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): February 10, 2020

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 8.01 Other Events.

On February 10, 2020, AVROBIO, Inc. (the "Company") issued a press release titled "AVROBIO Presents Positive Initial Data for its Investigational Cystinosis Program and plato™ Platform, as well as Positive Data Out to 32 Months for its Ongoing Investigational Fabry Program". A copy of the press release is filed as Exhibit 99.1 to this Current Report on Form 8-K and incorporated into this Item 8.01 by reference.

On February 10, 2020, the Company updated its corporate presentation for use in meetings with investors, analysts and others. A copy of the slide presentation is filed as Exhibit 99.2 to this Current Report on Form 8-K and incorporated into this Item 8.01 by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

99.1 Press release issued by AVROBIO, Inc., dated February 10, 2020.

99.2 AVROBIO, Inc. slide presentation, dated February 10, 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: February 10, 2020

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

Exhibit 99.1

AVROBIO Presents Positive Initial Data for its Investigational Cystinosis Program and plato™ Platform, as well as Positive Data Out to 32 Months for its Ongoing Investigational Fabry Program

Early data trends from first patient dosed in the AVR-RD-04 investigational gene therapy program for cystinosis show improvements across multiple measures

Data from the Phase 1 and Phase 2 trials of AVR-RD-01 support potential long-term engraftment and durable, endogenous production of functional enzyme in patients with Fabry disease

First Phase 2 Fabry patient treated using plato gene therapy platform shows plasma enzyme activity at one month 4.0 times higher than mean activity of other Phase 2 patients treated using academic platform at same timepoint

*Analyst and investor event will be webcast today, Feb. 10, 2020, at 7:00 p.m. ET, in conjunction with WORLD*Symposium™

CAMBRIDGE, Mass., Feb. 10, 2020 — AVROBIO, Inc. (NASDAQ: AVRO), a leading clinical-stage gene therapy company with a mission to free people from a lifetime of genetic disease, today announced new initial data from the first patient dosed in the investigational gene therapy program for cystinosis, showing improvements in early measures at three months compared to baseline. The company also unveiled new clinical data showcasing a sustained biomarker response in patients for up to 32 months after receiving the company's investigational gene therapy for Fabry disease across metrics including vector copy number (VCN), substrate levels and enzyme activity. Additionally, the company reported on the clinical debut of its plato™ gene therapy platform. These data showed improved enzyme activity, transduction efficiency and VCN in drug product manufactured using plato compared with drug product produced using the academic platform, as well as higher in vivo enzyme activity at one month in the first patient treated with plato, as compared to other patients treated using the academic platform. All these data will be presented today, during the 16th Annual WORLD*Symposium*™ in Orlando, Fla.

"We have now dosed 10 patients across three trials for two lysosomal disorders and we're delighted with the data we're seeing. We have followed six patients in our Fabry trial for more than a year and one for nearly three years, and they are consistently producing the functional enzyme that was missing as a consequence of their genetic disease, suggesting a potentially durable effect from a single dose," said Geoff MacKay, AVROBIO's president and CEO. "Furthermore, we believe that early data from the first clinical application of plato support our decision to invest heavily from AVROBIO's earliest days in this state-of-the-art gene therapy platform. We believe these data collectively indicate that we're making exciting progress toward our goal of freeing patients and families from the life-limiting symptoms and relentless progression of lysosomal disorders."

Three-month data from first patient in investigational AVR-RD-04 trial in cystinosis

AVROBIO reported initial data from the first patient dosed in the investigator-sponsored Phase 1/2 trial of the company's AVR-RD-04 investigational gene therapy for cystinosis, a progressive disease marked by the accumulation of cystine crystals in cellular organelles known as lysosomes. Patients with cystinosis accumulate the amino acid cystine, which can lead to crystal formation in the lysosomes of cells, causing debilitating symptoms including corneal damage, difficulty breathing and kidney failure, often leading to a shortened lifespan. The current standard of care for cystinosis, a burdensome treatment regimen that can amount to dozens of pills a day, may not prevent overall progression of the disease.

As of the safety data cut-off date of Jan. 27, 2020, which was approximately three months following administration of the investigational gene therapy to the first patient in the AVR-RD-04 program, there have been no reports of safety events attributed to the investigational drug product. In addition, no serious adverse events (SAEs) have been reported as of the safety data cut-off date. Adverse events did not suggest any unexpected safety signals or trends.

Three months following administration of AVR-RD-04, the first patient had a VCN of 2.0. VCN measures the average number of copies of the lentiviral-vector inserted transgene integrated into the genome of a cell and can be used to help assess the durability of a gene therapy. Initial data on another biomarker show that the patient's average granulocyte cystine level — one of the trial's primary endpoints — decreased from 7.8 nmol half cystine/mg protein two weeks after cysteamine discontinuation, to 1.5 at three months post-gene therapy.

The ongoing open-label, single-arm Phase 1/2 clinical trial evaluating the safety and efficacy of AVR-RD-04 is sponsored by AVROBIO's academic collaborators at the University of California San Diego (UCSD), led by Stephanie Cherqui, Ph.D. The trial is actively enrolling up to six participants at UCSD.

Interim data continue to support potential first line use of AVR-RD-01 in Fabry disease

Four patients have been dosed in the Phase 2 trial (FAB-201), and five patients in the Phase 1 investigator-led trial of AVR-RD-01 in Fabry disease.

VCN data continue to be stable at 32 months following AVR-RD-01 treatment for the first patient in the Phase 1 trial, suggesting successful engraftment, which is critical to the long-term success of investigational ex vivo lentiviral gene therapies. The VCN data trend was generally consistent across the seven other Phase 1 and Phase 2 trial participants out six to 24 months.

The first three AVR-RD-01 Phase 2 patients entered the study with minimal endogenous enzyme activity. At nine, 12 and 18 months after dosing, data from these three patients indicate sustained increased leukocyte and plasma enzyme activity, suggesting that they are now producing an endogenous supply of functional alpha-galactosidase (AGA) enzyme. This enzyme is essential for breaking down globotriaosylceramide (Gb3) in cells; without it, a toxic metabolite, lyso-Gb3, may accumulate, potentially causing cardiac and kidney damage and other symptoms.

For two Phase 2 patients, data indicate that their decreased plasma lyso-Gb3 levels, a key biomarker for monitoring Fabry disease, have been sustained below their baseline at six and 18 months after dosing. The third Phase 2 patient, a cardiac variant who does not have classic Fabry disease, did not show a decrease in plasma lyso-Gb3 levels, as expected. Cardiac and kidney function measures in the Phase 2 trial remained within normal range for patients who had available 12-month data.

As previously reported, a kidney biopsy taken at 12 months post-treatment for the first patient in the Phase 2 trial showed an 87-percent reduction in Gb3 inclusions per peritubular capillary. The company believes this data point, the primary efficacy endpoint for the Phase 2 trial, supports the potential of AVR-RD-01 to reduce Gb3 levels in tissue, including in the kidney.

In the Phase 1 trial of AVR-RD-01, four of the five patients had their plasma lyso-Gb3 levels reduced between 26 and 47 percent compared to their pre-treatment baseline levels. Data from the other patient in the trial, who remains off enzyme replacement therapy (ERT), through month six showed an initial decline and at month 12 showed a 23-percent increase in lyso-Gb3 levels, as compared to pre-treatment levels. This patient’s lyso-Gb3 levels remain within the range for the Fabry disease patients on ERT observed in this study.

Overall, three of the five Phase 1 patients have discontinued ERT and all three remain off ERT for six, 14 and 15 months.

As of the safety data cut-off date of Nov. 26, 2019, there have been no safety events attributed to AVR-RD-01 drug product in either the Phase 1 or Phase 2 trial. Through the safety data cut-off date, four SAEs have been reported in the FAB-201 trial and two SAEs in the Phase 1 trial. The fourth Phase 2 patient, who was dosed after the safety data cut-off date, has reported an SAE, which was not attributed to AVR-RD-01 and which subsequently resolved. Across both studies, each of the SAEs has been consistent with the conditioning regimen, stem cell mobilization, underlying disease or pre-existing conditions. Pre-existing low anti-AGA antibody titers have been detected in four patients in the Phase 1 trial and a transient low titer was observed but not detectable in subsequent measures in one patient in the Phase 2 trial.

The Phase 1 trial is fully enrolled. AVROBIO continues to actively enroll the Phase 2 trial in Australia, Canada and the U.S. The FAB-201 trial is an ongoing open-label, single-arm Phase 2 clinical trial evaluating the efficacy and safety of AVR-RD-01 in eight to 12 treatment-naïve patients with Fabry disease.

Successful clinical debut of plato™ gene therapy platform

AVROBIO also shared preliminary results from the first two patients to receive busulfan conditioning. Conditioning is an essential step in ex vivo lentiviral gene therapy designed to clear space in the bone marrow for the cells carrying the therapeutic transgene to engraft. The conditioning regimen developed as part of AVROBIO's plato platform includes therapeutic dose monitoring to assess how rapidly the individual patient metabolizes busulfan so physicians can adjust the dose as needed, with a goal of minimizing side effects while maximizing the potential of durable engraftment.

AVROBIO is implementing its precision dosing conditioning regimen across its company-sponsored clinical trials as part of the plato platform. The fourth patient in AVROBIO's Phase 2 Fabry trial received a precision dosing conditioning regimen with busulfan as part of the plato platform, while the first patient in the investigator-led cystinosis trial received busulfan but not as part of the plato platform.

These two patients both had rapid neutrophil and platelet count recovery, with a trajectory that was similar to the patients who enrolled earlier in the Fabry trials and who received a melphalan conditioning regimen. Side effects, which included nausea, mucositis, fever, rash and hair loss, developed eight to 10 days after dosing with busulfan and then resolved quickly.

The company also reported preliminary data from the first drug product produced using the plato gene therapy platform, which was used to dose the fourth patient in the Phase 2 Fabry trial (FAB-201). Early data indicate that enzyme activity and transduction efficiency for the drug product used to dose the fourth patient were 2.2 times higher than the mean of the drug product used to dose the first three patients in FAB-201. VCN for the drug product used to dose the fourth patient was 1.8 times higher than the mean of the drug product for the first three patients dosed in FAB-201. The drug product for the first three patients in FAB-201 was manufactured using a manual process first developed by AVROBIO's academic collaborators. The automated manufacturing embedded in plato leverages optimized processes developed at AVROBIO.

At one month following administration of the plato-produced investigational gene therapy for the fourth patient in the Phase 2 Fabry trial, initial data show the patient's plasma enzyme activity level to be 4.0 times higher than the mean activity level of the first three patients in the Phase 2 Fabry trial at the same timepoint.

The investigational drug product used to dose the first patient in the AVR-RD-04 program for cystinosis, which included a four-plasmid vector but not plato's automated manufacturing process, also showed increased performance in line with the increased performance recorded for the drug product in the Fabry trial. The investigational drug product and VCN assay are different for each trial.

"We believe these data are an early, but exciting, validation of our decision to invest in technological innovation rather than build expensive bricks-and-mortar manufacturing facilities," said MacKay. "The plato platform gives us control over the production and scaling of our investigational gene therapies through an efficient, automated manufacturing system that is designed to be deployed in standard contracted sites around the world. The four-plasmid vector, conditioning regimen with precision dosing and other elements of plato are designed to optimize the safety, potency and durability of our investigational lentiviral gene therapies."

About AVROBIO's ex vivo approach to gene therapy

Our investigational ex vivo gene therapies start with the patient's own stem cells. In the manufacturing facility, a lentiviral vector is used to insert a therapeutic gene designed to enable the patient to produce a functional supply of the protein they lack. These cells are then infused back into the patient, where they are expected to engraft in the bone marrow and produce generations of daughter cells, each containing the therapeutic gene. This approach is designed to drive durable production of the functional protein throughout the patient's body, including hard-to-reach tissues such as the brain, muscle and bone. It is a distinguishing feature of this type of gene therapy that the corrected cells are expected to cross the blood-brain barrier and thereby potentially address symptoms originating in the central nervous system.

