# 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): January 11, 2021**

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

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

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

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

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

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

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

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

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

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

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

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

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

Emerging growth company ☒

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

**Item 7.01 Regulation FD Disclosure.**

On January 11, 2021, AVROBIO, Inc. updated its corporate presentation for use in meetings with investors, analysts and others. A copy of the presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

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

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits

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

**SIGNATURES**

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

AVROBIO, INC.

Date: January 11, 2021

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

Exhibit 99.1

# AVROBIO
# Corporate Presentation

JANUARY 2021

# Disclaimer

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

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words and phrases such as "aims," "anticipates," "believes," "could," "designed to," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "seeks," "will," and variations of these words and phrases or similar expressions that are intended to identify forward-looking statements. These forward-looking statements include, without limitation, statements regarding our business strategy for and the potential therapeutic benefits of our current and prospective product candidates; the design, commencement, enrollment and timing of ongoing or planned clinical trials and regulatory pathways; the timing of patient recruitment and enrollment activities, clinical trial results, and product approvals; the timing and results of our ongoing preclinical studies; the anticipated benefits of our gene therapy platform including the potential impact on our commercialization activities, timing and likelihood of success; the anticipated benefits and safety profile of busulfan as a conditioning agent; the expected benefits and results of our manufacturing technology, including the implementation of our plato® platform in our clinical trials and gene therapy programs; the expected safety profile of our investigational gene therapies; the potential impact of the COVID-19 outbreak on our clinical trial programs and business generally, as well as our plans and expectations with respect to the timing and resumption of any development activities that may be temporarily paused as a result of the COVID-19 outbreak; and the market opportunity for and anticipated commercial activities relating to our investigational gene therapies. Any such statements in this presentation that are not statements of historical fact may be deemed to be forward-looking statements.

Any forward-looking statements in this presentation are based on our current expectations, estimates and projections about our industry as well as management's current beliefs and expectations of future events only as of today and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that any one or more of our product candidates will not be successfully developed or commercialized; the risk of cessation or delay of any ongoing or planned clinical trials of AVROBIO or our collaborators; the risk that we may not successfully recruit or enroll a sufficient number of patients for our clinical trials; the risk that we may not realize the intended benefits of our gene therapy platform, including the features of our plato® platform; the risk that our product candidates or procedures in connection with the administration thereof, including our use of busulfan as a conditioning agent, will not have the safety or efficacy profile that we anticipate; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or trials involving our product candidates; the risk that we will be unable to obtain and maintain regulatory approval for our product candidates; the risk that the size and growth potential of the market for our product candidates will not materialize as expected; risks associated with our dependence on third-party suppliers and manufacturers; risks regarding the accuracy of our estimates of expenses and future revenue; risks relating to our capital requirements and needs for additional financing; risks relating to clinical trial and business interruptions resulting from the COVID-19 outbreak or similar public health crises, including that such interruptions may materially delay our development timeline and/or increase our development costs or that data collection efforts may be impaired or otherwise impacted by such crises; and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause AVROBIO's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in AVROBIO's most recent 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 registered trademark of AVROBIO. Other trademarks referenced in this presentation are the property of their respective owners.

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



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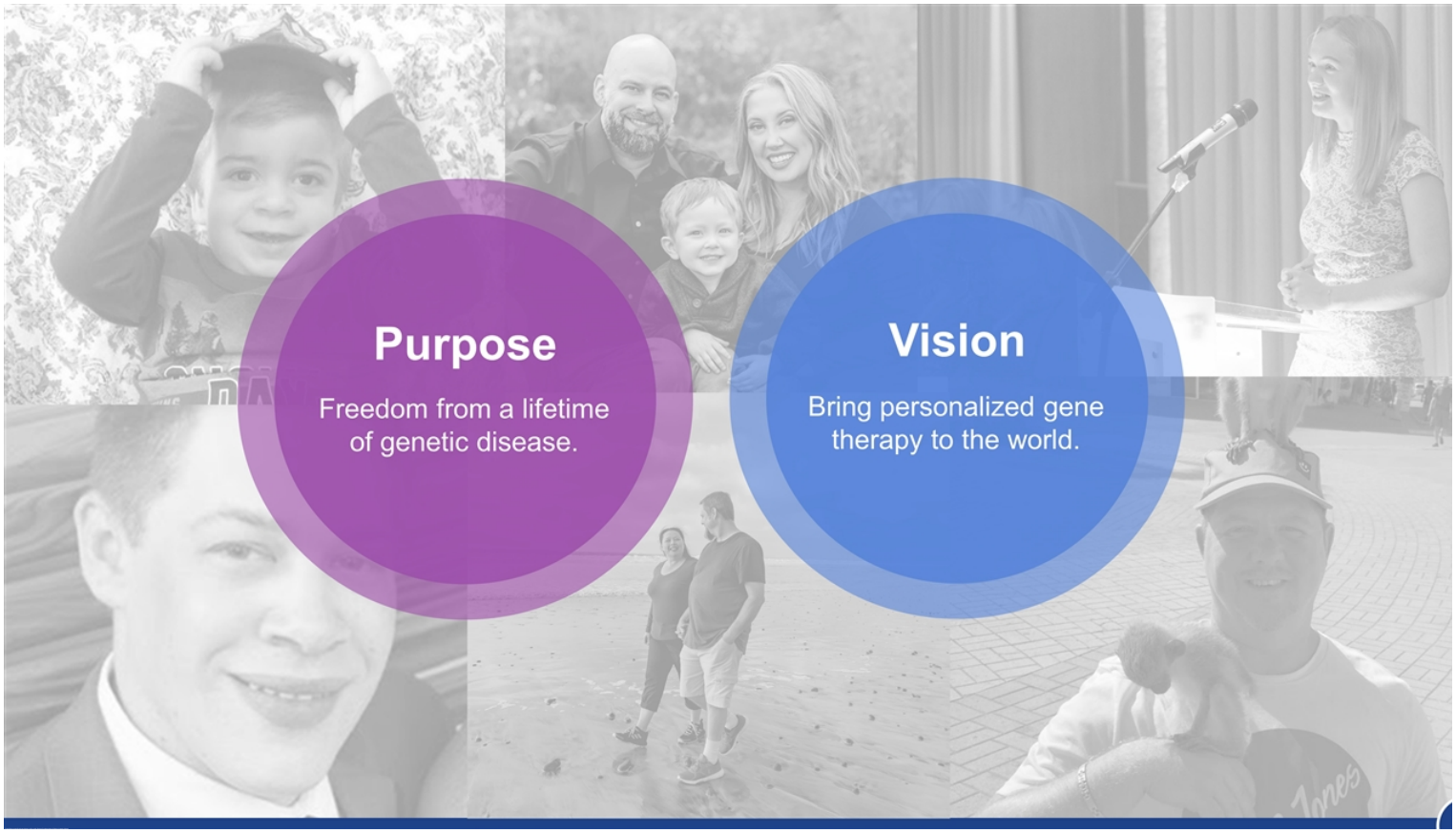
Purpose
Freedom from a lifetime of genetic disease.
Vision
Bring personalized gene therapy to the world.

# *Ex vivo* lentiviral gene therapy has emerged as a leading modality across multiple genetic diseases

**Industry-wide data demonstrate proven record, broad utility**

| EFFICACY | DURABILITY | TOLERABILITY | WIDE REACH | BROAD UTILITY |
|---|---|---|---|---|
| **Approved**<br>• ALD<br>• Beta thalassemia<br>• MLD<br>**Investigational**<br>• Fanconi anemia<br>• Hurler syndrome<br>• Sanfilippo A<br>• Sanfilippo B<br>• SCID-ADA<br>• SCID-X<br>• Sickle cell disease<br>• Wiskott-Aldrich syndrome<br>• X-CGD | • >12 years post-infusion | • >350 patients<br>• >1,000 patient years | • Head-to-toe, including:<br>– Brain<br>– Muscle<br>– Bone | • Pediatrics and adults<br>• All mutations<br>• No exclusions due to pre-existing antibodies |

*ALD: Adrenoleukodystrophy; SCID-ADA: Severe Combined Immunodeficiency-Adenosine Deaminase Deficiency; SCID-X: X-Linked Severe Combined Immunodeficiency; MLD: Metachromatic Leukodystrophy; X-CGD: X-Linked Chronic Granulomatous Disease*

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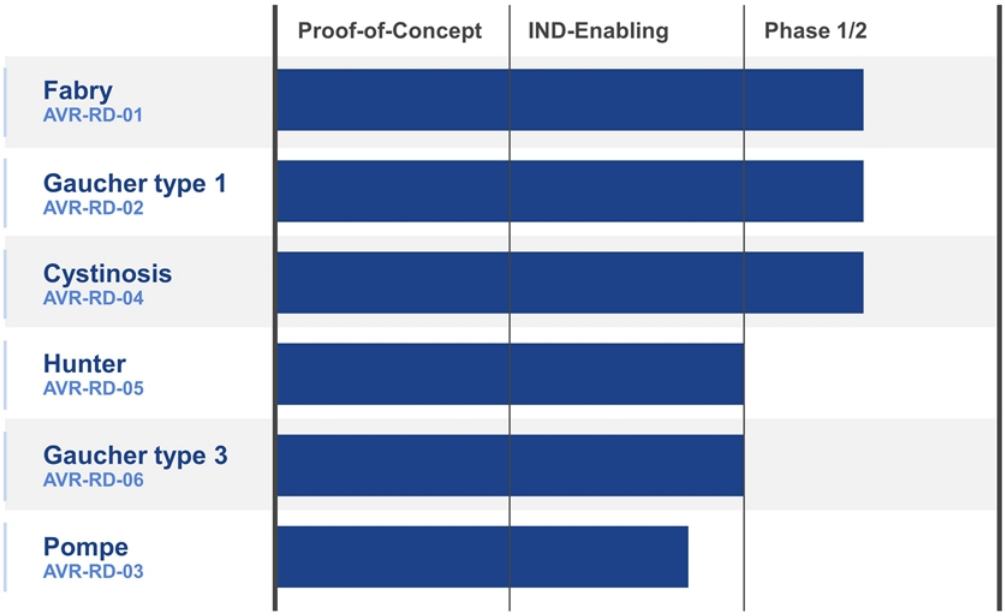
# Leading lysosomal disorder gene therapy pipeline

