AVROBIO

Freedom from a lifetime of disease

July 15, 2019

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AVROBIO

Freedom from a lifetime of disease

July 15, 2019

Key questions for today

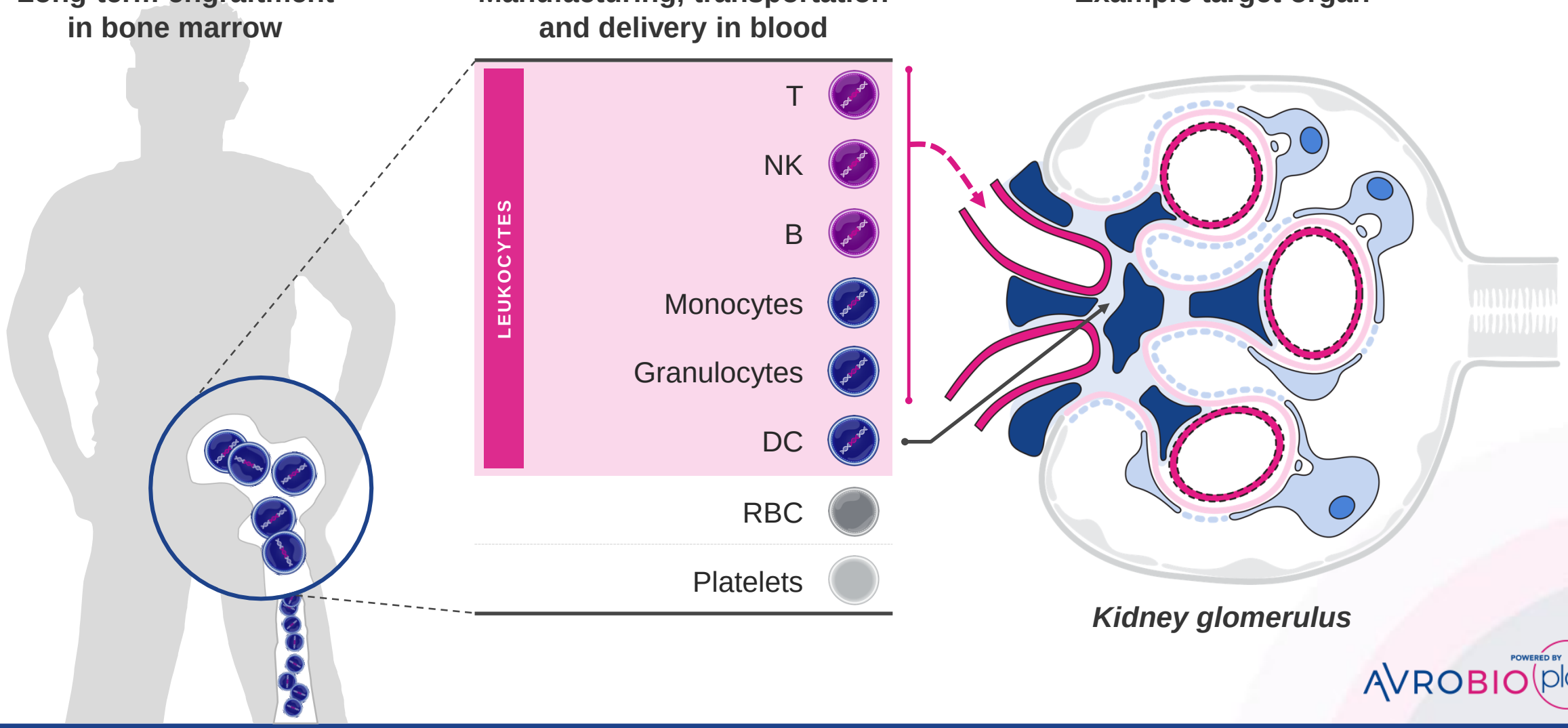
- What is the kidney biopsy (primary efficacy endpoint) result for the first patient in FAB-201?
- How well are the 5 Fabry patients in Phase 1 doing versus baseline ERT?
- What have we learned about the durability of AVR-RD-01?
- Will the Gaucher and cystinosis trials start in 2019?
- What is the status of our ongoing transition to plato™?

Endogenous enzyme delivered to tissues via multiple cell lineages

Long-term engraftment in bone marrow

Manufacturing, transportation and delivery in blood

Example target organ



Kidney glomerulus

Two AVR-RD-01 Fabry clinical trials

8 patients dosed across Phases 1 and 2

PHASE 1 Investigator-Sponsored Trial*	PHASE 2 AVRO – FAB-201 Trial
Patients **n = 5 (fully enrolled)** **On ERT > 6 months prior to enrollment** **18 - 50 year-old males**	**Patients** **n = 8-12 (3 patients dosed to-date)** **Treatment-naive** **16 - 50 year-old males**
Key Objective Safety and preliminary efficacy	**Key Objectives** Safety and efficacy

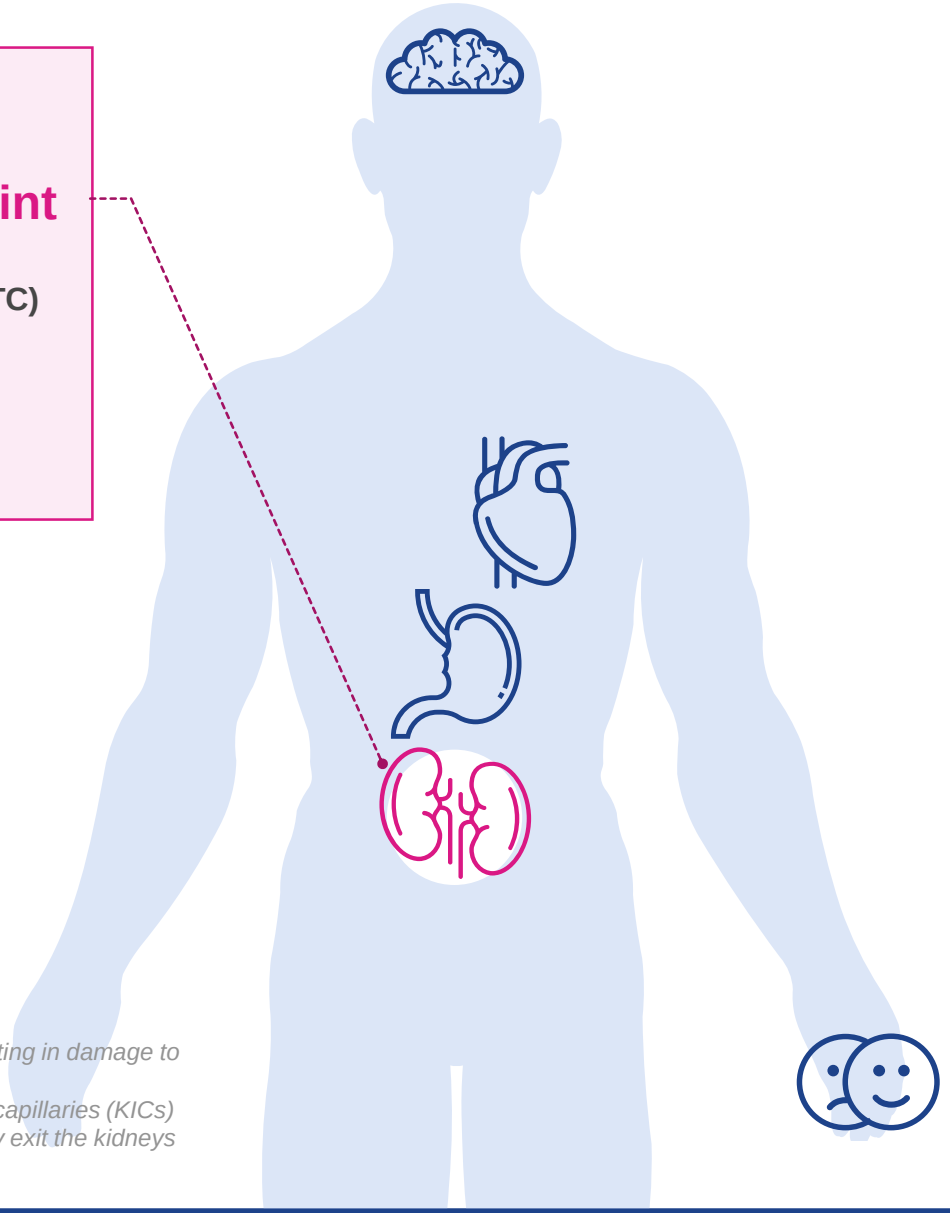
** Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada*

FAB-201 Primary and secondary endpoints

FAB-201
Primary efficacy endpoint

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

- Biopsy at 1 year vs. baseline
- FDA-recognized endpoint in Fabry



Primary safety endpoints

AEs, SAEs
Clinical labs, ECG, vital signs
Antibodies, RCL, ISA

Secondary efficacy endpoints

ORGAN AND SYSTEM FUNCTION

Kidney function
Cardiac function
GI distress
Pain

PATIENT WELL-BEING

Clinical status
Quality of life

BIOMARKERS

Toxic metabolite – lyso-Gb3 in plasma, urine
Substrate – Gb3 in plasma, urine, skin
Enzyme – AGA in leukocytes, plasma
VCN

