dose		Did not resume ERT after gene therapy dose	6 months after gene therapy dose	

\* RupaLab, ref range 24-56 nmol/hr/mg protein

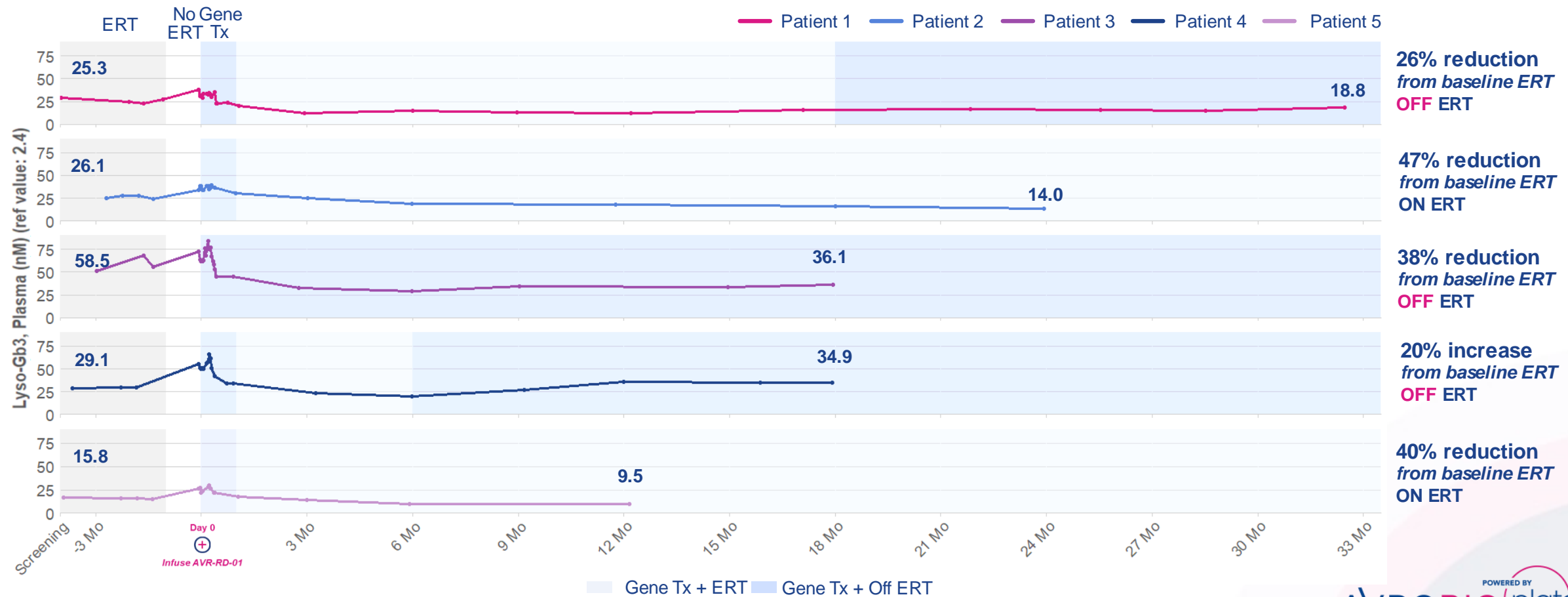
\*\* Reference value  $\leq 2.4$  nM protein

Note: AGA:  $\alpha$ -galactosidase A; ERT: Enzyme Replacement Therapy; GI: Gastrointestinal; Lyso-Gb3: Globotriaosylsphingosine



# Patients 1-5: Plasma lyso-Gb3 reduction sustained up to 32 months

All patients who have discontinued ERT remain off ERT\*



\* As of July 21, 2020

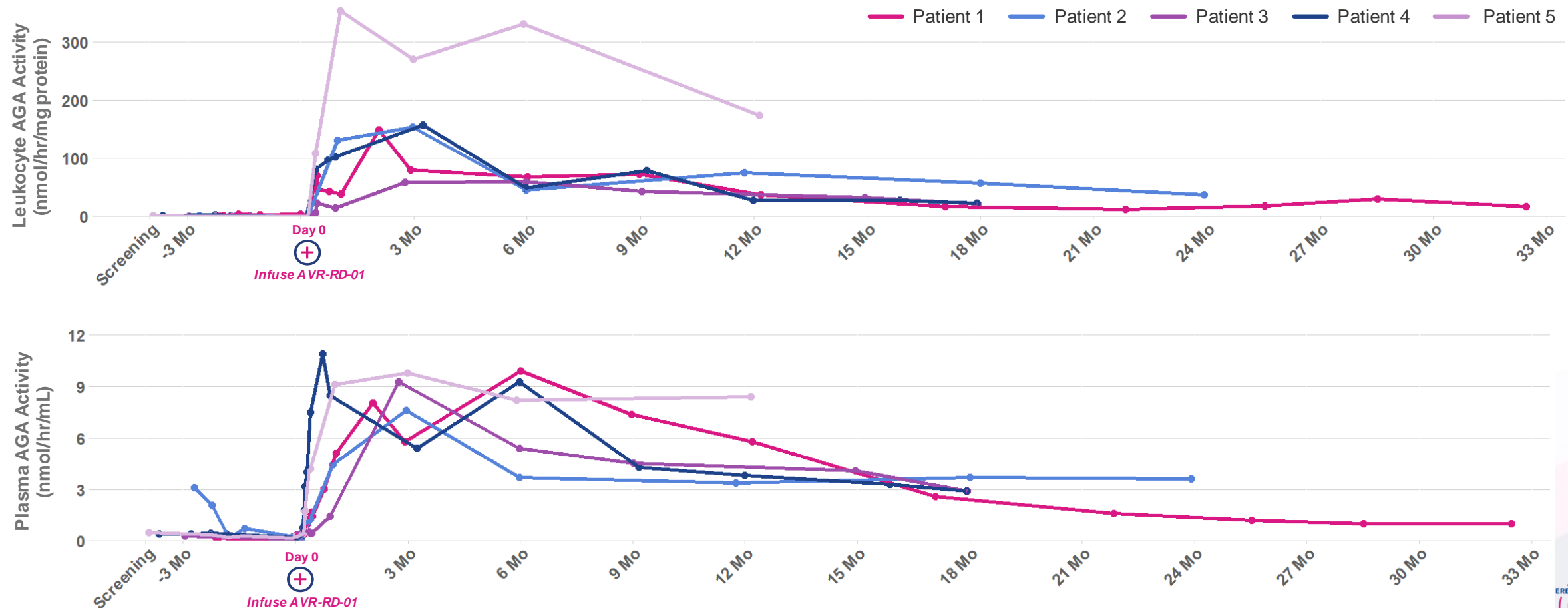
Lyso-Gb3 Plasma Reference Value: 2.4 nM; Lyso-Gb3: Globotriaosylsphingosine; ERT: Enzyme Replacement Therapy; Tx: Therapy





# Leukocyte and plasma enzyme activity sustained up to 32 months with consistent trend across all other patients

All 5 patients now out 1 year or more





# Patients 1-5: VCN stable at 32 months with consistent trend across all other patients

All 5 patients now out 1 year or more

Drug Product  
VCN/dg

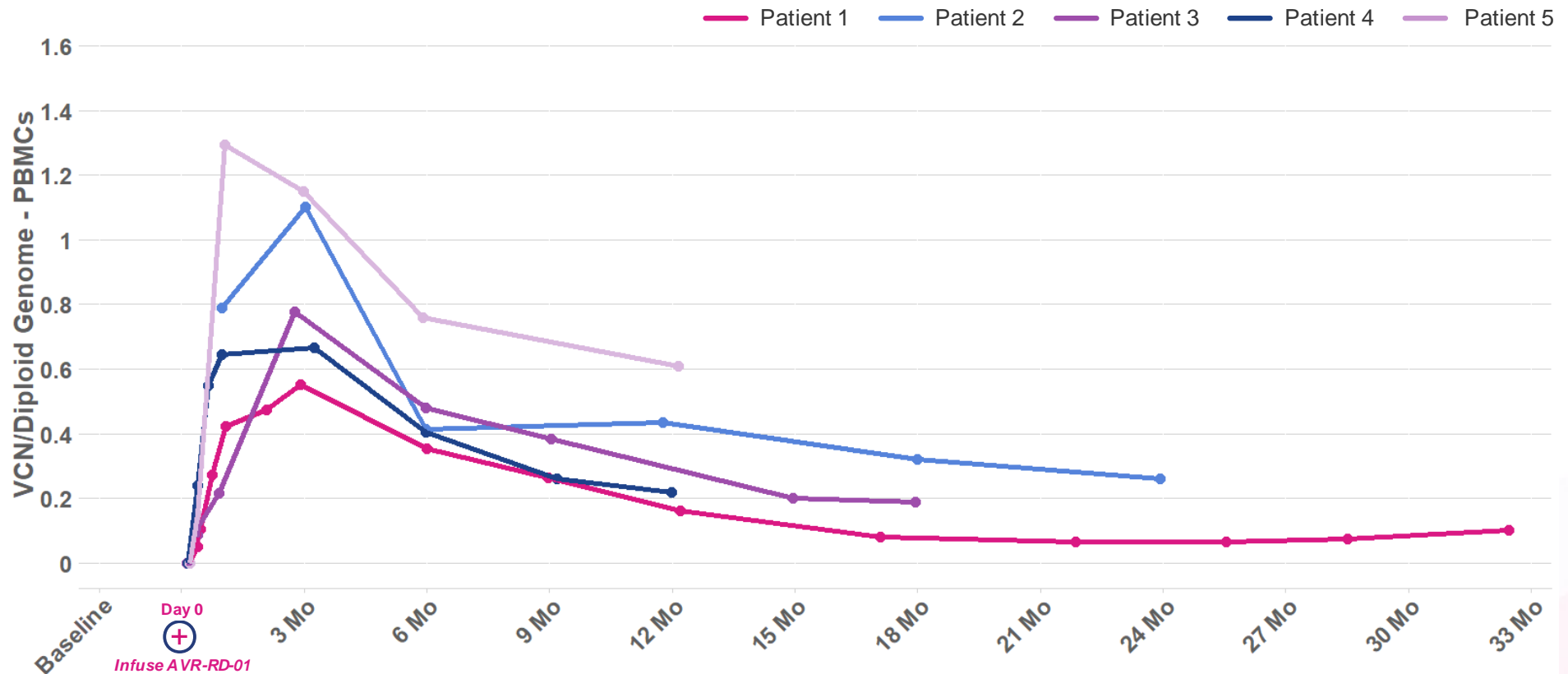
Patient 1 0.7

Patient 2 1.4

Patient 3 0.8

Patient 4 1.4

Patient 5 1.2



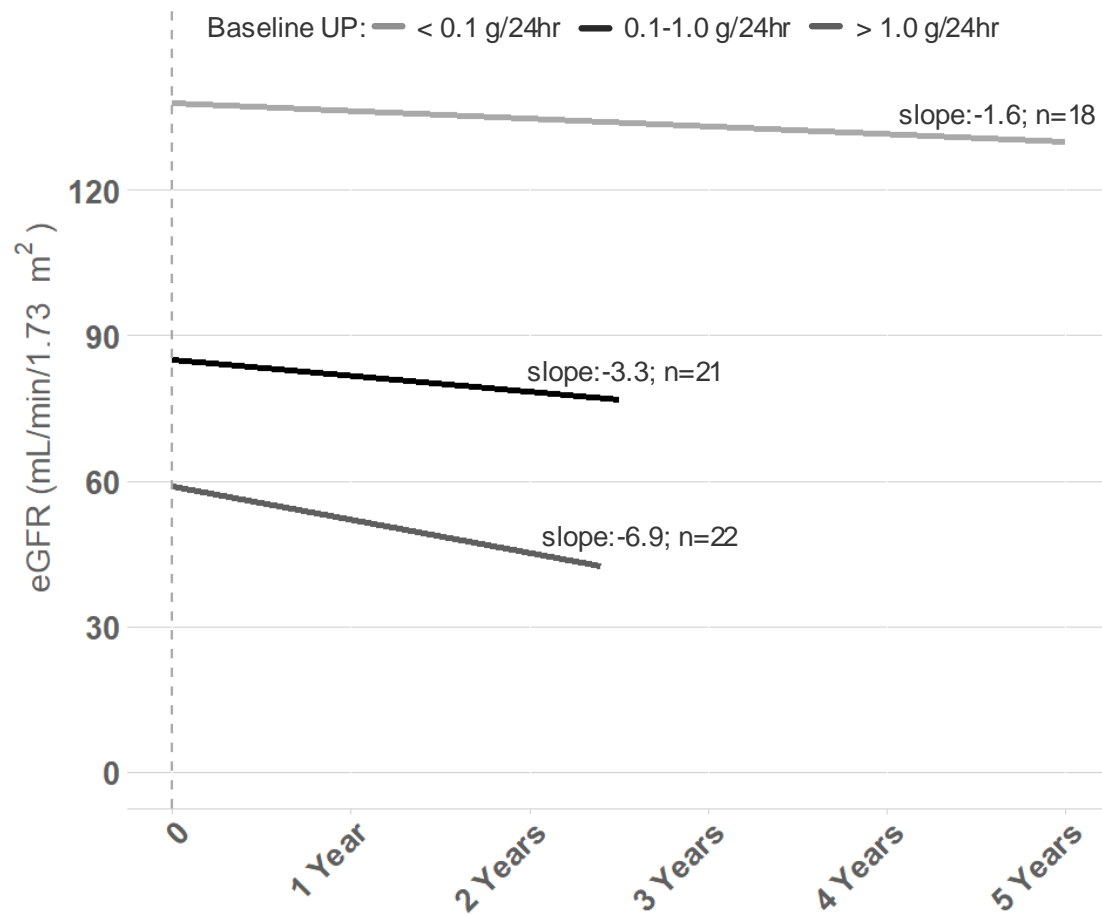
Note: 0.1 VCN is indicative of approx. 5-10% of all nucleated cells having an average of 1-2 copies of the transgene  
VCN: Vector Copy Number



