AVROBIO

Freedom from a lifetime of disease

Corporate Presentation

August 2019

Disclaimer

This presentation has been prepared by AVROBIO, Inc. ("AVROBIO") for informational purposes only and not for any other purpose. Certain information contained in this presentation and statements made orally during this presentation relate to or are based on studies, publications, surveys and other data obtained from third-party sources and AVROBIO's own internal estimates and research. While AVROBIO believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and AVROBIO makes no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. While AVROBIO believes its internal research is reliable, such research has not been verified by any independent source.

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts", "goal," "intends," "may" "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. These forward-looking statements include, without limitation, statements regarding our business strategy, prospective products and goals, the therapeutic potential of our investigational gene therapies, the design, enrollment and timing of ongoing or planned clinical trials, clinical trial results, product approvals and regulatory pathways, potential regulatory approvals and the timing thereof, anticipated benefits of our gene therapy platform, the expected safety profile of our investigational gene therapies, timing and likelihood of success, plans and objectives of management for future operations, future results of anticipated products, and the market opportunity for our investigational gene therapies. Any such statements in this presentation that are not statements of historical fact may be deemed to be forward-looking statements.

Any forward-looking statements in this presentation are based on AVROBIO's current expectations, estimates and projections about our industry as well as management's current beliefs and expectations of future events only as of today and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that any one or more of AVROBIO's investigational gene therapies will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials of AVROBIO or our collaborators, the risk that AVROBIO may not realize the intended benefits of our gene therapy platform, the risk that our investigational gene therapies or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or trials involving AVROBIO's investigational gene therapies, the risk that we will be unable to obtain and maintain regulatory approvals for our investigational gene therapies, the risk that the size and growth potential of the market for our investigational gene therapies will not materialize as expected, risks associated with our dependence on third-party suppliers and manufacturers, risks regarding the accuracy of our estimates of expenses and future revenue, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our investigational gene therapies. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause AVROBIO's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in AVROBIO's most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, uncertainties and other important factors in AVROBIO's subsequent filings with the Securities and Exchange Commission. AVROBIO explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

Note regarding trademarks: plato is a trademark of AVROBIO. Other trademarks referenced in this presentation are the property of their respective owners.

Developing gene therapies designed to cure rare diseases

- Deep pipeline targeting lysosomal storage disorders (LSDs) where SoC ~$4B 2018 net sales
- Compelling Fabry data across Phase 1 and Phase 2 trials
- Gaucher and cystinosis expected to enter the clinic this year
- Powered by plato™ - our commercial-stage manufacturing platform
- Management comprised of cell, gene and rare disease industry leaders
- Multiple 2H 2019 milestones anticipated

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

Addressing multi-billion dollar markets

CURRENT STANDARD OF CARE COSTS

Disease	Est. Cost Per Year	Approx. 2018 Net Sales	Selected Companies
Fabry	$320k	$1.4B	SANOFI GENZYME, Takeda Shire
Gaucher	$250k-400k	$1.4B	SANOFI GENZYME, Takeda Shire
Pompe	$500k	$1B	SANOFI GENZYME
Cystinosis	$625k-700k*	$0.2B	HORIZON PHARMA, Mylan, RECORDATI

Sources: *Rombach S et al, Orphanet J Rare Dis, 2013; van Dussen L et al, Orphanet J Rare Dis, 2014; WAC pricing from Redbook; 2018 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

Cell, gene and rare disease industry leaders

MANAGEMENT TEAM

Geoff MacKay
President and CEO

Organogenesis Inc. · Novartis

Birgitte Volck, PhD, MD
President of Research and Development

GSK · Sobi · Amgen

Kim Warren, PhD
Head of Operations

Lonza · CCRM

Erik Ostrowski
Chief Financial Officer

Summit Therapeutics · LEERINK · Organogenesis Inc.

Chris Mason, MD, PhD, FRCS
Chief Science Officer

UCL

Steven Avruch, JD
General Counsel

Biogen

Deanna Petersen, MBA
Chief Business Officer

Shire · agenus

Josie Yang, PhD
Head of Regulatory Affairs

PTC Therapeutics · FDA · ImClone Systems

Kathryn McNaughton, PhD
SVP Portfolio & Program Management

Shire · Synageva

BOARD OF DIRECTORS

Bruce Booth, DPhil
Chairman

ATLAS VENTURE

Ian Clark

Genentech
A Member of the Roche Group

Philip Vickers, PhD

Northern Biologics · Shire

Annalisa Jenkins, MBBS, FRCP

Merck Serono · Dimension Therapeutics

Phillip Donenberg

avexis

Chris Paige, PhD

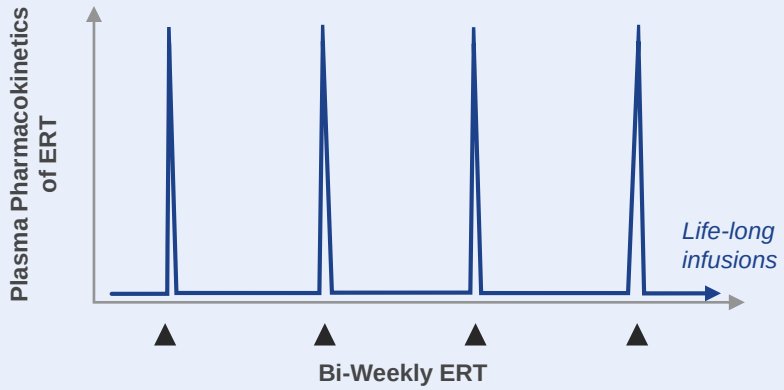
UHN

Geoff MacKay

AVROBIO

POWERED BY AVROBIOplato

Life-long treatments vs. potential single dose cure

	DISEASE PROGRESSION **CONTINUES**	DISEASE PROGRESSION **COULD HALT**
	Enzyme Replacement Therapy (ERT) Temporary bolus of enzyme, not curative	**AVROBIO Gene Therapy** 24/7 expression of protein, curative potential
		
Enzyme or protein level	Transient, intermittent elevation	Long-term, continuous elevation
Treatment burden	Bi-weekly IV infusions	Single IV infusion

One platform applied across our portfolio

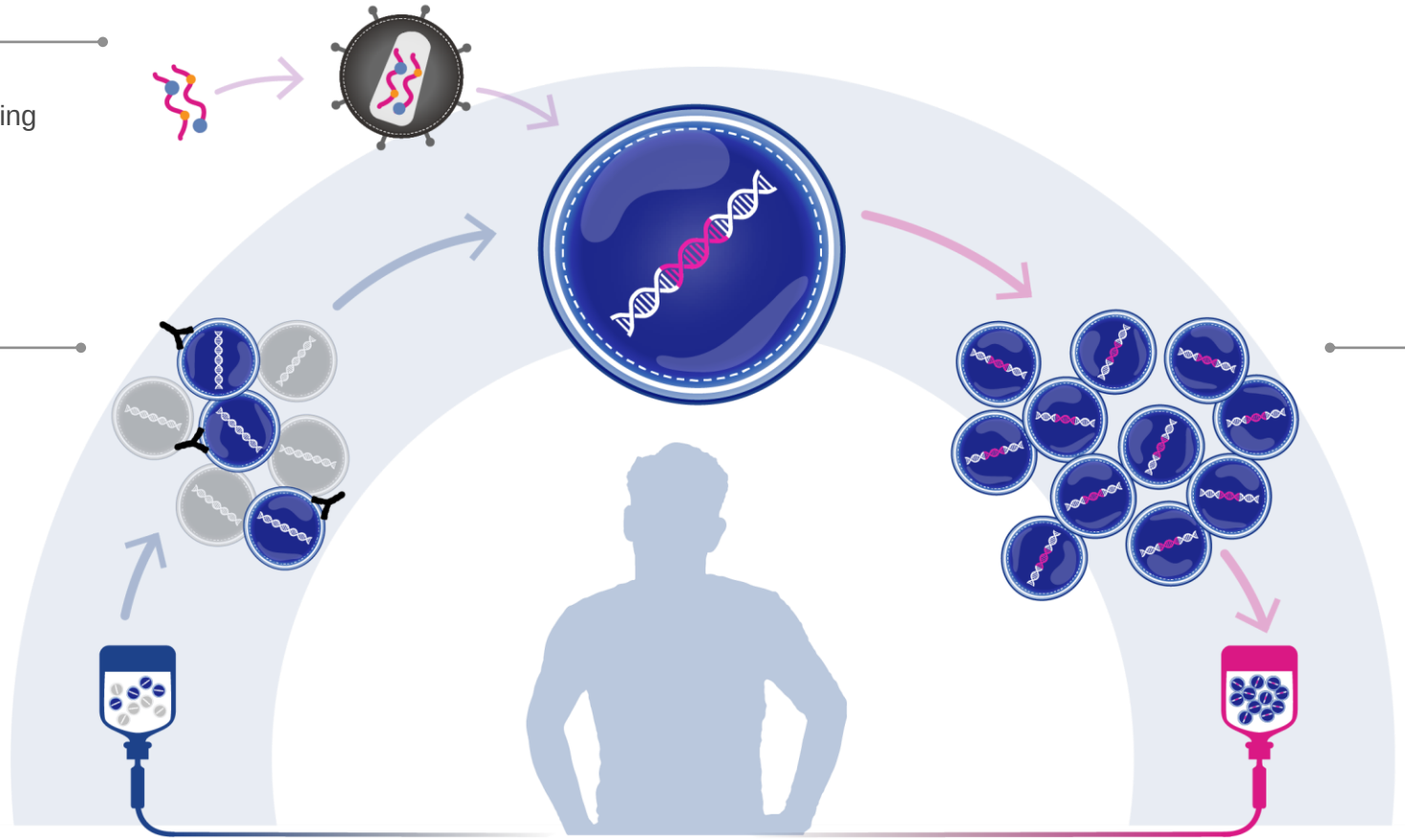
3 **Transduce** with lentiviral vector carrying normal gene