Lentiviral vectors are differentiated from other delivery mechanisms because of their large cargo capacity and their ability to integrate the therapeutic gene directly into the patient's chromosomes. This integration is designed to maintain the transgene's presence as the patient's cells divide, which may improve the expected durability of the therapy and potentially enable dosing of pediatric patients, whose cells divide rapidly as they grow. Because the transgene is integrated ex vivo into patients' stem cells, patients are not excluded from receiving the investigational therapy due to pre-existing antibodies to the viral vector.

Analyst and investor event and webcast information

AVROBIO will host an analyst and investor event today, Monday, Feb. 10, 2020, in conjunction with the WORLD*Symposium*™, an annual scientific meeting dedicated to lysosomal disorders, in Orlando, FL. The presentation at the event will be webcast beginning at 7:00 p.m. ET. The webcast and accompanying slides will be available under "Events and Presentations" in the Investors & Media section of the company's website at www.avrobio.com. An archived webcast recording of the event will be available on the website for approximately 30 days.

About AVROBIO

Our mission is to free people from a lifetime of genetic disease with a single dose of gene therapy. We aim to halt or reverse disease throughout the body by driving durable expression of functional protein, even in hard-to-reach tissues and organs including the brain, muscle and bone. Our clinical-stage programs include Fabry disease, Gaucher disease and cystinosis and we also are advancing a program in Pompe disease. AVROBIO is powered by the plato™ gene therapy platform, our foundation designed to scale gene therapy worldwide. We are headquartered in Cambridge, Mass., with an office in Toronto, Ontario. For additional information, visit avrobio.com, and follow us on Twitter and LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements, including 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 prospective product candidates, the design, commencement, enrollment and timing of ongoing or planned clinical trials, clinical trial results, product approvals and regulatory pathways, and anticipated benefits of our gene therapy platform including potential impact on our commercialization activities, timing and likelihood of success. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Results in preclinical or early-stage clinical trials may not be indicative of results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements, or the scientific data presented.

Any forward-looking statements in this press release 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 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 AVROBIO may not successfully recruit or enroll a sufficient number of patients for our 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 product candidates 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 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, 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 materially and adversely 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.

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Exhibit 99.2

WORLD Investor Event

February 10, 2020

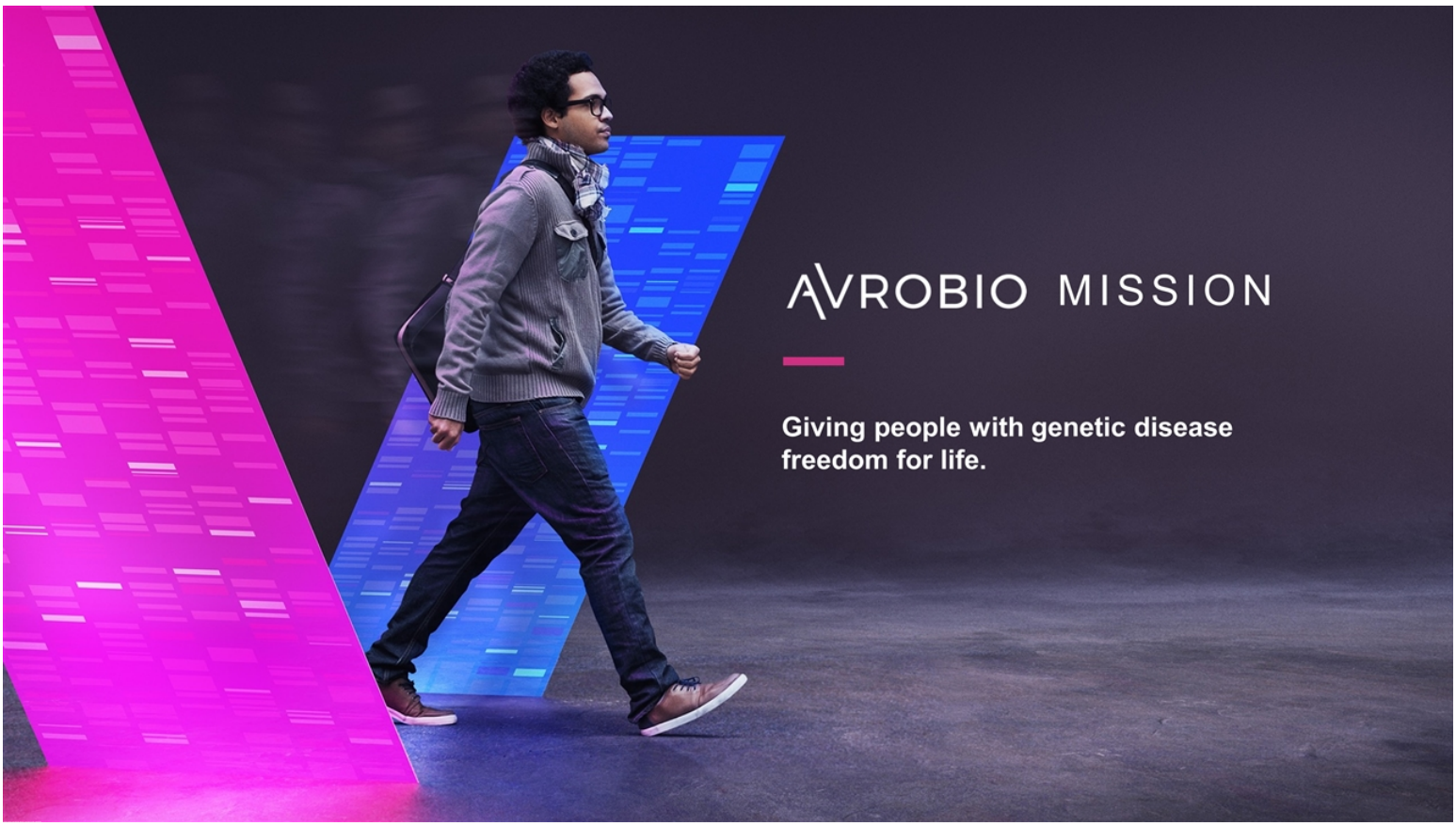
Disclaimer

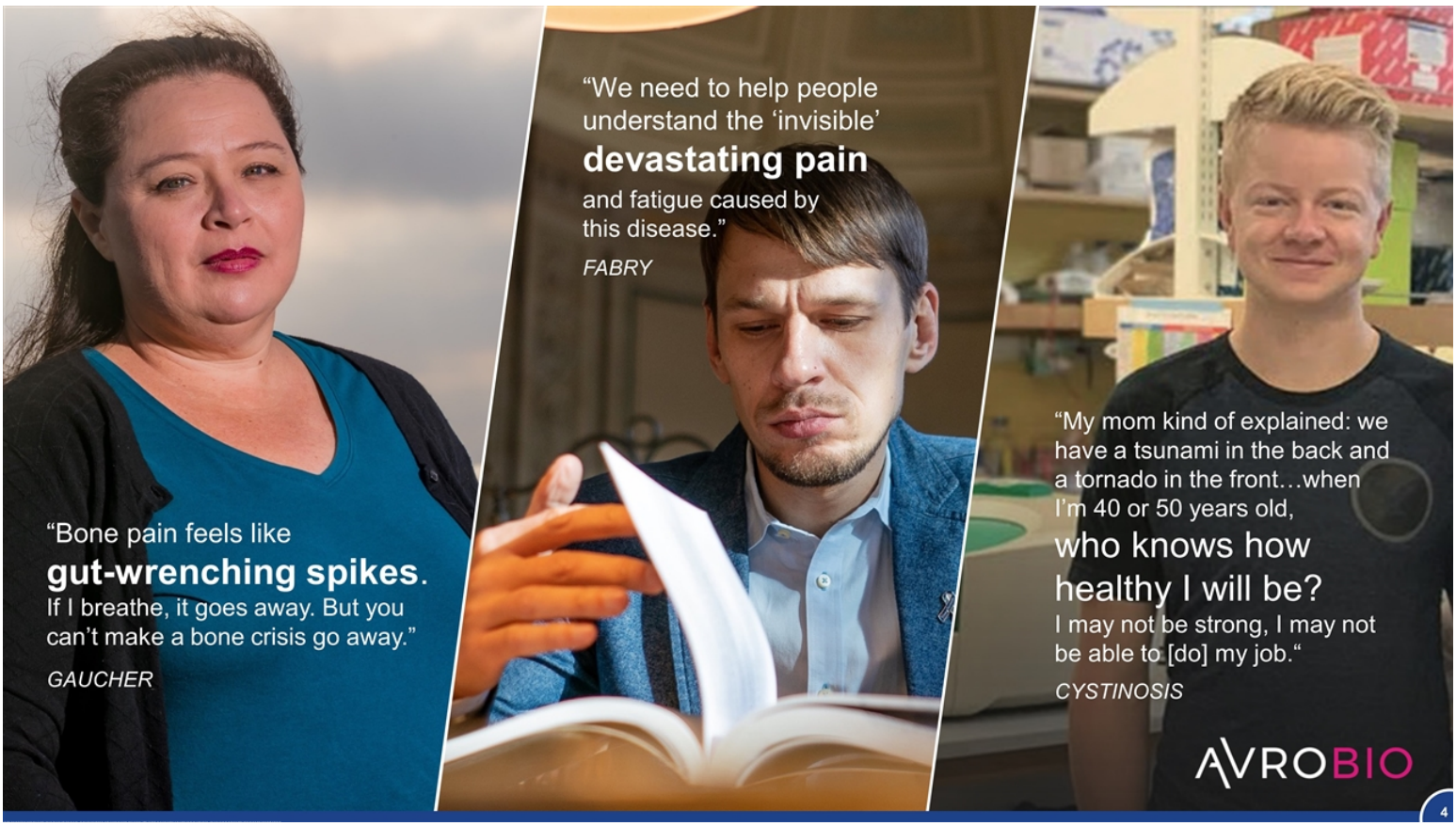
This presentation has been prepared by AVROBIO, Inc. ("AVROBIO") for informational purposes only and not for any other purpose. Certain information contained in this presentation and statements made orally during this presentation relate to or are based on studies, publications, surveys and other data 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, 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, the risk that our investigational gene therapies or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or trials involving AVROBIO's investigational gene therapies, the risk that we will be unable to obtain and maintain regulatory approvals for our investigational gene therapies, the risk that the size and growth potential of the market for our investigational gene therapies will not materialize as expected, risks associated with our dependence on third-party suppliers and manufacturers, risks regarding the accuracy of our estimates of expenses and future revenue, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our investigational gene therapies. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause AVROBIO's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in AVROBIO's most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, uncertainties and other important factors in AVROBIO's subsequent filings with the Securities and Exchange Commission. AVROBIO explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

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


AVROBIO MISSION
Giving people with genetic disease
freedom for life.