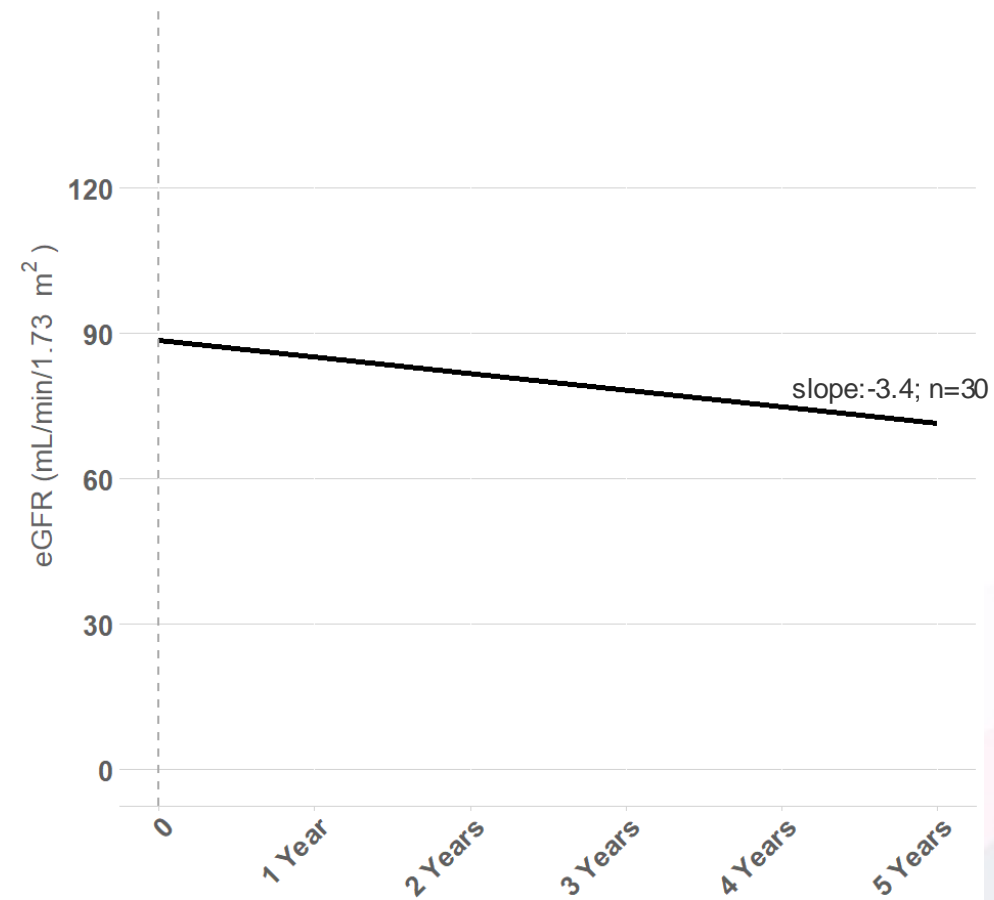
# eGFR declines in natural history and on ERT

## Classic Fabry male literature eGFR data

**Natural history annualized eGFR slopes of treatment naïve patients\***



**Annualized eGFR slope of ERT-treated patients\*\***

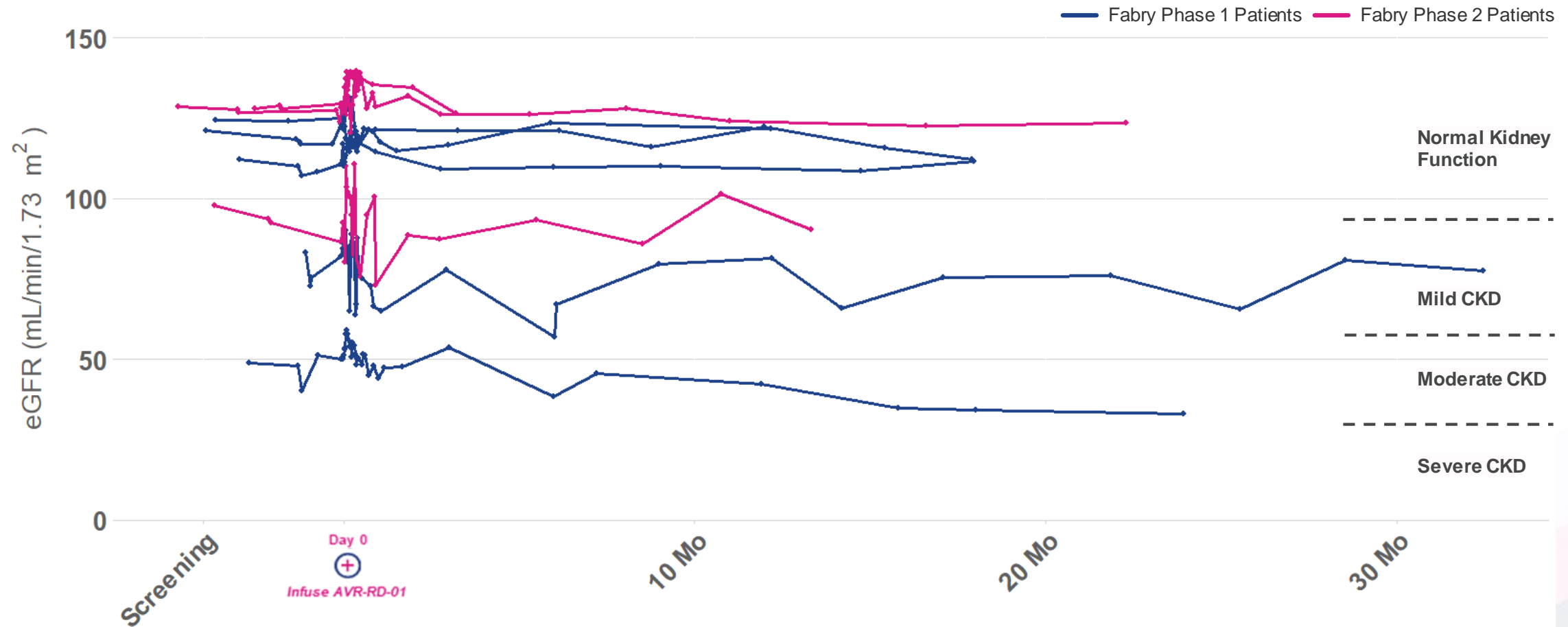


eGFR: Estimated Glomerular Filtration Rate; UP: Urinary Protein

Sources: \*Schiffmann R et al, Nephrol Dial Transplant, 2009 (Table 4); \*\*Rombach SM et al, Orphanet J Rare Dis 2013 (Table 2)



# Kidney function stable across Phase 1 and Phase 2 trials, up to 32 months\*



\* Eight of nine patients stable; other patient entered trial with more advanced kidney disease and a baseline eGFR level <50. As expected, this patient has not stabilized, and the patient remains on ERT.  
eGFR: Estimated Glomerular Filtration Rate. Patient #2 from the Phase 2 trial, who is a cardiac variant and as expected has stable eGFR, has been excluded above.





Phase 1 Fabry (5 patients) and  
FAB-201 (4 patients)

**No unexpected  
safety events  
or trends  
identified**



**No SAEs related to AVR-RD-01 drug product**



**AEs and SAEs reported**

**Phase 1 AEs (n = 100):**

- Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions

**FAB 201 AEs (n = 91):**

- Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
  - Grade 1 or 2 (n = 74)
  - Grade 3 or 4 (n = 17)

**Phase 1 SAEs (n = 2):**

- Febrile neutropenia (grade 3)
- Thrombophlebitis (grade 2)

**FAB 201 SAEs: (n = 6)**

**Pre-treatment and prior to conditioning**

- Seizure (grade 2)

**Post-treatment**

- Dehydration, nausea, vomiting (grade 3)
- Febrile neutropenia (2 patients, grade 3 & 4)
- Culture negative fevers (grade 2)
- Mucositis (grade 2)



**Anti-AGA antibodies**

- Anti-AGA antibody titers observed in 4 patients in the Phase 1 trial and 2 patients in FAB-201. We believe none of these are of clinical significance.

*Note: Safety data cut off April 23, 2020*

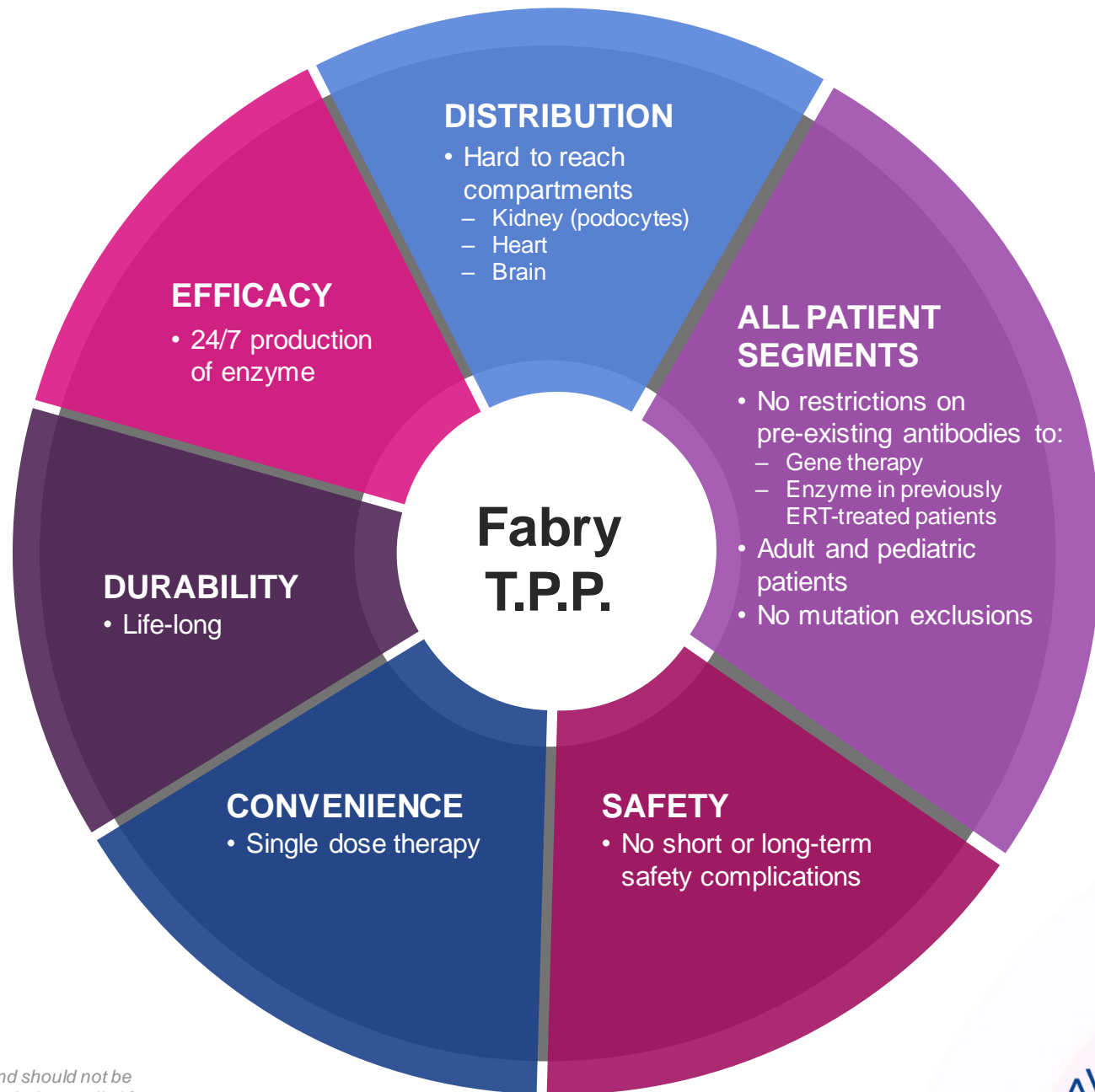
*AE: Adverse Event; SAE: Serious Adverse Event*

*NOTE: AVR-RD-01 is an investigational gene therapy*



# Fabry disease target product profile (T.P.P.)

Potential attributes intended to support first-line use



ERT: Enzyme Replacement Therapy

Note: Potential attributes represent desired target product profile, and are not intended, and should not be interpreted, to be attributes of AVROBIO's current investigational gene therapies, which are being studied for safety and efficacy and have not been approved by the FDA or any other regulatory body.

# Building commercial capabilities

44+ product launches, including 1 gene therapy



**Holly May**

*Chief Commercial Officer*



- Led commercial teams for LSDs at SanofiGenzyme
- Head of Commercial at SOBI, a rare disease company



**Jose Gomez**

*SVP, Global Market Access & Value*



- Led global strategic marketing and global market access functions at AveXis
- Led market access, global strategic pricing and reimbursement functions for LSDs at Shire



**Sean Ring**

*VP, Head of Commercial Operations*



- Extensive orphan drug commercial strategy and launch expertise
- Built out market development and commercial ops at Editas, Zafgen, Cubist, Shire, Biogen



**Ramesh Arjunji**

*VP, Global Health Economics and Outcomes Research / Value Demonstration*



- Led value demonstration for insurers globally at AveXis
- Significant access and reimbursement responsibilities at leading global biotech companies





# Cystinosis



AVR-RD-04



# Goals for gene therapy in cystinosis

## UNMET NEEDS:



### Kidney function

**Unmet needs:** renal Fanconi syndrome, proteinuria, chronic kidney disease, kidney failure



### Vision

**Unmet needs:** corneal cystine accumulation, photophobia, involuntary eyelid closure



### Endocrine disorders

**Unmet needs:** softening/weakening of bones, bone pain, rickets, long bone deformations, hypophosphatemia, delayed growth, hypothyroidism, pancreatic insulin insufficiency, diabetes, infertility



### CNS complications

**Unmet needs:** myopathy, hypotonia, tremors, difficulty swallowing, neurodevelopmental issues (speech and walking delay and cognitive impairment)



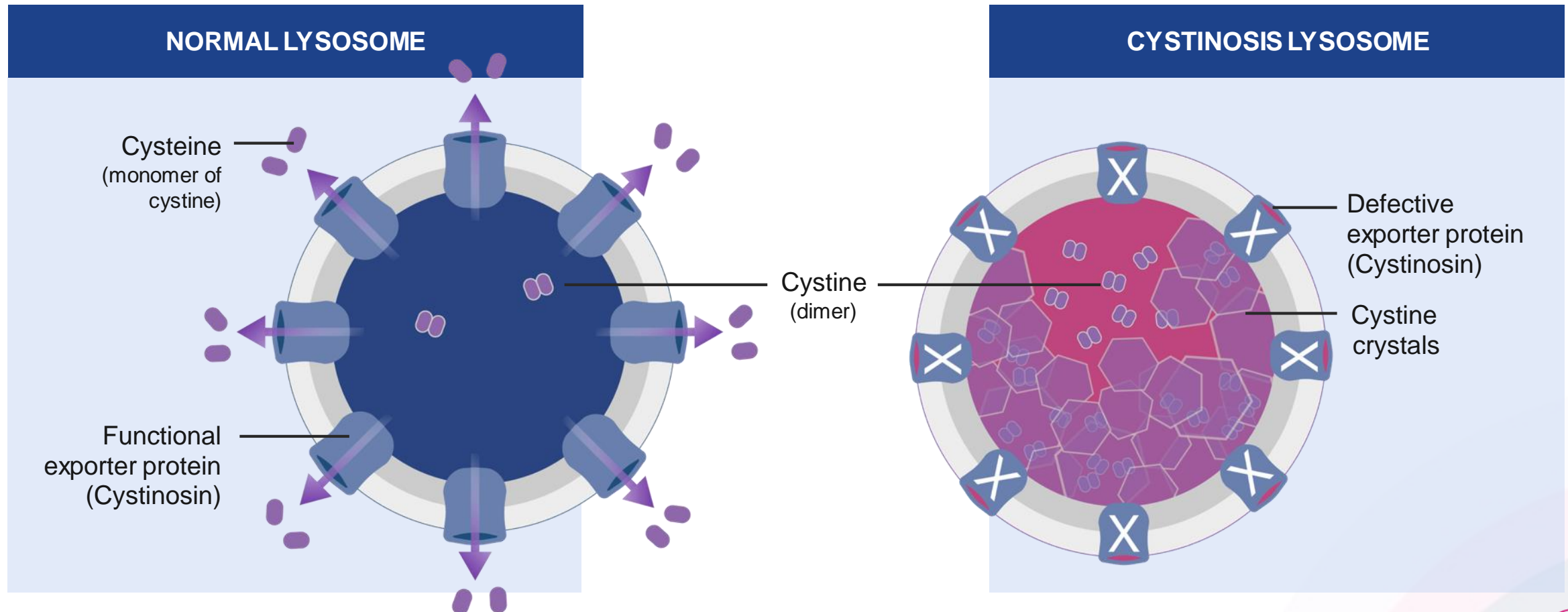
### Everyday burden of illness and life expectancy

