AVROBIO

Corporate Presentation

JANUARY 2021

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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.

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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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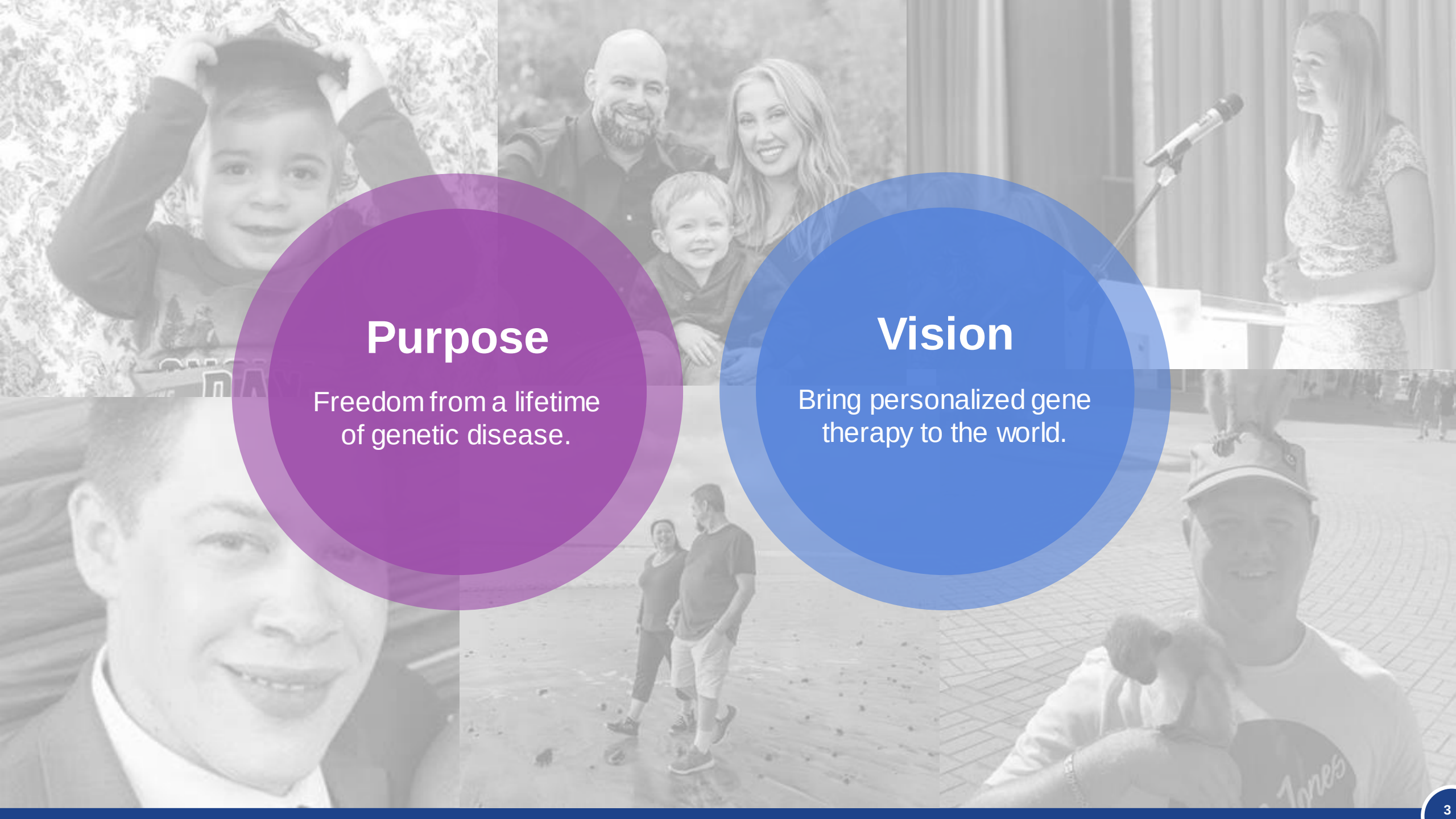

Purpose

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

Approved

- ALD
- Beta thalassemia
- MLD

Investigational

- Fanconi anemia
- Hurler syndrome
- Sanfilippo A
- Sanfilippo B
- SCID-ADA
- SCID-X
- Sickle cell disease
- Wiskott-Aldrich syndrome
- X-CGD

DURABILITY

- >12 years post-infusion

TOLERABILITY

- >350 patients
- >1,000 patient years

WIDE REACH

- Head-to-toe, including:
  - Brain
  - Muscle
  - Bone

BROAD UTILITY

- Pediatrics and adults
- All mutations
- 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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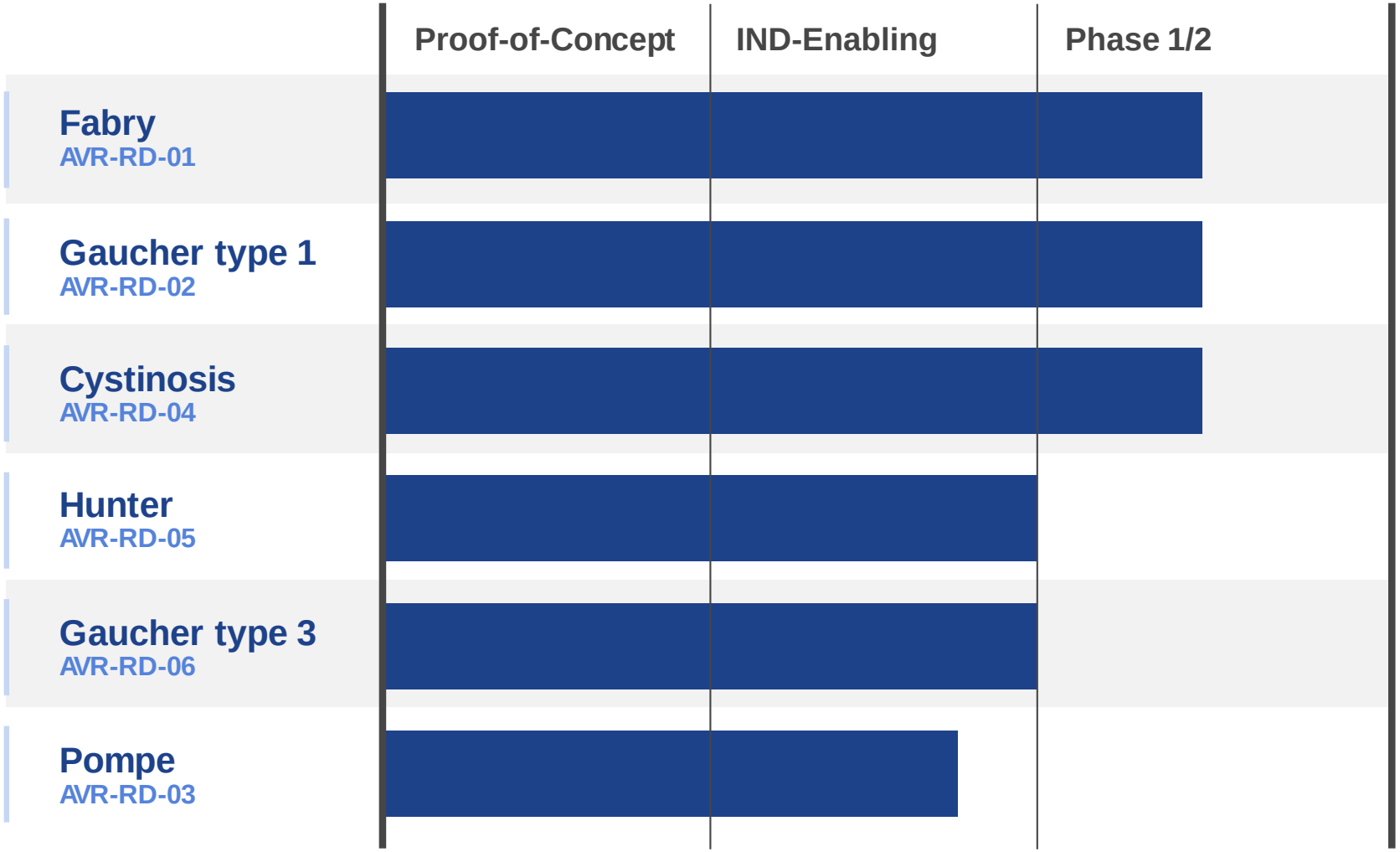
Leading lysosomal disorder gene therapy pipeline