“Bone pain feels like
gut-wrenching spikes.
If I breathe, it goes away. But you can’t make a bone crisis go away.”
GAUCHER
“We need to help people understand the ‘invisible’
devastating pain
and fatigue caused by this disease.”
FABRY
“My mom kind of explained: we have a tsunami in the back and a tornado in the front…when I’m 40 or 50 years old,
who knows how healthy I will be?
I may not be strong, I may not be able to [do] my job.“
CYSTINOSIS
AVROBIO
4

Key takeaways

Early cystinosis data suggests potential gene therapy impact
Cystine level reductions in granulocytes and skin; urine volume reduction

Growing Fabry data set continues to support potential first-line use
9 patients now dosed across Phase 1 and Phase 2 trials

Initial plato™ *in-vivo* enzyme levels 4x greater than academic process
1-month plasma enzyme level for first Fabry patient dosed with plato vs. initial Phase 2 patients

plato automated manufacturing operational in US and AU
Europe in progress

Reporting data across 3 gene therapy programs in 2020
Continued readouts expected across Fabry, cystinosis and Gaucher trials

Thought leaders

Stephanie Cherqui
Ph.D.
University of California,
San Diego, CA

Mark Thomas
MBBS (Syd)., FRACP
Royal Perth Hospital,
Perth, Australia

Jeffrey A. Medin
Ph.D.
Medical College of Wisconsin,
Milwaukee, WI

Multiple programs in the clinic

10 patients dosed; 3 programs actively recruiting

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				AVROBIO

IND: Investigational New Drug

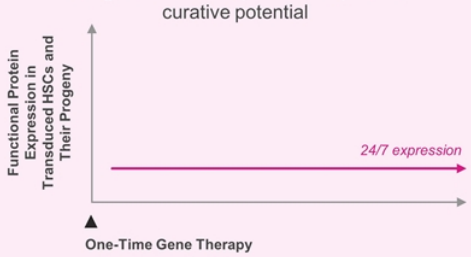
Addressing multi-billion dollar market opportunity

CURRENT STANDARD OF CARE COSTS

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

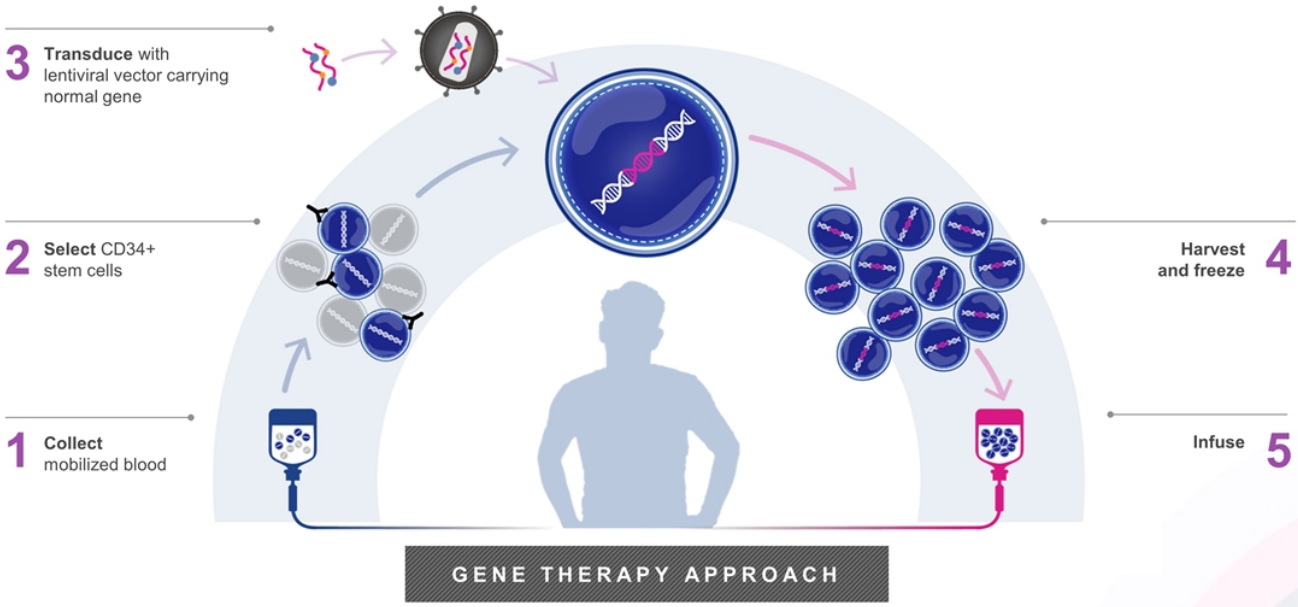
Sources: Rombach S et al, Orphanet J Rare Dis, 2013; van Dussen L et al, Orphanet J Rare Dis, 2014; WAC pricing from Redbook; 2018 Net Sales from company annual and other reports
** for Horizon's Procysbi oral therapy (delayed release cysteamine bitartrate)*
Note: Shire acquired by Takeda in 2019

Lifelong treatments vs. potential single-dose therapy

	DISEASE PROGRESSION CONTINUES	DISEASE PROGRESSION COULD HALT OR REVERSE
	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

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

Established *ex vivo* lentiviral approach



GENE THERAPY APPROACH

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

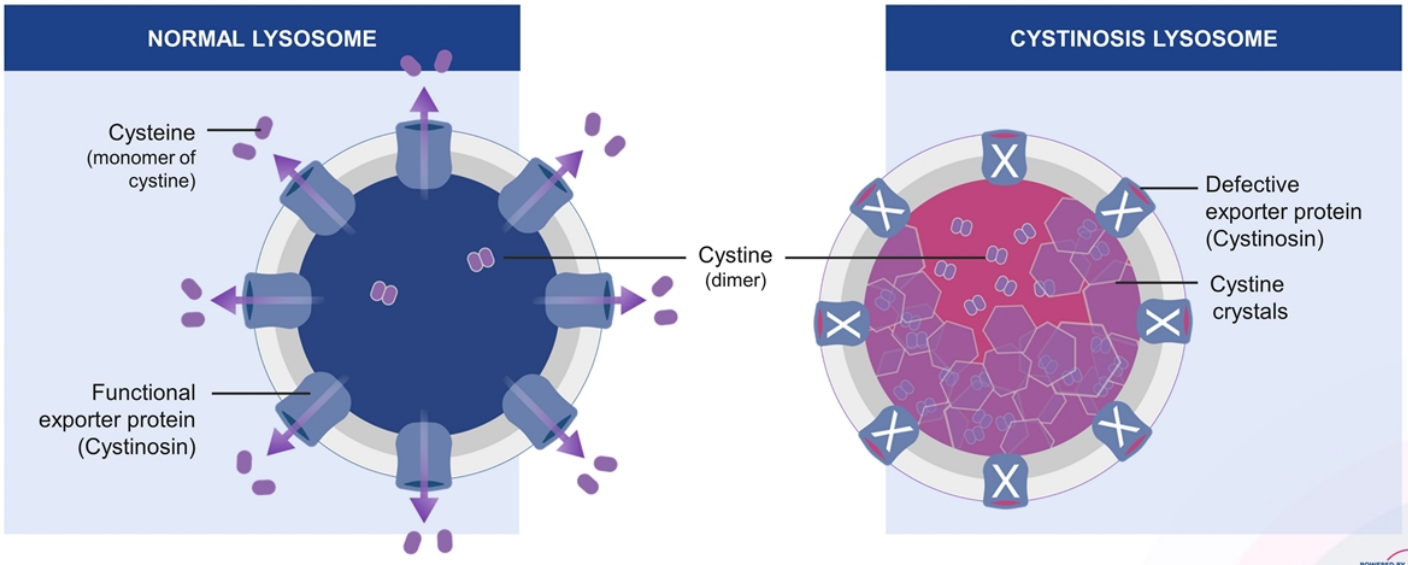
CNS complications
Unmet needs: myopathy, hypotonia, tremors, difficulty swallowing, neurodevelopmental issues (speech and walking delay and cognitive impairment)

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

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

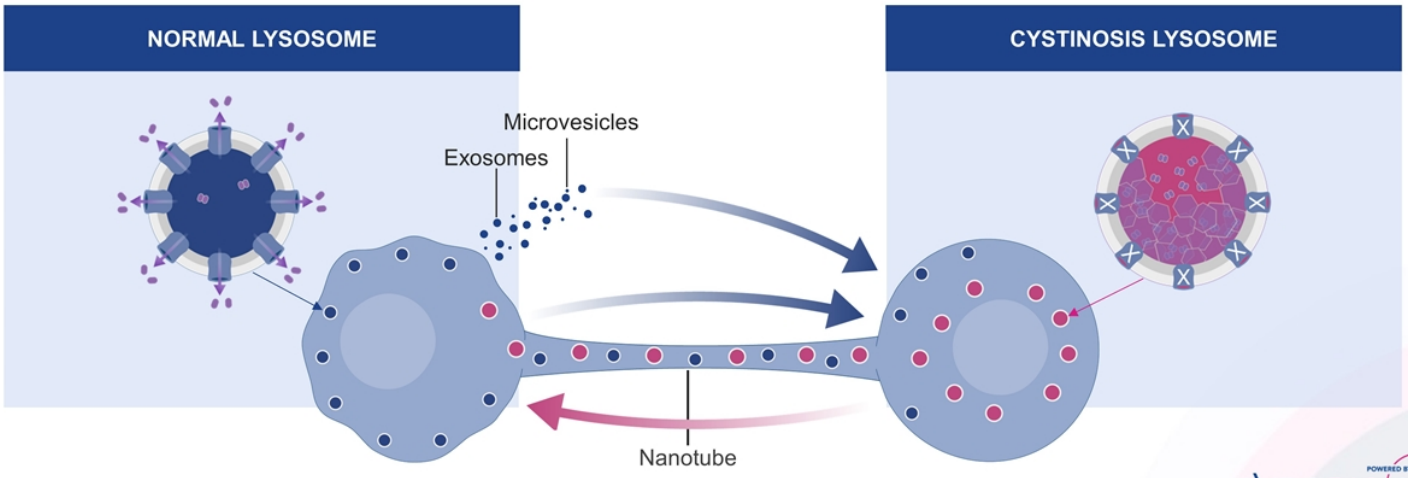
Drug product-derived macrophages restore normal cystine recycling

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



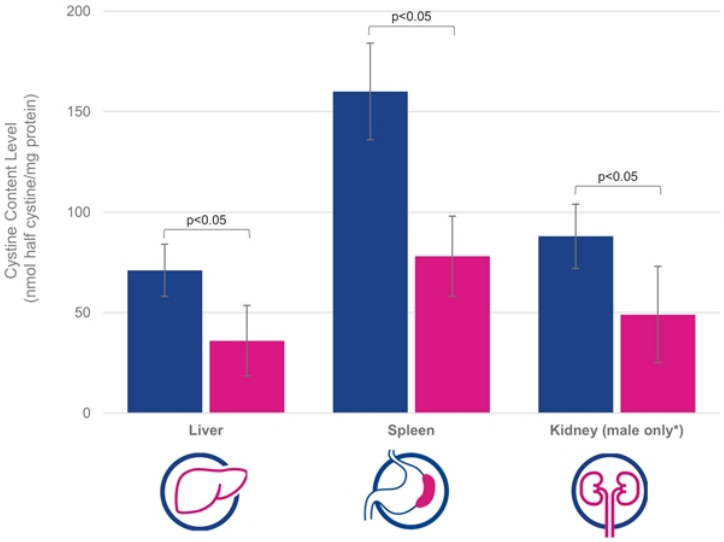
Sources: Naphade, Stem Cells, 2015. Harrison, Molecular Therapy, 2013.
CTNS: cystinosin, lysosomal cystine transporter; mRNA: Messenger Ribonucleic Acid

Preclinical cystinosis data

AVR-RD-04 preclinical proof-of-concept demonstrated[1]

Significantly decreased cystine levels in multiple tissues

- Untreated cystinosis KO mice
- Cystinosis KO mice post AVRO gene therapy AVR-RD-04



- Cytinosis KO mice[2] with established disease
- 32 weeks post-treatment
- Cystinosis KO mouse Sca1^{+} BM cells
- Human cystinosin gene
- n = 8–12 mice/group/experiment
- Data bars at the 95% confidence interval for the group

