

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): June 16, 2020

AVROBIO, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction
of incorporation)

001-38537
(Commission
File Number)

81-0710585
(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 June 16, 2020, AVROBIO, Inc. updated its corporate presentation for use in meetings with investors, analysts and others. A copy of the slide 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 June 16, 2020.](#)

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: June 16, 2020

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

AVROBIO

Company Presentation
June 2020



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, prospective products and goals, the therapeutic potential of our investigational gene therapies, the design, commencement, enrollment and timing of ongoing or planned clinical trials, clinical trial results, product approvals and regulatory pathways, potential regulatory approvals and the timing thereof, 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, anticipated benefits of our gene therapy platform including potential impact on our commercialization activities, the

expected benefits and results of our implementation of the plato™ platform in our clinical trials and gene therapy programs, 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, the market opportunity for and anticipated commercial activities relating to our investigational gene therapies, and statements regarding the Company's 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.

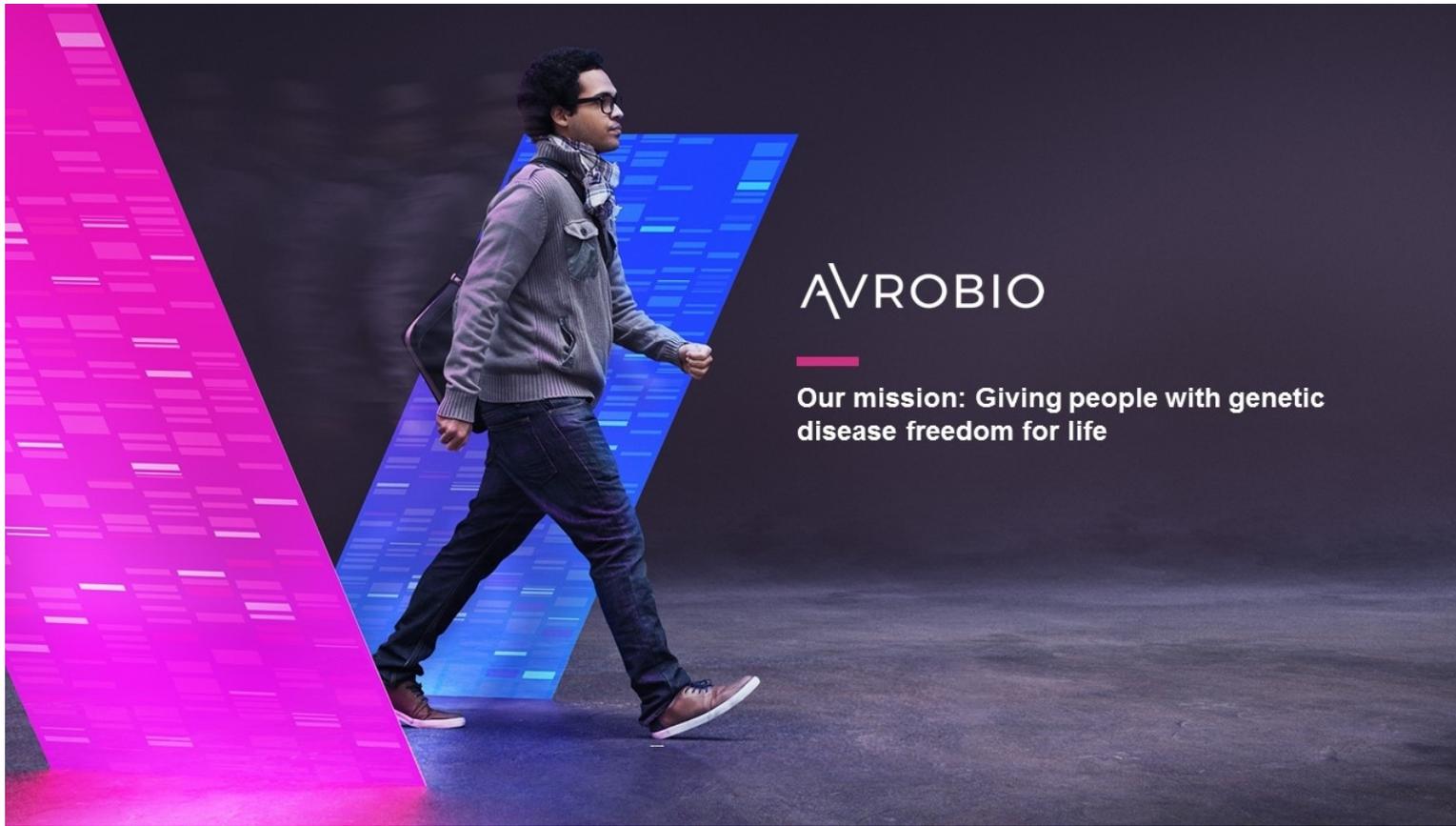
Any forward-looking statements in this presentation are based on AVROBIO's current expectations, estimates and projections about our industry as well as management's current beliefs and expectations of future events only as of today and are subject to a number of risks and uncertainties that could cause 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 or of encountering challenges in the enrollment or dosing in such clinical trials, the risk that AVROBIO may not realize the intended benefits of our gene therapy platform, including the features of our plato 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, 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 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.

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.





AVROBIO

Our mission: Giving people with genetic disease freedom for life



Multiple programs in the clinic

10 patients dosed to date

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

IND: Investigational New Drug

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Addressing multi-billion dollar market opportunity



CURRENT STANDARD OF CARE COSTS

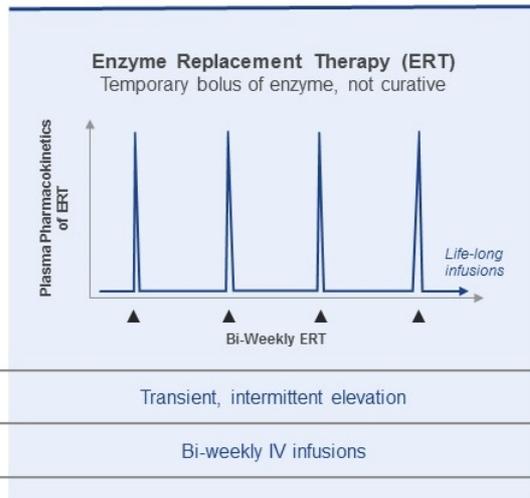
Disease	Est. Cost Per Patient Per Year	Approx. 2019 Net Sales	Selected Companies
Fabry	\$320k	\$1.4B	SANOFI GENZYME   
Gaucher	\$250k-400k	\$1.4B	SANOFI GENZYME   
Pompe	\$500k	\$1.0B	SANOFI GENZYME 
Cystinosis	\$625k-700k*	\$0.2B	  

Sources: Rombach S et al, Orphanet J Rare Dis, 2013; van Dussen L et al, Orphanet J Rare Dis, 2014; WAC pricing from Redbook; 2019 Net Sales from company annual and other reports
 * for Horizon's Procysbi oral therapy (delayed release cysteamine bitartrate)
 Note: Shire acquired by Takeda in 2019

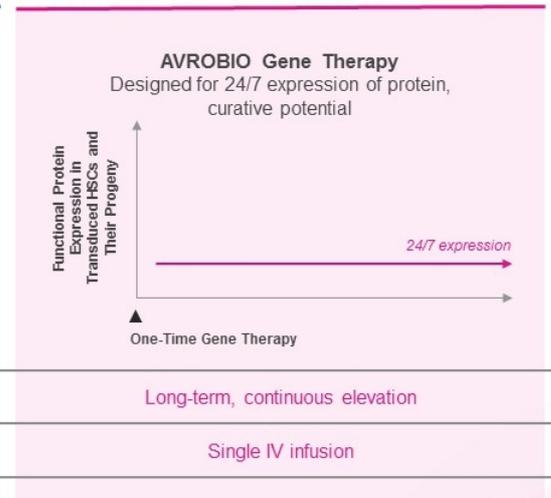
Lifelong treatments vs. potential single-dose therapy



DISEASE PROGRESSION CONTINUES



DISEASE PROGRESSION COULD HALT OR REVERSE



Enzyme or protein level

Transient, intermittent elevation

Long-term, continuous elevation

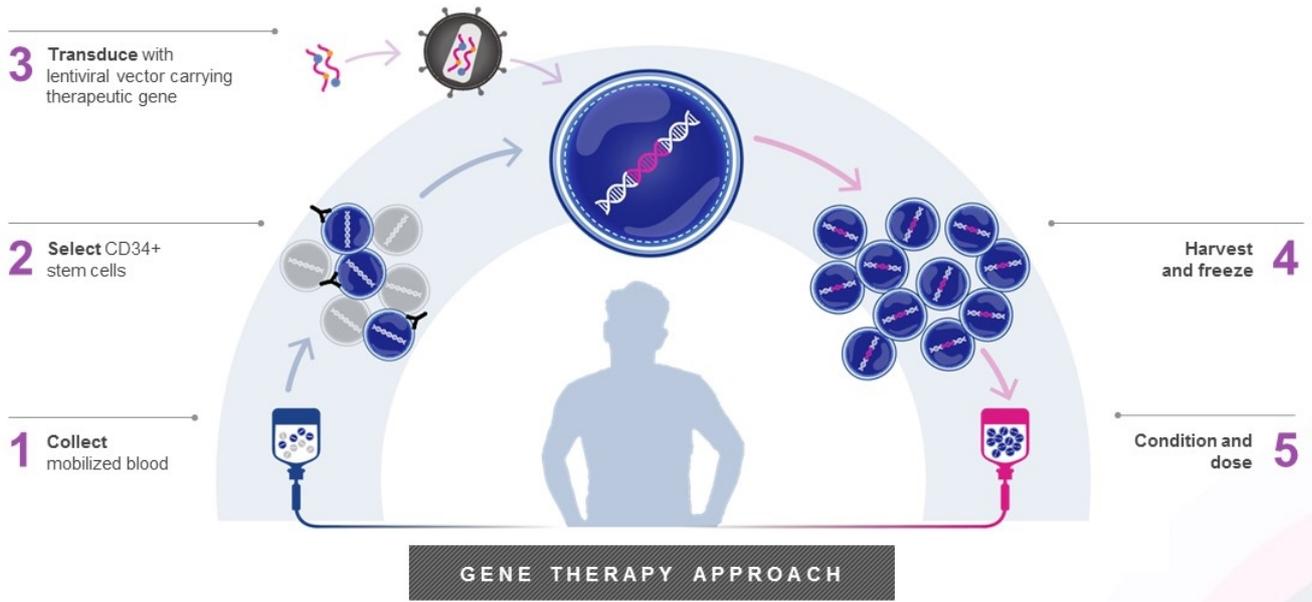
Treatment burden

Bi-weekly IV infusions

Single IV infusion

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

Established *ex vivo* lentiviral approach





⊕ Fabry Disease

AVR-RD-01



Goals for gene therapy in Fabry disease

UNMET NEEDS:



Kidney function

Unmet needs: proteinuria, polyuria, kidney failure



Cardiac function

Unmet needs: left ventricular hypertrophy, fibrosis, heart failure



Neuropathic pain

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



CNS complications

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



Everyday burden of illness and life expectancy

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

Sources: Wanner C et al, *Med Genetics and Metab*, 2018; Burlina A, *JIEMS*, 2016
CNS: Central Nervous System; TIA: Transient Ischemic Attack

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Two AVR-RD-01 Fabry clinical trials

9 patients dosed across Phases 1 and 2



PHASE 1

Investigator-Sponsored Trial*

Patients

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

Key Objective

Safety and preliminary efficacy

PHASE 2

AVRO – FAB-201 Trial

Patients

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

Key Objectives

Safety and efficacy

July 2019 data presented, unless otherwise specified
* Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada

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Fabry FAB-201 Patient Characteristics

