UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): March 23, 2021

AVROBIO, INC.
(Exact name of registrant as specified in its charter)

Delaware	001-38537	81-0710585
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

One Kendall Square
Building 300, Suite 201
Cambridge, MA 02139
(Address of principal executive offices, including zip code)

(617) 914-8420
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**AVRO**	**Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On March 23, 2021, AVROBIO, Inc. updated its corporate presentation for use in meetings with investors, analysts and others. A copy of the presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information in this Form 8-K shall not be deemed "filed" for purposes of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

99.1	AVROBIO, Inc. slide presentation, dated March 2021
104	The cover page from this Current Report on Form 8-K, formatted in Inline XBR

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

AVROBIO, INC.

Date: March 23, 2021

By: /s/ Geoff MacKay
Geoff MacKay
President and Chief Executive Officer


AVROBIO
Corporate
Presentation
MARCH 2021

Disclaimer

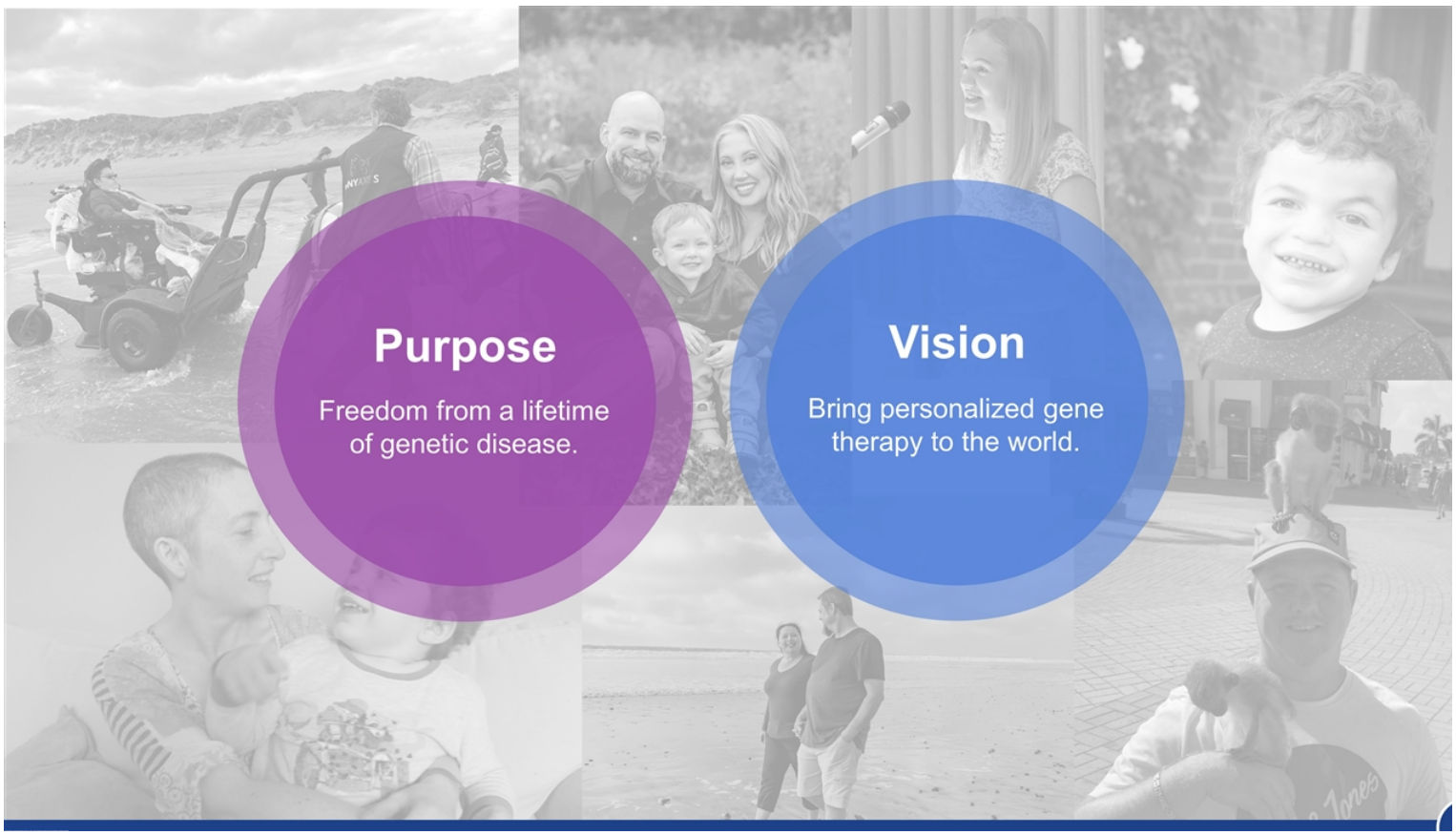
This presentation has been prepared by AVROBIO, Inc. ("AVROBIO") for informational purposes only and not for any other purpose. Certain information contained in this presentation and statements made orally during this presentation relate to or are based on studies, publications, surveys and other data 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 and phrases such as "aims," "anticipates," "believes," "could," "designed to," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "seeks," "will," and variations of these words and phrases or similar expressions that are intended to identify forward-looking statements. These forward-looking statements include, without limitation, statements regarding our business strategy for and the potential therapeutic benefits of our current and prospective product candidates; the design, commencement, enrollment and timing of ongoing or planned clinical trials and regulatory pathways; the timing of patient recruitment and enrollment activities, clinical trial results, and product approvals; the timing and results of our ongoing preclinical studies; the anticipated benefits of our gene therapy platform including the potential impact on our commercialization activities, timing and likelihood of success; the anticipated benefits and safety profile of busulfan as a conditioning agent; the expected benefits and results of our manufacturing technology, including the implementation of our plato® platform in our clinical trials and gene therapy programs; the expected safety profile of our investigational gene therapies; the potential impact of the COVID-19 outbreak on our clinical trial programs and business generally, as well as our plans and expectations with respect to the timing and resumption of any development activities that may be temporarily paused as a result of the COVID-19 outbreak; the market opportunity for and anticipated commercial activities relating to our investigational gene therapies; and statements regarding our financial and cash position and expected cash reserves. 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 our 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 our product candidates 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 we may not successfully recruit or enroll a sufficient number of patients for our clinical trials; the risk that we may not realize the intended benefits of our gene therapy platform, including the features of our plato® platform; the risk that our product candidates or procedures in connection with the administration thereof, including our use of busulfan as a conditioning agent, 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 our product candidates; the risk that we will be unable to obtain and maintain regulatory approval for our product candidates; the risk that the size and growth potential of the market for our product candidates 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; risks relating to clinical trial and business interruptions resulting from the COVID-19 outbreak or similar public health crises, including that such interruptions may materially delay our development timeline and/or increase our development costs or that data collection efforts may be impaired or otherwise impacted by such crises; and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. 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 Annual Report on Form 10-K, 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.

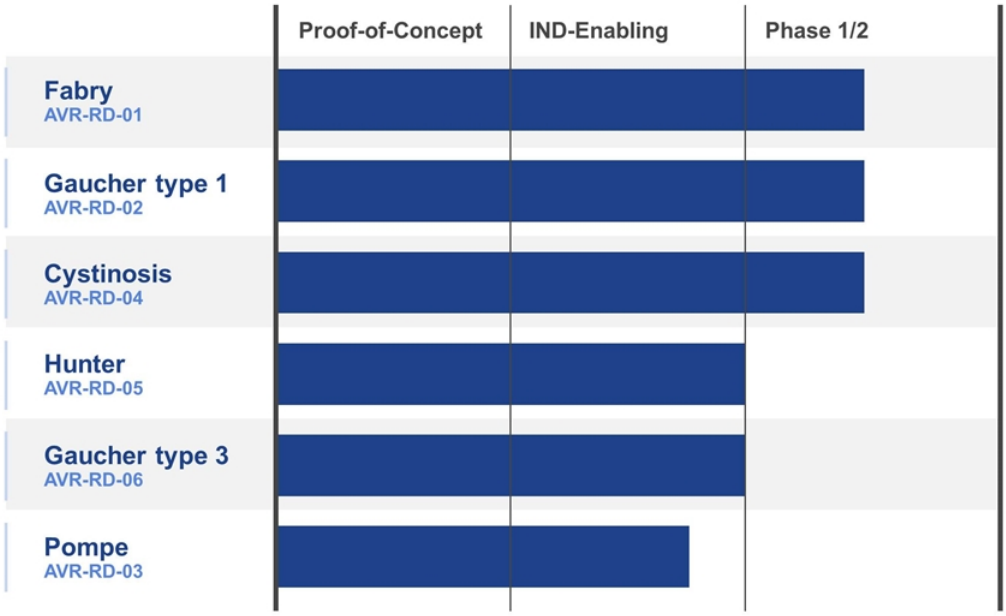
Note regarding trademarks: plato® is a registered trademark of AVROBIO. Other trademarks referenced in this presentation are the property of their respective owners.

Note regarding future updates: The statements contained in this presentation reflect our current views with respect to future events, which may change significantly as the global consequences of the COVID-19 pandemic rapidly develop. Accordingly, we do not undertake and specifically disclaim any obligation to update any forward-looking statements.


Purpose
Freedom from a lifetime of genetic disease.
Vision
Bring personalized gene therapy to the world.

Leading lysosomal disorder gene therapy pipeline

14 patients dosed to date across three indications



IND: Investigational New Drug

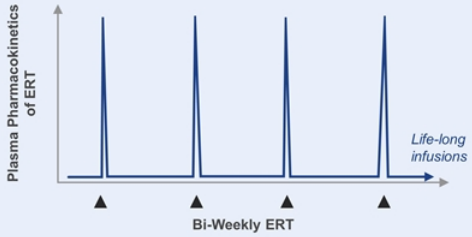
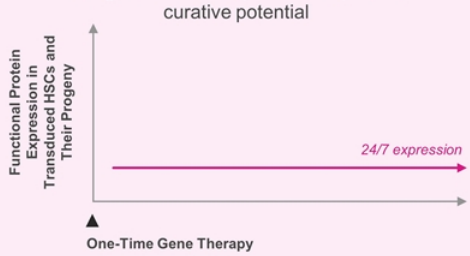
Multi-billion dollar market opportunity

Over 50,000 patients across target indications

Disease	Approx. 2020 Global Net Sales†	Five-Year SOC Cost per U.S. Patient*	Selected Companies w/ Marketed Therapies
Fabry	$1.4B	$1.7M	Sanofi Genzyme, Takeda/Shire
Cystinosis	$0.2B	$4.3M	Horizon‡
Gaucher	$1.5B	$2.3M	Sanofi Genzyme, Takeda/Shire
Hunter	$0.6B	$2.4M	Takeda/Shire
Pompe	$1.1B	$3.2M	Sanofi Genzyme
	Total: $4.8B		

Sources: Rombach S et al., Orphanet J Rare Dis, 2013; van Dussen L et al., Orphanet J Rare Dis, 2014
** WAC pricing from Redbook using standard dosing assumptions*
† 2020 Net Sales from company annual and other reports
‡ Horizon's Procysbi oral therapy (delayed release cysteamine bitartrate); midpoint between avg. adult and pediatric
Note: Shire acquired by Takeda in 2019
SOC: Standard of Care

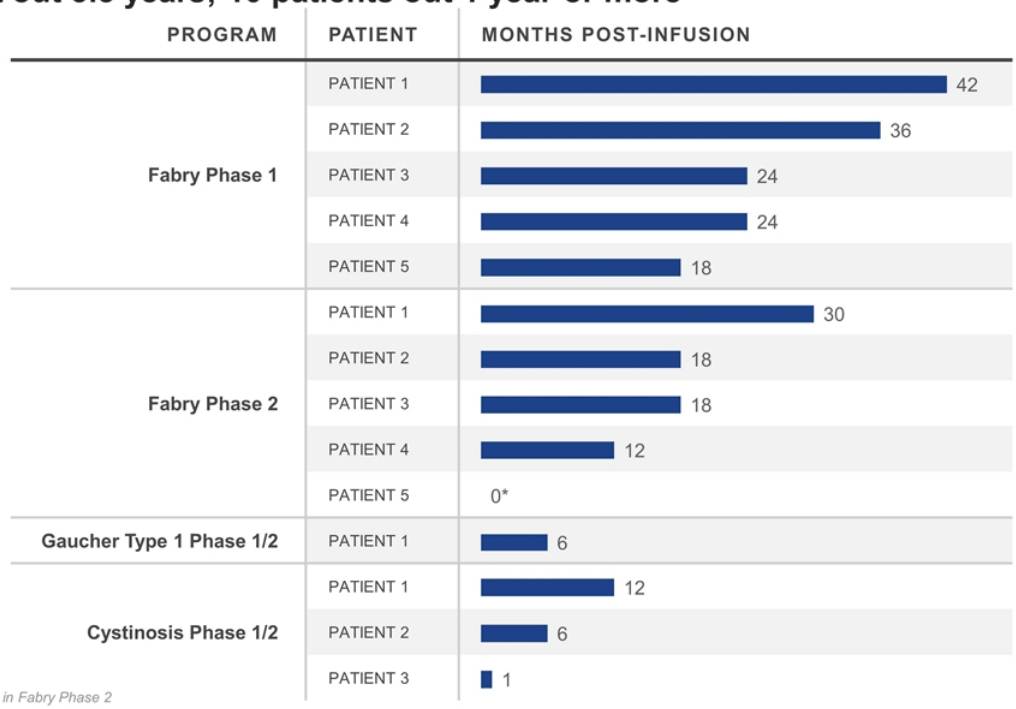
Lifelong treatments vs. potential single-dose therapy

	DISEASE PROGRESSION CONTINUES	COULD HALT, PREVENT OR REVERSE DISEASE
	Enzyme Replacement Therapy (ERT) Temporary bolus of enzyme, not curative  	**AVROBIO Gene Therapy** Designed for 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
Ability to impact CNS	No	Yes