**Unmet needs:** medications multiple times per day that cause GI discomfort and sulfur body and breath smell, shortened lifespan



# Cystinosis caused by defective gene that encodes cystinosin, an exporter protein

Cystine crystals build up in lysosomes causing tissue and organ damage







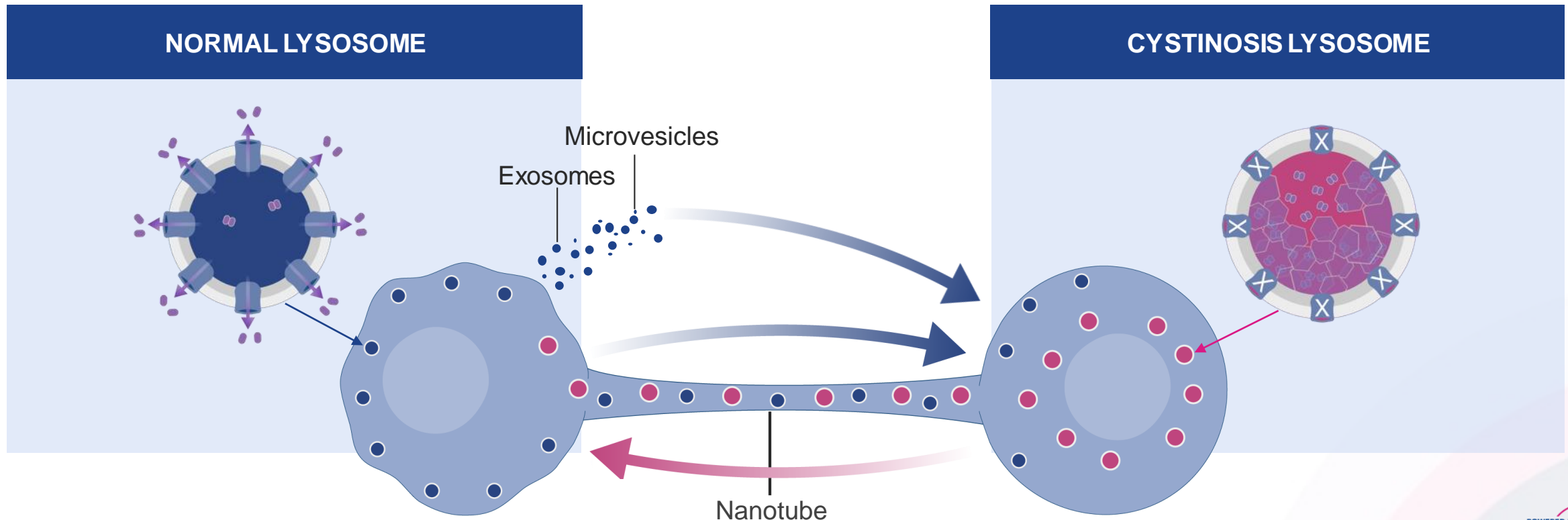
# Drug product-derived macrophages restore normal cystine recycling

## Mechanisms of action

Macrophages with CTNS transgene restore cystine recycling to CTNS<sup>-ve</sup> cells via:

1. Tunneling nanotubes – transfer of corrected lysosomes, cystinosin, CTNS mRNA
2. Exosomes / Microvesicles – transfer of cystinosin, CTNS mRNA

Net result: Corrected lysosomes in cells throughout the body



# Allogeneic transplant demonstrated stabilized renal function, corrected polyuria and improved photophobia



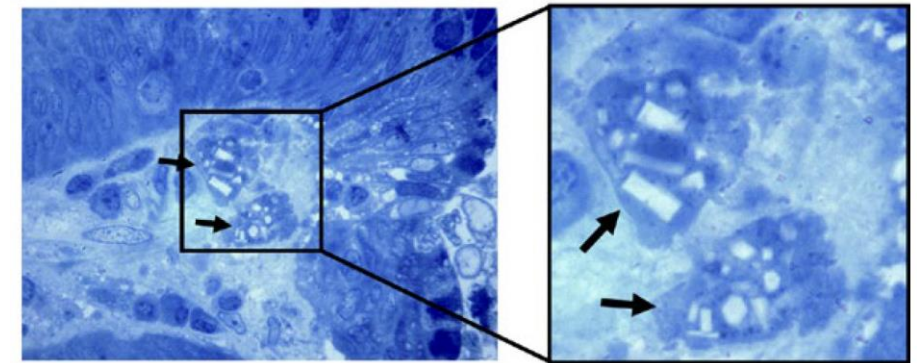
## Allogenic HSC Transplant

University Hospital Leuven

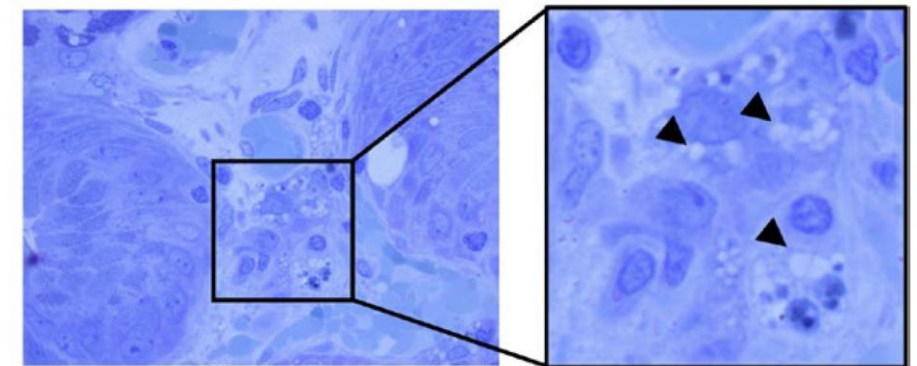
- 16 year old male
- Diagnosed at 2.7 years old, started on cysteamine
- Age 15 years – cysteamine toxicity
- Age 16 years – fully matched HLA transplant
- Acute GvHD
- **First few months**
  - Kidney function stabilized
  - Polyuria resolved
- **6 months**
  - Photophobia score reduced from 5 (unable to open eyes even inside dark room) to 0 (no photophobia)

**Cystine crystal reduction (31%) in macrophages in gastric mucosa at 30 months post transplant**

**BEFORE  
TRANSPLANT**



**30 MONTHS  
POST  
TRANSPLANT**



Arrows/arrowheads point to tissue macrophages



# Investigator-sponsored\* study of AVR-RD-04 in cystinosis patients

Two patients dosed



## PHASE 1/2

Investigator-Sponsored Trial\*

### Patients

Up to 6 patients

Adults and adolescents

Cohorts 1-2  $\geq 18$  years; Cohort 3  $\geq 14$  years

Male and Female

On oral and ophthalmic cysteamine



### Key Objectives

Safety and efficacy



## Cystinosis AVR-RD-04 Phase 1/2 Patient Characteristics

	PATIENT 1
Age of symptom onset / diagnosis	0 year / 8 months
Age dosed with AVR-RD-04	20 years
Gender	Male
Mutation	Allele 1: 57-kb deletion Allele 2: c.696dupC, p.Val233Argfs*63
Primary disease signs and SoC treatment related symptoms, including	<ul style="list-style-type: none"><li>Fanconi syndrome</li><li>Polyuria</li><li>Corneal abnormalities</li><li>Mild photophobia</li><li>Vomiting</li></ul>
Granulocyte Cystine levels at baseline (nmol half cystine per mg protein)*	7.8
Comments	<p>NO kidney transplant; stage 3 (moderate CKD) renal failure</p> <ul style="list-style-type: none"><li>Cysteamine 1125 mg p.o. every 12 h/day since 2009; discontinued prior to AVR-RD-04 infusion</li><li>Cysteamine eyedrops 4-5x/day</li><li>Concomitant medications not listed</li></ul>



Phase 1/2 Cystinosis

**No unexpected  
safety events  
or trends  
identified**



**No AEs or SAEs related to AVR-RD-04 drug product**



**No SAEs reported**



**AEs reported**

- Consistent with myeloablative conditioning and underlying disease
- N = 22 (moderate = 9, mild = 13)

**Pre-treatment and prior to conditioning** (n = 6, not all events listed)

- Diarrhea, hypokalemia, dizziness
- Dehydration, vomiting

**Post-treatment** (n = 16, not all events listed)

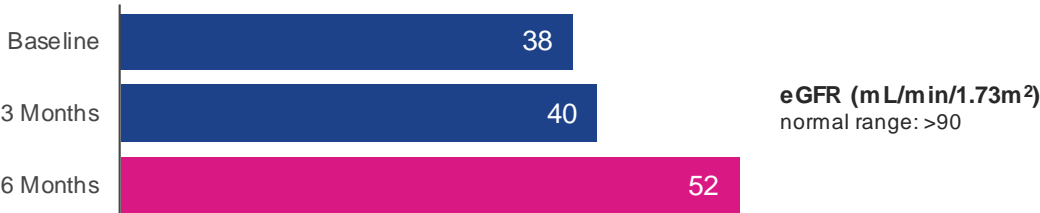
- Alopecia, intermittent diarrhea, vomiting
- Mucositis, intermittent febrile neutropenia, intermittent epistaxis
- Intermittent blurry vision, intermittent hypokalemia, mucocoeles
- Thrombocytopenia



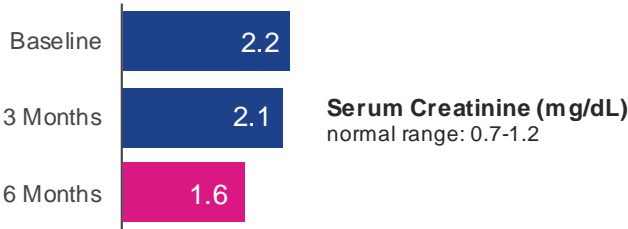
# Patient 1: Initial data indicate positive trends across multiple measures

## CLINICAL LAB MEASURES

### Kidney Function



### Serum Creatinine (mg/dL)



### Urine Volume

24 Hour Urine Volume in L



## BIOMARKER ENDPOINTS

### Levels of Cystine in Skin\*

µm³



- Experimental *in vivo* confocal microscopy
- Two skin areas, behind the ear and 'optional', averaged
- Analysis and quantification (3D Image-Pro software)

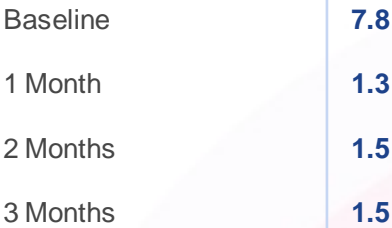
### VCN (vcn/dg)

(Drug Product = 2.1)



### Average Granulocyte Cystine Level

(µmol half cystine/g protein)



Asymptomatic Heterozygous Carrier Granulocyte Cystine Range: 0.2 – 1.9 µmol half cystine/g protein  
Source: Gertsman I et al., Clinical Chemistry, 2016  
VCN: Vector Copy Number; CTNS: Cystinosis, Lysosomal Cystine Transporter; mRNA: Messenger Ribonucleic Acid; eGFR: Estimated Glomerular Filtration Rate; SCr: Serum Creatinine  
\*Data obtained using a novel experimental methodology utilizing *in vivo* confocal microscopy, to image crystals in the skin behind the ear





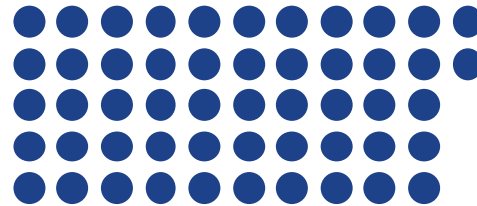
# Patient 1: Reduced treatment burden at 6 months

## Number of Medications and Supplements

(max per day)

**Before  
Gene Therapy**

ON Cysteamine

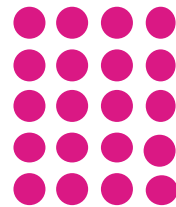


52

**After Gene  
Therapy**

(at 6 months  
post-gene therapy)

OFF Cysteamine



20



# Gaucher Disease



AVR-RD-02



# Goals for gene therapy in Gaucher Type 1 Disease

## UNMET NEEDS:



### Bone-related manifestations

**Unmet needs:** bone pain, avascular necrosis, bone crisis, osteoporosis, fractures, joint destruction, skeletal abnormalities



### Hemoglobin levels and platelet counts

**Unmet needs:** anemia, thrombocytopenia, easy bruising, bleeding



### Hepatosplenomegaly

**Unmet needs:** enlarged liver, enlarged spleen



### CNS complications

**Unmet needs:** Increased risk of GBA-Parkinson's disease



### Everyday burden of illness, and life expectancy

**Unmet needs:** fatigue, pain, lung disease, biweekly infusions, shortened lifespan

# Long-term follow-up study highlights significant unmet need in Gaucher Type 1



Despite standard-of-care ERT, **disease progression** continues and **unmet need** remains.

## Incomplete therapeutic response is common:

- **60%** of patients failed to achieve at least one of the six therapeutic goals evaluated after 4+ years of ERT<sup>1</sup>
- A clinically significant percentage of patients continue to exhibit **bone pain, organomegaly and cytopenia** after 10 years of ERT<sup>2</sup>
- **25%** of patients continue to suffer from physical limitations after two years of ERT, primarily due to bone disease<sup>3</sup>

Persistence after 10 years ERT <sup>†</sup>	Non-splenectomized Patients	Splenectomized Patients
Anemia	12.4%	8.8%
Thrombocytopenia*	22.7%	0.7%
Splenomegaly*	38.3%	N/A
Hepatomegaly*	14.3%	18.8%
Bone Pain	42.9%	62.5%
Bone Crisis	7.4%	16.7%

\* Higher persistence rates observed when more severe manifestations were present at baseline

<sup>†</sup> Persistence refers to the presence of anemia, bone pain, bone crisis, or at least moderate thrombocytopenia, splenomegaly, or hepatomegaly, present after 10 years of ERT among those with baseline involvement of these parameters (from a registry of 757 GD1 patients; Weinreb et al., 2013).

Following 10 years of treatment, ~26% of patients were receiving between 45-150 U/kg EOW, and 96% of these individuals were receiving doses between 45-90 U/kg EOW.

**Sources:** <sup>1</sup>Weinreb N et al. *Amer J Hematol*, 2008; <sup>2</sup>Weinreb N et al. *J Inherit Metab Dis*, 2013; <sup>3</sup>Giraldo P et al. *Qual Life Res*, 2005.

