
AVROBIO
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AVROBIO
R&D Day
NOVEMBER 2020

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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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AVROBIO

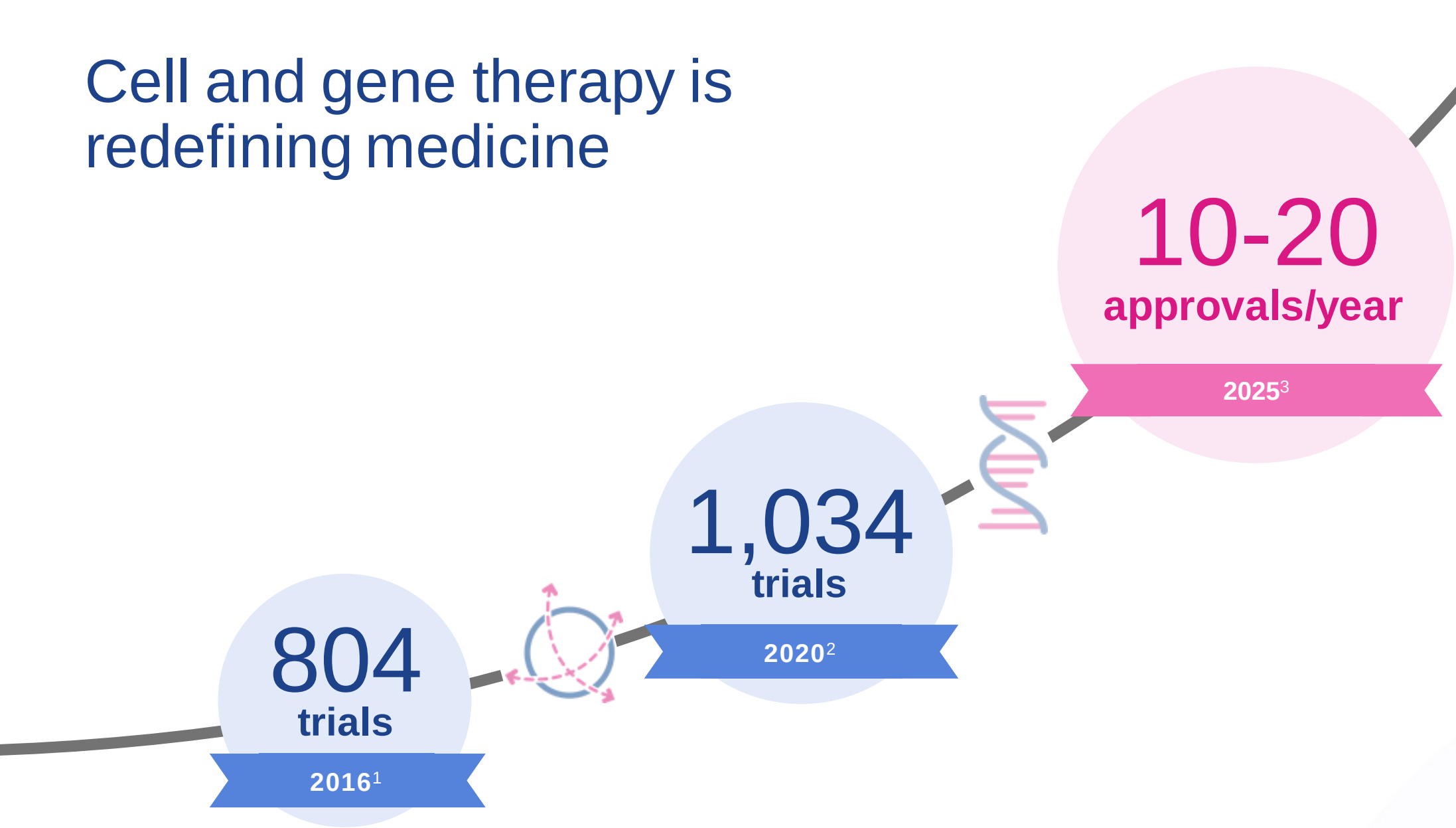
Purpose

Freedom from a lifetime of genetic disease.

Vision

Bring personalized gene therapy to the world.

Cell and gene therapy is redefining medicine



Sources: [1]Alliance for Regenerative Medicine: 2016 Annual Data Report; [2]Alliance for Regenerative Medicine: Sector Report 1H 2020; [3]FDA.gov press release at: https://bit.ly/2GcPftr

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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

Investigational
- Fanconi anemia
- Hurler syndrome
- MLD
- 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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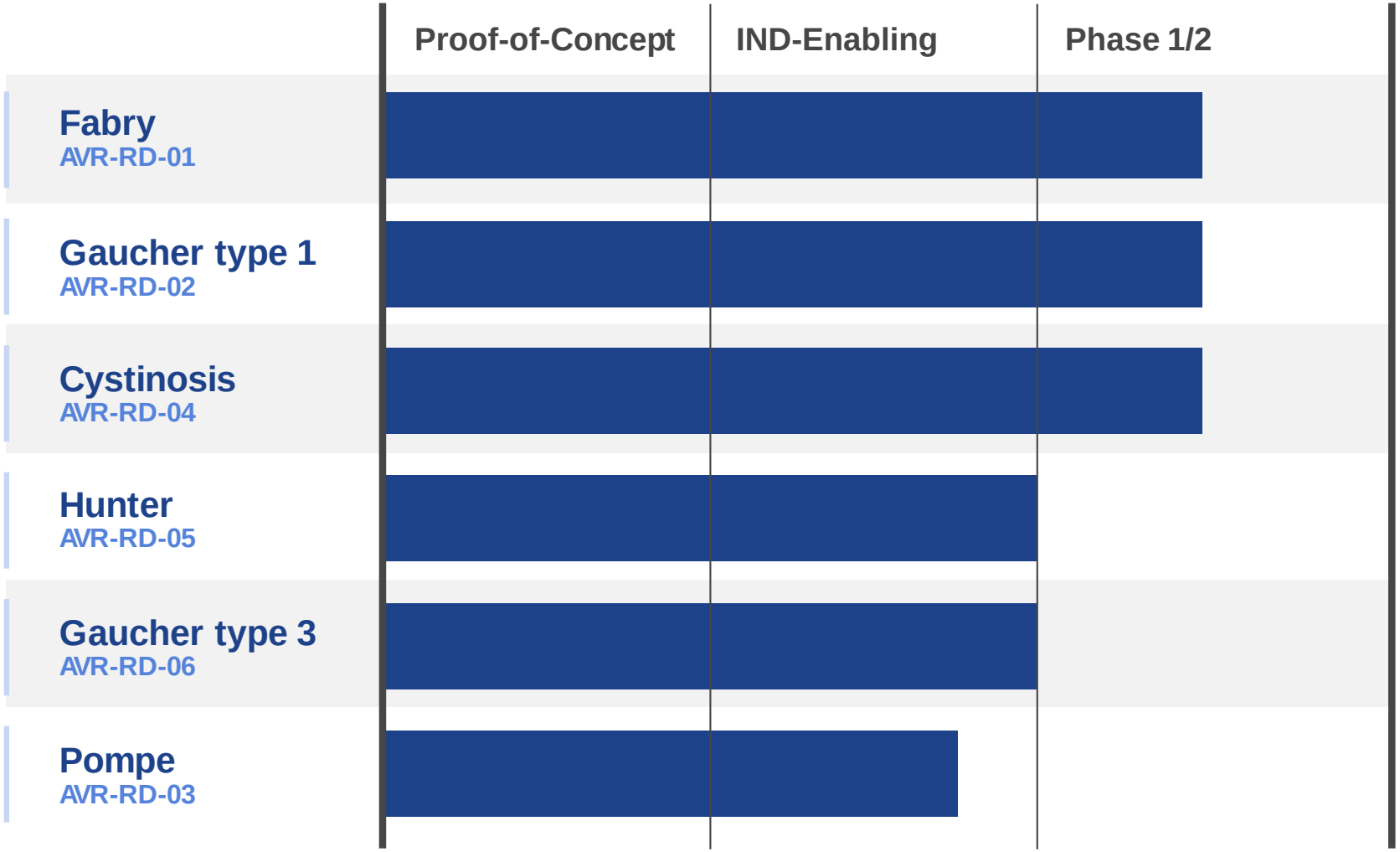
Leading lysosomal disorder gene therapy pipeline

Built on strong strategic fit



IND: Investigational New Drug

A multi-billion dollar market opportunity

Targeting larger rare lysosomal disorders

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 Pharma‡
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

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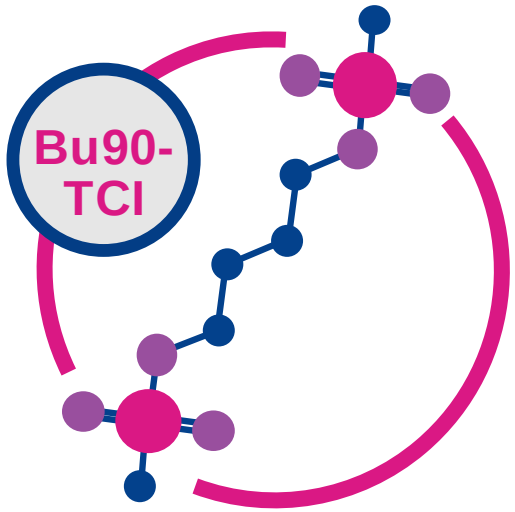
Durability across programs

PROGRAM	PATIENT	MONTHS POST-INFUSION
Fabry Phase 1	PATIENT 1	42
	PATIENT 2	24
	PATIENT 3	24
	PATIENT 4	18
	PATIENT 5	18
Fabry Phase 2	PATIENT 1	30
	PATIENT 2	18
	PATIENT 3	12
	PATIENT 4	9
Gaucher Phase 1/2	PATIENT 1	3
Cystinosis Phase 1/2	PATIENT 1	12
	PATIENT 2	3
	PATIENT 3	0

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

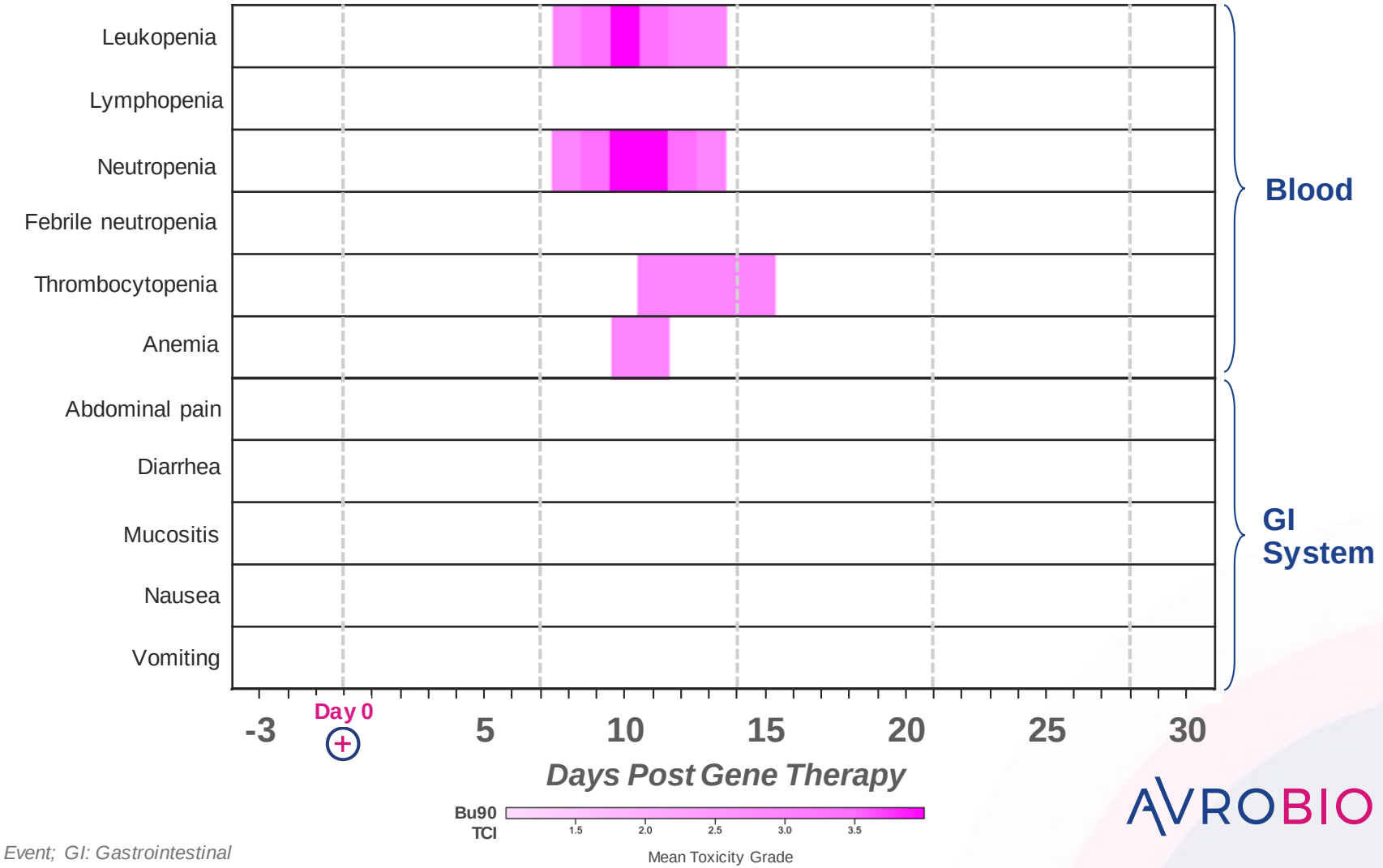
Emerging tolerability profile has been predictable and manageable

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

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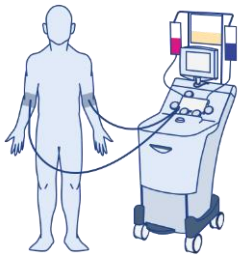
Unrivaled commercial-scale platform in plato®

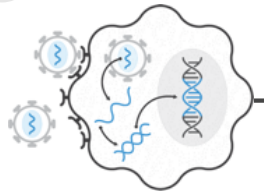
Patient **Consent & Screening**

1 **MOBILIZATION & APHERESIS**

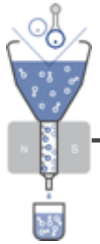


CLOSED, AUTOMATED SYSTEM

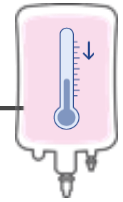
3 TRANSDUCTION

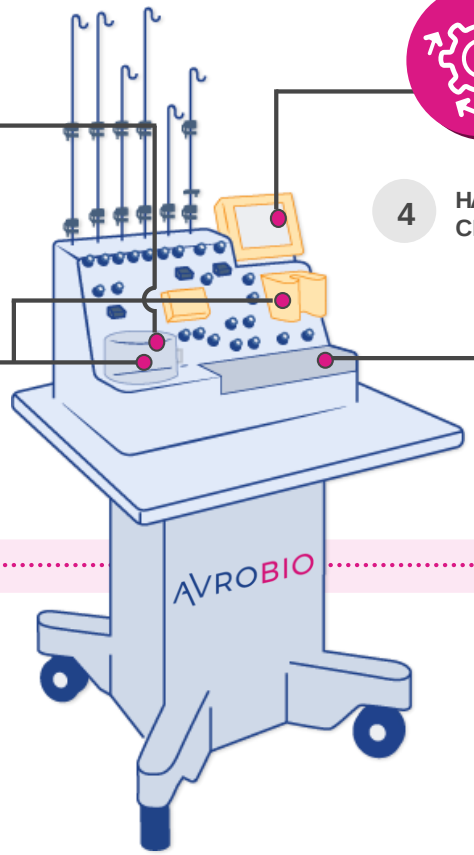


2 **CELL SEPARATION & CULTURE**

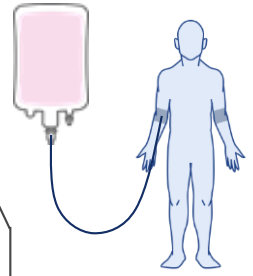


4 **HARVESTING & CRYOPRESERVATION**





5 **CONDITIONING & GENE THERAPY ADMINISTRATION**



DRUG PRODUCT TESTING

Patient **Monitoring**

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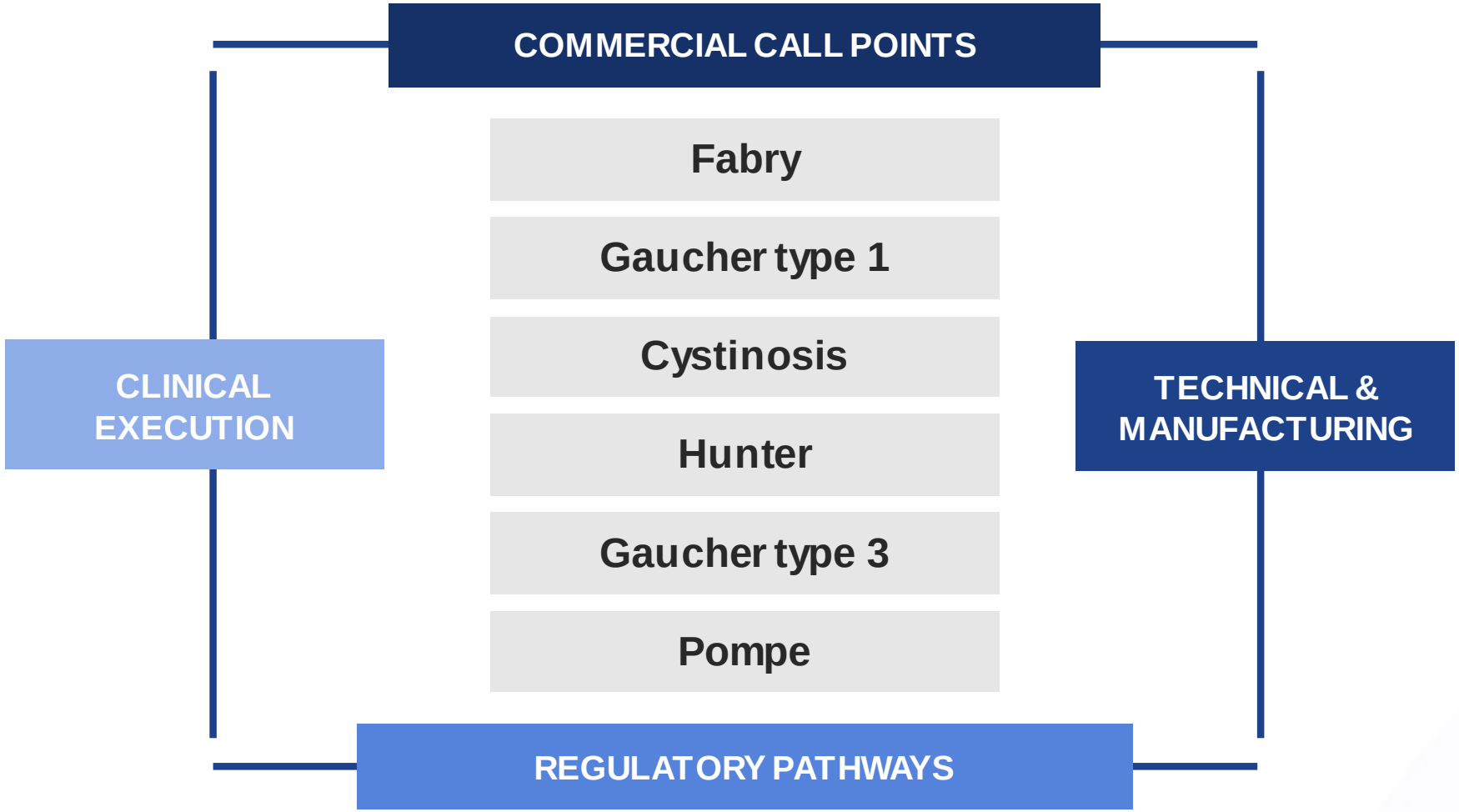
‘Halo effect’ driven by strong pipeline synergies