**13 patients dosed to date**

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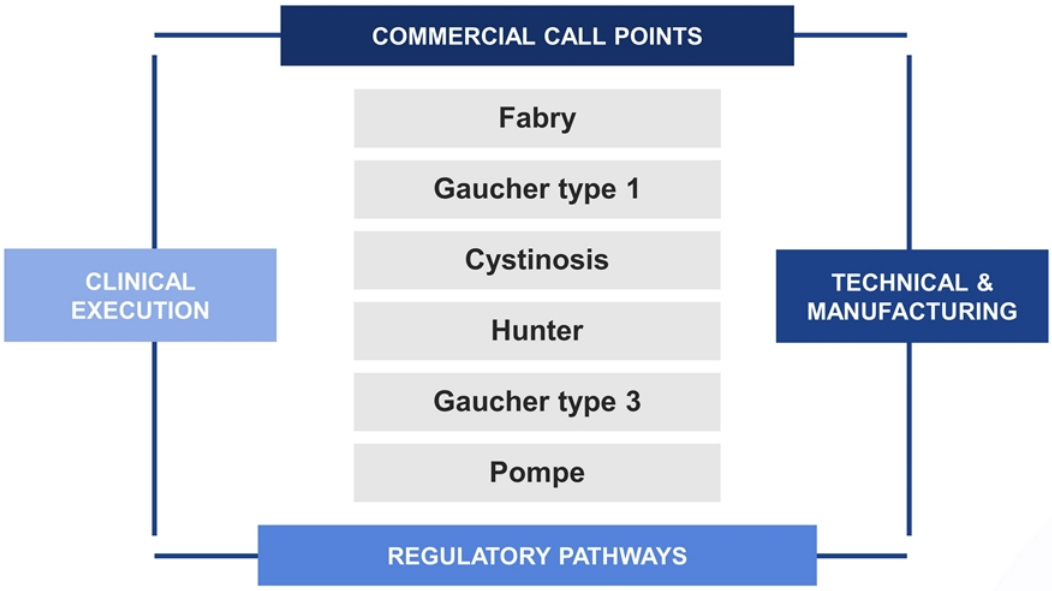
*IND: Investigational New Drug*

# ‘Halo effect’ driven by strong pipeline synergies

**Replicable path to market**

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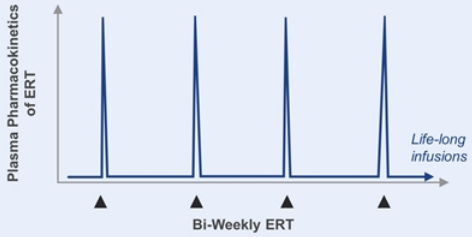
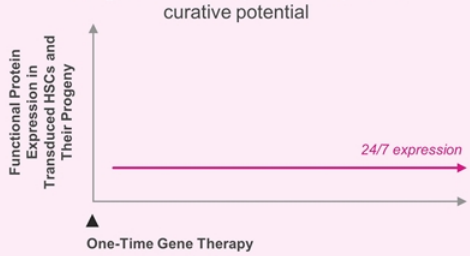
# Multi-billion dollar market opportunity

**Targeting rare lysosomal disorders with annual sales of ~$4.6 billion**

| Disease | Approx. 2019 Global Net Sales† | Five-Year SOC Cost per U.S. Patient* | Selected Companies w/ Marketed Therapies |
|---|---|---|---|
| Fabry | $1.4B | $1.7M | Sanofi Genzyme, Takeda/Shire |
| Cystinosis | $0.2B | $4.3M | Horizon‡ |
| Gaucher | $1.4B | $2.3M | Sanofi Genzyme, Takeda/Shire |
| Hunter | $0.6B | $2.4M | Takeda/Shire |
| Pompe | $1.0B | $3.2M | Sanofi Genzyme |
| | ***Total: $4.6B*** | | |

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

# Lifelong treatments vs. potential single-dose therapy

| | DISEASE PROGRESSION CONTINUES | COULD HALT, PREVENT OR REVERSE DISEASE |
|---|---|---|
| | **Enzyme Replacement Therapy (ERT)**<br>Temporary bolus of enzyme, not curative<br>  <br> | **AVROBIO Gene Therapy**<br>Designed for 24/7 expression of protein, curative potential<br>  <br> |
| **Enzyme or protein level** | Transient, intermittent elevation | Long-term, continuous elevation |
| **Treatment burden** | Bi-weekly IV infusions | Single IV infusion |
| **Ability to impact CNS** | No | Yes |

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

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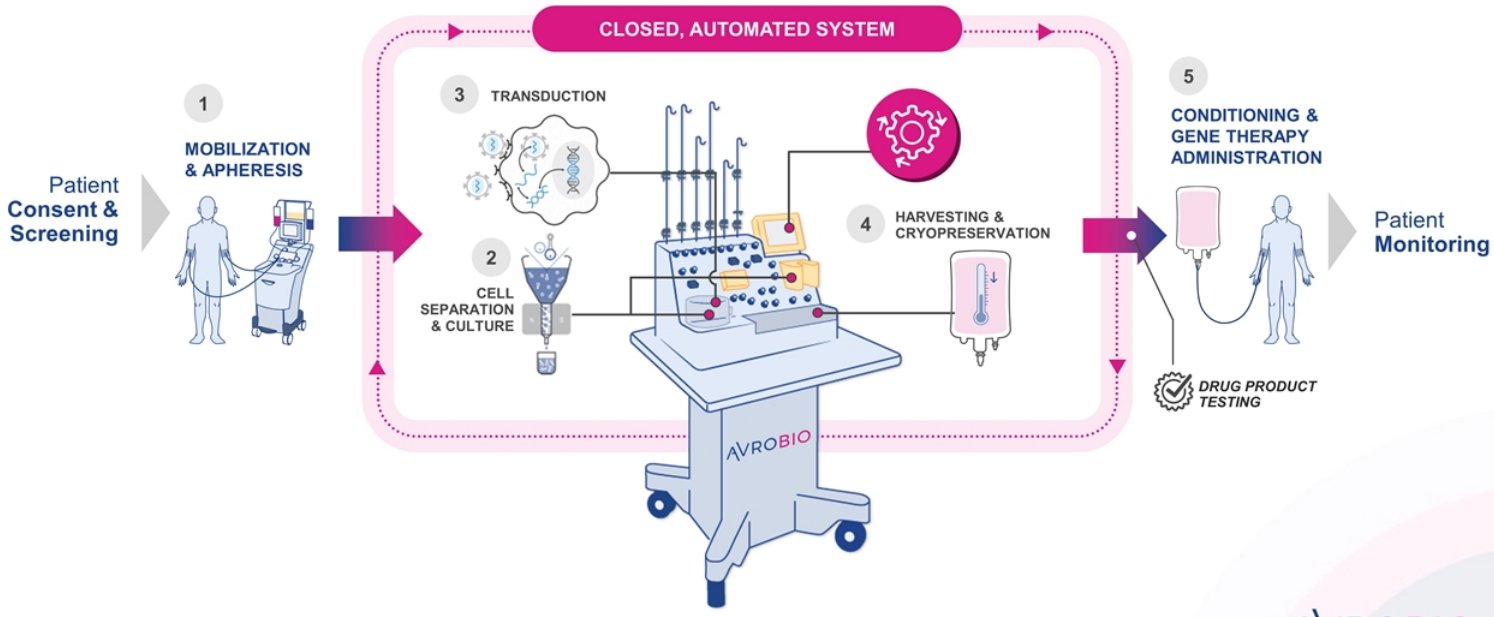
# Unrivaled commercial-scale platform in plato®

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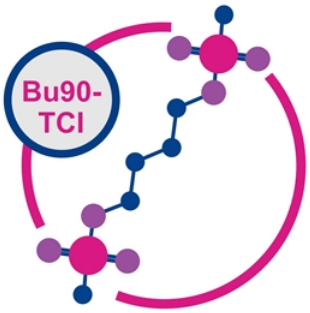
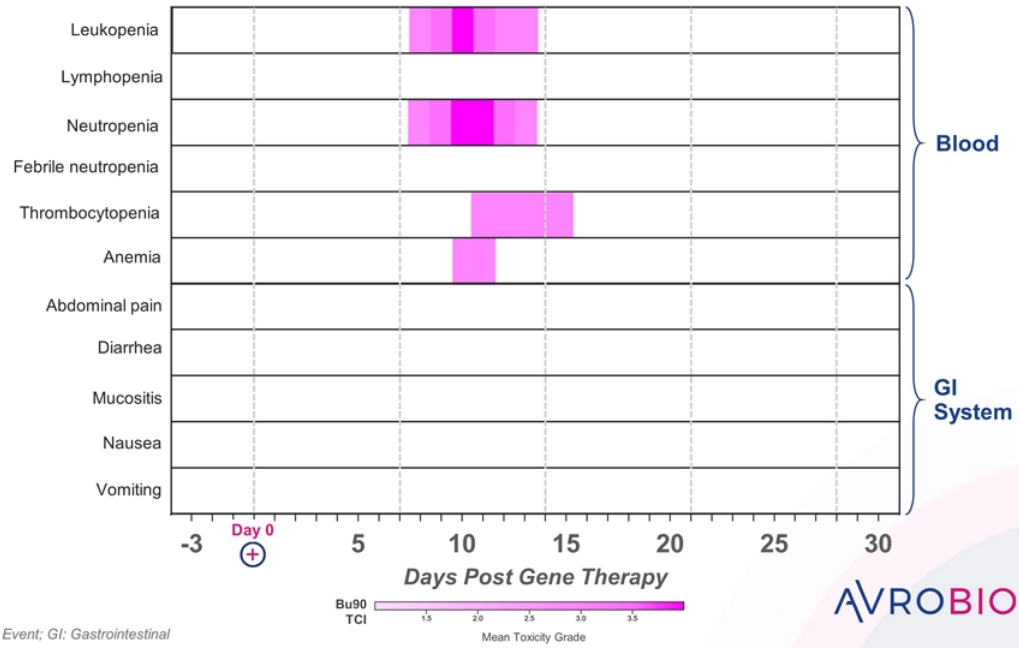
# Emerging tolerability profile has been predictable and manageable