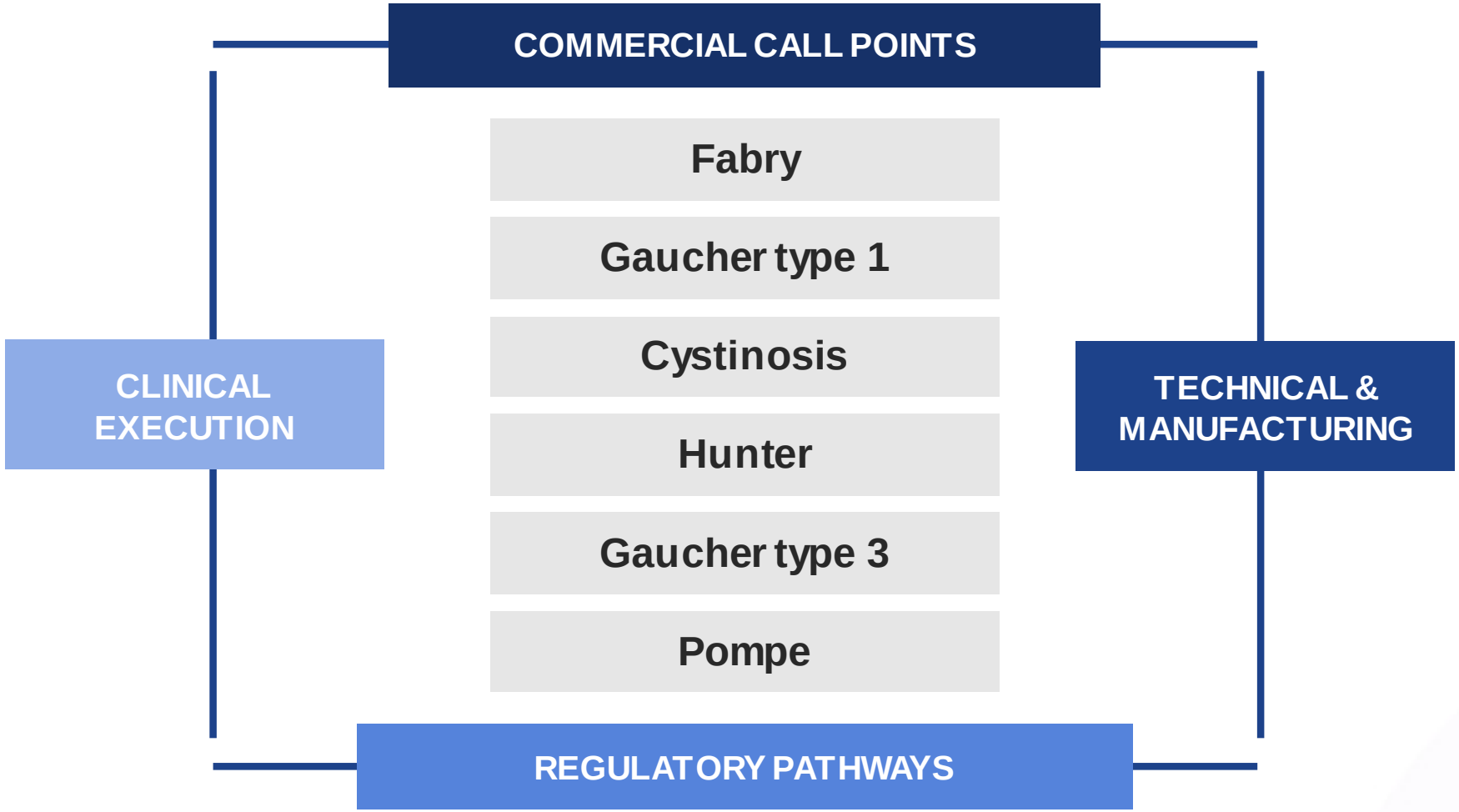
13 patients dosed to date



IND: Investigational New Drug

‘Halo effect’ driven by strong pipeline synergies

Replicable path to market



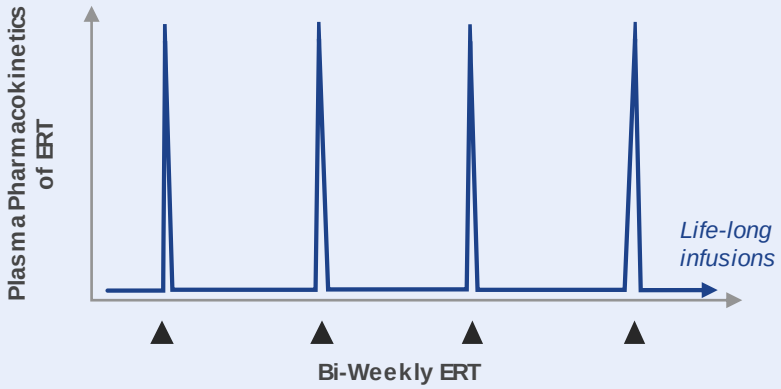
Multi-billion dollar market opportunity

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

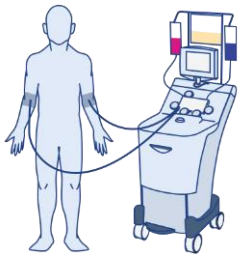
	DISEASE PROGRESSION CONTINUES	COULD HALT, PREVENT OR REVERSE DISEASE
	Enzyme Replacement Therapy (ERT) Temporary bolus of enzyme, not curative 	**AVROBIO Gene Therapy** Designed for 24/7 expression of protein, curative potential 
Enzyme or protein level	Transient, intermittent elevation	Long-term, continuous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

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

Unrivaled commercial-scale platform in plato®

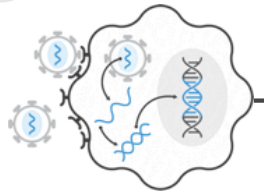
Patient **Consent & Screening**

1 **MOBILIZATION & APHERESIS**

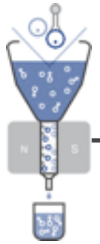


CLOSED, AUTOMATED SYSTEM

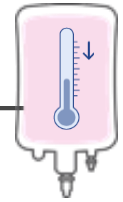
3 TRANSDUCTION

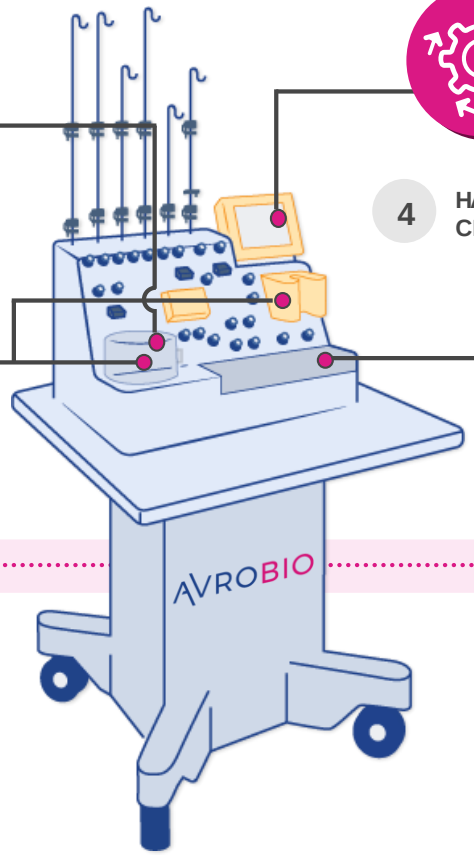


2 **CELL SEPARATION & CULTURE**

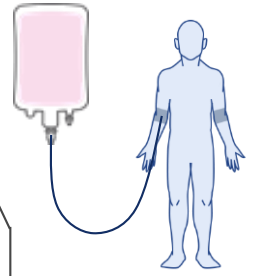


4 **HARVESTING & CRYOPRESERVATION**





5 **CONDITIONING & GENE THERAPY ADMINISTRATION**



DRUG PRODUCT TESTING

Patient **Monitoring**

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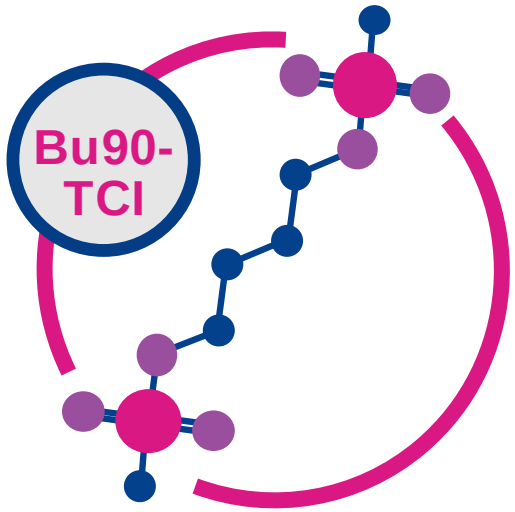
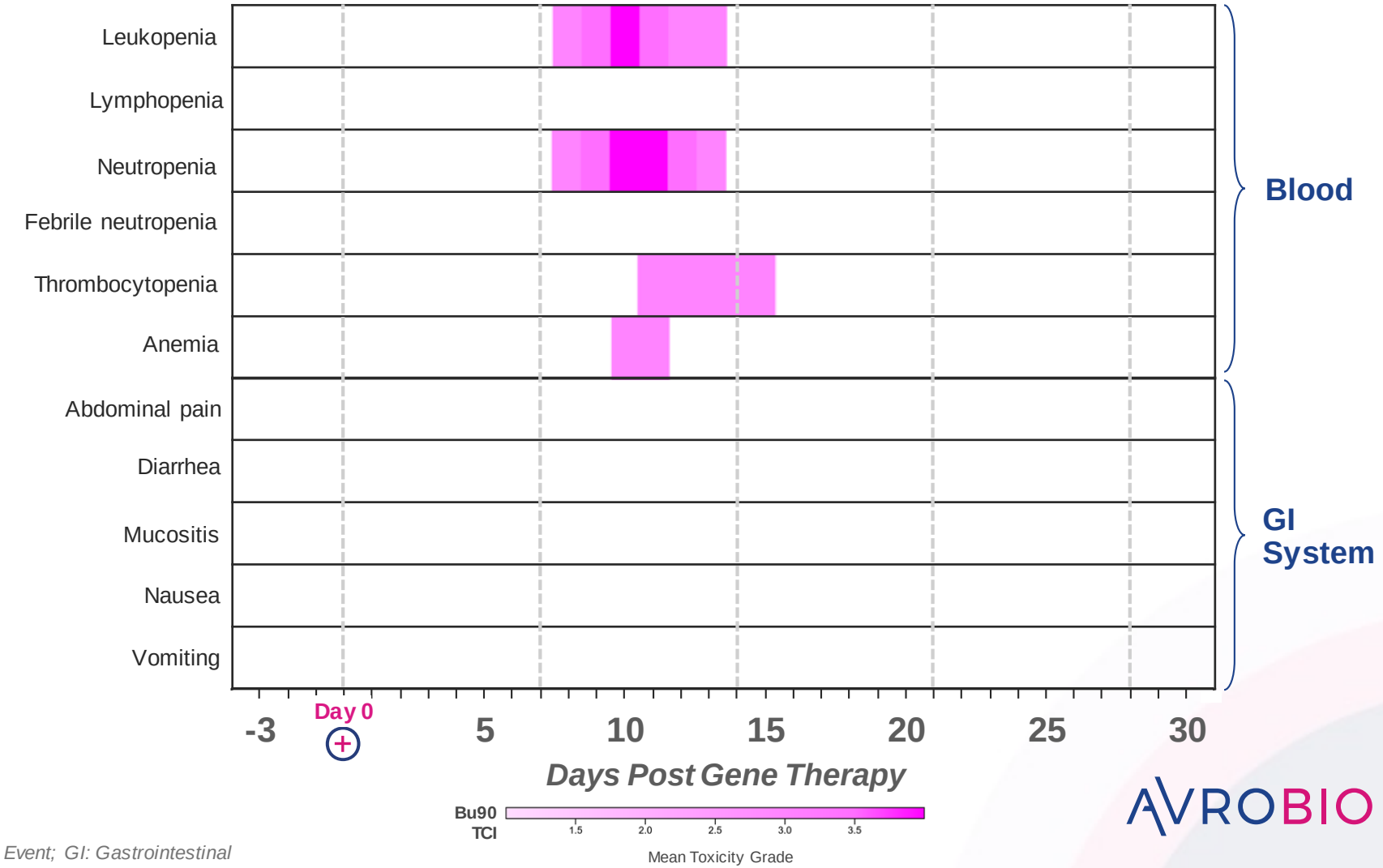
Emerging tolerability profile has been predictable and manageable

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



Busulfan 90 Target Concentration Intervention (TCI)