Gb3, also referred to as GL-3: a type of fat that builds in cells, resulting in damage to kidneys, heart and brain
Peritubular capillaries (PTCs), also referred to as kidney interstitial capillaries (KICs) convey blood after filtration in the glomeruli, enabling it to eventually exit the kidneys and return to the circulatory system

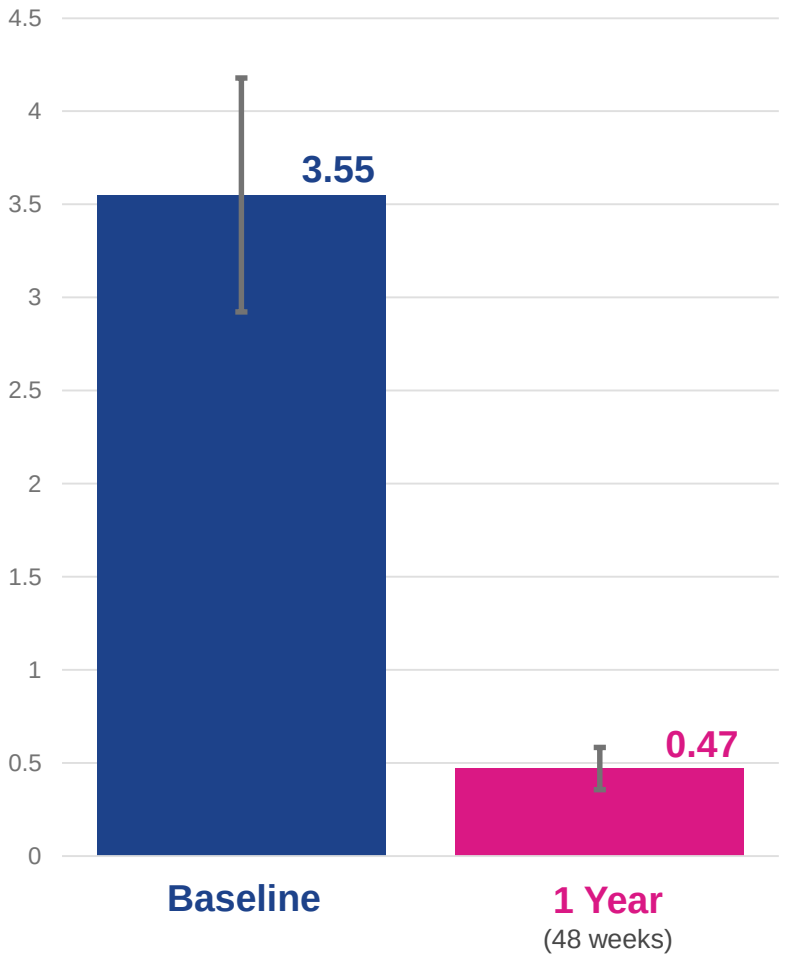
FAB-201 Patient Characteristics

	PATIENT 1	PATIENT 2	PATIENT 3
Age symptom onset / diagnosis	10 / 19 years	36 / 37 years	13 / 13 years
Age dosed with AVR-RD-01	21 years	46 years	40 years
Mutation	c.1021G>A (p.E341K)	c.644A>G (p.N215S)	c.639+1G>T
Primary disease signs and symptoms	• Kidney disease • Chronic pain • GI symptoms • Decreased cold sensation	• Cardiac disease • Peripheral neuropathy • Chronic pain • Increased tiredness • GI symptoms • Intermittent tinnitus • Mild high frequency hearing loss • Raynaud's syndrome	• Kidney disease • GI symptoms • Peripheral neuropathy • Bilateral deafness • Tinnitus • Peripheral edema • Decreased cold sensation
Leukocyte AGA enzyme activity at baseline (nmol/h/mg)	0.10*	2.38**	0.58**
Plasma lyso-Gb3 at baseline (nM)***	202	8	147
Comment	IgA deposits in kidney biopsy	Cardiac variant, not a classic Fabry male	

* *Mayo Lab, ref range ≥23.1 nmol/h/mg*
** *Rupar Lab, ref range 24-56 nmol/h/mg*
*** *Reference value ≤ 2.4 nM*
Note: *AGA is α-galactosidase A, Lyso-Gb3 is lyso-globotriaosylceramide*

FAB-201 Patient 1: 87% substrate reduction in kidney biopsy

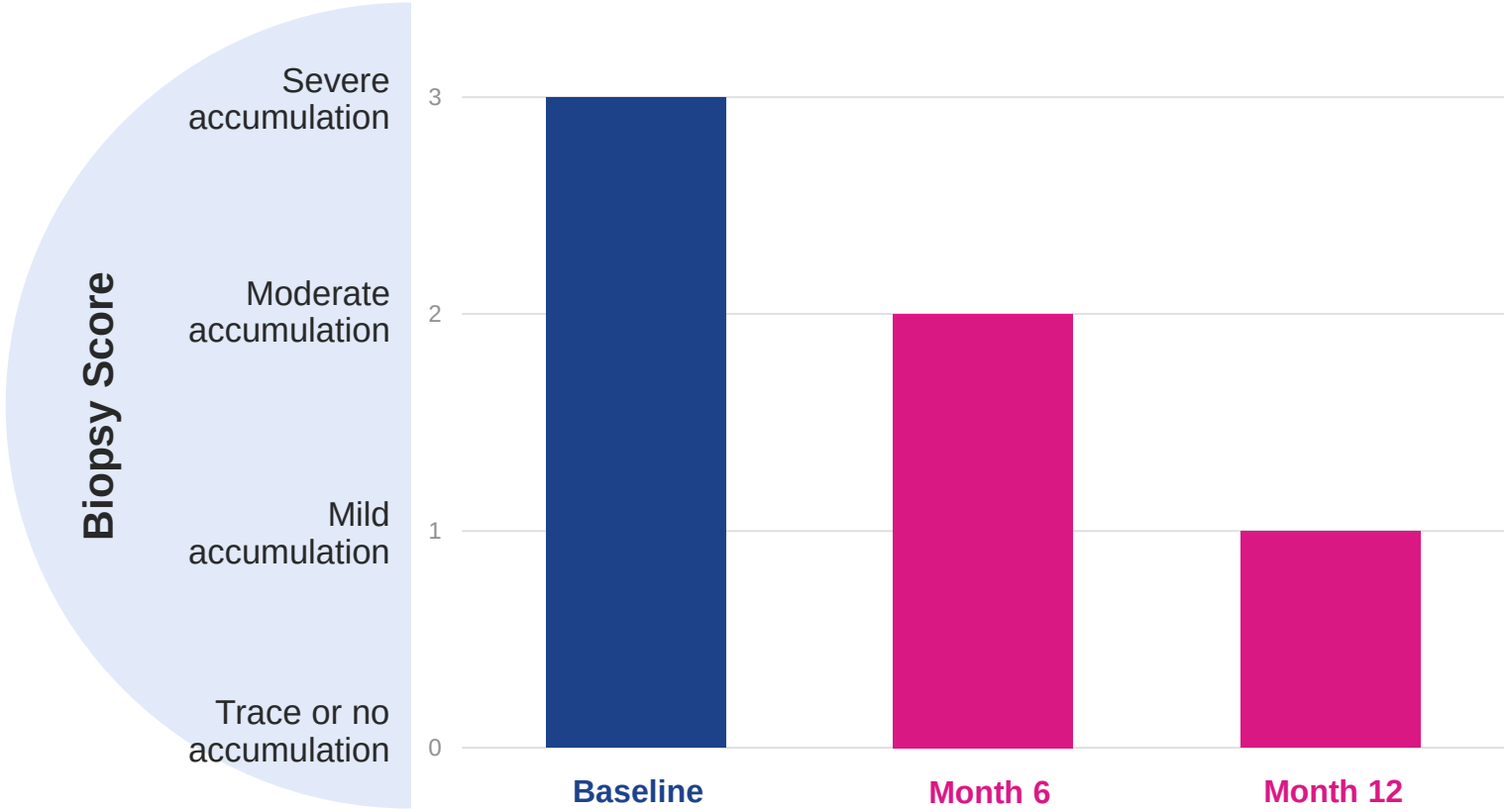
Average number of **Gb3 inclusions per peritubular capillary (PTC)**



- *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*

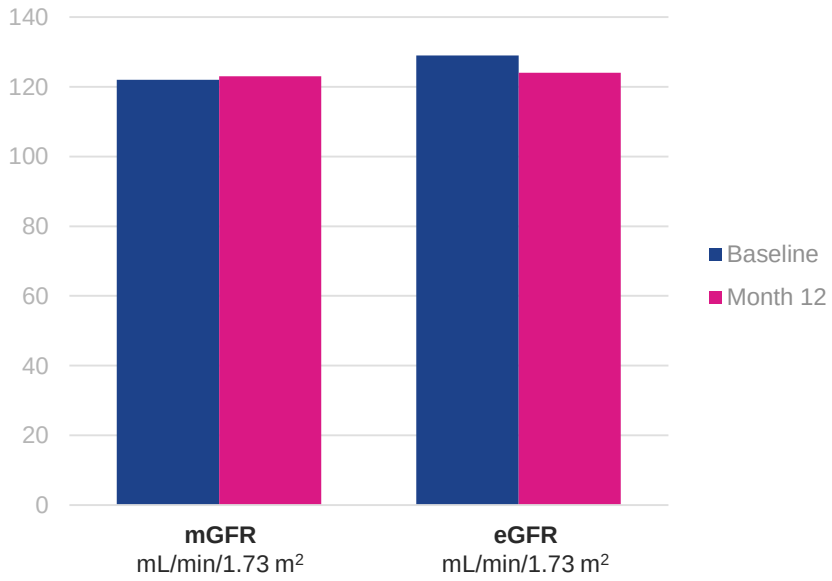
FAB-201 Patient 1: Continued reduction in substrate inclusions in skin endothelial cells