Sources: [1]Harrison et al., Molecular Therapy, 2013; [2]Cherqui et al., Mol Cell Biol, 2002;
Error bars represent means ±SD; Group comparisons of cystine content parameters were made with one-way analysis of variance, followed by t-test
Note: Females in CTNS$^{-/-}$ mouse model excessively accumulate cystine crystals in kidneys compared to males, unlike cystinosis patients where there is no difference in males and females
KO: Knockout; BM: Bone Marrow;

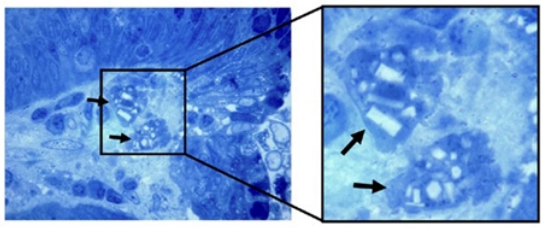
Allogeneic transplant demonstrated stabilized renal function, corrected polyuria and improved photophobia

Allogenic HSC Transplant
University Hospital Leuven

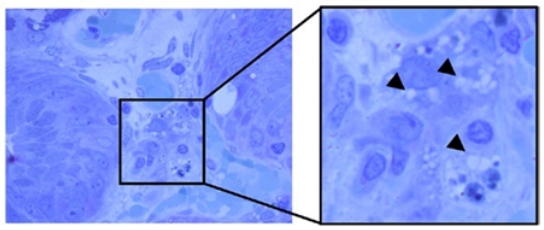
- 16 year old male
- Diagnosed at 2.7 years old, started on cysteamine
- Age 15 years – cysteamine toxicity
- Age 16 years – fully matched HLA transplant
- Acute GvHD
- **First few months**
  - **Kidney function stabilized**
  - **Polyuria resolved**
- **6 months**
  - **Photophobia score reduced from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

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

BEFORE TRANSPLANT



30 MONTHS POST TRANSPLANT



Arrows/arrowheads point to tissue macrophages

Elmonem M A et al, Am. J. Transplant, 2018; HSC: Hematopoietic Stem Cell; HLA: Human Leukocyte Antigen; GvHD: Graft vs Host Disease

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

Actively recruiting

Key Objectives

Safety and efficacy

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

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	• 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 • 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, mucoceles
- Thrombocytopenia

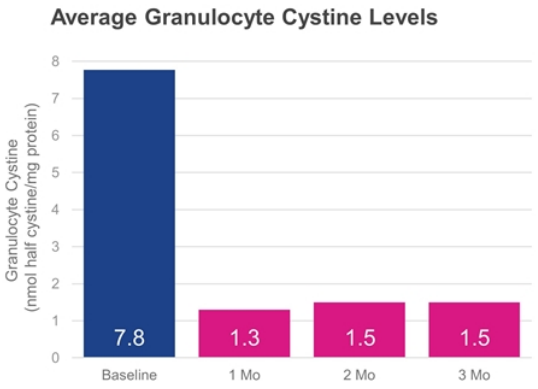
Note: Safety database cut as of January 27, 2020
AE: Adverse Event; SAE: Serious Adverse Event

Patient 1: Initial data suggest positive trends across multiple measures

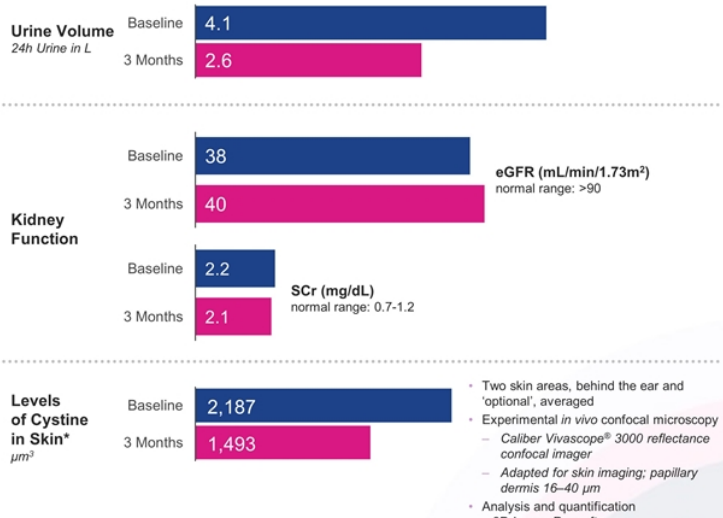
PRIMARY EFFICACY ENDPOINT

VCN
(Drug Product = 2.1)

1 month	2.9
2 months	3.0
3 months	2.0



SECONDARY ENDPOINTS



- Two skin areas, behind the ear and 'optional', averaged
- Experimental *in vivo* confocal microscopy
  - *Caliber Vivascope® 3000 reflectance confocal imager*
  - *Adapted for skin imaging; papillary dermis 16–40 µm*
- Analysis and quantification
  – 3D Image-Pro software

Asymptomatic Heterozygous Carrier Granulocyte Cystine Range: 0.2 – 1 .9 nmol half cystine/mg protein
Source: Gertsman I et al., Clinical Chemistry, 2016
VCN: Vector Copy Number; CTNS: Cystinosin, Lysosomal Cystine Transporter; mRNA: Messenger Ribonucleic Acid; eGFR: Estimated Glomerular Filtration Rate; SCr: Serum Creatinine
**Data obtained using a novel experimental methodology utilizing optical coherence tomography, to image crystals in the skin behind the ear*

Patient 1: Reduced treatment burden at 3 months

Number of Medications and Supplements

(max per day)

Before Gene Therapy
ON Cysteamine

52

After Gene Therapy
(at 3 months post-gene therapy)
OFF Cysteamine

21

NOTE: Investigational gene therapy

Thought Leader Q&A

Cystinosis

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

Two AVR-RD-01 Fabry clinical trials

9 patients dosed across Phases 1 and 2, including first patient dosed with plato™

PHASE 1
Investigator-Sponsored Trial*

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

Key Objectives
Safety and preliminary efficacy

PHASE 2
AVRO – FAB-201 Trial

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

Actively enrolling

Key Objectives
Safety and efficacy

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

Fabry FAB-201 Patient Characteristics

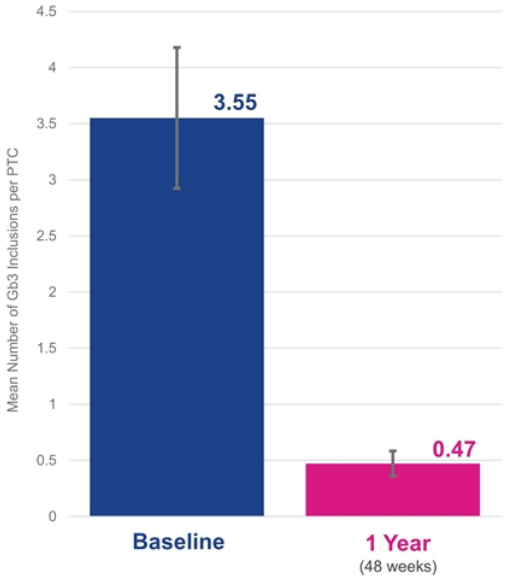
Treatment-naïve Fabry patients

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Age of symptom onset / diagnosis	10 / 19 years	36 / 37 years	13 / 13 years	9 / 9 years
Age dosed with AVR-RD-01	21 years	46 years	40 years	26 years
Mutation	c.1021G>A (p.E341K)	c.644A>G (p.N215S)	c.639+1G>T	c.833dupA
Primary disease signs and symptoms	• Kidney disease • Chronic pain • GI symptoms • Decreased cold sensation	• Cardiac disease • Peripheral neuropathy • Chronic pain • Increased tiredness • GI symptoms • Intermittent tinnitus • Mild high frequency hearing loss • Raynaud's syndrome	• Kidney disease • GI symptoms • Peripheral neuropathy • Bilateral deafness • Tinnitus • Peripheral edema • Decreased cold sensation	• 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*
*** Rupar 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)**

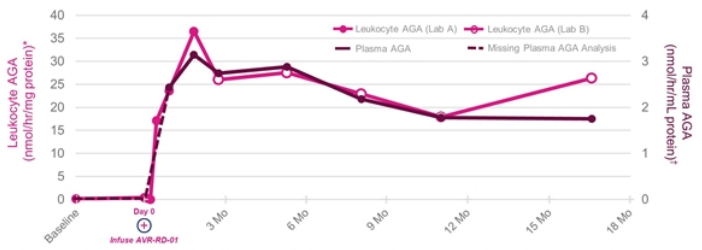


- *Unpaired t-test for difference between n=55 PTCs at baseline vs. n=101 PTCs at 1 year; p < 0.0001*
- *Error bar represents the standard deviation*

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

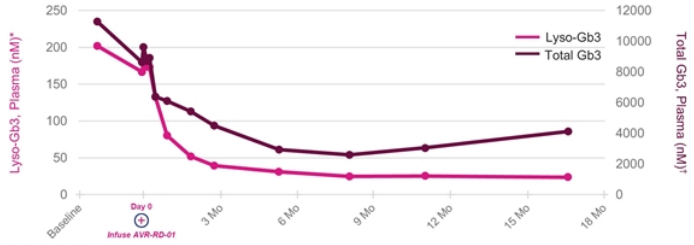
Patient 1: Multiple data trends sustained up to 18 months

Leukocyte + Plasma AGA Enzyme Activity



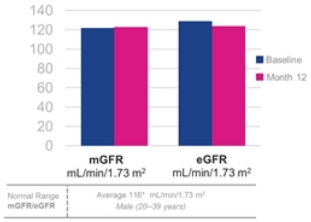
*Lab A: Mayo Clinic Laboratories; Lab B: Rupar Laboratory; Lab A Reference Range: >23.1 nmol/hr/mg; Lab B Reference Range: 24–56 nmol/hr/mg
†Reference Range: 5.1–9.2 nmol/hr/mL
AGA: α-galactosidase A

Plasma Lyso-Gb3 and Total Gb3



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

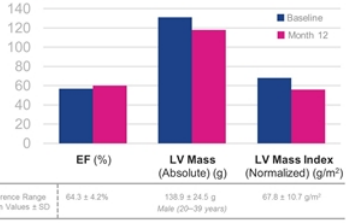
KIDNEY FUNCTION
remains within normal range at 12 mos.



	mGFR mL/min/1.73 m²	eGFR mL/min/1.73 m²
Normal Range mGFR/eGFR	Average 116* mL/min/1.73 m² Male (20–39 years)	

*Source: https://www.kidney.org/atoz/content/gfr
mGFR: Measured Glomerular Filtration Rate; eGFR: Estimated Glomerular Filtration Rate

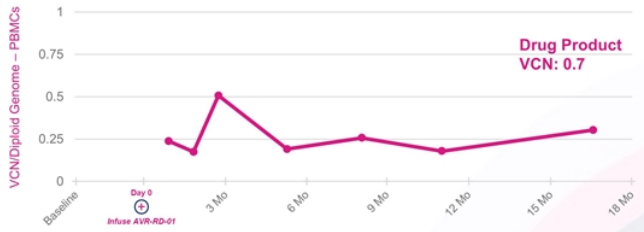
CARDIAC FUNCTION
remains within normal range at 12 mos.