2 **Select** CD34+ stem cells

1 **Collect** mobilized blood

Harvest and freeze **4**

Infuse **5**



GENE THERAPY PLATFORM

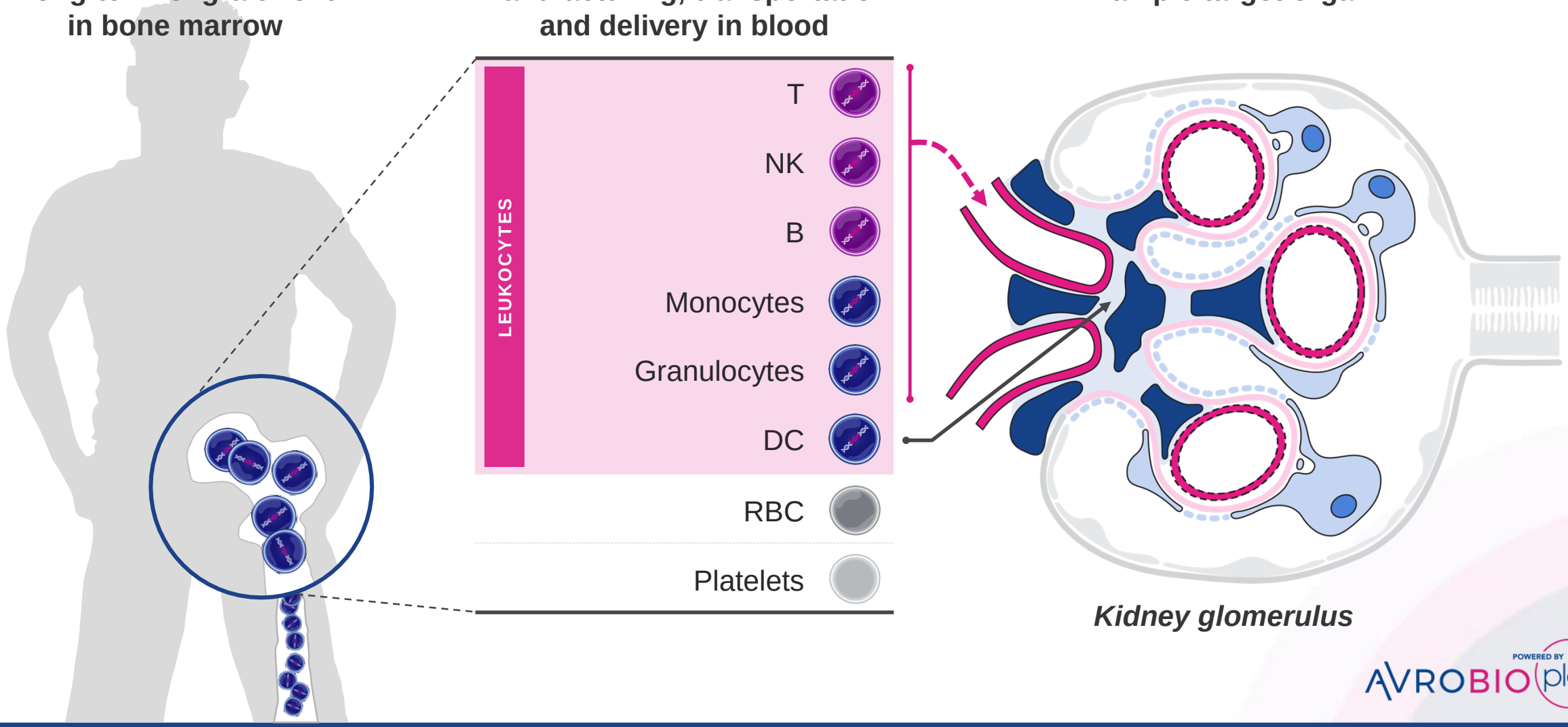
POWERED BY AVROBIO plato

Endogenous enzyme delivered to tissues via multiple cell lineages

Long-term engraftment in bone marrow

Manufacturing, transportation and delivery in blood

Example target organ

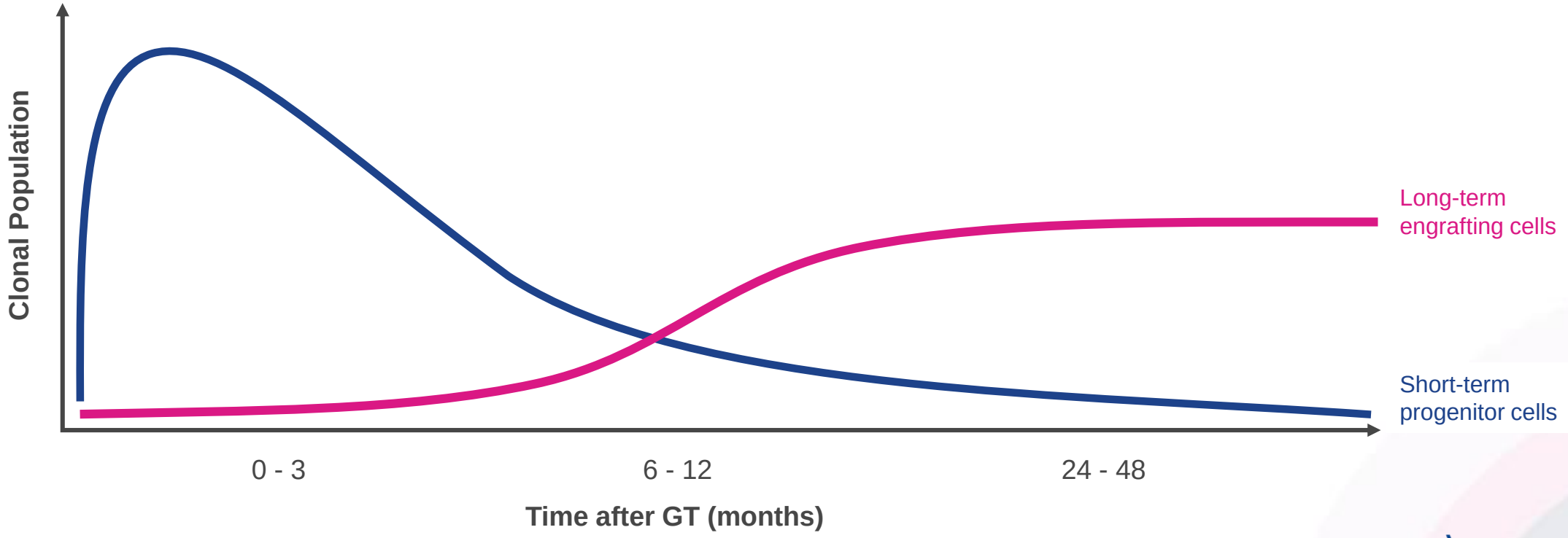


Kidney glomerulus

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



Source: Biasco L et al, Cell Stem Cell, 2016

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

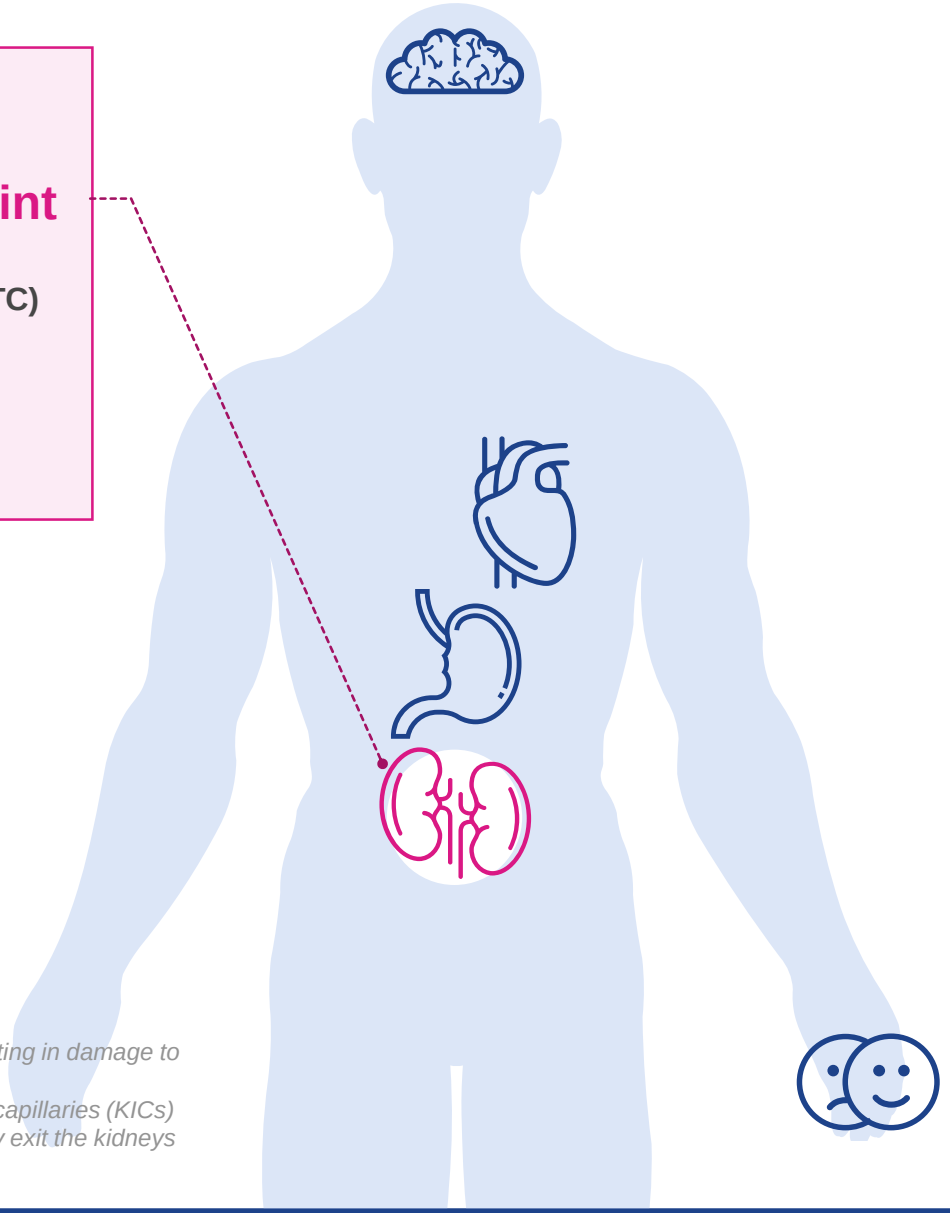
** Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada*