GD1: Gaucher Disease Type 1; SOC: Standard of Care; ERT: Enzyme Replacement Therapy; EOW: Every Other Week

# GuardOne: Phase 1/2 study in Gaucher Type 1 patients

First patient dosed



## PHASE 1/2

AVR-RD-02 Trial

### Patients

n = 8 - 16

Type 1 Gaucher

Treatment naïve or on ERT

16 - 35 year-old

Male and Female



### Key Objectives

Safety, Engraftment, Efficacy,  
ERT-independence



# Pompe disease



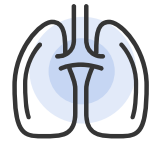
AVR-RD-03





# Goals for gene therapy in Pompe Disease

## TO PREVENT OR IMPROVE:



### Pulmonary function

**Unmet needs:** respiratory insufficiency, chronic respiratory infections, sleep apnea, artificial ventilation



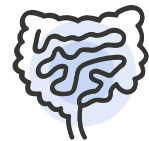
### Physical endurance and strength

**Unmet needs:** proximal myopathy, progressive muscle weakness in diaphragm, trunk and lower limbs, wheel-chair bound



### CNS complications

**Unmet needs:** neuromuscular control, reduction in executive function, cognitive impairment



### GI complications

**Unmet needs:** macroglossia (childhood onset), difficulty chewing and swallowing, GI symptoms, including irritable bowel-like symptoms



### Everyday burden of illness, and life expectancy

**Unmet needs:** fatigue, hepatomegaly, independent living, biweekly infusions, shortened lifespan

# Pompe lentiviral gene therapy program advancing

## Integrated three-part approach



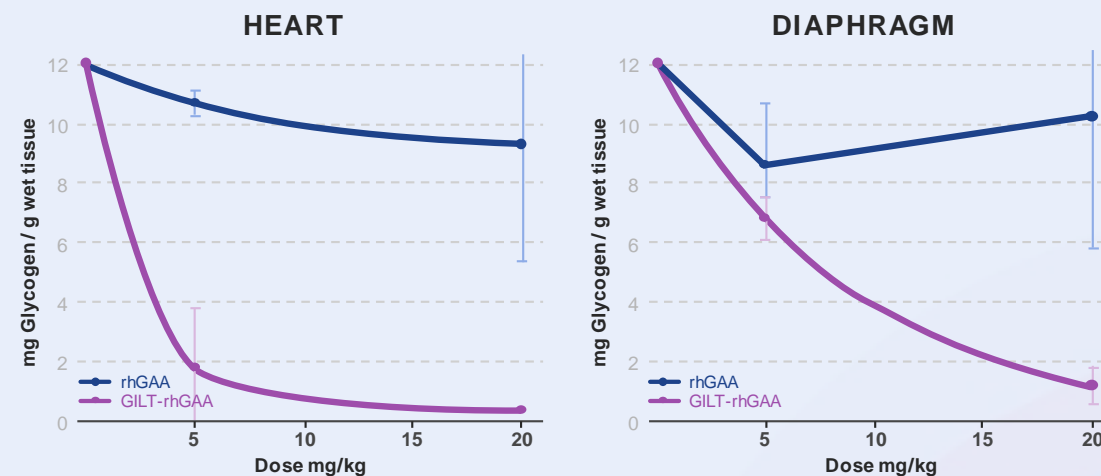
### THE CHALLENGE

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

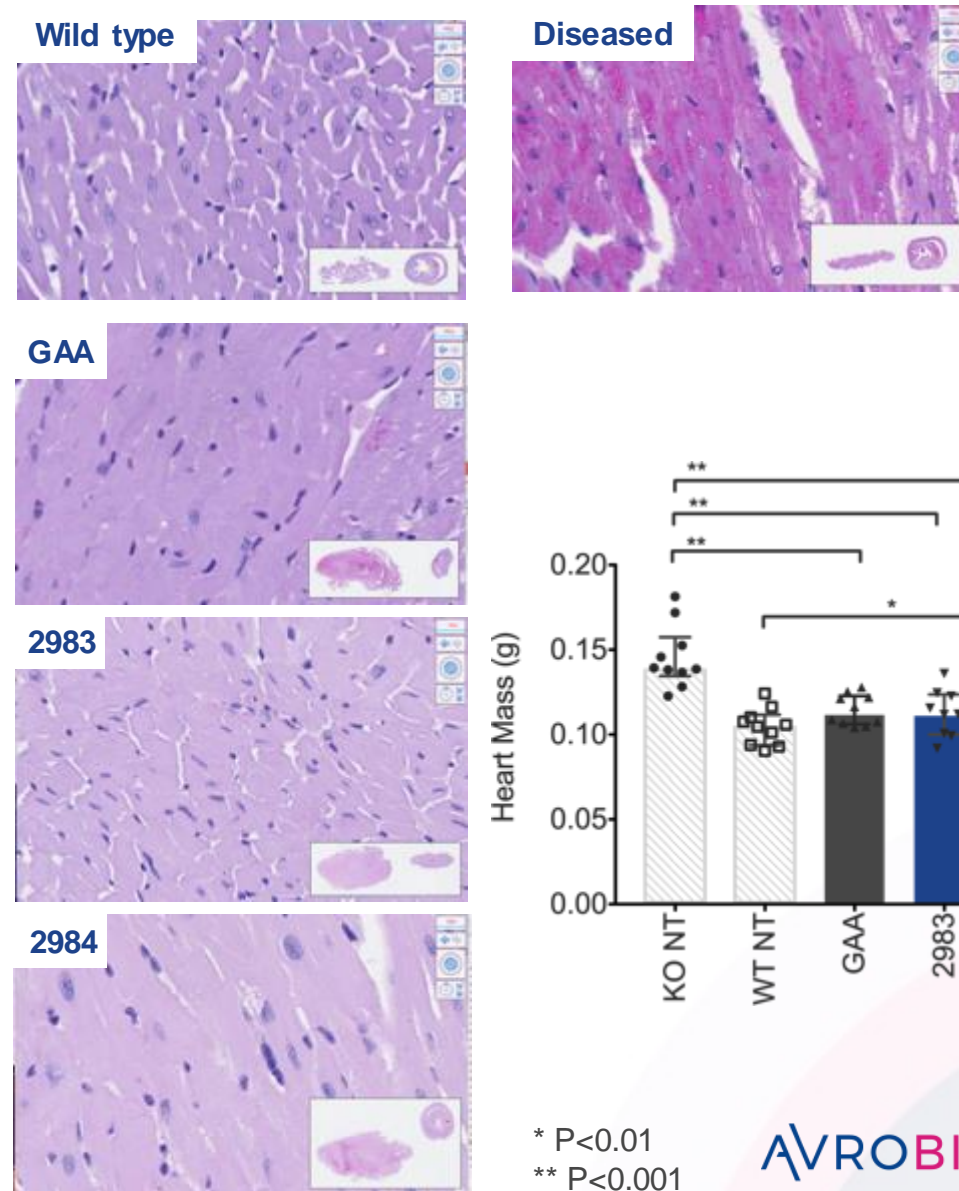
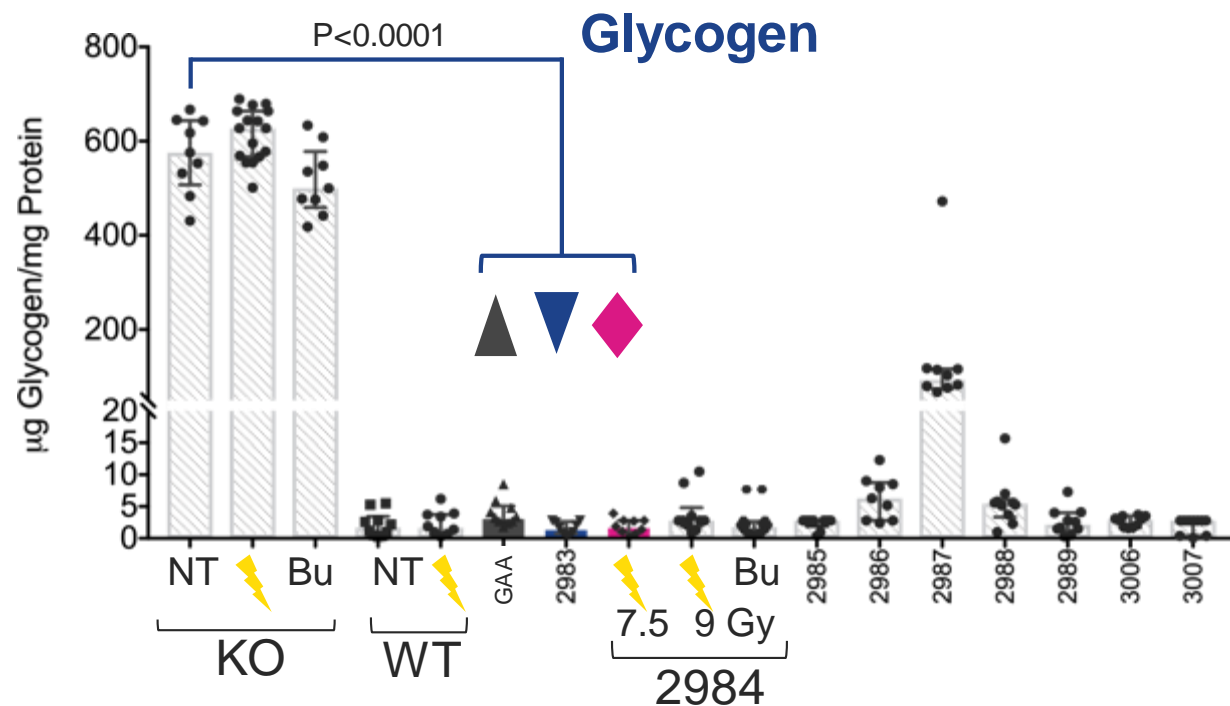
### AVROBIO's APPROACH

- Potent transgene promoter
- GILT uptake tag
- Bu90-TDM 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

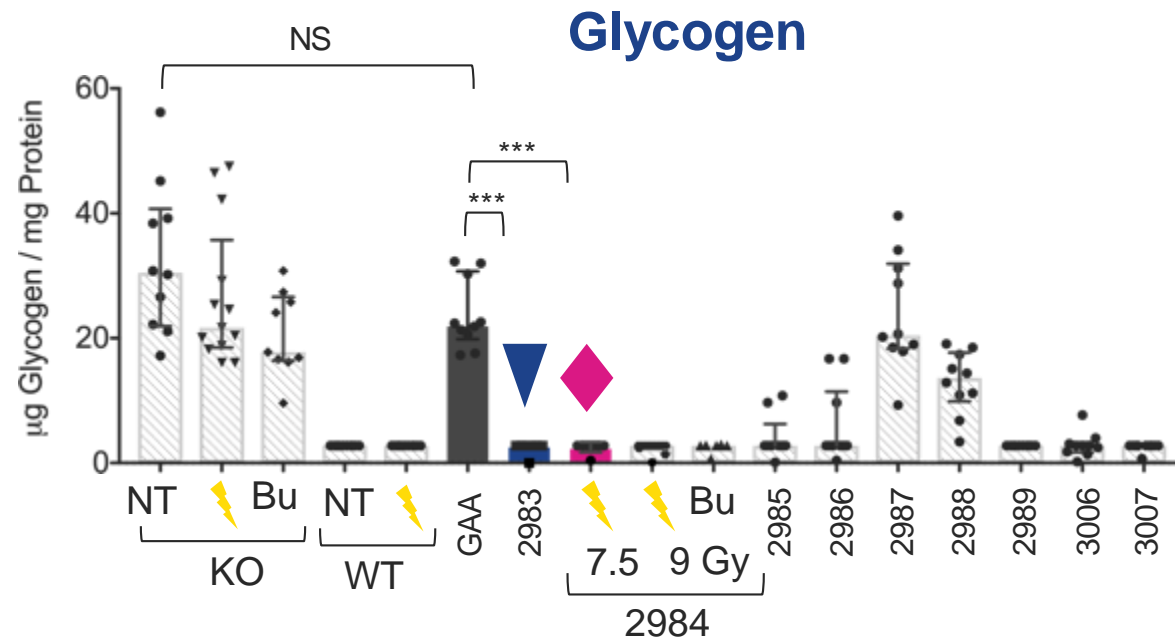


# GILT and GILT mutant v1 reduce glycogen by >99% in heart



# Glycogen and GILT and GILT mutant v1 similar to wildtype mice

GILT tag is essential for glycogen clearance in CNS



	Cerebrum	Spinal cord
WT		
KO		
GAA		
2983		
2984		

\*\*\* P<0.001



# plato<sup>®</sup>

—  
AVROBIO's foundation designed to  
scale gene therapy worldwide

*State-of-the-art technologies including  
automated manufacturing platform*










+ Optimized  
for performance

+ Redefines manufacturing  
best practices



# plato<sup>®</sup>: Three upgrades designed to optimize potency, safety and durability



 UPGRADES	Increase enzyme activity	Increase transduction efficiency	Increase VCN	Increase marrow space / engraftment	Increase consistency and safety
					
					 *
					

*Upgrades designed to increase Vector Copy Number (VCN), enzyme activity, chimerism and durability*

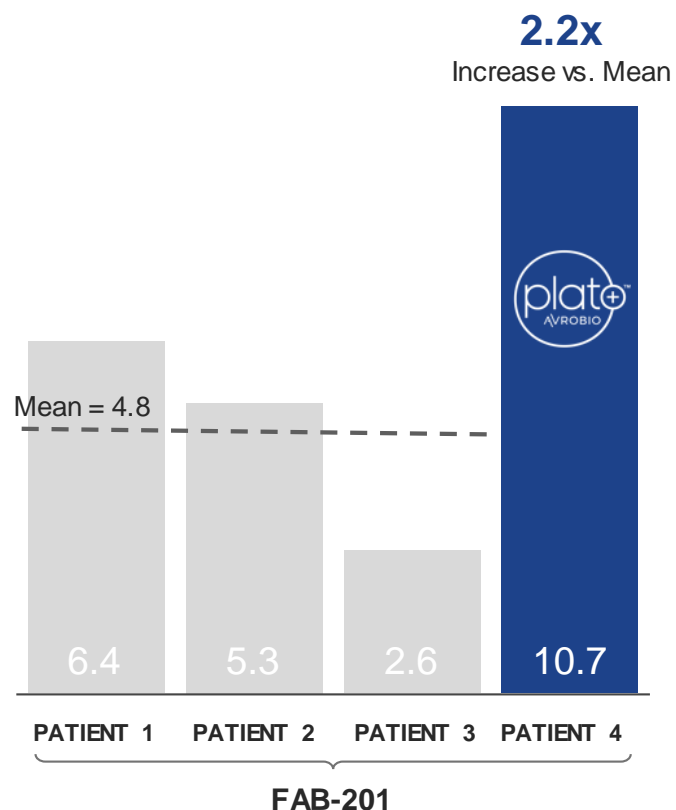
\* TDM (therapeutic drug monitoring)