Replicable path to market



Patient enrollment activities accelerating across trials

Q4 '20 Recruiting Objective

ENROLLED

CONSENTED

DOSED

Clinical Trial Site Expansion

Active clinical sites:

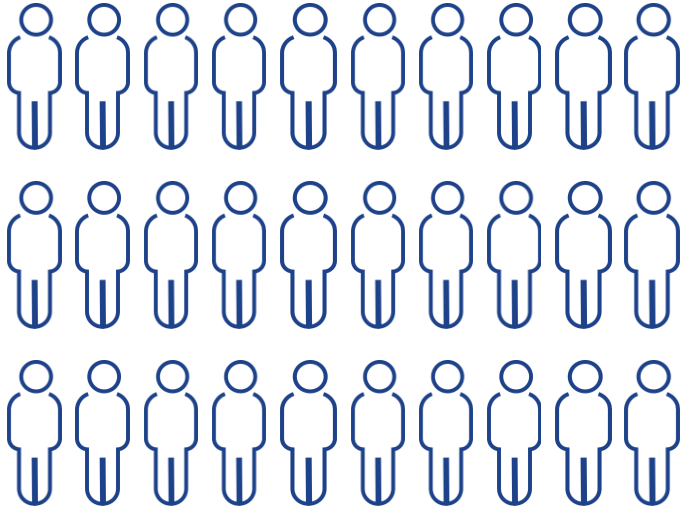
7

CURRENTLY

23

PLANNED BY Q4 2021

Cumulative 2021 Patient Dosing Goal



By the end of 2021, we expect to have dosed a total of **30 patients.**

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Key takeaways for today

- Fabry advancing toward potential accelerated approval pathway in one or more major markets
- Exciting early data in cystinosis and Gaucher
- Clear advantages of Bu90-TCI conditioning
- plato® platform reimagines CMC / analytics
- Leading lysosomal disorder gene therapy franchise

Bu90-TCI: Busulfan 90-Target Concentration Intervention; CMC: Chemistry, Manufacturing, and Controls

Today's agenda

	Time
Clinical updates New data and update on future regulatory plans	9:15
Precision conditioning designed to enable durability and head-to-toe reach The Bu90-TCI advantage	10:00
Addressing industry manufacturing challenges with advanced CMC and analytic solutions AVROBIO's platform for global gene therapy commercialization	10:35
The second wave Working to prevent irreversible damage to body and brain	11:30

Bu90-TCI: Busulfan 90-Target Concentration Intervention; CMC: Chemistry, Manufacturing, and Controls

Perspective from leading KOLs

Rob Hopkin, M.D.

Genetic Medicine Specialist, Fabry KOL at Cincinnati Children's Hospital

Harry Malech, M.D.

Chief of Genetic Immunotherapy Section and Deputy Chief of Laboratory of Clinical Immunology and Microbiology, NIAID, NIH

Anthony Davies, Ph.D.

Founder and CEO, Dark Horse Consulting Group

Dr. Rob Hopkin is a consultant to AVROBIO and Dr. Anthony Davies is the CEO of Dark Horse, an AVROBIO vendor
KOL: Key Opinion Leader; NIAID: National Institute of Allergy and Infectious Diseases; NIH: National Institutes of Health; CEO: Chief Executive Officer

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Gaucher Disease Type 1

Adrianna, living with Gaucher disease type 1

DIFFERENTIATED TARGET PRODUCT PROFILE *for*

Gaucher Disease Type 1

First-Line Therapy and Functional Cure

Prevents, halts or reverses disease; normalizes lifespan

- Bone-related manifestations, prevention of physical deformity, bone crises, bone pain, avascular necrosis
- Low hemoglobin and platelets
- Hepatosplenomegaly, risk of cirrhosis and splenectomy
- Risk of multiple myeloma
- Fatigue
- CNS: risk of GBA-Parkinson's disease

Lifelong durability

- Single infusion for life
- Off ERT/chaperone
- No waning of efficacy
- Save millions of dollars in healthcare costs per patient

Addresses all patient segments

- All Gaucher disease type 1 genetic mutations
- All age groups
- Male and female
- No AAV or ERT neutralizing antibody limitations

Impacts hard-to-reach organs

- Diseased macrophages (Gaucher cells) replaced by functional macrophages
- Brain: global distribution of genetically modified microglia
- Bone and bone marrow: global distribution of genetically modified macrophages and osteoclasts

Well-tolerated

- No ERT/SRT-related side effects
- Mild-to-moderate, transient side effect profile consistent with Bu90-TCI
- No splenectomy medication and complications
- No liver toxicity or adverse immunogenicity

Note: These are target attributes for a first-line therapy

AAV: Adeno-Associated Viral vector; Bu90-TCI: Busulfan 90-Target Concentration Intervention; CNS: Central Nervous System; ERT: Enzyme Replacement Therapy; GBA: Glucocerebrosidase; SRT: Substrate Reduction Therapy

Even on ERT, patients endure debilitating symptoms

Incomplete therapeutic response is common:

- **60% failed to achieve** at least one of six therapeutic goals after 4+ yrs of ERT[1]
- Many continue to exhibit **bone pain, organomegaly and cytopenia** after 10 yrs of ERT[2]
- **25% have physical limitations** after 2 yrs of ERT, primarily due to bone disease[3]

Prospective registry of 757 GD1 patients on ERT after 10 years

Persistence after **10 years ERT†**	**Non-splenectomized** Patients	**Splenectomized** Patients
Bone Pain	43%	63%
Splenomegaly*	38%	N/A
Thrombocytopenia*	23%	1%
Hepatomegaly*	14%	19%
Anemia	12%	9%
Bone Crisis	7%	17%

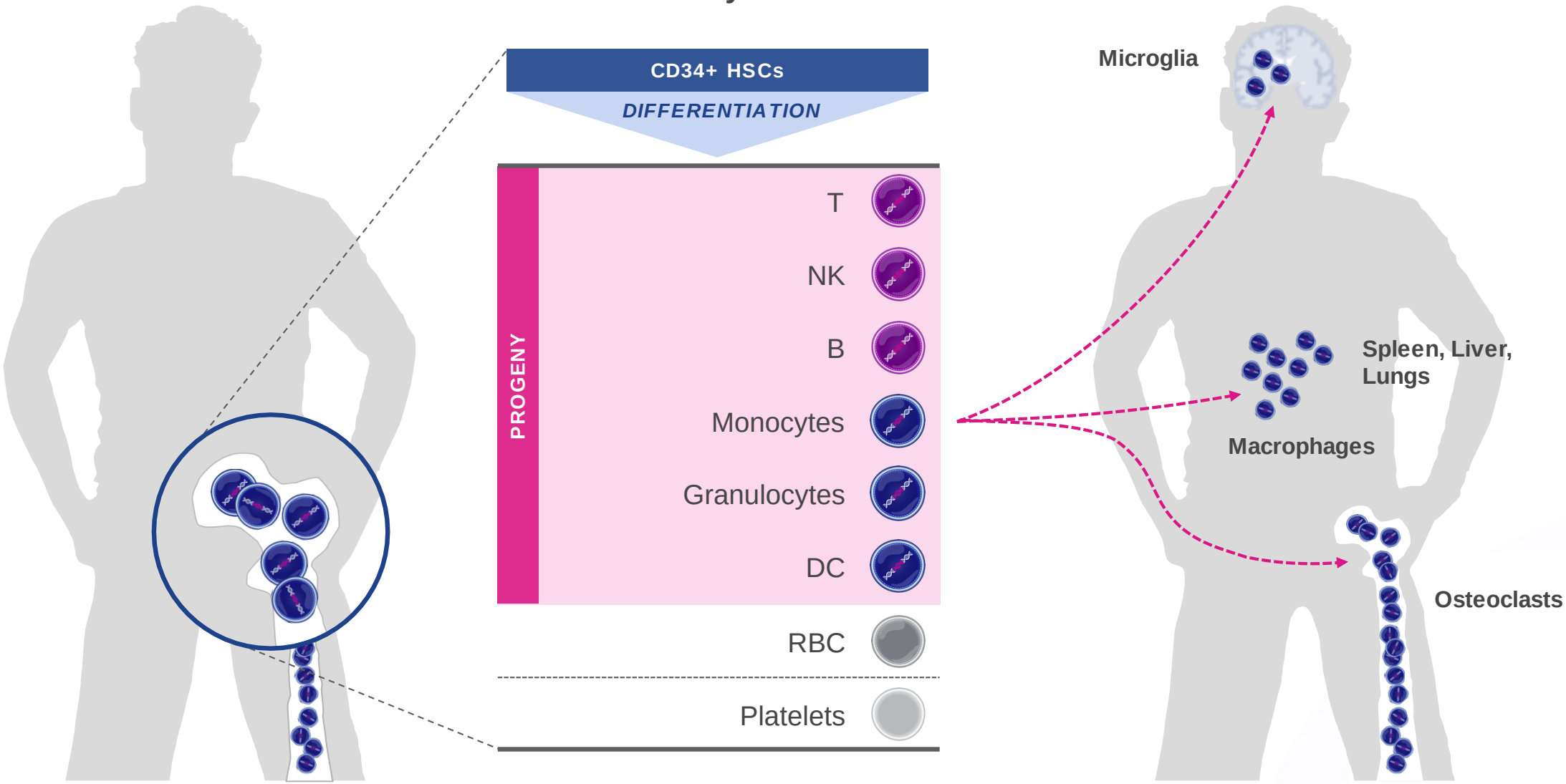
** Higher persistence rates observed when more severe manifestations were present at baseline*
† Persistence refers to the presence of anemia, bone pain, bone crisis, or at least moderate thrombocytopenia, splenomegaly, or hepatomegaly, present after 10 years of ERT among those with baseline involvement of these parameters (from a registry of 757 GD1 patients; Weinreb et al., 2013)
Following 10 years of treatment, ~26% of patients were receiving between 45-150 U/kg EOW, and 96% of these individuals were receiving doses between 45-90 U/kg EOW.
Data rounded to complete integer.
GD1: Gaucher Disease Type 1; ERT: Enzyme Replacement Therapy; EOW: Every Other Week
[1]Weinreb N et al., Amer J Hematol, 2008; [2]Weinreb N et al., J Inherit Metab Dis, 2013; [3]Giraldo P et al., Qual Life Res, 2005

Delivering genetically modified cells head-to-toe

Long-term engraftment in bone marrow

'Manufacturing', transportation and delivery in blood

Target organs



HSC: Hematopoietic Stem Cell; NK: Natural Killer; DC: Dendritic Cell; RBC: Red Blood Cell

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

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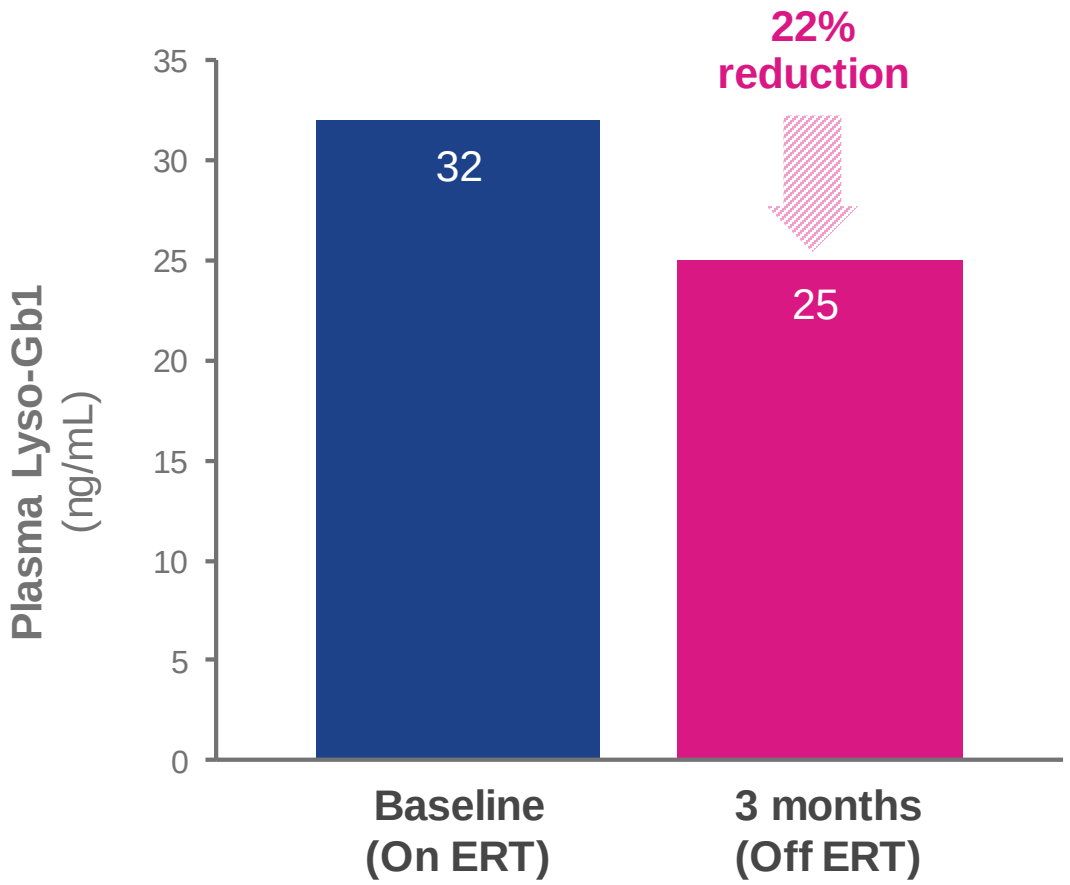
GD1: Gaucher Disease Type 1; ERT: Enzyme Replacement Therapy; SRT: Substrate Reduction Therapy; 1H: First Half

Toxic metabolite lyso-Gb1 reduced below ERT levels at 3 months

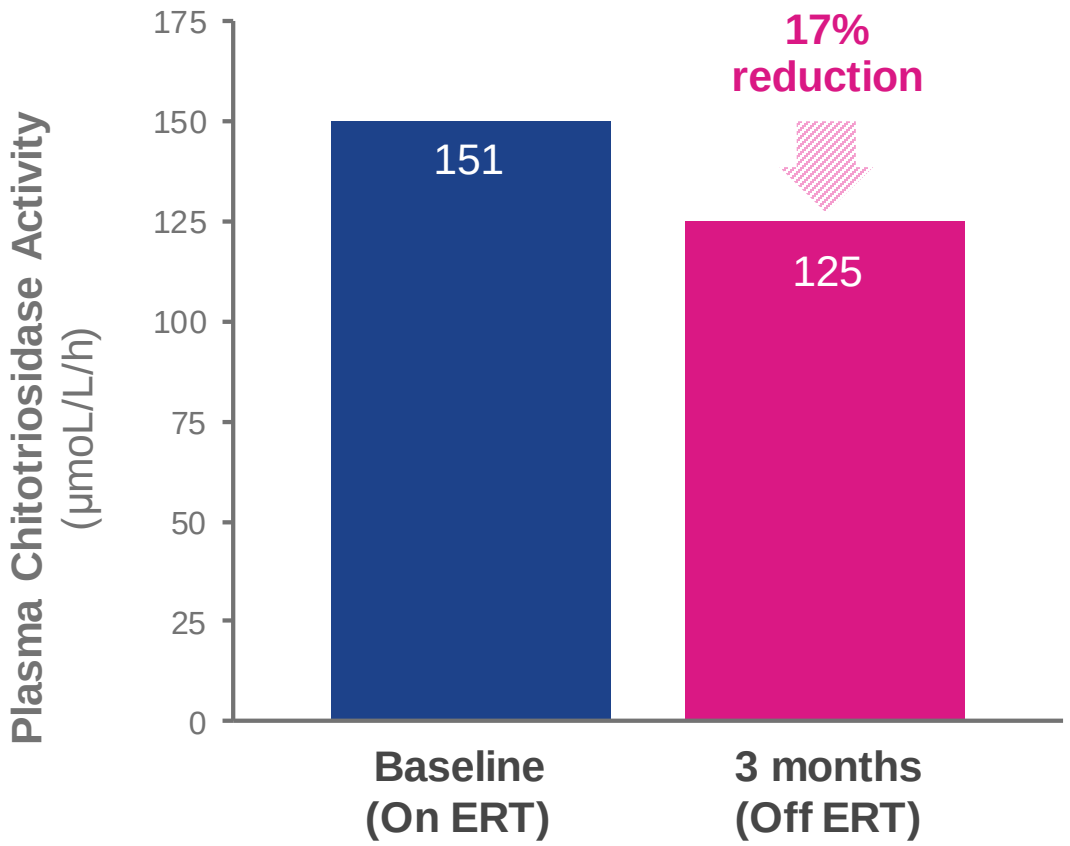
Lyso-Gb1, a sensitive and specific marker of metabolite accumulation in Gaucher disease is decreased relative to baseline on ERT