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

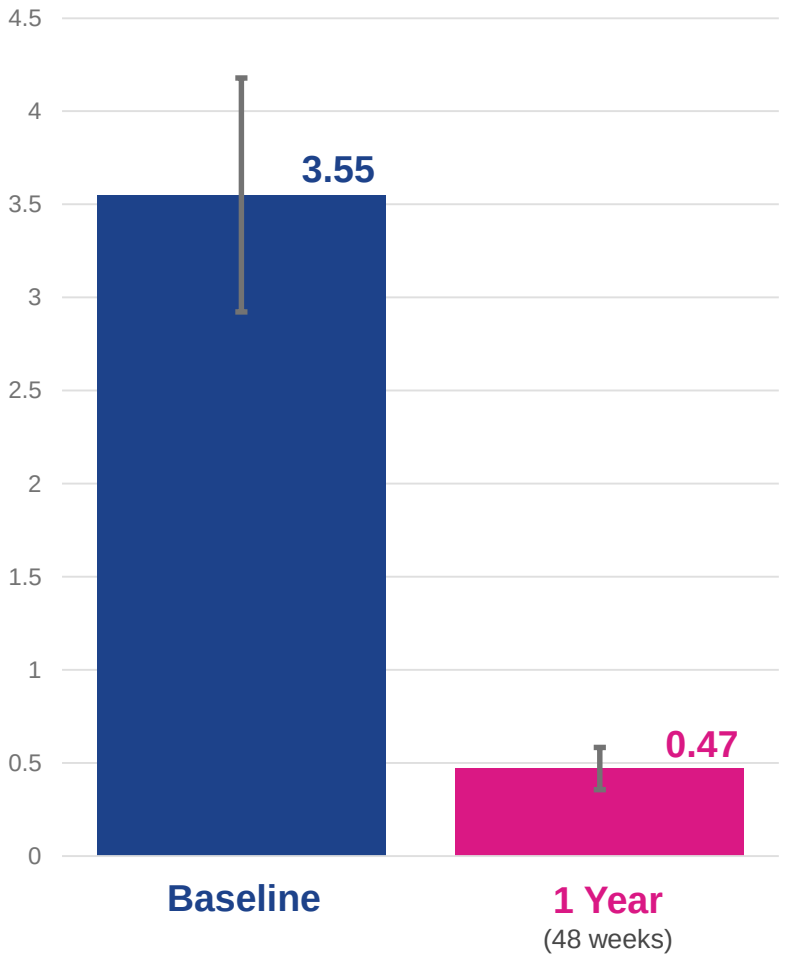
FAB-201 Patient Characteristics

	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*

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

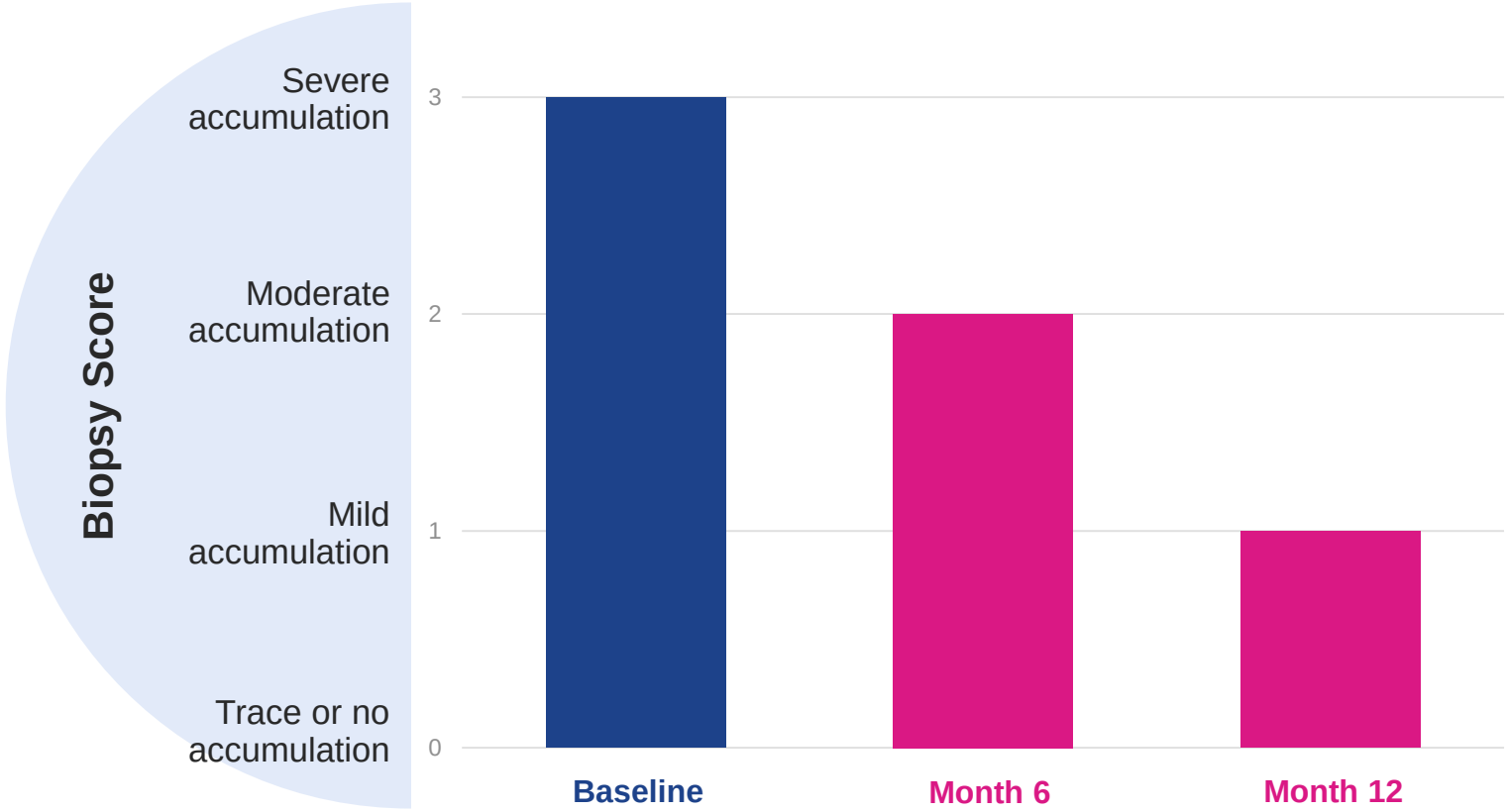
Average number of **Gb3 inclusions per peritubular capillary (PTC)**



- *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*

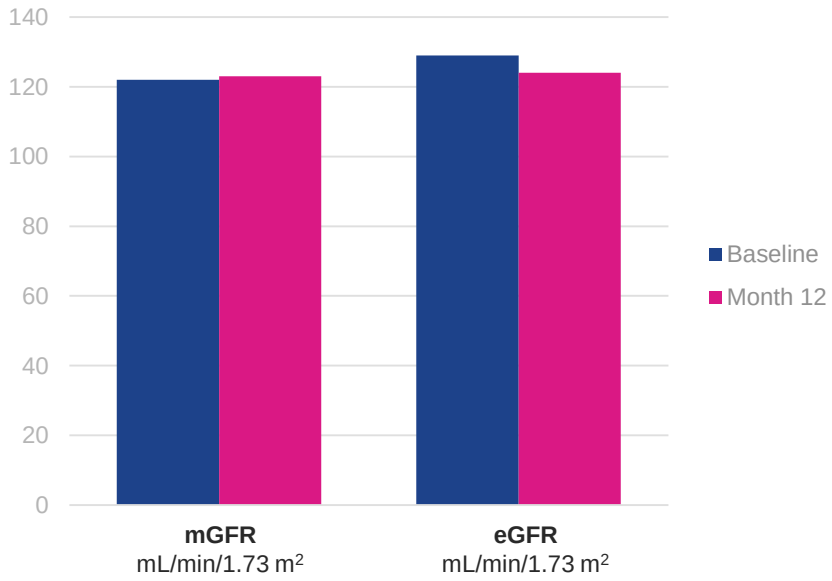
FAB-201 Patient 1: Continued reduction in substrate inclusions in skin endothelial cells