Treatment-naïve
Fabry patients

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

* Mayo Lab, ref range ≥ 23.1 nmol/hr/mg

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

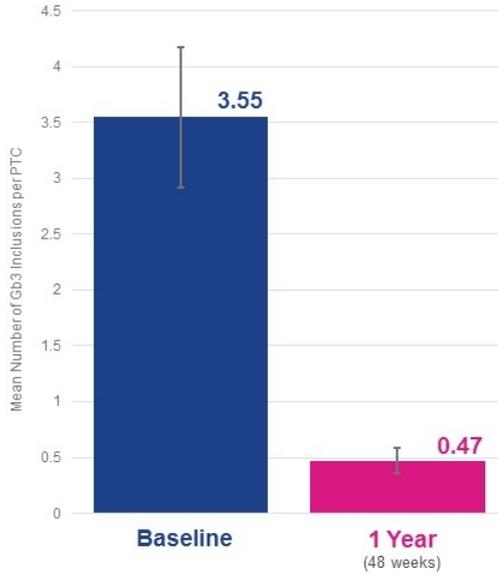
*** Reference value ≤ 2.4 nM

AGA: α -galactosidase A; Lyso-Gb3: Globotriaosylsphingosine; GI: Gastrointestinal; IgA: Immunoglobulin-A



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

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

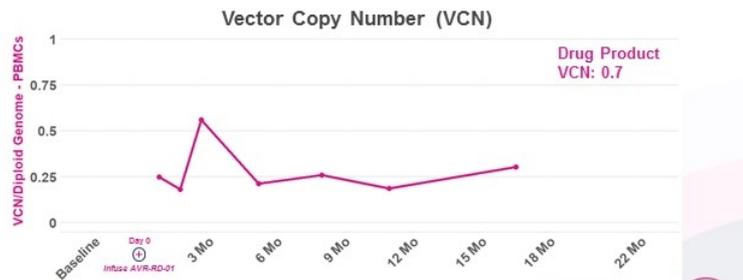
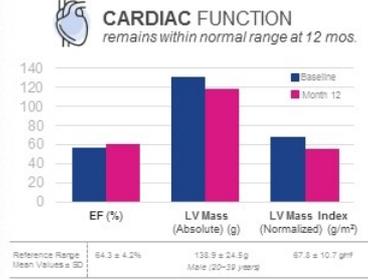
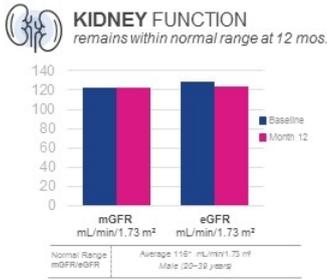
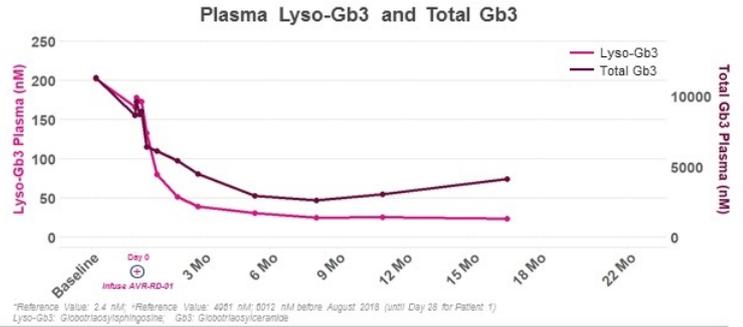
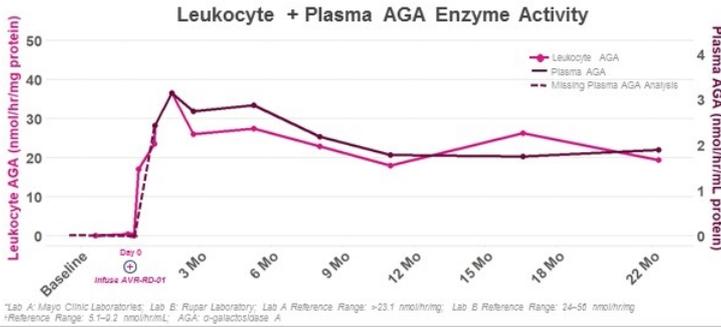


- Unpaired t-test for difference between n=55 PTCs at baseline vs. n=101 PTCs at 1 year; $p < 0.0001$
- Error bar represents the standard deviation

Baseline: The last available, non-missing observation prior to AVR-RD-01 infusion
 Note: With respect to Fabry disease, Gb3 inclusions per PTC is interchangeable with GL-3 inclusions per KIC
 FAB-201-1: First patient in FAB-201 clinical trial
 PTC: Peritubular Capillary; Gb3: Globotriaosylceramide; GL-3: Globotriaosylceramide; KIC: Kidney Interstitial Capillary



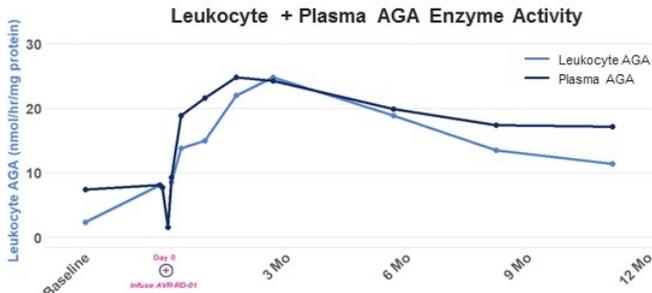
Patient 1: Multiple data trends sustained up to 22 months



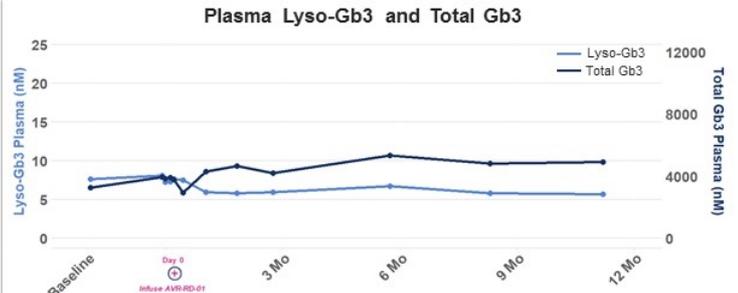
Note: Patient #1 had a skin biopsy score of 3 (severe accumulation) at baseline, a score of 2 (moderate accumulation) at 6 months and a score of 1 (mild accumulation) at 12 months
 Note: Visualization of multiple biomarkers adjusted to utilize the same statistical scaling ratio across biomarkers (as compared to prior presentation)



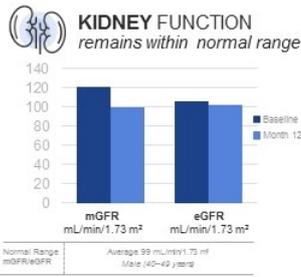
Patient 2: Multiple data trends sustained up to 1 year*



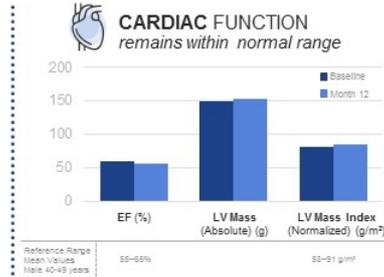
*Data from Ripar Laboratory; Reference Range: 24–50 nmol/hr/mg; †Reference Range: 5.1–2.2 nmol/hr/mL; AGA: α-galactosidase A



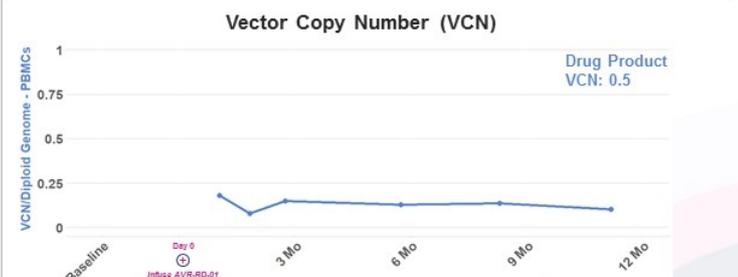
*Reference Value: 2.4 nM; †Reference Value: 4001 nM. Note: Patient #2 has normal substrate, consistent with late-onset cardiac variant phenotype. Lyso-Gb3: Globotriaosylsphingosine; Gb3: Globotriaosylceramide



Normal Range mGFR/eGFR: Average 90 mL/min/1.73 m² Male (40–49 years)



Reference Range Mean Values Male 40–49 years: EF: 55–65%; LV Mass: 50–91 g/m²

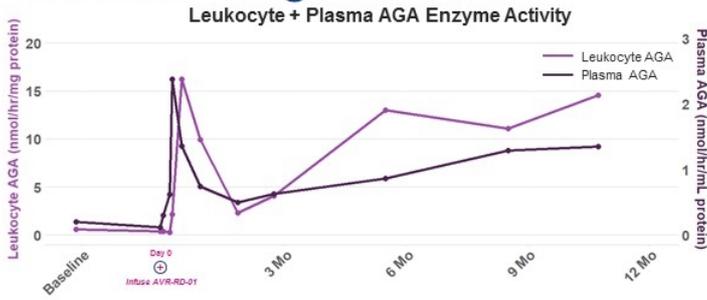


VCN: Vector Copy Number; PBMcs: Peripheral Blood Mononuclear Cells

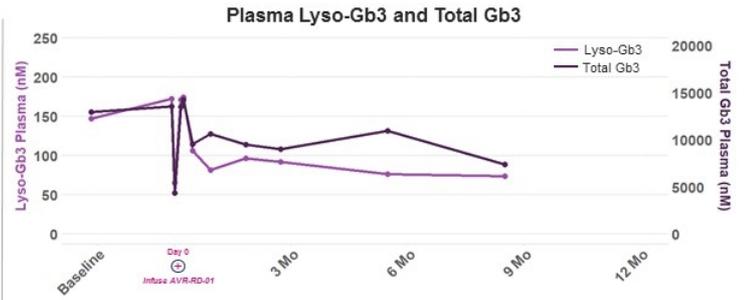
Note: As patient #2 is a cardiac variant of Fabry disease, this patient had a skin biopsy score of 0 (trace or no accumulation) at baseline and at 6 months
 Note: Visualization of multiple biomarkers adjusted to utilize the same statistical scaling ratio across biomarkers (as compared to prior presentation)
 * Latest data points for this patient are at the 1-year follow-up which = 48 weeks per protocol



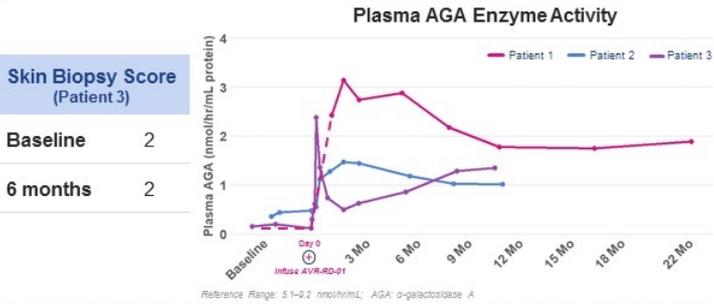
Patient 3: Data up to 1 year* suggest trend towards durable engraftment



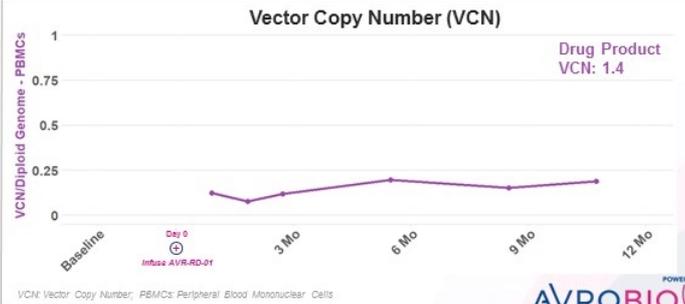
*Data from Rupa Laboratory; Reference Range: 24-50 nmol/hr/mg; †Reference Range: 5.1-0.2 nmol/hr/mL; AGA: α-galactosidase A