Lyso-Gb1 Plasma Normal Range: 0.5 – 1.2 ng/mL
ERT: Enzyme Replacement Therapy; Lyso-Gb1: Glucosylsphingosine

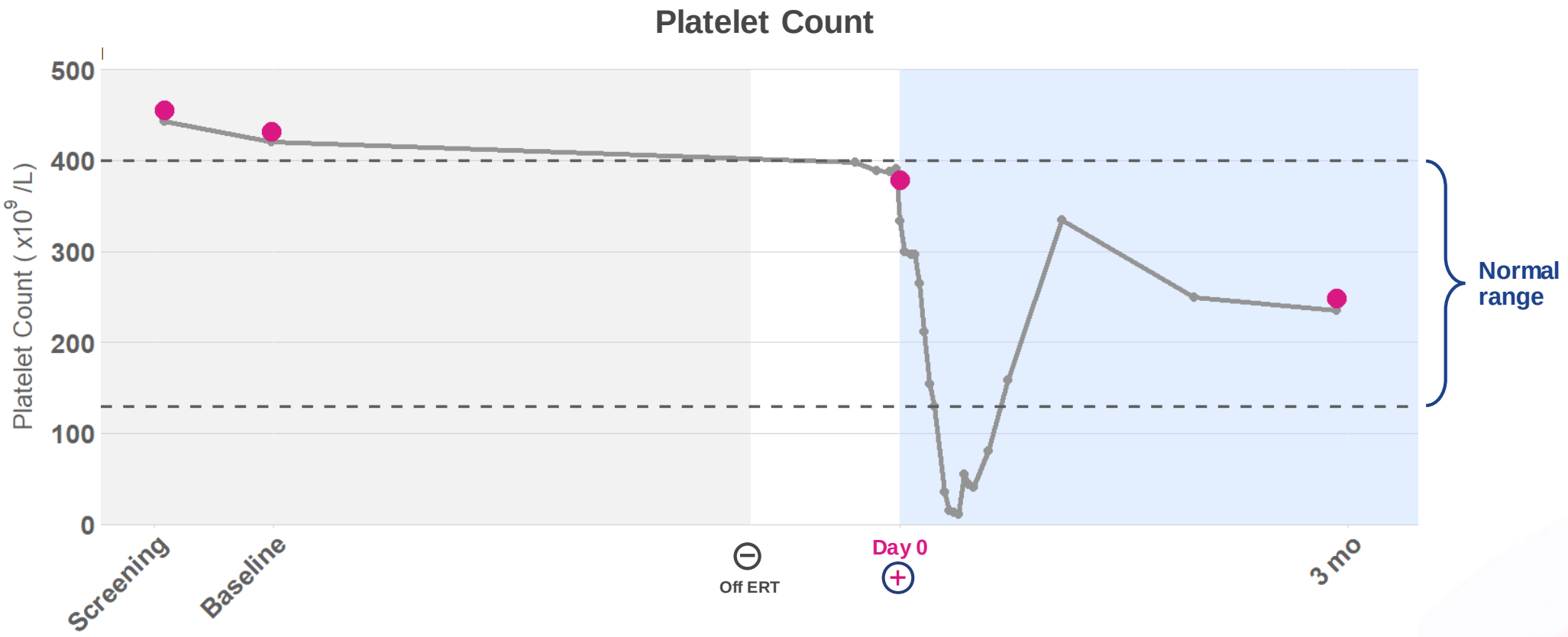
Plasma chitotriosidase reduced below ERT levels at 3 months

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



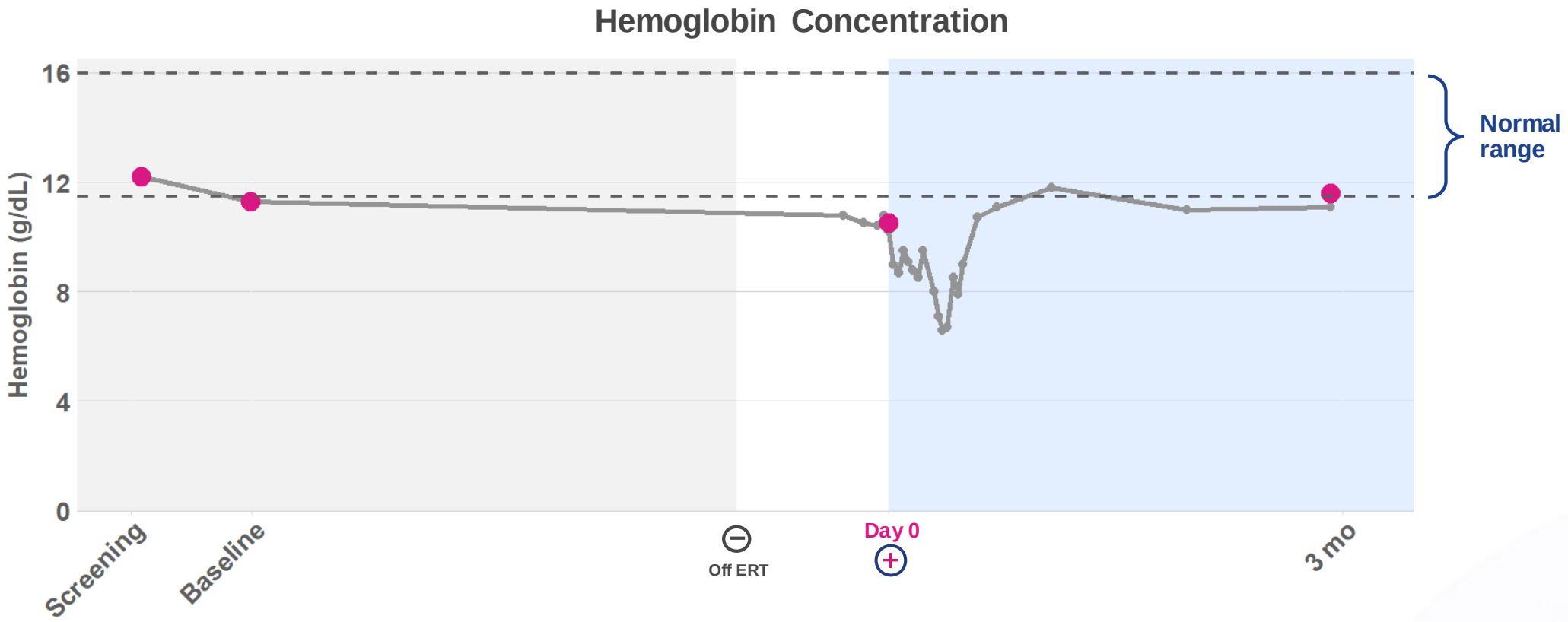
Chitotriosidase Plasma Activity Normal Range: 0.0–44.2 µmoL/L/h
ERT: Enzyme Replacement Therapy

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



Platelet Count Reference Value Adult: 130-400x10^9/L; grey line: local (safety) lab values; pink dots: central (efficacy) lab values
ERT: Enzyme Replacement Therapy

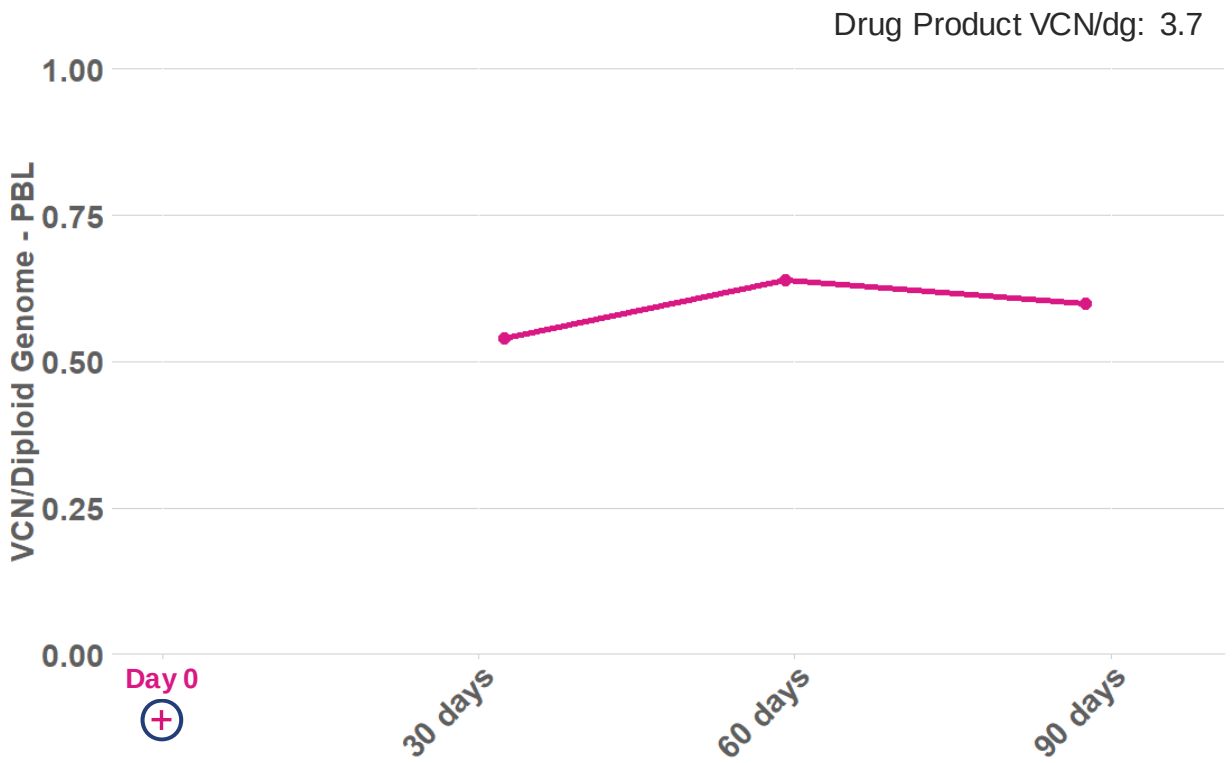
Hemoglobin normal at 3 months, despite being off ERT



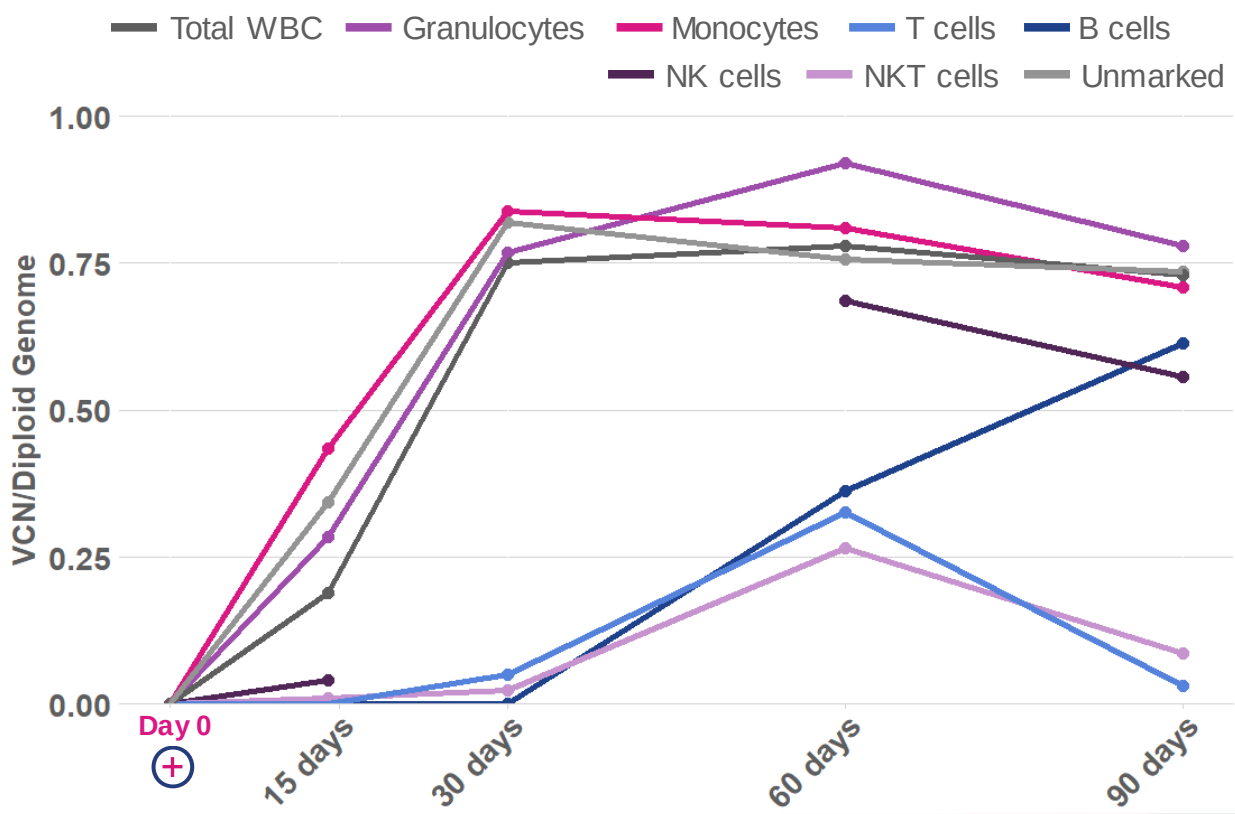
Hemoglobin Reference Value: Males: 13.5-17.5 g/dL; Females: 11.5-16.0 g/dL; grey line: local (safety) lab values; pink dots: central (efficacy) lab values
ERT: Enzyme Replacement Therapy

VCN reflects stable presence of transgene in macrophages

Average VCN



Exploratory Cell Subtype VCN



VCN: Vector Copy Number; PBL: Peripheral Blood Leukocytes; dg: Diploid Genome; WBC: White Blood Cell; NK: Natural Killer; NKT: Natural Killer T

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

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

QOL: Quality Of Life; ERT: Enzyme Replacement Therapy

AVR-RD-02

Anticipated Next Steps

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

Fabry Disease

Travis, living with Fabry disease

DIFFERENTIATED TARGET PRODUCT PROFILE *for*

Fabry Disease

First-Line Therapy and Functional Cure

Prevents, halts or reverses disease; normalizes lifespan

- Cardiovascular disease
- Renal disease
- TIA/stroke, peripheral pain
- GI issues, hearing loss, fatigue
- CNS: executive function deficit, depression

Lifelong durability

- Single infusion for life
- No waning of efficacy
- Off ERT/chaperone
- Off concomitant medication
- Save millions of dollars in healthcare costs per patient

Addresses all patient segments

- All genetic mutations
- All age groups
- Male and female
- No AAV or ERT neutralizing antibody limitations

Impacts hard-to-reach organs

- Brain: global distribution of genetically modified microglia
- Heart, kidney: tissue-resident cells penetrate and distribute into all organs

Well-tolerated

- No ERT/chaperone-related side effects
- Mild-to-moderate, transient side effect profile consistent with Bu90-TCI
- No liver toxicity or adverse immunogenicity

Note: These are target attributes for a first-line therapy

AAV: Adeno-Associated Virus; Bu90-TCI: Busulfan 90-Target Concentration Intervention; CNS: Central Nervous System; GI: Gastrointestinal; TIA: Transient Ischemic Attack; ERT: Enzyme Replacement Therapy