## Conditioning-related grade 3-4 AEs were transient in first 2 plato® patients




**Busulfan 90 Target Concentration Intervention (TCI)**

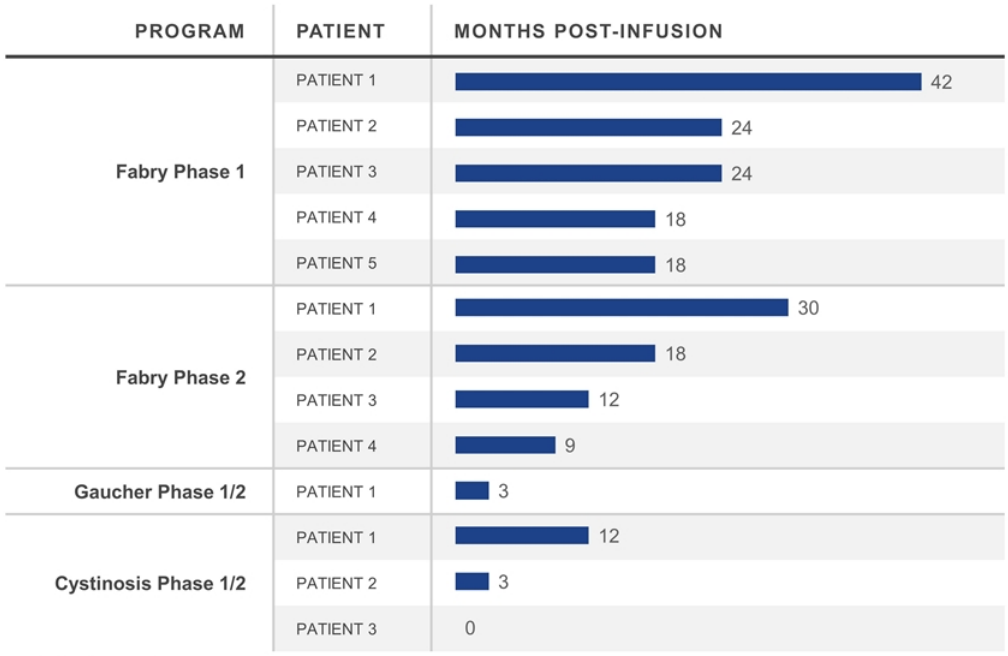
*Observations to-date show short-term side effects start ~1 week after infusion, peak over the next 3-5 days and subside*




*Bu90-TCI: Busulfan 90-Target Concentration Intervention; AE: Adverse Event; GI: Gastrointestinal*

# Durability across programs

**9 patients out 1 year or more; first patient out 3.5 years**




*Note: Based on data cut-off date of Nov. 12, 2020*

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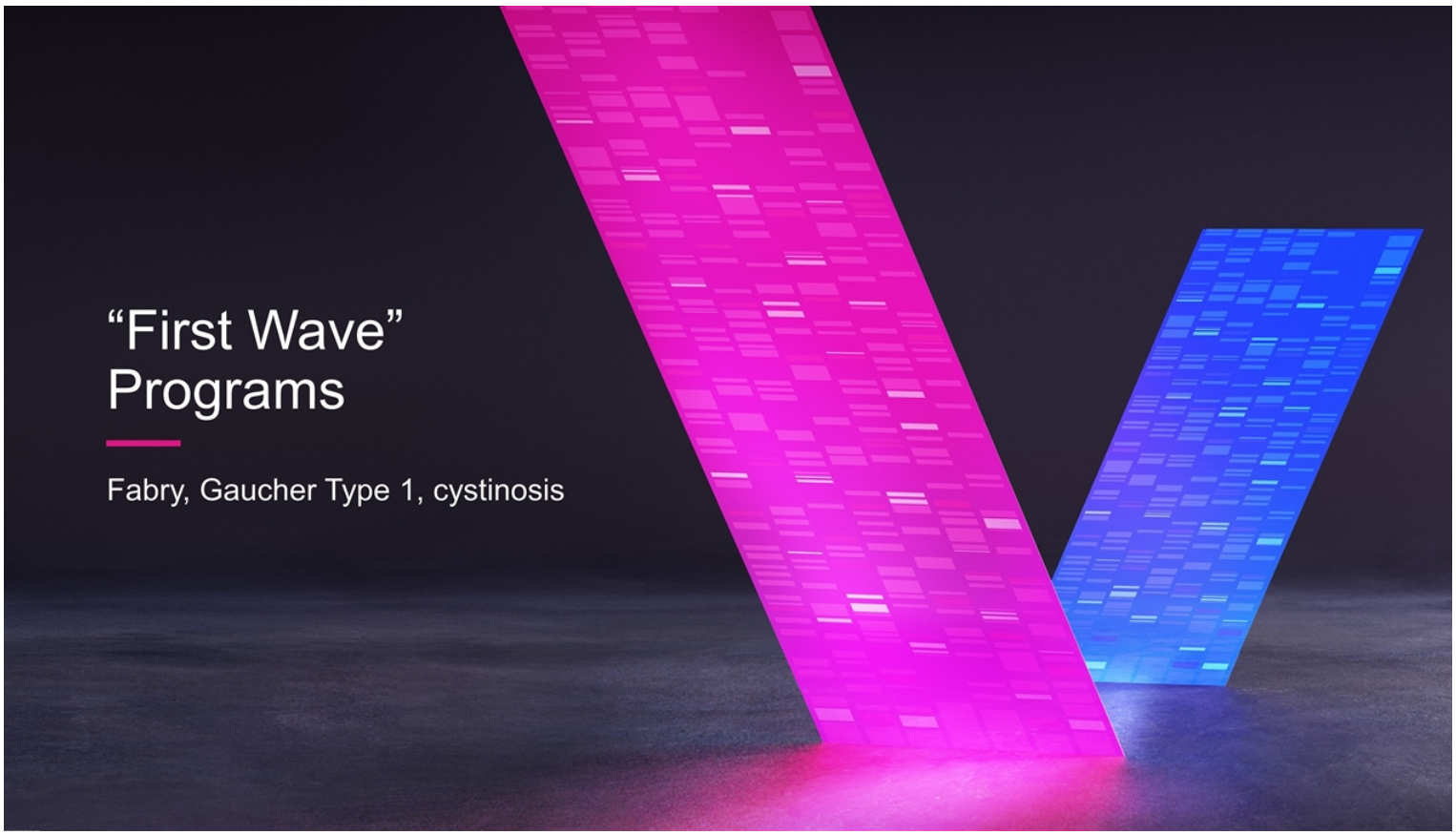
“First Wave”
Programs
Fabry, Gaucher Type 1, cystinosis

# Fabry disease opportunity

**Travis,** living with Fabry disease

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

## Standard of care (SOC): ERT

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

## Unmet needs with SOC:

**Kidney function**
Proteinuria, polyuria, kidney failure

**Cardiac function**
Left ventricular hypertrophy, fibrosis, heart failure

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

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

**CNS complications**
TIA/stroke, depression, mild cognitive deficiency, white matter hyperintensities

## Fabry Disease Target Product Profile:

- Prevents, halts or reverses disease; normalizes lifespan
- Addresses all patient segments – all genetic mutations, male and female, all ages
- Lifelong durability – single infusion; off ERT
- Impacts hard-to-reach organs – e.g., brain, heart, kidney
- Well tolerated – no ERT/chaperone therapy-related side effects

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

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** WAC pricing from Redbook using standard dosing assumptions*

# 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

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

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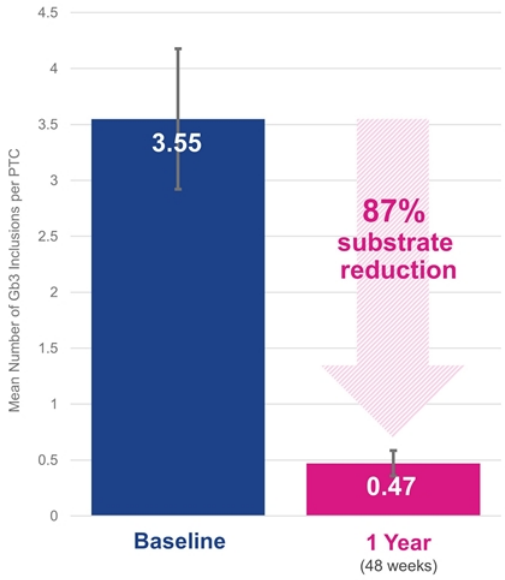
# Substantial reduction of substrate in kidney biopsy at 1 year