Source: *Thurberg BL, 2011, https://everylifefoundation.org/wp-content/uploads/images/workshopseries/16-Thurberg-Fabry-pathology-Nov-2011-compr-dc.pdf*

FAB-201 Patient 1: Kidney and cardiac function stable at one year

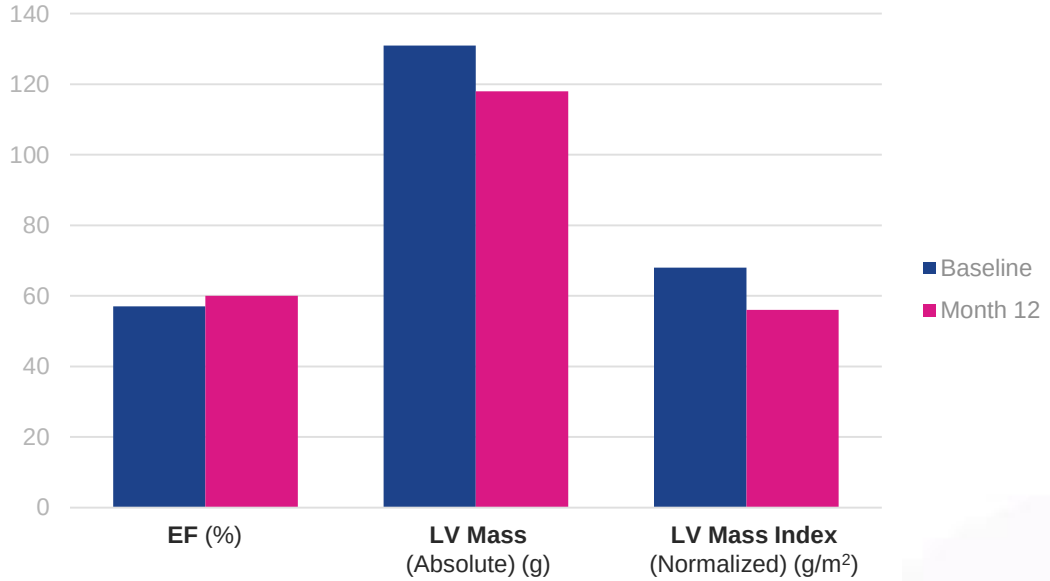
KIDNEY FUNCTION
remains within normal range



Normal Range	mGFR/eGFR
Male (20-29 years)	Average 116*

Source: https://www.kidney.org/atoz/content/gfr
Note: *mGFR is measured Glomerular Filtration Rate, eGFR is estimated Glomerular Filtration Rate*

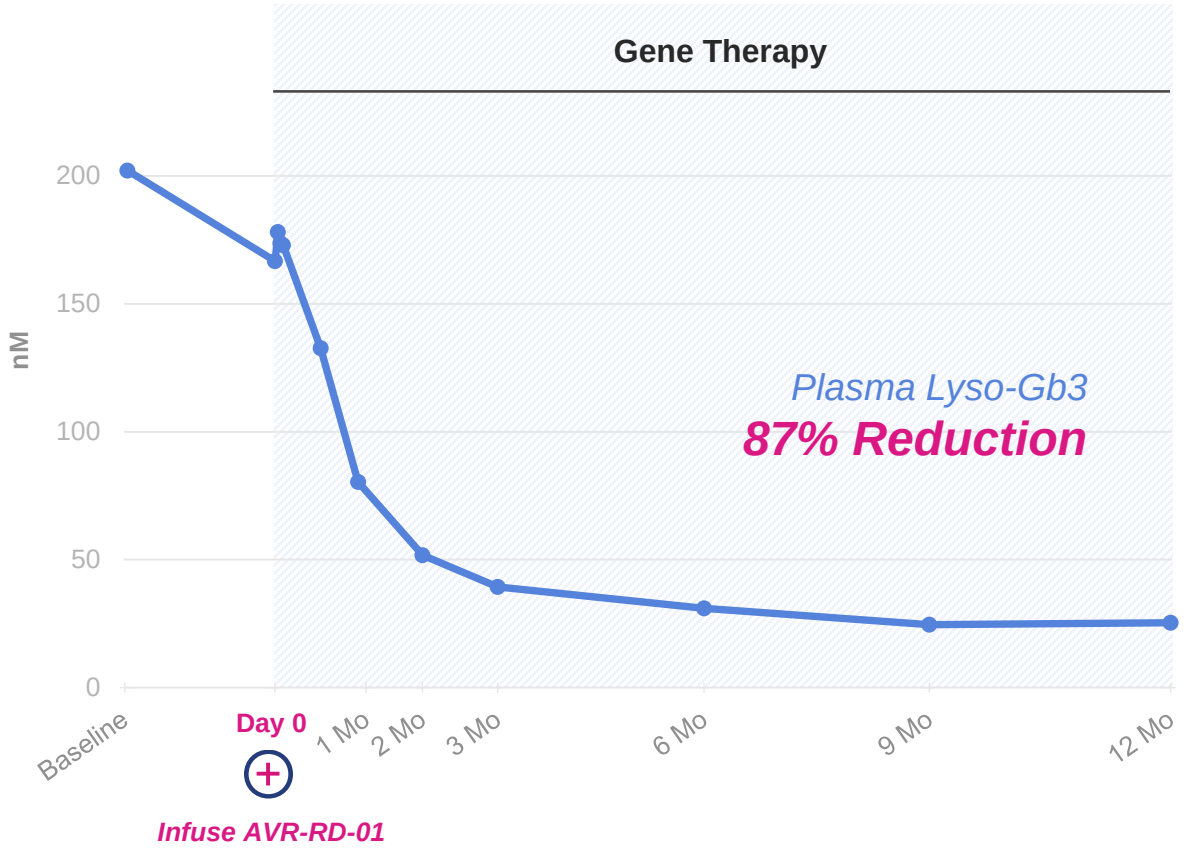
CARDIAC FUNCTION
remains within normal range

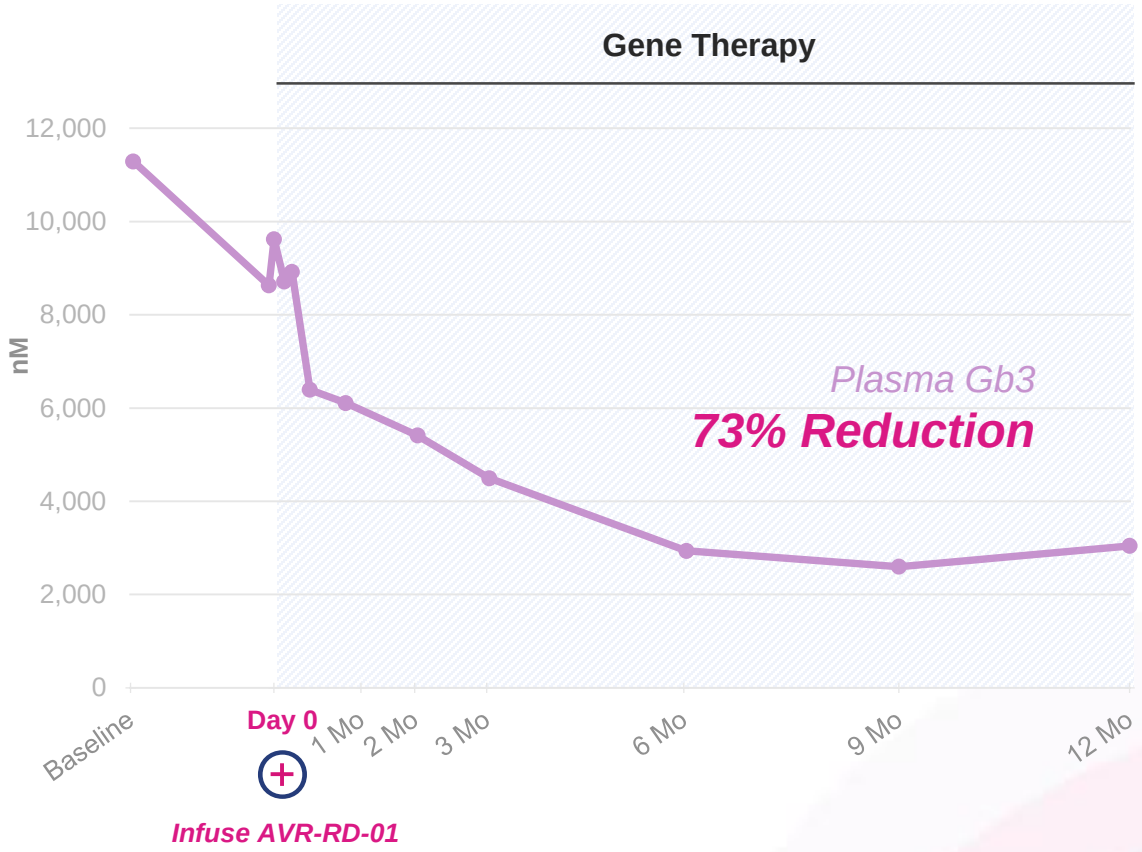


Reference Range Mean Values ± SD	EF (%)	LVM (g)	LVMI (g/m²)
Male (20-39 years)	64.3 ± 4.2	138.9 ± 24.5	67.8 ± 10.7