ERT: Enzyme Replacement Therapy; IV: Intravenous; HSC: Hematopoietic Stem Cells

Durability demonstrated across clinical programs

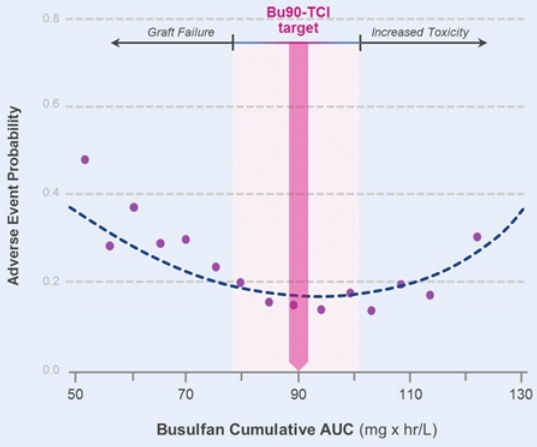
First patient out 3.5 years; 10 patients out 1 year or more



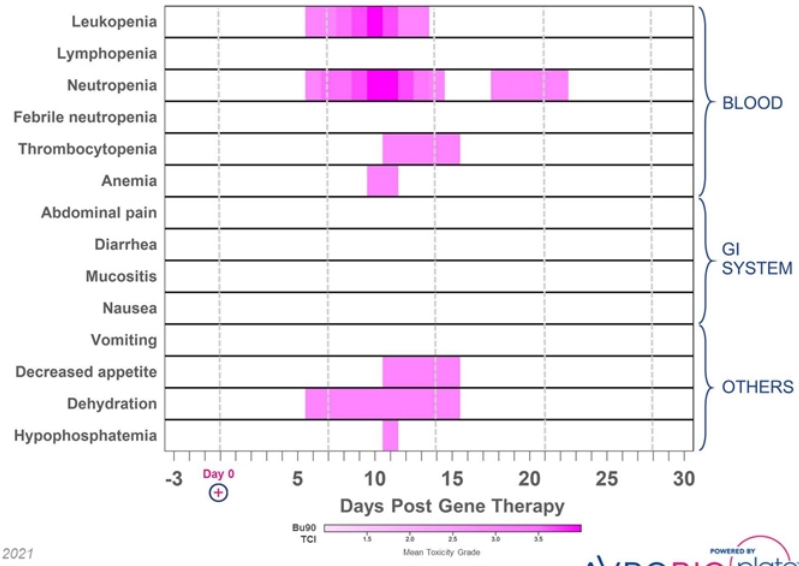
** Data not yet available for patient #5 in Fabry Phase 2*
Note: Based on data cut-off date of January 11, 2021

Bu90-TCI conditioning-related side effects have been predictable and transient in first two plato® patients

Analysis of 465 non-malignant patients identified optimum exposure for busulfan conditioning:*



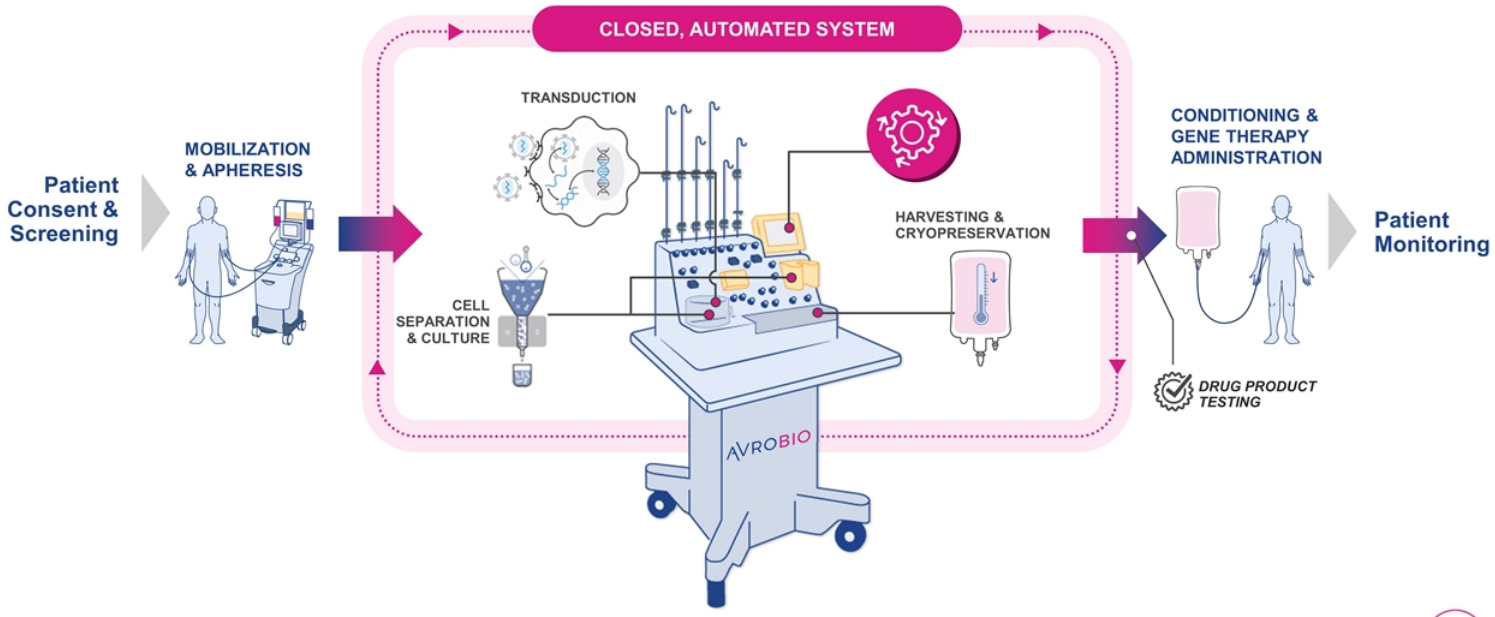
Conditioning-related grade 3-4 AEs in first two plato® patients



Note: FAB-GT, f-k-a FAB-201, safety data cut-off December 7, 2020; Gaucher safety data cut-off January 4, 2021
** Source: Bartelink IH et al., Lancet Haematol, 2016*
Bu90-TCI: Busulfan 90-Target Concentration Intervention; AUC: Area Under the Curve; TCI: Target Concentration Intervention

AVROBIO (plato) POWERED BY

Unrivaled commercial-scale platform in plato®



POWERED BY AVROBIO plato


“First Wave”
Programs
Fabry, Gaucher Type 1, cystinosis

Fabry disease opportunity

Tom, living with Fabry disease

Caused by mutation in gene encoding for alpha-galactosidase A enzyme

Standard of care (SOC): ERT

- Not curative, relentless progression of disease continues
- Burdensome and expensive – bi-weekly ERT infusions required; 5-year treatment cost of ERT = ~$1.7 million*

Unmet needs with SOC:

Kidney function
Proteinuria, polyuria, kidney failure

Cardiac function
Left ventricular hypertrophy, fibrosis, heart failure

Neuropathic pain
Pain and burning sensations in hands and feet, pain crises

Everyday burden of illness, and life expectancy
Not curative, relentless progression of disease, shortened lifespan

CNS complications
TIA/stroke, depression, executive function deficit, white matter lesions

Fabry Disease Target Product Profile**:

- Prevents, halts or reverses disease; extends/normalizes lifespan
- Addresses all patient segments – all genetic mutations, male and female, all ages
- Lifelong durability – single infusion; off ERT
- Impacts hard-to-reach organs – e.g., brain, heart, kidney
- Well tolerated

Affects ~ 1:40,000 males and 1:118,000 females in U.S.

** WAC pricing from Redbook using standard dosing assumptions*
*** Note: these are target attributes for a first-line therapy*

POWERED BY AVROBIO plato

Two AVR-RD-01 Fabry clinical trials

10 patients dosed across Phase 1 and 2

PHASE 1

Investigator-Sponsored Trial*

FULLY ENROLLED

OBJECTIVES	PATIENTS
• Safety and tolerability • Preliminary efficacy	• n = 5 patients • 18 – 59 year-old males • On ERT >6 months prior to enrollment

PHASE 2

AVROBIO FAB-GT Trial **

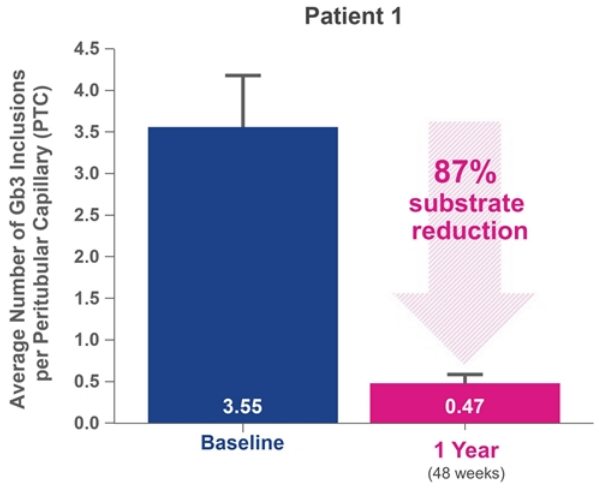
ACTIVELY RECRUITING

OBJECTIVES	PATIENTS
• Safety and tolerability • Efficacy	• n = 8-12 patients (5 dosed to-date) • 16 – 50 year-old males • Treatment naïve

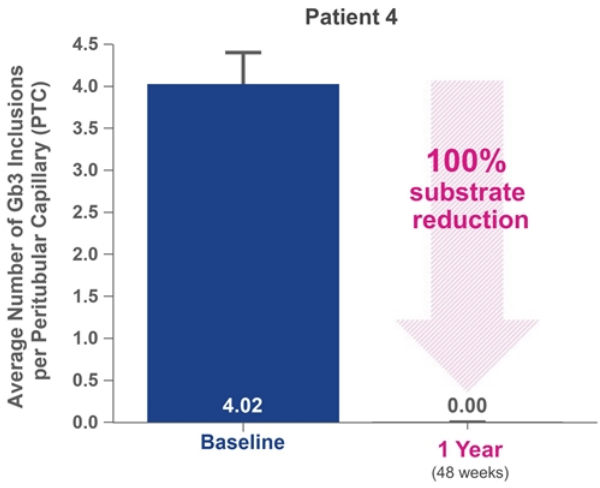
** Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada*
*** FAB-GT fka FAB-201*

POWERED BY AVROBIO plato

Clinically meaningful and statistically significant reduction in substrate in first two evaluable kidney biopsies



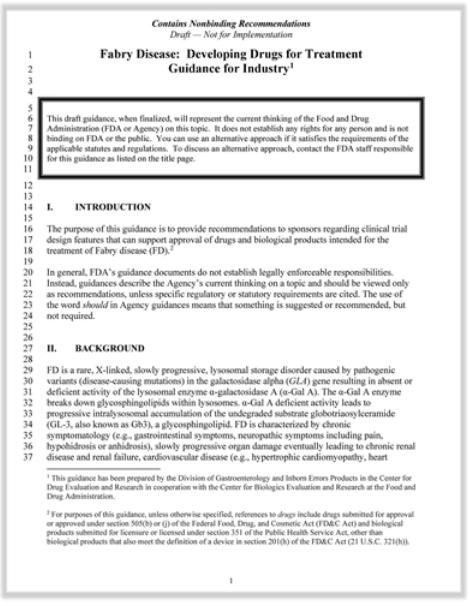
Two-sample t-test for difference between average PTCs at Baseline vs. 48 weeks; $p < 0.0001$; Error bar represents the standard error at Baseline (n=48 PTCs) and 48 weeks (n=101 PTCs). Scored by 2 independent, blinded pathologists



Two-sample t-test for difference between average PTCs at Baseline vs. 48 weeks; $p < 0.0001$; Error bar represents the standard error at Baseline (n=103 PTCs) and 48 weeks (n=99 PTCs). Scored by 2 independent, blinded pathologists

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

FDA guidance cites kidney biopsy as surrogate endpoint for accelerated approval



Contains Nonbinding Recommendations
Draft — Not for Implementation

Fabry Disease: Developing Drugs for Treatment
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors regarding clinical trial design features that can support approval of drugs and biological products intended for the treatment of Fabry disease (FD).[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FD is a rare, X-linked, slowly progressive, lysosomal storage disorder caused by pathogenic variants (disease-causing mutations) in the galactosidase alpha (*GLA*) gene resulting in absent or deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal A). The α-Gal A enzyme breaks down glycosphingolipids within lysosomes. α-Gal A deficient activity leads to progressive intralysosomal accumulation of the undegraded substrate globotriaosylceramide (GL-3, also known as Gb3), a glycosphingolipid. FD is characterized by chronic symptomatology (e.g., gastrointestinal symptoms, neuropathic symptoms including pain, hypohidrosis or anhidrosis), slowly progressive organ damage eventually leading to chronic renal disease and renal failure, cardiovascular disease (e.g., hypertrophic cardiomyopathy, heart

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For purposes of this guidance, unless otherwise specified, references to *drugs* include drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and biological products submitted for licensure or licensed under section 351 of the Public Health Service Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

1

"The purpose of this guidance is to provide recommendations to sponsors regarding clinical trial design features that can support approval of drugs and biological products intended for the treatment of Fabry disease"

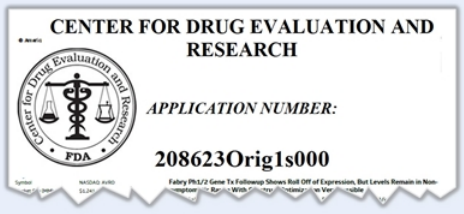
"Sponsors can use histological reduction of GL-3 inclusion burden in biopsied kidney interstitial capillaries (KIC) as a surrogate endpoint reasonably likely to predict clinical benefit to support accelerated approval"

"When assessing (counting) KIC GL-3 inclusions in histology specimens, the sponsor should use validated and standardized assay methodologies, and scoring of KIC GL-3 inclusions should be conducted by experienced pathologists in a blinded and systematic fashion"

Complete guidance available at fda.gov

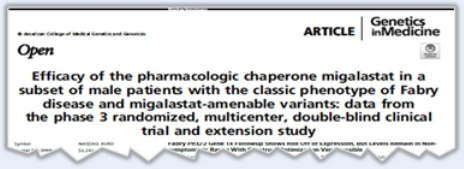
POWERED BY AVROBIO plato

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


CENTER FOR DRUG EVALUATION AND RESEARCH

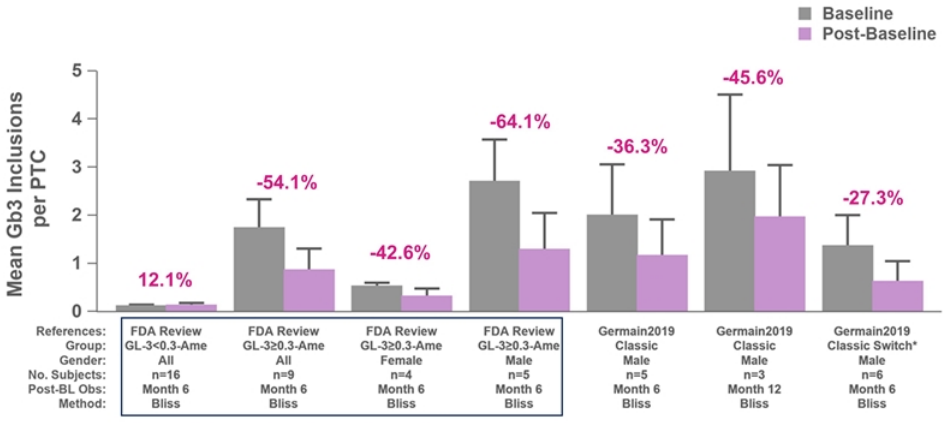
APPLICATION NUMBER:

208623Orig1s000


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



Abbreviations: Ame=Amenable; NonAme=Non-Amenable; Classic=Classic Fabry Patients; PTC=Peritubular Capillary; BL=Baseline; Obs=Observation.