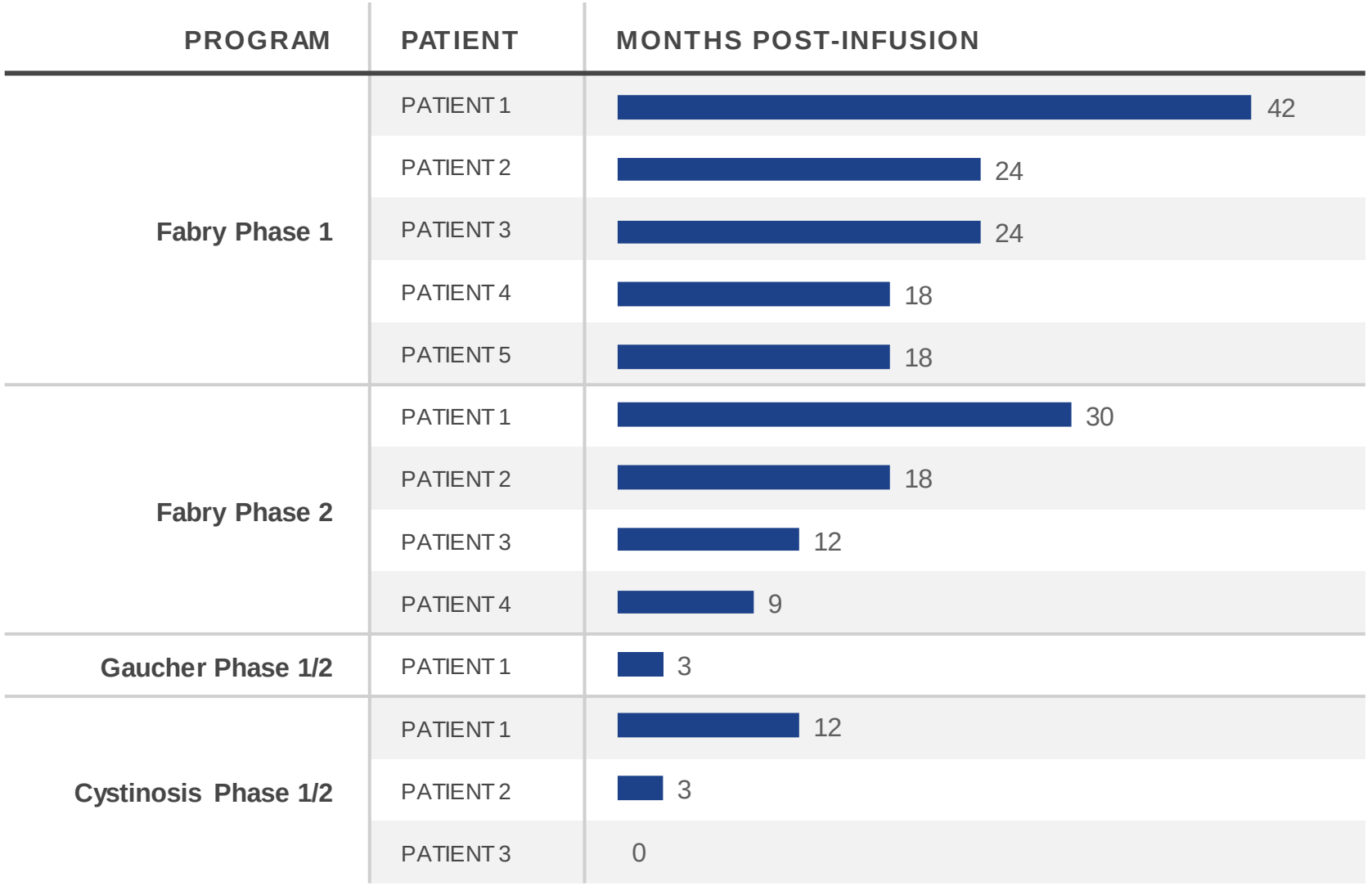
Observations to-date show short-term side effects start ~1 week after infusion, peak over the next 3-5 days and subside



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

Durability across programs

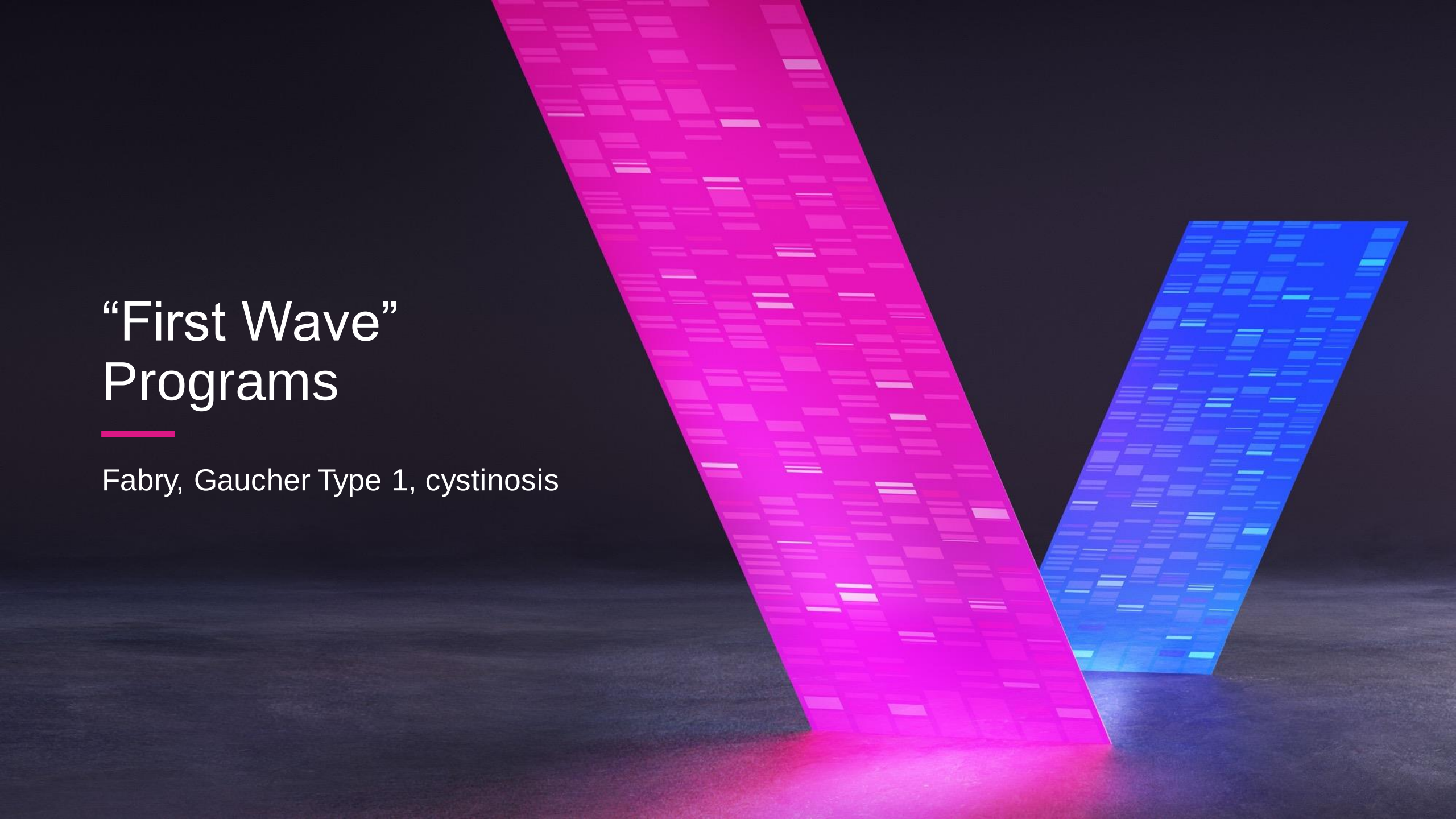
9 patients out 1 year or more; first patient out 3.5 years



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

“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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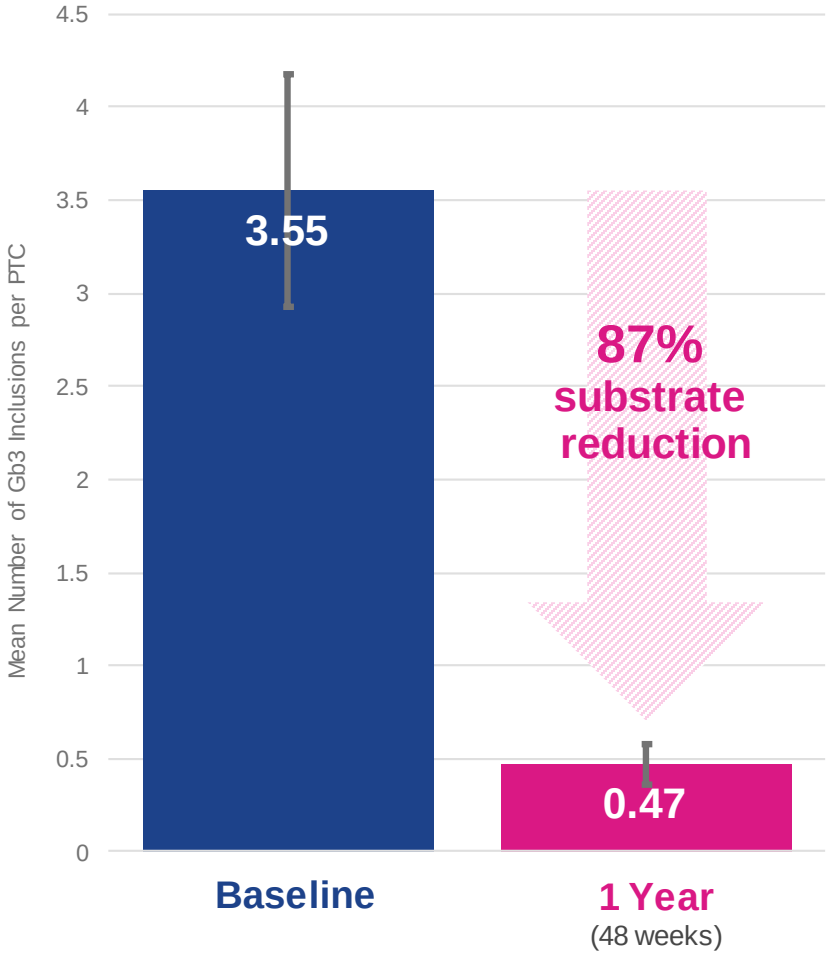
Substantial reduction of substrate in kidney biopsy at 1 year

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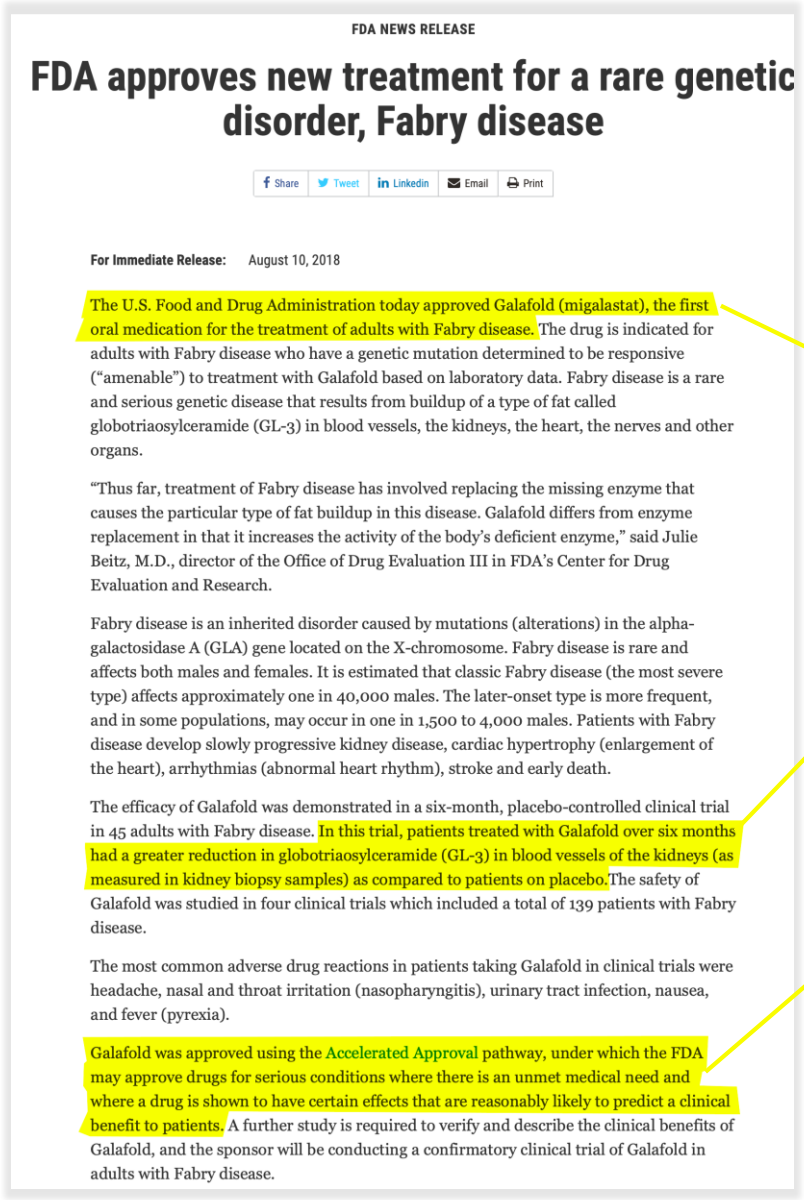
Precedent for use of kidney biopsy data for FDA approval of drug candidate for Fabry disease