## VECTOR UPGRADE:

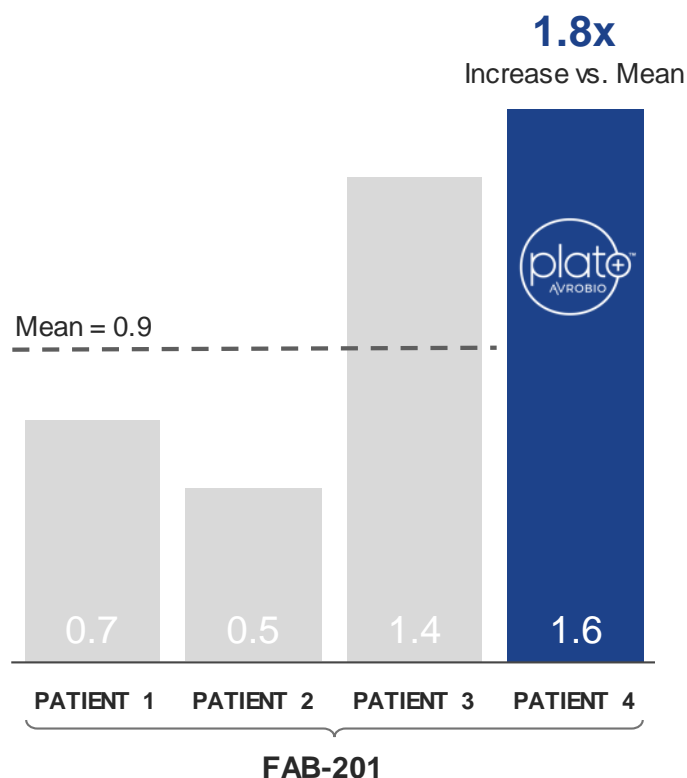
# Metrics compared to academic process

FAB-201 patient #4 drug product data with plato<sup>®</sup>

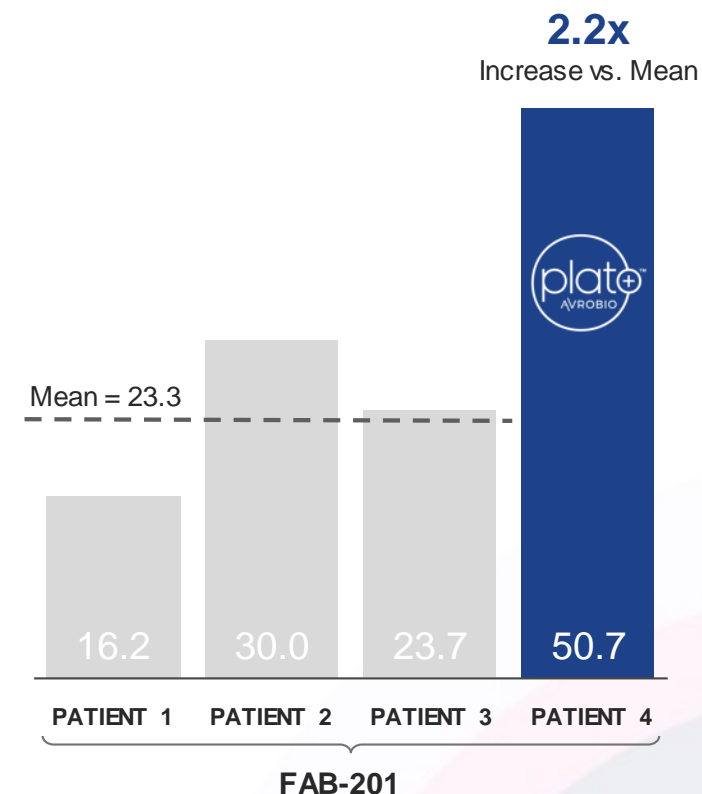
### Enzyme Activity (nmol/hr/mL)



### VCN (per diploid genome)



### Transduction Efficiency (%)





## VECTOR UPGRADE:

# Metrics compared to academic process

## FAB-201 and AVR-RD-04 drug product data

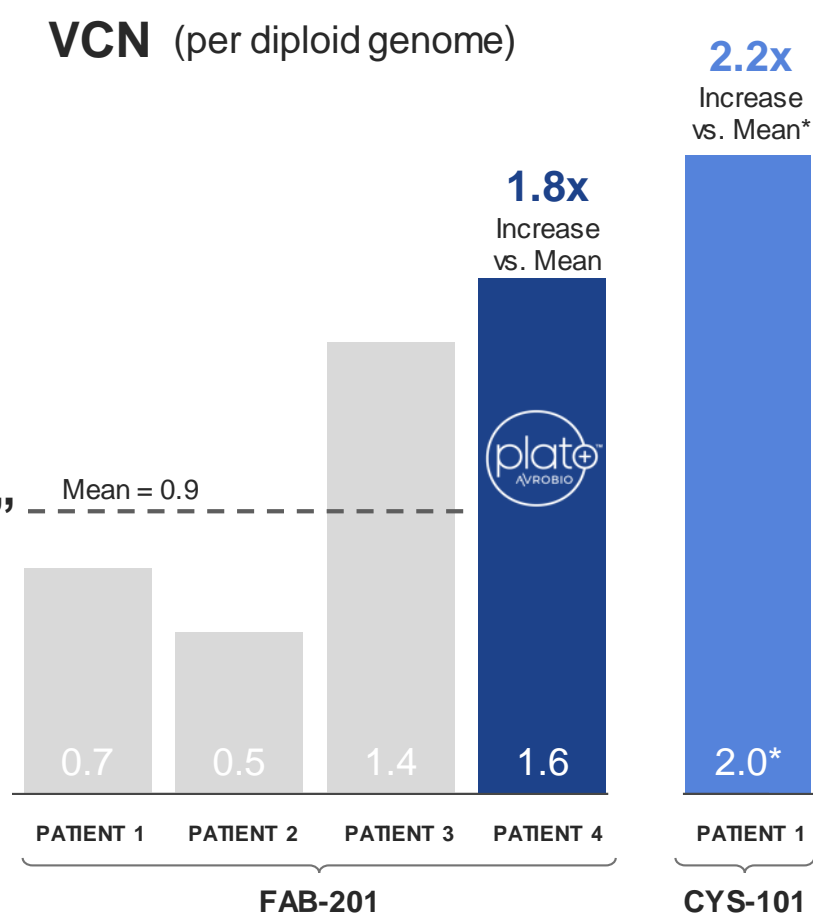
### FAB-201 with plato<sup>™</sup>

- 4-plasmid vector (LV2)
- Bu TDM conditioning
- Automated manufacturing

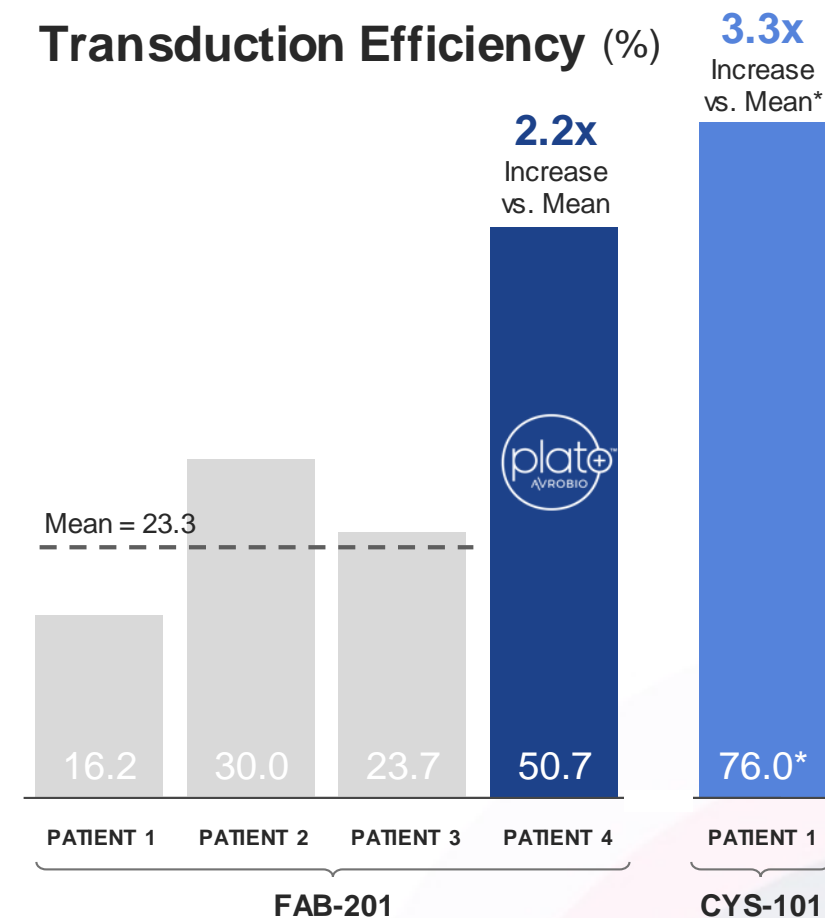
### AVR-RD-04 with “plato<sup>™</sup>-like”

- 4-plasmid vector
- Bu TDM conditioning
- Manual manufacturing

#### VCN (per diploid genome)



#### Transduction Efficiency (%)



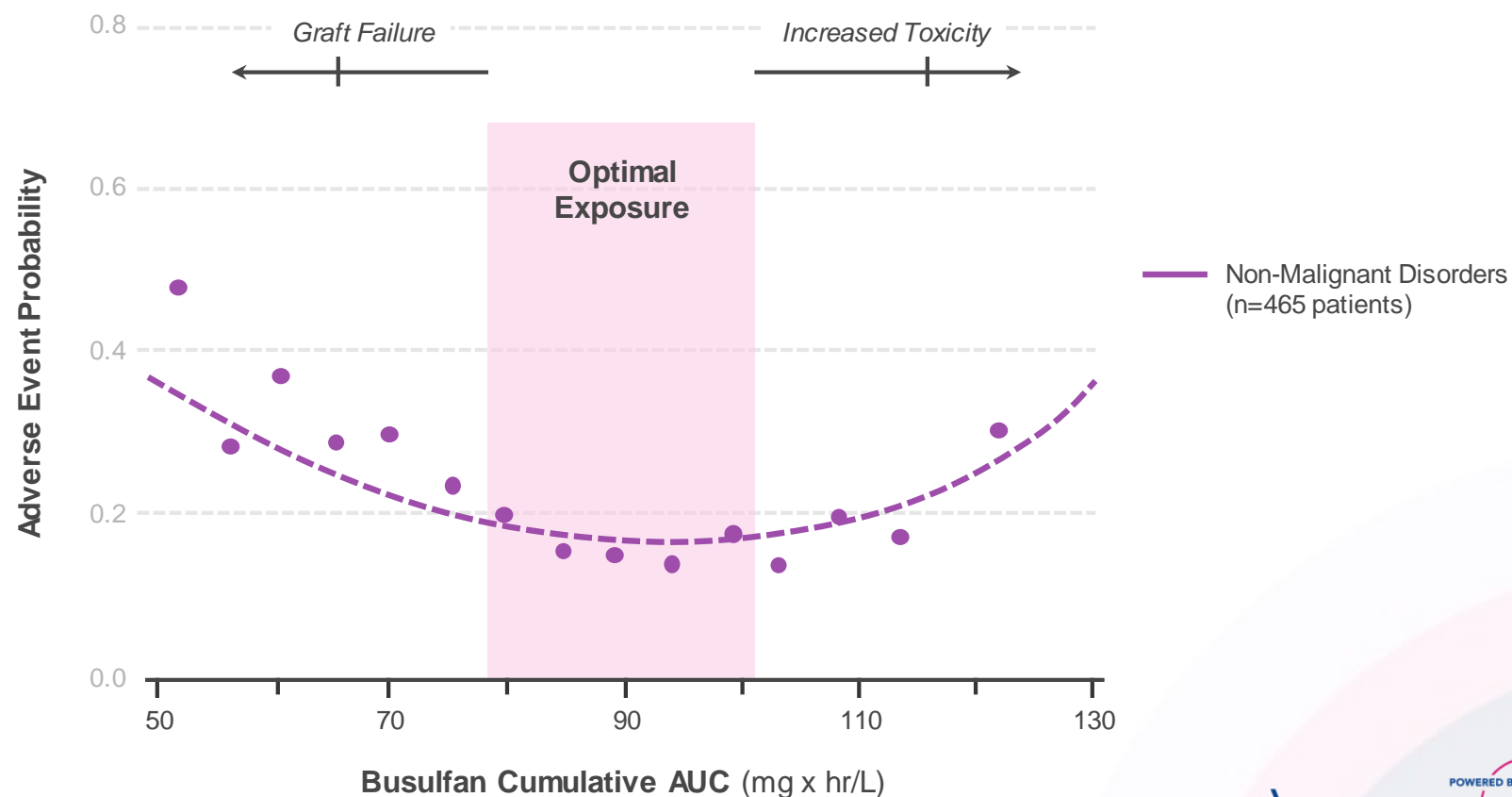
## PRECISION CONDITIONING UPGRADE:

# Targeted busulfan intended to balance optimal engraftment with enhanced safety

Meta-analysis of 465 patients identified optimal exposure

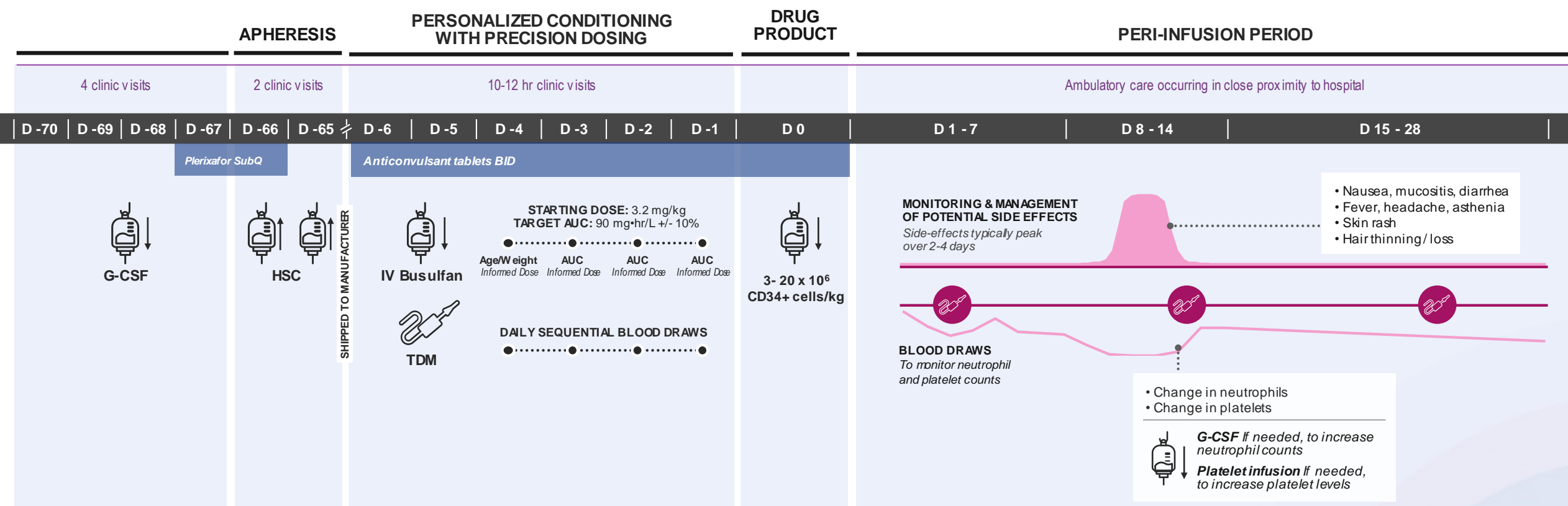
**Optimized precision dosing designed to enhance tolerability**

*Lowest rate of adverse events in the Bu90 range*



# PRECISION CONDITIONING UPGRADE:

## Precision dosing via state-of-the-art patient therapeutic drug monitoring (TDM)



G-CSF: granulocyte colony stimulating factor; PERI-INFUSION PERIOD: time from infusion to discharge; TDM: therapeutic drug monitoring; HSC: hematopoietic stemcell

Notes: Illustrative only. AEs will vary patient by patient, see busulfan label for a complete list of side-effects. Ambulatory care based on oncology setting with higher intensity conditioning



## PRECISION CONDITIONING UPGRADE:

Busulfan used in chemotherapy has a different purpose and side-effect profile than busulfan used in cell therapy