	EF (%)	LV Mass (Absolute) (g)	LV Mass Index (Normalized) (g/m²)
Reference Range Mean Values ± SD	64.3 ± 4.2%	138.9 ± 24.5 g Male (20–39 years)	67.8 ± 10.7 g/m²

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

Vector Copy Number (VCN)

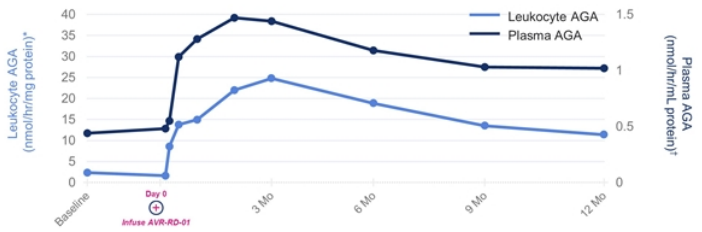


VCN: Vector Copy Number; PBMCs: Peripheral Blood Mononuclear Cells

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

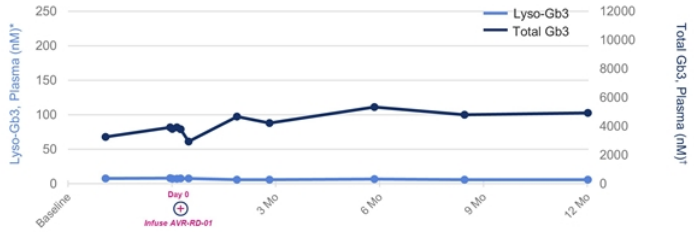
Patient 2: Multiple data trends sustained up to 12 months

Leukocyte + Plasma AGA Enzyme Activity



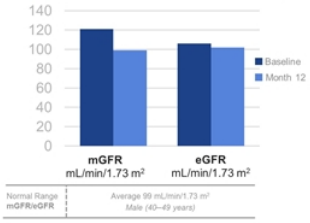
*Data from Rupar Laboratory; Reference Range: 24–56 nmol/hr/mg
†Reference Range: 5.1–9.2 nmol/hr/mL
AGA: α-galactosidase A

Plasma Lyso-Gb3 and Total Gb3



*Reference Value: 2.4 nM; †Reference Value: 4961 nM
Note: Patient #2 has normal substrate, consistent with late-onset cardiac variant phenotype
Lyso-Gb3: Globotriaosylsphingosine; Gb3: Globotriaosylceramide

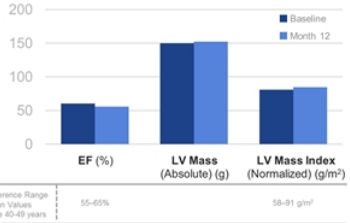
KIDNEY FUNCTION *remains within normal range*



	mGFR	eGFR
Normal Range mGFR/eGFR	Average 99 mL/min/1.73 m² Male (40–49 years)	

Source: https://www.kidney.org/atoz/content/gfr
mGFR: Measured Glomerular Filtration Rate; eGFR: Estimated Glomerular Filtration Rate

CARDIAC FUNCTION *remains within normal range*



	EF (%)	LV Mass (Absolute) (g)	LV Mass Index (Normalized) (g/m²)
Reference Range Mean Values Male 40-49 years	55–65%		58–91 g/m²

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

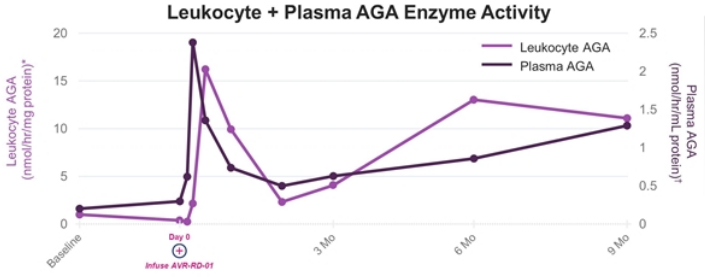
Vector Copy Number (VCN)

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

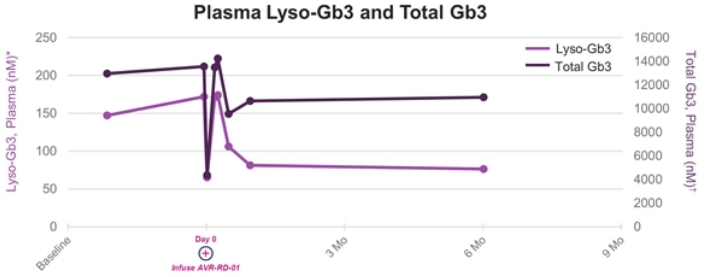
Patient 3: Initial divergent profile with 9 months data trending toward anticipated long-term engraftment

Leukocyte + Plasma AGA Enzyme Activity



*Data from Rupar Laboratory; Reference Range: 24–56 nmol/hr/mg
†Reference Range: 5.1–9.2 nmol/hr/mL
AGA: α-galactosidase A

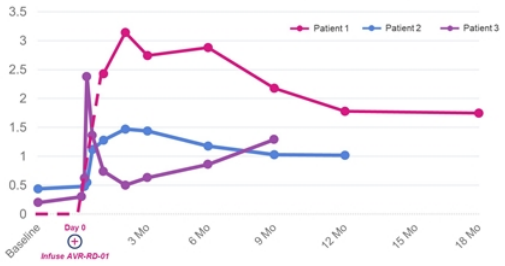
Plasma Lyso-Gb3 and Total Gb3



*Reference Value: 2.4 nM
†Reference Value: 4961 nM
Lyso-Gb3: Globotriaosylsphingosine; Gb3: Globotriaosylceramide

Skin Biopsy Score (Patient 3)	
Baseline	2
6 months	2

Plasma AGA Enzyme Activity



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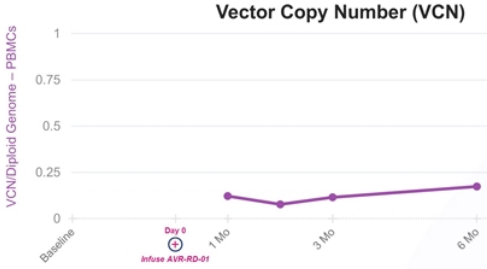


Drug Product
VCN: 1.4

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

FAB-201

No unexpected safety events or trends identified

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

AEs and SAEs reported

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)

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

- Transient low titer in 1 patient

Note: The first three patients in the FAB-201 trial had been dosed prior to the safety data cut-off date of November 26, 2019; the fourth patient, who was dosed following the safety cut-off date, has reported an SAE related to non-neutropenic fever, which was not attributed to AVR-RD-01
AE: Adverse Event; SAE: Serious Adverse Event
NOTE: AVR-RD-01 is an investigational gene therapy

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

Actively enrolling

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

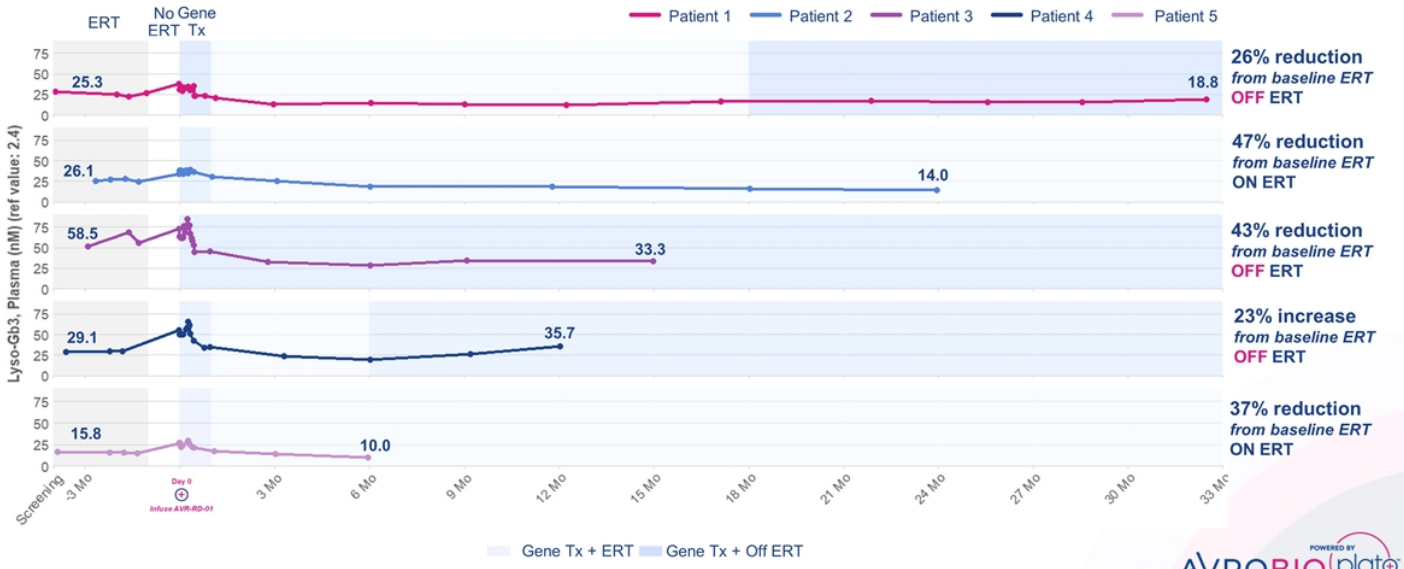
ERT-Treated Fabry Patients

	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	• Kidney disease • Cardiac disease • GI pain • GI diarrhea • Angiokeratoma • Insomnia	• Kidney disease • Cardiomyopathy • Hypohidrosis • Corneal verticillata • Peripheral neuropathy • GI symptoms • Angiokeratoma • Lymphedema • Acroparesthesia	• Cardiac Disease • Tinnitus • Headaches • Dizziness • Acroparesthesia	• Cardiac Disease • Hypohidrosis • Tinnitus • Corneal verticillata • Angiokeratoma • GI symptoms	• Kidney disease • Hypertension • Hypohidrosis • Tinnitus • Migraines • Impaired hearing • Angiokeratoma • Sleep apnea • Asthma • Depression
Leukocyte AGA activity at baseline (nmol/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	

** Rupar Lab, ref range 24-56 nmol/hr/mg*
*** Reference value ≤ 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

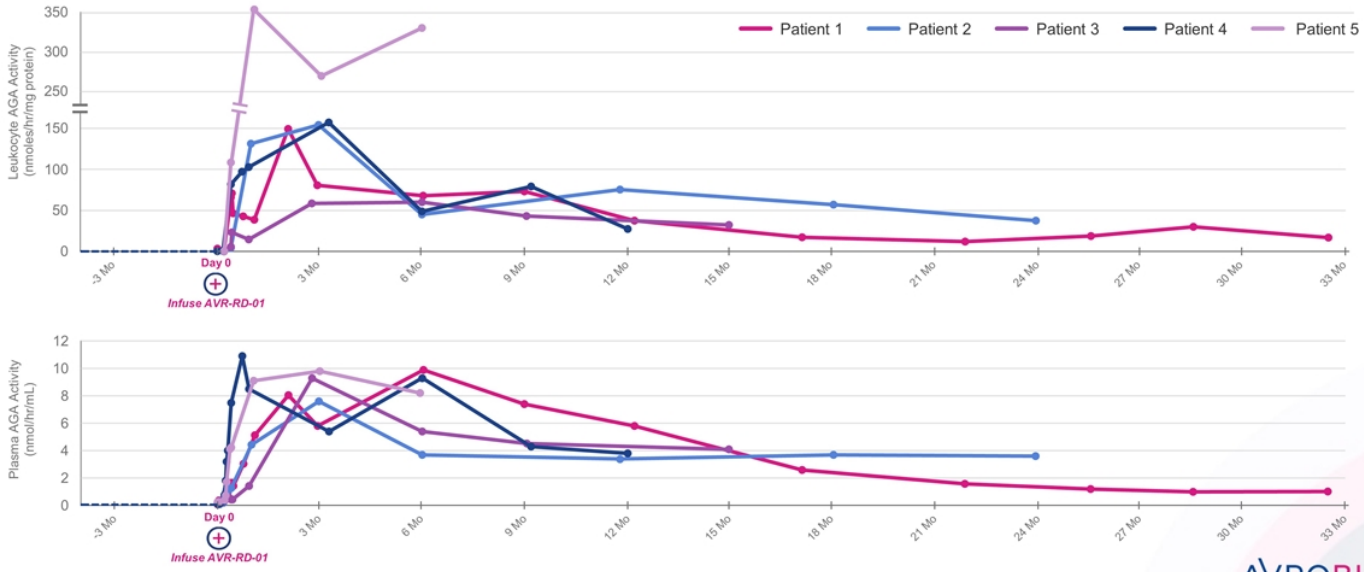
All patients who have discontinued ERT remain off ERT