FDA NEWS RELEASE

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

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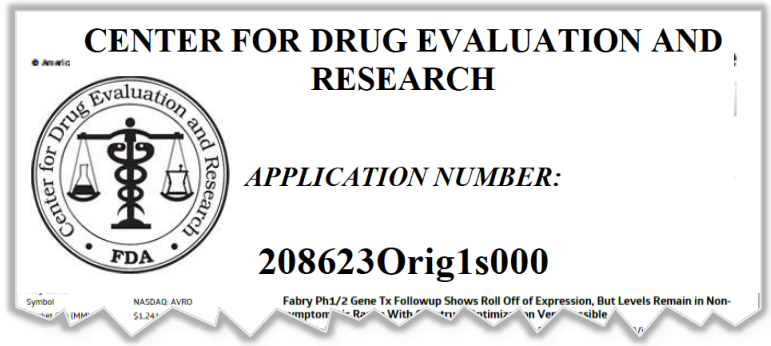
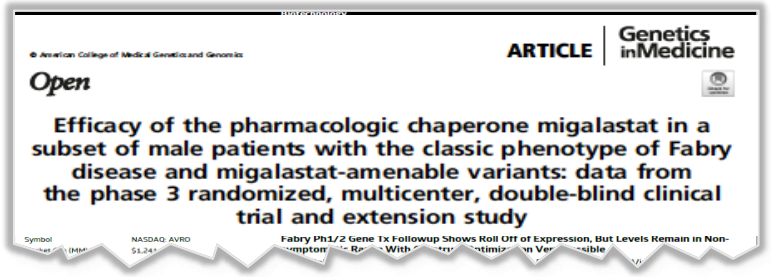
Precedent for use of kidney biopsy data for FDA approval of drug candidate for Fabry disease


CENTER FOR DRUG EVALUATION AND RESEARCH

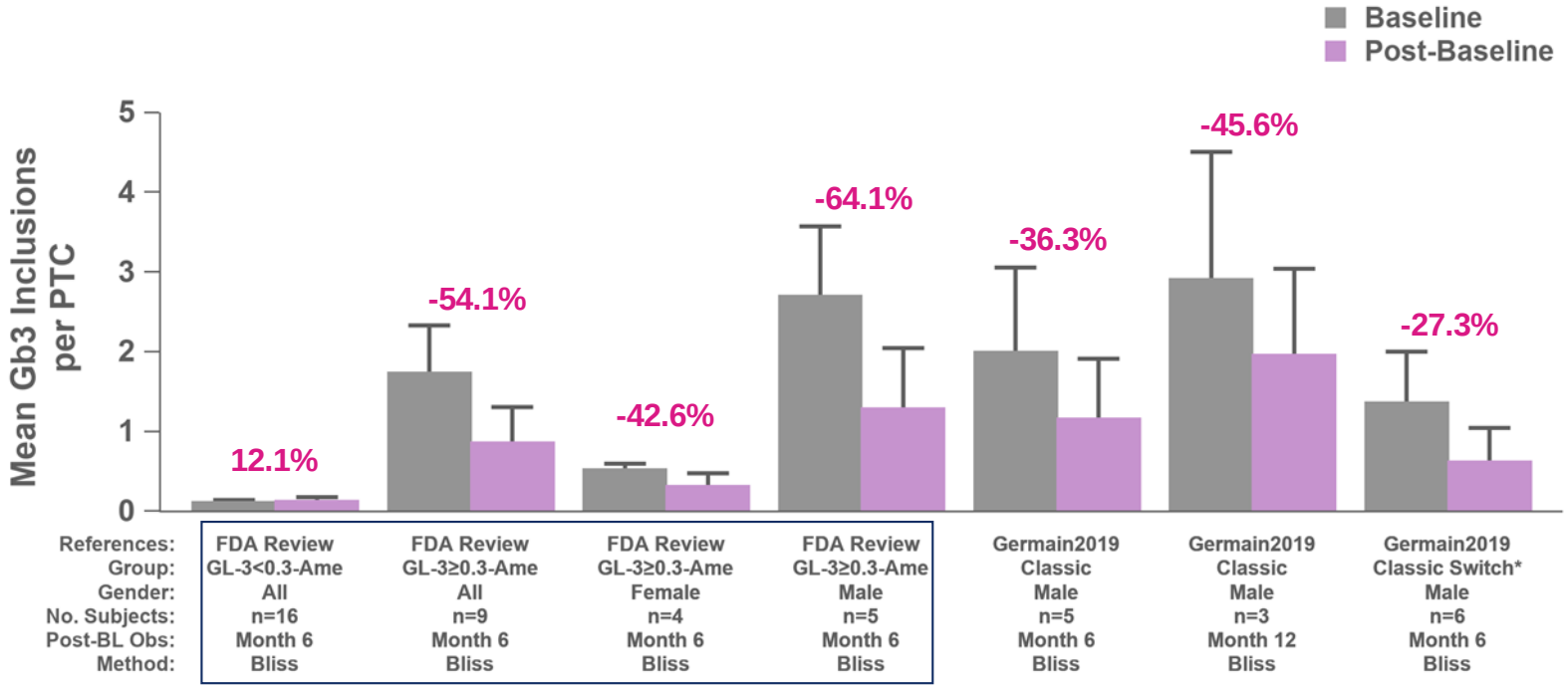
APPLICATION NUMBER:

208623Orig1s000


ARTICLE | Genetics inMedicine

Open

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



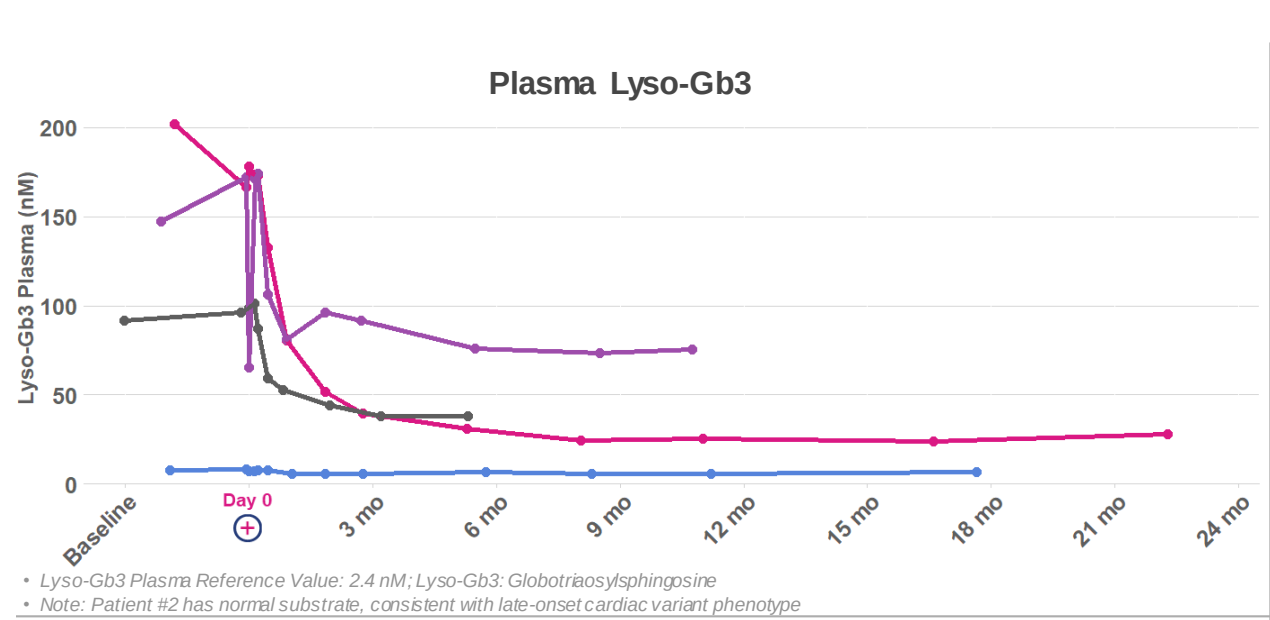
Abbreviations: Ame=Amenable; NonAme=Non-Amenable; Classic=Classic Fabry Patients; PTC=Peritubular Capillary; BL=Baseline; Obs=Observation.

Notes: All data on substrate changes presented are from Migalastat-treated subjects who participated in the Phase 3 FACETS study (NCT00925301). Substrate changes were determined using BLISS (Barisoni Lipid Inclusion Scoring System).
Error bar represents the standard error of the mean.
* Denotes patients who were randomized to Placebo (Months 0-6) and switched to Migalastat starting at Month 6 post study start. The Baseline at Month 6 was derived as the sum of the PTC Gb3 inclusions at Baseline (Month 0) and the Change in PTC Gb3 inclusions from Baseline to Month 6. Percent change is associated with Change from Month 6 to Month 12.