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

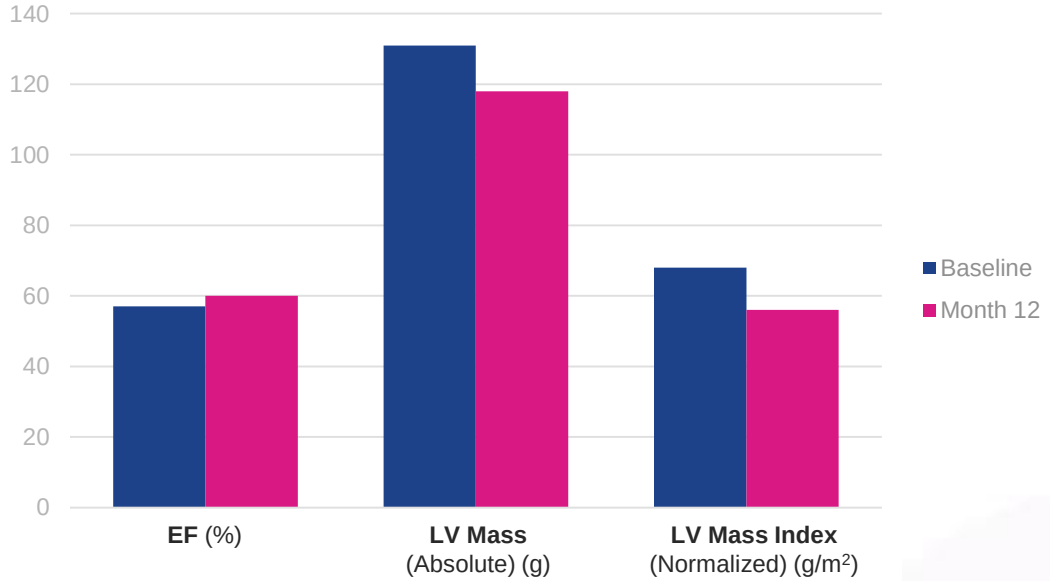
KIDNEY FUNCTION
remains within normal range



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*

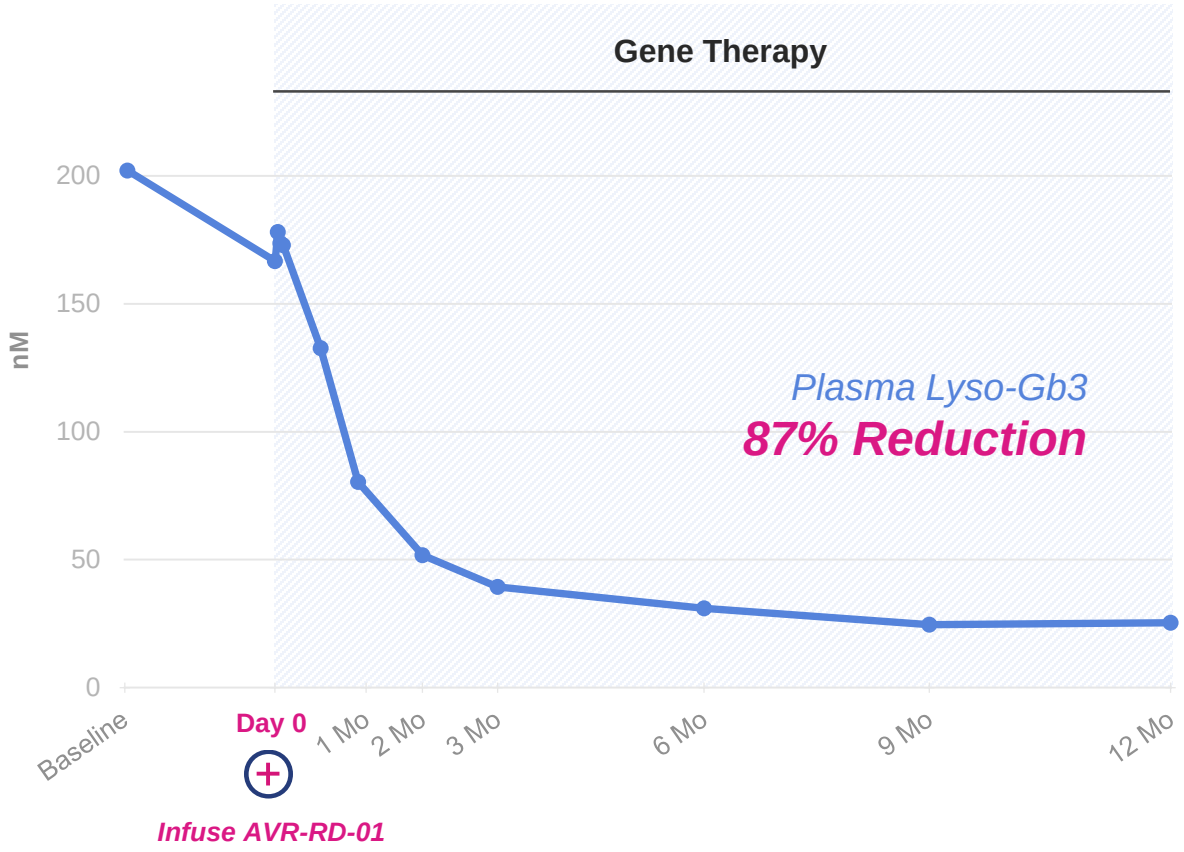
CARDIAC FUNCTION
remains within normal range

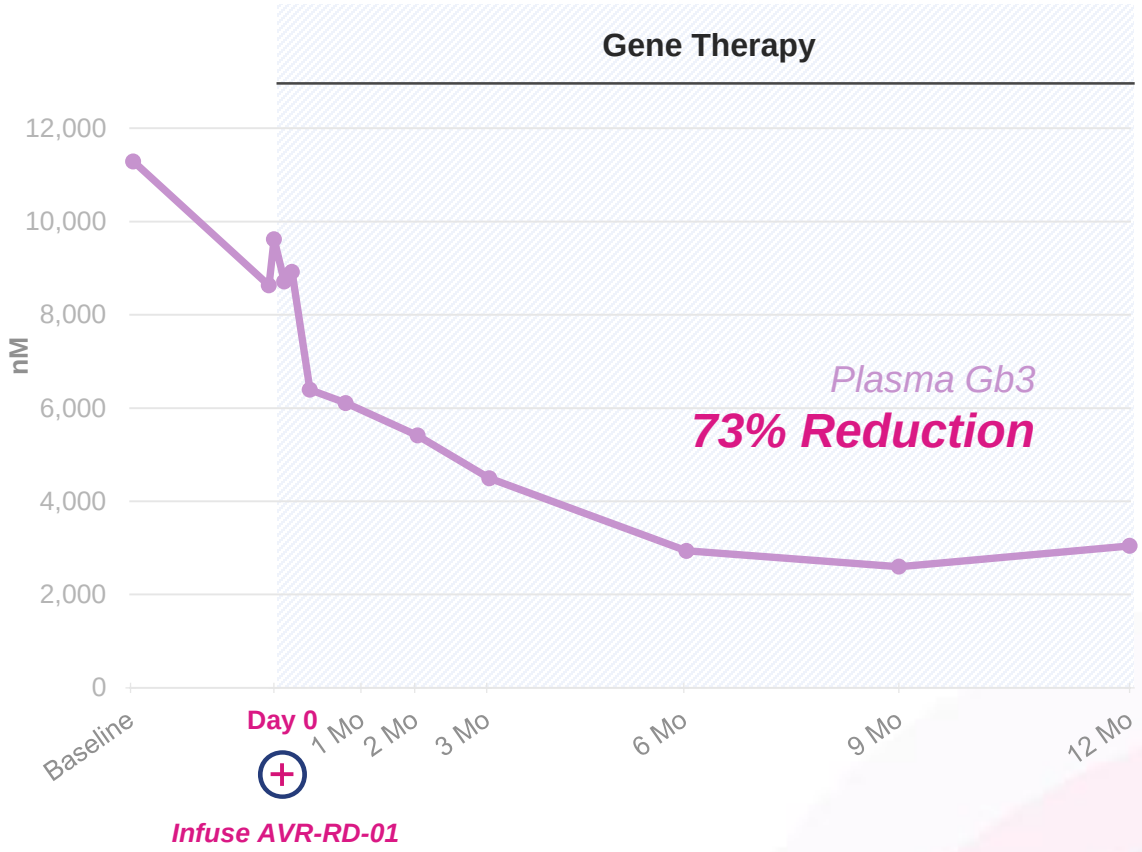


Reference Range Mean Values ± SD	EF (%)	LVM (g)	LVMI (g/m^2)
Male (20-39 years)	64.3 ± 4.2	138.9 ± 24.5	67.8 ± 10.7

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

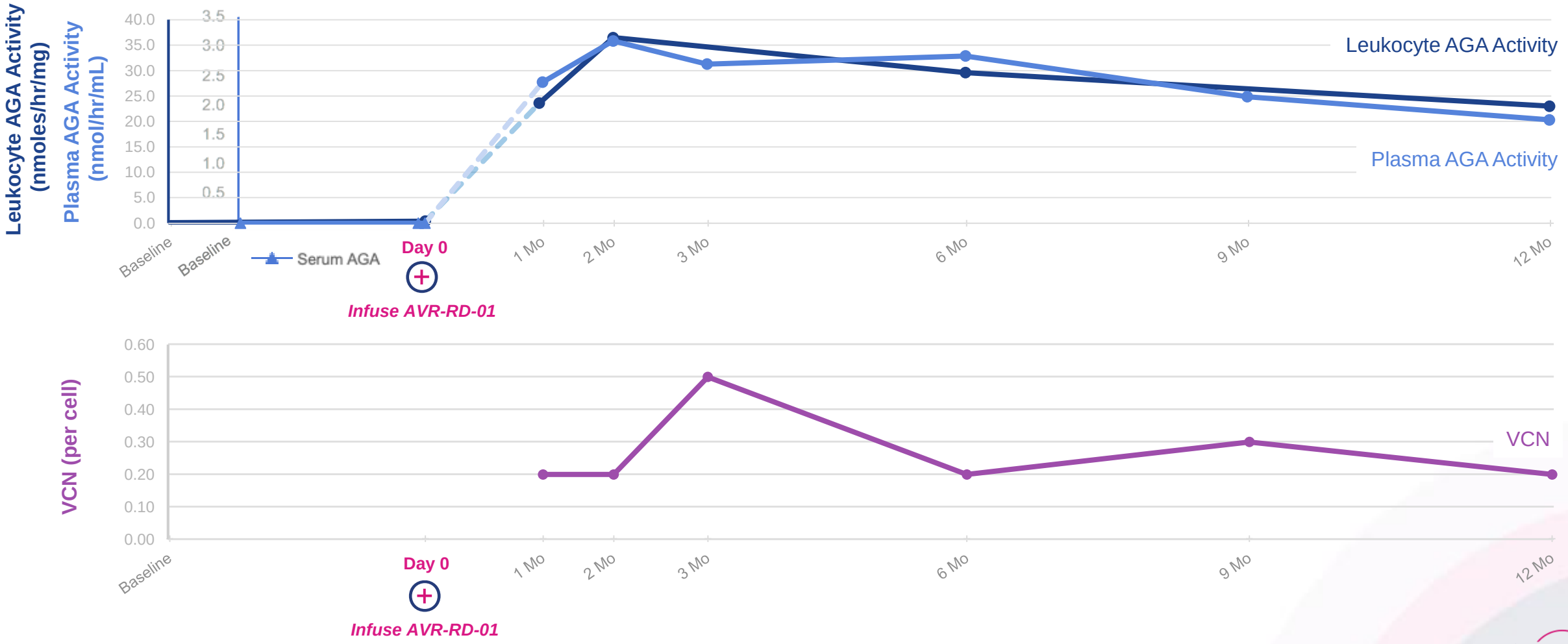
FAB-201 Patient 1: Substantial reduction in plasma substrate / metabolite levels, sustained at 1 year