Notes: All data on substrate changes presented are from Migalastat-treated subjects who participated in the Phase 3 FACETS study (NCT00925301). Substrate changes were determined using BLISS (Barisoni Lipid Inclusion Scoring System). Error bar represents the standard error of the mean.

* Denotes patients who were randomized to Placebo (Months 0-6) and switched to Migalastat starting at Month 6 post study start. The Baseline at Month 6 was derived as the sum of the PTC Gb3 inclusions at Baseline (Month 0) and the Change in PTC Gb3 inclusions from Baseline to Month 6. Percent change is associated with Change from Month 6 to Month 12.

Sources: Galafold (Migalastat), Multi-Discipline FDA Review; Germain 2019, Genet Med 21, 1987–1997 (2019)

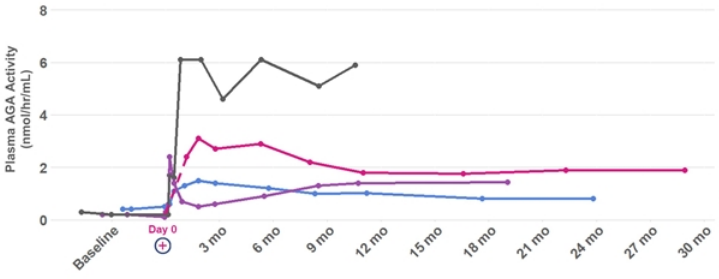
POWERED BY AVROBIO plato

FABRY PHASE 2

Durability demonstrated over multiple measures up to 2.5 years

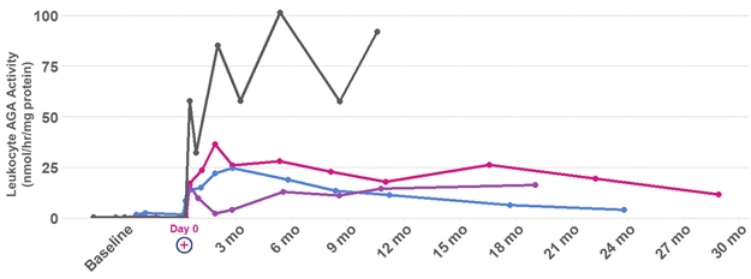
Patient 4 dosed using plato®

Plasma AGA Enzyme Activity



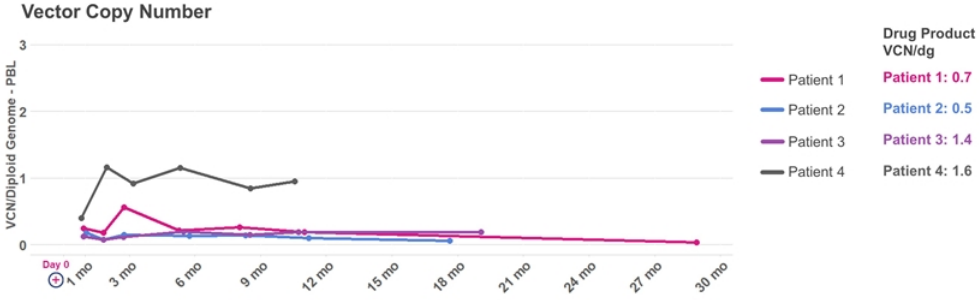
Plasma AGA Activity Reference Range: 5.1–9.2 nmol/hr/mL; AGA: α-galactosidase A

Leukocyte AGA Enzyme Activity



Leukocyte AGA Activity Reference Range: 24–56 nmol/hr/mg protein; AGA: α-galactosidase A

Vector Copy Number

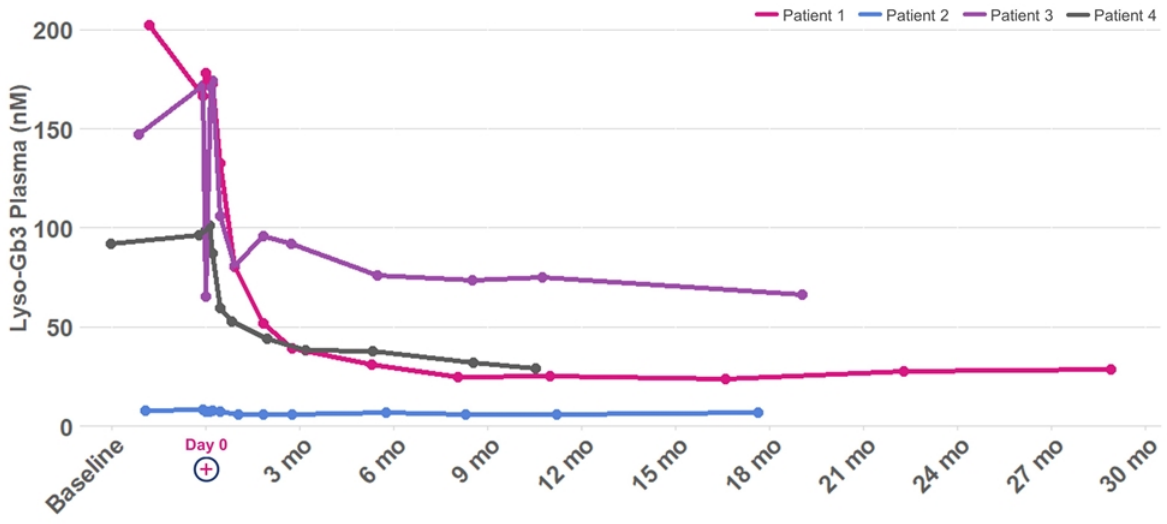


VCN: Vector Copy Number; PBL: Peripheral Blood Leukocytes; dg: Diploid Genome

AVROBIO powered by plato

FABRY PHASE 2

70% average plasma lyso-Gb3 reduction



Reduction from Baseline to Last Observation	
Patient 1	86%
Patient 2	N/A
Patient 3	55%
Patient 4	69%

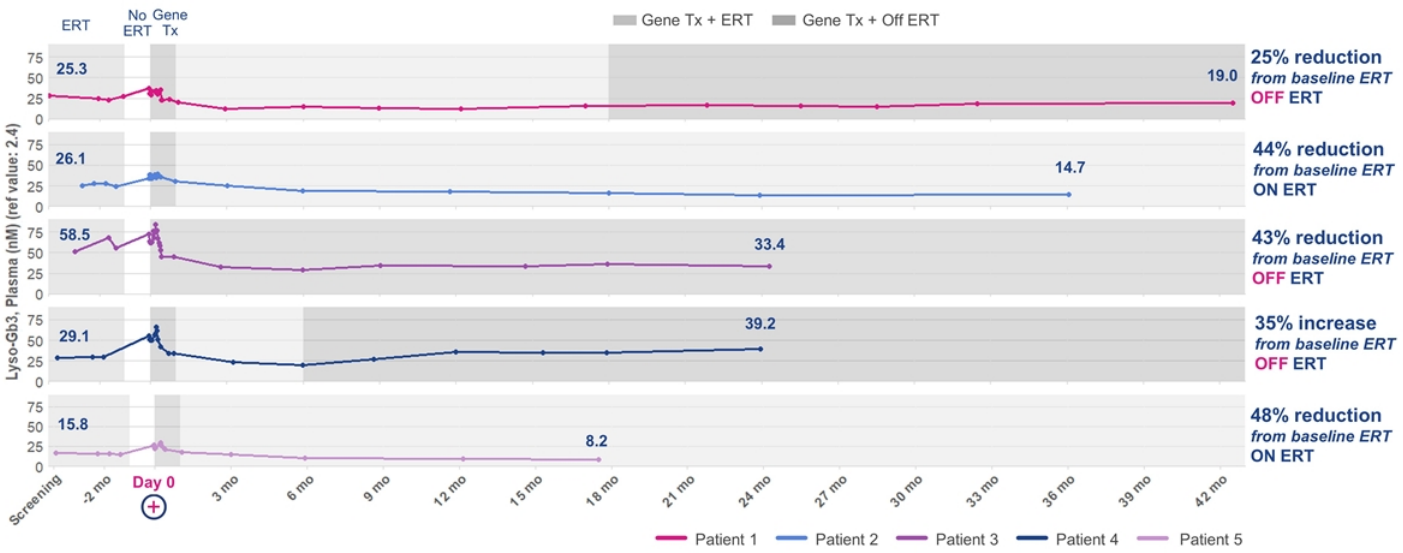
Lyso-Gb3 Plasma Reference Value: 2.4 nM; Lyso-Gb3: Globotriaosylsphingosine
Note: Patient 2 has normal substrate, consistent with late-onset cardiac variant phenotype

AVROBIO plato

FABRY PHASE 1

25% average plasma lyso-Gb3 reduction below baseline ERT

All patients who have discontinued ERT remain off ERT*

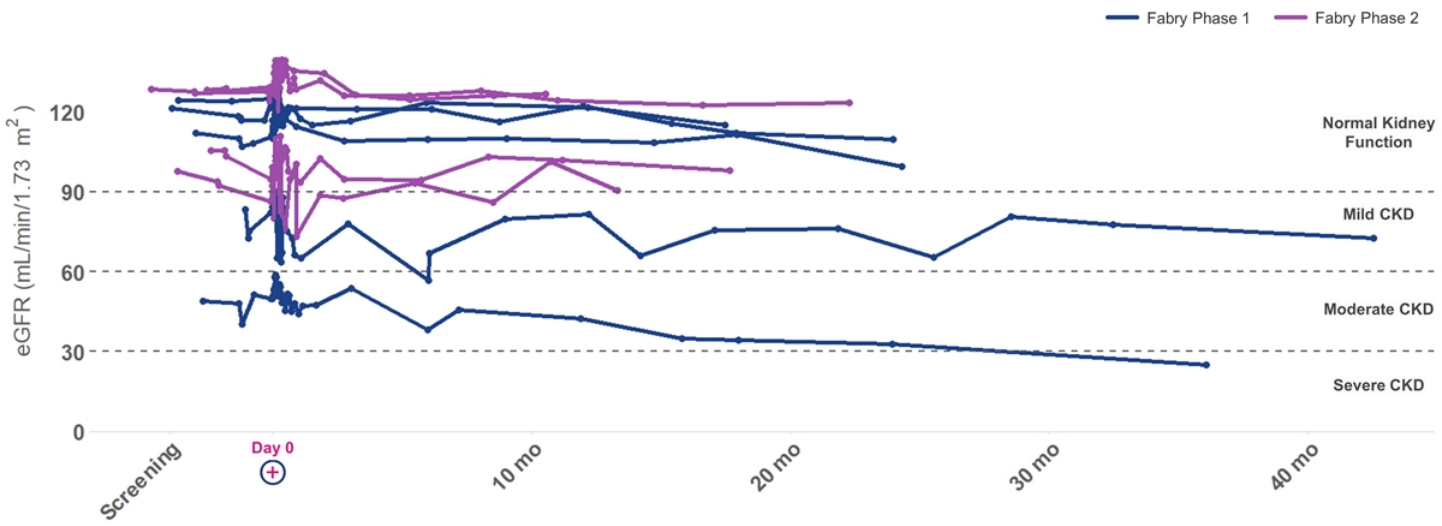


** As of January 11, 2021*

Lyso-Gb3: Globotriaosylsphingosine; ERT: Enzyme Replacement Therapy; Tx: Therapy

POWERED BY AVROBIO plato

Kidney function (eGFR) stable up to 3.5 years*



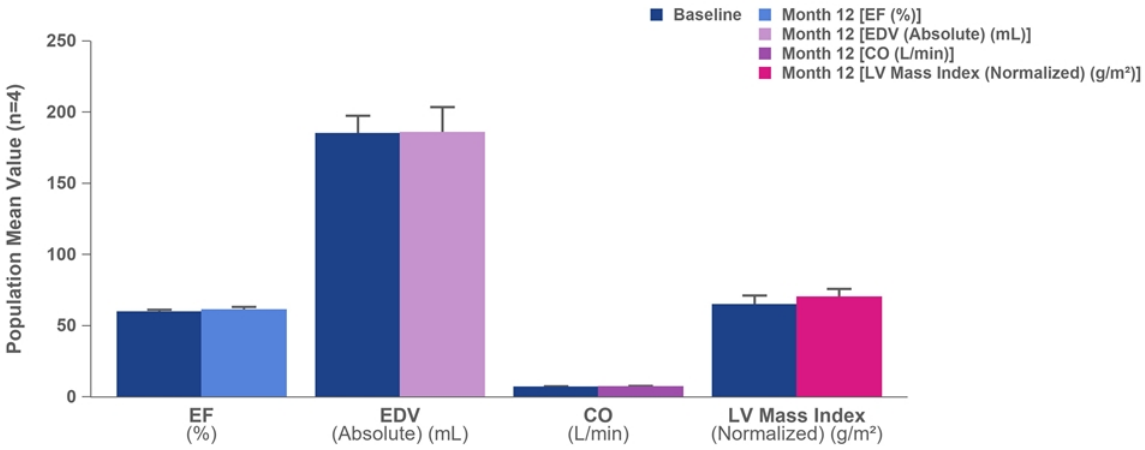
** Eight of nine patients stable; other patient entered trial with more advanced kidney disease and a baseline eGFR level <50 mL/min/1.73m2; as expected, this patient has not stabilized, and the patient remains on ERT*