Source: *Alfakih K et al, J Magn Reson Imaging, 2003*
Note: *EF is Ejection Fraction, LVMI is Left Ventricular Mass Index*

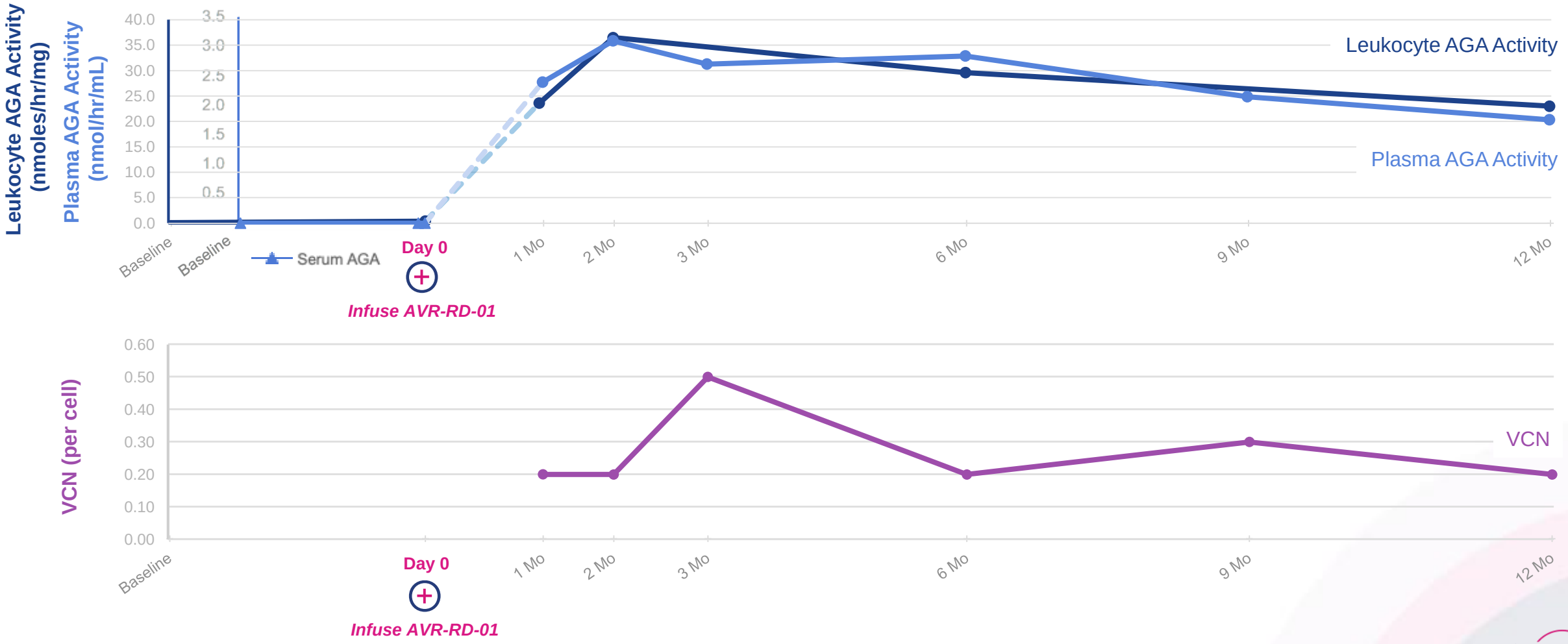
FAB-201 Patient 1: Substantial reduction in plasma substrate / metabolite levels, sustained at 1 year





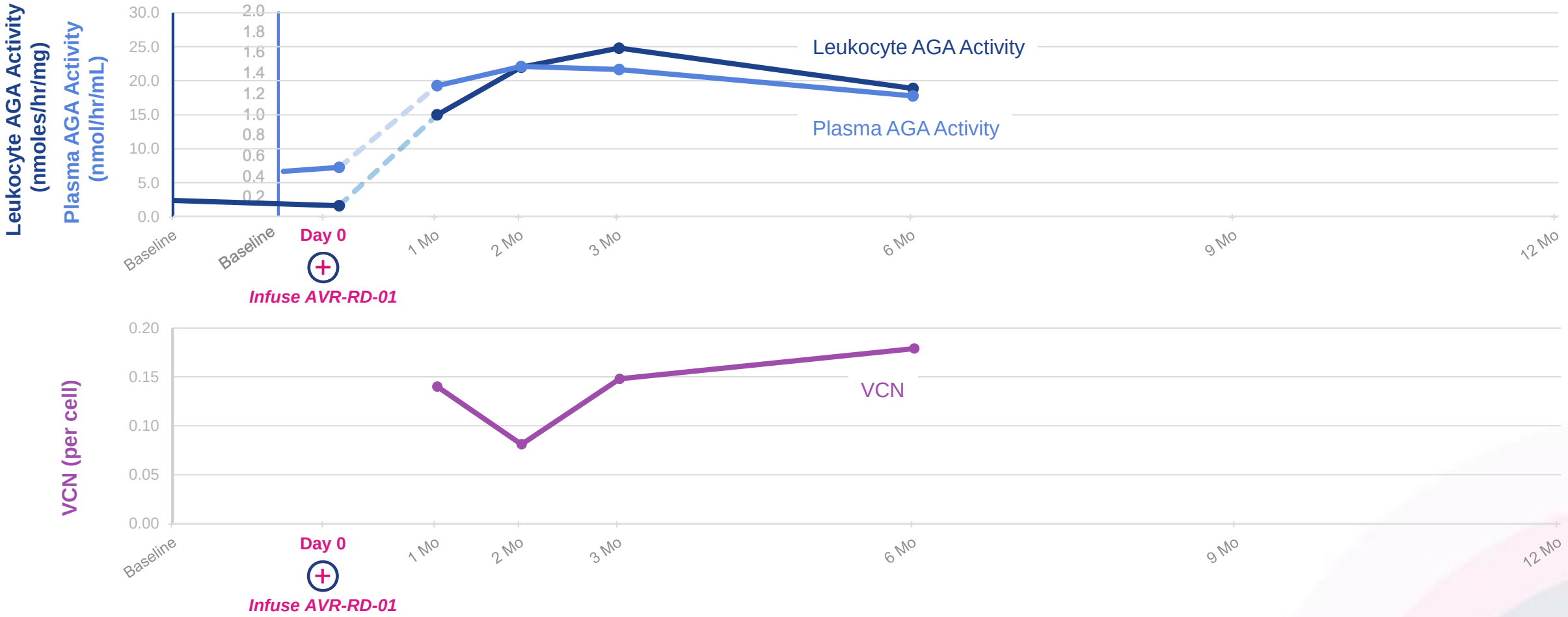
Baseline: *The last available, non-missing observation prior to AVR-RD-01 infusion*
Note: *AVR-RD-01 is an investigational gene therapy*

FAB-201 Patient 1: Sustained leukocyte and plasma enzyme activity at 1 year; VCN stable



Note: *0.1 VCN is indicative of approx. 5-10% of all nucleated cells having an average of 1-2 copies of the transgene*
Baseline: *The last available, non-missing observation prior to AVR-RD-01 infusion*

FAB-201 Patient 2: Sustained leukocyte and plasma enzyme activity and VCN at 6 months



Note: *Patient 3 had plasma AGA activity of 0.740, leukocyte AGA activity of 9.94 and VCN of 0.12 as of 1 month*
Note: 0.1 *VCN is indicative of approx. 5-10% of all nucleated cells having an average of 1-2 copies of the transgene*
Baseline: *The last available, non-missing observation prior to AVR-RD-01 infusion*

FAB-201
3 patients dosed

No unexpected trends or safety events identified

No AEs or SAEs related to AVR-RD-01 drug product

AEs and SAEs reported

- **AEs**
  - Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
- **SAEs**
  - **Pre-treatment**
    - Seizure (resolved)
  - **Post-treatment**
    - Dehydration, nausea, vomiting (resolved)
    - Febrile neutropenia (resolved)

Anti-AGA antibodies

- Transient low titer in 1 subject (resolved)