*Reference Value: 2.4 nM; †Reference Value: 4001 nM; Lyso-Gb3: Globotriaosylsphingosine; Gb3: Globotriaosylceramide



Reference Range: 5.1-0.2 nmol/hr/mL; AGA: α-galactosidase A



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

Skin Biopsy Score (Patient 3)

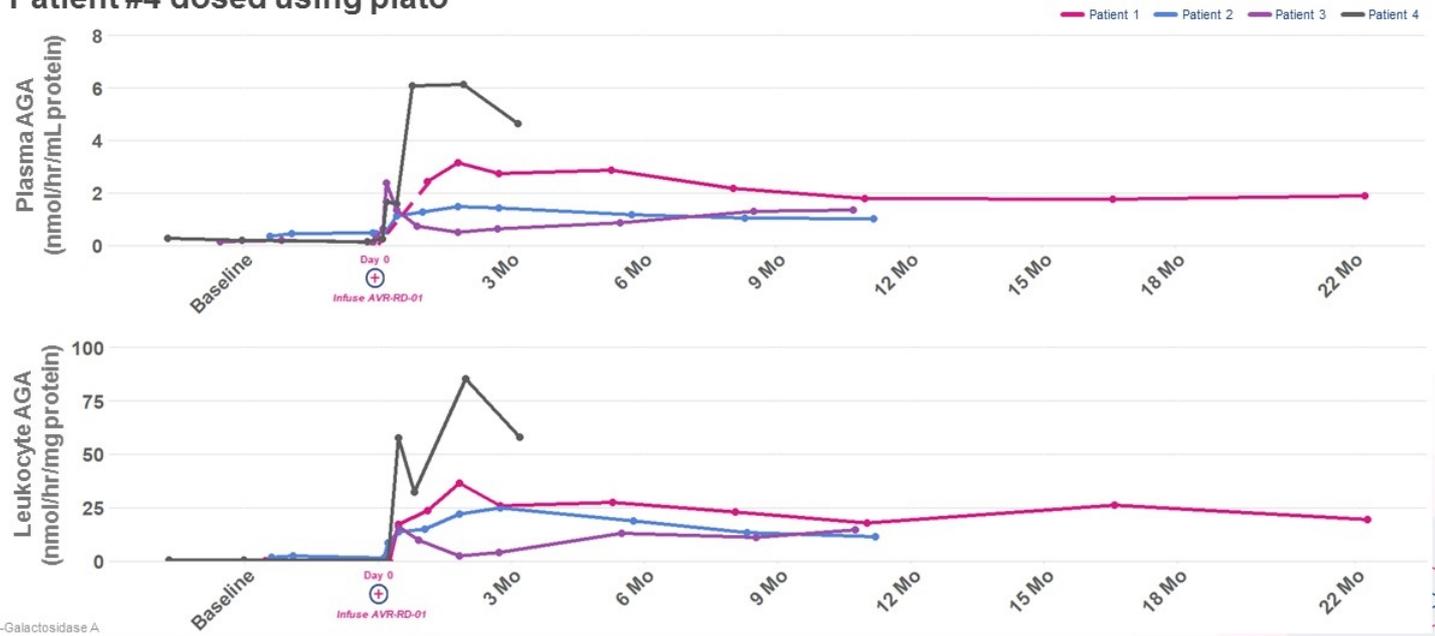
Baseline	2
6 months	2

Note: Visualization of multiple biomarkers adjusted to utilize the same statistical scaling ratio across biomarkers (as compared to prior presentation)
 *1-year follow-up = 48 weeks per protocol



Patients 1-4: Plasma and leukocyte enzyme activity sustained up to 22 months

Patient #4 dosed using plato™

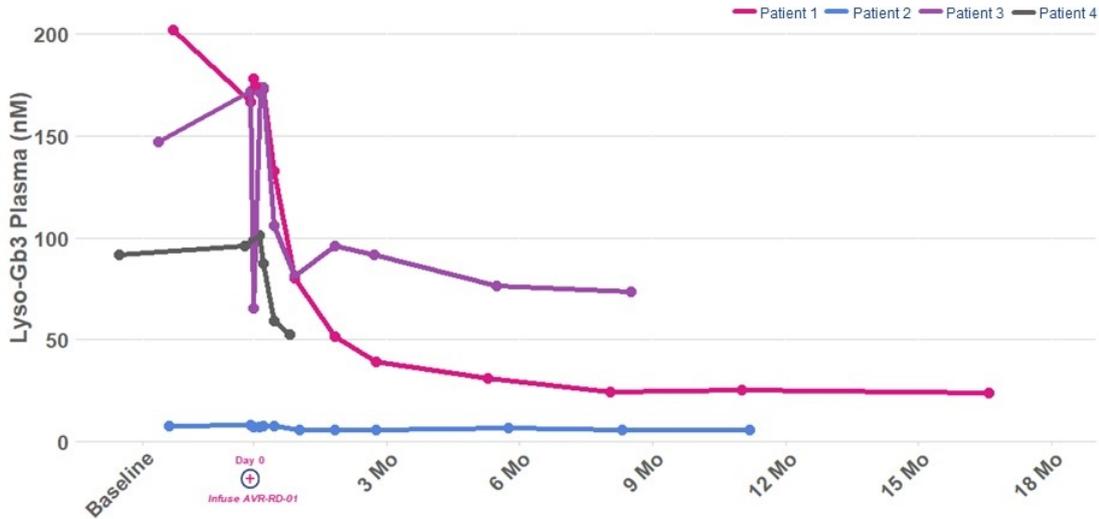


AGA: α-Galactosidase A

plato



Patients 1-4: Plasma lyso-Gb3 reduction sustained up to 18 months



Reduction from Baseline to Last Observation

Patient 1 88%

Patient 2 NA

Patient 3 50%

Patient 4 43%



• Lyso-Gb3: Globotriaosylsphingosine

• Note: Patient #2 has normal substrate, consistent with late-onset cardiac variant phenotype



Two AVR-RD-01 Fabry clinical trials

9 patients dosed across Phases 1 and 2



PHASE 1

Investigator-Sponsored Trial*

Patients

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

Key Objectives

Safety and preliminary efficacy

PHASE 2

AVRO – FAB-201 Trial

Patients

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



Key Objectives

Safety and efficacy

FAB-201 = AVRO-RD-01-201 Study
* Sponsored by FACTs team (Fabry Disease Clinical Research and Therapeutics) in Canada
ERT: Enzyme Replacement Therapy



Fabry Phase 1 Patient Characteristics

ERT-Treated Fabry Patients

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

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

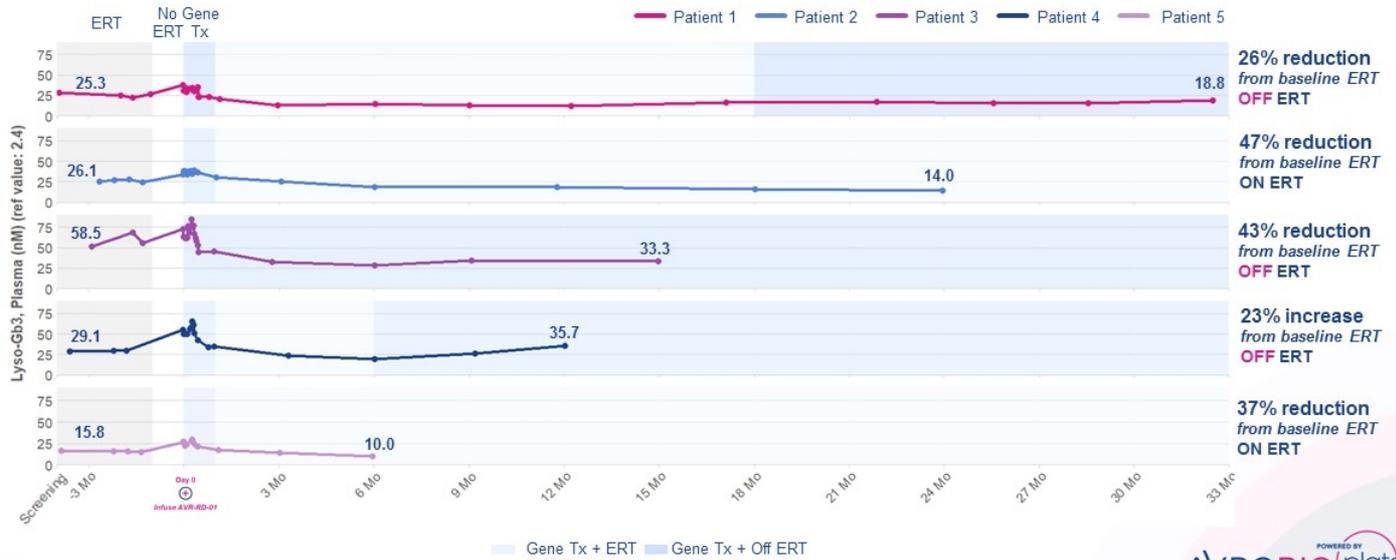
** Reference values ≤ 2.4 nM

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



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

All patients who have discontinued ERT remain off ERT*

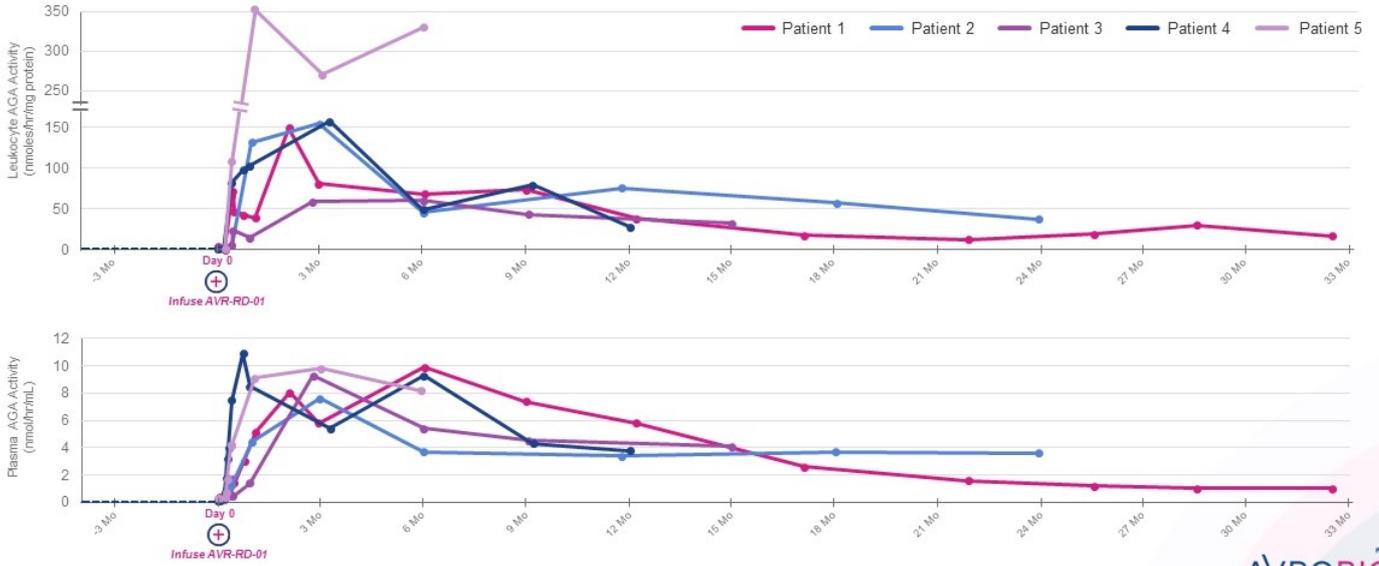


* As of April 27, 2020
Lyso-Gb3: Globotriaosylsphingosine; ERT: Enzyme Replacement Therapy; Tx: Therapy