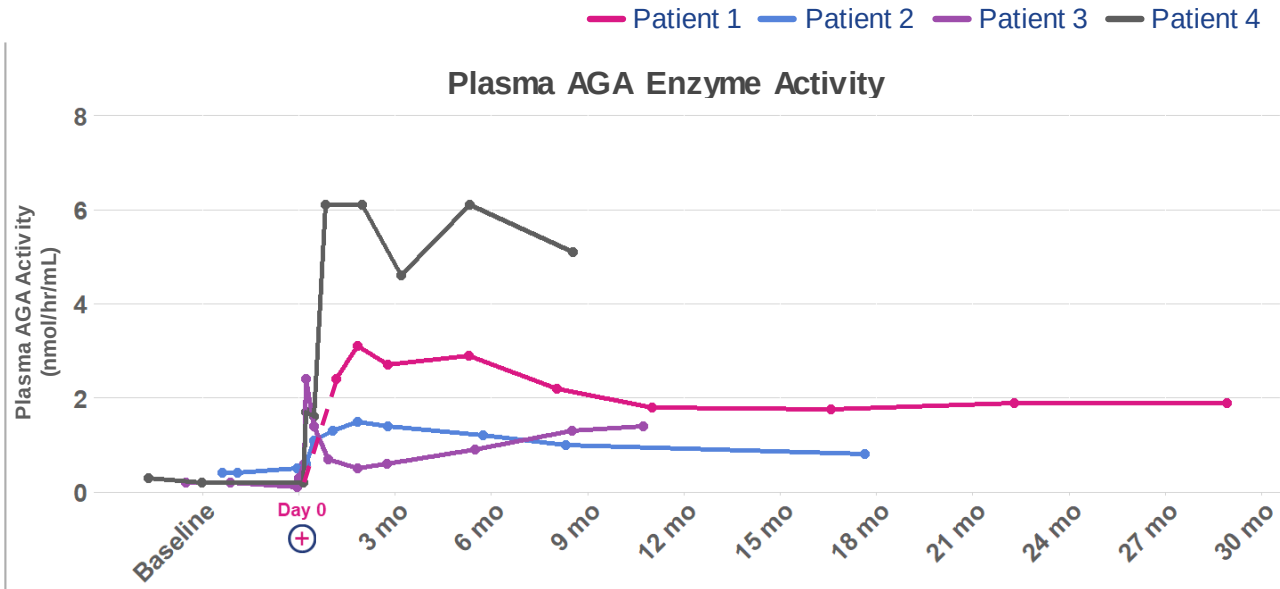
Sources: Galafold (Migalastat), Multi-Discipline FDA Review; Germain 2019, Genet Med 21, 1987–1997 (2019)

Sustained trends over multiple measures up to 2.5 years

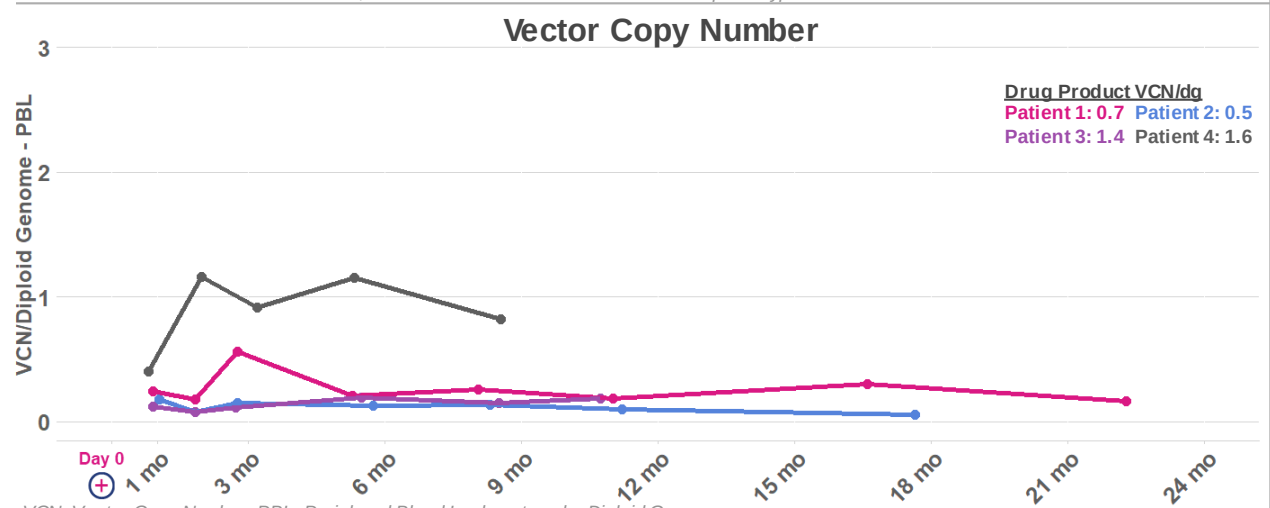
Patient 4 dosed using plato®



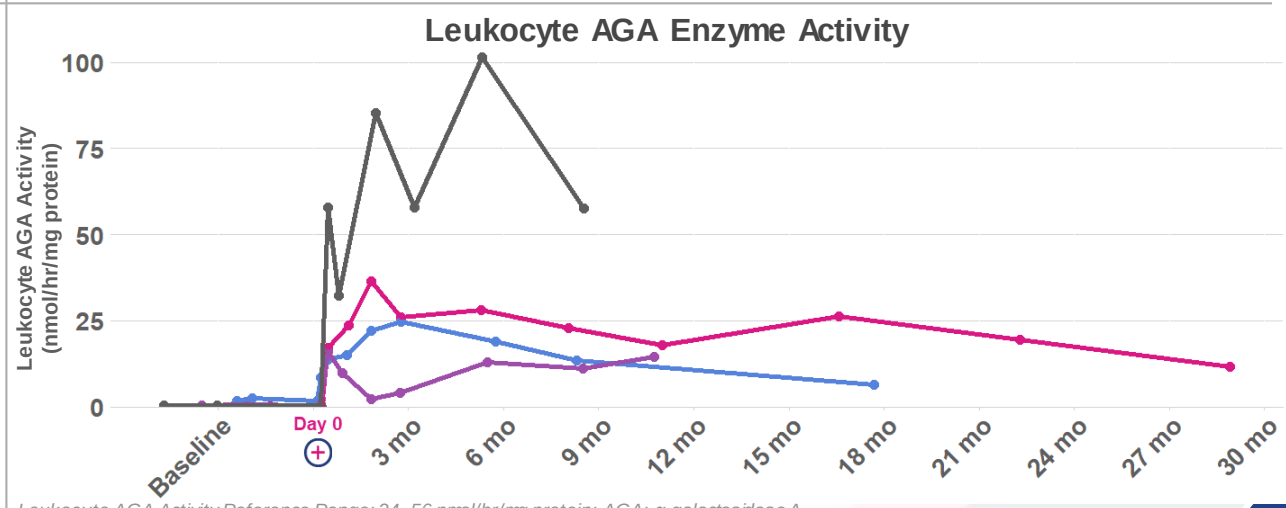
- *Lyso-Gb3 Plasma Reference Value: 2.4 nM; Lyso-Gb3: Globotriaosylsphingosine*
- *Note: Patient #2 has normal substrate, consistent with late-onset cardiac variant phenotype*



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



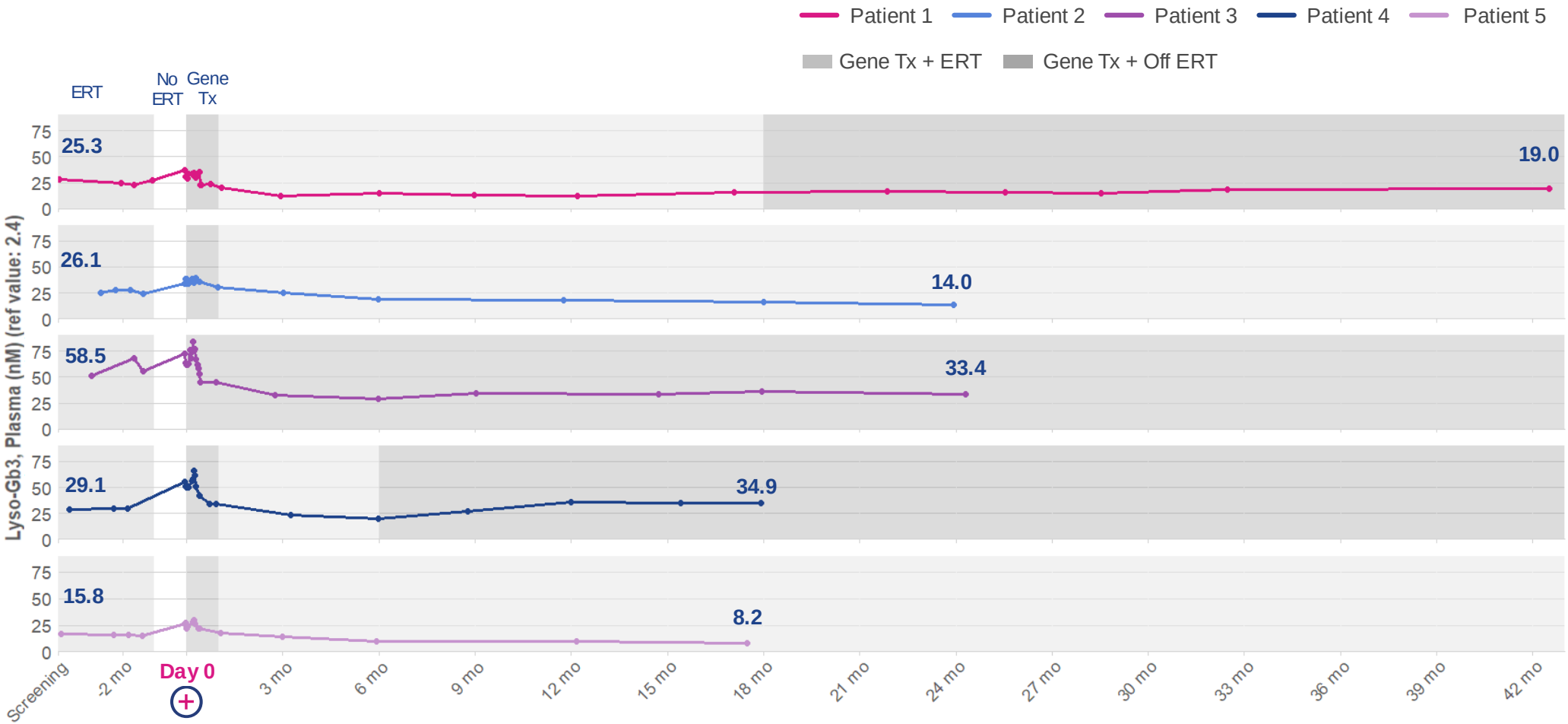
VCN: Vector Copy Number; PBL: Peripheral Blood Leukocytes; dg: Diploid Genome