Note: eGFR was calculated using the CKD-EPI formula

eGFR: Estimated Glomerular Filtration Rate; CKD: Chronic Kidney Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

POWERED BY AVROBIO plato

Cardiac function and mass stable across multiple measures up to 1 year



Abbreviations: EF=Ejection Fraction; EDV=End Diastolic Volume; LV=Left Ventricular.
Error bar represents the standard error of the population mean (n=4).
*Reference Range Mean Values Male 20-39 yrs; EF: 64.3 ± 4.2%; EDV: 178.6 ± 30.1 mL; CO: 4-8 L/min; LV Mass Index: 67.8 ± 10.7 g/m²
**Reference Range Mean Values Male 40-49 yrs; EF: 58-75 %; EDV: 117-200 mL; CO: 4-8 L/min; LV Mass Index: 58-91 g/m²

*Source: *Alfakih K et al, J Magn Reson Imaging, 2003 ; **Maceira AM et al, J of Cardiovascular Magnetic Resonance, 2006*

No unexpected safety events identified

Conditioning-related side effects have been manageable and transient

Phase 1 & 2 AEs and SAEs

- No AEs or SAEs related to AVR-RD-01 drug product
- AEs across trials generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions

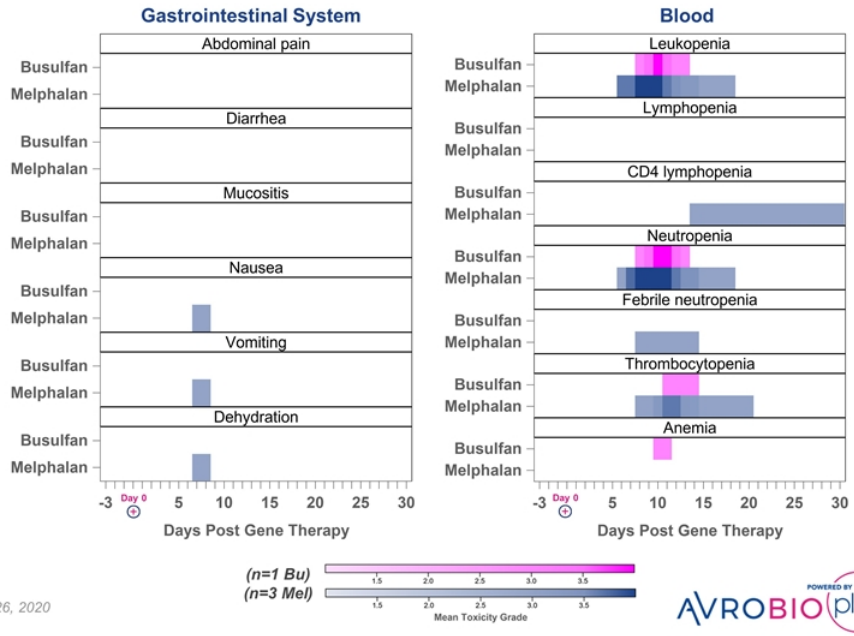
---

- Phase 1 AEs (n=94)
  - Grade 3 or 4 (n=14)
- Phase 1 SAEs (n=2) resolved without clinical sequelae
  - Post-AVR-RD-01 treatment: febrile neutropenia; thrombophlebitis

---

- Phase 2 AEs (n=111)
  - Grade 3 or 4 (n=22)
- Phase 2 SAEs (n=6) resolved without clinical sequelae
  - Post-AVR-RD-01 treatment: dehydration; nausea; vomiting; febrile neutropenia

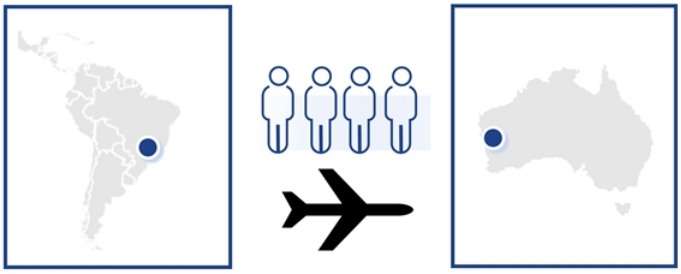
Phase 2 conditioning-related grade 3/4 AEs



Note: Phase 2 safety data cut-off December 7, 2020; Phase 1 safety data cut-off November 26, 2020
AE: Adverse Event; Bu: Busulfan; Mel: Melphalan

Accelerating enrollment by adding international referrals

ONE Fabry patient from Brazil has been dosed and **THREE** have been enrolled in Australia



Long-term follow-up expected to take place in Brazil

Global patient recruitment

- Expands pool of potential patients
- Helps navigate COVID-19 issues
- First global center of excellence established in Australia

AVROBIO plato

Planned global regulatory strategy for Fabry disease

Planned ERT-switch

CONFIRMATORY TRIAL

- Males, mutation-independent
- Efficacy, durability, safety
- Cardiac and kidney function
- Cognition scoring and CNS imaging
- Biomarker data
- Quality of life

Phase 2 Partially Enrolled ERT-naïve

EXPANDED FOR POTENTIAL ACCELERATED APPROVAL

- n=8-12
- Treatment-naïve classic males
- Efficacy, durability, and safety
- Biomarker data, kidney and cardiac function, Gb3 in kidney biopsy
- Expand n, including adding females

Fully Enrolled ERT-switch

PHASE 1 – INVESTIGATOR SPONSORED TRIAL

- n=5, fully enrolled
- ERT-switch in classic males
- Safety, preliminary efficacy, durability
- Biomarker data, kidney function

Anticipated Next Steps:

- Discuss accelerated approval approach with FDA in Q1 '21
- Expand Phase 2 study and complete enrollment
- Initiate confirmatory ERT-switch trial activities in 2021
- Seek early FDA agreement on potency assay matrix
- Advance commercial readiness activities including payors / HTA interactions

ERT: Enzyme Replacement Therapy;
CNS: Central Nervous System;
Gb3: Globotriaosylceramide

Cystinosis opportunity

Jaxon, living with cystinosis

Caused by CTNS gene defect, resulting in cystine buildup in lysosomes

Standard of care (SOC): Cysteamine pills & eye drops

- Not curative, relentless progression of disease continues; significantly shortened lifespan; kidney transplant often required
- Burdensome and expensive – high pill burden and hourly eye drops; 5-year treatment cost with SOC ~$4.3 million*

Unmet needs with SOC:

Kidney function
Renal Fanconi syndrome, proteinuria, CKD, kidney failure

Vision
Corneal cystine accumulation, photophobia, involuntary eyelid closure

Endocrine disorders
Softening & deformation of bones, hypothyroidism, diabetes, infertility

CNS complications
Myopathy, hypotonia, tremors, swallowing, neurodevelopmental issues

Everyday burden of illness, reduced life expectancy
High pill burden causes GI discomfort; sulfur body odor and breath

Cystinosis Target Product Profile**:

- Prevents, halts or reverses disease; extends/normalizes lifespan
- Addresses all patient segments – male & female; kidney transplant independent; all ages
- Lifelong durability – single infusion; off cysteamine pills and eye drops
- Impacts hard-to-reach organs – e.g., eye, endocrine organs, brain
- Well tolerated

Affects ~ 1:170,000 people

** WAC pricing from Redbook using standard dosing assumptions*
*** Note: these are target attributes for a first-line therapy*

POWERED BY AVROBIO plato

Steady enrollment in AVR-RD-04 IST trial in cystinosis

PHASE 1/2
AVR-RD-04

ACTIVELY RECRUITING:

OBJECTIVES	PATIENTS
• Safety and tolerability • Hypothesis generation of endpoints	• Up to 6 patients (3 patients enrolled to-date) • Adults and adolescents • Cohorts 1-2 >18 years; Cohort 3 >14 years • Male and female • Oral and ophthalmic cysteamine

AVR-RD-04 trial sponsored by University of California, San Diego; IST does not use plato® platform
Note: AVR-RD-04 aka CTNS-RD-04
IST: Investigator Sponsored Trial

AVROBIO powered by plato

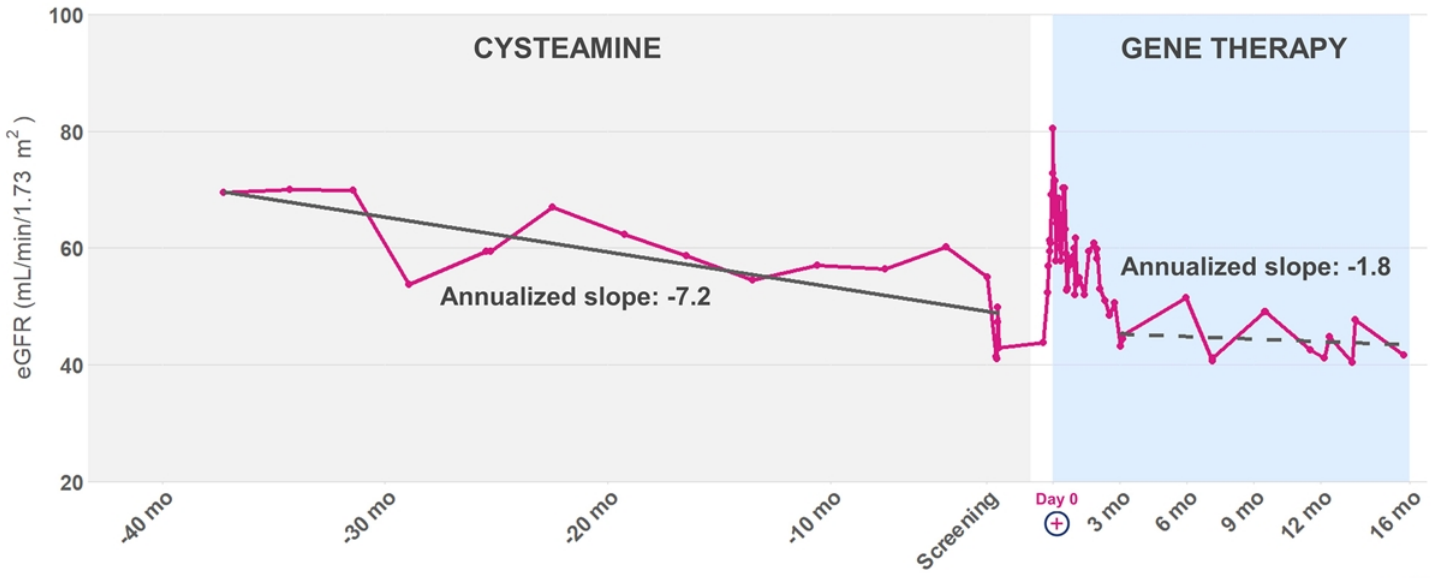
All patients continue to be cysteamine-independent

CYSTINOSIS	PATIENT	MONTHS OFF CYSTEAMINE PILLS AND EYE DROPS POST AVR-RD-04 INFUSION
OFF cysteamine pills	PATIENT 1	16
	PATIENT 2	6
	PATIENT 3	2
OFF cysteamine eye drops	PATIENT 1	16
	PATIENT 2	5
	PATIENT 3	1

Note: All 3 subjects remain off cysteamine pills and eye drops.
Subjects 2 and 3 stopped cysteamine eye drops 1-month post-transplant (per protocol).
Subject 1 stopped cysteamine eye drops prior to baseline.
Data as of January 20, 2021

CYSTINOSIS PHASE 1/2: PATIENT 1

eGFR data at 16 months suggest renal function stabilization post-gene therapy after years of pathological decline

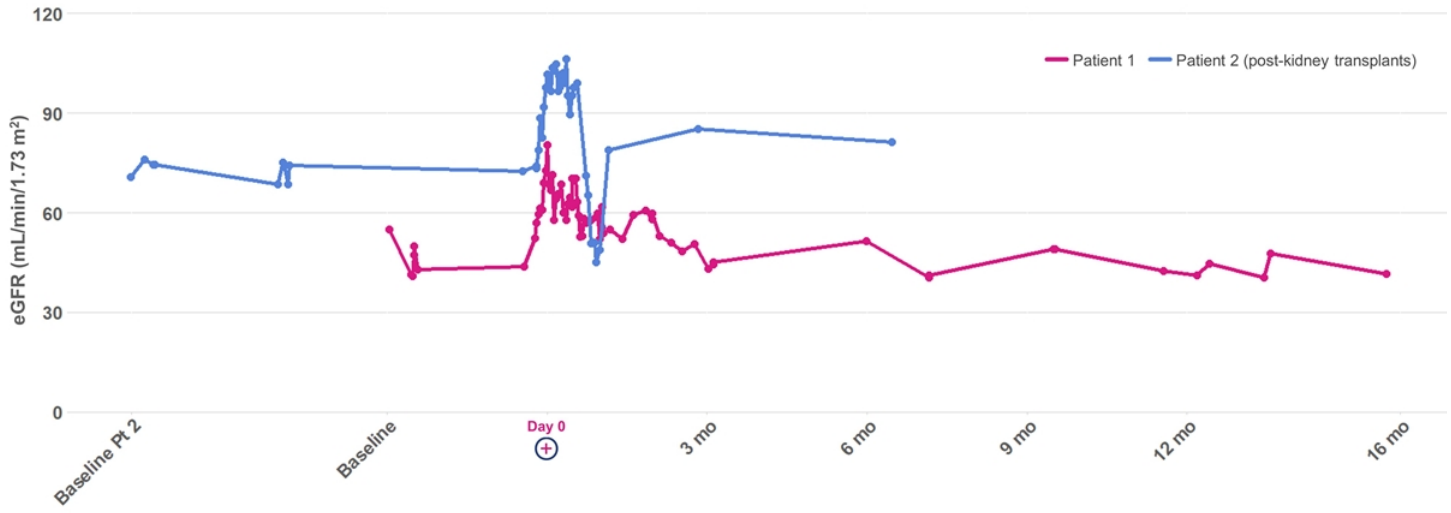


Note: These results are for a single patient only and may vary in the study population; eGFR calculated using CKD-EPI formula; eGFR: Estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