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*

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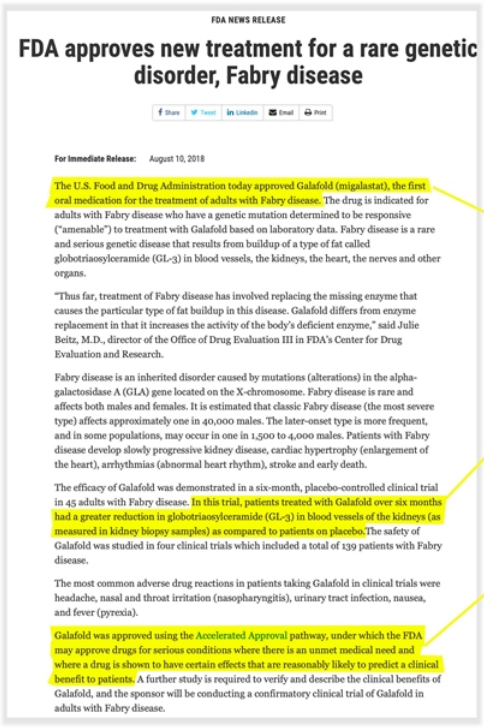
# Precedent for use of kidney biopsy data for FDA approval of drug candidate for Fabry disease



FDA NEWS RELEASE

**FDA approves new treatment for a rare genetic disorder, Fabry disease**

Share Tweet LinkedIn Email Print

**For Immediate Release:** August 10, 2018

The U.S. Food and Drug Administration today approved Galafold (migalastat), the first oral medication for the treatment of adults with Fabry disease. The drug is indicated for adults with Fabry disease who have a genetic mutation determined to be responsive ("amenable") to treatment with Galafold based on laboratory data. Fabry disease is a rare and serious genetic disease that results from buildup of a type of fat called globotriaosylceramide (GL-3) in blood vessels, the kidneys, the heart, the nerves and other organs.

"Thus far, treatment of Fabry disease has involved replacing the missing enzyme that causes the particular type of fat buildup in this disease. Galafold differs from enzyme replacement in that it increases the activity of the body's deficient enzyme," said Julie Beitz, M.D., director of the Office of Drug Evaluation III in FDA's Center for Drug Evaluation and Research.

Fabry disease is an inherited disorder caused by mutations (alterations) in the alpha-galactosidase A (GLA) gene located on the X-chromosome. Fabry disease is rare and affects both males and females. It is estimated that classic Fabry disease (the most severe type) affects approximately one in 40,000 males. The later-onset type is more frequent, and in some populations, may occur in one in 1,500 to 4,000 males. Patients with Fabry disease develop slowly progressive kidney disease, cardiac hypertrophy (enlargement of the heart), arrhythmias (abnormal heart rhythm), stroke and early death.

The efficacy of Galafold was demonstrated in a six-month, placebo-controlled clinical trial in 45 adults with Fabry disease. In this trial, patients treated with Galafold over six months had a greater reduction in globotriaosylceramide (GL-3) in blood vessels of the kidneys (as measured in kidney biopsy samples) as compared to patients on placebo. The safety of Galafold was studied in four clinical trials which included a total of 139 patients with Fabry disease.

The most common adverse drug reactions in patients taking Galafold in clinical trials were headache, nasal and throat irritation (nasopharyngitis), urinary tract infection, nausea, and fever (pyrexia).

Galafold was approved using the Accelerated Approval pathway, under which the FDA may approve drugs for serious conditions where there is an unmet medical need and where a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit to patients. A further study is required to verify and describe the clinical benefits of Galafold, and the sponsor will be conducting a confirmatory clinical trial of Galafold in adults with Fabry disease.

"The U.S. Food and Drug Administration today approved Galafold (migalastat), the first oral medication for the treatment of adults with Fabry disease."

"In this trial, patients treated with Galafold over six months had a greater reduction in globotriaosylceramide (GL-3) in blood vessels of the kidneys (as measured in kidney biopsy samples) as compared to patients on placebo."

"Galafold was approved using the Accelerated Approval pathway, under which the FDA may approve drugs for serious conditions where there is an unmet medical need and where a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit to patients."

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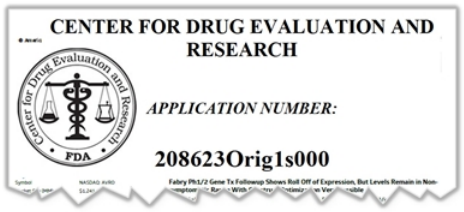
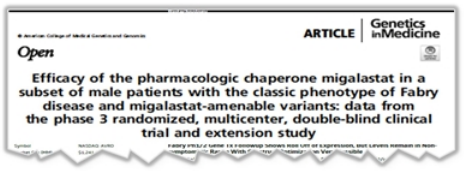


CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

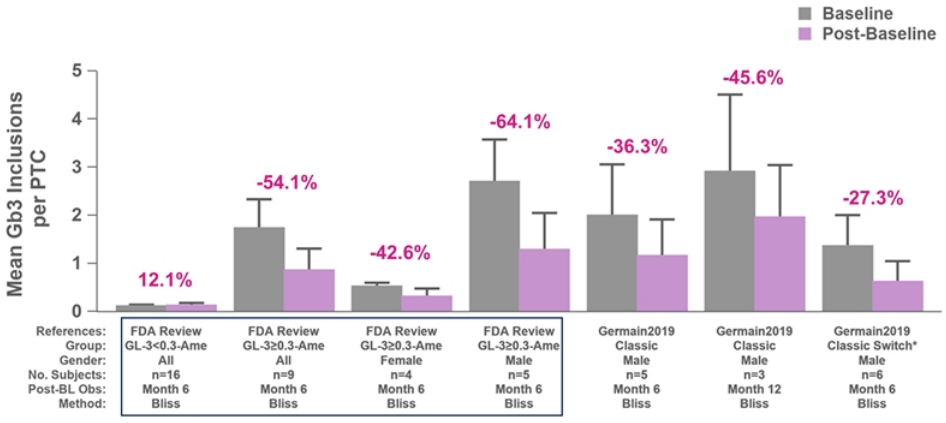
208623Orig1s000



ARTICLE | Genetics inMedicine

*Open*

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




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

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

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

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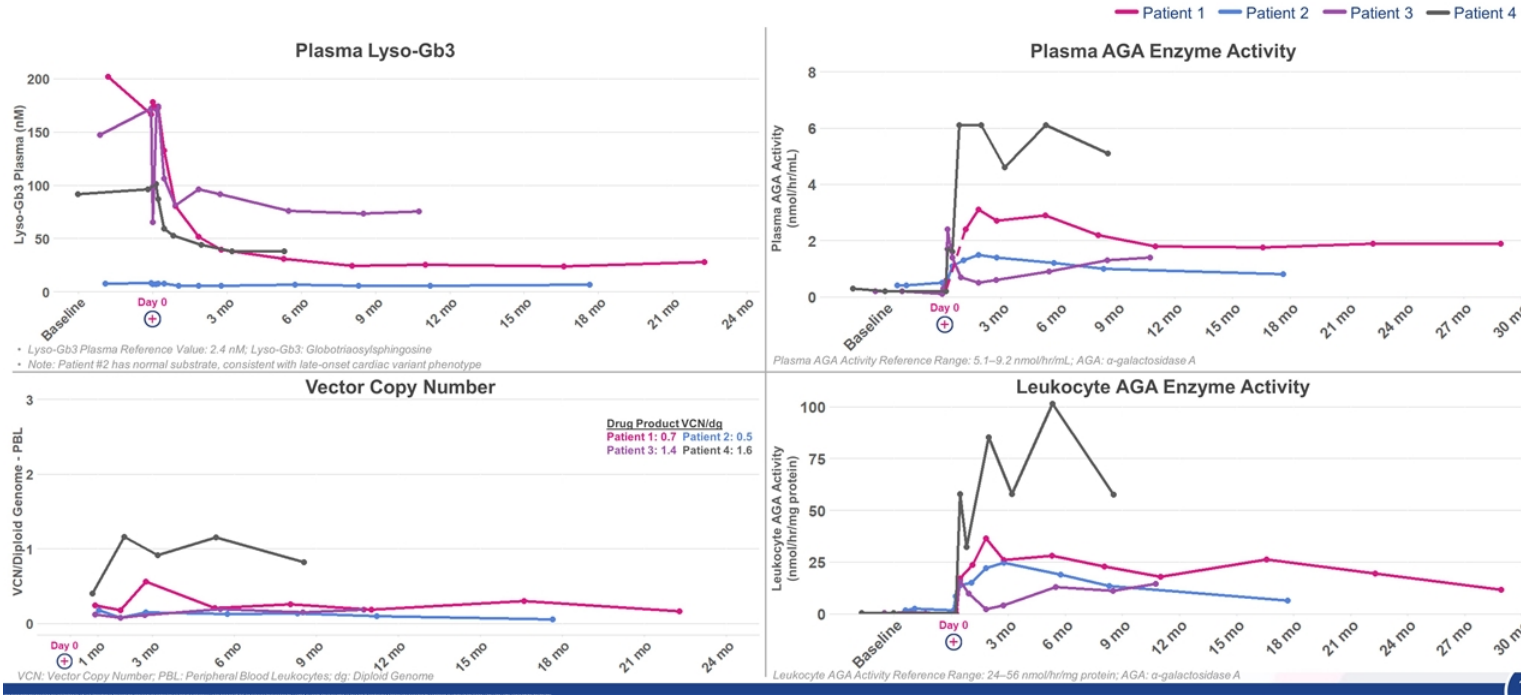
*Sources: Galafold (Migalastat), Multi-Discipline FDA Review; Germain 2019, Genet Med* 21, 1987–1997 (2019)