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

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**

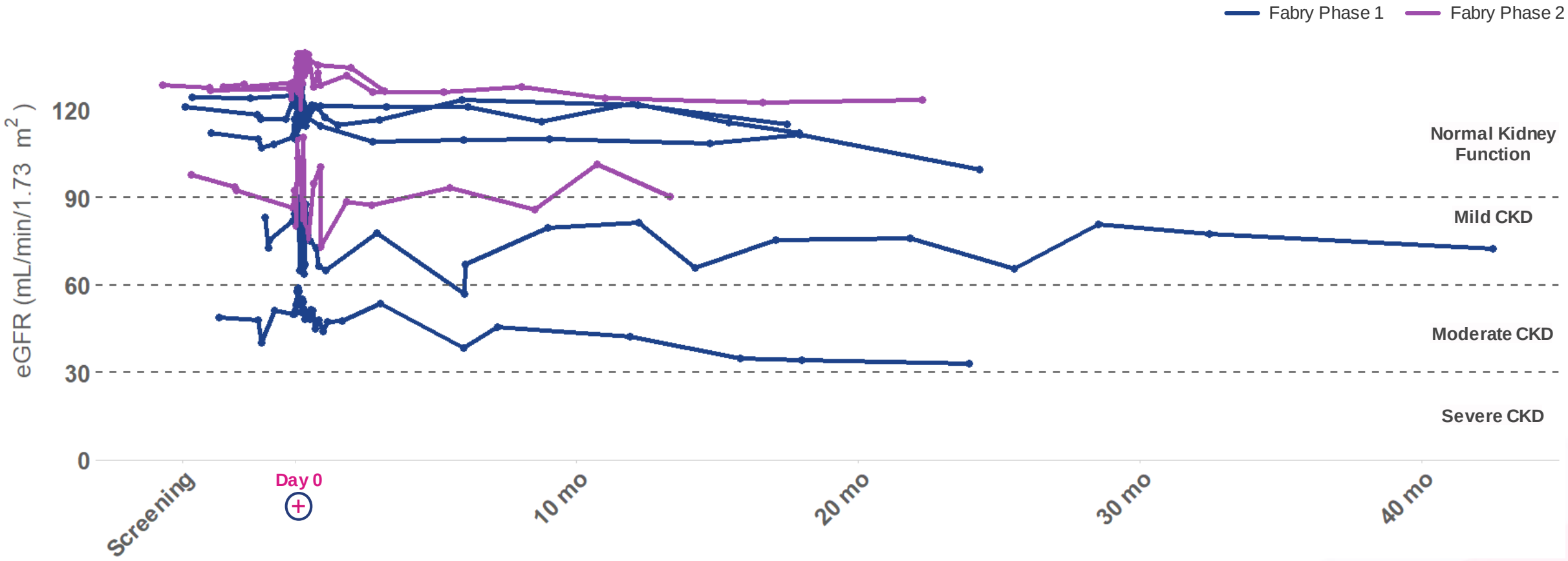
43% reduction *from baseline ERT* **OFF ERT**

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

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

** 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/1.73m^2. 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 • Hypothesis generation of endpoints	• Up to 6 patients • Adults and adolescents • Cohorts 1-2 >18 years; Cohort 3 >14 years • Male and female • Oral and ophthalmic cysteamine

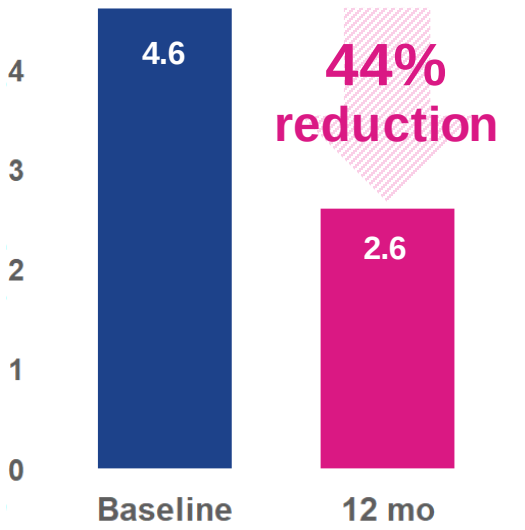
AVR-RD-04 trial sponsored by University of California, San Diego; IST does not use plato® platform
Note: AVR-RD-04 aka CTNS-RD-04
IST: Investigator Sponsored Trial

AVROBIO

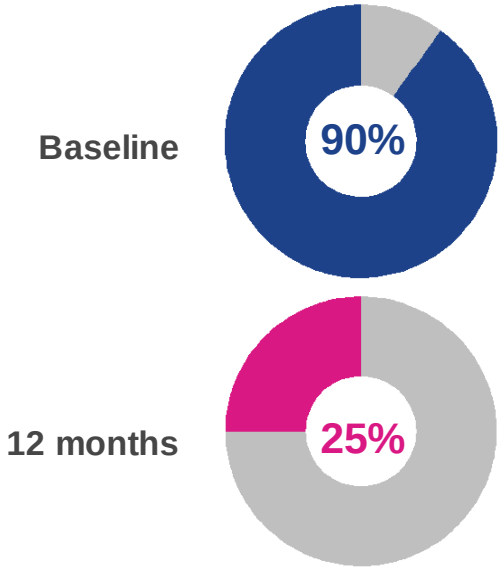
Sharp drop in the number and size of cystine crystals in skin and rectal biopsies

Skin Biopsy

Average intracytoplasmic crystals per cell

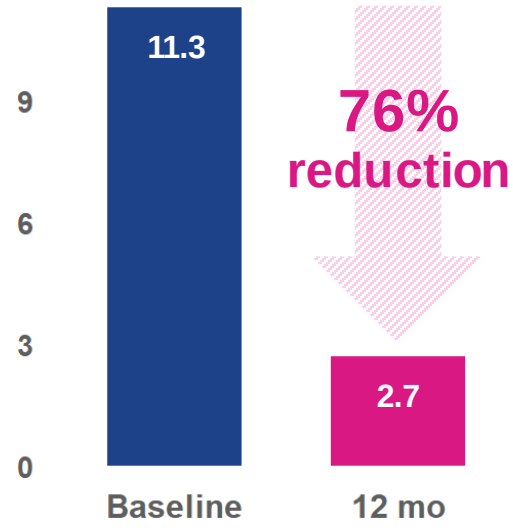


Occupancy of cytoplasmic volume

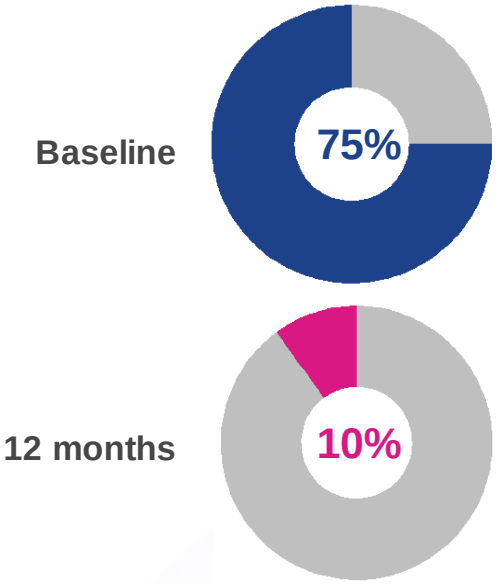


Rectal Biopsy

Average intracytoplasmic crystals per cell



Occupancy of cytoplasmic volume



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

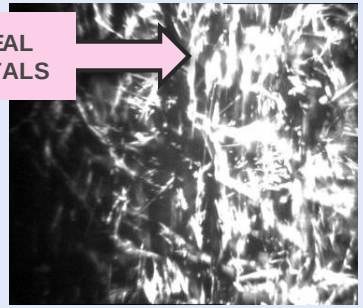
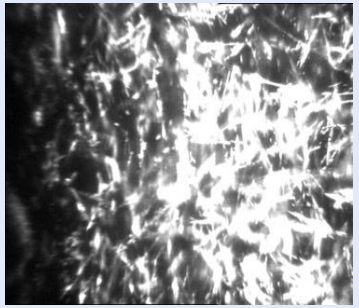
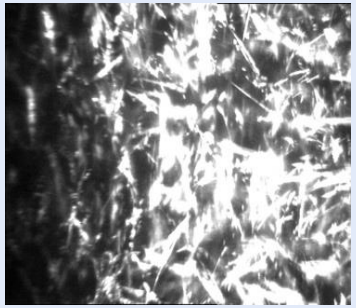
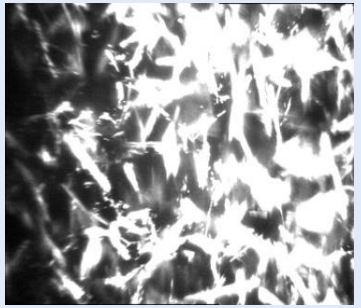
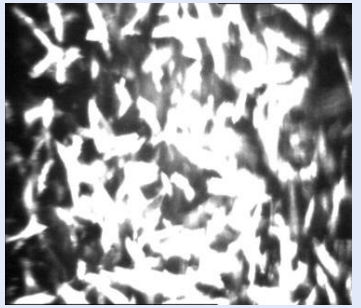
Substantial decline in corneal crystals observed at 1 year

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

Baseline

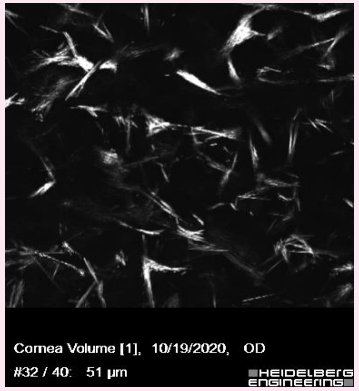
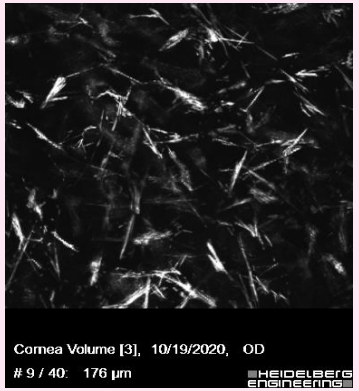
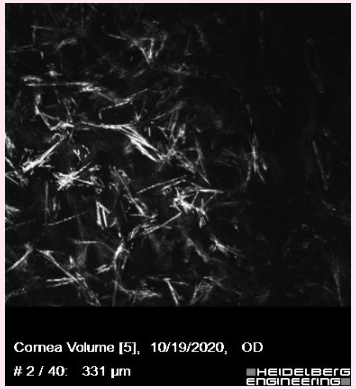
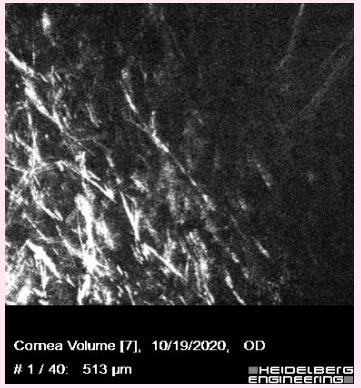
IVCM images from Nidek Confoscan

CORNEAL CRYSTALS

111 µm, OD	174 µm, OD	330 µm, OD	515 µm, OD	724 µm, OD
				

12 months post-gene therapy

IVCM images from Heidelberg HRT3 w/ Rostock Corneal Module

51 µm, OD	176 µm, OD	331 µm, OD	513 µm, OD
			

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

AVROBIO

First patient remains off cysteamine and eye drops at 1 year

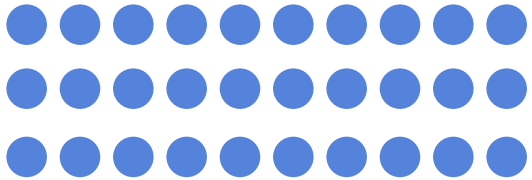
Daily cysteamine regimen

(max per day)

Before AVR-RD-04

***ON** cysteamine*

30 pills / day



***ON** cysteamine eye drops*

Prescribed 8 drops / day

After AVR-RD-04

(1 year post-gene therapy)