Note: *Safety database cut as of July 10, 2019*

Two AVR-RD-01 Fabry clinical trials

8 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

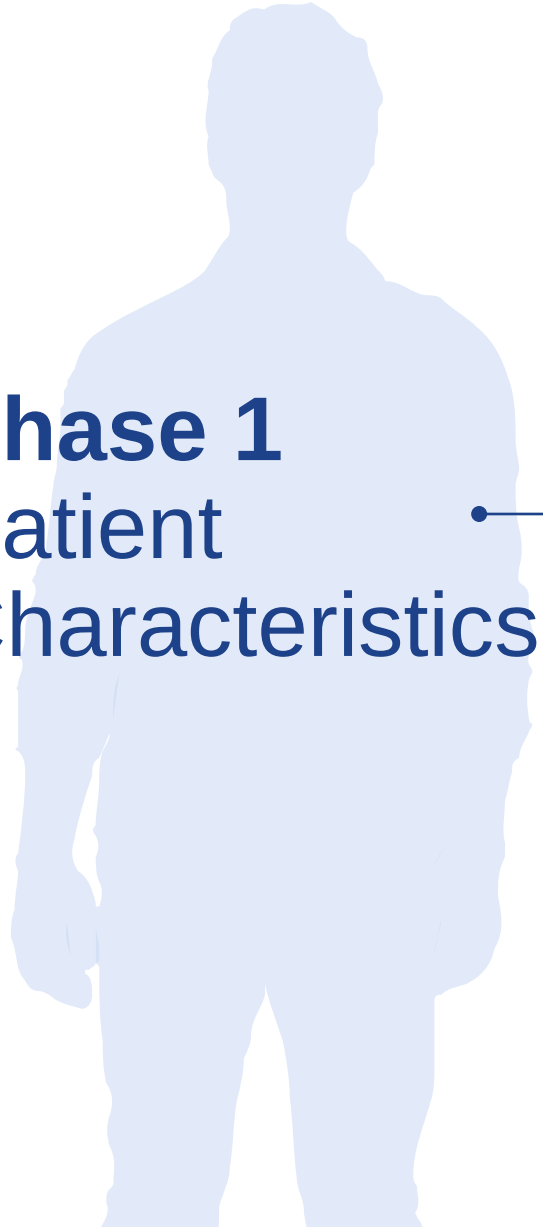
Patients

n = 8-12 (3 patients dosed to-date)
Treatment-naive
16 - 50 year-old males

Key Objectives

Safety and efficacy

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



Phase 1 Patient Characteristics

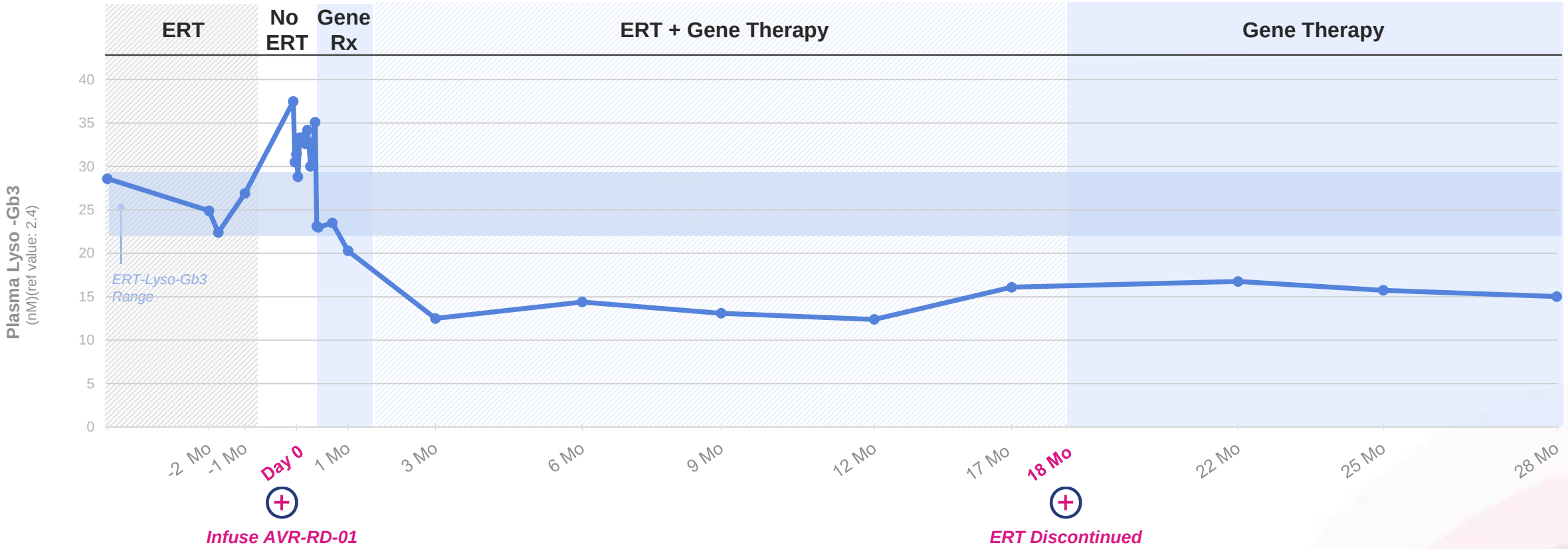
	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Age symptom onset / diagnosis	18 / 37	9 / 29	10 / 0	7 / 4	10 / 14
Years on ERT	11	6	4	11	2
Age dosed with AVR-RD-01	48	39	40	37	30
Mutation	c.962A>G (p.Q321R)	c.1033T>C (p.S345P)	c.427G>C (p.A143P)	c.427G>C (p.A143P)	(p.Y134S)
Primary disease signs and symptoms	• Kidney disease • Cardiac disease • GI pain • GI diarrhea • Angiokeratoma • Insomnia	• Kidney disease • Cardiomyopathy • Hypohidrosis • Corneal verticillata • Peripheral neuropathy • GI symptoms • Angiokeratoma • Lymphedema • Acroparesthesia	• Cardiac Disease • Tinnitus • Headaches • Dizziness • Acroparesthesia	• Cardiac Disease • Hypohidrosis • Tinnitus • Corneal verticillata • Angiokeratoma • GI symptoms	• Kidney disease • Hypertension • Hypohidrosis • Tinnitus • Migraines • Impaired hearing • Angiokeratoma • Sleep apnea • Asthma • Depression
Leukocyte AGA activity at baseline* (nmol/h/mg)	2.1	1.1	0.6	2.2	1.0
Plasma lyso-Gb3 at baseline (nM)**	25	26	59	29	16
Discontinued ERT	18 months after gene therapy dose		Did not resume ERT after gene therapy dose	ERT discontinuation planned	

** Rupar Lab, ref range 24-56 nmol/h/mg*
*** Reference value ≤ 2.4 nM*
Note: *AGA is α-galactosidase A, Lyso-Gb3 is lyso-globotriaosylceramide*