Patients 1-5: Leukocyte and plasma enzyme activity sustained up to 32 months

Consistent trends across all patients, 4 patients > 1 year

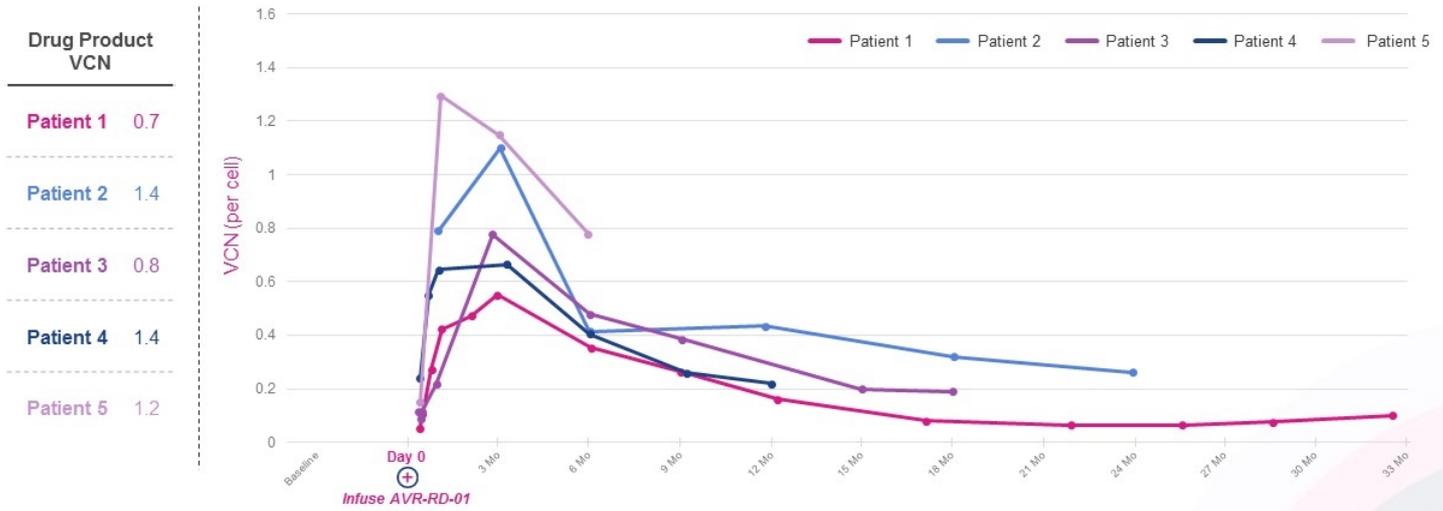


AGA: α -Galactosidase A



VCN stable at 32 months with consistent trend across all other patients

4 patients with 1+ years data



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



Patient 1: Kidney function stable at 32 months



eGFR: Estimated Glomerular Filtration Rate; ERT: Enzyme Replacement Therapy; TX: Therapy; CKD: Chronic Kidney Disease



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

**No unexpected
safety events
or trends
identified**

No SAEs related to AVR-RD-01 drug product

AEs and SAEs reported

Phase 1 AEs (n = 128):

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

FAB 201 AEs (n = 98):

- Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
 - Grade 1 or 2 (n = 72)
 - Grade 3 or 4 (n = 30)

Phase 1SAEs (n = 2):

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

FAB 201 SAEs: (n = 4)

Pre-treatment and prior to conditioning

- Seizure (grade 2)

Post-treatment

- Dehydration, nausea, vomiting (grade 3)
- Febrile neutropenia (2 patients, grade 3 & 4)

Anti-AGA antibodies

- Pre-existing low titers detected in 4 patients

Note: Safety data cut November 26, 2019
AE: Adverse Event; SAE: Serious Adverse Event
NOTE: AVR-RD-01 is an investigational gene therapy

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

Potential attributes intended to support first-line use



ERT: Enzyme Replacement Therapy

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

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Building commercial capabilities

44+ product launches, including 1 gene therapy



Holly May
Chief Commercial Officer



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

Jose Gomez
SVP, Global Market Access & Value



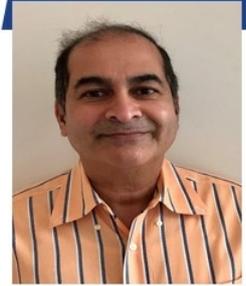
- Led global strategic marketing and global market access functions at AveXis
- Led market access, global strategic pricing and reimbursement functions for LSDs at Shire

Sean Ring
VP, Head of Commercial Operations



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

Ramesh Arjunji
VP, Global Health Economics and Outcomes Research / Value Demonstration



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





⊕ Cystinosis

AVR-RD-04



Goals for gene therapy in cystinosis

UNMET NEEDS:



Kidney function

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



Vision

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



Endocrine disorders

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



CNS complications

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



Everyday burden of illness and life expectancy

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

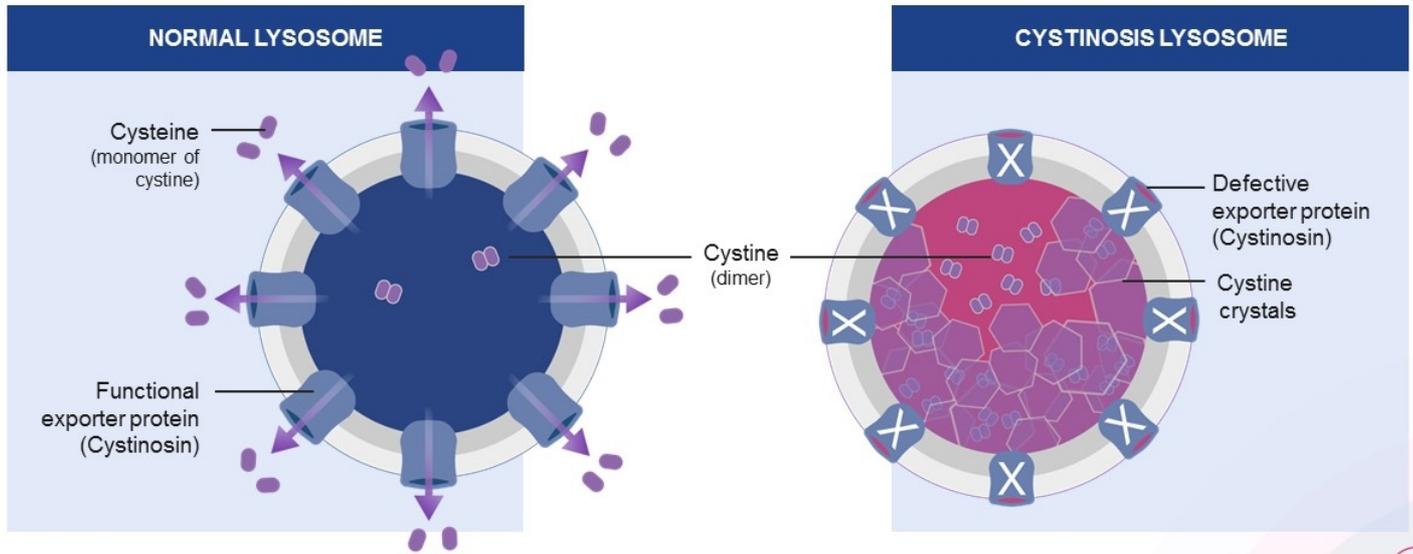
Sources: Ariceta G et al, *Nephrol Dial Transplant*, 2015; Elmonem M et al, *Orphanet Journal of Rare Diseases*, 2016; Gahl et al, *NEJM*, 2002; Bois et al, *J Med Genet*, 1976
CNS: Central Nervous System; GI: Gastrointestinal

POWERED BY
AVROBIO plato



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

Cystine crystals build up in lysosomes causing tissue and organ damage



Source: Cherqui et al, Nat Rev Nephrol. 2017



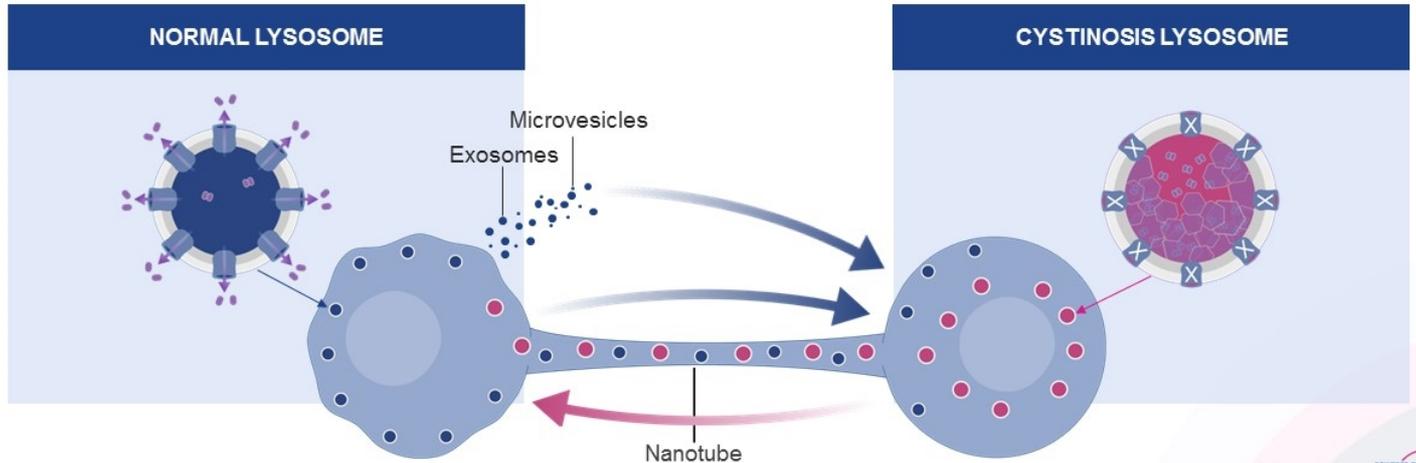
Drug product-derived macrophages restore normal cystine recycling

Mechanisms of action

Macrophages with CTNS transgene restore cystine recycling to CTNS^{-ve} cells via:

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

Net result: Corrected lysosomes in cells throughout the body



Sources: Naphade, Stem Cells, 2015; Harrison, Molecular Therapy, 2013.
CTNS: cystinosin, lysosomal cystine transporter; mRNA: Messenger Ribonucleic Acid

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

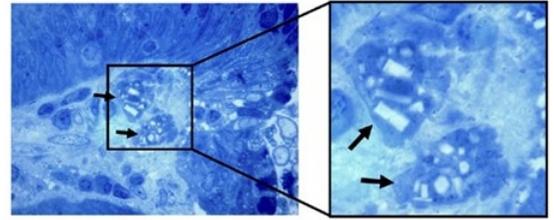
Allogeneic HSC Transplant

University Hospital Leuven

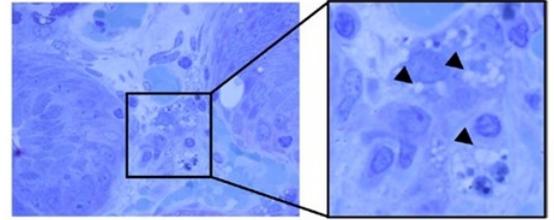
- 16 year old male
- Diagnosed at 2.7 years old, started on cysteamine
- Age 15 years – cysteamine toxicity
- Age 16 years – fully matched HLA transplant
- Acute GvHD
- **First few months**
 - Kidney function stabilized
 - Polyuria resolved
- **6 months**
 - Photophobia score reduced from 5 (unable to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

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

BEFORE
TRANSPLANT



30 MONTHS
POST
TRANSPLANT



Arrows/arrowheads point to tissue macrophages



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

First patient dosed



PHASE 1/2

Investigator-Sponsored Trial*

Patients

Up to 6 patients
Adults and adolescents
Cohorts 1-2 ≥18 years; Cohort 3 ≥14 years
Male and Female
On oral and ophthalmic cysteamine