***OFF** cysteamine*

0 pills / day

***OFF** cysteamine eye drops*

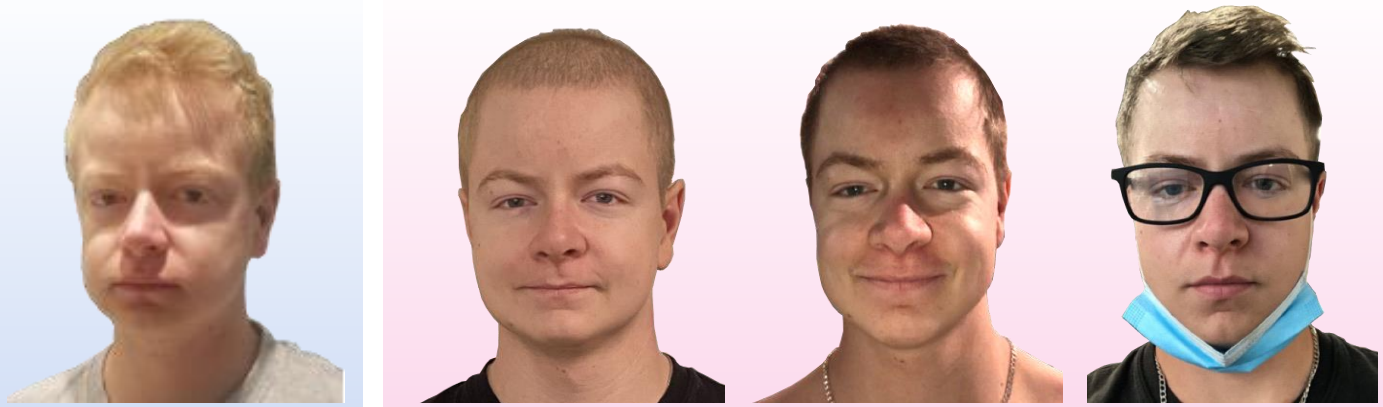
0 drops / day

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

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

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

AVROBIO

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 • Efficacy • Engraftment	• Enrollment goal: 8-16 patients • 18-45-year-old males and females • Have a confirmed diagnosis of GD1 based on: – Deficient glucocerebrosidase enzyme activity – Clinical features consistent with GD1

Gaucher disease type 1 patients who are:

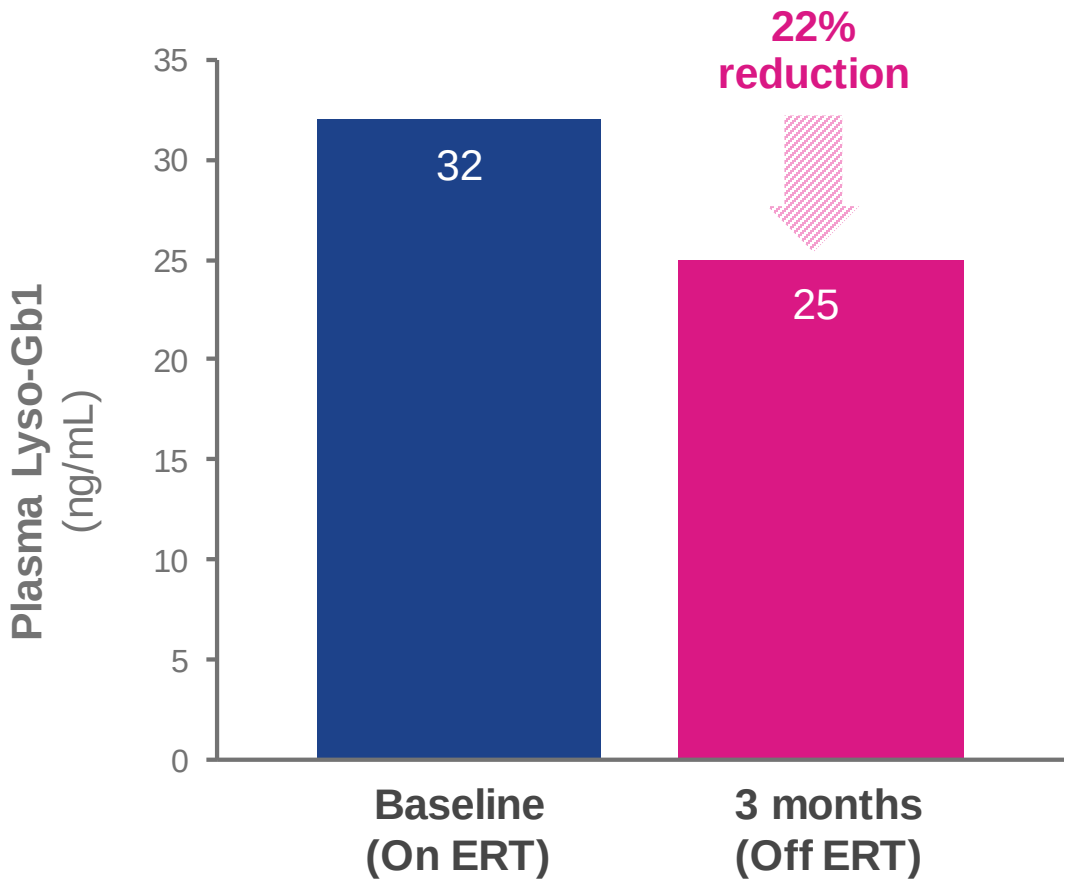
- ERT-stable for >24 months *or*
- Treatment-naïve *or*
- Have not received ERT or SRT in the last 12 months

AVROBIO

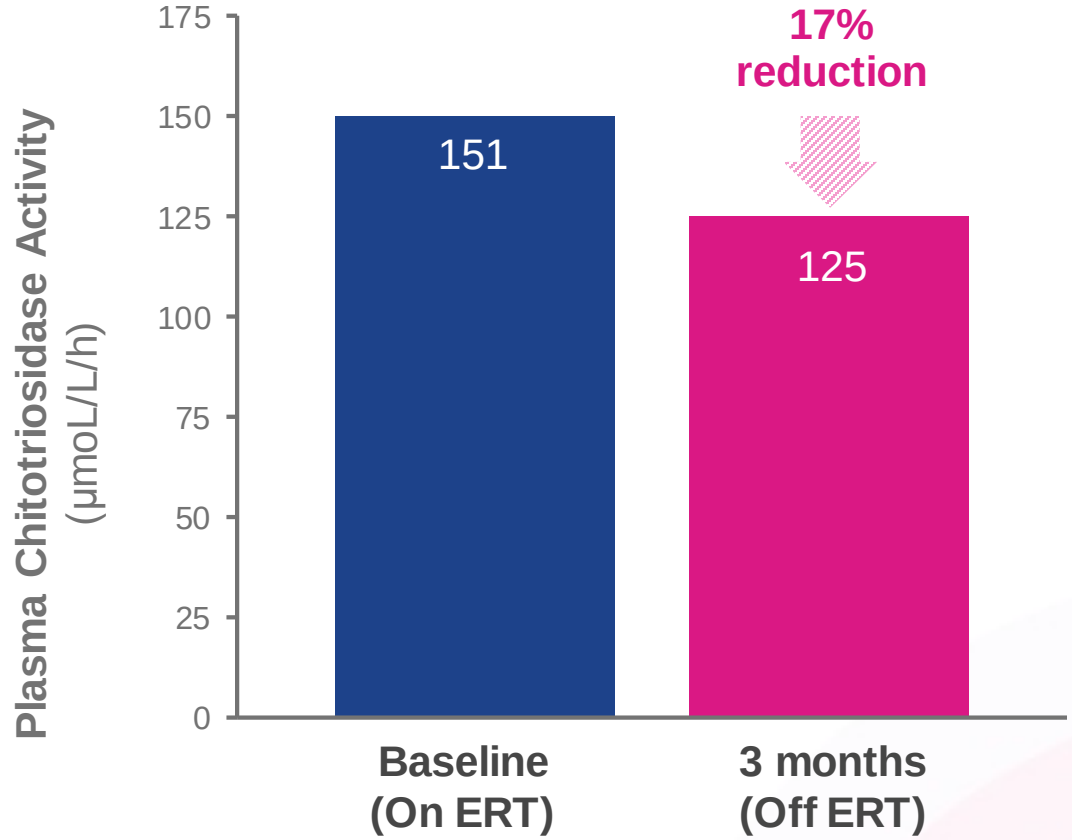
GD1: Gaucher Disease Type 1; ERT: Enzyme Replacement Therapy; SRT: Substrate Reduction Therapy; 1H: First Half

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



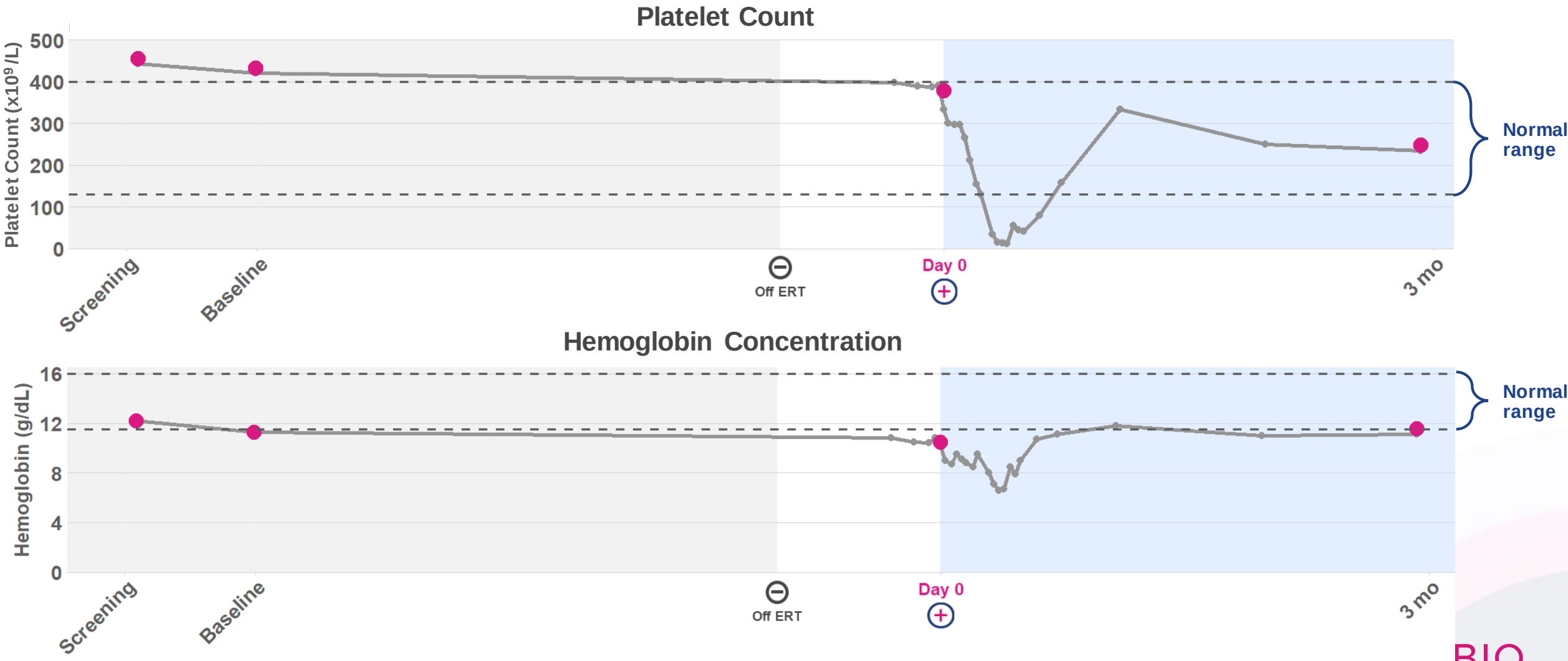
Chitotriosidase, a marker of activated macrophages (Gaucher cells), is also decreased