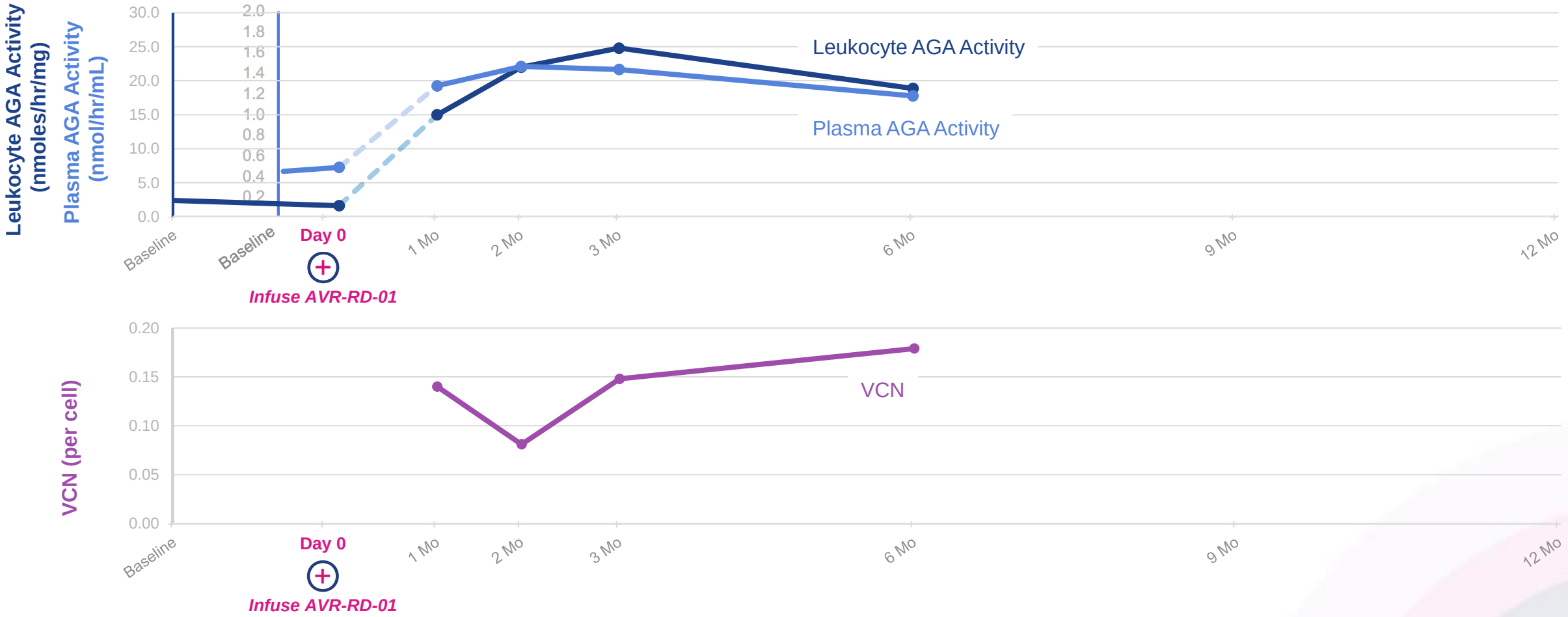
Baseline: *The last available, non-missing observation prior to AVR-RD-01 infusion*
Note: *AVR-RD-01 is an investigational gene therapy*

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

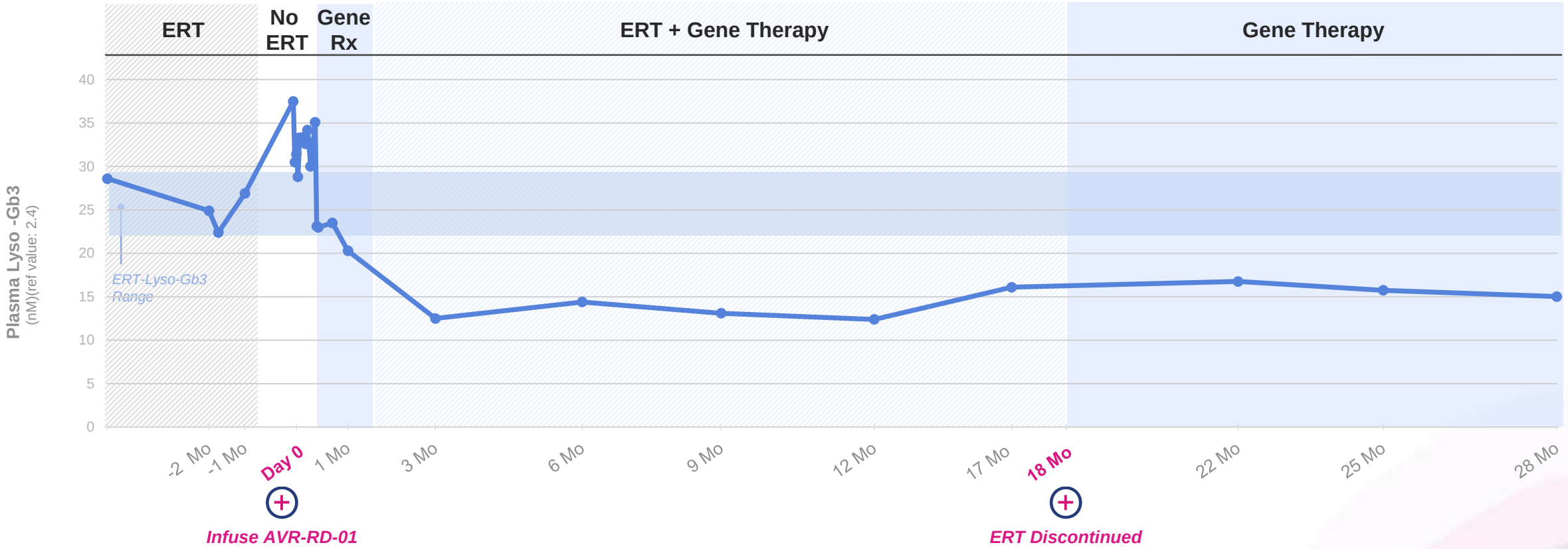
	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Age symptom onset / diagnosis	18 / 37	9 / 29	10 / 0	7 / 4	10 / 14
Years on ERT	11	6	4	11	2
Age dosed with AVR-RD-01	48	39	40	37	30
Mutation	c.962A>G (p.Q321R)	c.1033T>C (p.S345P)	c.427G>C (p.A143P)	c.427G>C (p.A143P)	(p.Y134S)
Primary disease signs and 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	7 months after gene therapy dose	