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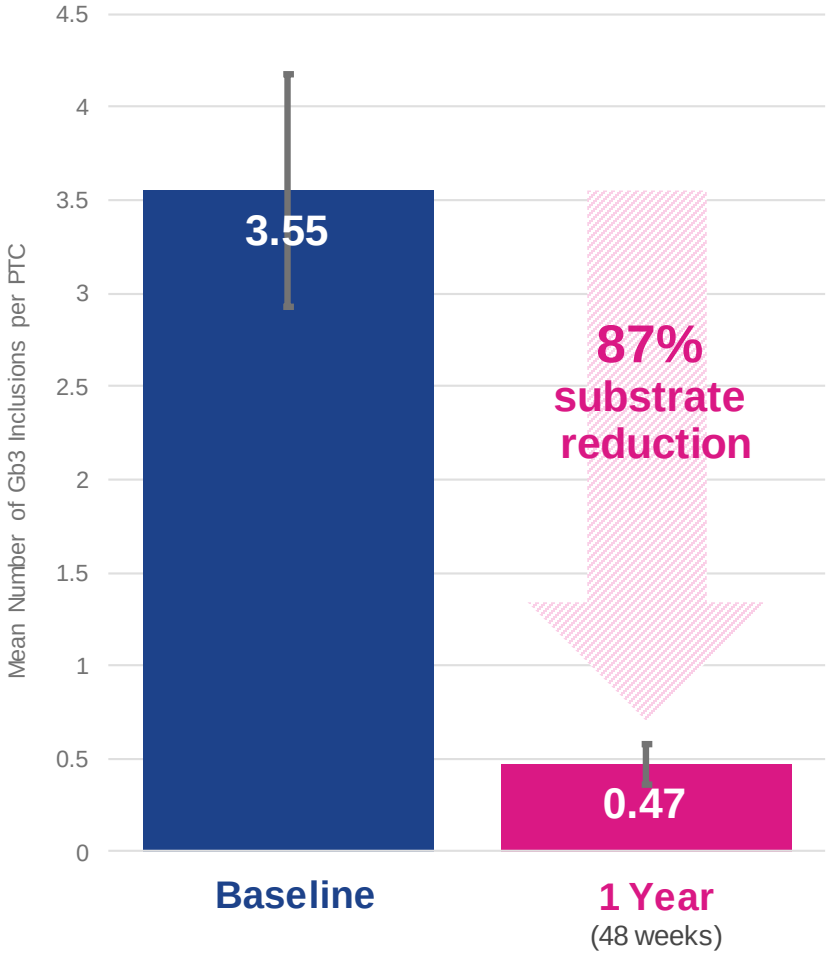
Substantial reduction of substrate in kidney biopsy at 1 year

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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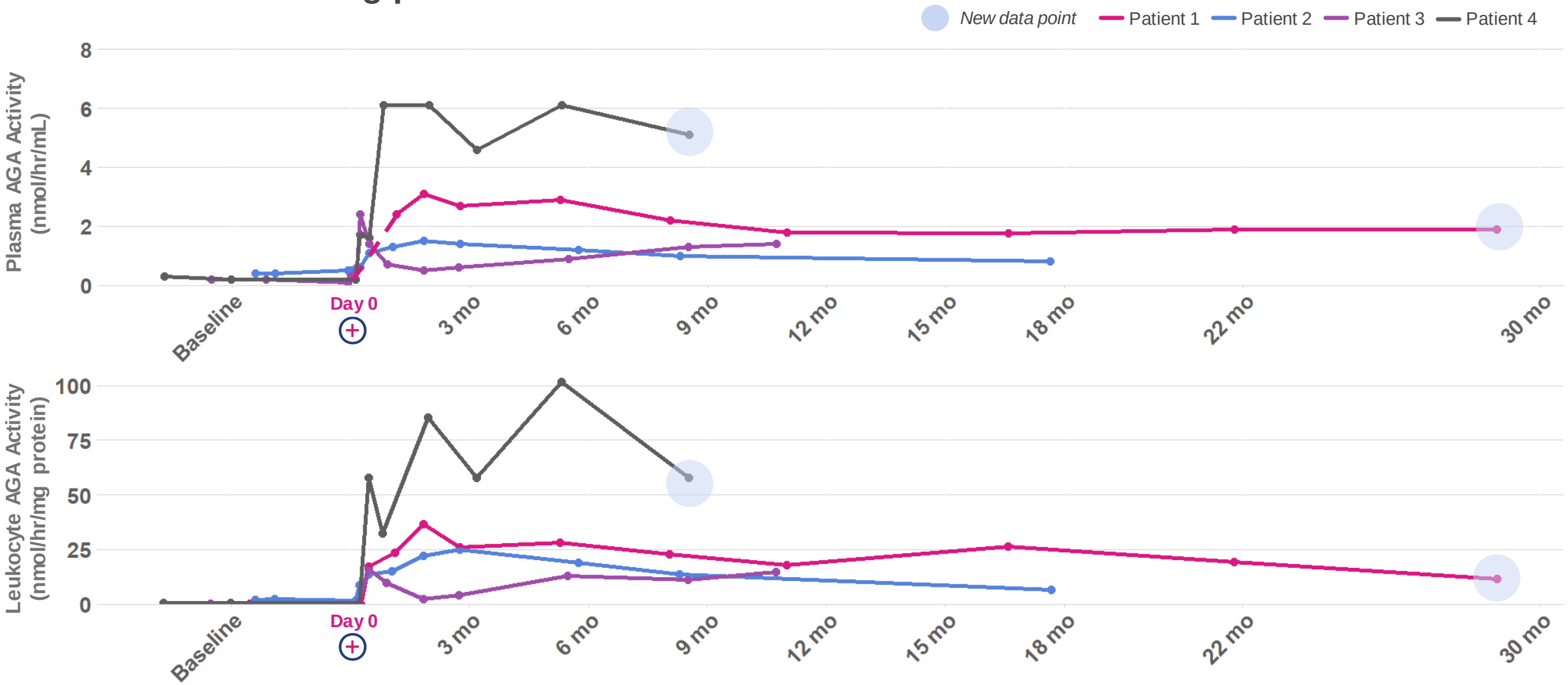
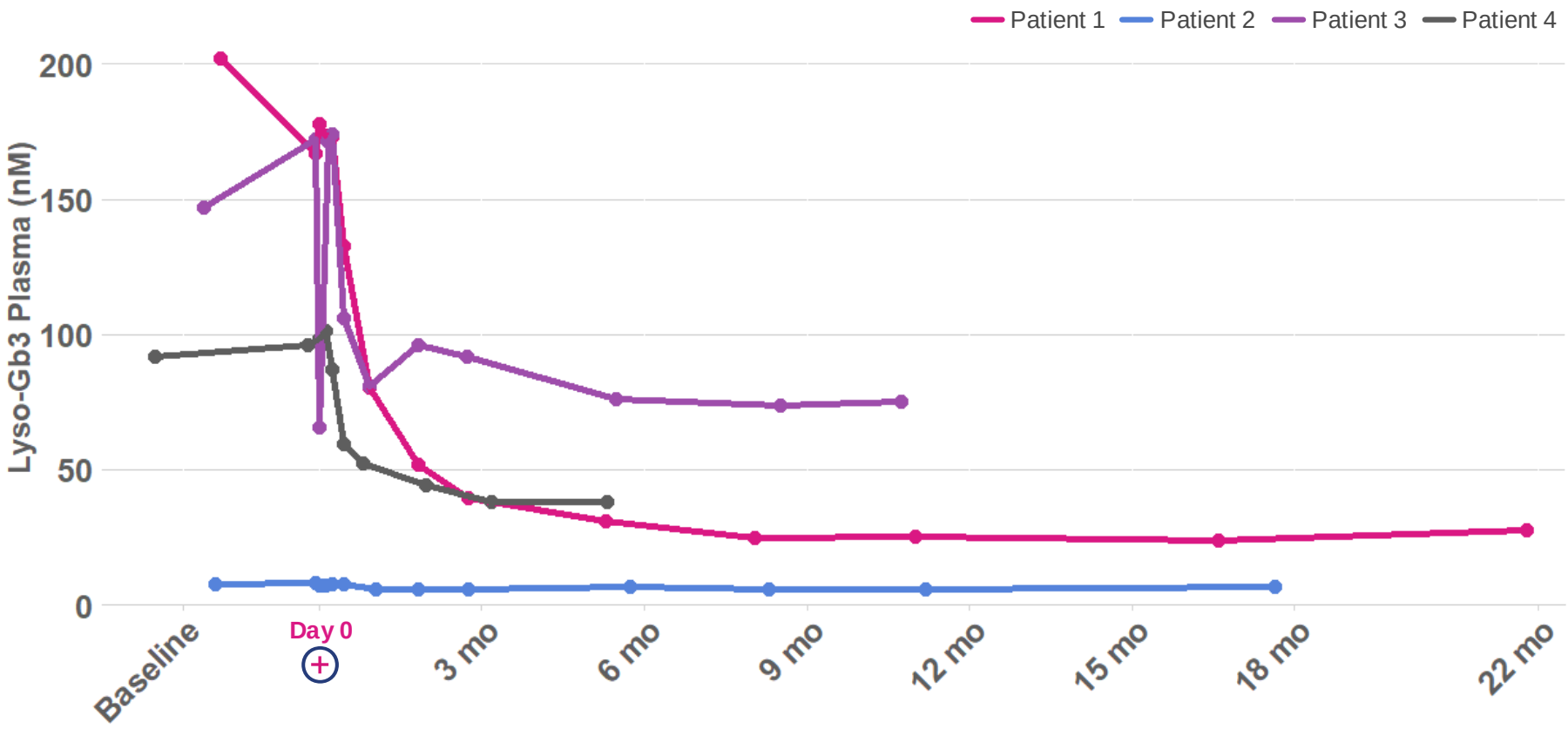
Plasma, leukocyte enzyme activity sustained up to 2.5 yrs

Patient 4 dosed using plato®



Leukocyte AGA Activity Reference Range: 24–56 nmol/hr/mg protein; Plasma AGA Activity Reference Range: 5.1–9.2 nmol/hr/mL; AGA: α-galactosidase A

Plasma lyso-Gb3 reduction sustained up to 1.8 years



Reduction from Baseline to Last Observation	
Patient 1	86%
Patient 2	N/A
Patient 3	49%
Patient 4	59%

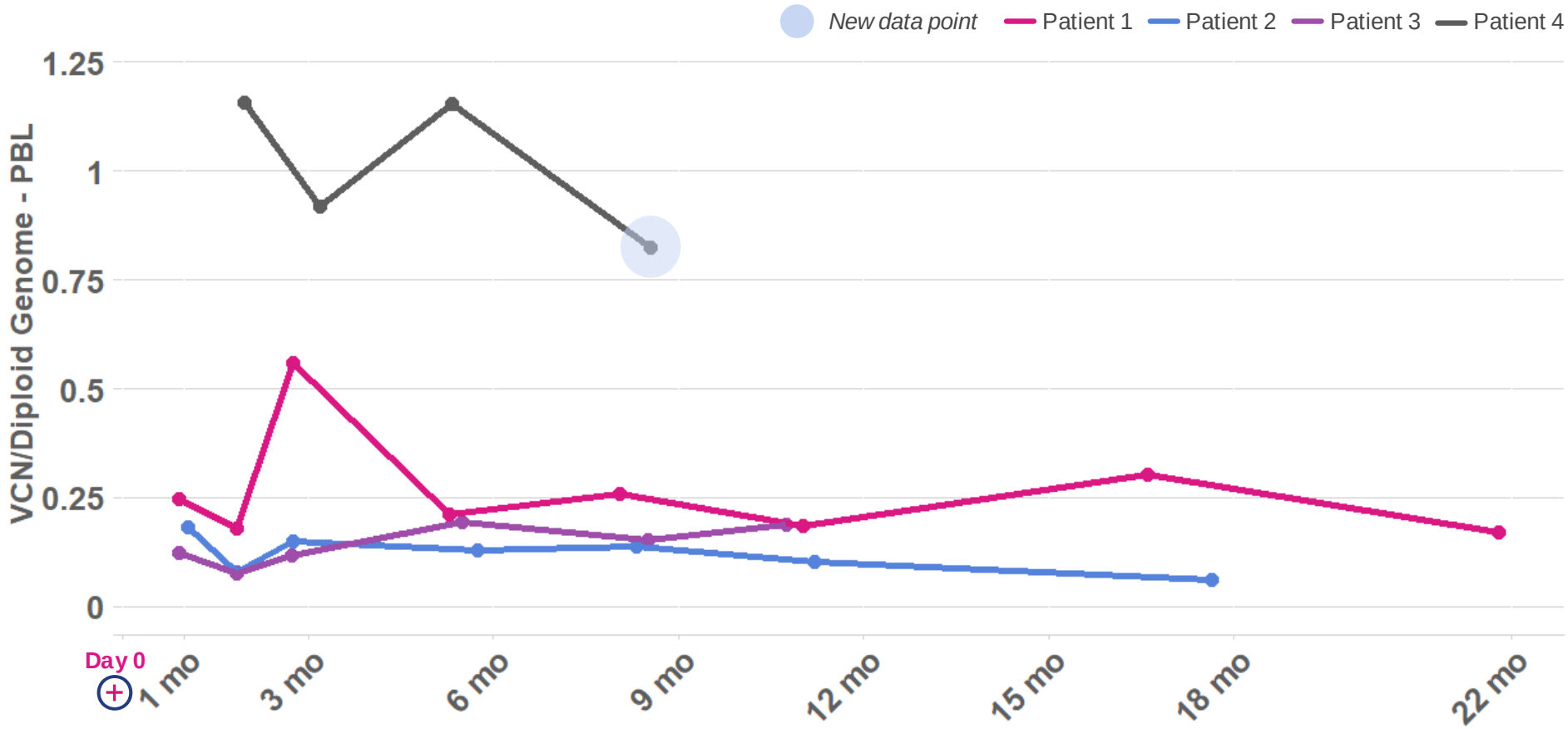
Lyso-Gb3 Plasma Reference Value: 2.4 nM; Lyso-Gb3: Globotriaosylsphingosine
Note: Patient 2 has normal substrate, consistent with late-onset cardiac variant phenotype

AVROBIO

VCN trends stable up to 1.8 years

Patient 4 dosed using plato®

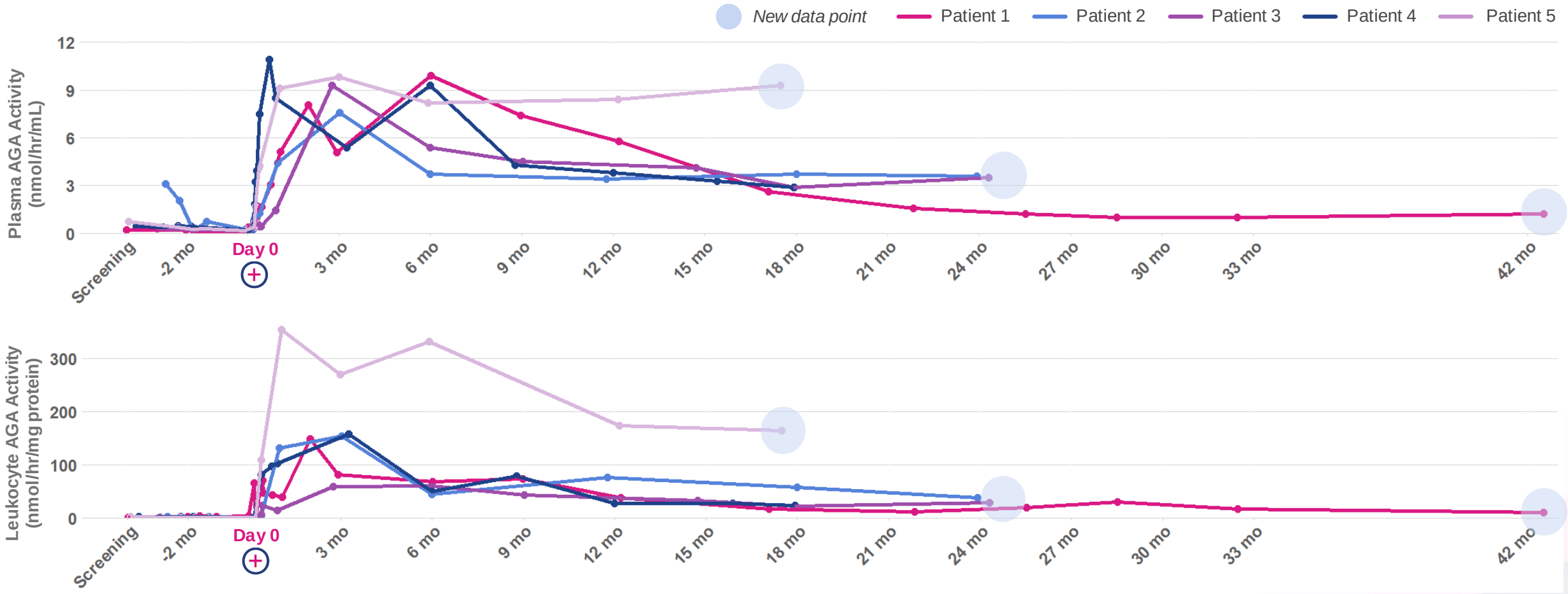
Drug Product VCN/dg	
Patient 1	0.7
Patient 2	0.5
Patient 3	1.4
Patient 4	1.6