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

AVROBIO

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

AVROBIO

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

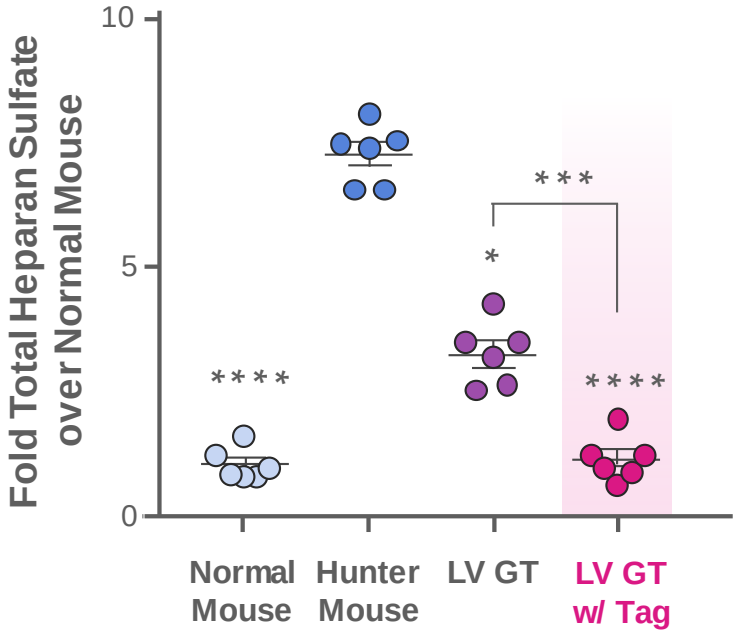
“Second Wave” Programs

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

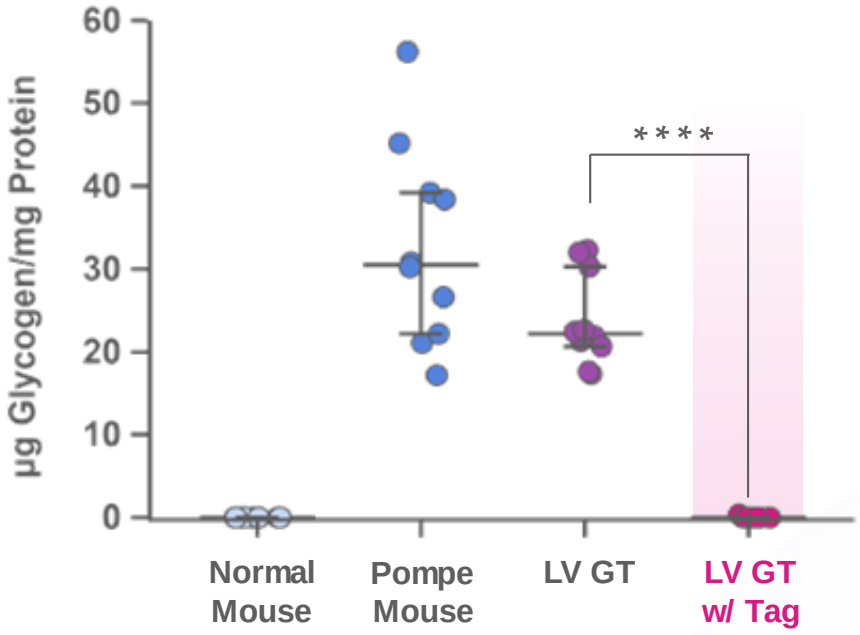


*Figure adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 3A; *P<0.05, ***P<0.001, ****P<0.0001; LV GT: Lentiviral Gene Therapy*

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

AVROBIO

** 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

** WAC pricing from Redbook using standard dosing assumptions*

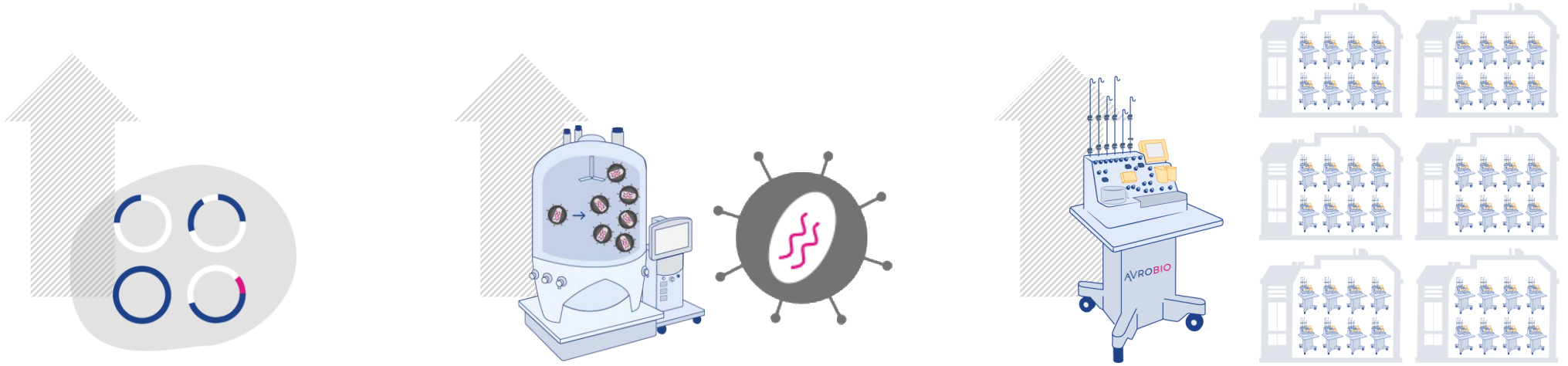
plato®

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

Note: This diagram is for illustrative purposes only

AVROBIO

Poised to manufacture at scale

Global infrastructure already in place

VECTOR	DRUG PRODUCT
2,400 PATIENTS ANNUALLY	2,400 PATIENTS ANNUALLY
>50 patients per run	**100** patients per unit per year
12 runs per year per suite (200L scale bioreactor runs (10^9 titer))	**8** automated units per suite
4 production suites	**3+** global production suites

Note: This diagram is for illustrative purposes only

CMC achievements have defined the plato® story

Strategic investment in technology laid the foundation for our manufacturing leadership

Manufacturing

Robust production platform

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

Global footprint

- Cleared for the clinic from multiple agencies

Cost effective

- Intended to address key COGs issues

Analytics

Robust platform analytics

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

Deep product characterization

- First-in-class single cell analytics

Potency assay matrix

- Intended to accelerate regulatory approvals

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

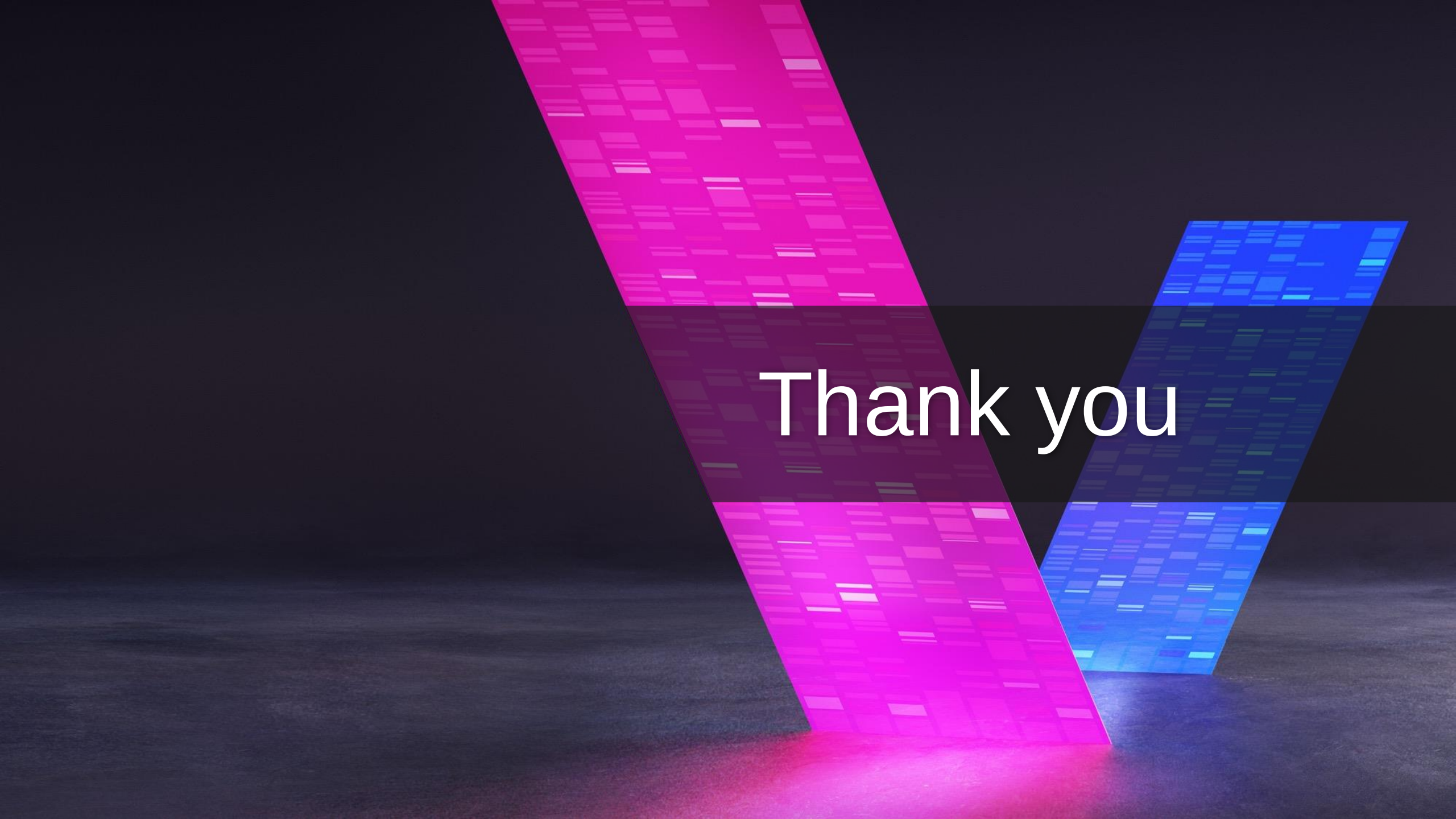
Key anticipated 2021 milestones

Goal:
30 patients dosed cumulatively by end of 2021

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

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

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


Thank you