** Rupar Lab, ref range 24-56 nmol/h/mg*
*** Reference value ≤ 2.4 nM*

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

Reduced 41% from ERT baseline*

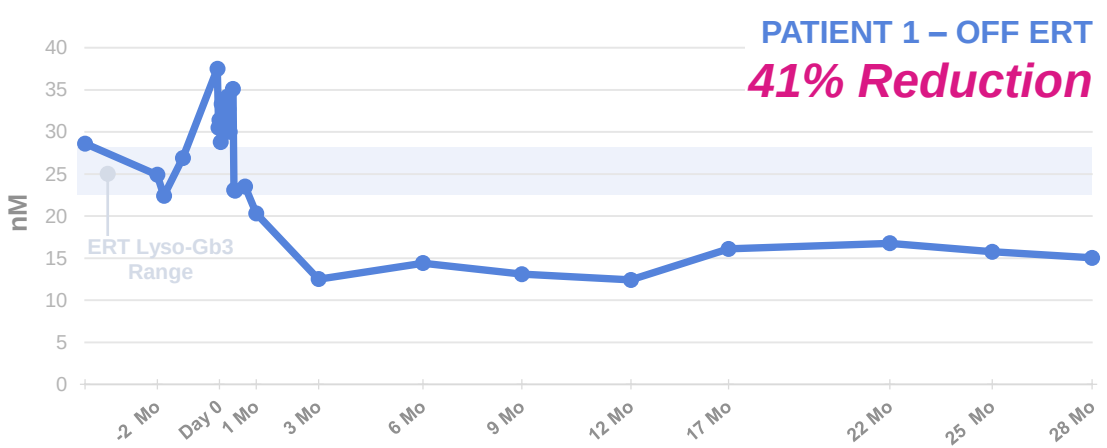
Patient #1

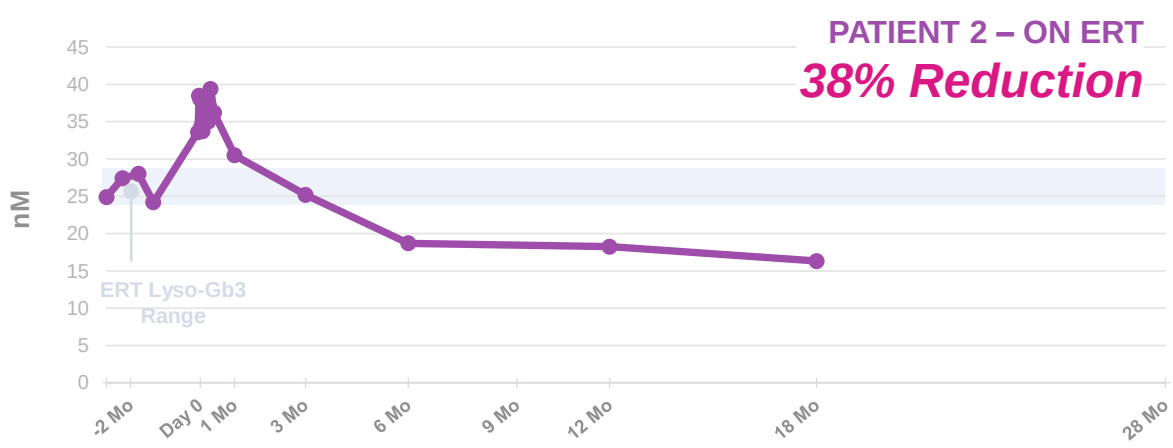


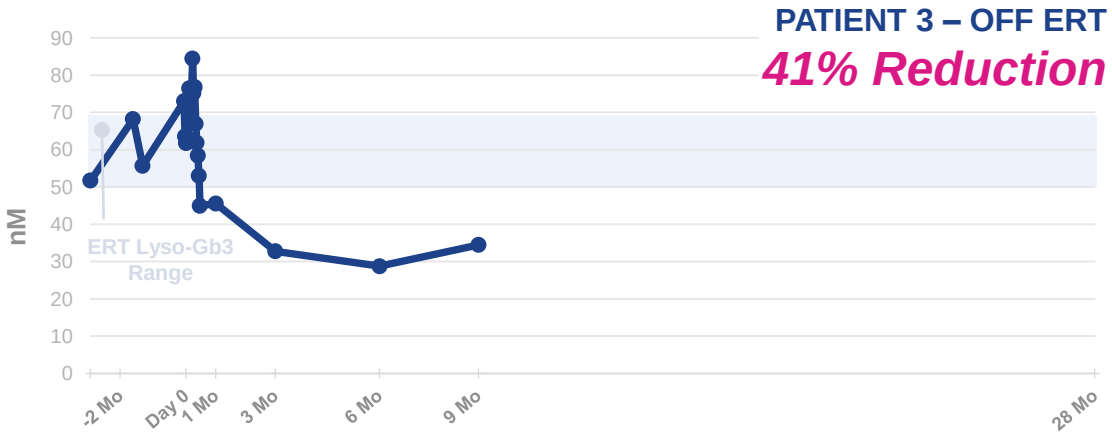
*Baseline: The mean of the values reported prior to initiating mobilization

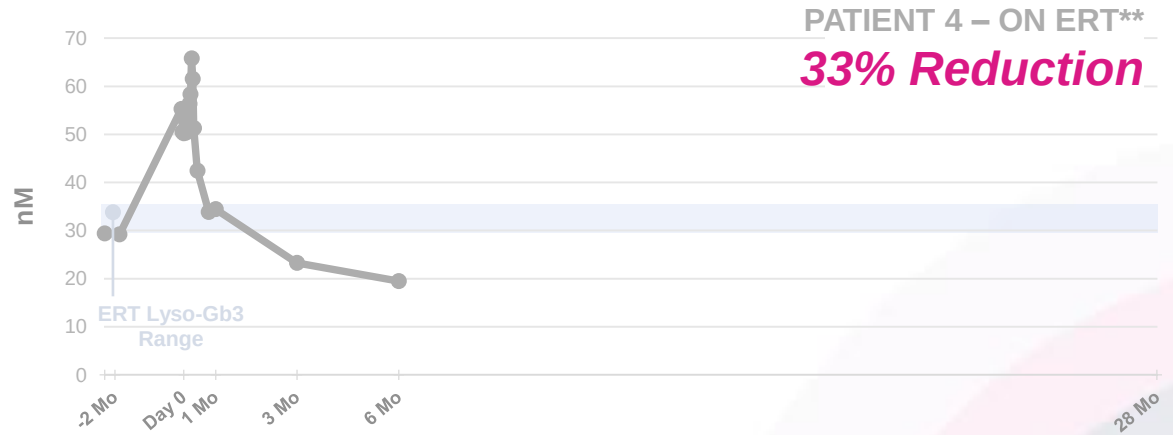
Note: AVR-RD-01 is an investigational gene therapy candidate

Phase 1: Plasma lyso-Gb3 consistently reduced by 33-41% vs. baseline* ERT at 6+ months post AVR-RD-01 treatment





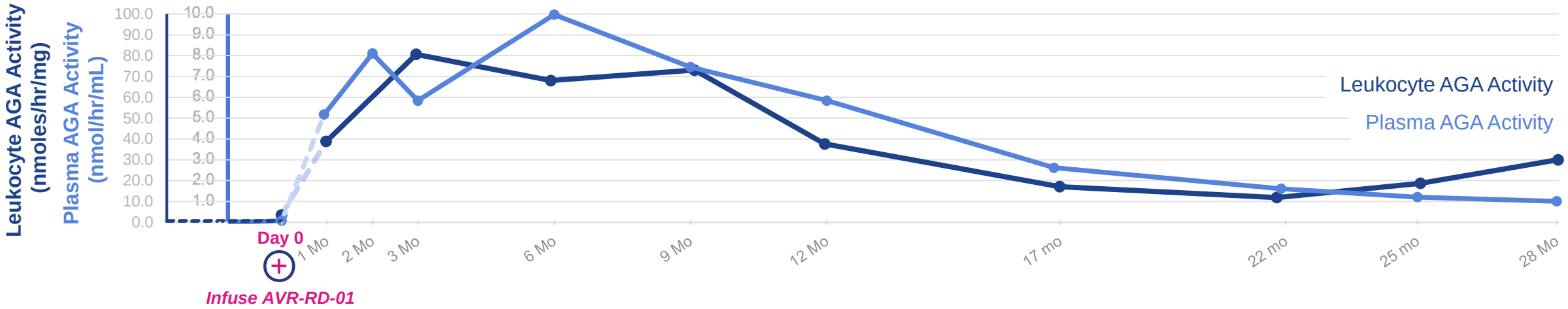


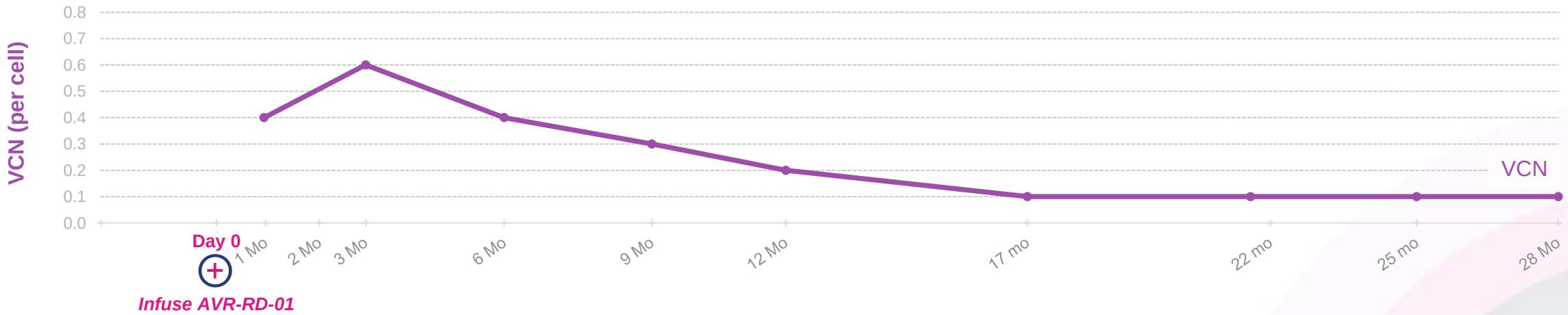


__Baseline:__ The mean of the values reported prior to initiating mobilization
__Percent reduction:__ As measured from baseline to last assessment
***Patient 4 discontinued ERT 7 months after gene therapy dose*