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

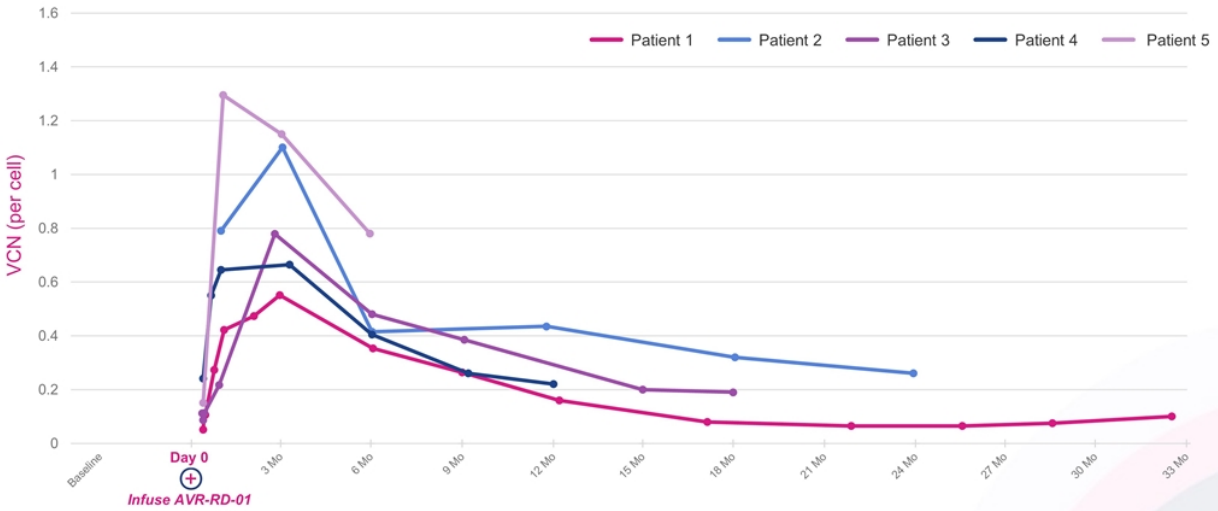


AGA: α-Galactosidase A

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

4 patients with 1+ years data

Drug Product VCN	
Patient 1	0.7
Patient 2	1.4
Patient 3	0.8
Patient 4	1.4
Patient 5	1.2

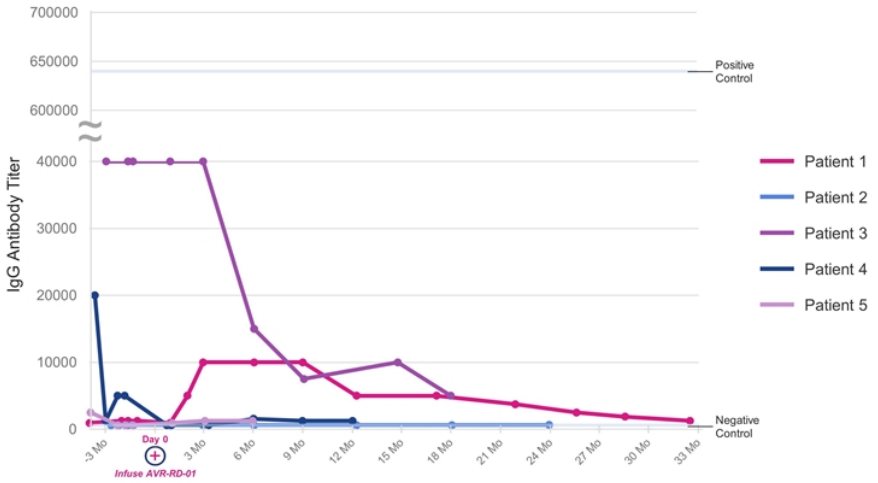


Note: 0.1 VCN is indicative of approx. 5-10% of all nucleated cells having an average of 1-2 copies of the transgene
VCN: Vector Copy Number

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



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

Similar Results Observed in Other Studies

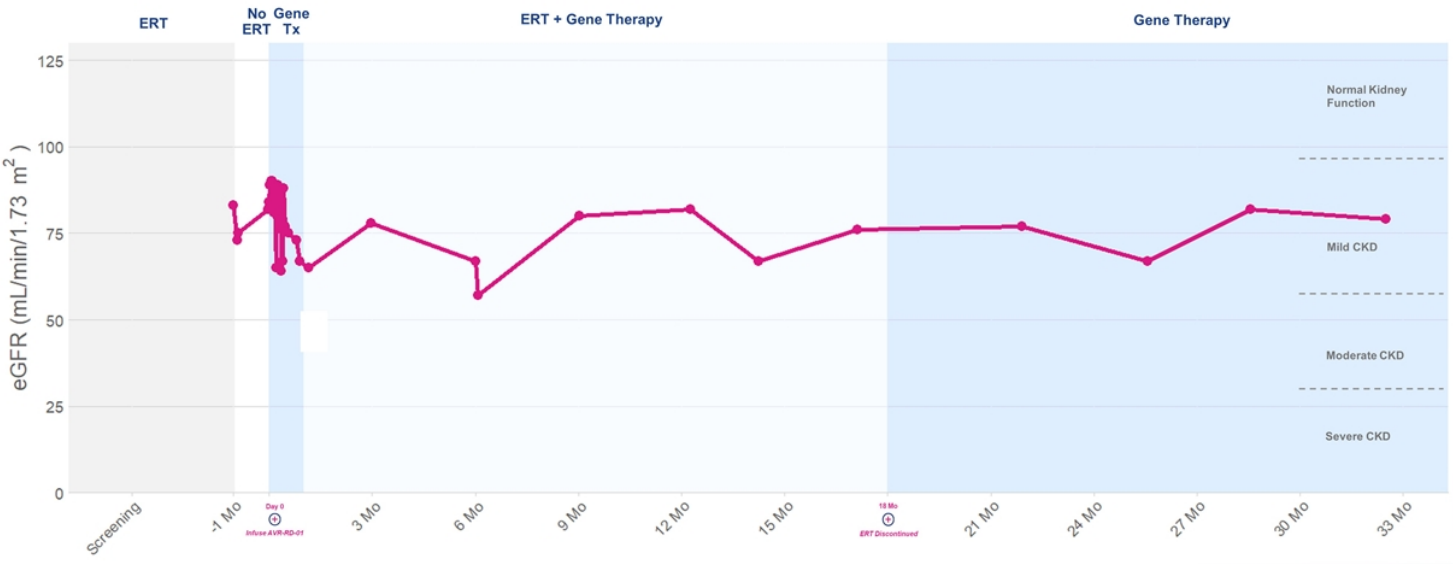
San Raffaele Telethon Institute for Gene Therapy (SR-TIGET)

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*

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 dosed

No unexpected safety events or trends identified

No SAEs related to AVR-RD-01 drug product

AEs and SAEs reported

AEs (n = 128):

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

SAEs (n = 2):

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

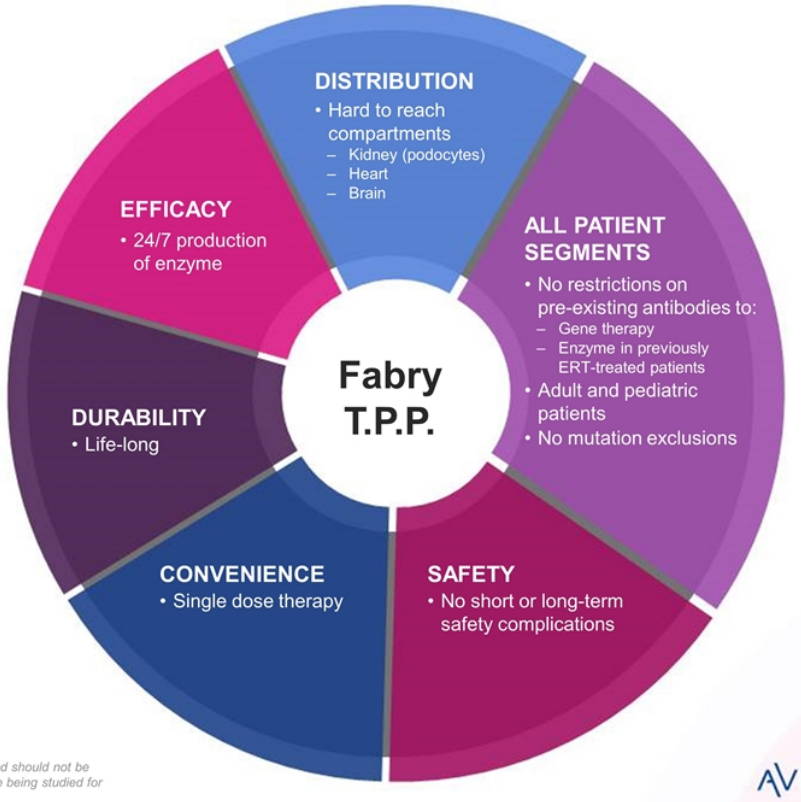
Anti-AGA antibodies

- 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

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

Potential attributes intended to support first-line use



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

Building commercial capabilities

50+ product launches, including 2 gene therapies

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

Monique da Silva
SVP, Corporate Communications

- Led communications strategy through launch at Spark Therapeutics
- Led communications functions at Biogen and OgilvyPR

Deanna Petersen
Chief Business Officer

- Led Shire's rare disease business development and M&A
- Responsible for Shire's rare disease pipeline strategy

SANOFI GENZYME avexis Spark THERAPEUTICS Shire sobi Pioneer in Rare Diseases Biogen AVROBIO POWERED BY plato

Thought Leader Q&A

Fabry disease

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

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

Actively recruiting

Key Objectives

Safety, Engraftment, Efficacy, ERT-independence

GAU-201: AVR-RD-02 Study; ERT: Enzyme Replacement Therapy

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

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)

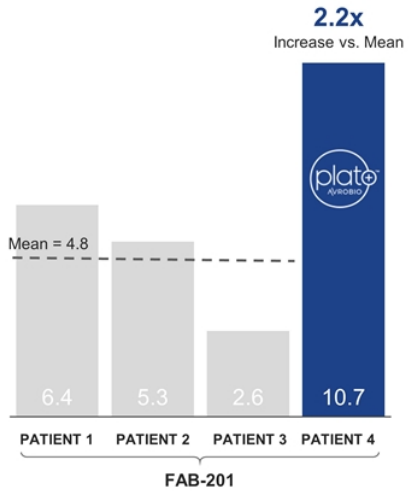
plato™ UPGRADE 1

VECTOR UPGRADE:

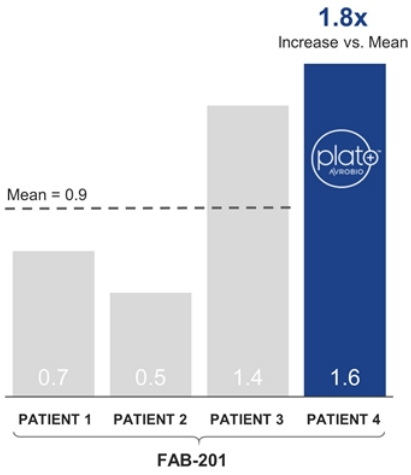
Metrics compared to academic process

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

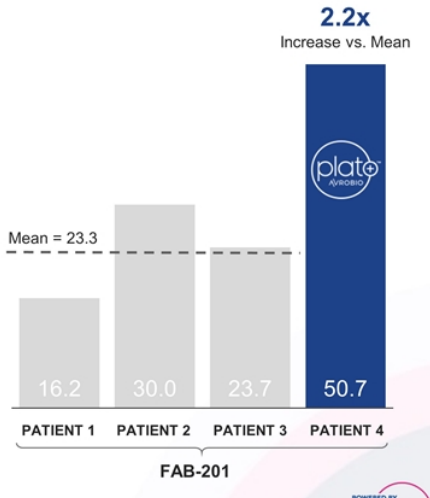
Enzyme Activity (nmol/hr/mL)