AVROBIO plato

Trial designed to demonstrate broad applicability across cystinosis patient population

Positive eGFR trends independent of kidney transplant status



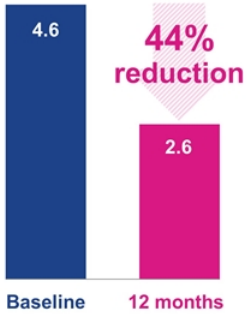
Note: eGFR calculated using CKD-EPI formula
Patient 2 is post two kidney transplants
eGFR: Estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

CYSTINOSIS PHASE 1/2: PATIENT 1

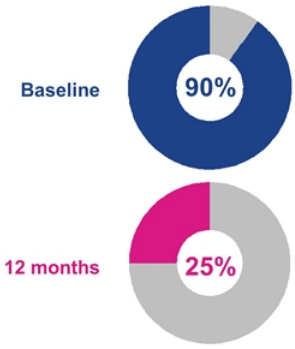
Sharp drop in the number and size of cystine crystals in skin and rectal biopsies

SKIN BIOPSY

Average intracytoplasmic crystals per cell

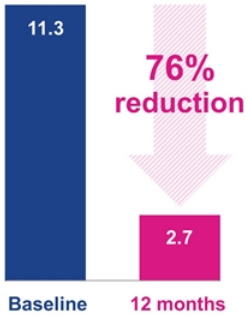


Occupancy of cytoplasmic volume

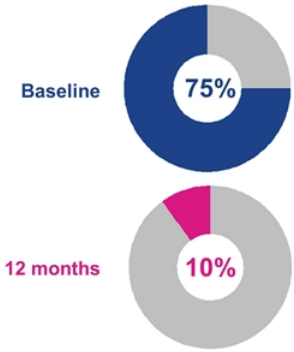


RECTAL BIOPSY

Average intracytoplasmic crystals per cell



Occupancy of cytoplasmic volume



Note: These results are for a single patient only and may vary in the study population

AVROBIO plato

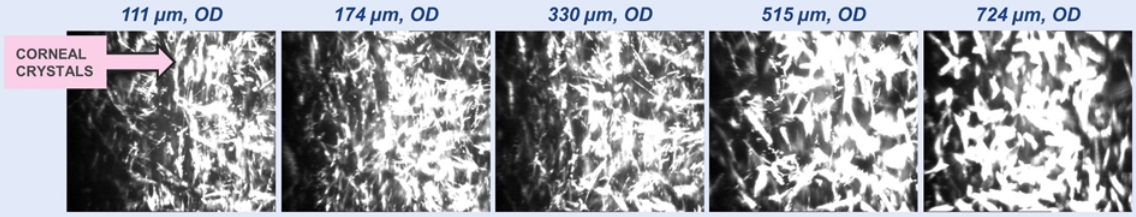
CYSTINOSIS PHASE 1/2: PATIENT 1

Substantial decline in corneal crystals observed at 1 year

***Front** of cornea* — ***Back** of cornea*

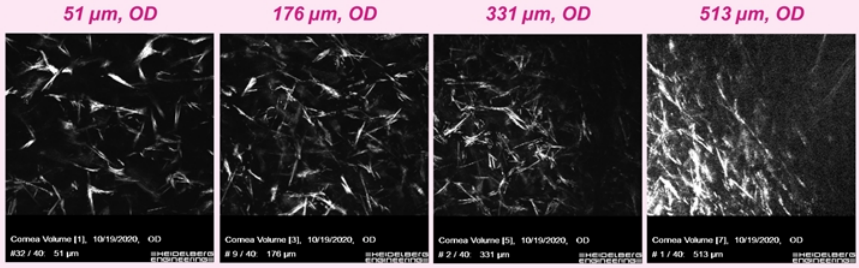
Baseline

IVCM images from Nidek Confoscan



12 months post-gene therapy

IVCM images from Heidelberg HRT3 w/ Rostock Corneal Module



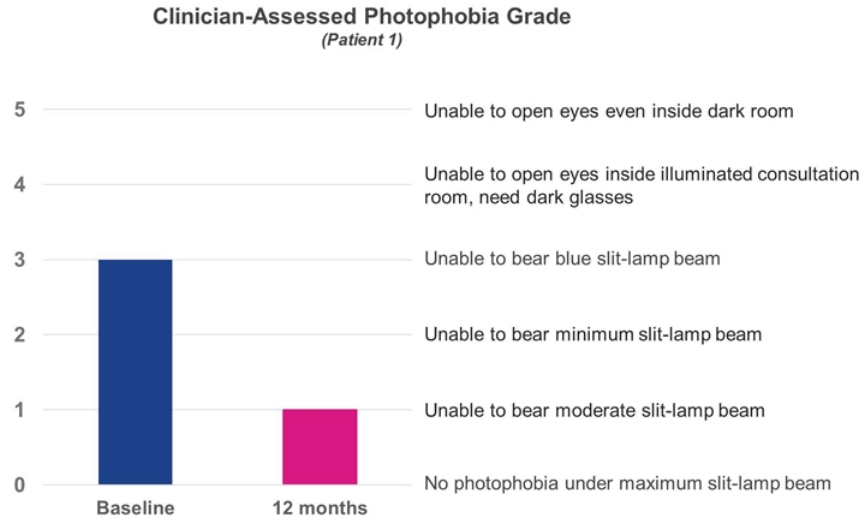
Note: These results are for a single patient only and may vary in the study population; IVCM: In Vivo Confocal Microscopy; OD: Oculus Dexter (right eye); HRT3: Heidelberg Retina Tomograph 3

Photophobia improved meaningfully at 1 year

Photophobia, or extreme sensitivity to light, is a hallmark of cystinosis

Cystinosis photophobia intensity associated with:

- Crystal density (light scattering)
- Inflammatory cell infiltration
- Corneal nerve damage



Liang, H. IONS May 2015

Darker pigmentation may be a sign of multi-functional cystinosin activity post-gene therapy

Cystinosin is located in melanosomes and regulates melanin synthesis

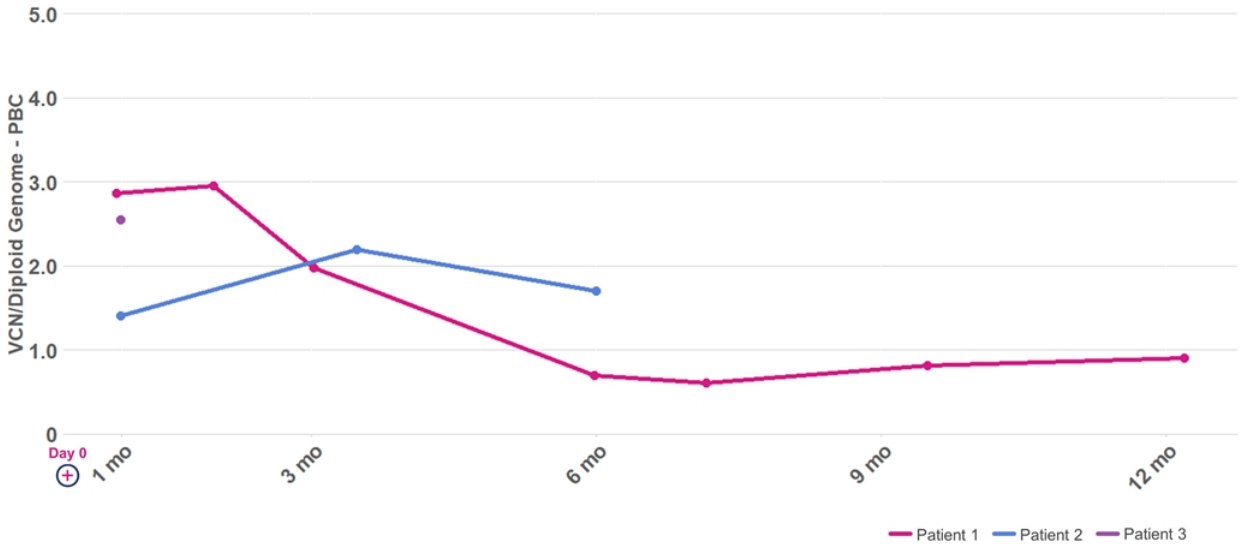
Patient 1 appears to exhibit **progressively darkening skin, eyebrows and hair color post-infusion**, suggesting a possible impact of cystinosin protein on melanin

Note: These results are for a single patient only and may vary in the study population; Background removed for clarity
Source: Chiaverini et al., FESEB, 2012

VCN trending as expected across patients

Patient 1 reached VCN therapeutic plateau

DRUG PRODUCT VCN/dg	
Patient 1	2.1
Patient 2	1.3*
Patient 3	1.6



** From second apheresis*

VCN: Vector Copy Number; PBCs: Peripheral Blood Cells; dg: Diploid Genome

No unexpected safety events

Conditioning-related side effects have been manageable and transient

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

AEs & SAEs reported

- AEs (n=48)
  - Majority of AEs are mild or moderate and resolved
- SAE (n=1)
  - Post AVR-RD-04 treatment: appendicitis unrelated to study treatment or procedures

- AEs are generally consistent with myeloablative conditioning or underlying disease:

Pre-AVR-RD-04 treatment and prior to conditioning (not all events listed)
- Diarrhea, hypokalemia, dizziness
- Dehydration, vomiting

Post-AVR-RD-04 treatment (not all events listed)
- Alopecia, intermittent diarrhea, vomiting, loss of appetite
- Mucositis, intermittent febrile neutropenia, intermittent epistaxis
- Intermittent blurry vision, intermittent hypokalemia, mucoceles
- Thrombocytopenia

Note: Safety database cut as of January 27, 2021
AE: Adverse Event; SAE: Serious Adverse Event

Planned global regulatory strategy for cystinosis

Planned

POTENTIAL REGISTRATION

- Adults and pediatrics, males and females
- Mutation-independent, kidney transplant-independent
- Efficacy, durability, safety
- Ophthalmology, kidney, and other undisclosed
- Multiple crystal measures
- Quality of life

50% Enrolled

PHASE 1/2 – INVESTIGATOR SPONSORED TRIAL

- n ≤6
- Adults and adolescents, males and females
- Mutation-independent, kidney transplant-independent
- Safety, durability, preliminary efficacy
- Biomarker data, kidney function, vision
- Quality of life

Anticipated Next Steps:

- Complete Phase 1/2 enrollment in 2021
- Engage with FDA on registration trial design
- Identify global sites for registration trial
- Prepare plato® CMC / analytics requirements

FDA: Food and Drug Administration; CMC: Chemistry, Manufacturing, and Controls

Gaucher disease type 1 opportunity

Adrianna, living with Gaucher disease type 1

Caused by mutation in the gene encoding for glucocerebrosidase (GCase) enzyme

Standard of care (SOC): ERT

- Not curative, relentless progression of disease continues, including bone crisis and fatigue
- Burdensome and expensive – bi-weekly infusions required; 5-year treatment cost with ERT = ~$2.3 million*

Unmet needs with SOC:

Bone-related manifestations
Skeletal abnormalities, avascular necrosis, osteoporosis

Hemoglobin levels and platelet counts
Anemia, thrombocytopenia, easy bruising, bleeding

Hepatosplenomegaly
Enlarged liver, enlarged spleen

Everyday burden of illness, and life expectancy
Fatigue, pain, lung disease, biweekly infusions, shortened lifespan

CNS complications
Increased risk of GBA-Parkinson's disease

Gaucher Disease Type 1 Target Product Profile**:

- Prevents, halts or reverses disease; extends/normalizes lifespan
- Addresses all patient segments – all GD1 genetic mutations, all ages, male & female
- Lifelong durability – single infusion; off ERT/chaperone therapy
- Impacts hard-to-reach organs – e.g., brain, bone and bone marrow
- Well tolerated

Affects ~ 1:44,000 people worldwide

** WAC pricing from Redbook using standard dosing assumptions*
*** Note: these are target attributes for a first-line therapy*

Guard1: Phase 1/2 study in Gaucher disease type 1

PHASE 1/2
AVR-RD-02

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 Gaucher disease type 1

ACTIVELY RECRUITING:

RECRUITING PLANNED 2021:

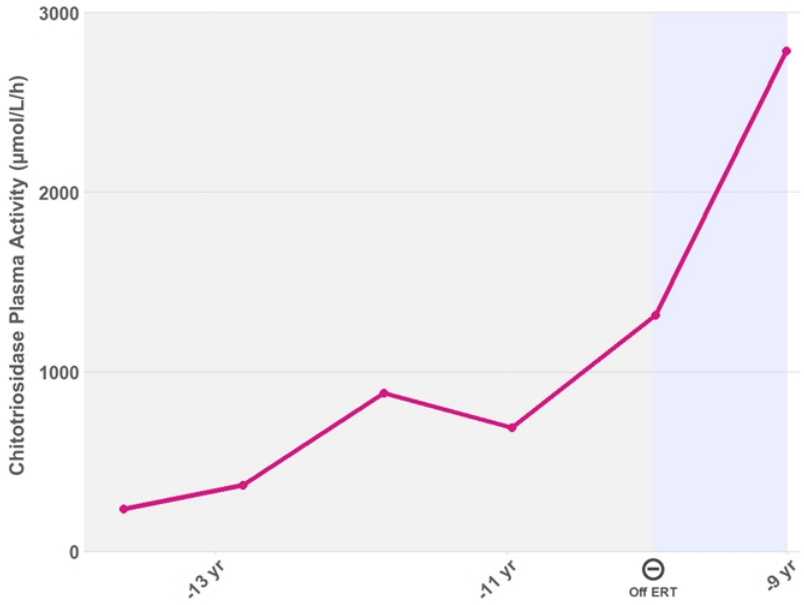
OBJECTIVES	PATIENTS	
• Safety • Efficacy • Engraftment	• Enrollment goal 8-16 patients • 18-45-year-old males and females • Have a confirmed diagnosis of GD1 based on: – Deficient glucocerebrosidase enzyme activity – Clinical features consistent with GD1	**Gaucher disease type 1 patients who are:** • ERT-stable for >24 months *or* • Treatment-naïve *or* • Have not received ERT or SRT in the last 12 months