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

Plasma, leukocyte enzyme activity sustained up to 3.5 yrs

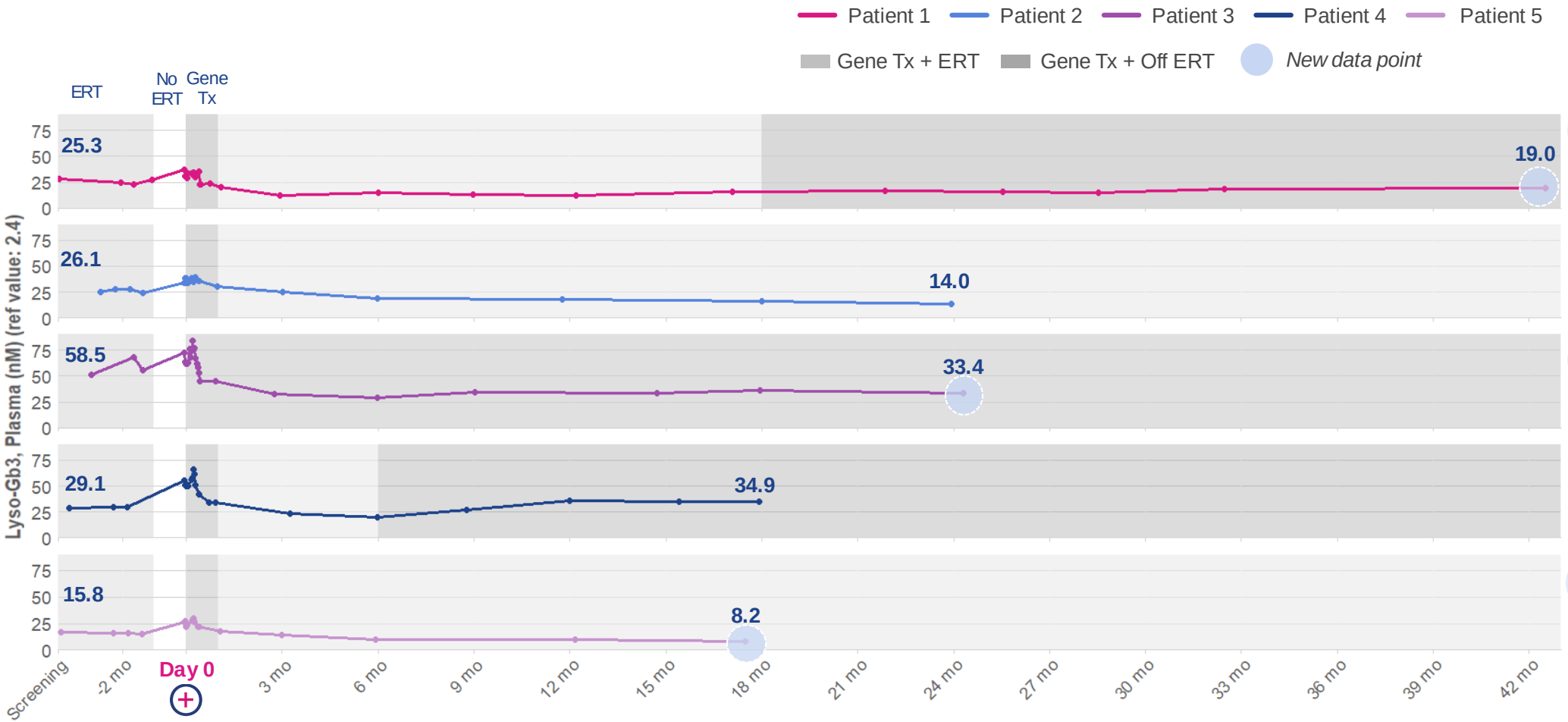
All 5 patients now out 18 months or more



Leukocyte AGA Activity Reference Range: 24–56 nmol/hr/mg protein; Plasma AGA Activity Reference Range: 5.1–9.2 nmol/hr/mL; AGA: α-galactosidase A

29% average lyso-Gb3 reduction below baseline ERT

All patients who have discontinued ERT remain off ERT*



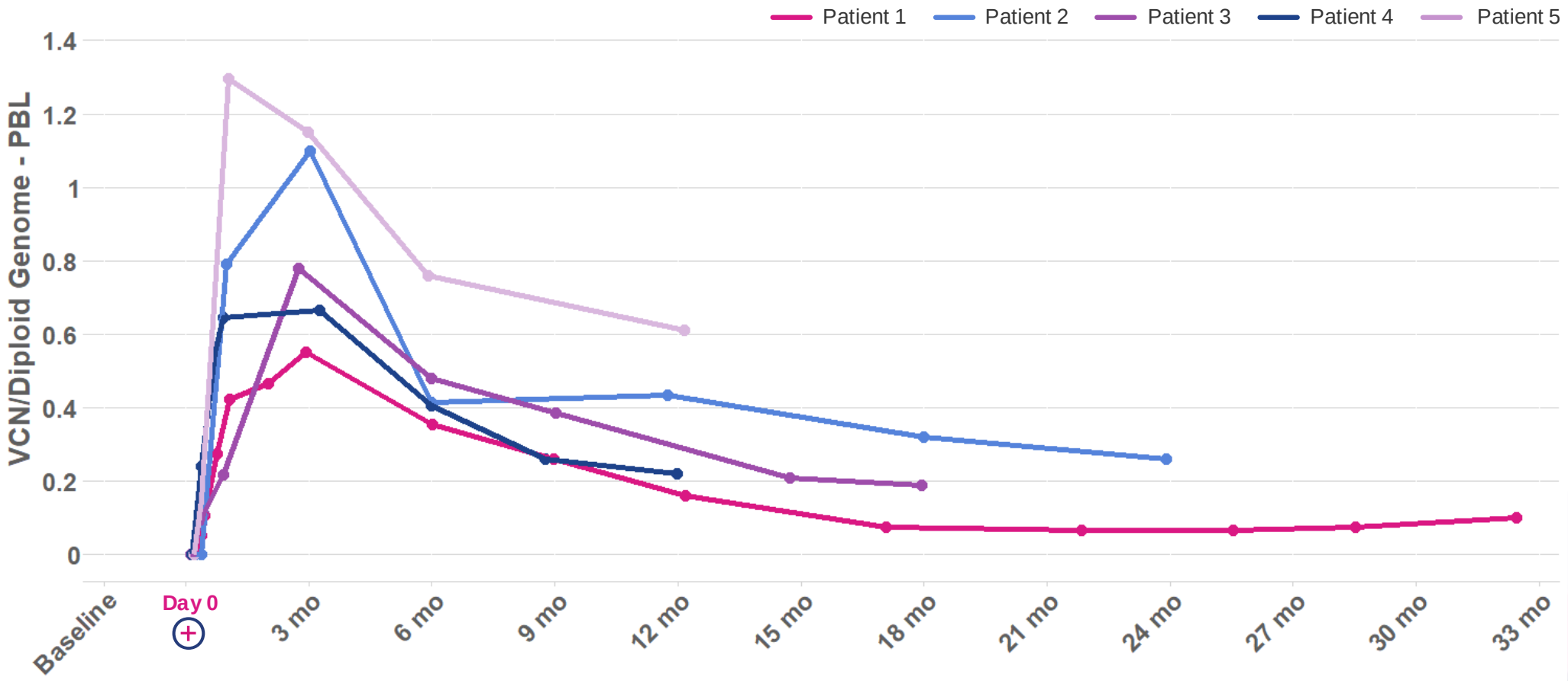
** As of October 26, 2020*

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

VCN stable up to 2.7 years

All 5 patients now out 1 year or more

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

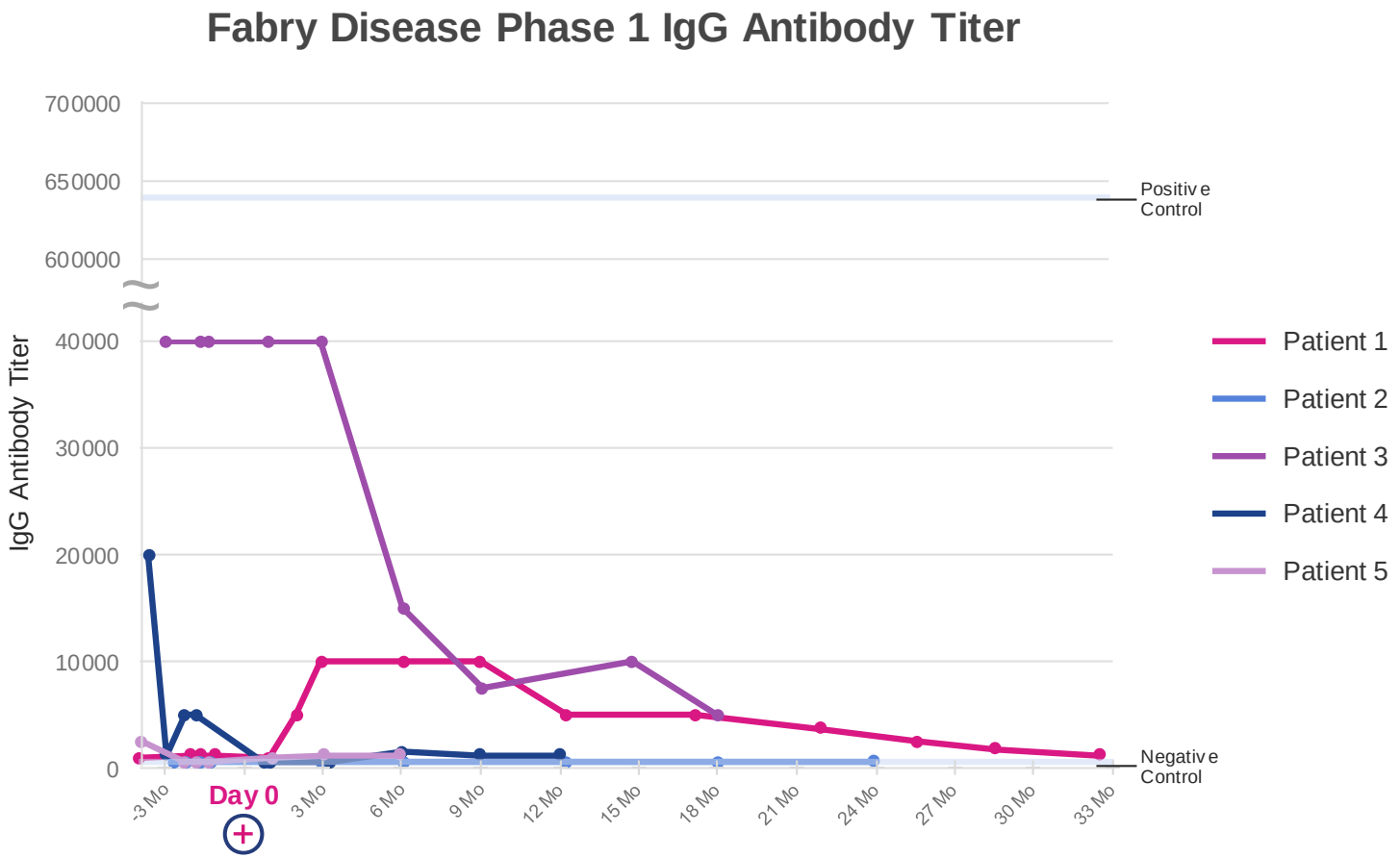


Note: 0.1 VCN is indicative of approx. 5-10% of all nucleated cells having an average of 1-2 copies of the transgene; Some data points delayed due to COVID vendor laboratory employment furloughs

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

Reduction of pre-existing anti-ERT drug IgG antibodies

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



Similar results observed in other studies

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

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

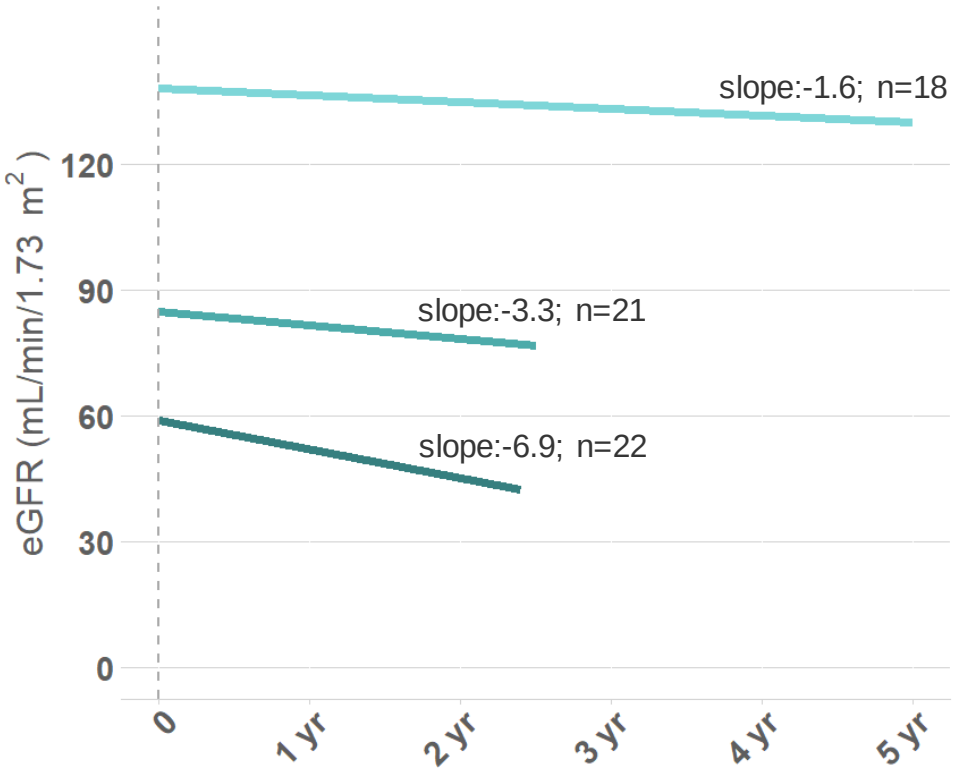
- *Ex vivo* LV gene therapy with conditioning
- n=6
- Evaluable patients (5/6) demonstrated sustained, supraphysiologic blood IDUA activity
- 4/5 prior ERT (rhIDUA) exposure (5-28 months)
- 4/5 pre-existing ERT-induced IgG antibodies
- 6/6 anti-rhIDUA IgGs undetectable 2 months post-gene therapy

Source: Gentner B et al., Blood, 2019
ERT: Enzyme Replacement Therapy; IgG: Immunoglobulin G; MPS-1: Mucopolysaccharidosis Type 1; IDUA: Iduronidase: SR-TIGET: San Raffaele Telethon Institute for Gene Therapy; LV: Lentiviral; rhIDUA: Recombinant Human alpha-L-Iduronidase

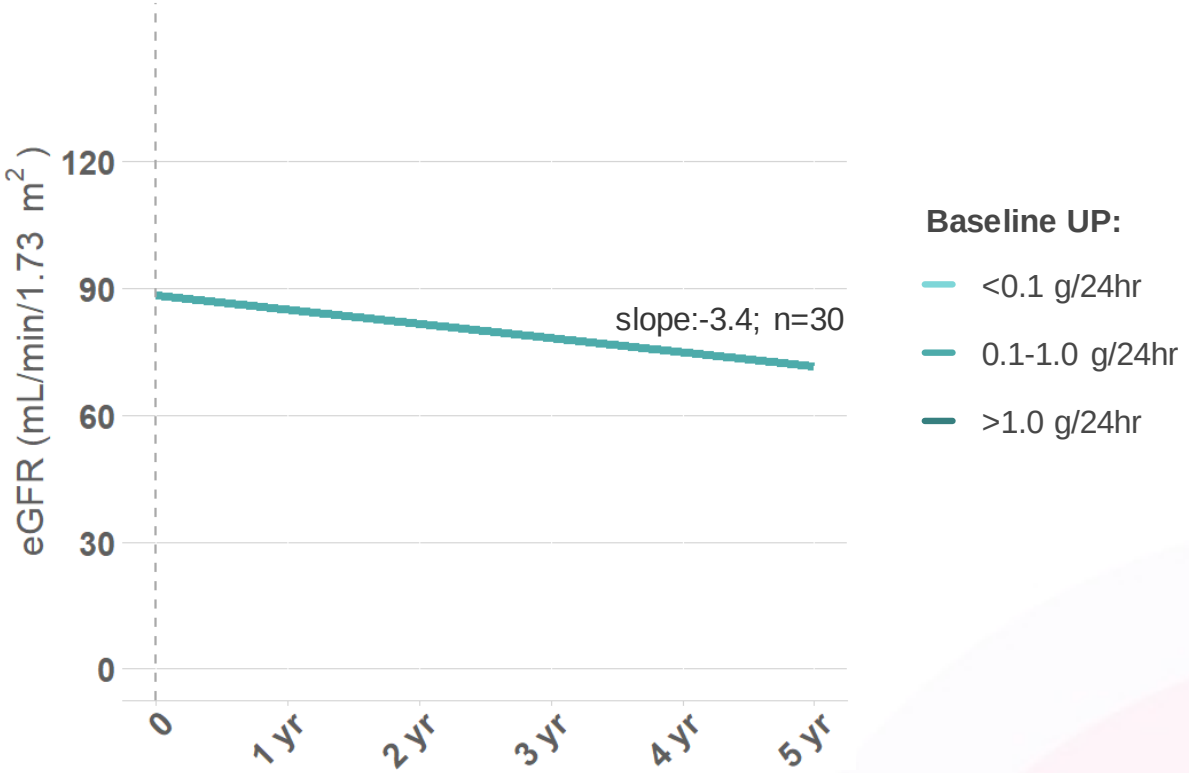
eGFR declines in natural history and on ERT

Classic Fabry male literature eGFR data

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

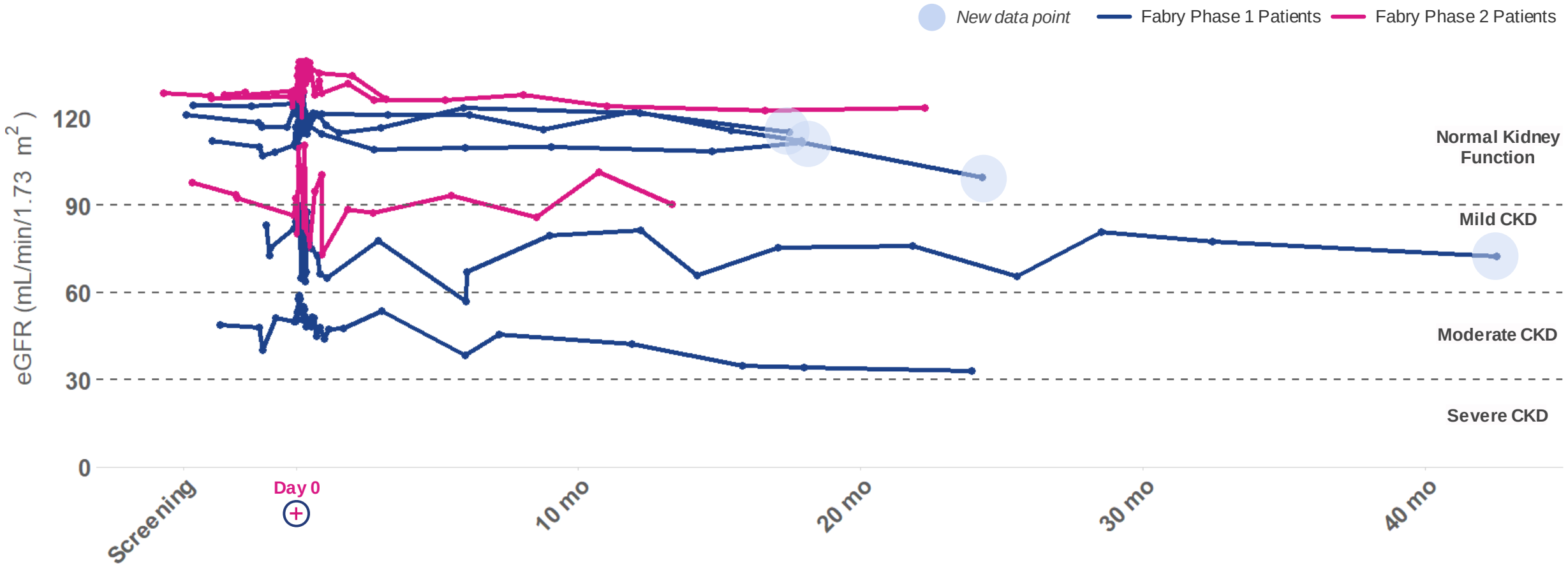


Annualized eGFR slope of ERT-treated patients[2]



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

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

AVROBIO

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

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

AVR-RD-01

Anticipated Next Steps

- Phase 2 study additional kidney biopsy data by EOY ‘20
- Discuss accelerated approval approach with FDA by Q1 ‘21
- Expand Phase 2 study and complete enrollment
- Initiate confirmatory ERT-switch trial in 2021
- Seek early FDA agreement on potency assay matrix
- Advance commercial readiness activities including payors / HTA interactions

EOY: End Of Year; FDA: Food and Drug Administration; ERT: Enzyme Replacement Therapy; HTA: Health Technology Assessment

Cystinosis

"To know that your child, he could live a life 'til he's 30... Or he could not. That's a reality we live with every day."