### Chemotherapy

– *to eradicate cancer cells*

- Used in combinations
- Intensive high-dose chemo\*
- Multiple cycles (palliative)
- Weight-based dosing

\*Requires rescue HSC Tx

Busulfan **IS** the therapy

### Cell Therapy

– *create space in bone marrow and CNS*

- Used as a single agent
- Less intensive
- Single cycle
- Precision TDM dosing

Busulfan **IS NOT** the therapy

**PRECISION CONDITIONING UPGRADE:**

Lysosomal disorder patient characteristics are typically favorable compared to oncology patients and other gene therapy indications



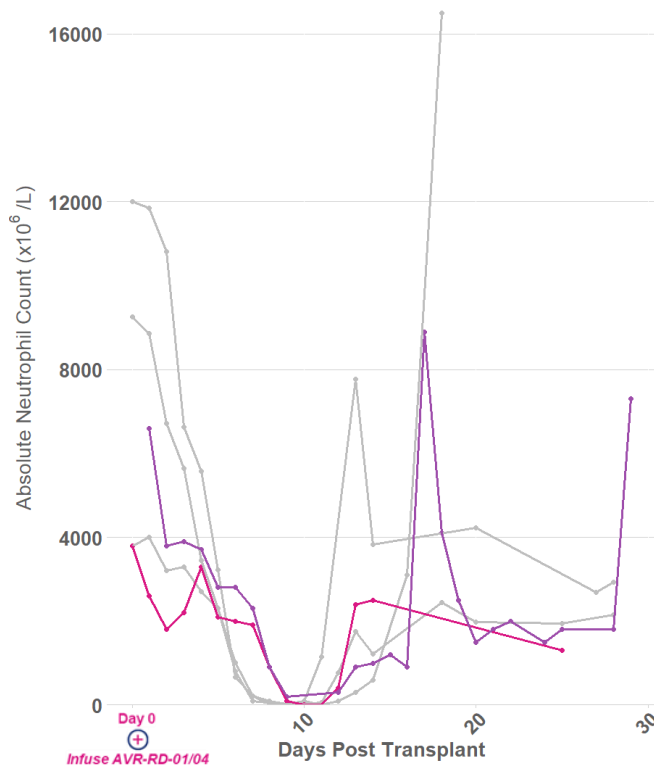
Typical characteristics	Cancer patients	Other LV GT patients (eg. SCD, TDT)	AVROBIO LD patients (Fabry, Gaucher*, cystinosis, Pompe)
Healthy bone marrow	x	x	✓
Healthy immune systems	x	✓	✓
Healthy livers	x	x	✓
Fewer co-morbidities	x	✓	✓
Younger	x	✓	✓

\* Potentially excludes treatment-naïve Gaucher Type 1  
LV GT: Lentiviral Gene Therapy; SCD: Sickle Cell Disease; TDT: Transfusion-Dependent  $\beta$ -Thalassemia; LDs: Lysosomal Disorders

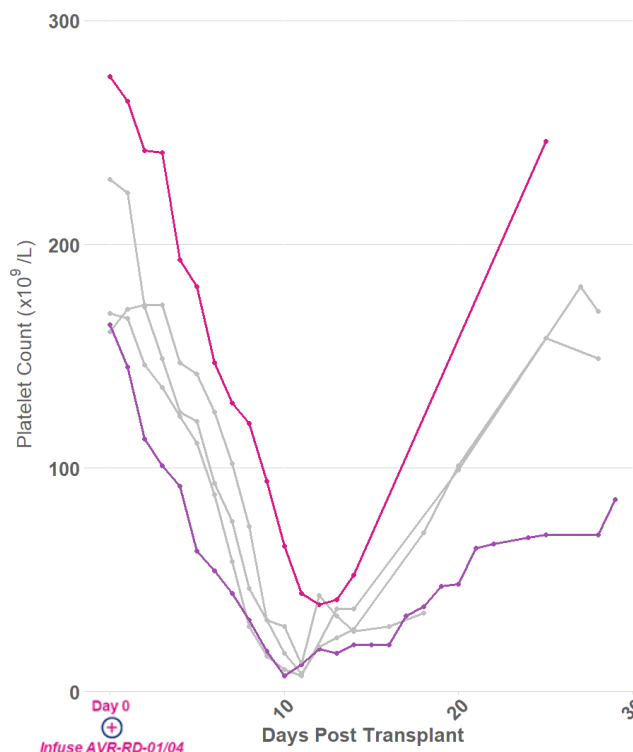
## PRECISION CONDITIONING UPGRADE:

# Rapid neutrophil and platelet recovery with minimal lymphocyte depletion using Busulfan TDM

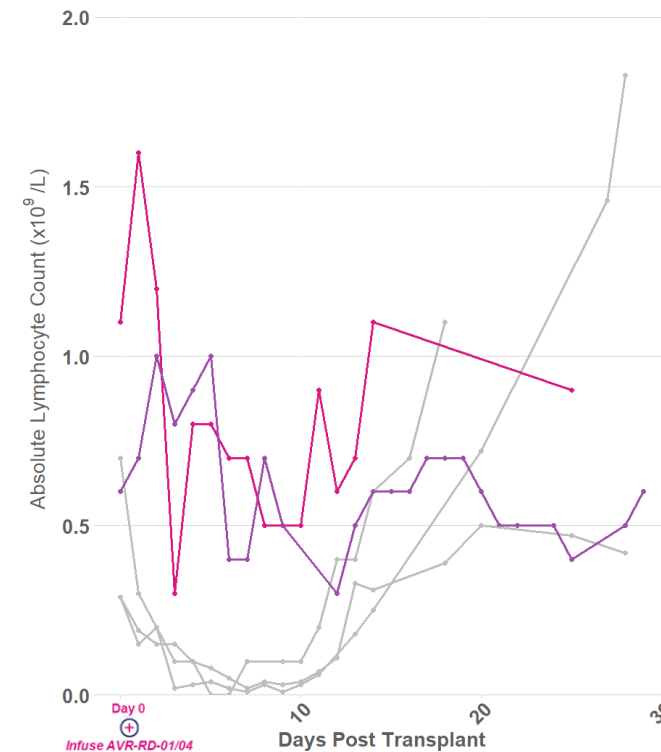
### Absolute Neutrophil Count (ANC)



### Platelet Count



### Absolute Lymphocyte Count



— Cystinosis Patient 1: Busulfan — Fabry Patients 1 – 3: Mel — Fabry Patient 4: Bu90-TDM

Fabry: Patients #1-3 Melphalan 100mg/m<sup>2</sup>; Patient #4 Busulfan 'AUC 90'; Cystinosis: Patient #1 Busulfan 'AUC 90'

Threshold levels for prophylactic supportive care in HSC Tx; ANC <0.5 x 10<sup>9</sup> per liter (AABB); Platelets <10 X 10<sup>9</sup> cells/L (AABB)

NOTE: Neutrophil counts - G-CSF administration post gene therapy: Pt 1: 7 Doses, Day 7 – 14, Pt 2: 11 Doses, Day 7 – 17, Pt 3: 6 Doses, Day 7 – 12, Pt 4: 5 Doses, Day 8 – 12

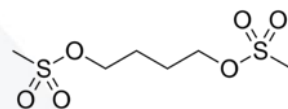
NOTE: Platelet counts - Platelet Transfusion: Pt 1: Day 10; Pt 2, 3: Day 11, Pt 4: no transfusion

TDM = Therapeutic Drug Monitoring; G-CSF = Granulocyte-colony stimulating factor

# PRECISION CONDITIONING UPGRADE: Designed to access “hard-to-reach” compartments

## BRAIN

Busulfan crosses blood-brain barrier and eliminates resident microglia cells making space for gene-modified cells

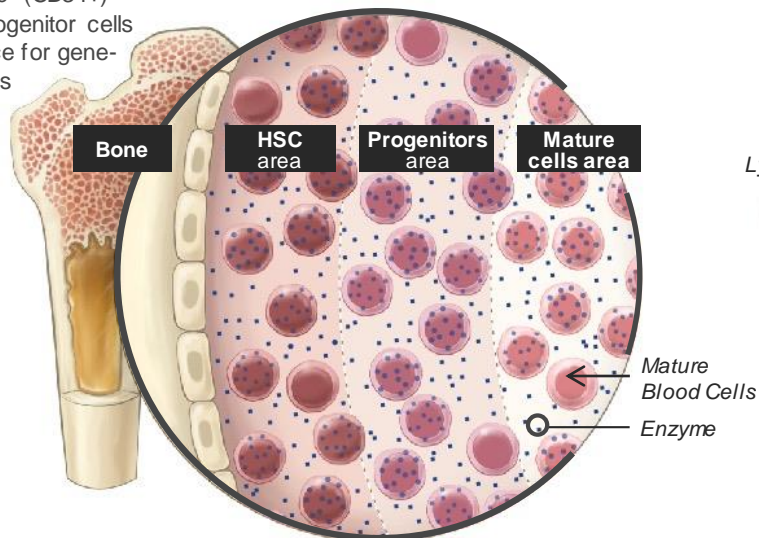


## IN THE BONE MARROW

Busulfan eliminates hematopoietic (CD34+) stem and progenitor cells making space for gene-modified cells

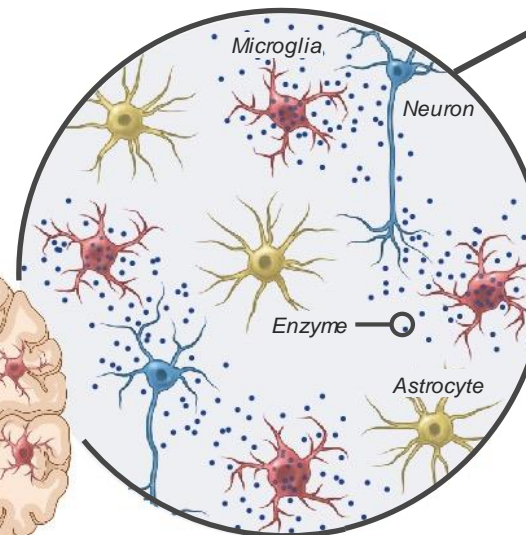
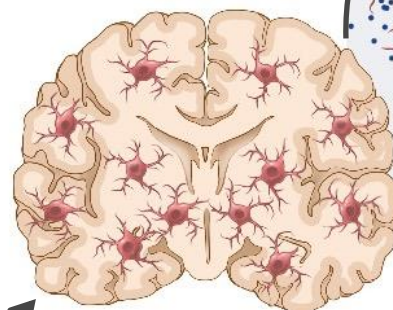
TRANSDUCE  
CD34+ CELLS

## BONE MARROW

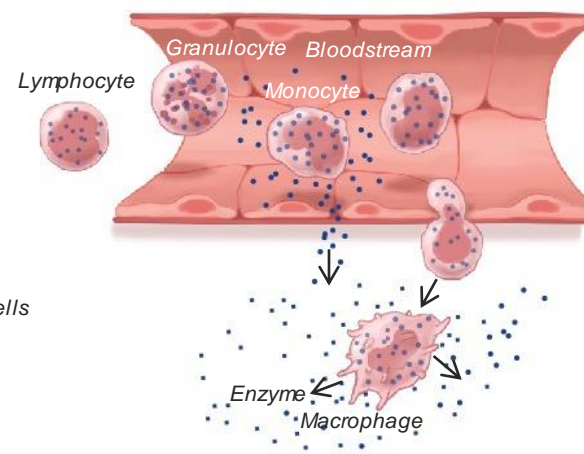


## MICROGLIA

Potential for widespread microglia engraftment throughout the brain



## PERIPHERAL TISSUE



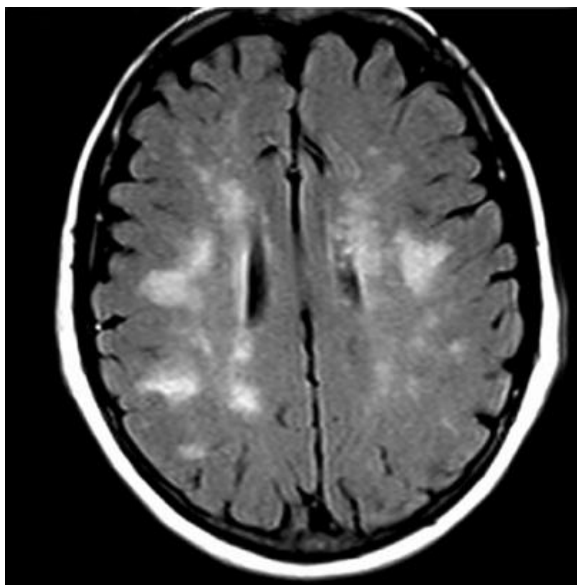
CNS/PNS

Viscera

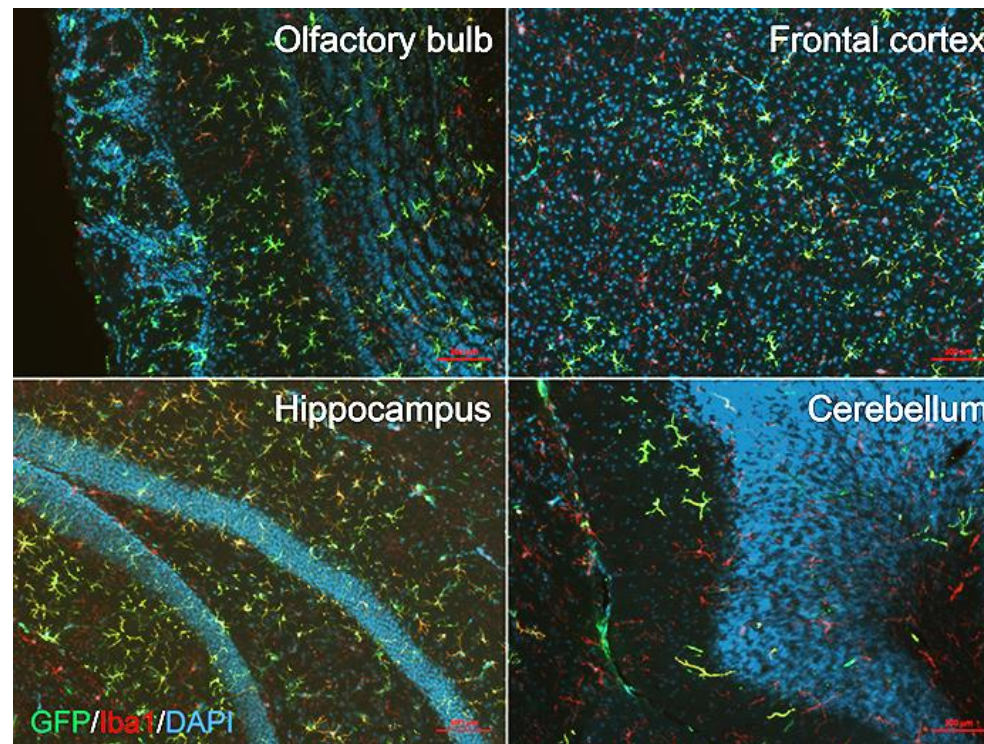




## PRECISION CONDITIONING UPGRADE: Designed to access “hard-to-reach” compartments, including the brain



**MRI:** 54 year old with Fabry disease demonstrating white matter lesions (WMLs)



**GFP:** Marker of engrafted cells  
**Iba1:** Marker of microglia cells  
**DAPI:** Nuclear stain irrespective of cell type