Key Objectives

Safety and efficacy

* Sponsored by University of California, San Diego
Note: AVR-RD-04 aka CTNS-RD-04

POWERED BY
AVROBIO plato



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

	PATIENT 1
Age of symptom onset / diagnosis	0 year / 8 months
Age dosed with AVR-RD-04	20 years
Gender	Male
Mutation	Allele 1: LDM ₁ Allele 2: Nt1035 (insC)
Primary disease signs and SoC treatment related symptoms, including	<ul style="list-style-type: none">• Fanconi syndrome• Polyuria• Corneal abnormalities• Mild photophobia• Vomiting
Granulocyte Cystine levels at baseline (nmol half cystine per mg protein)*	7.8
Comments	NO kidney transplant <ul style="list-style-type: none">• Cysteamine 1125 mg p.o. every 12 h/day since 2009; discontinued prior to AVR-RD-04 infusion• Cysteamine eyedrops 4-5x/day• Concomitant medications not listed

Note: AVR-RD-01 aka CTNS-RD-04



Phase 1/2 Cystinosis
1 patient dosed

**No unexpected
safety events
or trends
identified**

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

+ No SAEs reported

+ AEs reported

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

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

- Diarrhea, hypokalemia, dizziness
- Dehydration, vomiting

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

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

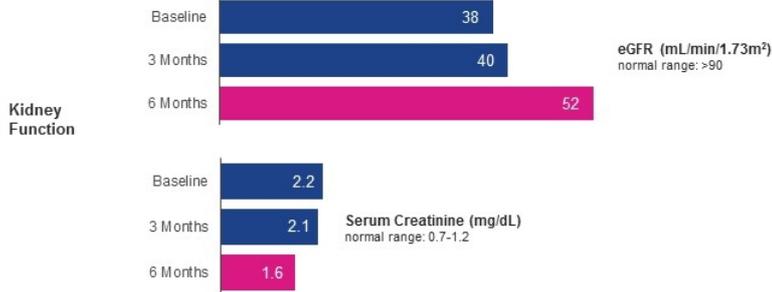
Note: Safety database cut as of January 27, 2020
AE: Adverse Event; SAE: Serious Adverse Event

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Patient 1: Initial data indicate positive trends across multiple measures

CLINICAL LAB MEASURES



BIOMARKER ENDPOINTS



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

VCN (vcn/dg) (Drug Product = 2.1)

1 Month	2.9
2 Months	3.0
3 Months	2.0

Average Granulocyte Cystine Level (μmol half cystine/g protein)

Baseline	7.8
1 Month	1.3
2 Months	1.5
3 Months	1.5

Asymptomatic Heterozygous Carrier Granulocyte Cystine Range: 0.2 – 1.9 μmol half cystine/g protein

Source: Gertsman I et al., *Clinical Chemistry*, 2016

VCN: Vector Copy Number; CTNS: Cystinosis, Lysosomal Cystine Transporter; mRNA: Messenger Ribonucleic Acid; eGFR: Estimated Glomerular Filtration Rate; SCR: Serum Creatinine

*Data obtained using a novel experimental methodology utilizing *in vivo* confocal microscopy, to image crystals in the skin behind the ear



Patient 1: Reduced treatment burden at 6 months

Number of Medications and Supplements

(max per day)

**Before
Gene Therapy**

ON Cysteamine



52

**After Gene
Therapy**

(at 6 months
post-gene therapy)

OFF Cysteamine



20

NOTE: Investigational gene therapy



Gaucher Disease



AVR-RD-02



Goals for gene therapy in Gaucher Type 1 Disease

UNMET NEEDS:



Bone-related manifestations

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



Hemoglobin levels and platelet counts

Unmet needs: anemia, thrombocytopenia, easy bruising, bleeding



Hepatosplenomegaly

Unmet needs: enlarged liver, enlarged spleen



CNS complications

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



Everyday burden of illness, and life expectancy

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

Sources: Grabowski G et al, *Online Metabolic and Molecular Bases of Inherited Disease*, 2018; Weinreb N et al, *AJH*, 2008; Pastores G et al, *Semin Hematol*, 2004
CNS: Central Nervous System; GBA: gene coding for glucocerebrosidase

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



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

Incomplete therapeutic response is common:

- **60%** of patients failed to achieve at least one of the six therapeutic goals evaluated after 4+ years of ERT¹
- A clinically significant percentage of patients continue to exhibit **bone pain, organomegaly and cytopenia** after 10 years of ERT²
- **25%** of patients continue to suffer from physical limitations after two years of ERT, primarily due to bone disease³

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

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

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

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

Sources: ¹Weinreb N et al. *Amer J Hematol*, 2008; ²Weinreb N et al. *J Inherit Metab Dis*, 2013; ³Giraldo P et al. *Qual Life Res*, 2005.
GD1: Gaucher Disease Type 1; SOC: Standard of Care; ERT: Enzyme Replacement Therapy; EOW: Every Other Week

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



PHASE 1/2

AVR-RD-02 Trial

Patients

n = 8 - 16
Type 1 Gaucher
Treatment naïve or on ERT
16 - 35 year-old
Male and Female



Key Objectives

Safety, Engraftment, Efficacy,
ERT-independence



⊕ Pompe disease

AVR-RD-03



TO PREVENT OR IMPROVE:



Pulmonary function

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



Physical endurance and strength

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



CNS complications

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



GI complications

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



Everyday burden of illness, and life expectancy

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

Goals for gene therapy in Pompe Disease

Sources: Barba-Romero M et al, Rev Neurol, 2012; Dasouki M et al, Neurol Clin, 2014; Hagemans M et al, J Neurol, 2007; Musumeci O et al, Eur J of Neurol, 2018

Pompe lentiviral gene therapy program advancing

Integrated three-part approach



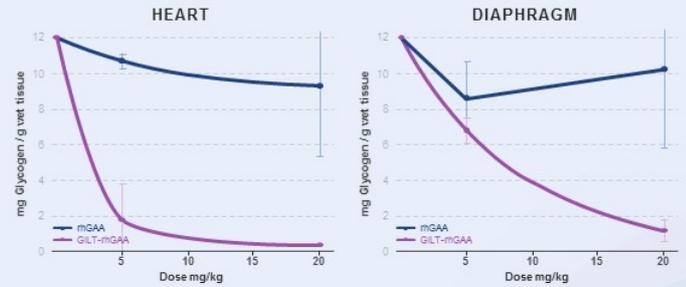
THE CHALLENGE

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

AVROBIO's APPROACH

- Potent transgene promoter
- GILT uptake tag
- Bu90-TDM for CNS impact

GILT-tagged Recombinant Human (rh)GAA impacts levels of stored glycogen compared to non GILT-tagged Recombinant Human (rh)GAA in a Pompe mouse model

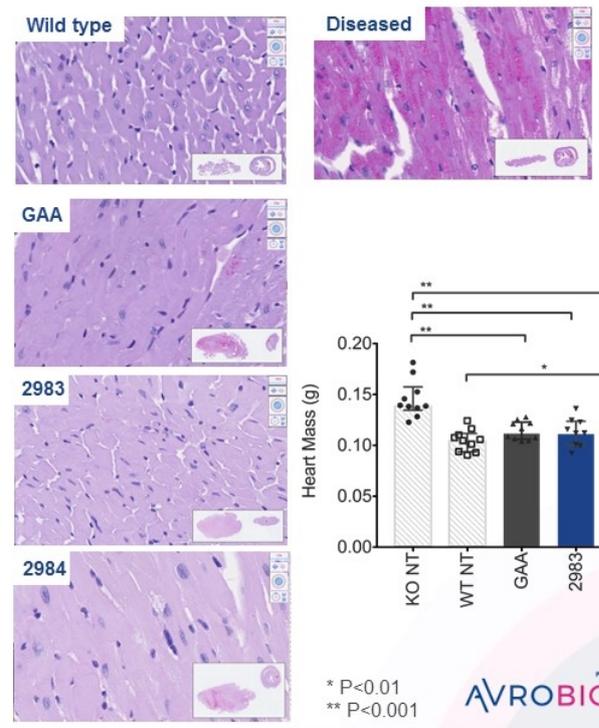
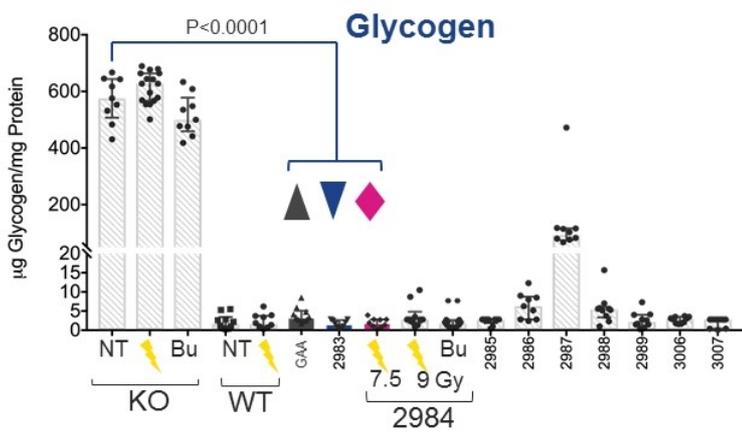


• GILT: Glycosylation-Independent Lysosomal Targeting

• 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; Mago JA et al, J of Bio Chem, 2013; Bartelink, Lancet Haematol, 2016.

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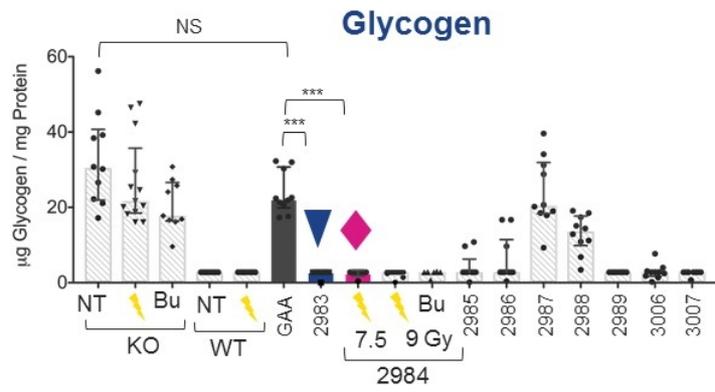
GILT and GILT mutant v1 reduce glycogen by >99% in heart



Glycogen and GILT and GILT mutant v1 similar to wildtype mice



GILT tag is essential for glycogen clearance in CNS



	Cerebrum	Spinal cord
WT		
KO		
GAA		
2983		
2984		

*** P<0.001



plato™

—
AVROBIO's foundation designed to
scale gene therapy worldwide

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

+ Optimized
for performance

+ Redefines manufacturing
best practices

POWERED BY
AVROBIO plato



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



 UPGRADES	Increase enzyme activity	Increase transduction efficiency	Increase VCN	Increase marrow space/ engraftment	Increase consistency and safety
1 Vector					
2 Conditioning					 *
3 Automation					

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

* TDM (therapeutic drug monitoring)



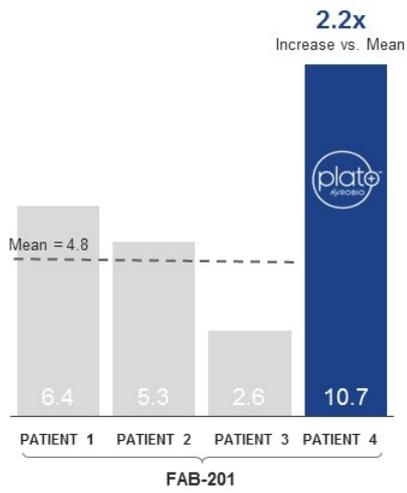
VECTOR UPGRADE:

Metrics compared to academic process

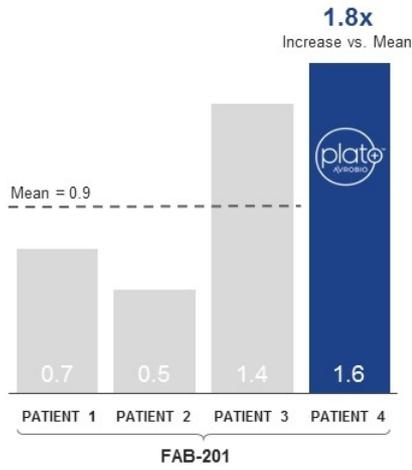
FAB-201 patient #4 drug product data with plato™



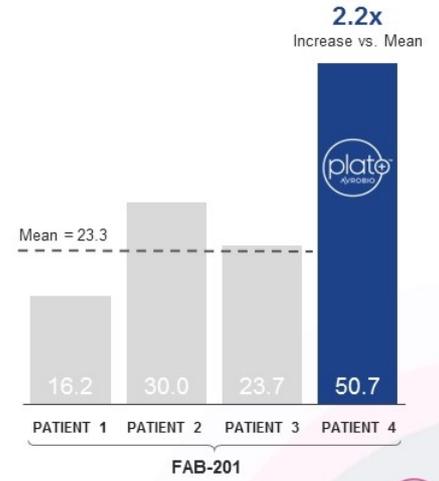
Enzyme Activity (nmol/hr/mL)



VCN (per diploid genome)



Transduction Efficiency (%)



VCN: Vector Copy Number; FAB-201: AVR-RD-01 Study
NOTE: Data is from drug product





VECTOR UPGRADE:

Metrics compared to academic process

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



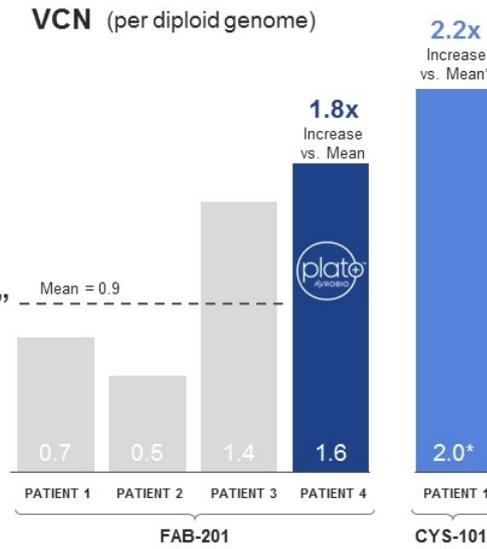
FAB-201 with plato™

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

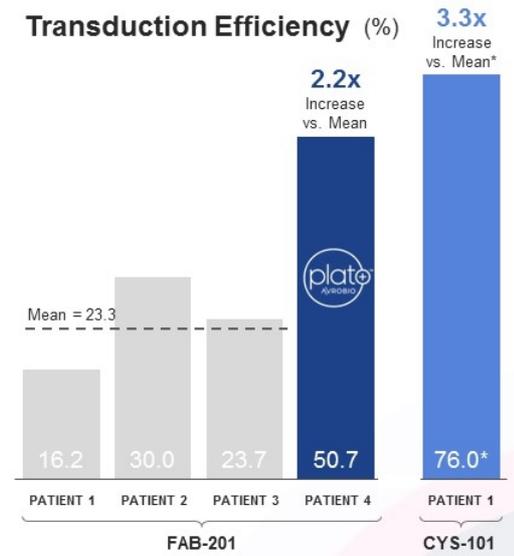
AVR-RD-04 with “plato™-like”

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

VCN (per diploid genome)



Transduction Efficiency (%)



BU TDM: Busulfan Therapeutic Drug Monitoring; VCN: Vector Copy Number; FAB-201: AVR-RD-01 Study; CYS-101: AVR-RD-04 Study; LV: Lentiviral Vector
* Manufactured at UCLA using UCLA's assays and methodologies
NOTE: Data is from drug product



PRECISION CONDITIONING UPGRADE:

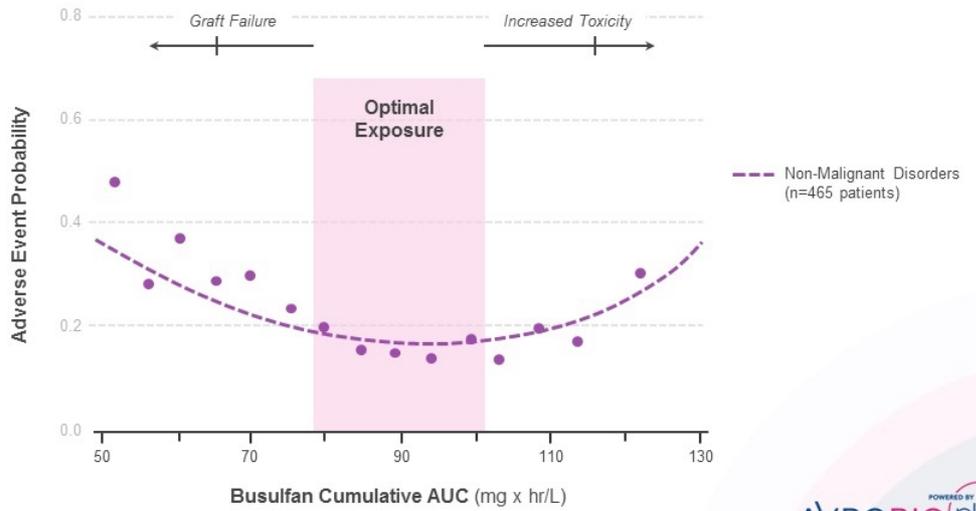
Targeted busulfan intended to balance optimal engraftment with enhanced safety

Meta-analysis of 465 patients identified optimal exposure



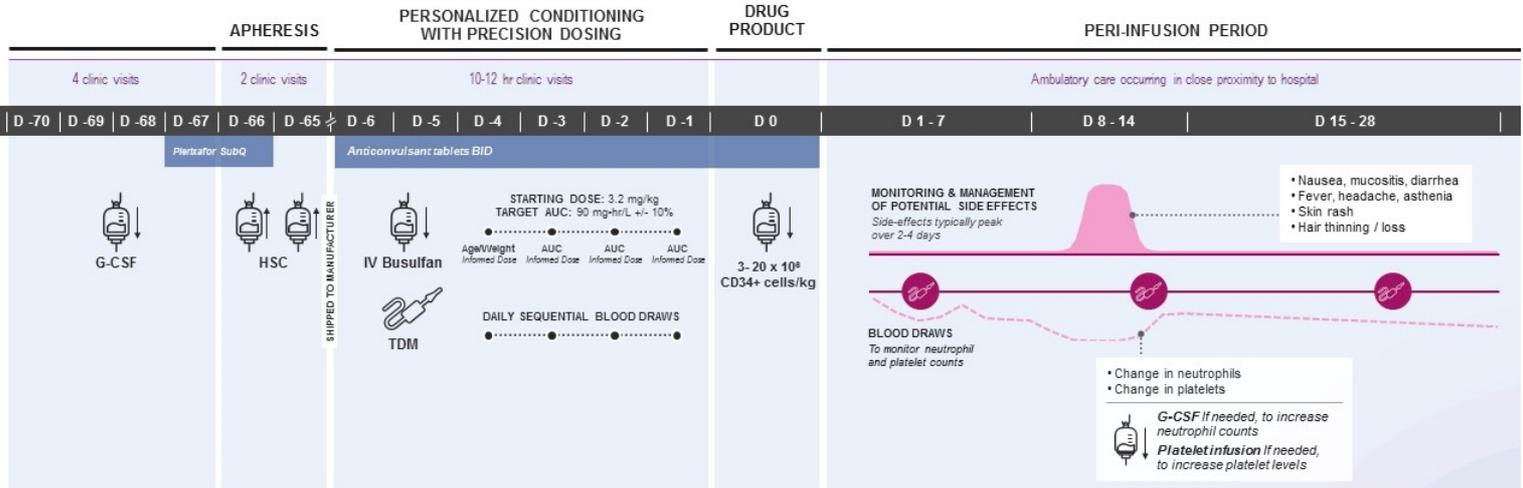
Optimized precision dosing designed to enhance tolerability

Lowest rate of adverse events in the Bu90 range



Bu: Busulfan; AUC: Area Under the Curve
Sources: Bartelink IH et al, Lancet Haematol, 2016

PRECISION CONDITIONING UPGRADE: Precision dosing via state-of-the-art patient therapeutic drug monitoring (TDM)



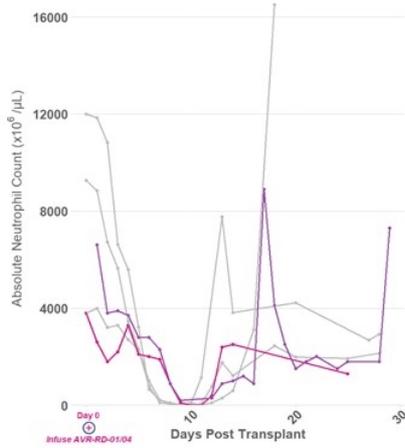
G-CSF: granulocyte colony stimulating factor; PERI-INFUSION PERIOD: time from infusion to discharge; TDM: therapeutic drug monitoring; HSC: hematopoietic stem cell
 Notes: Illustrative only. AEs will vary patient by patient, see busulfan label for a complete list of side-effects. Ambulatory care based on oncology setting with higher intensity conditioning

PRECISION CONDITIONING UPGRADE:

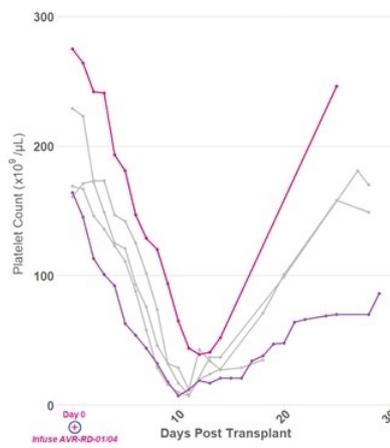
Rapid neutrophil and platelet recovery with minimal lymphocyte depletion using Busulfan TDM



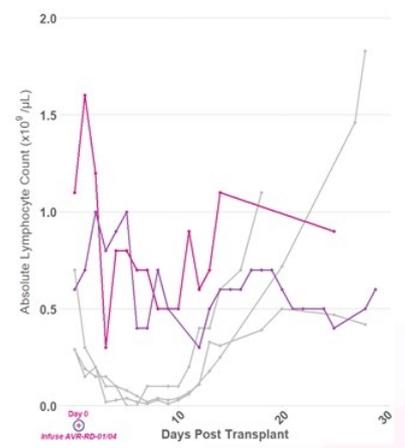
Absolute Neutrophil Count (ANC)



Platelet Count



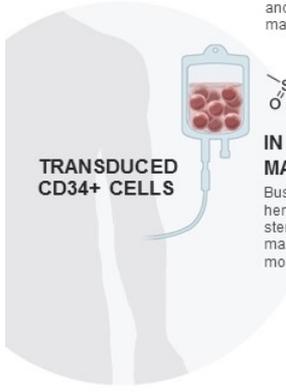
Absolute Lymphocyte Count



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

Fabry: Patients #1-3 Melphalan 100mg/m²; Patient #4 Busulfan 'AUC 90'; Cystinosis: Patient #1 Busulfan 'AUC 90'
 Threshold levels for prophylactic supportive care in HSC Tx; ANC <0.5 x 10⁹ per liter (AABB); Platelets <10 x 10⁹ cells/L (AABB)
 NOTE: Neutrophil counts - G-CSF administration post gene therapy: Pt 1: 7 Doses, Day 7 – 14, Pt 2: 11 Doses, Day 7 – 17, Pt 3: 6 Doses, Day 7 – 12, Pt 4: 5 Doses, Day 8 – 12
 NOTE: Platelet counts - Platelet Transfusion: Pt 1: Day 10; Pt 2, 3: Day 11, Pt 4: no transfusion
 TDM = Therapeutic Drug Monitoring; G-CSF = Granulocyte-colony stimulating factor