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

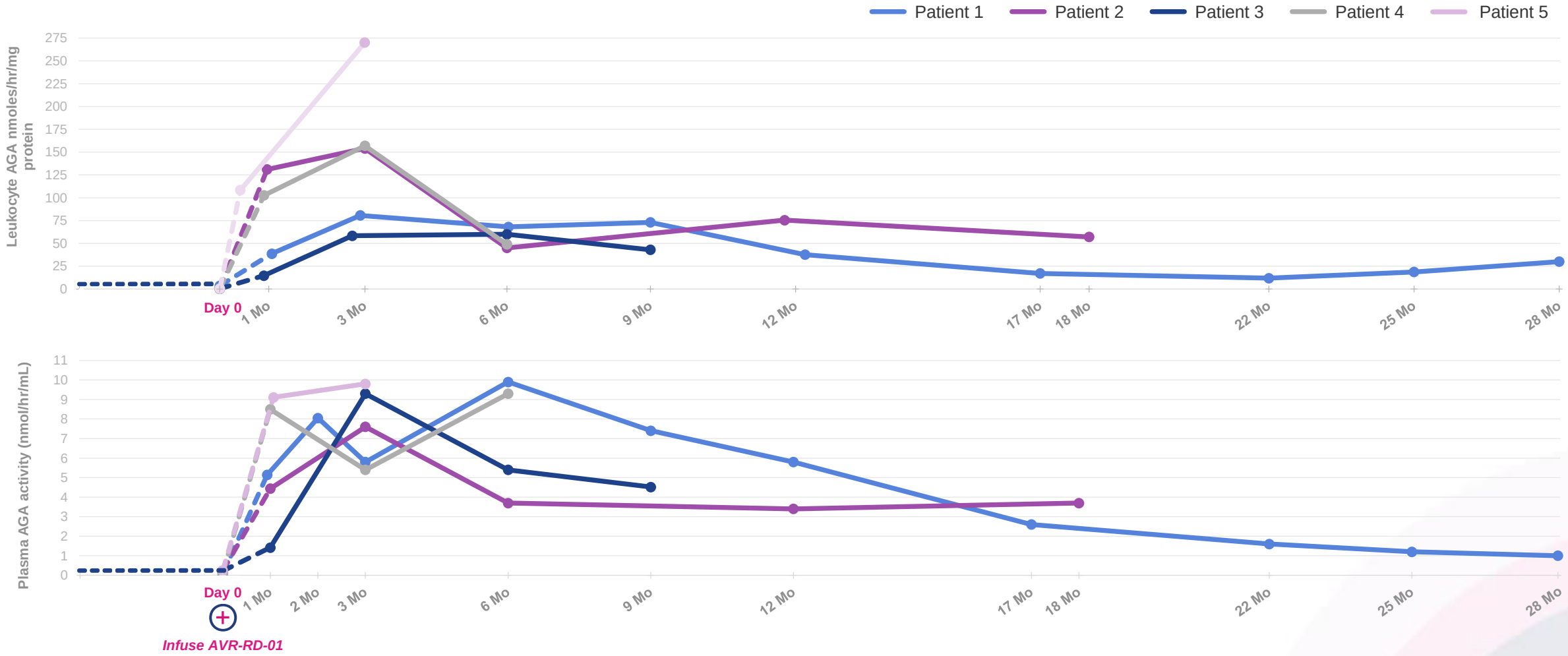
Patient #1





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

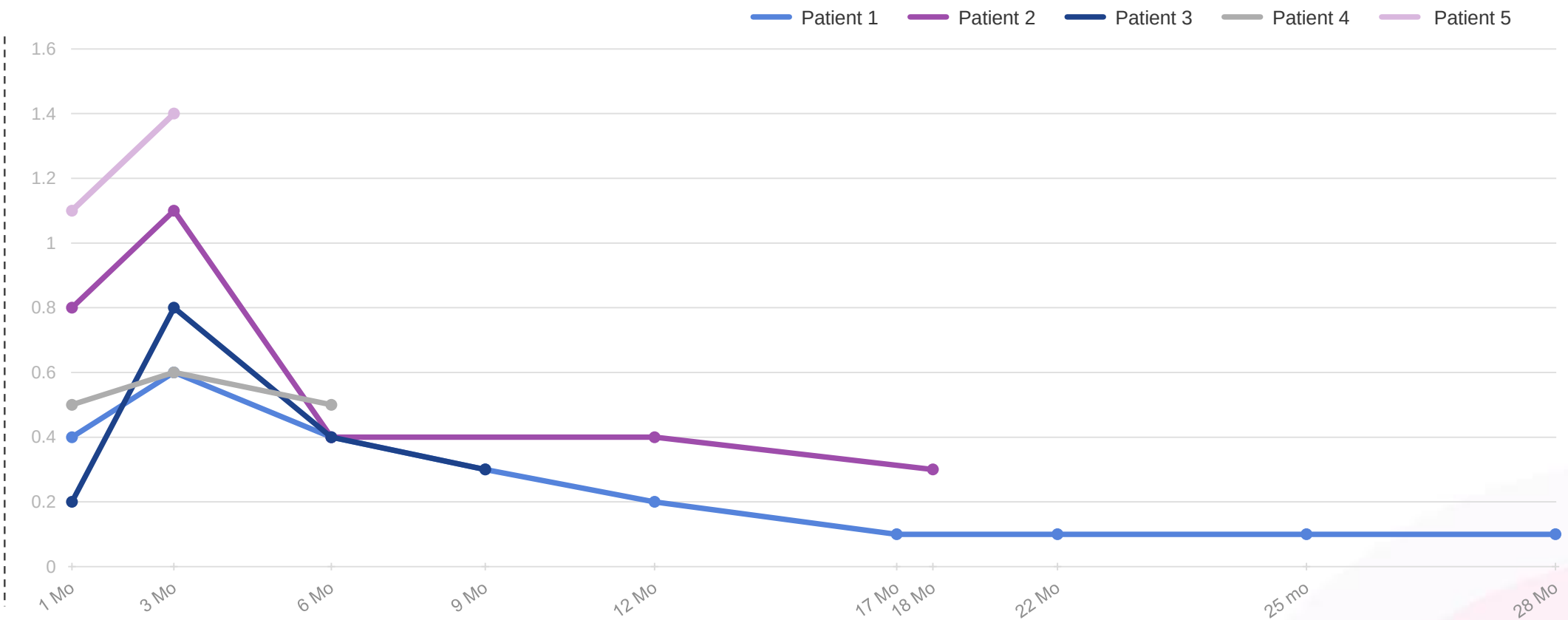
Phase 1: Leukocyte and plasma enzyme activity levels trend consistently across all patients



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*

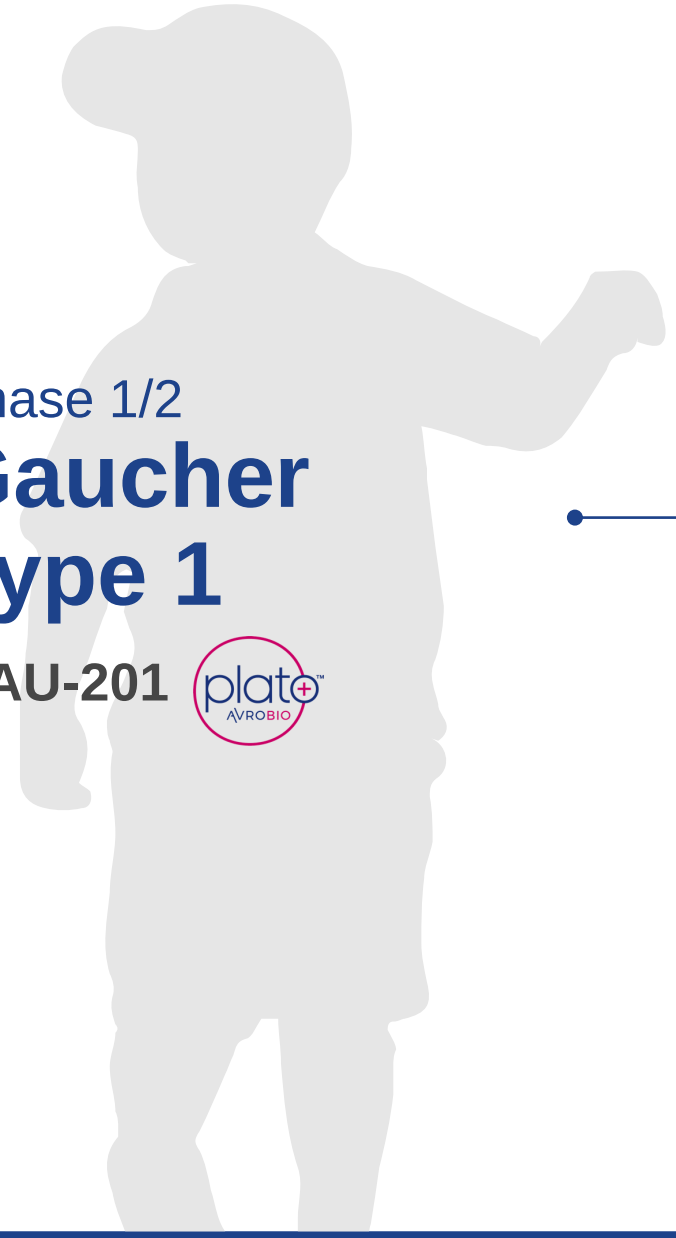
**Resolved post-safety database cut-off date*

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



Phase 1/2

Gaucher Type 1

GAU-201

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

GAU-201: Phase 1/2 study in Gaucher Type 1 patients

GAUCHER DISEASE TYPE 1 ERT-STABLE and TREATMENT NAÏVE PATIENTS

Day -60	Day -4	Day 0	Day 28	Months
Mobilize stem cells Patients on ERT: ERT discontinued D -14	Conditioning	Infuse AVR-RD-02	Post-treatment assessment	3, 6, 9 & 12 Safety & efficacy assessments

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 patients with Type 1 Gaucher disease

OBJECTIVES	PATIENTS	ASSESS
• Safety • Engraftment • Efficacy (functional endpoints and biomarkers)	• 8-16 patients • 16-35 year old males and females • Two arms – Treatment naïve – Stable receiving ERT	• Vector Copy Number (VCN) • Chimerism • GCase activity, including in CSF • Efficacy – Hematologic values – End-organ volumes and BMD – Biomarkers and QoL • Safety

Phase 1/2

Cystinosis

Investigator-Sponsored Trial

- US IND achieved
- Clinical site actively recruiting
- First patient expected to be dosed this year
- $12M Tier 1 CIRM grant funding to UCSD announced

Investigator-sponsored* Phase 1/2 study in Cystinosis

CYSTINOSIS PATIENTS

Day -140	Day -70	Day -20	Day -5	Day 0	Day 28	Weeks 6-14 / Months 6, 12, 18 & 24
Discontinue cysteamine eye drops	Mobilize stem cells	Discontinue oral cysteamine	Conditioning	Infuse AVR-RD-04	Post-treatment assessment	Safety & efficacy assessments