Phase 1: Plasma lyso-Gb3 reduction sustained >2 yrs

Reduced 41% from ERT baseline*

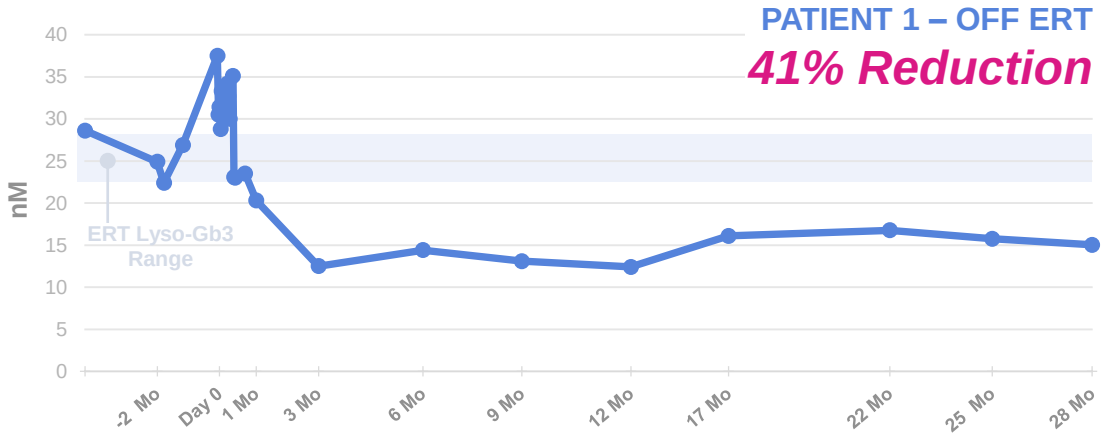
Patient #1

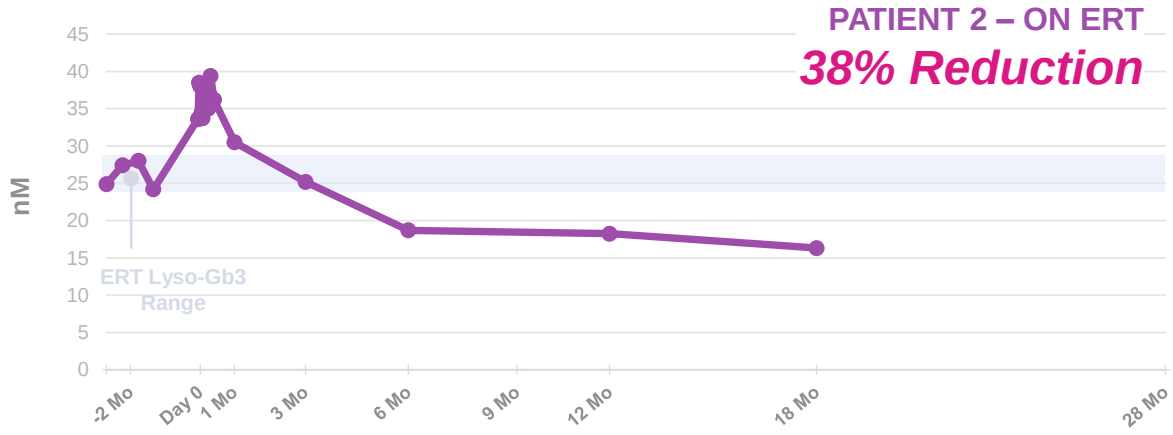


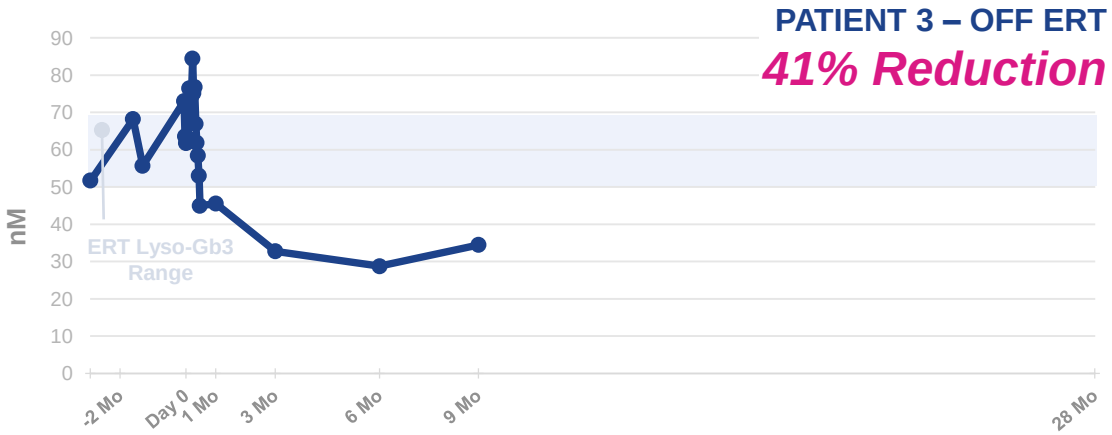
*Baseline: The mean of the values reported prior to initiating mobilization

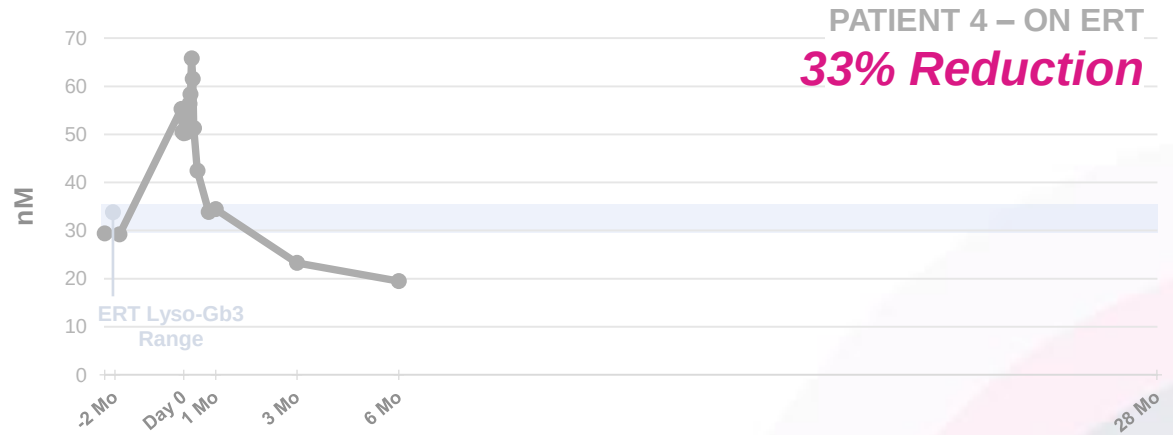
Note: AVR-RD-01 is an investigational gene therapy candidate

Phase 1: Plasma lyso-Gb3 consistently reduced by 33-41% vs. baseline* ERT





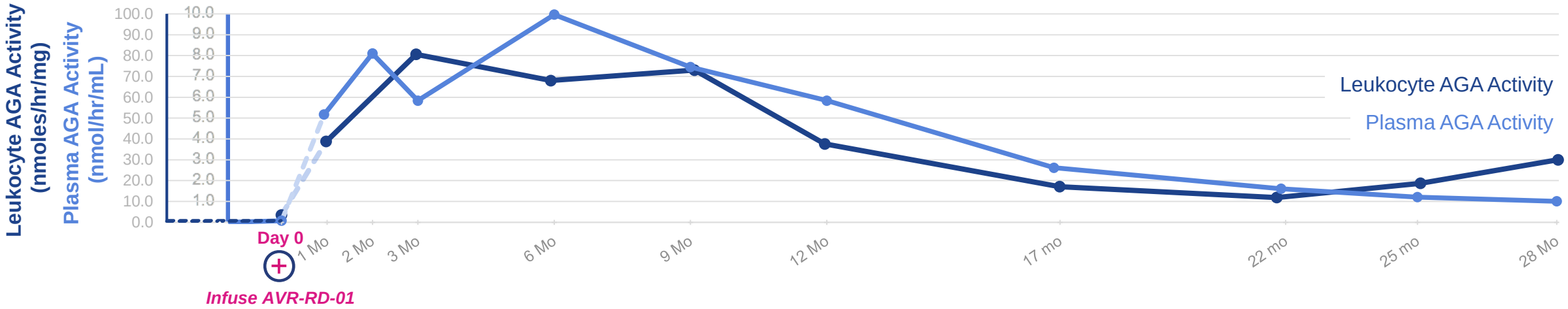


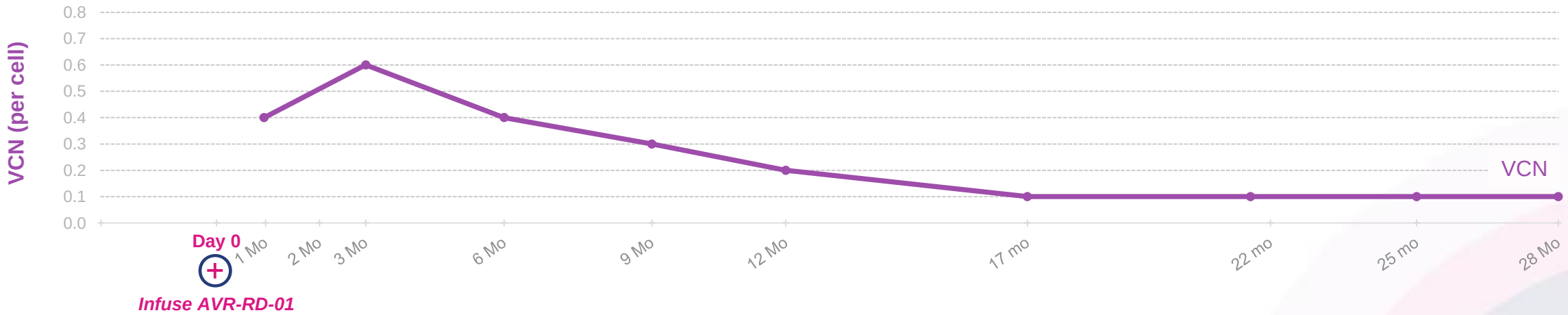


***Baseline:** The mean of the values reported prior to initiating mobilization*
***Percent reduction:** As measured from baseline to last assessment*