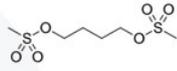
PRECISION CONDITIONING UPGRADE: Designed to access “hard-to-reach” compartments



**TRANSDUCED
CD34+ CELLS**

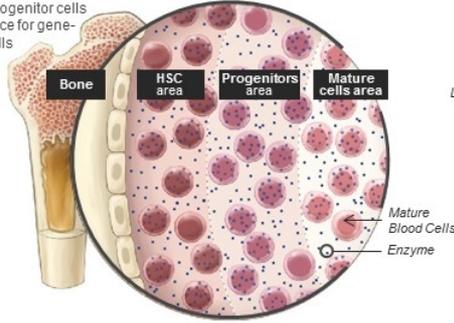
BRAIN

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



**IN THE BONE
MARROW**

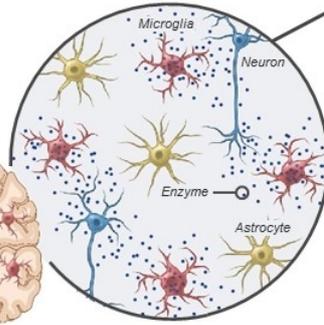
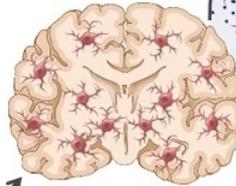
Busulfan eliminates hematopoietic (CD34+) stem and progenitor cells making space for gene-modified cells



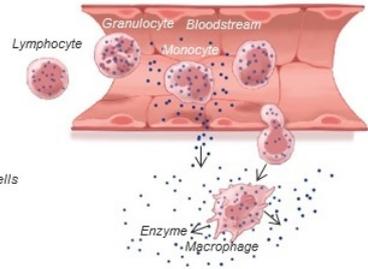
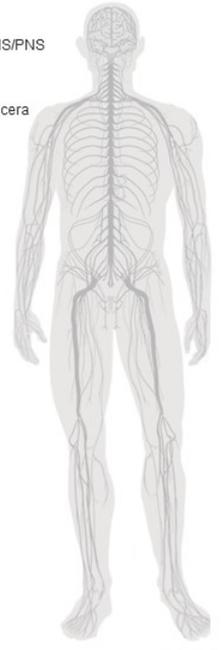
BONE MARROW

PERIPHERAL TISSUE

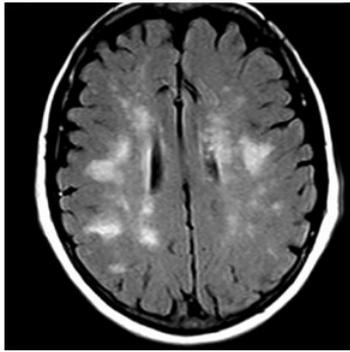
MICROGLIA
Potential for widespread microglia engraftment throughout the brain



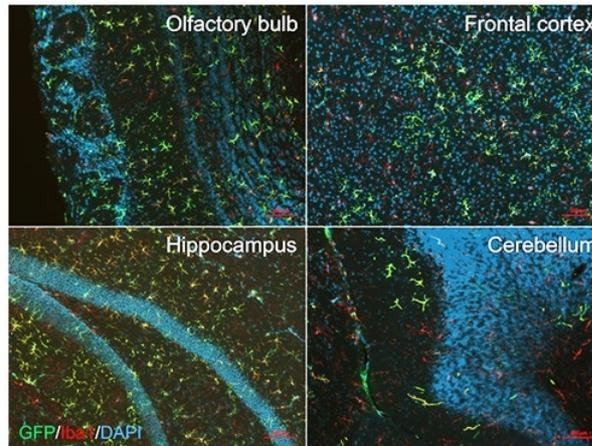
CNS/PNS
Viscera



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



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



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

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

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

Source: Buechner S, J. *Neuro, Neurosurg, Psychiatry*, 2008
MRI: Magnetic Resonance Imaging; ERT: Enzyme Replacement Therapy; WMLs: White Matter Lesions; HSC: Hematopoietic Stem Cell

AUTOMATION UPGRADE:

Automated, scalable manufacturing system

Designed to elevate quality and overcome historic CMC bottlenecks



Expanded Scale

Potential to reach thousands of patients per year



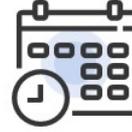
Broader Reach

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



High Quality

Automated, closed system designed to improve quality and consistency



Enhanced Convenience

Cryopreservation simplifies logistics and patient scheduling



Lower Costs

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

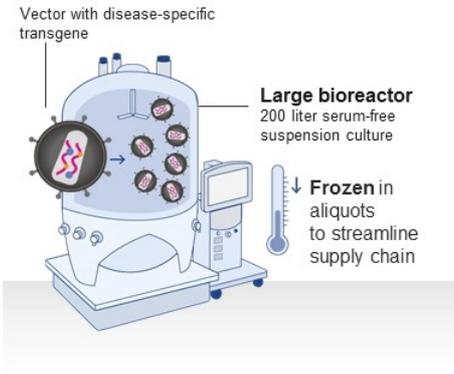
AUTOMATION UPGRADE:

Designed to deliver large-scale manufacturing

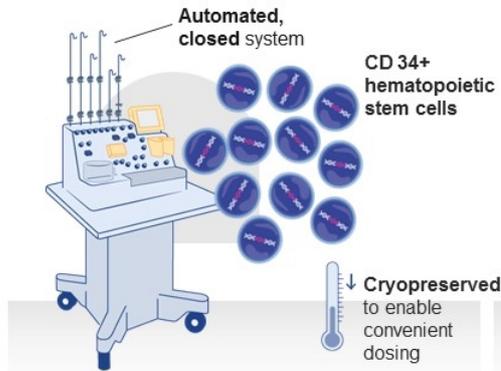
Differentiated, cost-effective approach



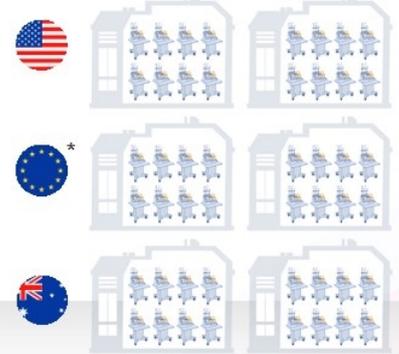
HIGH VOLUME / TITRE



INCREASE CONSISTENCY



COST-EFFECTIVE SCALE-OUT



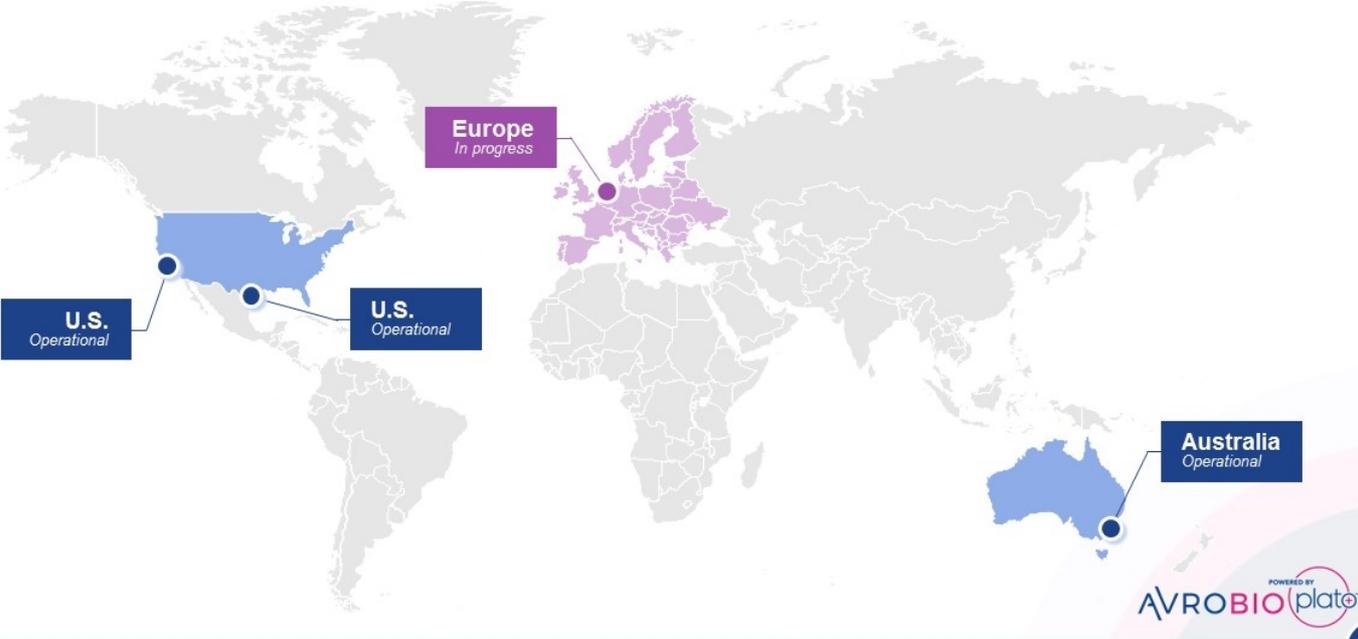
Illustrative

* European manufacturing capabilities planned for 2H 2020; manufacturing capabilities currently in place in U.S. & Australia

AUTOMATION UPGRADE:

Global manufacturing established

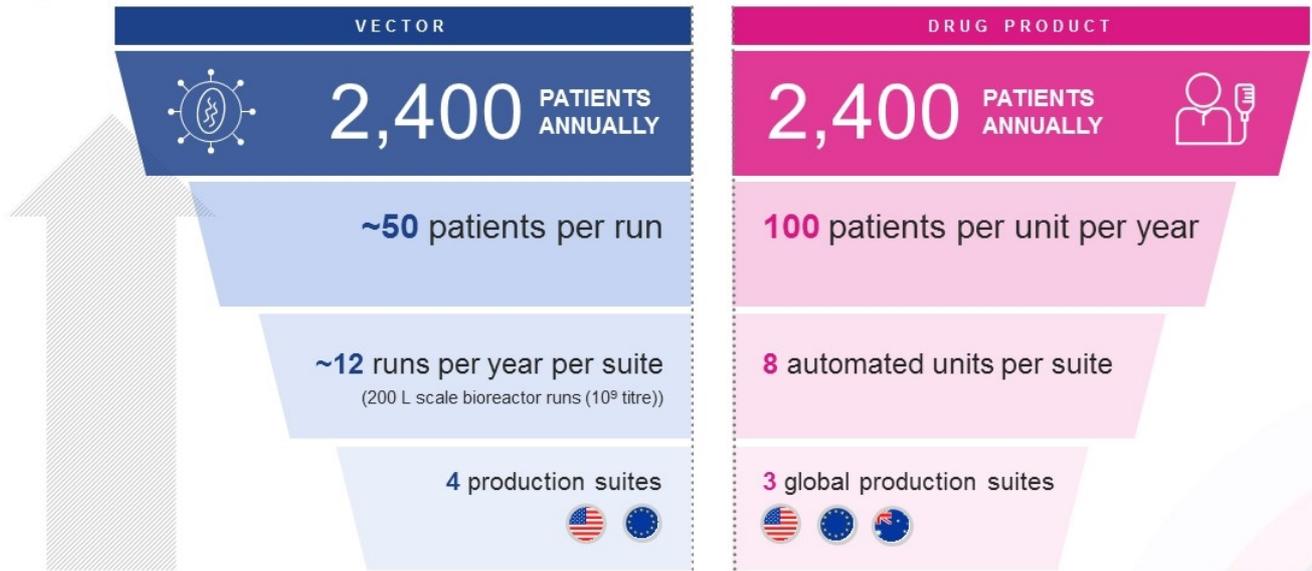
Automated systems operational in 3 sites with 4th in progress