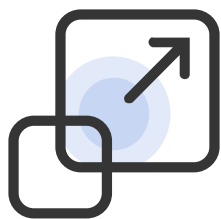
### Global microglial coverage of mouse brain at 4 months post gene-modified HSC transplantation

- Widespread engraftment in regions critical for cognitive, motor, olfactory, and visual function
- Engrafted microglia/microglia-like cells have comparable morphology and classical lineage markers with endogenous microglia

## AUTOMATION UPGRADE:

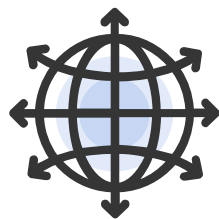
# Automated, scalable manufacturing system

Designed to elevate quality and overcome historic CMC bottlenecks



### Expanded Scale

Potential to reach thousands of patients per year



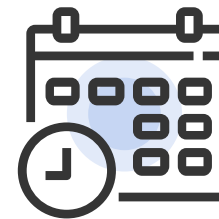
### Broader Reach

Portable platform designed for flexible global production using low grade clean rooms



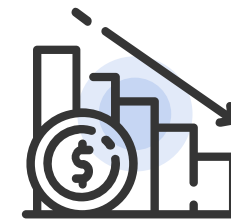
### High Quality

Automated, closed system designed to improve quality and consistency



### Enhanced Convenience

Cryopreservation simplifies logistics and patient scheduling



### Lower Costs

Designed to create efficiencies in vector design / scalable cell and vector production

## AUTOMATION UPGRADE:

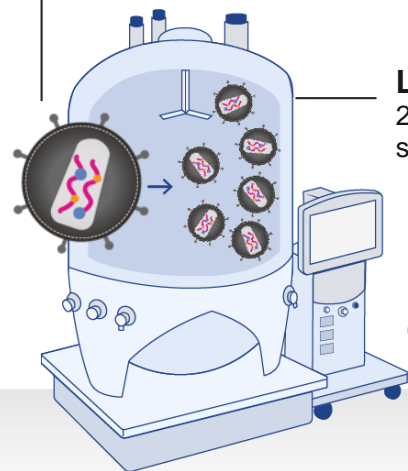
# Designed to deliver large-scale manufacturing

Differentiated, cost-effective approach

### 1 Vector production

HIGH VOLUME/ TITRE

Vector with disease-specific transgene



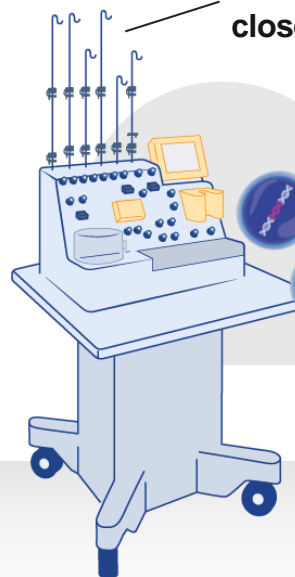
**Large bioreactor**  
200 liter serum-free  
suspension culture

↓ **Frozen in aliquots**  
to streamline  
supply chain

### 2 Drug product production

INCREASE CONSISTENCY

Automated,  
closed system

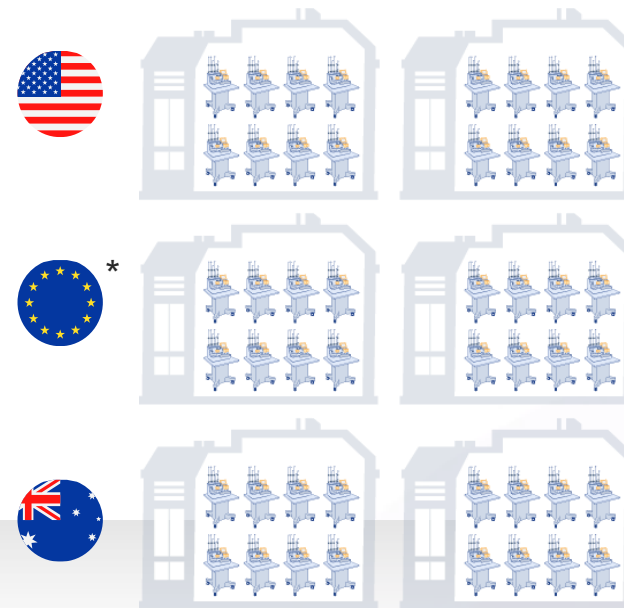


**CD 34+  
hematopoietic  
stem cells**

↓ **Cryopreserved**  
to enable  
convenient  
dosing

### 3 Scalable, global production suites

COST-EFFECTIVE SCALE-OUT

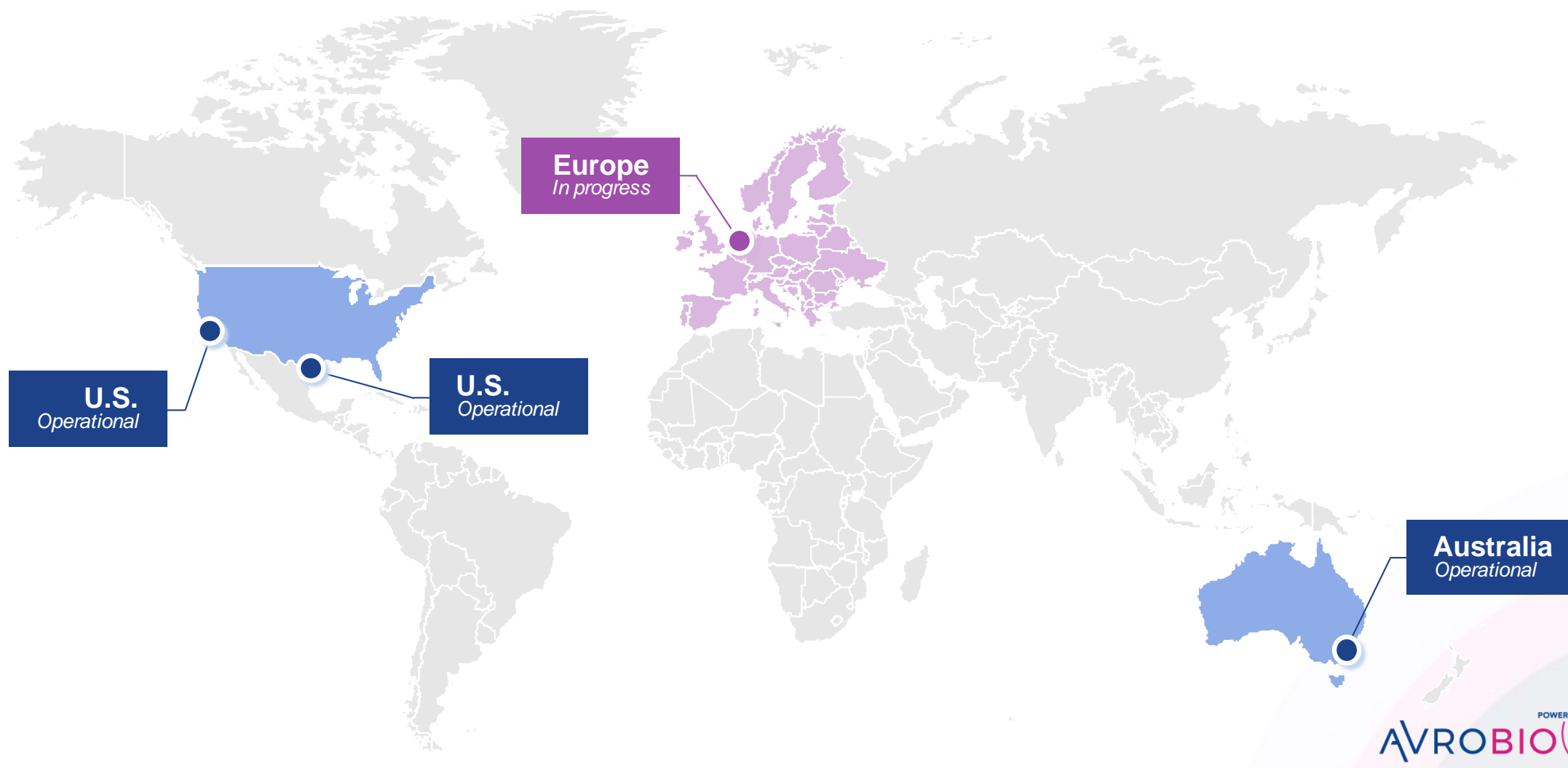


Illustrative

## AUTOMATION UPGRADE:

# Global manufacturing established

Automated systems operational in 3 sites with 4<sup>th</sup> in progress



## AUTOMATION UPGRADE:

# Poised to manufacture at scale

Designed to optimize potency and safety, and overcome historic CMC bottlenecks

### VECTOR



**2,400** PATIENTS  
ANNUALLY

**~50** patients per run

**~12** runs per year per suite  
(200 L scale bioreactor runs ( $10^9$  titre))

**4** production suites



### DRUG PRODUCT

**2,400** PATIENTS  
ANNUALLY



**100** patients per unit per year

**8** automated units per suite

**3** global production suites



*Illustrative*

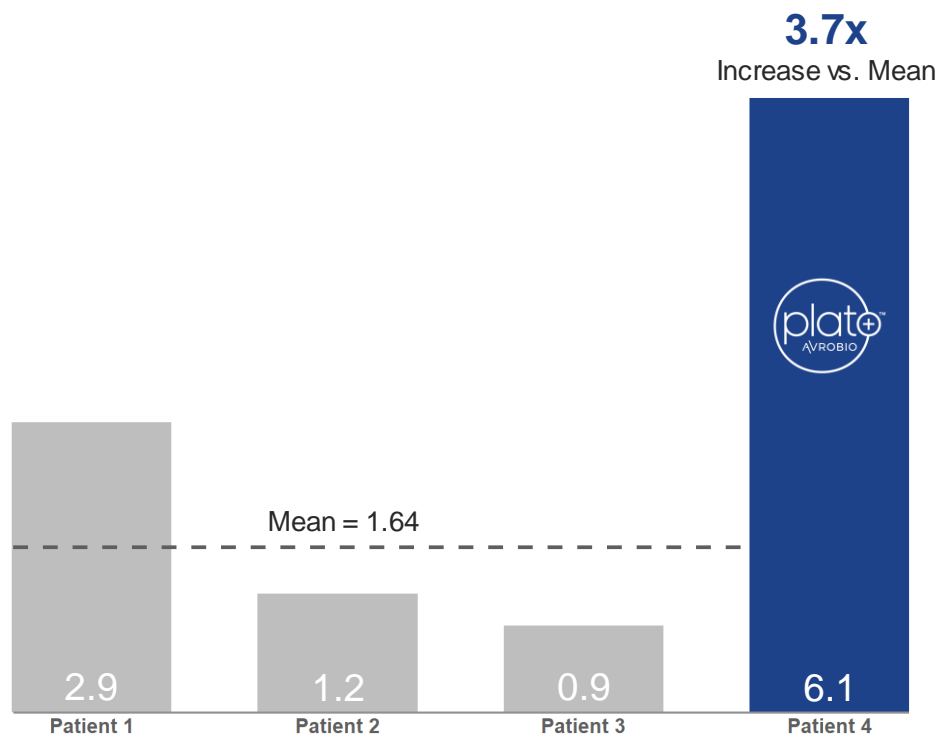
### 3 UPGRADES IN PLACE:

## plato<sup>®</sup> metric compared to academic process

FAB-201 SIX MONTH data for patient #4 with plato<sup>®</sup> vs. patients #1-3

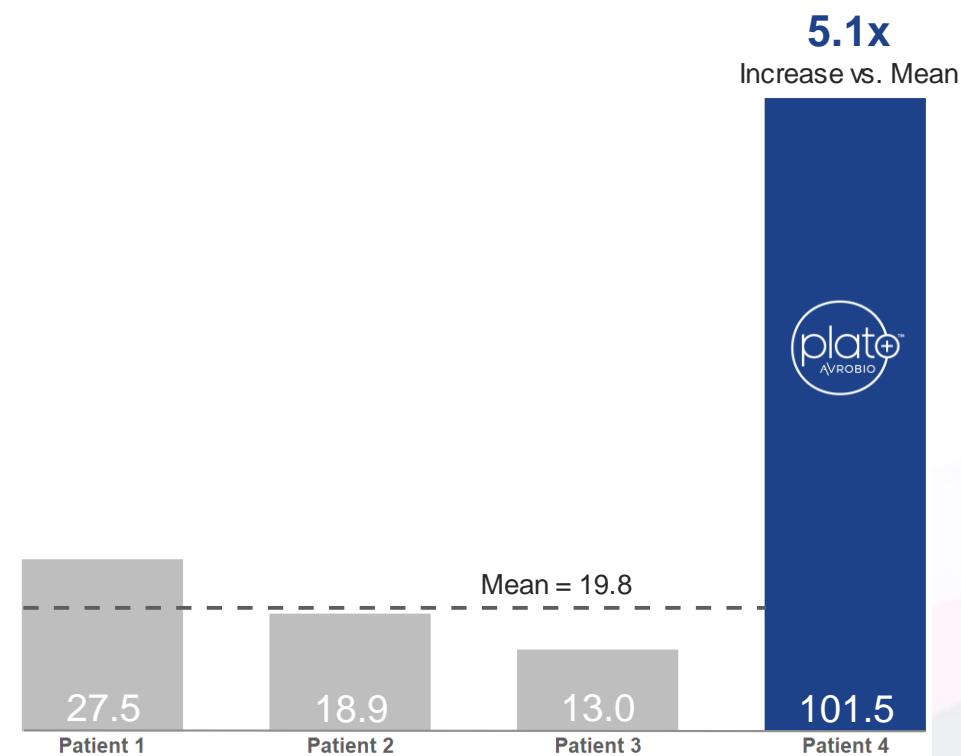
### Plasma Enzyme Activity

(nmol/hr/mL)



### Leukocyte Enzyme Activity

(nmol/hr/mg protein)

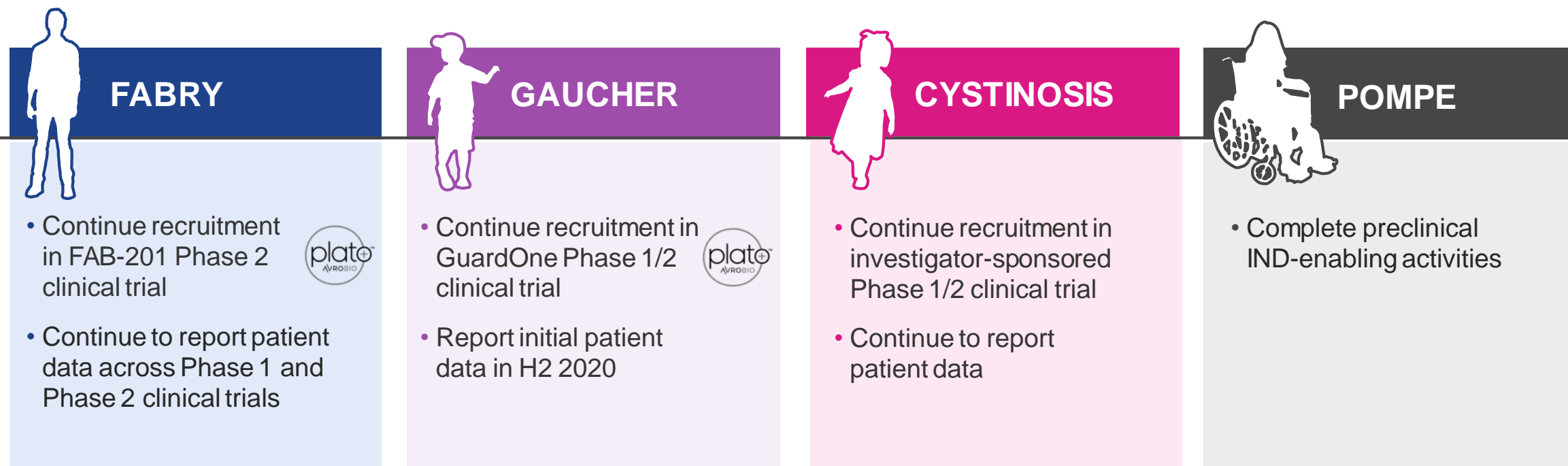




# Milestones anticipated across the pipeline in 2020



Clinical activities and timelines subject in all respects to ongoing and evolving COVID-19 pandemic\*



**AVROBIO to hold first R&D Day in Q4 2020**

\* For additional information, see the Company's Quarterly Report on Form 10-Q filed with the SEC on August 6, 2020.