FABRY PHASE 2

# Sustained trends over multiple measures up to 2.5 years

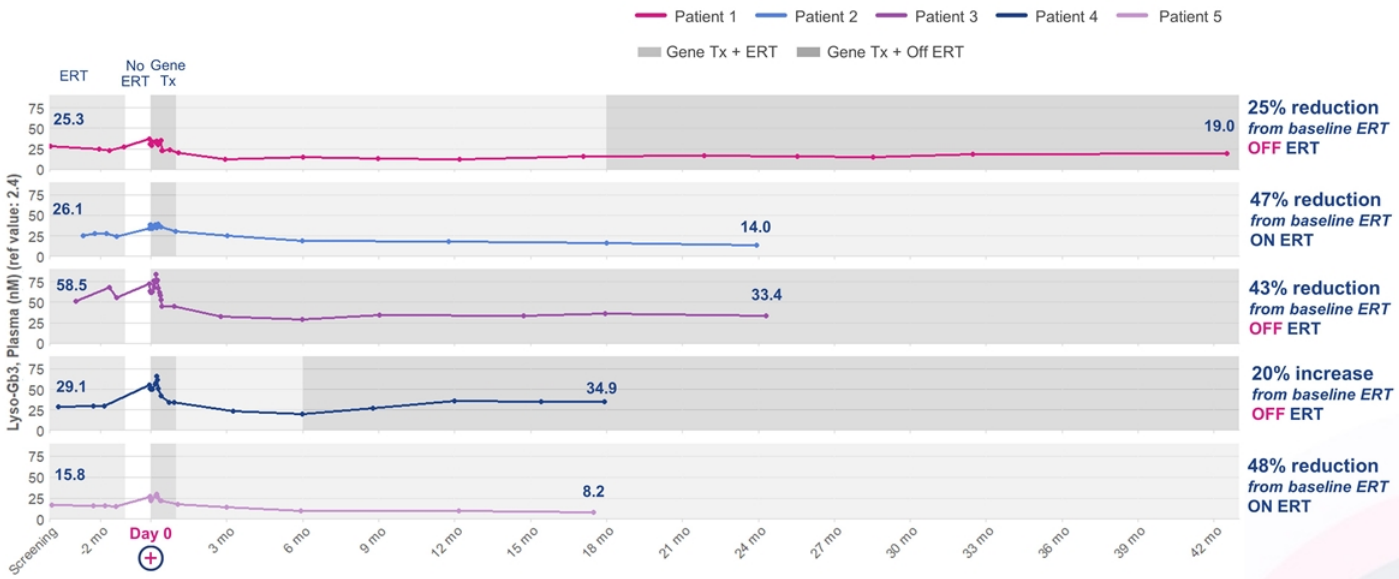
## Patient 4 dosed using plato®



FABRY PHASE 1

# 29% average lyso-Gb3 reduction below baseline ERT

## All patients who have discontinued ERT remain off ERT*




**25% reduction** *from baseline ERT* **OFF ERT**

**47% reduction** *from baseline ERT* **ON ERT**

**43% reduction** *from baseline ERT* **OFF ERT**

**20% increase** *from baseline ERT* **OFF ERT**

**48% reduction** *from baseline ERT* **ON ERT**

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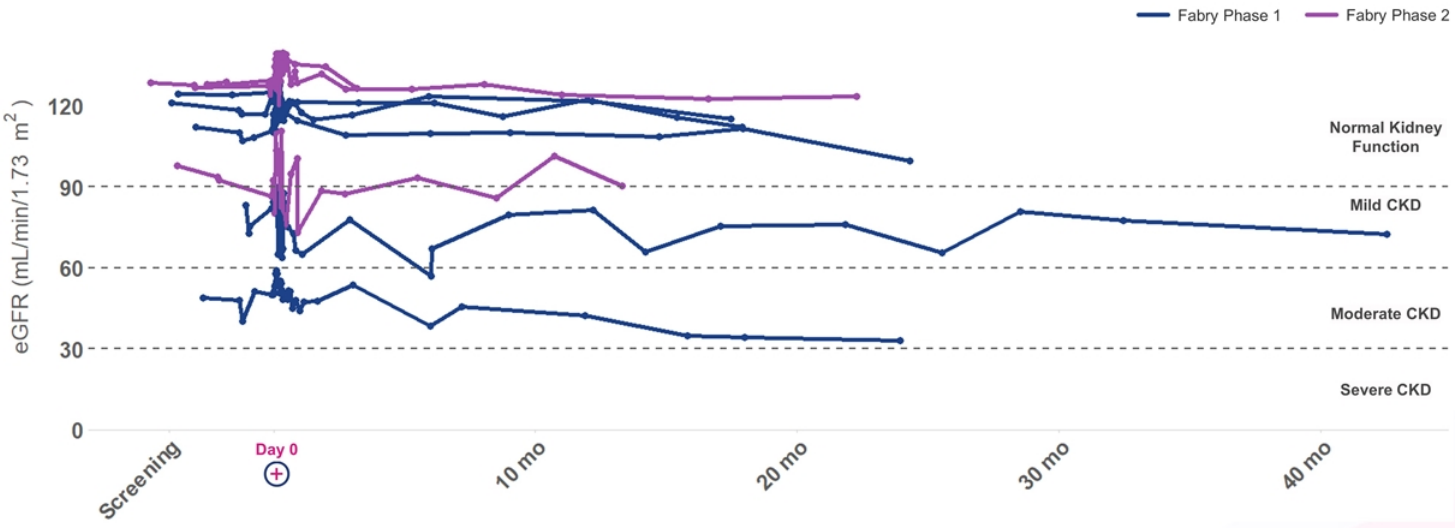
** As of October 26, 2020*

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

# Kidney function (eGFR) stable up to 3.5 years*




** Eight of nine patients stable; other patient entered trial with more advanced kidney disease and a baseline eGFR level <50 mL/min/1.73m².*
*As expected, this patient has not stabilized, and the patient remains on ERT*
*Note: eGFR was calculated using the CKD-EPI formula*
*eGFR: Estimated Glomerular Filtration Rate; CKD: Chronic Kidney Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration*

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# No unexpected safety events or trends identified

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

## Anti-AGA antibodies

- Anti-AGA antibody titers observed in 4 patients in the Phase 1 trial and 2 patients in FAB-201. We believe none of these are of clinical significance

## AEs and SAEs reported

**Phase 1 AEs** (n=101)

- Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
  - Grade 3 or 4 (n=17)

**Phase 1 SAEs** (n=2)

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

**FAB 201 AEs** (n=111)

- Generally consistent with myeloablative conditioning, underlying disease or pre-existing conditions
  - Grade 3 or 4 (n=22)

**FAB 201 SAEs** (n=6)

**Pre-AVR-RD-01 treatment and prior to conditioning**

- Seizure (grade 2)

**Post-AVR-RD-01 treatment**

- Dehydration, nausea, vomiting (grade 3)
- Febrile neutropenia (2 patients, grade 3 & 4)
- Culture negative fevers (grade 2)
- Mucositis (grade 2)

*Note: Safety data cut off October 8, 2020; AVR-RD-01 is an investigational gene therapy*
*AE: Adverse Event; SAE: Serious Adverse Event; AGA: Aspartylglucosaminidase*

AVROBIO

# Planned global regulatory strategy for Fabry disease

**Planned ERT-switch**

**CONFIRMATORY TRIAL**

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

**Phase 2 Partially Enrolled ERT-naïve**

**EXPANDED FOR POTENTIAL ACCELERATED APPROVAL**

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

**Fully Enrolled ERT-switch**

**PHASE 1 – INVESTIGATOR SPONSORED TRIAL**

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

## Anticipated Next Steps:

- Present new data, including second kidney biopsy, at World*Symposium* Q1 '21
- Discuss accelerated approval approach with FDA by Q1 '21
- Expand Phase 2 study and complete enrollment
- Initiate confirmatory ERT-switch trial activities in 2021
- Seek early FDA agreement on potency assay matrix
- Advance commercial readiness activities including payors / HTA interactions

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

# Cystinosis opportunity

**Jaxson,** living with cystinosis

***Caused by CTNS gene defect, resulting in cystine build up in lysosomes***

## Standard of care (SOC): Cysteamine oral & eye drops

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

## Unmet needs with SOC:

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

**Vision**
Corneal cystine accumulation, photophobia, involuntary eyelid closure

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

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

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

## Cystinosis Target Product Profile:

- Prevents, halts or reverses disease; normalizes lifespan
- Addresses all patient segments – male & female; kidney transplant independent; all ages
- Lifelong durability – single infusion; off cysteamine oral and eye drops
- Impacts hard-to-reach organs – e.g., eye, endocrine organs, brain
- Well tolerated – no cysteamine-related side effects

**Affects ~ 1:170,000 people**

AVROBIO

** WAC pricing from Redbook using standard dosing assumptions*

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

**3 patients dosed to date**

## PHASE 1/2

AVR-RD-04

**ACTIVELY RECRUITING:**

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

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

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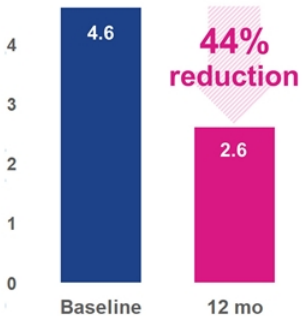
CYSTINOSIS PHASE 1/2: PATIENT 1

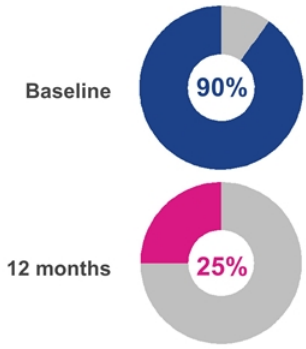
# Sharp drop in the number and size of cystine crystals in skin and rectal biopsies