– Chelsea, mother of Jaxon, a 3-year-old living with cystinosis

DIFFERENTIATED TARGET PRODUCT PROFILE *for*

Cystinosis

First-Line Therapy and Functional Cure

Prevents, halts or reverses disease; normalizes lifespan

- Fanconi syndrome and renal failure
- Compromised stature, myopathy, respiratory failure, swallowing dysfunction
- Vision: acuity, photophobia
- Endocrine disorders: hypothyroidism and diabetes
- Premature skin aging, coarse facial features
- Fatigue
- CNS: encephalopathy and learning difficulties

Lifelong durability

- Single infusion for life
- No waning of efficacy
- Off cysteamine oral and eye drops
- Off Fanconi syndrome supplements
- Save millions in healthcare costs per patient

Addresses all patient segments

- All age groups
- Male and female
- Infantile, nephropathic, late-onset, ocular
- Kidney transplant-independent

Impacts hard-to-reach organs

- Eye, endocrine organs, skin: global distribution of genetically modified macrophages
- Brain: global distribution of genetically modified microglia

Well-tolerated

- No cysteamine-related side effects, such as nausea, vomiting, dehydration, pill burden, sulfur halitosis or compliance challenges
- Mild-to-moderate, transient side effect profile consistent with Bu90-TCI
- Reduction in psychosocial impact

Note: These are target attributes for a first-line therapy

Bu90-TCI: Busulfan 90-Target Concentration Intervention; CNS: Central Nervous System

AVROBIO

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

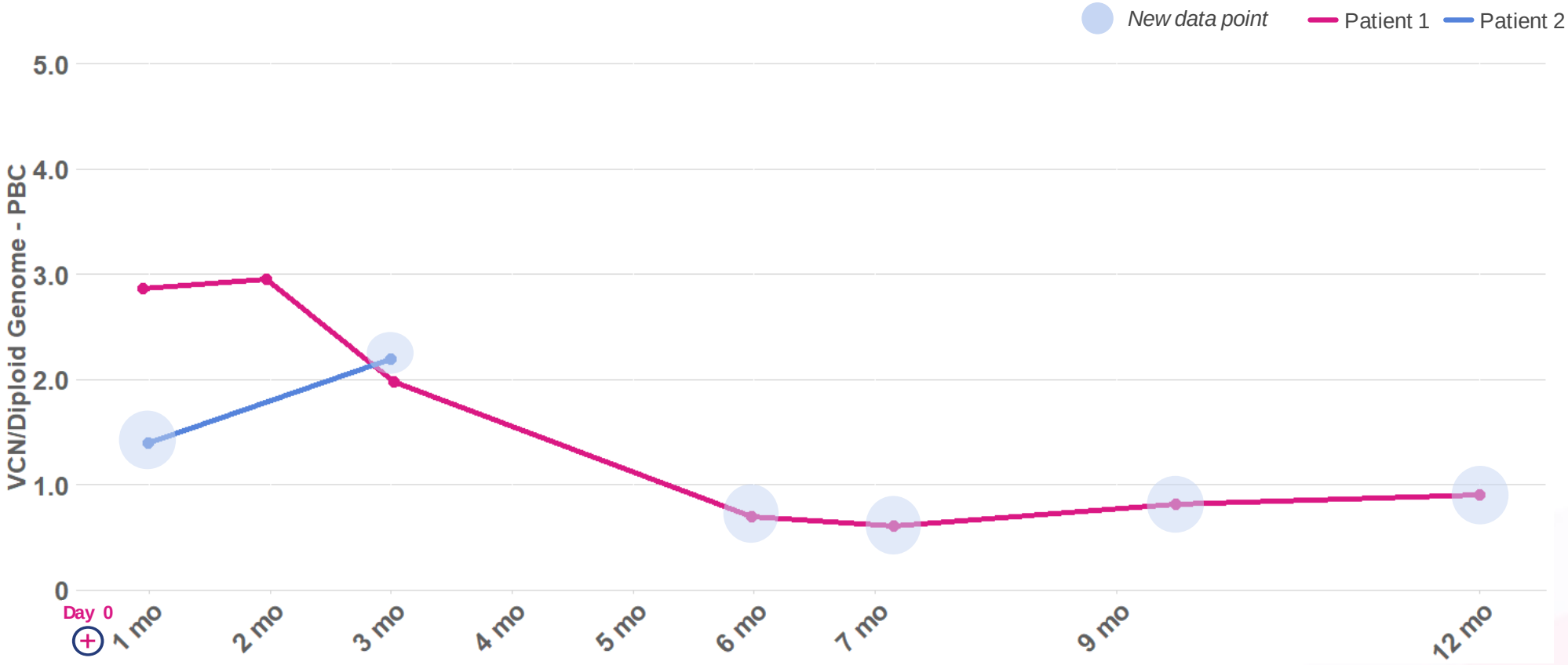
AVR-RD-04 trial sponsored by University of California, San Diego; IST does not use plato® platform
Note: AVR-RD-04 aka CTNS-RD-04
IST: Investigator Sponsored Trial

AVROBIO

Patient 1 reached VCN therapeutic plateau

Consistent with pattern seen across other clinical trials

Drug Product VCN/dg	
Patient 1	2.1
Patient 2	1.3*
Patient 3	1.6



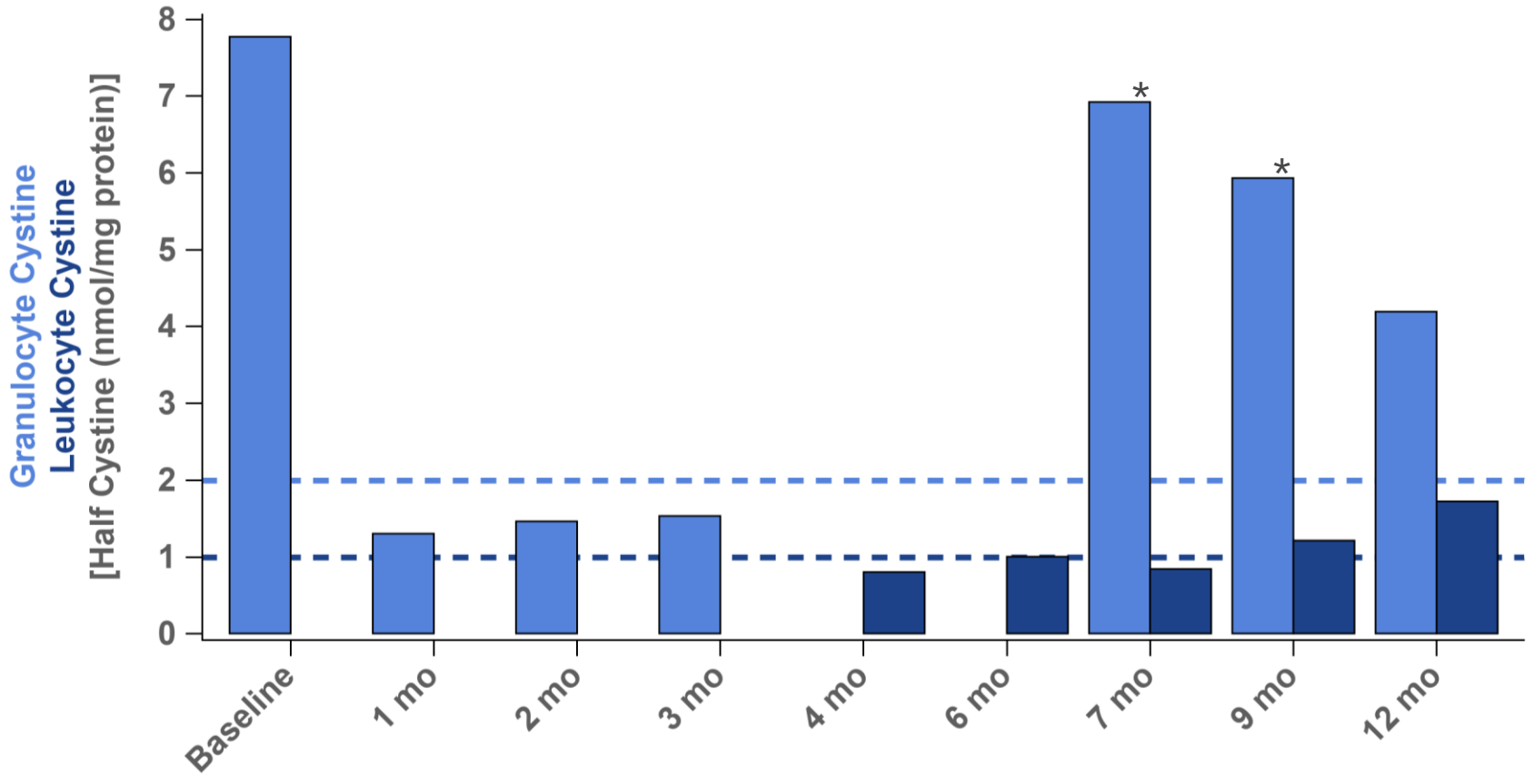
** From second apheresis*

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

Cystinosin is a multi-functional protein

mTORC1: Mechanistic/Mammalian Target of Rapamycin Complex 1; LAMP2A: Lysosome-Associated Membrane Protein 2A

Biomarkers for cysteamine are not biomarkers for gene therapy



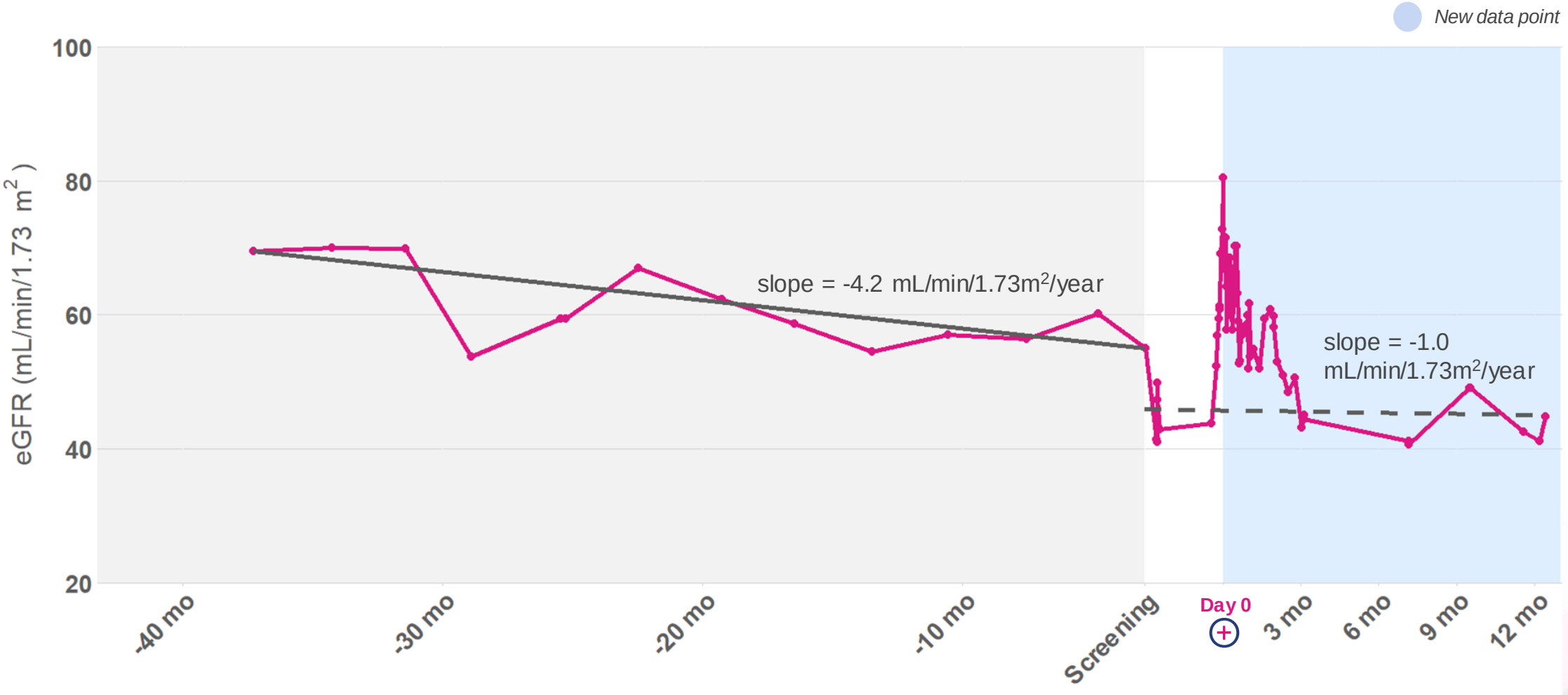
Granulocyte Cystine Carrier Asymptomatic Heterozygous Range: <1.9 µmol half cystine/g protein

Leukocyte Cystine Carrier Asymptomatic Heterozygous Range: <1 µmol half cystine/g protein

AVROBIO

** Samples handled differently (shipped) due to COVID travel restriction*

eGFR data at 1 year suggest renal function plateau post-treatment after years of pathological decline



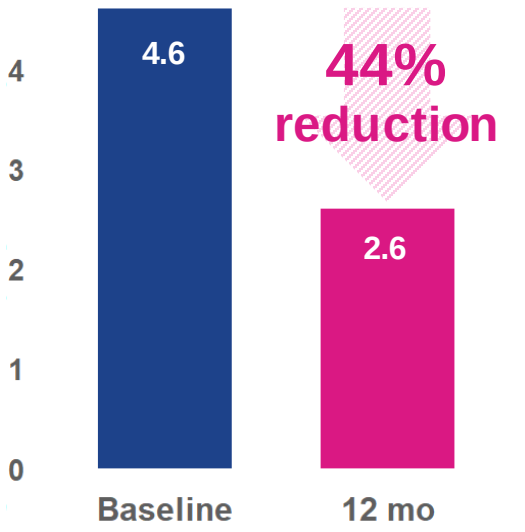
Note: These results are for a single patient only and may vary in the study population; eGFR calculated using CKD-EPI formula; eGFR: Estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