VCN (per diploid genome)



Transduction Efficiency (%)



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

plato™ UPGRADE 1

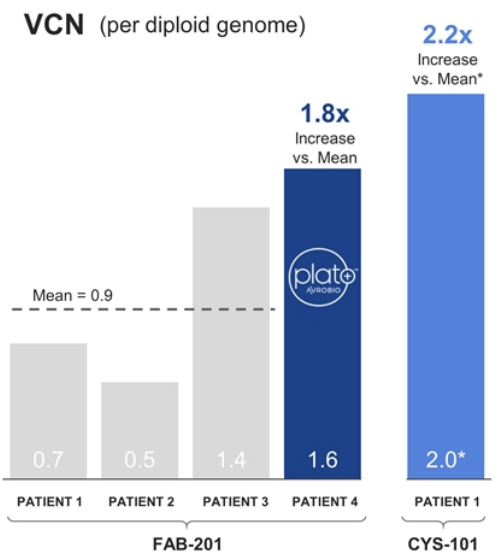
VECTOR UPGRADE:

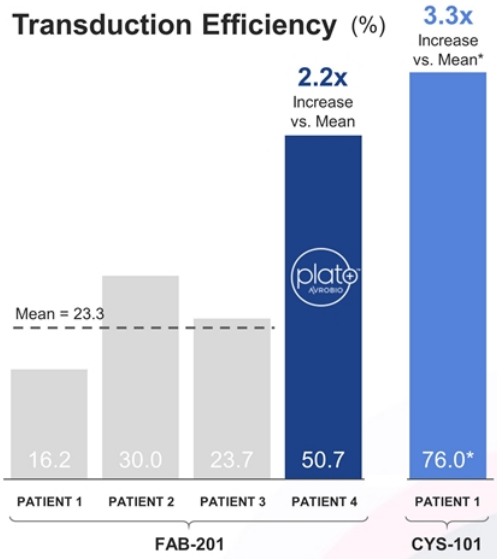
Metrics compared to academic process

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





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

plato™ UPGRADE 2

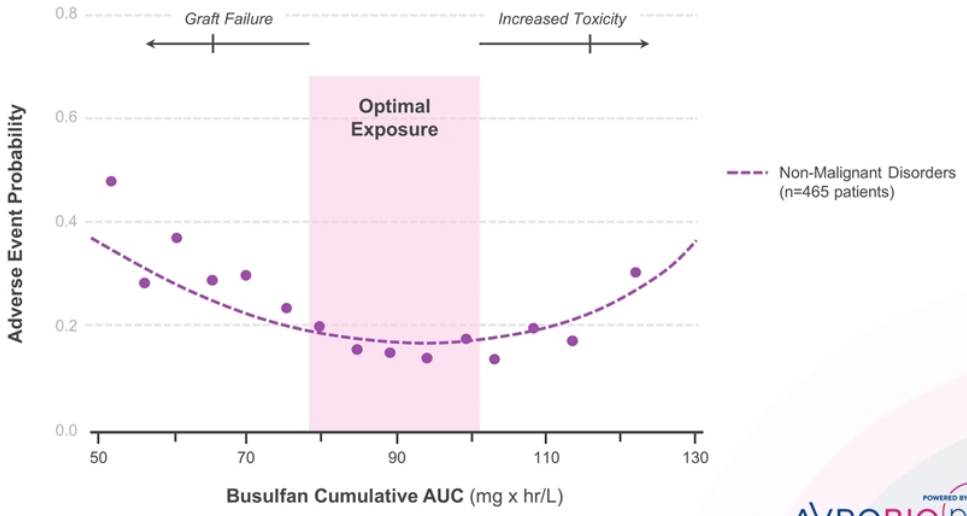
PRECISION CONDITIONING UPGRADE:

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

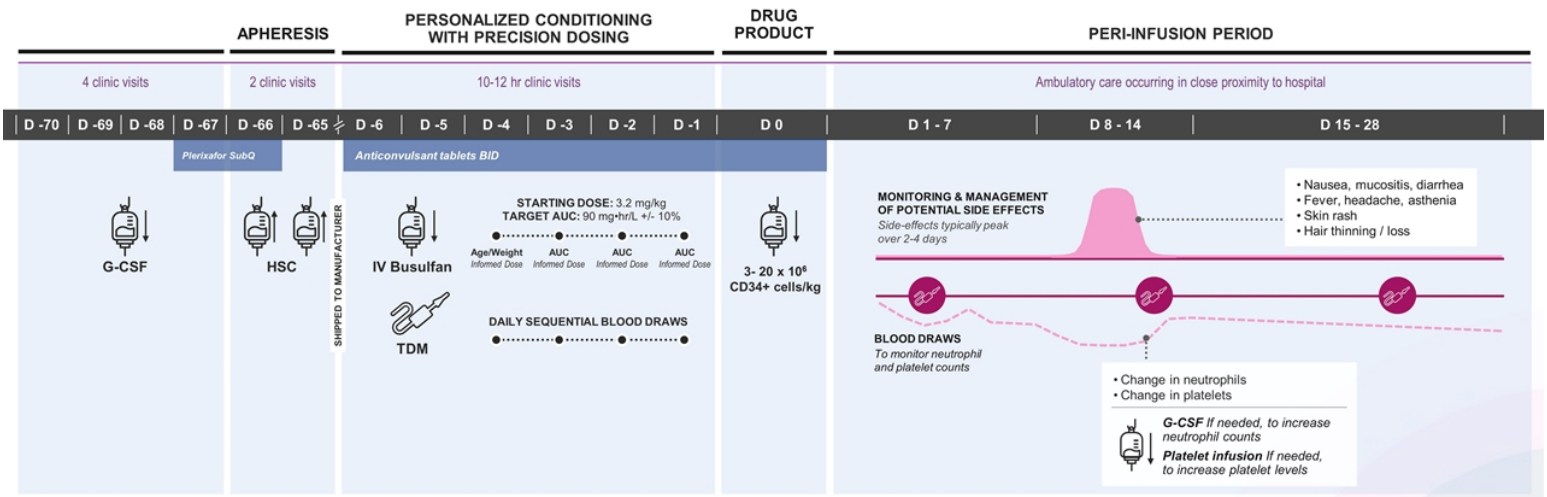


Bu: Busulfan; AUC: Area Under the Curve
Sources: Bartelink IH et al, Lancet Haematol, 2016

plato™ UPGRADE 2

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

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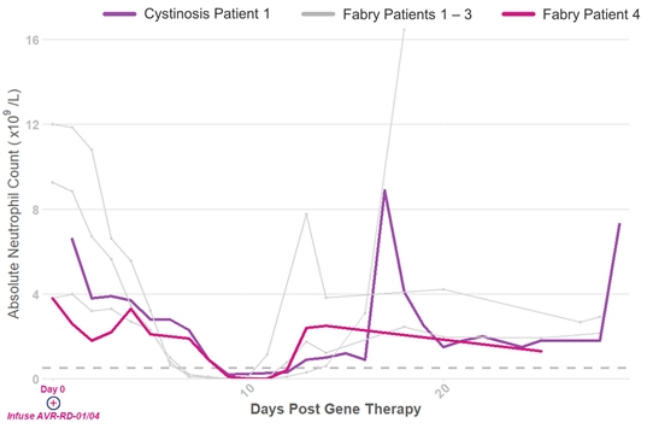
plato™ UPGRADE 2

PRECISION CONDITIONING UPGRADE:

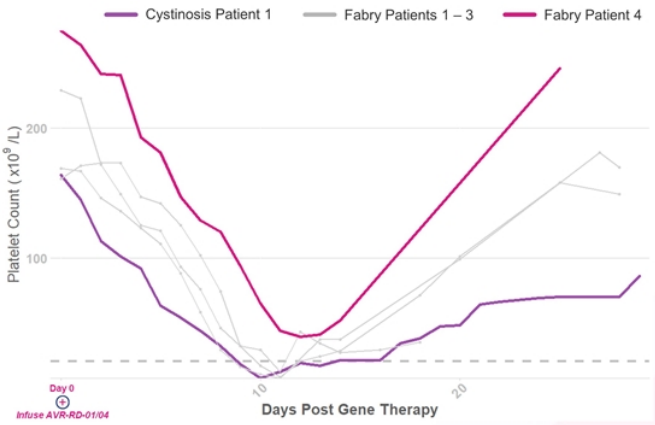
Rapid neutrophil and platelet count recovery

Similar for busulfan and melphalan across Fabry and cystinosis patients

Absolute Neutrophil Counts



Platelet Counts



Fabry: Patients #1-3 Melphalan 100mg/m2; Patient #4 Busulfan 'AUC 90'; Cystinosis: Patient #1 Busulfan 'AUC 90'
Dashed Lines: Threshold levels for prophylactic supportive care in HSC Tx; ANC <0.5 x 10^9 per liter (AABB); Platelets <10 X 10^9 cells/L (AABB)
NOTE: Neutrophil counts - Cystinosis G-CSF administration post gene therapy: Pt 1: 5 Doses, Day 15 – 19; Fabry 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 - Cystinosis Platelet Transfusion: Pt 1: Day 17 & 18; Fabry Platelet Transfusion: Pt 1: Day 10; Pt 2, 3: Day 11, Pt 4: no transfusion

plato™ UPGRADE 2

PRECISION CONDITIONING UPGRADE:

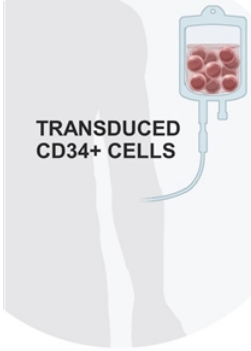
Designed to access “hard-to-reach” compartments

BRAIN

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

MICROGLIA

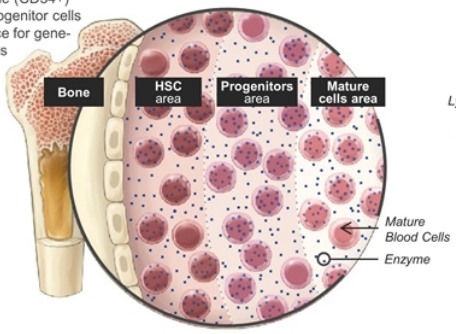
Potential for widespread microglia engraftment throughout the brain



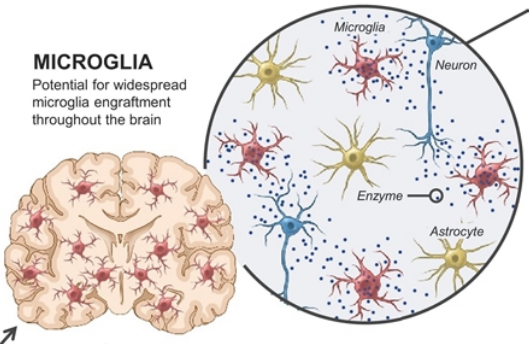
TRANSDUCED CD34+ CELLS

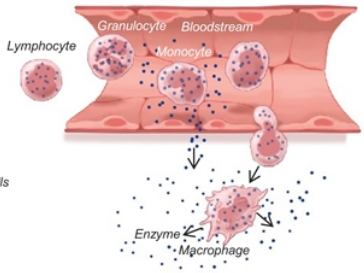
IN THE BONE MARROW

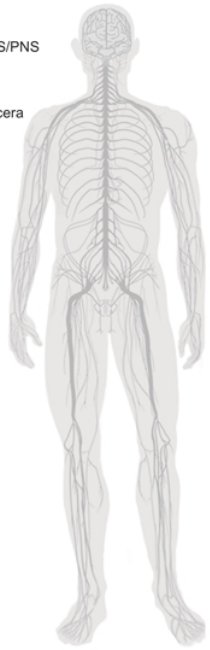
Busulfan eliminates hematopoietic (CD34+) stem and progenitor cells making space for gene-modified cells