## Skin Biopsy

### Average intracytoplasmic crystals per cell

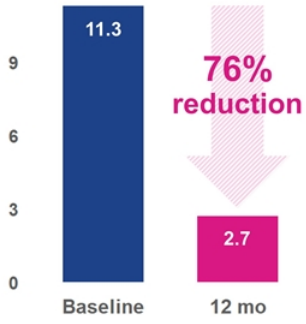



### Occupancy of cytoplasmic volume

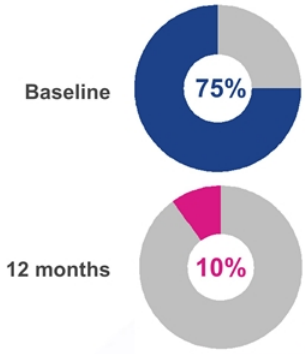



## Rectal Biopsy

### Average intracytoplasmic crystals per cell




### Occupancy of cytoplasmic volume

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

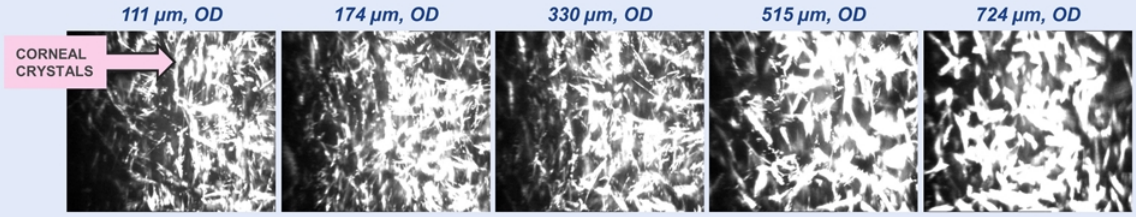
CYSTINOSIS PHASE 1/2: PATIENT 1

# Substantial decline in corneal crystals observed at 1 year

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

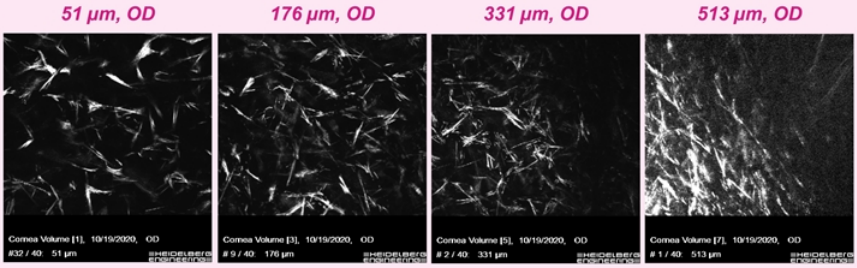
## Baseline

**IVCM images from Nidek Confoscan**




## 12 months post-gene therapy

**IVCM images from Heidelberg HRT3 w/ Rostock Corneal Module**




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

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CYSTINOSIS PHASE 1/2: PATIENT 1

# First patient remains off cysteamine and eye drops at 1 year

## Daily cysteamine regimen

*(max per day)*

| | *ON* cysteamine | *ON* cysteamine eye drops |
|---|---|---|
| **Before AVR-RD-04** | **30 pills / day**  | **Prescribed 8 drops / day**  |
| **After AVR-RD-04** (1 year post-gene therapy) | *OFF* cysteamine **0 pills / day** | *OFF* cysteamine eye drops **0 drops / day** |

*Note: These results are for a single patient only and may vary in the study population; Investigational gene therapy; Does not include supplements and other medications*

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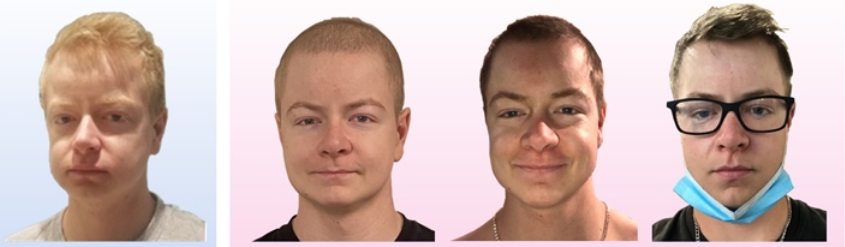
# Darker pigmentation may be a sign of the fully multi-functional cystinosin protein

- *In vitro* studies show that cystinosin is located in melanosomes, and regulates melanin synthesis
- Due to reduced melanin content, patients typically have blond hair and pale skin
- Protocol amended to assess the impact on melanin synthesis and turnover

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




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

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# No unexpected safety events or trends related to AVR-RD-04 identified in first two patients

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

## AEs reported

- n=29 for subject 1 (12 mo. observation period), n=16 for subject 2 (3 mo. observation period)
- Majority of AEs are mild or moderate and resolved
  - 1 severe AE of appendicitis unrelated to study treatment or procedures
- AEs are generally consistent with myeloablative conditioning or underlying disease:

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

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

*Note: Safety database cut Nov 2, 2020 (patients 1 and 2)*
*AE: Adverse Event; SAE: Serious Adverse Event*

# Planned global regulatory strategy for cystinosis

**Planned**

**POTENTIAL REGISTRATION**

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

**50% Enrolled**

**PHASE 1/2 – INVESTIGATOR SPONSORED TRIAL**

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

## Anticipated Next Steps:

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

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

# Gaucher disease type 1 opportunity

**Adrianna,** living with Gaucher disease type 1

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

## Standard of care (SOC): ERT

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

## Unmet needs with SOC:

**Bone-related manifestations**
Skeletal abnormalities, avascular necrosis, osteoporosis

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

**Hepatosplenomegaly**
Enlarged liver, enlarged spleen

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

**CNS complications**
Increased risk of GBA-Parkinson's disease

## Gaucher Disease Type 1 Target Product Profile:

- Prevents, halts or reverses disease; normalizes lifespan
- Addresses all patient segments – all GD1 genetic mutations, all ages, male & female
- Lifelong durability – single infusion; off ERT/chaperone therapy
- Impacts hard-to-reach organs – e.g., brain, bone and bone marrow
- Well tolerated – no ERT/SRT-related side effects

**Affects ~ 1:44,000 people worldwide**

** WAC pricing from Redbook using standard dosing assumptions*

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

**1 patient dosed to date**

## PHASE 1/2

AVR-RD-02

An **adaptive, open-label, multinational phase 1/2 study of the safety and efficacy** of *ex vivo*, lentiviral vector-mediated gene therapy AVR-RD-02 for patients with Gaucher disease type 1.

**ACTIVELY RECRUITING:**

**RECRUITING PLANNED 1H '21:**

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

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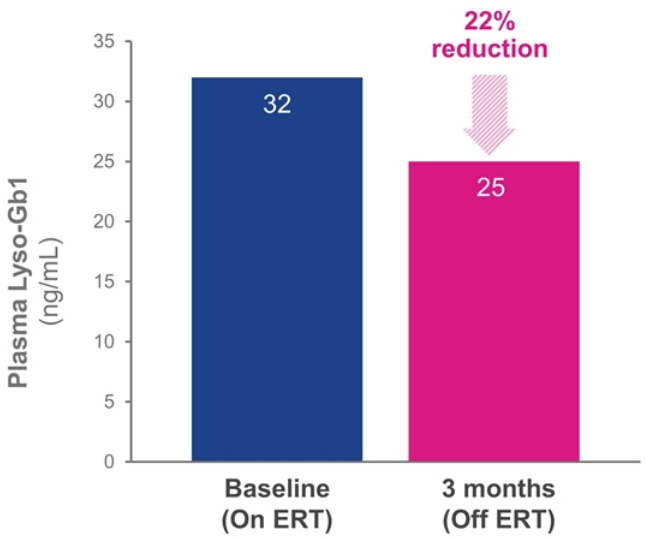
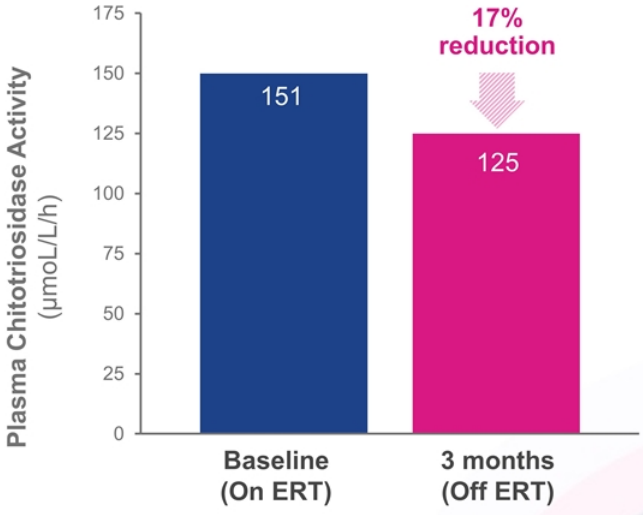
*GD1: Gaucher Disease Type 1; ERT: Enzyme Replacement Therapy; SRT: Substrate Reduction Therapy; 1H: First Half*

# Key biomarkers below ERT levels at 3 months

**Lyso-Gb1**, a sensitive and specific marker of metabolite accumulation in Gaucher disease is decreased relative to baseline on ERT




**Chitotriosidase,** a marker of activated macrophages (Gaucher cells), is also decreased




*Lyso-Gb1 Plasma Normal Range: 0.5 – 1.2 ng/mL*
*Chitotriosidase Plasma Activity Normal Range: 0.0–44.2 µmoL/L/*
*ERT: Enzyme Replacement Therapy; Lyso-Gb1: Glucosylsphingosine*