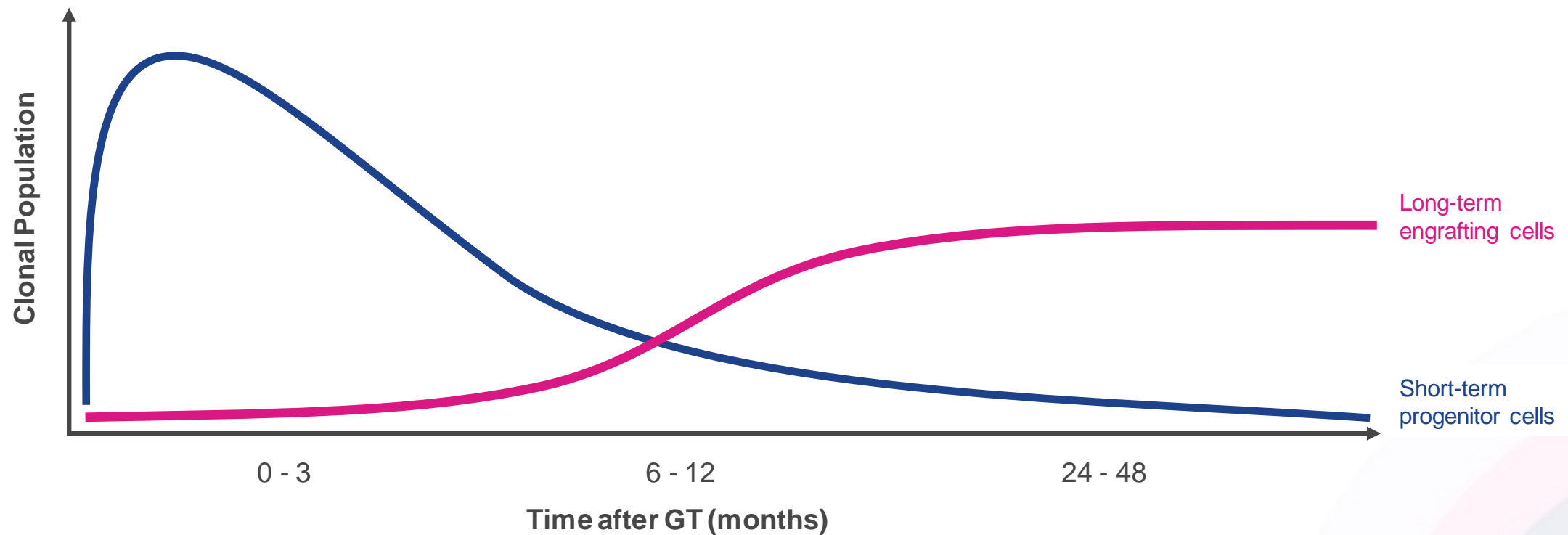


# Appendix

# Hematopoietic reconstitution occurs in two distinct phases

A few thousand long-term engrafting cells stably sustain levels of transgene product

*First wave of short-term progenitor cells start to exhaust with progressive takeover by a smaller population of long-term engrafting cells*





# Precedent for use of kidney biopsy data for FDA approval of drug candidate for Fabry disease

Migalastat approved on % reduction in GL-3 inclusions per KIC as compared to placebo



## 45 Amenable patients\* (16 males / 29 females)

Group	Migalastat (BL -M6)	Placebo (BL -M6)
Males (N=16)	5/7 (71%) -1.10 (-1.94, -0.02)	4/9 (44%) -0.03 (-1.00, 1.69)
Patients with baseline GL-3 $\geq 0.3$ (N=17; 9 males, 8 females)	7/9 (78%) -0.91 (-1.94, 0.19)	2/8 (25%) -0.02 (-1.00, 1.69)
Patients with baseline GL-3 < 0.3 (N=28; 7 males, 21 females)	6/16 (38%) -0.02 (-0.10, 0.26)	7/12 (58%) -0.05 (-0.16, 0.14)

**7/9 males  $\geq 50\%$  reduction**  
(at 6 months from baseline)

Treatment Group	n	Baseline Median (min, max)	Month 6 Median (min, max)	Change from Baseline Median (min, max)
Average number of GL-3 inclusions per KIC (N=13)				
GalaFold	7	3.6 (0.2, 6.0)	2.6 (0.1, 6.0)	-0.7 (-1.7, 1.2)
Placebo	6	1.8 (0.1, 2.8)	2.0 (0.05, 4.3)	-0.04 (-0.5, 1.5)

**28% average reduction**  
(at 6 months from baseline)



## Classic Fabry patient level data

0-6 months randomized clinical trial and 6-12 months open label extension

	Male Patients with the Classic Phenotype													
	Migalastat (Months 0-24)							Placebo (Months 0-6) → Migalastat (Months 6-24)						
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14
PTC GL-3 inclusions at BL	0.16	0.03	n/a	5.69	1.22	n/a	2.88	2.41	1.55	0.16	0.03	0.11	0.94	0.88
Change in PTC GL-3 inclusions from BL to M6	-0.08	0.01	n/a	-1.77	-1.10	n/a	-1.25	1.21	-0.21	0.01	0.09	-0.07	1.94	-0.83
Change in PTC GL-3 inclusions from BL/M6 to M12	-0.12	n/a	n/a	-1.92	n/a	n/a	-0.81	-0.94	-1.13	-0.09	-0.05	n/a	-2.28	0.06

**46% average reduction**  
(average of patients with 12 month data)

Source: Germain D et al, Genetics in Medicine, 2019

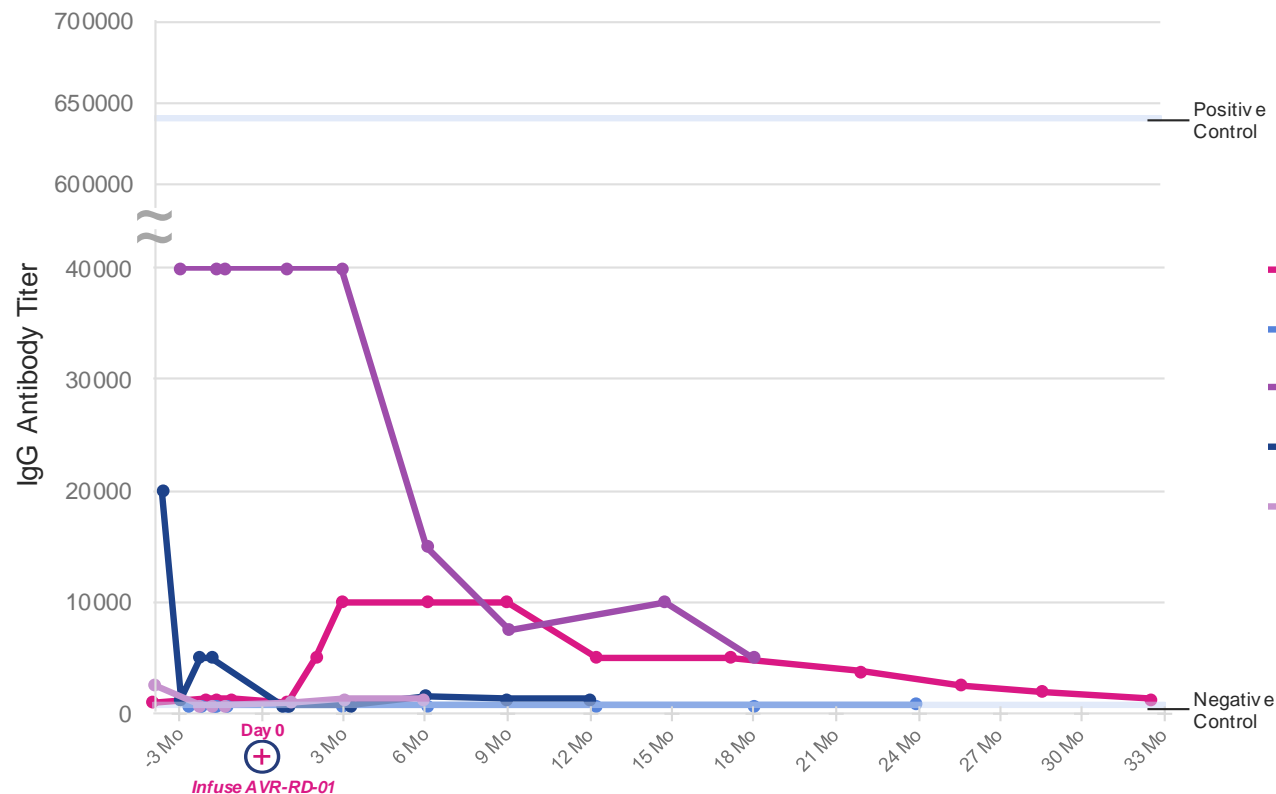
- Classic Fabry disease (AGA activity <1%)
- NOTE:** For informational purposes; differences exist between trial designs and subject populations; AVROBIO has not conducted any head-to-head trials comparing migalastat to AVR-RD-01



# Reduction of pre-existing anti-ERT drug IgG antibodies following AVR-RD-01

Suggests potential as a therapeutic option independent of pre-existing antibodies

## Fabry Disease Phase 1 IgG Antibody Titer



## Similar Results Observed in Other Studies

### San Raffaele Telethon Institute for Gene Therapy (SR-TIGET)

#### Change in pre-existing antibodies reported for Hurler disease (MPS-1)

- Ex vivo LV-CD34+ gene therapy with conditioning
- N = 6
- Evaluable patients (5/6) demonstrated sustained, supraphysiologic blood IDUA activity
- 4/5 prior ERT (rhIDUA) exposure (5-28 months)
- 4/5 pre-existing ERT-induced IgG antibodies
- 6/6 anti-rhIDUA IgGs undetectable 2 months post gene therapy

Source: Gentner B et al., Blood, 2019

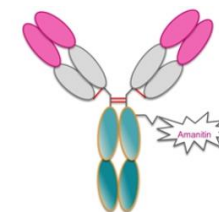


# New collaborations advancing leadership in lentiviral gene therapy



## Fully Automated Bu-TDM Immunoassay

- AVROBIO and Saladax announced agreement to develop and validate Saladax's fully automated nanoparticle immunoassay kit
- Designed to work on most automated hospital analyzers
- Regular technician, 24/7 analysis possible with results anticipated in minutes using only microLs of blood
- Designed to analyze 10-100s samples per machine/hour
- Expected to eliminate Bu degradation errors as assay conducted in real-time at the point of care
- Scalable



## Antibody-Drug Conjugate

- AVROBIO and Magenta announced research & clinical collaboration agreement to evaluate Magenta's preclinical CD117-targeted antibody conjugate to amanitin (MGTA-117) in conjunction with AVROBIO investigational gene therapies
- Designed to deplete only hematopoietic stem and progenitor cells
- Has shown promising data in non-human primates
- MGTA-117 currently in IND-enabling studies
- Each party retains commercial rights to its own programs





# AAV (liver-directed) data raises durability and safety questions

## Adverse safety and durability signals emerging

- **Safety**
  - Multiple recent reports of liver toxicity and adverse immune responses, esp. with high doses
    - 3 recent deaths due to liver toxicity in Audentes' MM trial
    - SAEs in Solid Bioscience's MDM trial (still on hold)
    - SAEs in Pfizer's DMD trial
    - SAEs in Dimension's hemophilia B trial
  - Recent UPenn 10-year AAV canine Factor 8 dog data suggests adverse integration for the first time
    - AAV integration in hepatocytes (>2000 unique integration sites across 3 biopsies per dog)
    - Clonal expansions with integration near genes associated with growth control and transformation in humans
- **Durability**
  - BioMarin's waning Factor 8 activity in hemophilia A
  - FDA is now requiring BioMarin to provide additional durability data

## AAV transduction of primate liver is highly efficient but not durable

- Population of stably expressing cells: integration?
- Evidence for genome inactivation
- Any inflammation essentially extinguishes residual expression

*Jim Wilson, ASGCT, 2019*

## Limitations to treating broad populations

- **Patients with pre-existing AAV capsid antibodies**
  - 30-70% of patients
- **Pediatric and adolescent patients**
  - Wash-out due to lack of integration
  - Important target market for rare diseases
- **Patients with CNS manifestations**
  - AAV primary target in the brain is neurons
  - AAV has low tropism for other cells in the brain, like microglia
  - Focused on targeted CNS diseases (not global)
- **Patients requiring medium-to-high doses**
  - Hepatotoxicity and adverse immune responses

## AAV modifications currently in development

### Current Generation

- AAV capsid design and selection
- Therapeutic protein selection
- Low dose, steroids

### Future Generations

- Scalable, re-dosable, capsid-free gene therapy
- Selective regulatory elements for precise cell targeting and controllable gene expression

# LV gene therapy data shows favorable track record of safety, efficacy and durability



## Favorable safety, efficacy and durability demonstrated in third party data

- **Strong safety profile**
  - LVs naturally integrate, integration/safety issues are rare
  - Low number of transgenes per cell reduces stress on cells
  - >350 patients treated, 1,000+ patient years of experience
- **Efficacy has been demonstrated**
  - In inherited blood disorders (sickle cell disease, thalassemia), primary immune deficiencies, SCID, WAS, MLD, ALD
  - LV integration expected to provide durability
  - Ex vivo LV provides systemic distribution throughout the body and brain
  - LDs are especially good disease targets for LV GT because only partial enzyme activity is required
- **Durability has been demonstrated >10 years**
  - Supported by data going out >10 years in thalassemia and ALD

## Potential to reach all patient segments

- **Patients with pre-existing drug product antibodies**
  - Patient limitations not anticipated
- **Pediatric patients**
  - Integration overcomes wash-out concerns
  - Important target market for rare diseases
- **Patients with CNS manifestations**
  - LV-transduced CD34+ cells produce daughter cells with transgene including microglia in CNS
  - Potential to treat global CNS diseases/manifestations

## New tailored, optimized busulfan conditioning regimens specifically for gene therapy

- **Potential to treat CNS**
- **Principally targets myeloid cells, not B and T cells**
- **Therapeutic drug monitoring designed to avoid out-of-range toxicities**
- **Proactive approach toward management of side-effects**