GD1: Gaucher Disease Type 1; ERT: Enzyme Replacement Therapy; SRT: Substrate Reduction Therapy

First patient's plasma chitotriosidase levels spike off ERT

Personal history documents response to intermittent and halted ERT use

Chitotriosidase is a marker of inappropriately activated macrophages (Gaucher cells)

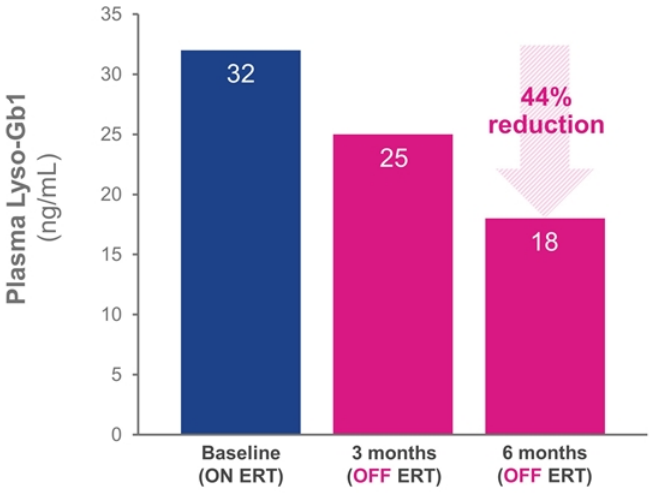


Chitotriosidase Plasma Activity Normal Range: 0.0–44.2 µmoL/L/h
ERT: Enzyme Replacement Therapy

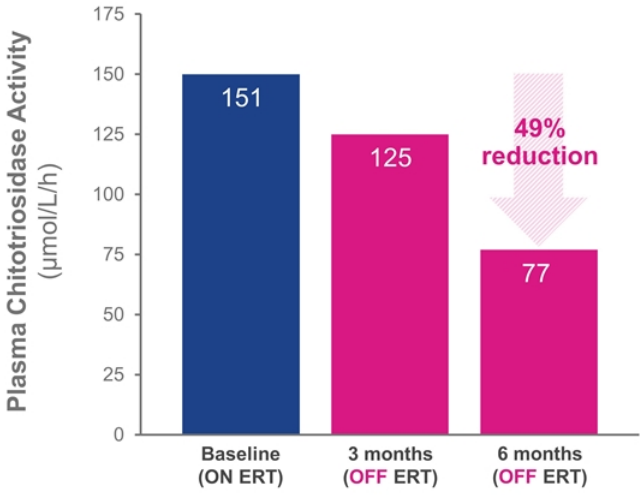
GUARD1: PATIENT 1

Key biomarkers below ERT baseline at 6 months

Lyso-Gb1 is a sensitive and specific marker of toxic metabolite accumulation in Gaucher disease



Chitotriosidase is a marker of inappropriately activated macrophages (Gaucher cells)

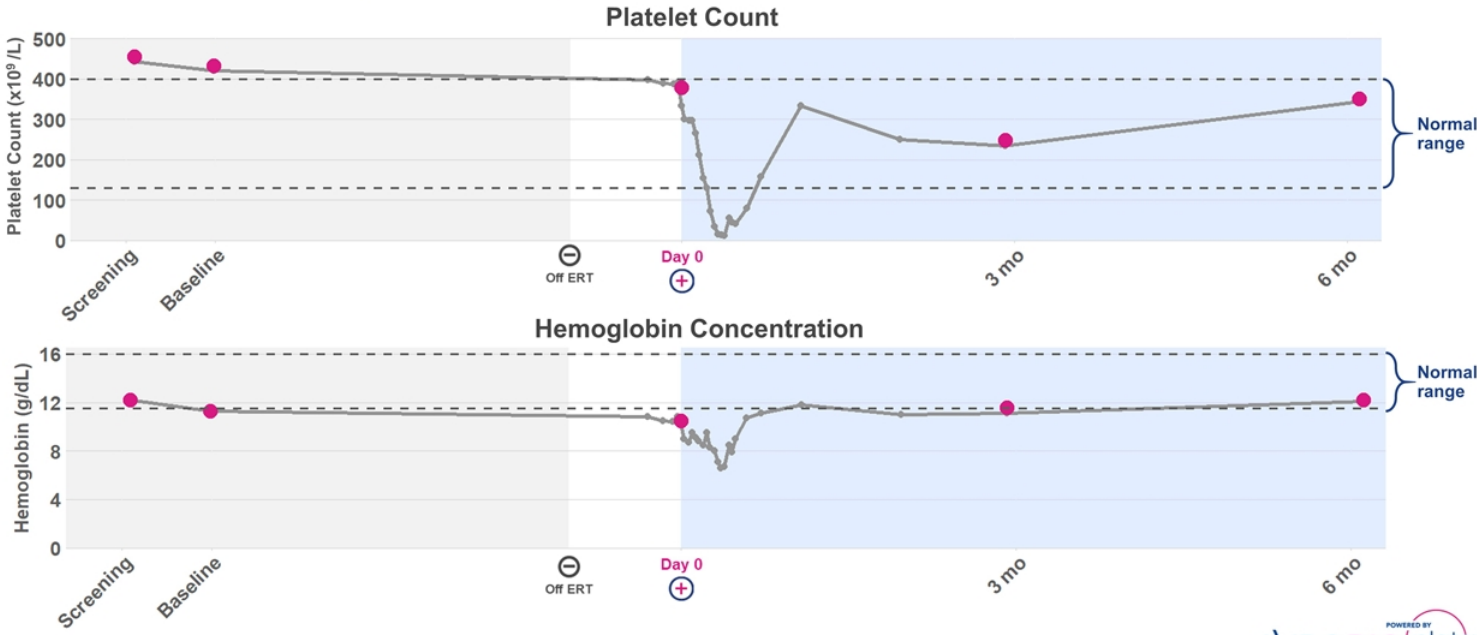


Baseline taken one month prior to gene therapy which is when ERT is discontinued
Lyso-Gb1 Plasma Normal Range: 0.5 – 1.2 ng/mL
Plasma chitotriosidase activity normal range: 0.0 – 44.2 µmoL/L/h
ERT: Enzyme Replacement Therapy

AVROBIO powered by plato

GUARD1: PATIENT 1

Platelet counts and hemoglobin in normal range at 6 months, despite being off ERT



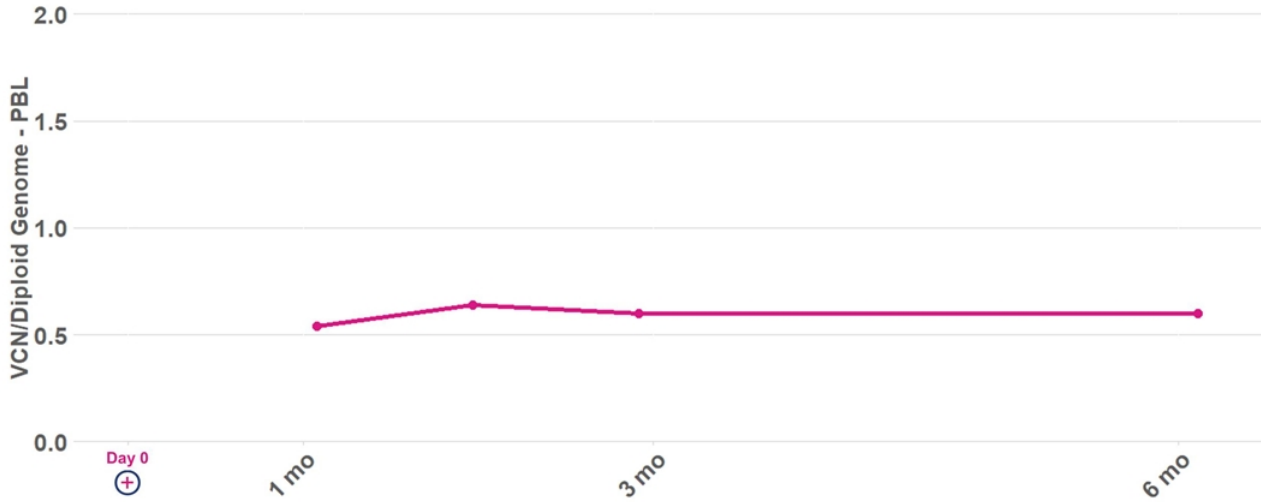
Platelet Count Reference Value Adult: 130-400x109/L; Hemoglobin Reference Value: Males: 13.5-17.5 g/dL; Females: 11.5-16.0 g/dL; grey line: local (safety) lab values; pink dots: central (efficacy) lab values; ERT: Enzyme Replacement Therapy

AVROBIO POWERED BY plato

GUARD1: PATIENT 1

VCN trending as expected at 6 months

Drug Product VCN/dg	
Patient 1	3.7



VCN, vector copy number; PBL, peripheral blood leukocytes; dg, diploid genome

GUARD1: PATIENT 1

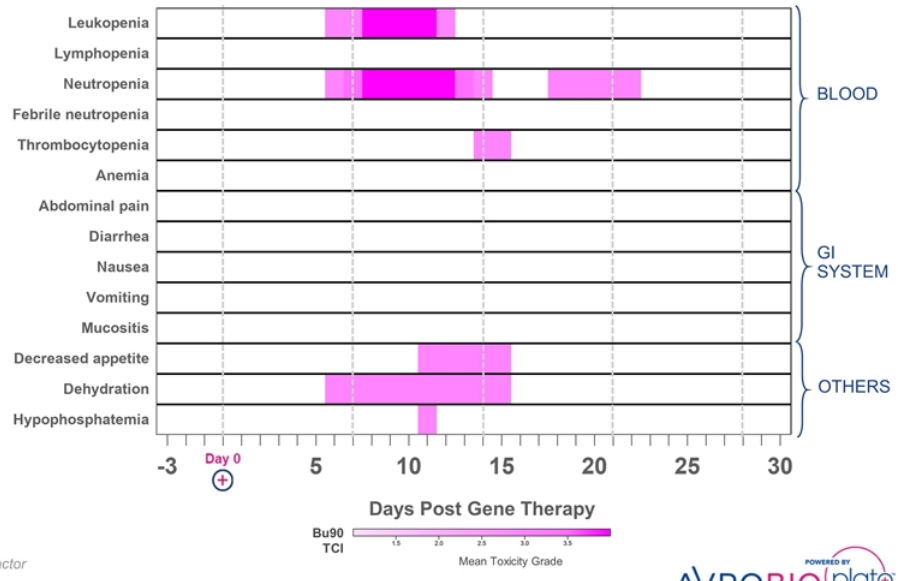
No unexpected safety events identified in first patient

Conditioning-related side effects have been predictable and transient

AEs (no SAEs reported)

- No AEs or SAEs related to AVR-RD-02 drug product
- AEs generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
- AEs n=29
  - Grade 3 (n=7)
    - Eye pain, decreased appetite, dehydration, headache, hypophosphatemia, neutropenia, thrombocytopenia
  - Grade 4 (n=2)
    - Leukopenia and neutropenia
- AEs resolved without clinical sequelae

Conditioning-related grade 3/4 AEs



Note: Safety database cut as of January 04, 2021
AE: Adverse Event; SAE: Serious Adverse Event; G-CSF: Granulocyte Colony Stimulating Factor
G-CSF 5 µg/kg @ Days 5, 6, 7, 10, 11, and 14 post-infusion of AVR-RD-02
Bu90-TCI: Busulfan 90-Target Concentration Intervention; GI: Gastrointestinal

Planned global development strategy for Gaucher disease type 1

Planned

POTENTIAL REGISTRATION PATH

- Phase 1/2 expansion
- Safety, efficacy, durability
- Organ volumes, hematologic measures, bone assessments, pain, and QOL

Enrolling

PHASE 1/2

- n=8-16
- Adults, males and females, ages 18-45 years old
- ERT-switch and ERT-naïve
- Safety, efficacy, durability
- Biomarker data, organ volumes, hematologic measures, bone assessments, pain, and QOL

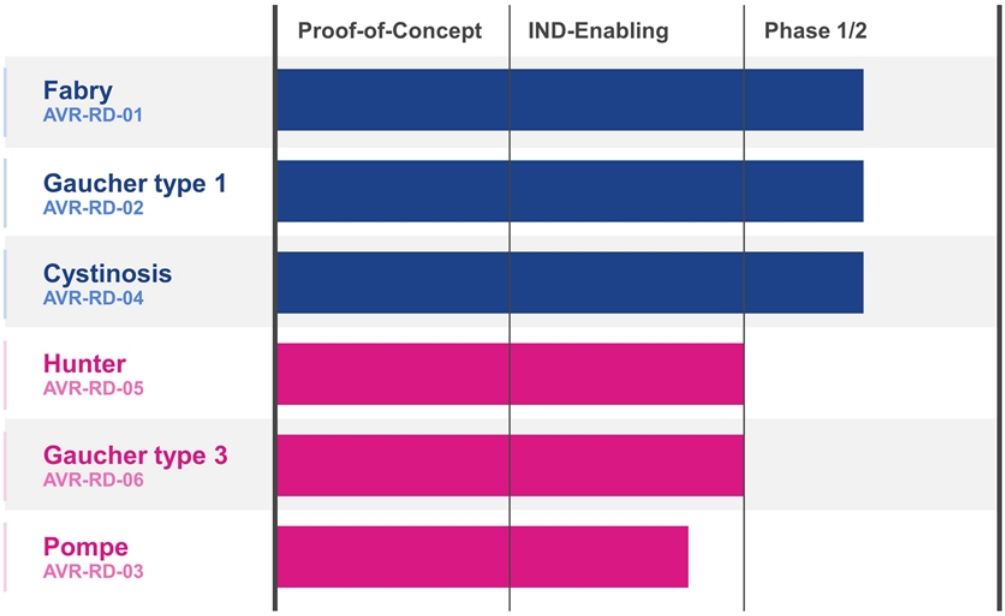
Anticipated Next Steps:

- Advance patient enrollment
- Advance regulatory dialogue on registration pathway

QOL: Quality Of Life; ERT: Enzyme Replacement Therapy


“Second Wave”
Programs
Hunter, Gaucher Type 3 and Pompe

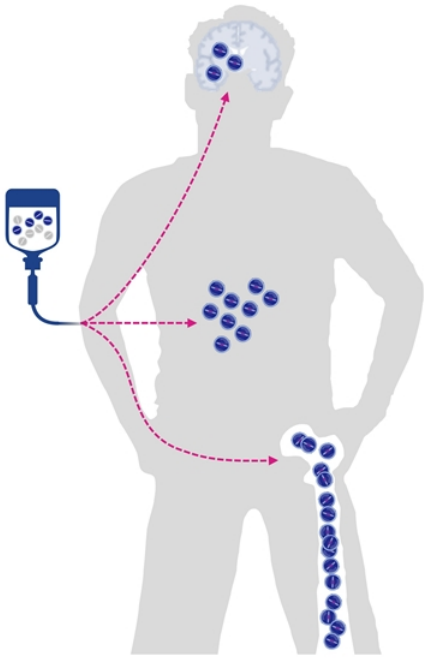
Bold expansion of our leadership in lysosomal disorders

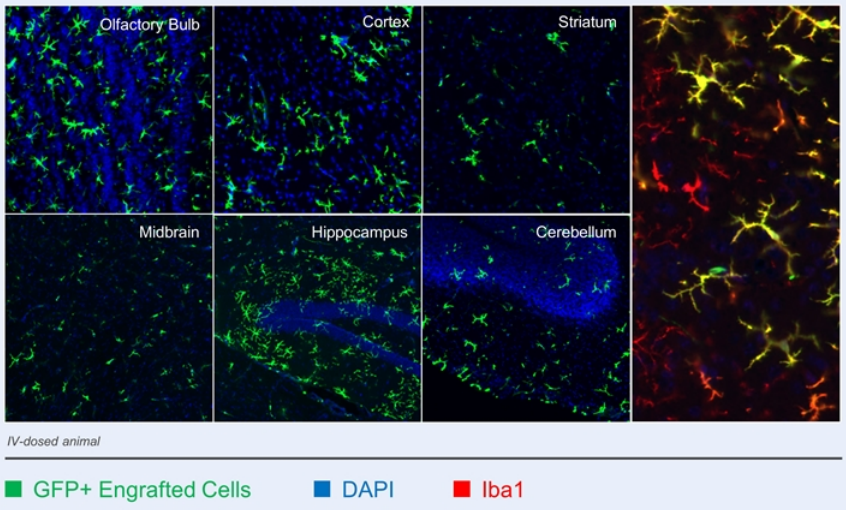


IND: Investigational New Drug

PRECLINICAL DATA

Lentiviral gene therapy enables global distribution of functional enzyme to brain and bone in preclinical studies





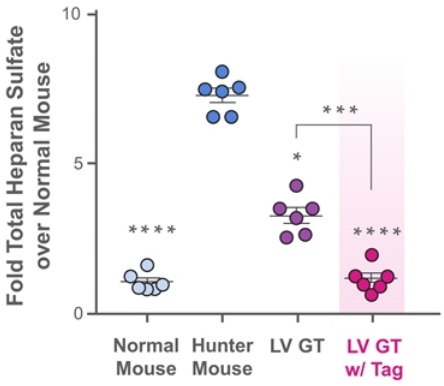
GFP: Green Fluorescent Protein; DAPI: 4',6-diamidino-2-phenylindole; Iba1: Ionized Calcium-Binding Adapter Molecule 1; IV: Intravenous

POWERED BY AVROBIO plato

Proprietary tags deliver therapeutic protein into hard-to-reach organs

Hunter syndrome

Tag normalizes heparan sulfate in brain



Pompe disease

Tag normalizes glycogen substrate in brain

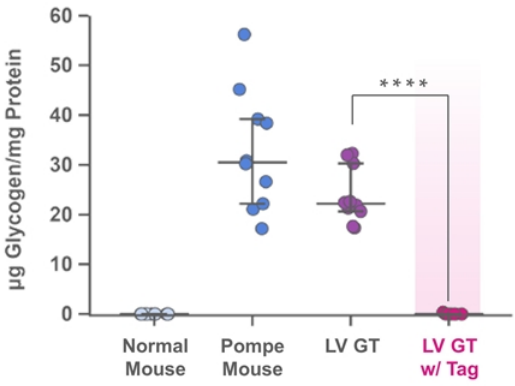


*Figure adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 3A; *P<0.05, ***P<0.001, ****P<0.0001; LV GT: Lentiviral Gene Therapy*

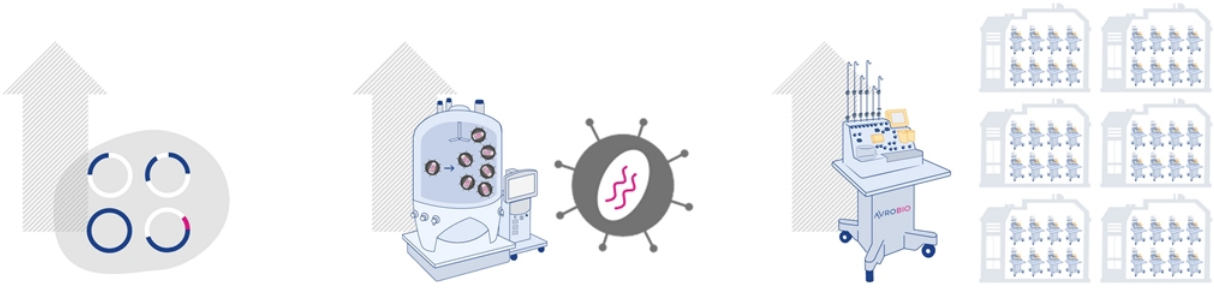
plato®

AVROBIO's platform for global gene therapy commercialization

- Redefines manufacturing best practices
- Solves key industry challenges

Designed to be fully scalable

Common components and automation leveraged across manufacturing



PLASMID

3 of 4 component plasmids used in every vector

Each plasmid can be mass produced and stored for use

VECTOR

State of the art, largest scale, 200L vector production

Expansion through simple installation of additional units, mass produced, frozen, and stored for use

DRUG PRODUCT

Closed system automated platform

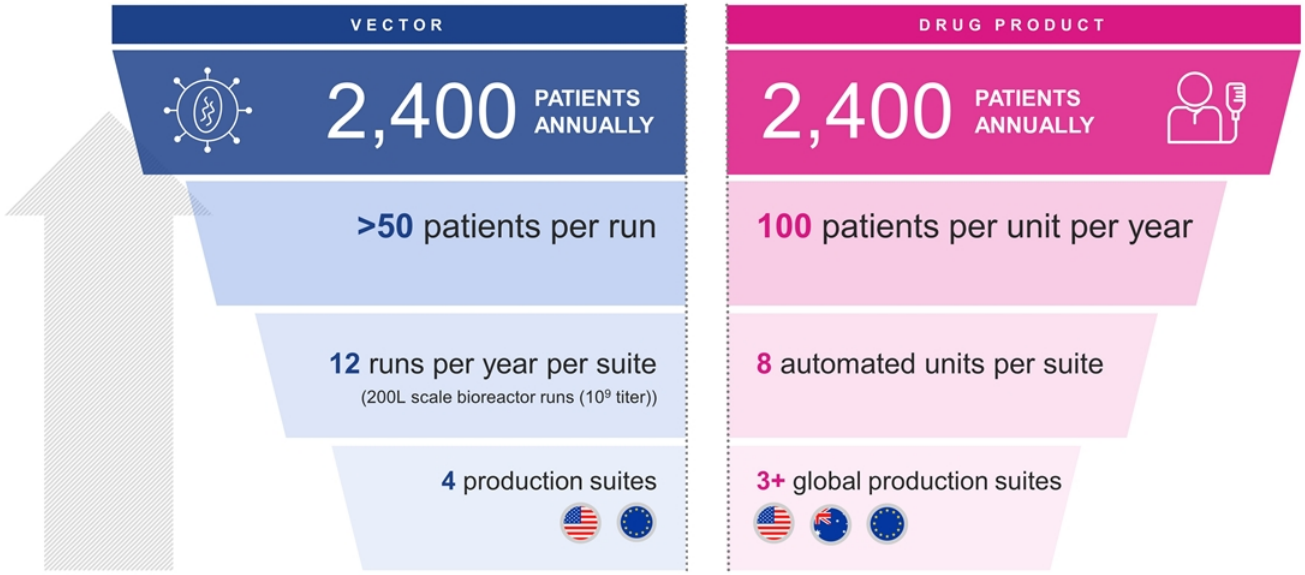
Scale out of manufacturing suites and automation units to meet patient demand

Note: This diagram is for illustrative purposes only

POWERED BY AVROBIO plato

Poised to manufacture at scale

Global infrastructure already in place



Note: This diagram is for illustrative purposes only

CMC achievements have defined the plato® story

Strategic investment in technology laid the foundation for our manufacturing leadership

Manufacturing

Robust production platform

- Best-in-class LV manufacturing
- Scalable from plasmid to drug product

Global footprint

- Cleared for the clinic from multiple agencies

Cost effective

- Intended to address key COGs issues

Analytics

Robust platform analytics

- Best-in-class VCN assay
- First-in-class transduction assay

Deep product characterization

- First-in-class single cell analytics

Potency assay matrix

- Intended to accelerate regulatory approvals

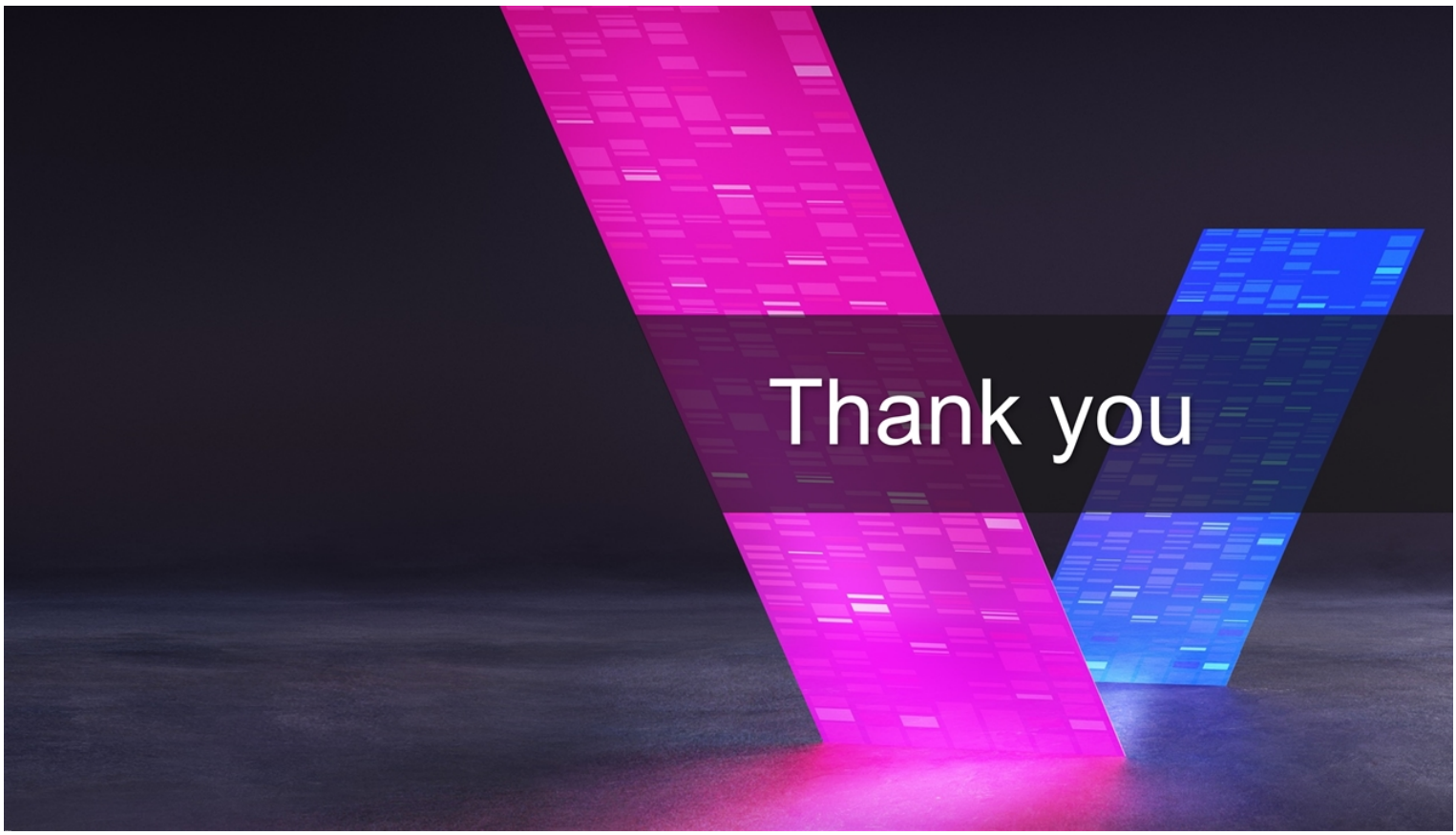
CMC: Chemistry, Manufacturing, and Controls; VCN: Vector Copy Number; LV: Lentiviral; COGs: Cost Of Goods

Key anticipated 2021 milestones

Goal: 30 patients dosed cumulatively by end of 2021

Fabry AVR-RD-01	Seek agreement with regulators on approval pathway in one or more major markets
Gaucher type 1 AVR-RD-02	Execute on global phase 1/2 trial
Cystinosis AVR-RD-04	Complete phase 1/2 enrollment Engage w/ FDA on pivotal trial design
Hunter AVR-RD-05	Conduct Phase 1/2 trial initiation activities
Gaucher type 3 AVR-RD-06	FDA dialogue on path to clinic
Pompe AVR-RD-03	Prepare for classic infantile-onset study