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
• Safety • Efficacy	• 6 patients • adults and potentially adolescents 14–17 years old • Using oral and ophthalmic cysteamine	• Cystine levels in granulocytes • Vector Copy Number (VCN) • Chimerism • Renal, respiratory and endocrine function, ophthalmologic findings, muscle strength, growth, bone density, neurologic and psychometric measures • Safety

* *Sponsored by UCSD*

POWERED BY AVROBIO plato

Pompe preclinical program **advancing**

Integrated 3-part approach

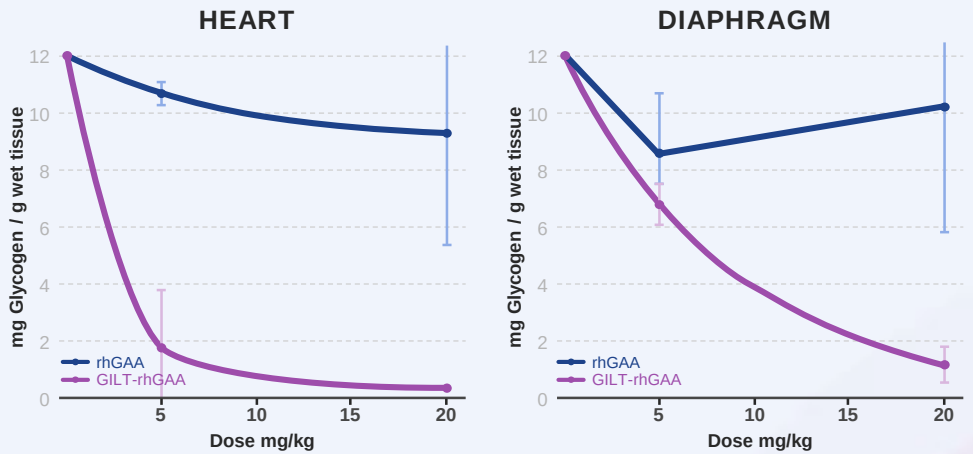
THE CHALLENGE

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

AVROBIO's APPROACH

1. Potent transgene promoter
2. GILT uptake tag
3. 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



GILT: Glycosylation-Independent Lysosomal Targeting
Sources: Burton B et al, J Pediatr, 2017; Ausems 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

plato™

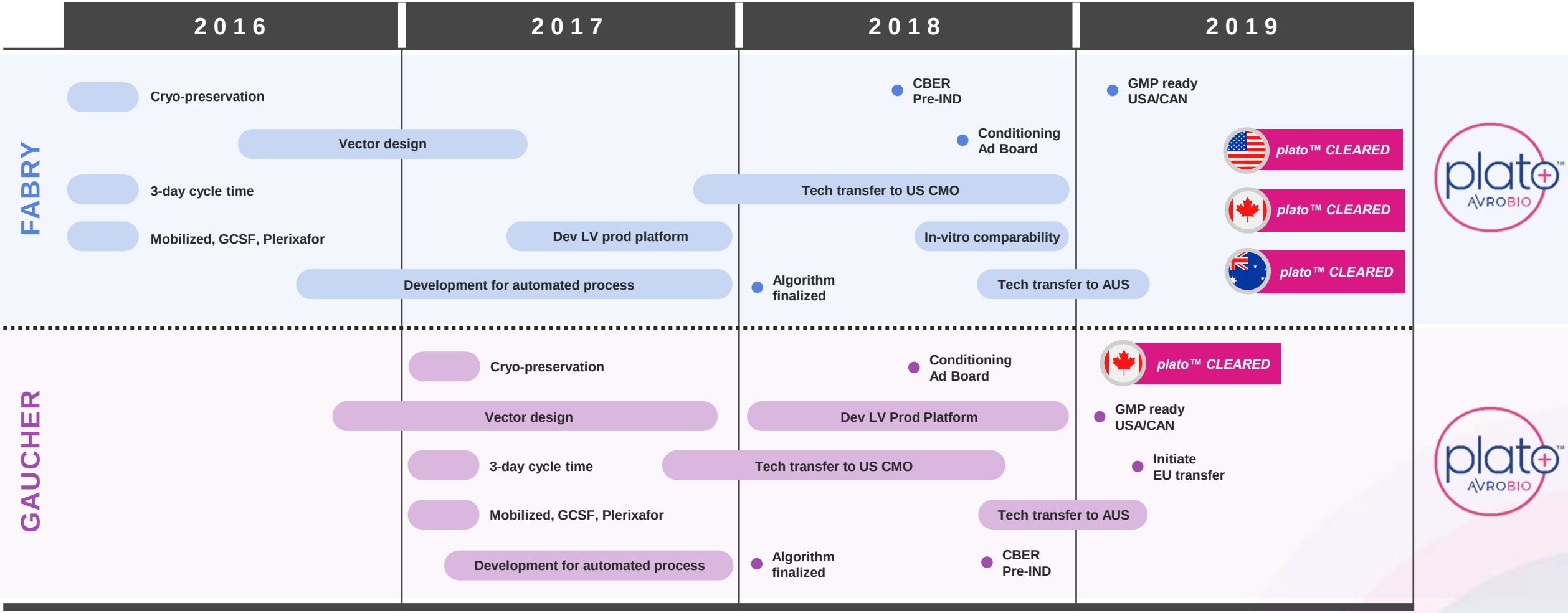
AVROBIO's foundation for worldwide commercialization

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



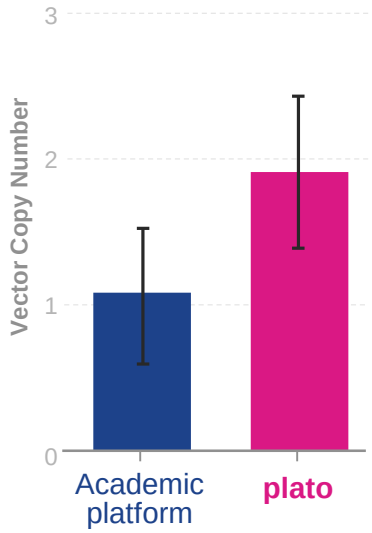
Note: *plato in Fabry cleared for use in US via IND, in Canada via protocol and CMC CTA amendment, and in AUS via CTN and HREC clearance; plato in Gaucher cleared for use in Canada via CTA and protocol CTA amendment*

plato™ optimized for performance

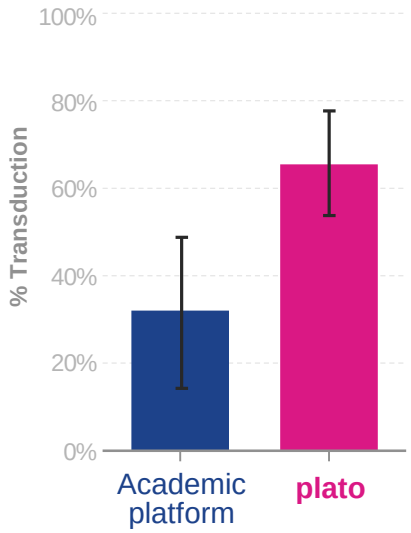
Proprietary Vector Toolbox

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

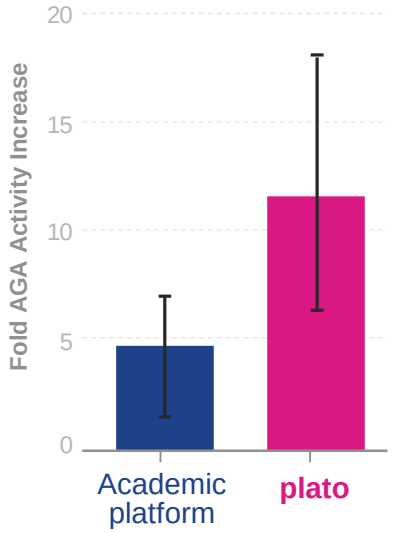
VCN



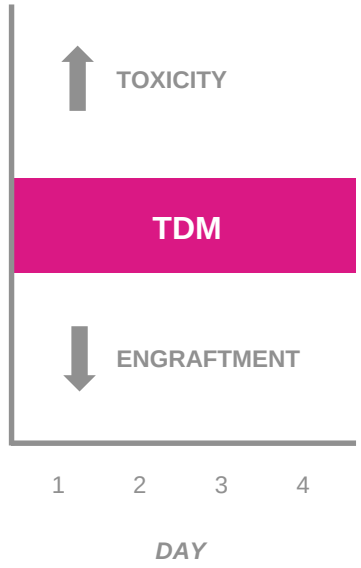
Transduction Efficiency



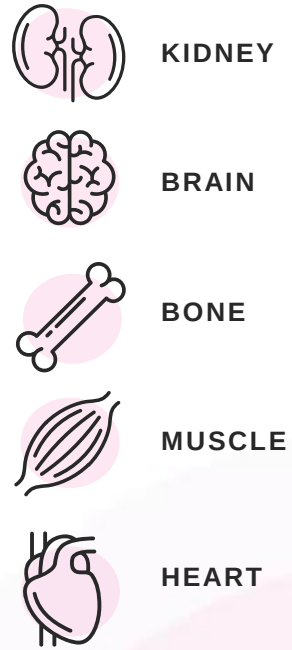
Enzyme Activity



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

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-

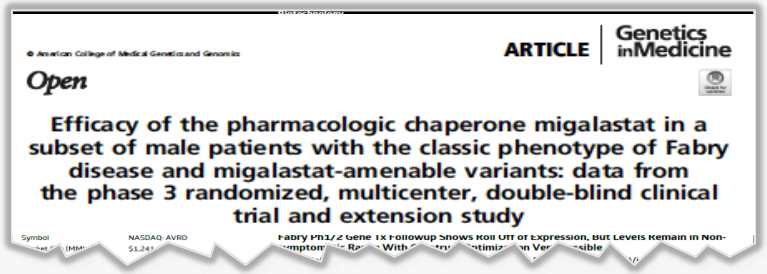
45 Amenable patients* (16 males / 29 females)

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*