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

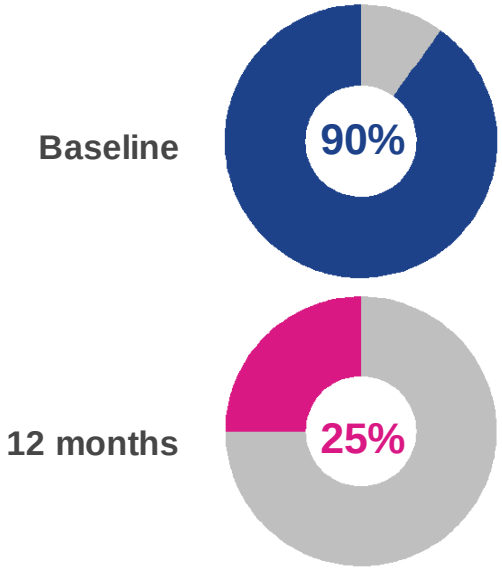
New data point

Skin Biopsy

Average intracytoplasmic crystals per cell

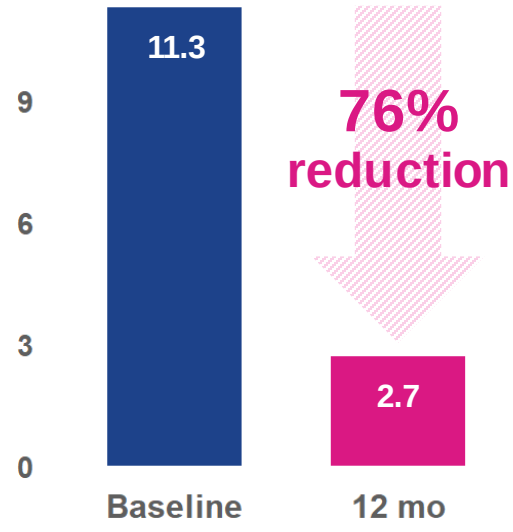


Occupancy of cytoplasmic volume

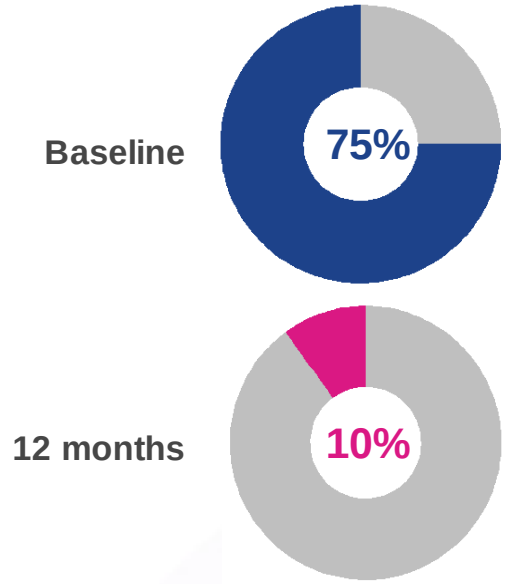


Rectal Biopsy

Average intracytoplasmic crystals per cell



Occupancy of cytoplasmic volume



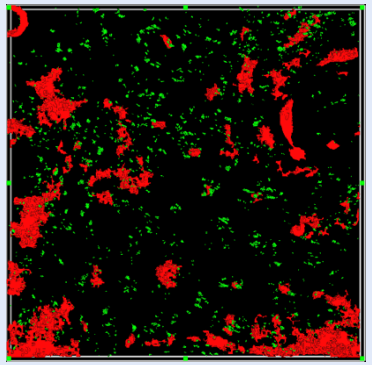
Note: These results are for a single patient only and may vary in the study population

Steady decline in crystal number and volume in the skin

New data point

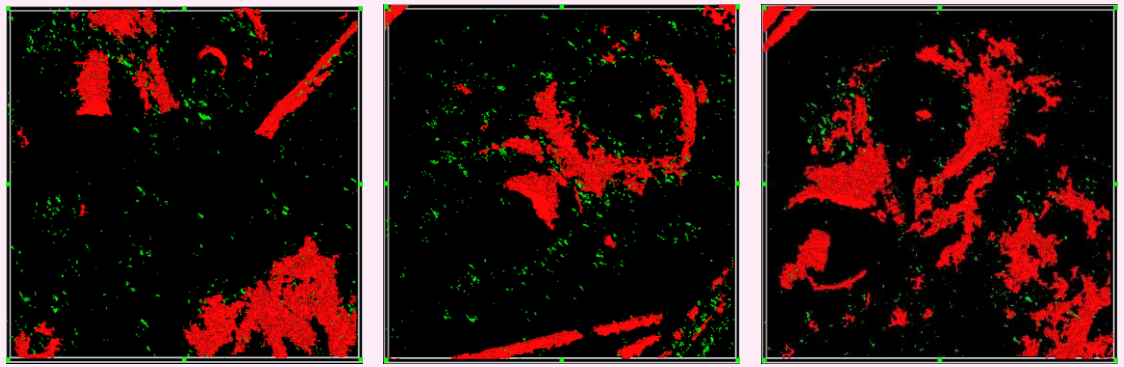
3D Crystal Reconstruction

Baseline

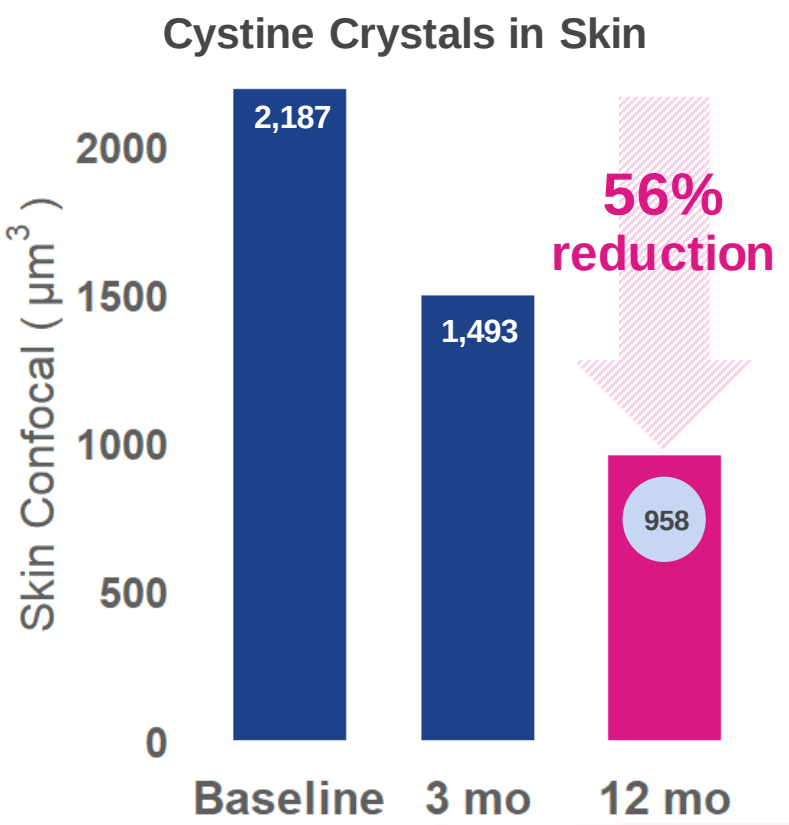


- skin structure in red
- cystine crystals in green

12 months



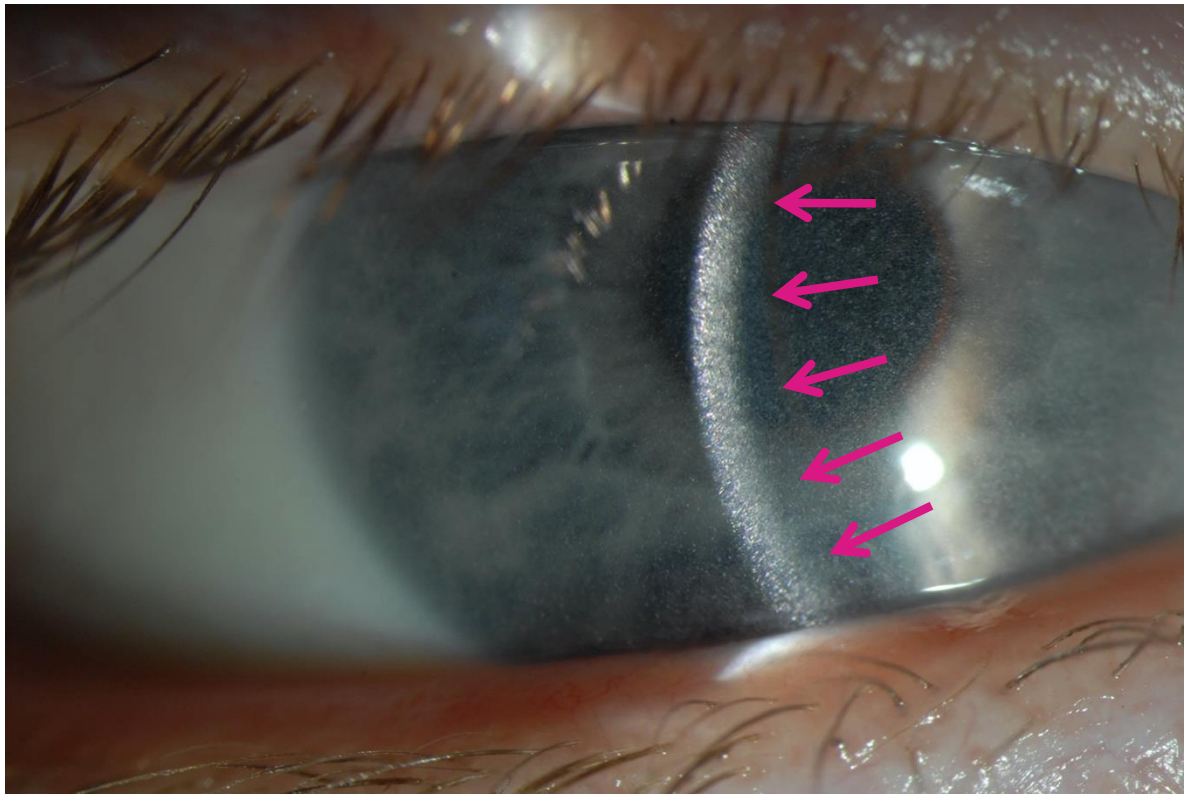
3D Normalized Crystal Volume



Note: These results are for a single patient only and may vary in the study population
Method: Experimental in vivo confocal microscopy; two skin areas, behind the ear and 'optional', averaged; analysis and quantification (3D Image-Pro software)

Crystal buildup in eye clearly visible before gene therapy

Patient 1 at baseline



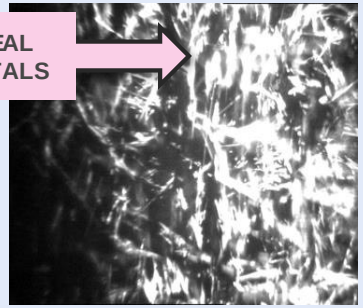
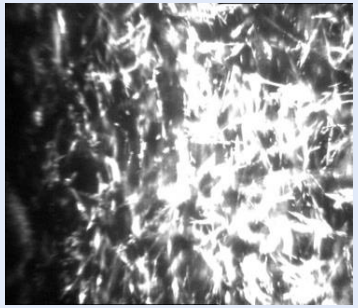
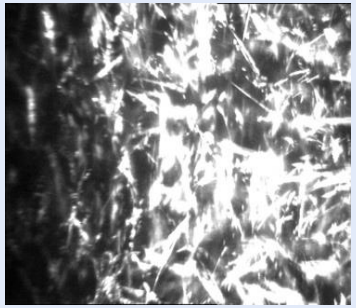
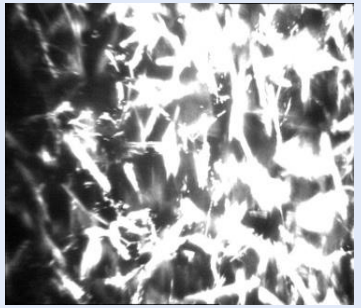
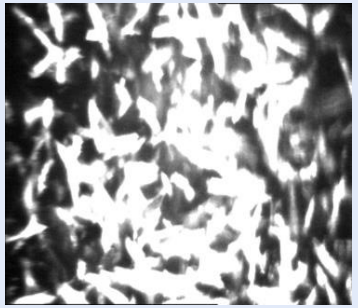
Substantial decline in corneal crystals observed at 1 year

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

Baseline

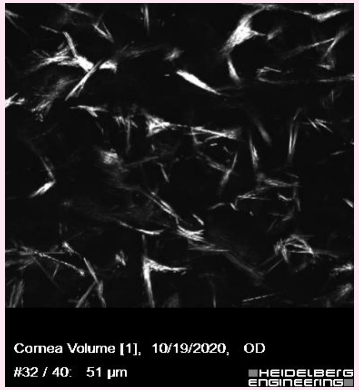
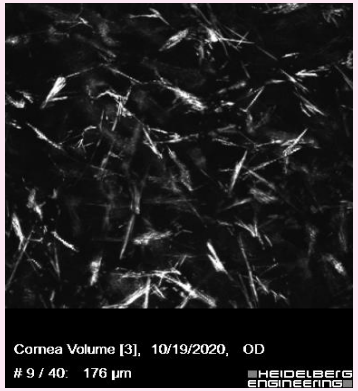
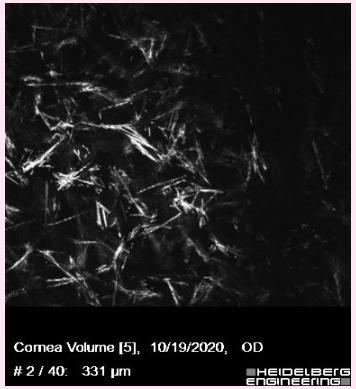
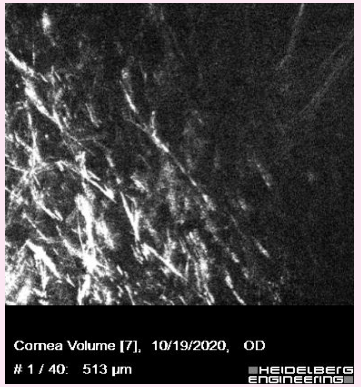
IVCM images from Nidek Confoscan

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

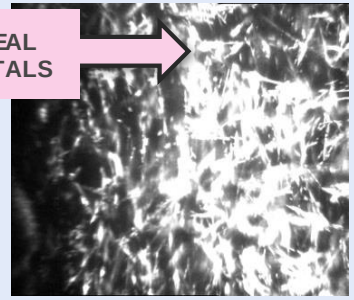
51 µm, OD	176 µm, OD	331 µm, OD	513 µm, OD
			

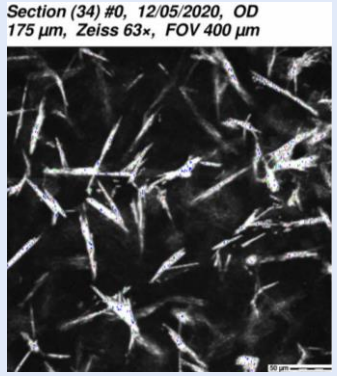
Note: These results are for a single patient only and may vary in the study population; IVCM: In Vivo Confocal Microscopy; OD: Oculus Dexter (right eye); HRT3: Heidelberg Retina Tomograph 3

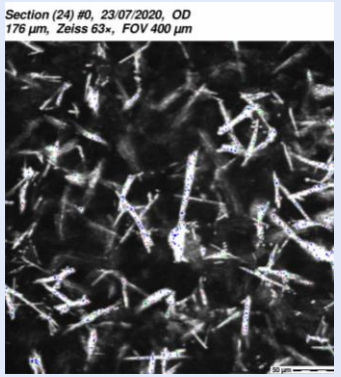
AVROBIO

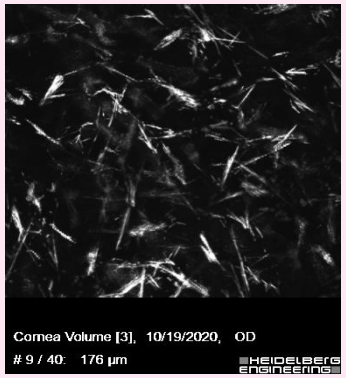
Substantial decline in corneal crystals observed over 1 year

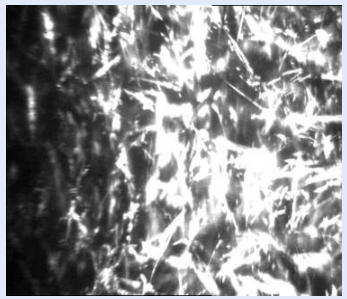
	Baseline IVCM Nidek images	7 months IVCM Heidelberg images	9 months IVCM Heidelberg images	12 months IVCM Heidelberg images
Front of cornea	*174 µm, OD* CORNEAL CRYSTALS	*175 µm, OD*	*176 µm, OD*	*176 µm, OD*
Back of cornea	*330 µm, OD*	*331 µm, OD*	*317 µm, OD*	*331 µm, OD*

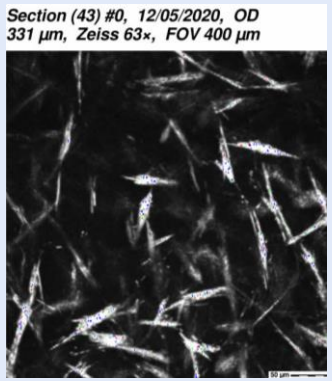


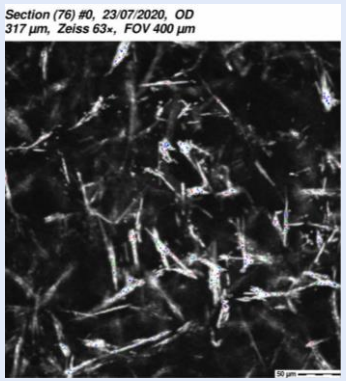


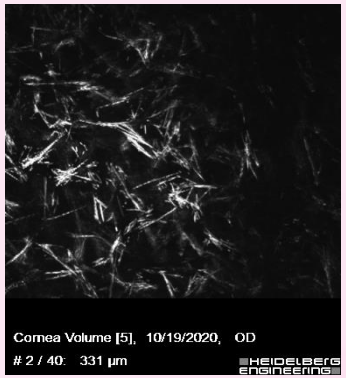












Note: These results are for a single patient only and may vary in the study population; IVCM: In Vivo Confocal Microscopy; OD: Oculus Dexter (right eye); Nidek and Heidelberg with Rostock Corneal Module are different IVCM instruments