FDA: Food and Drug Administration


Thank you

Appendix

Reported cases of potential lentiviral gene therapy-related oncogenesis

Zero cases reported outside of sickle cell disease

SICKLE CELL DISEASE (SCD)	NON-SCD MONOGENIC DISEASES	CAR-T
2 or 3 cases out of 47 patients	**0 cases** out of >300 patients	**0 cases** out of >1,000 patients

CAR-T: Chimeric Antigen Receptor T-cell

Sources: bluebird bio, Inc. 2/16/21 press release and conference call; Genes (Basel). 2019 Mar; 10(3): 218

Fabry Phase 1 & 2 Patient Characteristics

	PHASE 1: 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)
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
eGFR (mL/min/1.73m²) at baseline**	83	49	112	124	121
ERT discontinuation status	18 months after gene therapy dose		Did not resume ERT after gene therapy dose	6 months after gene therapy dose	

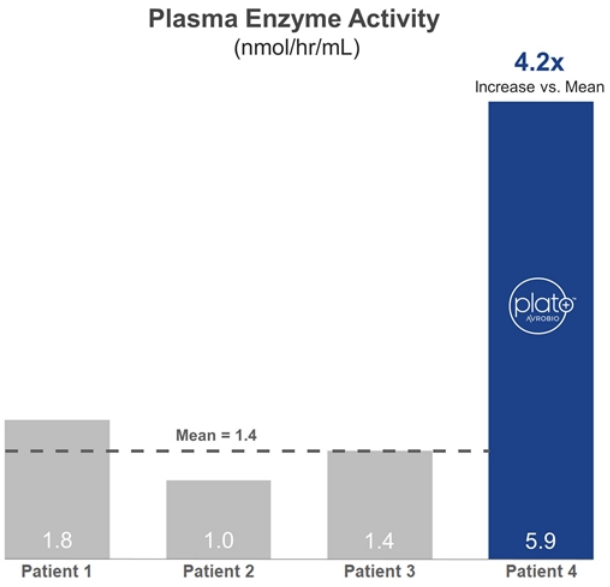
	PHASE 2: Treatment-naïve Fabry patients			
	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Age of symptom onset/diagnosis	10 / 19 years	36 / 37 years	13 / 13 years	9 / 9 years
Age dosed with AVR-RD-01	21 years	46 years	40 years	26 years
Mutation	c.1021G>A (p.E341K)	c.644A>G (p.N215S)	c.639+1G>T	c.833dupA
Leukocyte 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
eGFR (mL/min/1.73m²) at baseline**	128	106	98	129
Comment	Few IgA deposits in kidney biopsy, no mesangial proliferation	Cardiac variant, not a classic Fabry male		

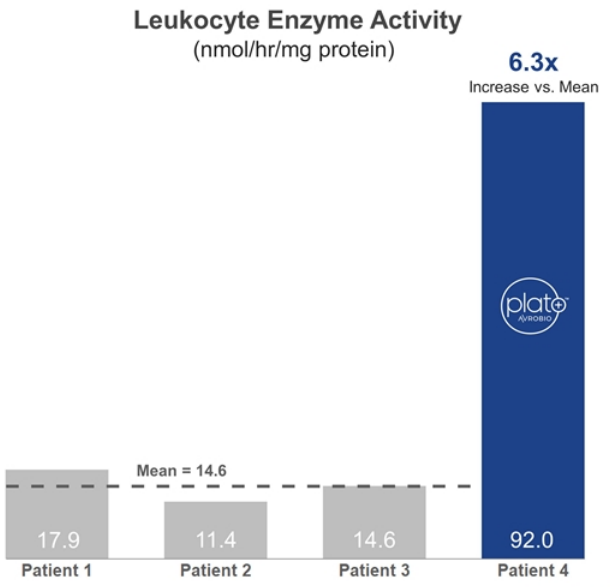
** Mayo Lab, ref range ≥23.1 nmol/hr/mg protein; ** Rupar Lab, ref range 24-56 nmol/hr/mg protein; *** Reference value ≤ 2.4 nM; **** eGFR: Estimated Glomerular Filtration Rate; calculated using CKD-EPI formula*
AGA: α-galactosidase A; Lyso-Gb3: Globotriaosylsphingosine;

POWERED BY AVROBIO plato

Patient #4 is first Fabry patient dosed with plato®

FAB-GT 12 month data for patient #4 with plato® vs. patients #1-3

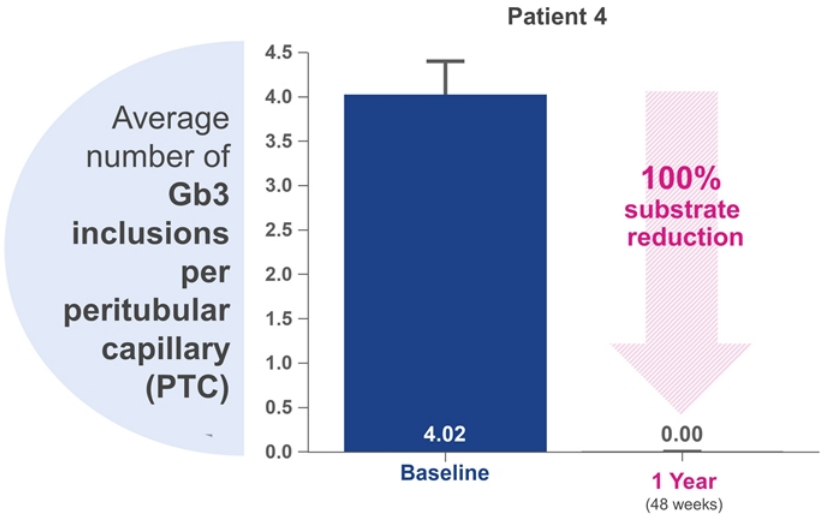




POWERED BY AVROBIO plato

100% clearance of substrate in kidney biopsy at 1 year

Patient dosed using plato®

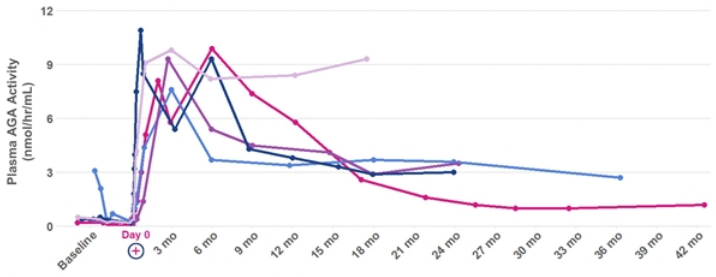


- *Two-sample t-test for difference between average PTCs at Baseline vs. 48 weeks; $p < 0.0001$; Error bar represents the standard error at Baseline (n=103 PTCs) and 48 weeks (n=99 PTCs); scored by 2 independent, blinded pathologists*

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

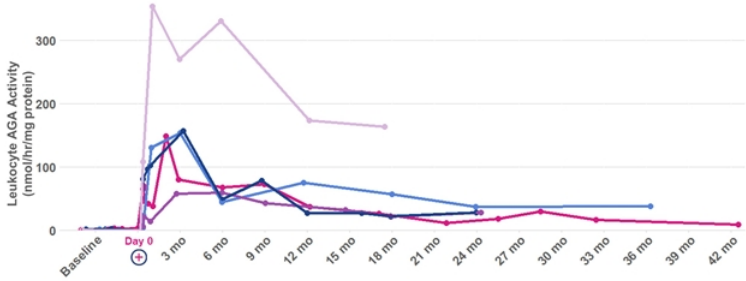
Durability demonstrated over multiple measures up to 3.5 years

Plasma AGA Enzyme Activity



Plasma AGA Activity Reference Range: 5.1–9.2 nmol/hr/mL; AGA: α-galactosidase A

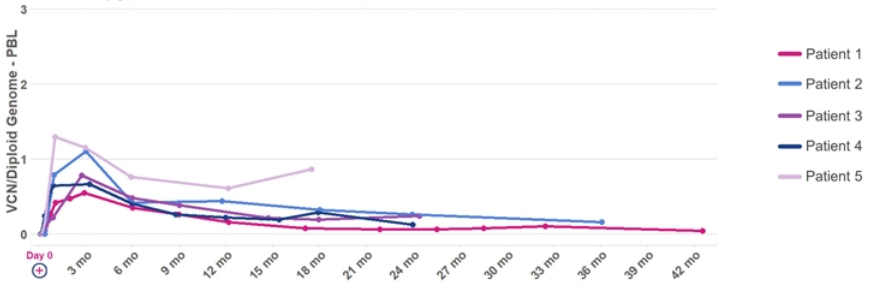
Leukocyte AGA Enzyme Activity



Leukocyte AGA Activity Reference Range: 24–56 nmol/hr/mg protein; AGA: α-galactosidase A

Drug Product VCN/dg
Patient 1: 0.7 **Patient 2: 1.4**
Patient 3: 0.8 **Patient 4: 1.4**
Patient 5: 1.2

Vector Copy Number



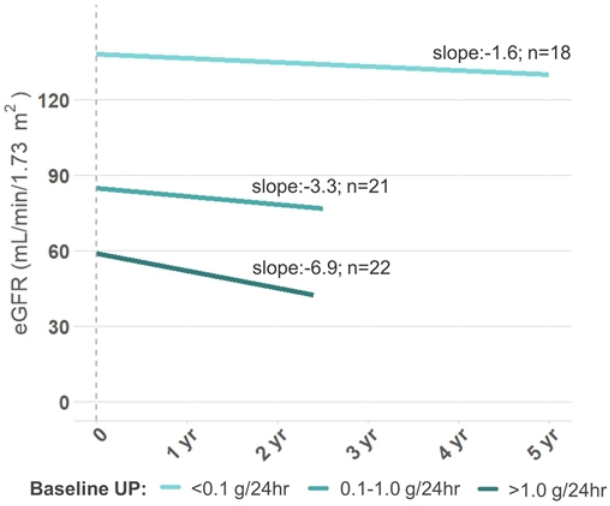
VCN: Vector Copy Number; PBL: Peripheral Blood Leukocytes; dg: Diploid Genome

AVROBIO powered by plato

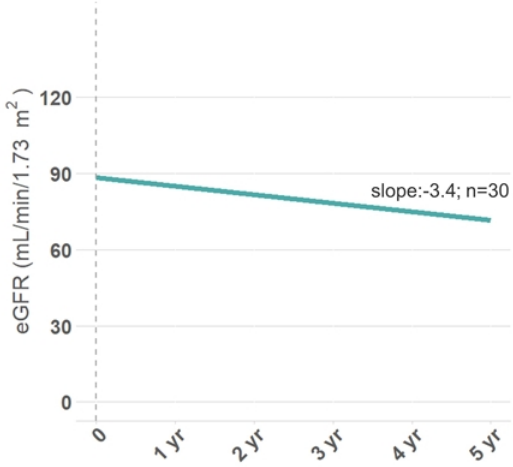
eGFR declines in natural history and on ERT

Classic Fabry male literature eGFR data

Natural history annualized eGFR slopes of treatment-naïve patients[1]



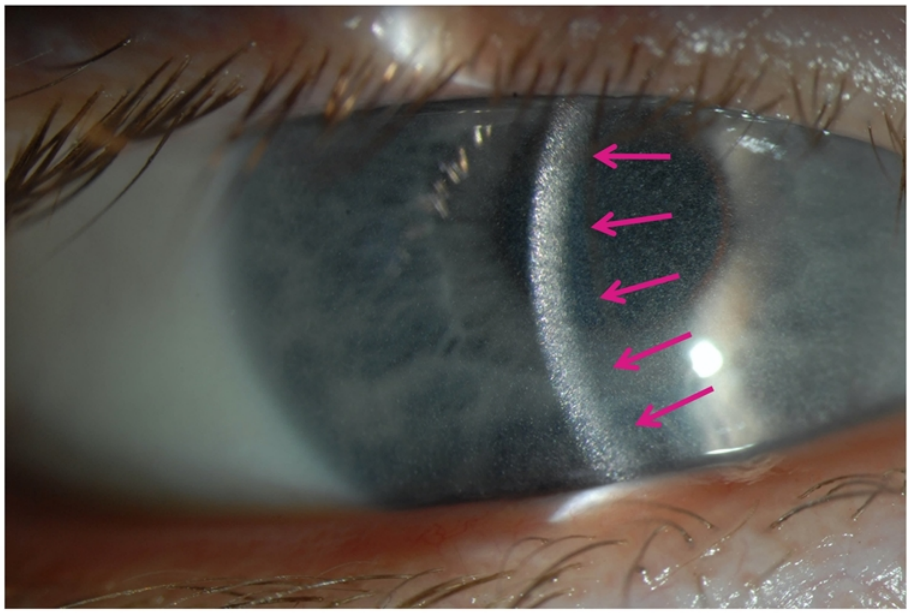
Annualized eGFR slope of ERT-treated patients[2]



Sources: [1]Schiffmann R et al., Nephrol Dial Transplant, 2009 (Table 4); [2]Rombach SM et al., Orphanet J Rare Dis, 2013 (Table 2)
eGFR: Estimated Glomerular Filtration Rate; UP: Urinary Protein; ERT: Enzyme Replacement Therapy

Crystal buildup in eye clearly visible before gene therapy

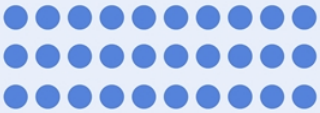
Patient 1 at baseline



Impact of cysteamine independence

Daily cysteamine regimen

(max per day)

Before AVR-RD-04	***ON*** *cysteamine pills* **30 pills / day** 	***ON*** *cysteamine eye drops* **Prescribed 8 drops / day** 
After AVR-RD-04 (16 months post-gene therapy)	***OFF*** *cysteamine pills* **0 pills / day**	***OFF*** *cysteamine eye drops* **0 drops / day**

Note: These results are for a single patient only and may vary in the study population; does not include supplements and other medications