Phase 1: Leukocyte and plasma enzyme activity sustained >2 years; VCN stable

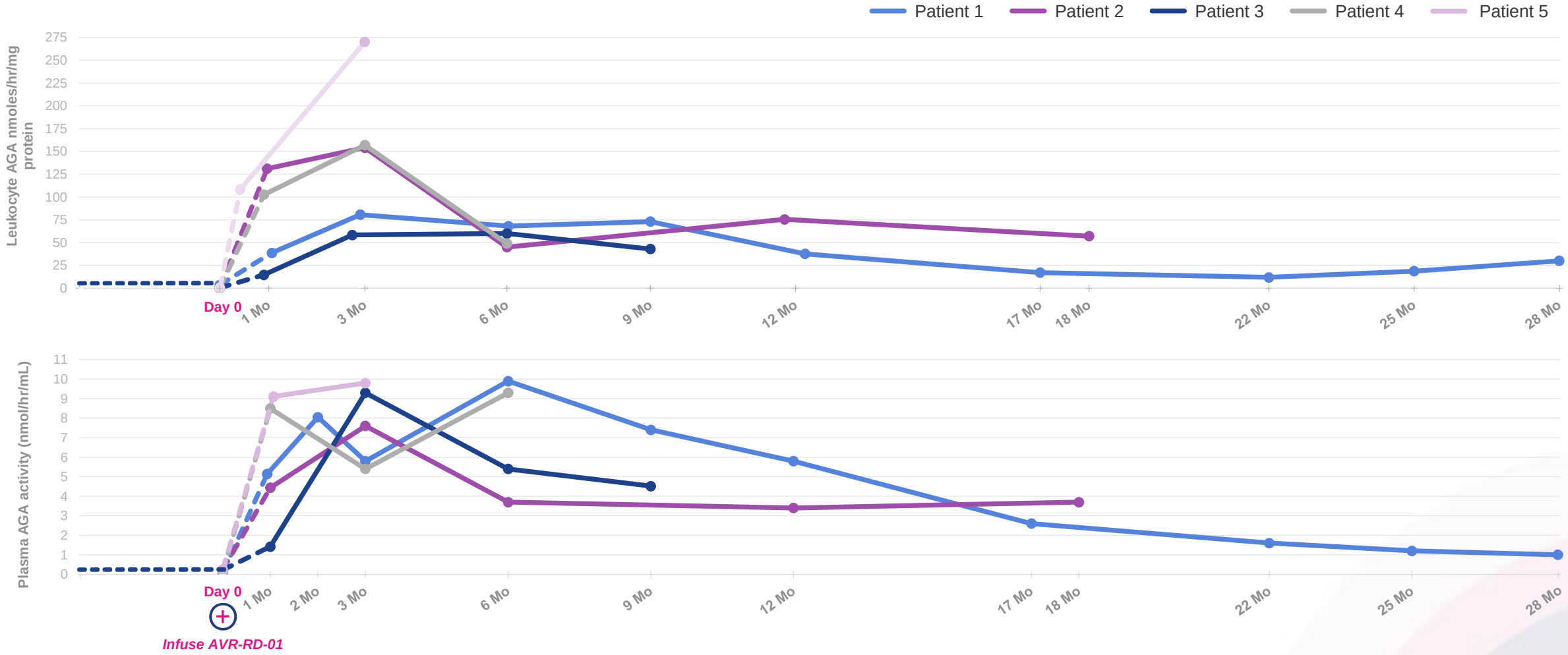
Patient #1





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

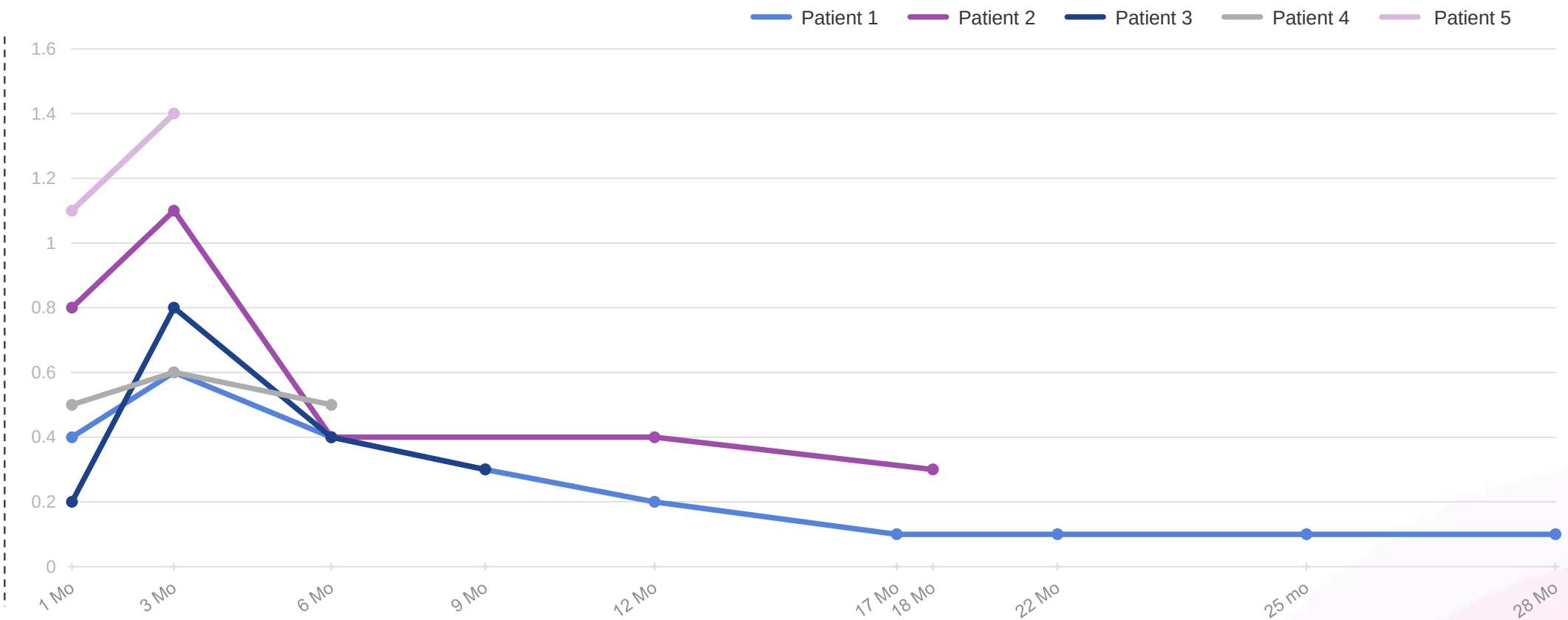
Phase 1: Leukocyte and plasma enzyme activity levels trend consistently across all patients



Note: *Enzyme measurements are taken at ERT troughs; Note: Dotted line illustrative only*
Patient #5's Day 12 data point was utilized since the one month data was not obtained

Phase 1: Consistent VCN trend across all patients

Drug Product VCN	
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*

Phase 1
5 patients dosed

No unexpected trends or safety events identified

No SAEs related to AVR-RD-01 drug product

AEs and SAEs reported

- **AEs**
  - Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
- **SAEs**
  - Febrile neutropenia (resolved)
  - Thrombophlebitis (resolved)*

Anti-AGA antibodies

- Mild titer rise in 1 patient

Note: *Safety database cut as of May 24, 2019*

**Resolved post-safety database cut-off date*

8 patients
dosed across
2 trials

longest follow-up
>2 years

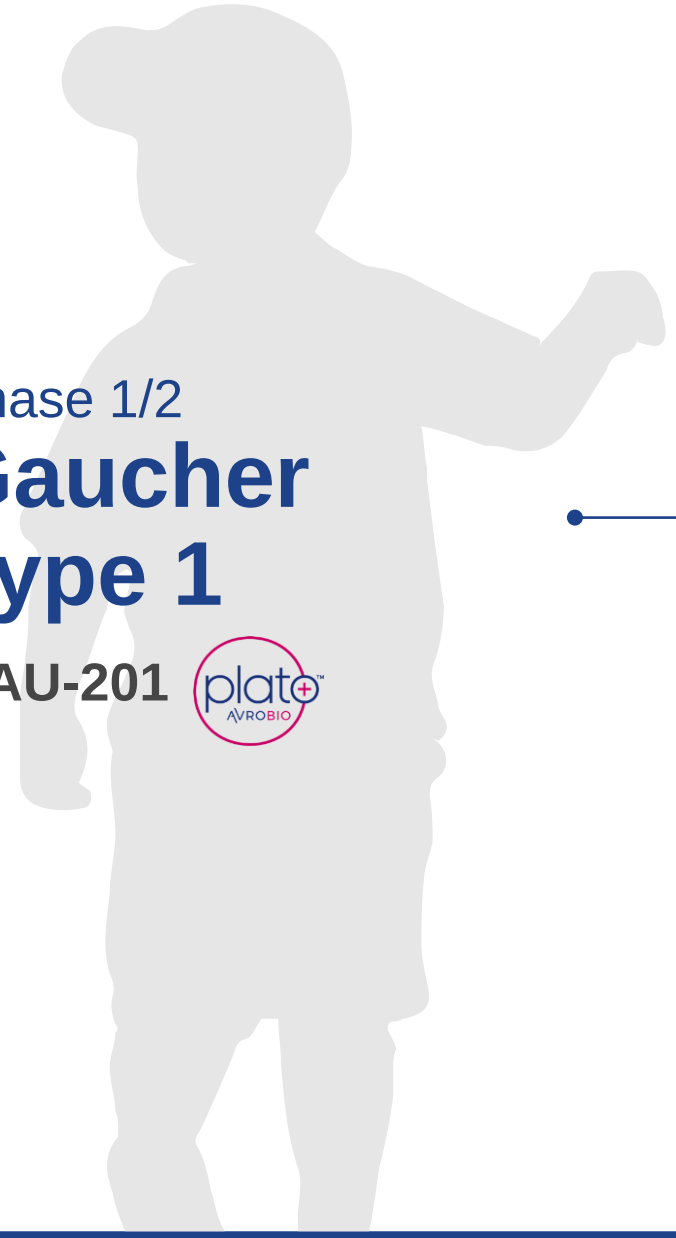
Emerging data support potential first-line use in Fabry disease

- 87% decrease in Gb3 in first kidney biopsy at 1 year
  in first Phase 2 patient
- Plasma lyso-Gb3 reduced by 30-40% vs. baseline ERT
  in four Phase 1 patients
- Kidney and cardiac function stable at 1 year
  in first Phase 2 patient
- Durability sustained >2 years for enzyme activity and VCN
  in first Phase 1 patient
- No unexpected trends or safety events identified
  8 patients across 2 trials

Steady stream of clinical programs

4 clinical trials up and running

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



Phase 1/2

Gaucher Type 1

GAU-201

- Clinical sites in CA, AUS actively recruiting
- First patient expected to be dosed 2H 2019
- US, CA, AUS manufacturing in place
- Pre-clinical data demonstrates bone improvement