AUTOMATION UPGRADE:

Poised to manufacture at scale

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



Illustrative



3 UPGRADES IN PLACE:

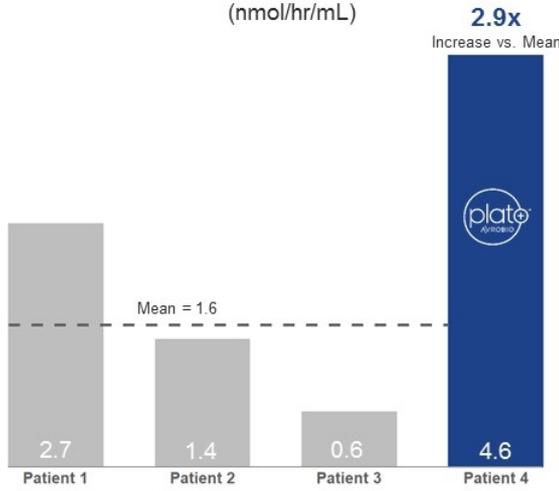
plato™ metric compared to academic process

FAB-201 THREE MONTH data for patient #4 with plato™ vs. patients #1-3



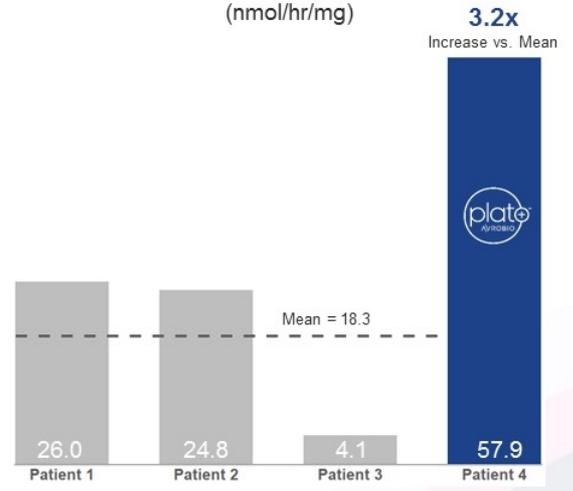
Plasma Enzyme Activity

(nmol/hr/mL)



Leukocyte Enzyme Activity

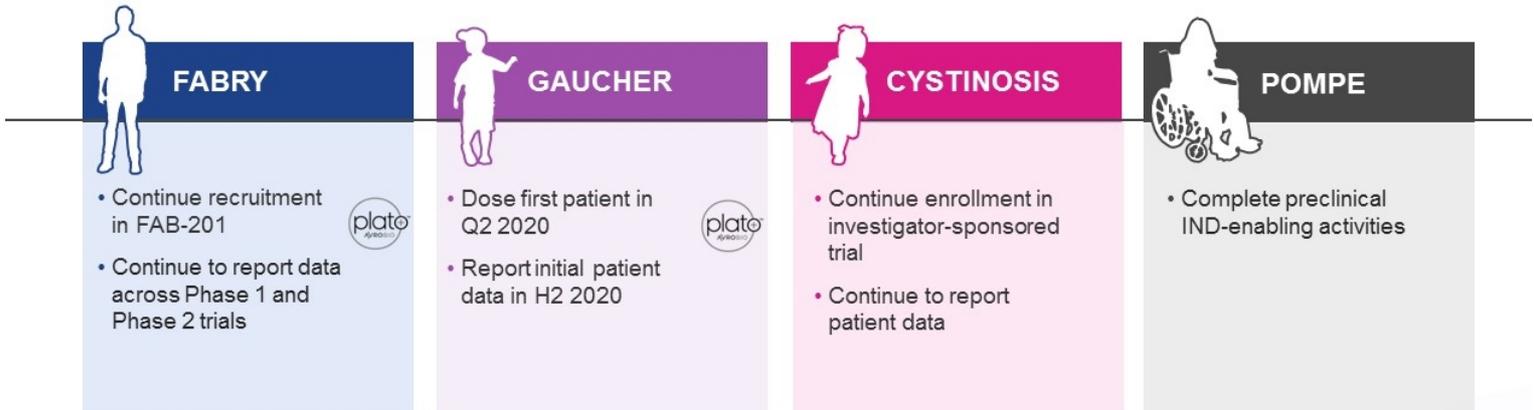
(nmol/hr/mg)





Milestones anticipated across the pipeline in 2020

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



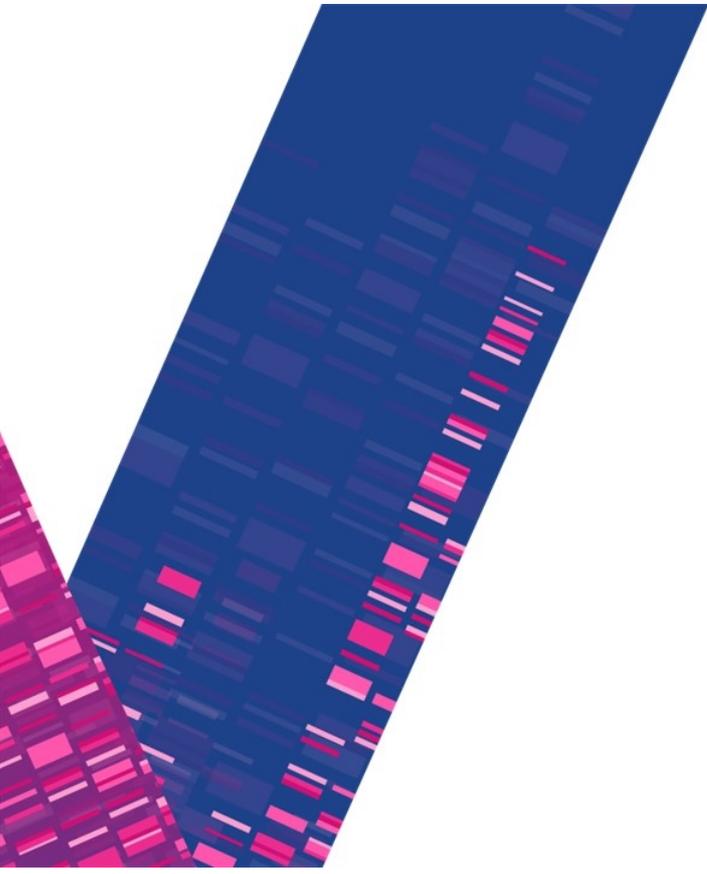
AVROBIO to hold first R&D Day in 2020

* For additional information, see the Company's Current Report on Form 8-K filed with the SEC on March 30, 2020, and the Company's risk factor related to COVID-19 in the Company's Annual Report on Form 10-K filed with the SEC on March 16, 2020.



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plato+™



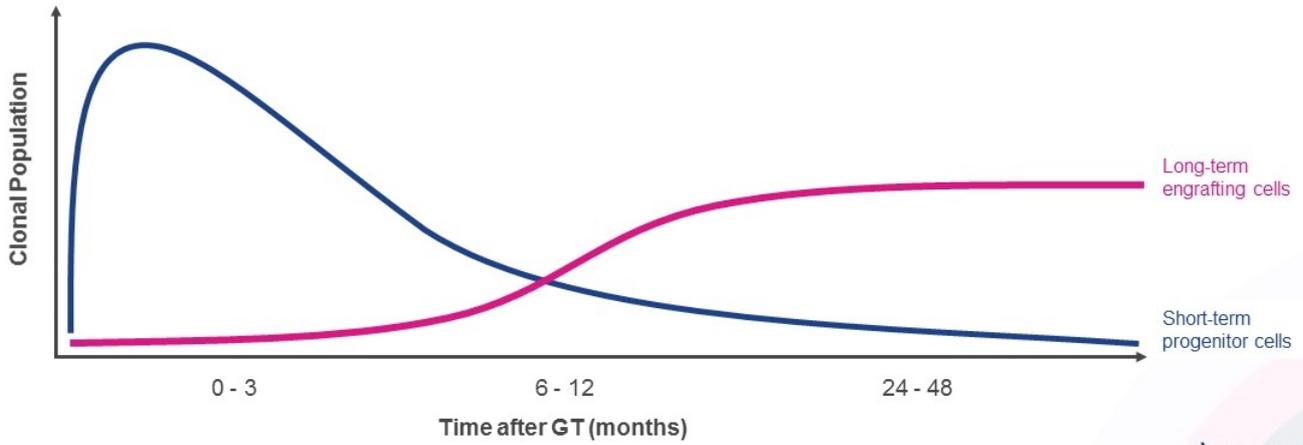


Appendix

Hematopoietic reconstitution occurs in two distinct phases

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

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



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



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

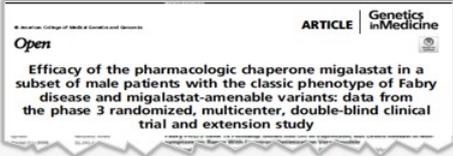
45 Amenable patients* (16 males / 29 females)

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 (70%) -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, 0.06)	7/12 (58%) -0.05 (-0.16, 0.14)

Treatment Group	n	Baseline Median (min, max)	Month 6 Median (min, max)	Change from Baseline Median (min, max)
Galaftod	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)

7/9 males ≥ 50% reduction
(at 6 months from baseline)

28% average reduction
(at 6 months from baseline)



Open | **ARTICLE** | **Genetics in Medicine**

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

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	1.65	0.16	0.03	0.11	0.94	0.88
Change in PTC GL-3 Inclusions from BL to M6	-0.08	0.01	n/a	-1.77	-1.10	n/a	-1.25	1.21	-0.21	0.01	0.09	-0.07	1.94	-0.83
Change in PTC GL-3 Inclusions from BL/M6 to M12	-0.12	n/a	n/a	-1.92	n/a	n/a	-0.51	-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

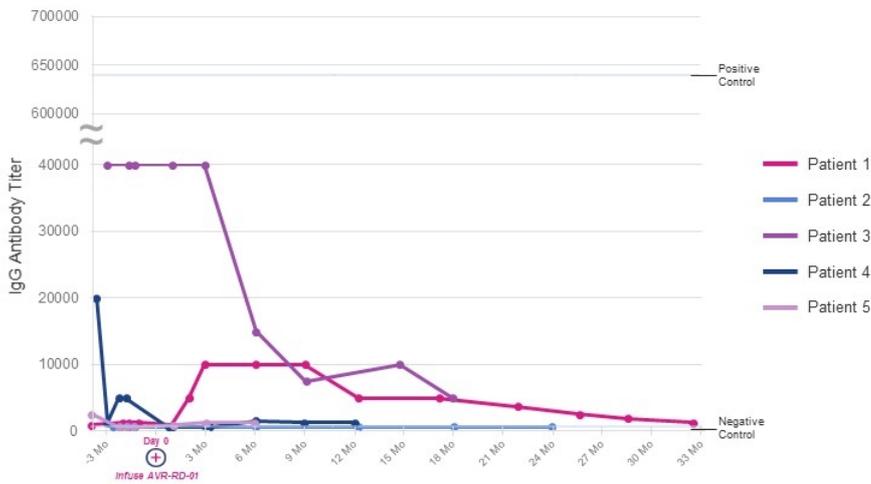




Reduction of pre-existing anti-ERT drug IgG antibodies following AVR-RD-01

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

Fabry Disease Phase 1 IgG Antibody Titer



Similar Results Observed in Other Studies

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

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

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

Source: Gentner B et al., Blood, 2019

ERT: Enzyme Replacement Therapy; IgG: Immunoglobulin G; MPS-1: Mucopolysaccharidosis Type 1; IDUA: Iduronidase; SR-TIGET: San Raffaele Telethon Institute for Gene Therapy; LV: Lentiviral; rhIDUA: Recombinant Human alpha-L-Iduronidase

New collaborations advancing leadership in lentiviral gene therapy



Fully Automated Bu-TDM Immunoassay

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



Antibody-Drug Conjugate

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