BONE MARROW → PERIPHERAL TISSUE





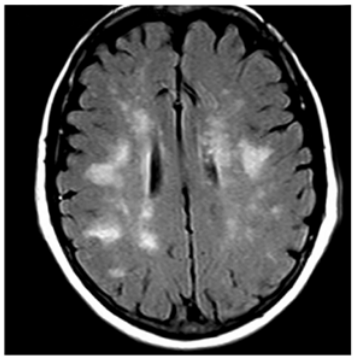


AVROBIO powered by plato™

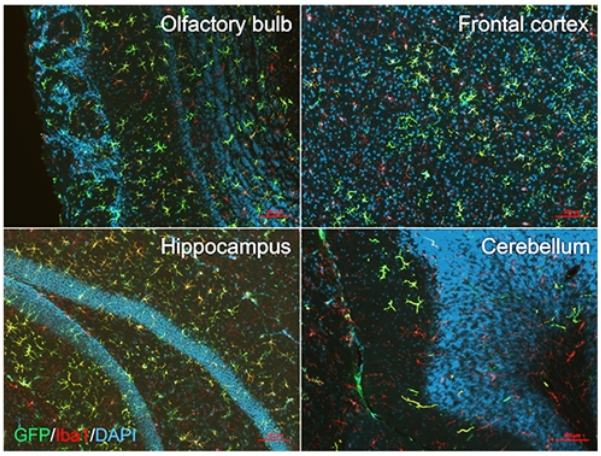
plato™ UPGRADE 2

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. Neurol, Neurosurg, Psychiatry, 2008
MRI: Magnetic Resonance Imaging; ERT: Enzyme Replacement Therapy; WMLs: White Matter Lesions; HSC: Hematopoietic Stem Cell

plato™ UPGRADE 3

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

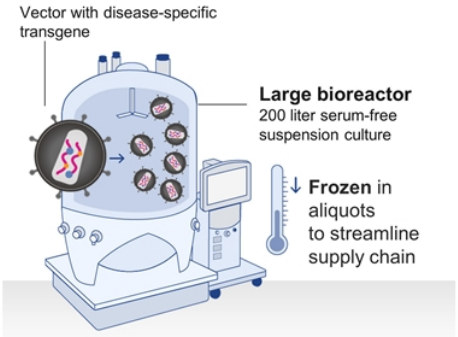
plato™ UPGRADE 3

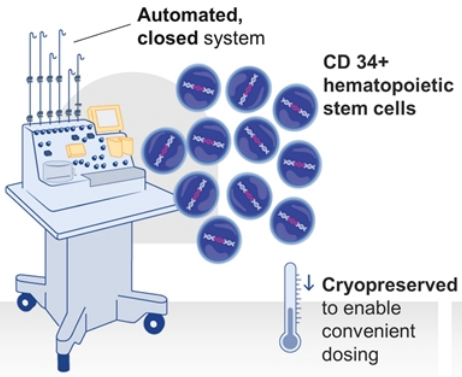
AUTOMATION UPGRADE:

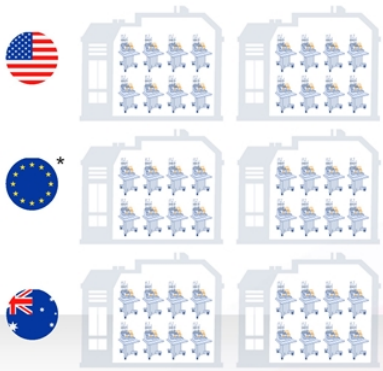
Designed to deliver large-scale manufacturing

Differentiated, cost-effective approach

1 Vector production	2 Drug product production	3 Scalable, global production suites
HIGH VOLUME / TITRE	INCREASE CONSISTENCY	COST-EFFECTIVE SCALE-OUT







Illustrative

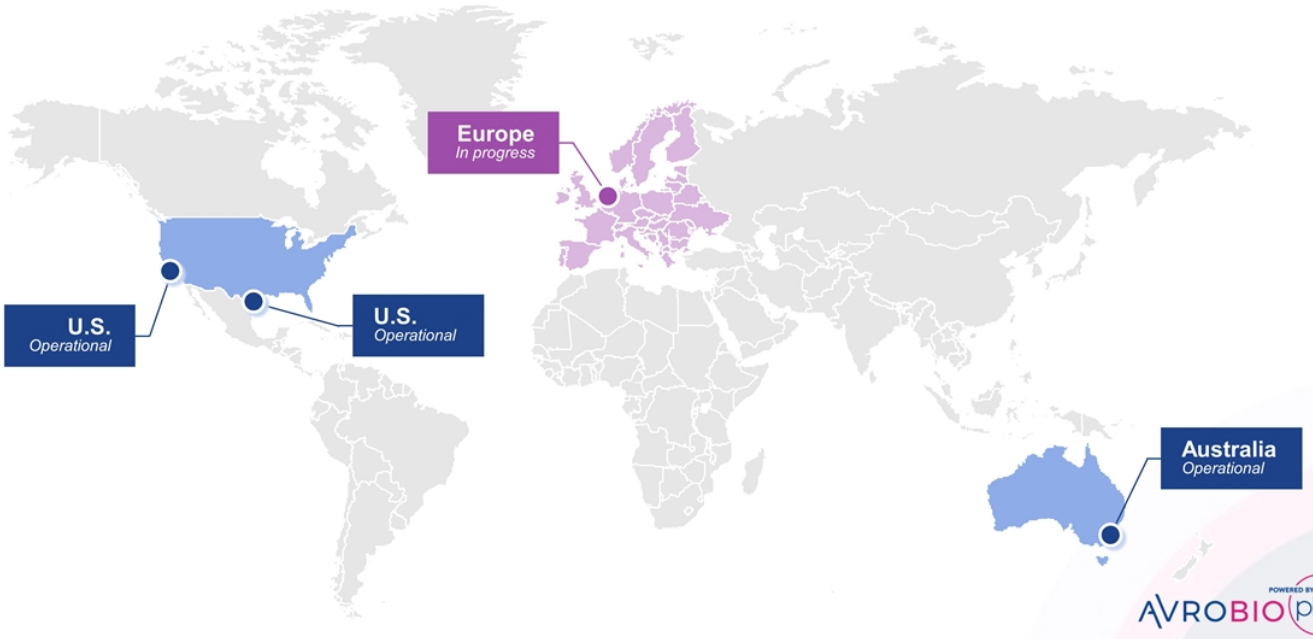
* European manufacturing capabilities planned for 2H 2020; manufacturing capabilities currently in place in U.S. & Australia

plato™ UPGRADE 3

AUTOMATION UPGRADE:

Global manufacturing established

Automated systems operational in 3 sites with 4th in progress



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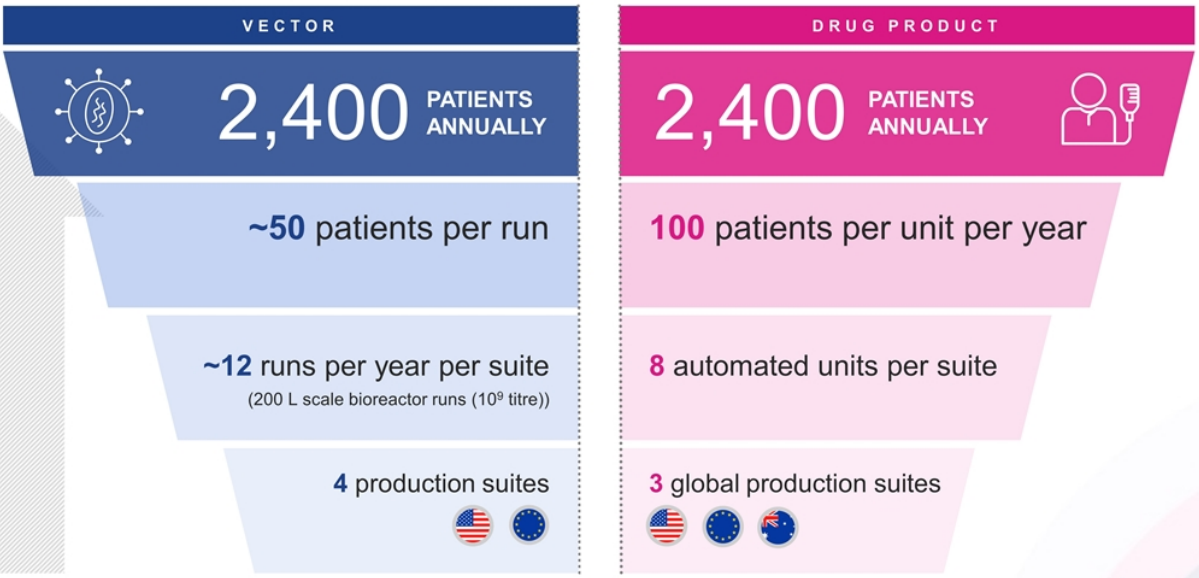
plato™ UPGRADE 3

AUTOMATION UPGRADE:

Poised to manufacture at scale

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



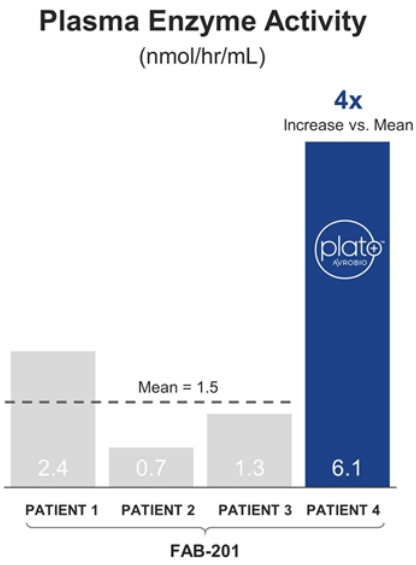
Illustrative

plato™ UPGRADE 1, 2, 3

3 UPGRADES IN PLACE:

plato™ metric compared to academic process

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



FAB-201: AVR-RD-01 Study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plato™

Milestones anticipated across the pipeline in 2020

FABRY

- Continue recruitment in FAB-201
- Continue to report data, including initial plato™ patient data

GAUCHER

- Enroll first patient in GAU-201 in Q1 2020 with dosing in Q2 2020
- Report initial patient data in H2 2020

CYSTINOSIS

- Continue enrollment in investigator-sponsored trial
- Continue to report patient data

POMPE

- Complete preclinical IND-enabling activities

AVROBIO to hold first R&D Day in 2020

Key takeaways

Early cystinosis data suggests potential gene therapy impact
Cystine level reductions in granulocytes and skin; urine volume reduction

Growing Fabry data set continues to support potential first-line use
9 patients now dosed across Phase 1 and Phase 2 trials

Initial plato™ *in-vivo* enzyme levels 4x greater than academic process
1-month plasma enzyme level for first Fabry patient dosed with plato vs. initial Phase 2 patients

plato automated manufacturing operational in US and AU
Europe in progress

Reporting data across 3 gene therapy programs in 2020
Continued readouts expected across Fabry, cystinosis and Gaucher trials