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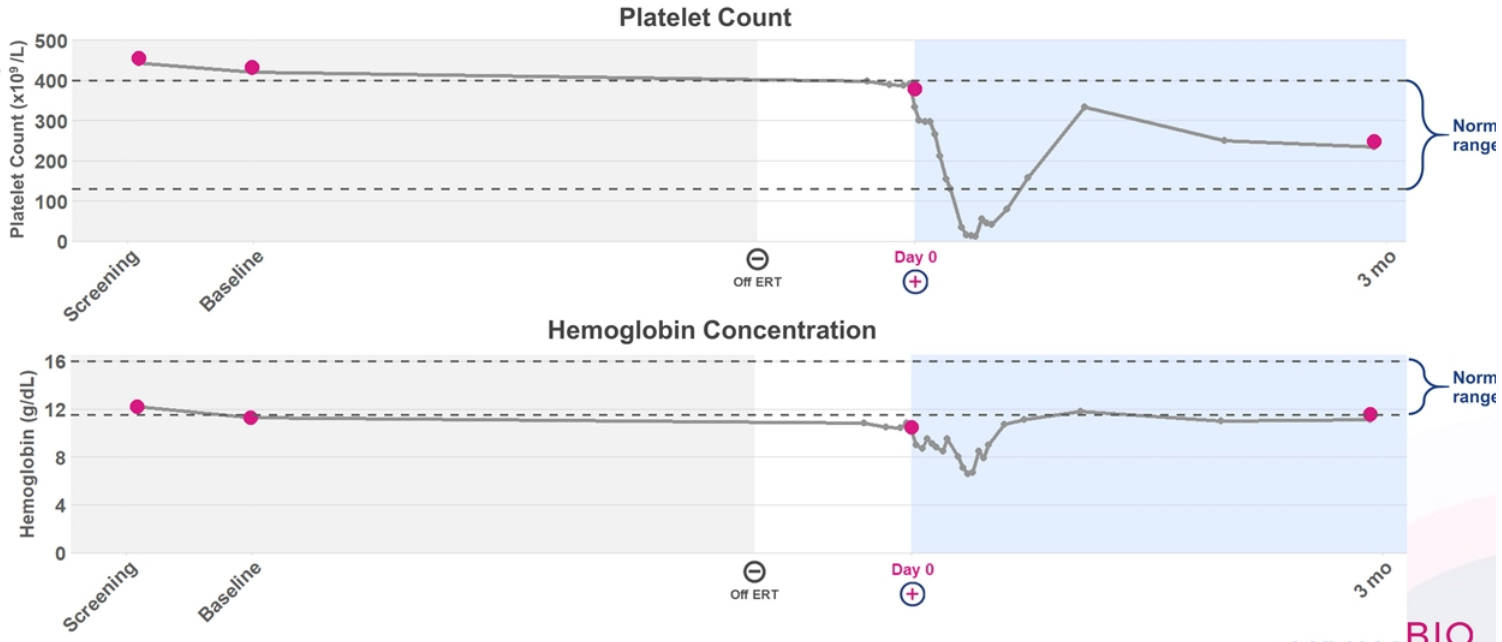
GUARD1: PATIENT 1

# Platelet counts and hemoglobin in normal range at 3 months, despite being off ERT







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

# No unexpected safety events or trends identified

**No SAEs or AEs related to AVR-RD-02 drug product**

**No SAEs reported**

## AEs reported

- n=26 (3-month observation period)
- Majority of AEs are mild or moderate
  - 8 grade 3 and 1 grade 4 AEs: 5 definitely or possibly related to busulfan, 1 definitely related to G-CSF, 1 (eye pain) with unknown relatedness, and 1 unrelated
- AEs are generally consistent with myeloablative conditioning or underlying disease:

**Pre-AVR-RD-02 treatment and prior to conditioning**

- Nausea & vomiting

**Post-AVR-RD-02 treatment**

- Nausea, intermittent headache
- Mucositis, alopecia, febrile neutropenia
- Anemia, thrombocytopenia
- Increased ocular pressure

*Note: These results are for Patient 1 only and may not be representative of the total study population; Safety database cut as of Nov. 3, 2020*
*AE: Adverse Event; SAE: Serious Adverse Event; G-CSF: Granulocyte Colony Stimulating Factor*

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# Planned global development strategy for Gaucher disease type 1

**Planned**

**PHASE 1/2 EXPANSION: POTENTIAL REGISTRATION**

- Safety, efficacy, durability
- Organ volumes, hematologic measures, bone assessments, pain, and QOL

**Enrolling**

**PHASE 1/2**

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

## Anticipated Next Steps:

- Present 6-month data at World*Symposium* Q1 ’21
- Advance patient enrollment
- Advance regulatory dialogue on registration pathway

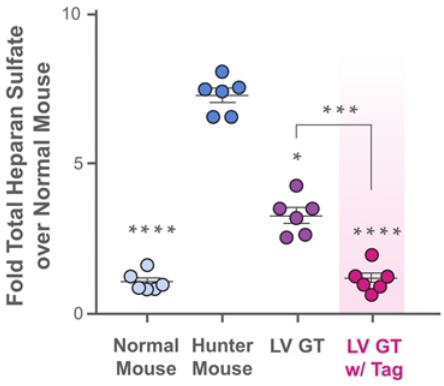
*QOL: Quality Of Life; ERT: Enzyme Replacement Therapy*


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

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

**Hunter syndrome**

Tag normalizes heparan sulfate in brain




**Pompe disease**

Tag normalizes glycogen substrate in brain

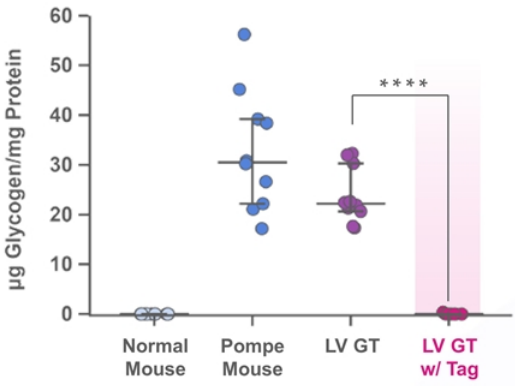



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*Figure adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 3A; *P<0.05, ***P<0.001, ****P<0.0001; LV GT: Lentiviral Gene Therapy*

# Hunter syndrome opportunity

**Danny,** living with Hunter syndrome

***Caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase (IDS)***

## Standard of care (SOC): ERT

- Not curative, significantly reduced lifespan; ERT not able to penetrate the blood-brain barrier
- Burdensome and expensive – weekly infusions required; 5-year ERT treatment cost = ~$2.4 million*

## Unmet needs with SOC:

**Neurological complications**
Cognitive deficits, seizures or behavior changes

**Skeletal and connective tissue issues**
Deformities of neck, face, teeth and skin; joint stiffness (movement)

**Respiratory and cardiac system impacts**
Chronic infections, respiratory distress, cardiac valve disease

**Everyday burden of illness and life expectancy**
Impaired vision, loss of hearing, hepatosplenomegaly, inguinal hernias, weekly infusions, significantly reduced life span

## Hunter Syndrome Target Product Profile:

- Prevents, halts or reverses disease; normalizes lifespan
- Addresses all patient segments – all genetic mutations, neuropathic and non-neuropathic, all ages
- Lifelong durability – single infusion; off ERT
- Impacts hard-to-reach organs, including brain and heart
- Well tolerated – no ERT-related side effects

**Affects ~ 1:100,000 to 1:170,000 male births worldwide**

**Anticipated next steps: Dose first patient in 2H 2021**

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** WAC pricing from Redbook using standard dosing assumptions*

# Gaucher disease type 3 opportunity

**Maddie,** living with Gaucher disease Type 3

***Subacute neurological form of Gaucher disease characterized by progressive encephalopathy and associated with the systemic manifestations of Gaucher type 1***

## Standard of care (SOC): ERT

- Not curative, relentless progression of disease continues; utility of ERT minimized by its inability to impact the CNS
- Burdensome and expensive – bi-weekly infusions required; 5-year treatment cost with ERT = ~$2.3 million*

## Unmet needs with SOC:

**CNS complications**
Seizures, cognitive problems, poor coordination

**Bone-related manifestations**
Bone crises, bone pain, avascular necrosis

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

**Hepatosplenomegaly**
Enlarged liver, enlarged spleen

**Everyday burden of illness, and life expectancy**
Fatigue, pain, shortened lifespan

## Gaucher Disease Type 3 Target Product Profile:

- Prevents, halts or reverses disease; normalizes lifespan
- Addresses all patient segments – all genetic mutations, all ages, male & female
- Lifelong durability – single infusion; off ERT/SRT
- Impacts hard-to-reach organs – e.g., brain, bone and bone marrow
- Well tolerated – no ERT-related side effects

**Anticipated next steps: Dialogue with FDA about path to clinic**

AVROBIO

** WAC pricing from Redbook using standard dosing assumptions*

# Pompe disease opportunity

**Sam and Sean,** living with Pompe disease

***Caused by mutation in acid alpha-glucosidase (GAA) gene***

**Standard of care (SOC): ERT**

- Not curative, significantly reduced lifespan; ERT not able to impact hard-to-reach organs, i.e., brain and heart
- Burdensome and expensive – bi-weekly infusions required; 5-year treatment cost = ~$3.2 million*

**Unmet needs with SOC:**

**Pulmonary function**
Chronic respiratory infections, sleep apnea, artificial ventilation

**Physical endurance and strength**
Progressive muscle weakness, wheel-chair bound

**CNS complications**
Neuromuscular control, cognitive impairment

**GI complications**
Macroglossia, difficulty chewing and swallowing

**Everyday burden of illness, and life expectancy**
Biweekly infusions, shortened lifespan

**Pompe Disease Target Product Profile:**

- Prevents, halts or reverses disease; normalizes lifespan
- Addresses all patient segments – all genetic mutations (classic infantile-onset, non-classic infantile-onset, and late-onset), all ages, male & female
- Lifelong durability – single infusion; off ERT
- Impacts hard-to-reach organs – brain, spinal cord, PNS: global distribution of genetically modified microglia; skeletal and cardiac muscle
- Well tolerated – no ERT-related side effects