Phase 1/2

Cystinosis

Investigator-Sponsored Trial

- US IND achieved
- Clinical site actively recruiting
- First patient expected to be dosed 2H 2019
- $12M Tier 1 CIRM grant funding to UCSD

plato™

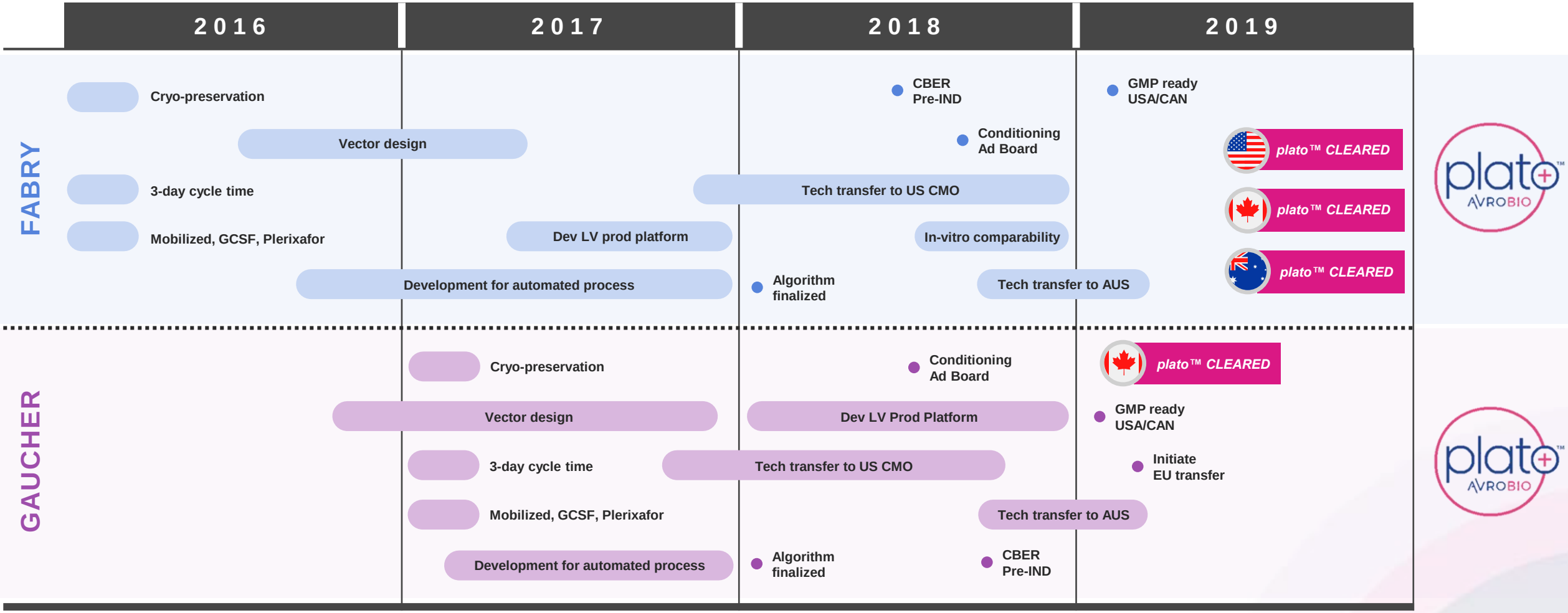
AVROBIO's foundation for worldwide commercialization

Beginning-to-end manufacturing platform

- **Optimized** for performance
- **Redefines** manufacturing best practices

POWERED BY AVROBIO plato™

Multiple plato™ IND and CTA regulatory clearances achieved 1H 2019



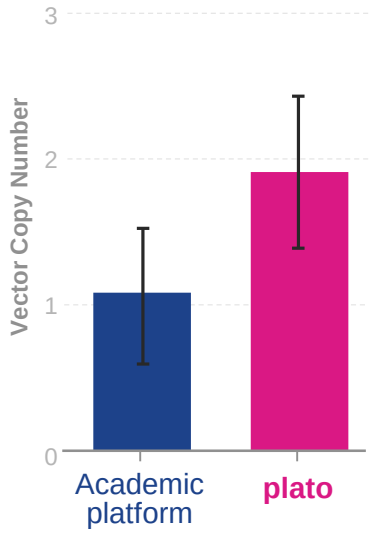
Note: *plato in Fabry cleared for use in US via IND, in Canada via protocol and CMC CTA amendment, and in AUS via CTN and HREC clearance; plato in Gaucher cleared for use in Canada via CTA and protocol CTA amendment*

plato™ optimized for performance

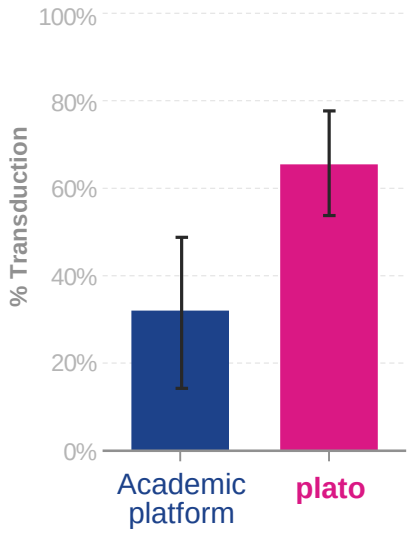
Proprietary Vector Toolbox

- OPTIMIZED VECTOR
- PROMOTERS
- OPTIMIZED TRANSCRIPTION
- OPTIMIZED TRANSLATION
- TAGS
- KOZAK SEQUENCE
- CODON OPTIMIZATION

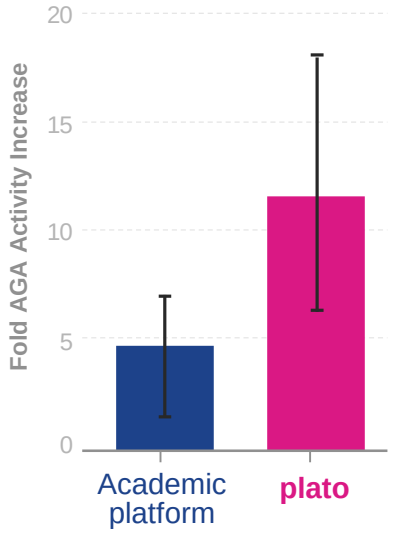
VCN



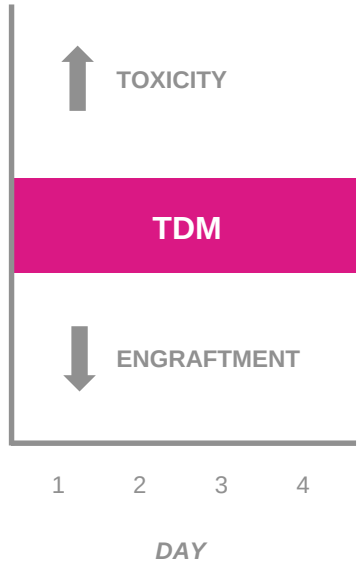
Transduction Efficiency



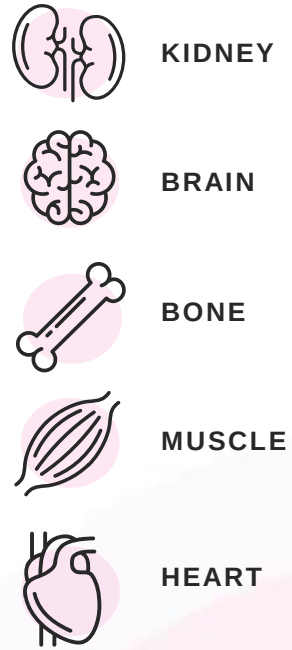
Enzyme Activity



Therapeutic Drug Monitored (TDM) Conditioning



Distribution



Note: Data from appropriate runs from normal donors and patients are included in the analysis; Data cutoff March 12, 2019

plato™ platform designed to be scalable for commercial supply

VECTOR	DRUG PRODUCT
2,400 PATIENTS ANNUALLY	2,400 PATIENTS ANNUALLY
~50 patients per run	**100** patients per unit per year
~12 runs per year per suite (200 L scale bioreactor runs (10^9 titre))	**8** automated units per suite
4 production suites	**3** global production suites

POWERED BY plato™

Multiple 2H 2019 milestones anticipated

FABRY

- Continued recruitment in FAB-201, with plato™ to be incorporated
- FAB-201 clinical sites to expand into USA and Canada

GAUCHER

- Dose first patient in GAU-201, incorporating plato™ from the outset

CYSTINOSIS

- Dose first patient in investigator-sponsored trial

POMPE

- Pre-clinical IND-enabling study to be initiated

Key take-aways for today

- 87% substrate reduction in first kidney biopsy, an endpoint used by FDA and EMA
  in first Phase 2 patient
- Toxic metabolite levels of patients treated with AVR-RD-01 are 30-40% below baseline ERT levels
  in first four Phase 1 patients
- Durability of AVR-RD-01 sustained >2 years and stable across multiple measures
  in first Phase 1 patient
- On track to achieve goal of 3 investigational gene therapies in the clinic 2H 2019
- Commercially scalable plato™ platform in place

Appendix

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


CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208623Orig1s000

Fabry Ph1/2 Gene Tx Followup Shows Roll Off of Expression, But Levels Remain in Non-

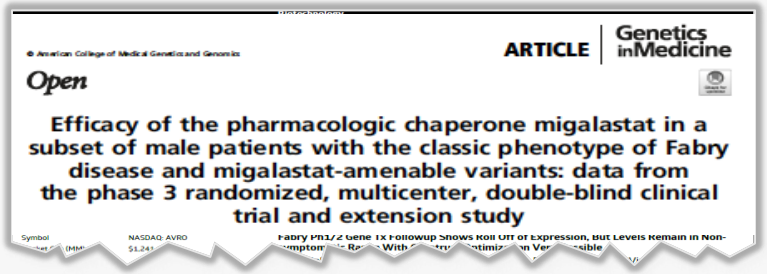
45 Amenable patients* (16 males / 29 females)

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 ≥ 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 ≥ 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)


ARTICLE | Genetics inMedicine

Open

Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of Fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study

Fabry Ph1/2 Gene Tx Followup Shows Roll Off of Expression, But Levels Remain in Non-

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

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[b] 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)

- *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*