**Affects ~ 1:58,000 people**

**Anticipated next steps: Align with FDA on classic infantile-onset trial design**

AVROBIO

** WAC pricing from Redbook using standard dosing assumptions*

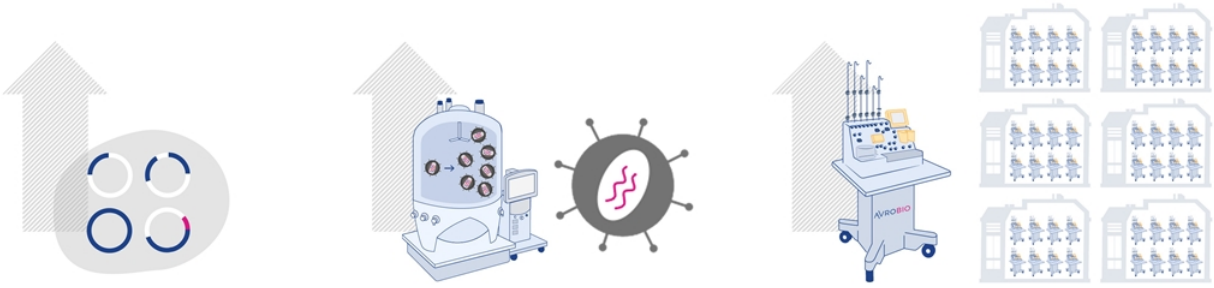
# plato®

AVROBIO's platform for global gene therapy commercialization

- Redefines manufacturing best practices
- Solves key industry challenges

# Designed to be fully scalable

## Common components and automation leveraged across manufacturing



**PLASMID**

### 3 of 4 component plasmids used in every vector

Each plasmid can be mass produced and stored for use

**VECTOR**

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

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

**DRUG PRODUCT**

### Closed system automated platform

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

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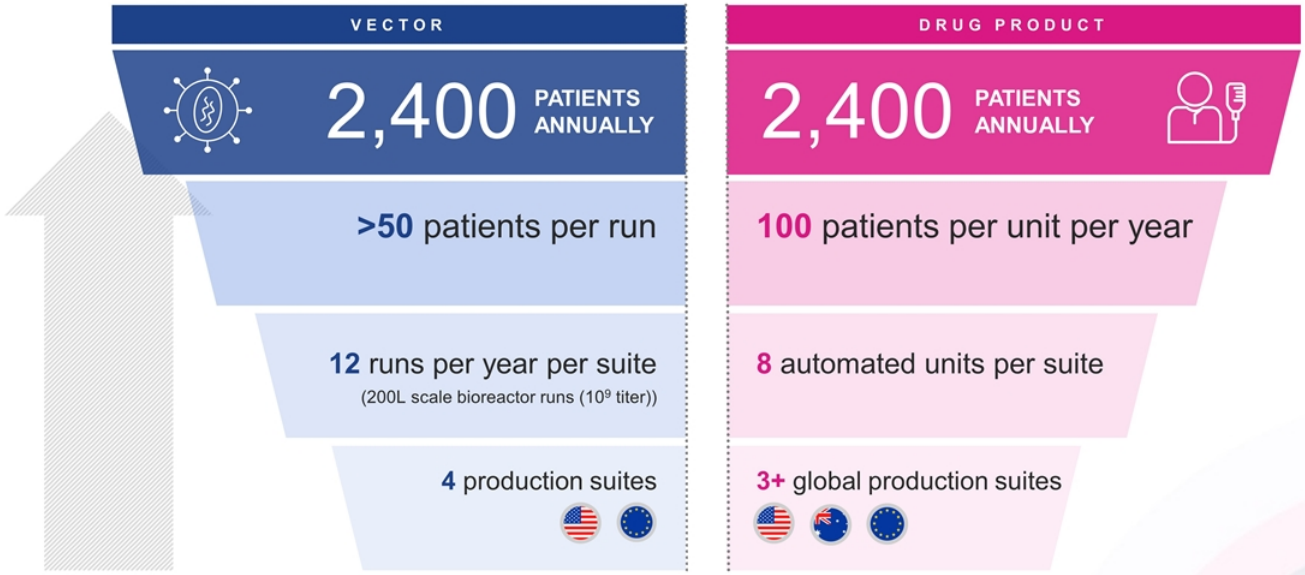
*Note: This diagram is for illustrative purposes only*

# Poised to manufacture at scale

**Global infrastructure already in place**




*Note: This diagram is for illustrative purposes only*

# CMC achievements have defined the plato® story

**Strategic investment in technology laid the foundation for our manufacturing leadership**

## Manufacturing

**Robust production platform**

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

**Global footprint**

- Cleared for the clinic from multiple agencies

**Cost effective**

- Intended to address key COGs issues

## Analytics

**Robust platform analytics**

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

**Deep product characterization**

- First-in-class single cell analytics

**Potency assay matrix**

- Intended to accelerate regulatory approvals

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

# Key anticipated 2021 milestones

**Goal:**
**30 patients dosed cumulatively by end of 2021**

| | |
|---|---|
| **Fabry**<br>AVR-RD-01 | Seek agreement with regulators on approval pathway in one or more major markets |
| **Gaucher type 1**<br>AVR-RD-02 | Execute on global phase 1/2 trial |
| **Cystinosis**<br>AVR-RD-04 | Complete phase 1/2 enrollment<br>Engage w/ FDA on pivotal trial design |
| **Hunter**<br>AVR-RD-05 | Dose first patient in 2H of 2021 |
| **Gaucher type 3**<br>AVR-RD-06 | FDA dialogue on path to clinic |
| **Pompe**<br>AVR-RD-03 | Prepare for classic infantile-onset study |

**Next planned data release: WORLD*Symposium* 2021 (week of February 8)**

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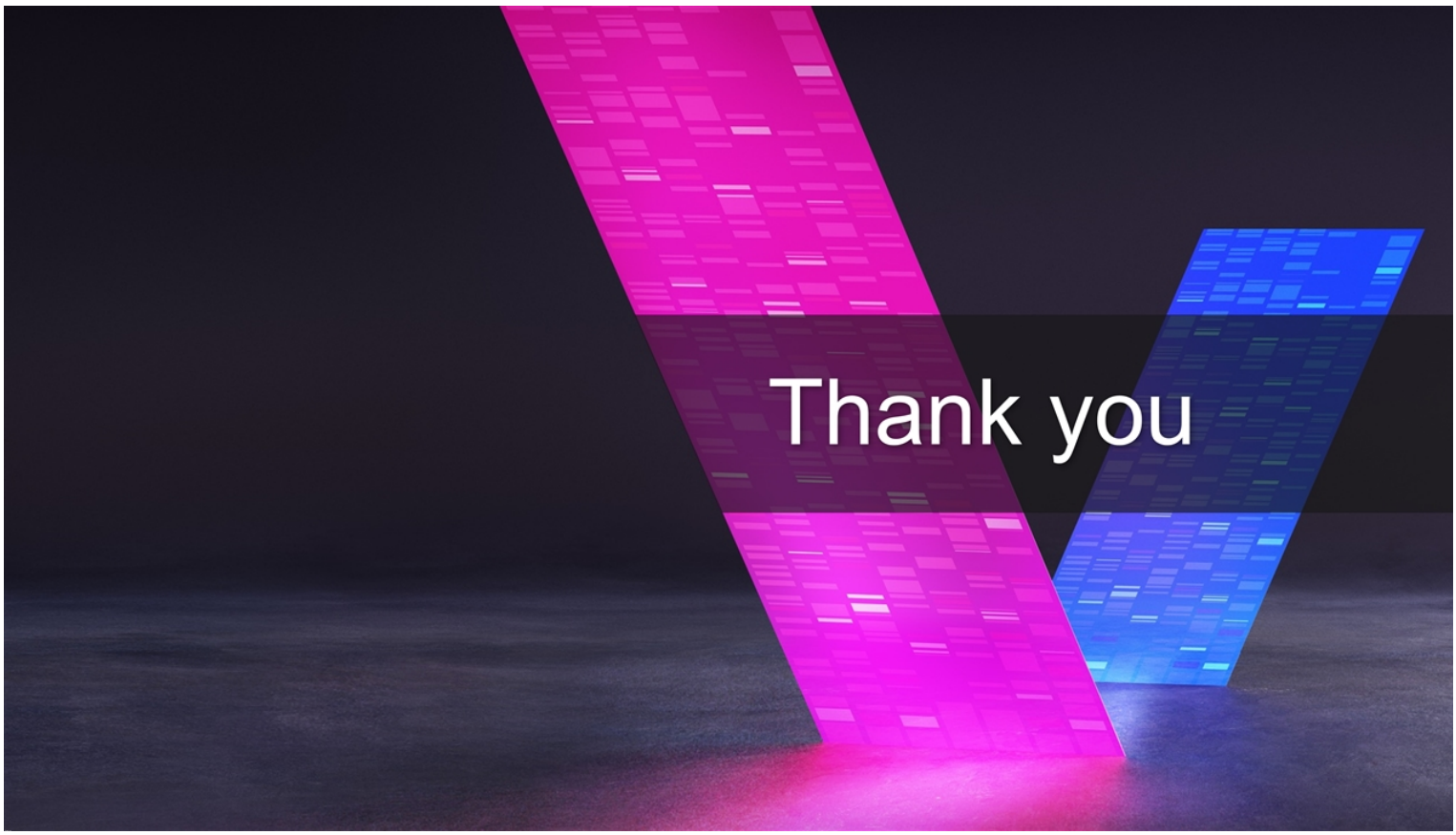
*FDA: Food and Drug Administration; 2H: Second Half*


Thank you