AVROBIO

Patient remains off cysteamine and eye drops at 1 year

Daily cysteamine regimen

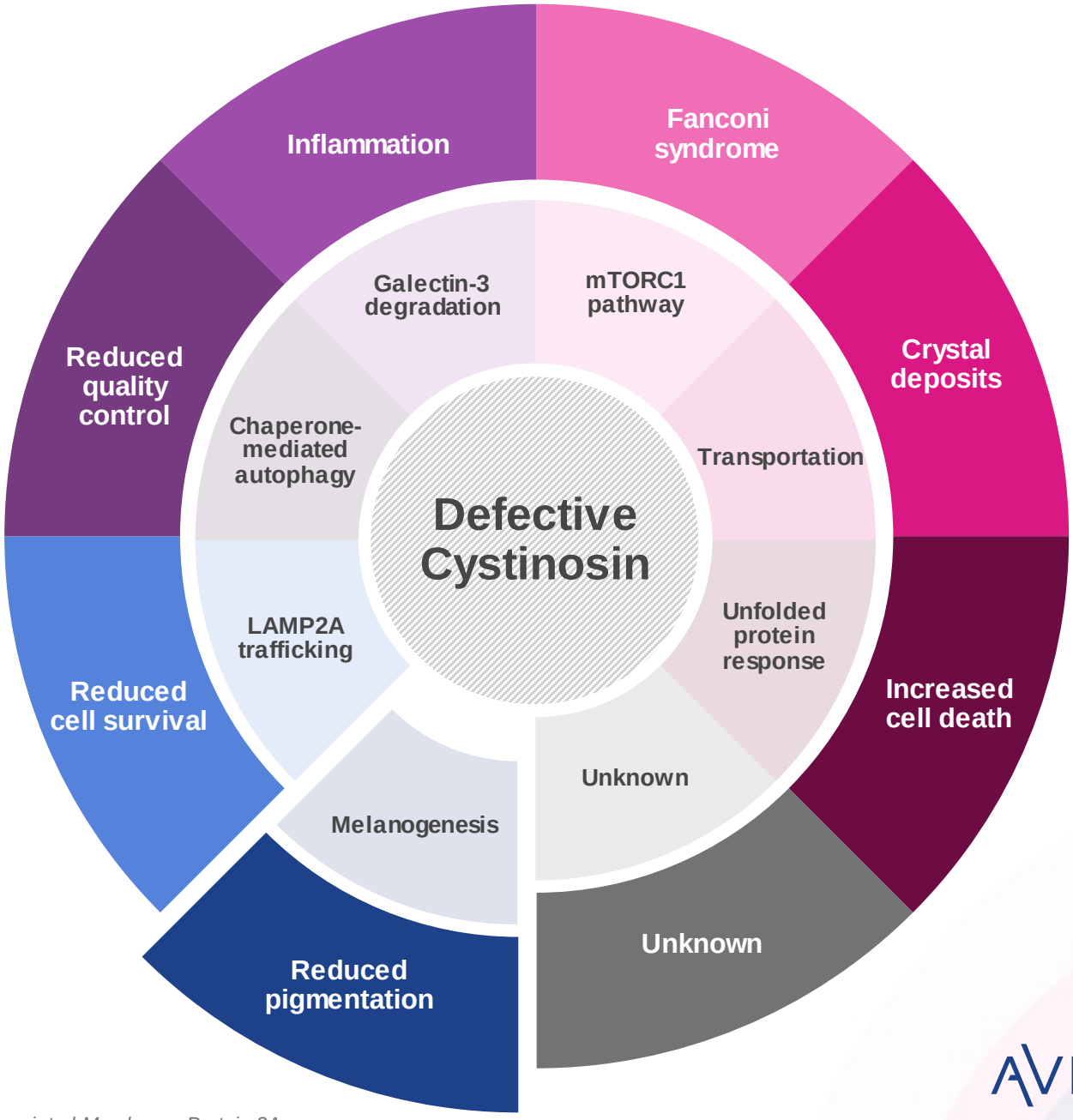
(max per day)

New data point

	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

Cystinosin is a multi-functional protein

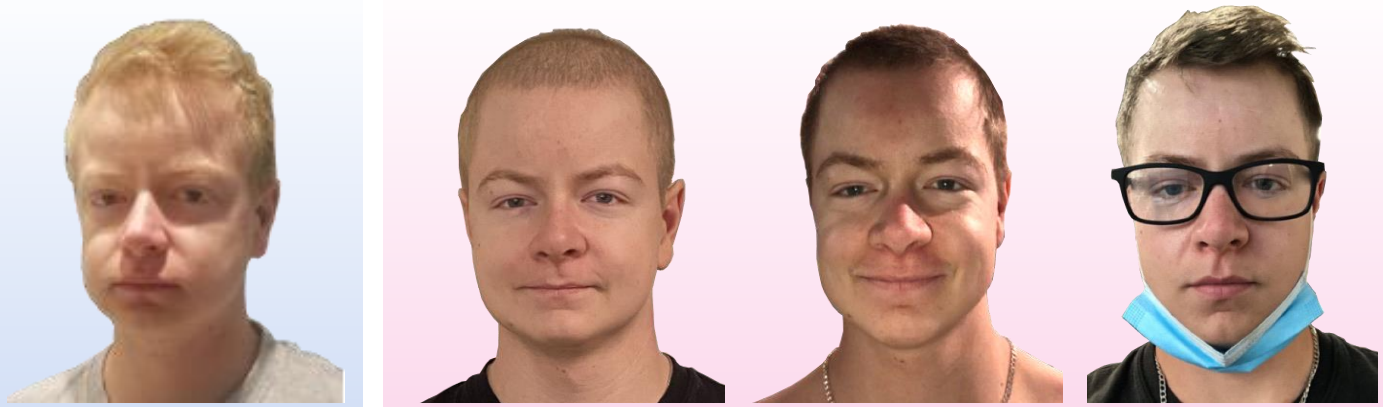


mTORC1: Mechanistic/Mammalian Target of Rapamycin Complex 1; LAMP2A: Lysosome-Associated Membrane Protein 2A

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

First patient in trial shares update on CRF website

One year post-gene therapy administration

…I definitely don't feel as sick all the time like I used to, and I physically feel better in many ways…

…The one thing that is drastically changed is the odor caused by … the medicine I used to take for cystinosis. The odor is completely gone now and that has made me feel more confident about myself. I'm not as self-conscious when I'm around people because the smell is gone.

…Going through this experience has definitely given me a different outlook on life. Today, I feel like I can do anything or become whomever I want. There isn't anything holding me back…

…I hope one day what I did will help your children or someone you know with the disease and we can all be cured together!

These are one patient's observations and may not be indicative of other patients' experience and should not be interpreted to suggest safety or efficacy. AVR-RD-04 is an investigational gene therapy and it is not approved by any regulatory agency.

CRF: Cystinosis Research Foundation

AVROBIO

Advisory board guiding planning for potential global registration trial

Detlef Bockenhauer, MD, PhD, FRCPCH
University College London & Great Ormond Street Hospital for Children

Stephanie Cherqui, PhD
Pediatrics, University of California, San Diego

Monte Del Monte, MD
Kellogg Eye Center, University of Michigan

Francesco Emma, MD
Pediatric Nephrology, Bambino Gesù Children's Hospital

Katharina Hohenfellner, MD, PhD
Pediatric Nephrology, Children's Hospital, Rosenheim Germany

Hong Liang, MD, PhD
Quinze-Vingts National Ophthalmology Hospital

Amrit Kaur, MB, ChB, BSc Hons, MRCPCH, MSc
Pediatric Nephrology, Royal Manchester Children's Hospital

Craig Langman, MD
Pediatric Nephrology, Northwestern University & Lurie Children's Hospital

Jess Thoene, MD
Pediatric Genetics, University of Michigan & C.S. Mott Children's Hospital

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

AVR-RD-04

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

Today's agenda

	Time
Clinical updates New data and update on future regulatory plans	9:15
Precision conditioning designed to enable durability and head-to-toe reach The Bu90-TCI advantage	10:00
Addressing industry manufacturing challenges with advanced CMC and analytic solutions AVROBIO's platform for global gene therapy commercialization	10:35
The second wave Working to prevent irreversible damage to body and brain	11:30

Bu90-TCI: Busulfan 90-Target Concentration Intervention; CMC: Chemistry, Manufacturing, and Controls

Bu90-TCI Advantages

Targeted-exposure conditioning + smart indication selection intended to transform patient experience

		Conventional Use *Hematologic-oncology*	**Optimized Use** *Used prior to lentiviral gene therapy for lysosomal disorders*
Busulfan Conditioning	**Purpose**	Busulfan ***is*** the therapy ***Substantial*** patient exposure to eliminate cancer cells	Busulfan ***is not*** the therapy ***Controlled*** patient exposure to make space in bone marrow
	Single agent or combination	Multiple agents, or multiple cycles over long periods	Single agent, single cycle
	Targeted exposure	Target exposure generally not optimized	Precision dosing (TCI) to hit precise target
	Management of side effects	Wide-ranging side effects requiring complex solutions	Proactive approach to managing side effects
	Infertility risk	Known risk when used in polypharmacy	Unknown risk when used as a single agent
	Ability to impact CNS	Generally not required	Essential
Patient Characteristics	**Bone marrow and immune system**	Both compromised	Both normal*
	Age/serious comorbidities	Patients often older, comorbidities common	Patients often younger, comorbidities less common
	Veno-occlusive disease (VOD) risk	Increased	Decreased

Head-to-head trials have not been conducted so we cannot assess relative safety profiles

** Potentially excludes treatment-naïve Gaucher type 1*
CNS: Central Nervous System; TCI: Target Concentration Intervention
Sources: Bartelink IH et al., Lancet Haematol, 2016; Myers AL et al., Expert Opin Drug Metab Toxicol, 2017

AVROBIO

Optimizing Busulfan Exposure

Busulfan used in chemotherapy has a different purpose and side effect profile than busulfan used in cell therapy

Chemotherapy

– to eradicate cancer cells

- Used in combinations
- Intensive high-dose chemo*
- Multiple cycles (palliative)
- Weight-based dosing

*Requires rescue HSC Tx

Busulfan **IS** the therapy

Cell Therapy

– create space in bone marrow and CNS

- Used as a single agent
- Less intensive
- Single cycle
- Precision TCI dosing

Busulfan **IS NOT** the therapy

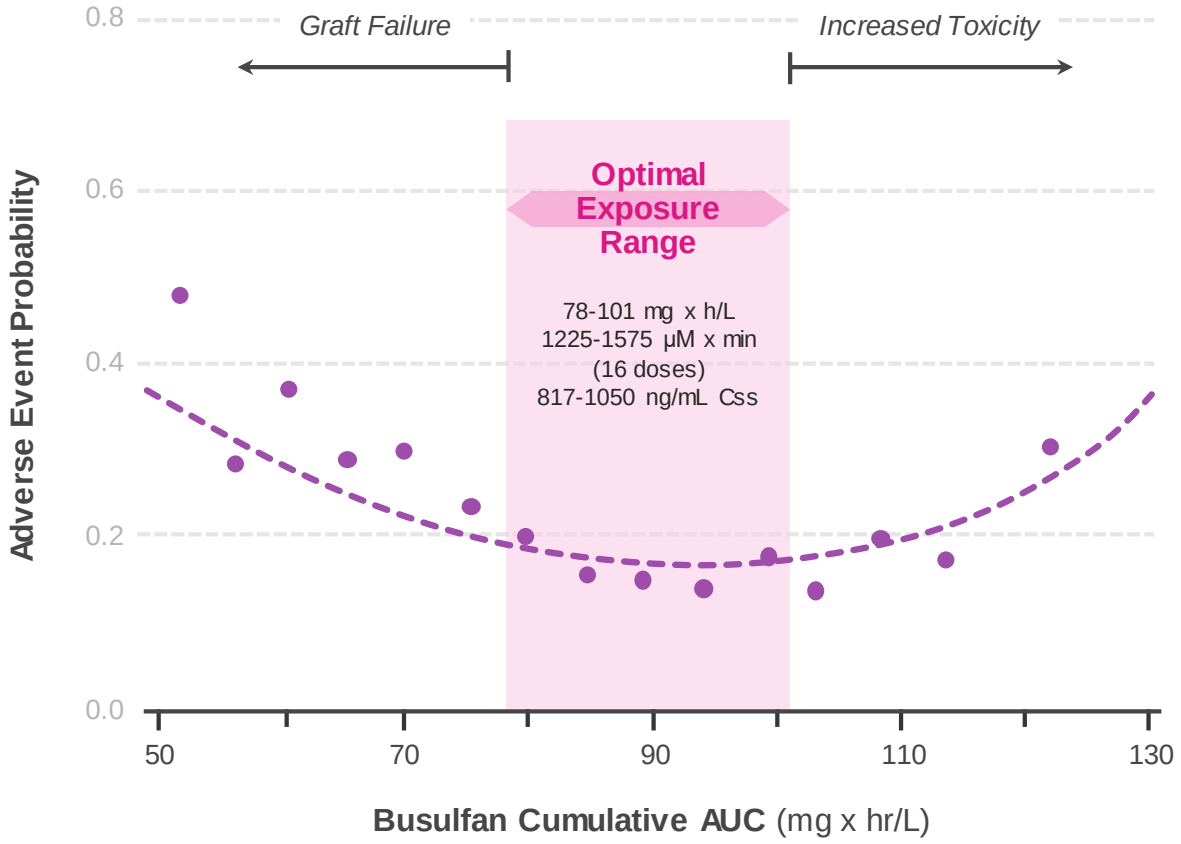
AVROBIO

HSC Tx: Hematopoietic Stem Cell Therapy; TCI: Target Concentration Intervention; CNS: Central Nervous System

Optimal exposure range for busulfan has been established

Improved clinical outcomes expected to be achieved by targeting Bu90

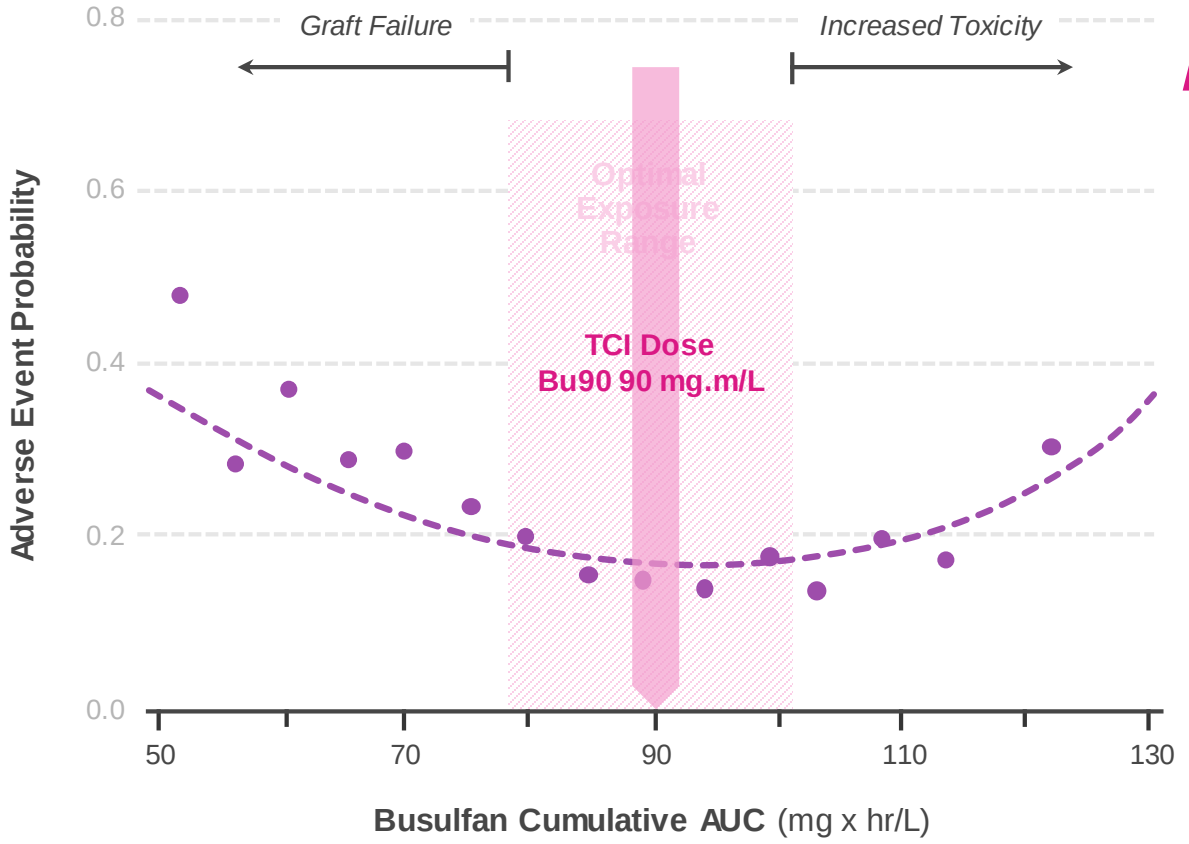
Meta-analysis of 465 non-malignant patients identified optimum exposure



AUC: Area Under the Curve; Bu90: Busulfan 90; Css: Concentration at Steady State
Source: Bartelink IH et al., Lancet Haematol, 2016

Bu90-TCI: personalized dosing to achieve target exposure

Meta-analysis of 465 non-malignant patients identified optimum exposure



Simple, fast, fully automated immunoassay kits being developed in AVROBIO-Saladax collaboration

In/out-patient

Source: Bartelink IH et al., Lancet Haematol, 2016
Bu90-TCI: Busulfan 90-Target Concentration Intervention; AUC: Area Under the Curve; TCI: Target Concentration Intervention

Single agent, single cycle administration reduces risks

Number of alkylating agents

1 : Bu

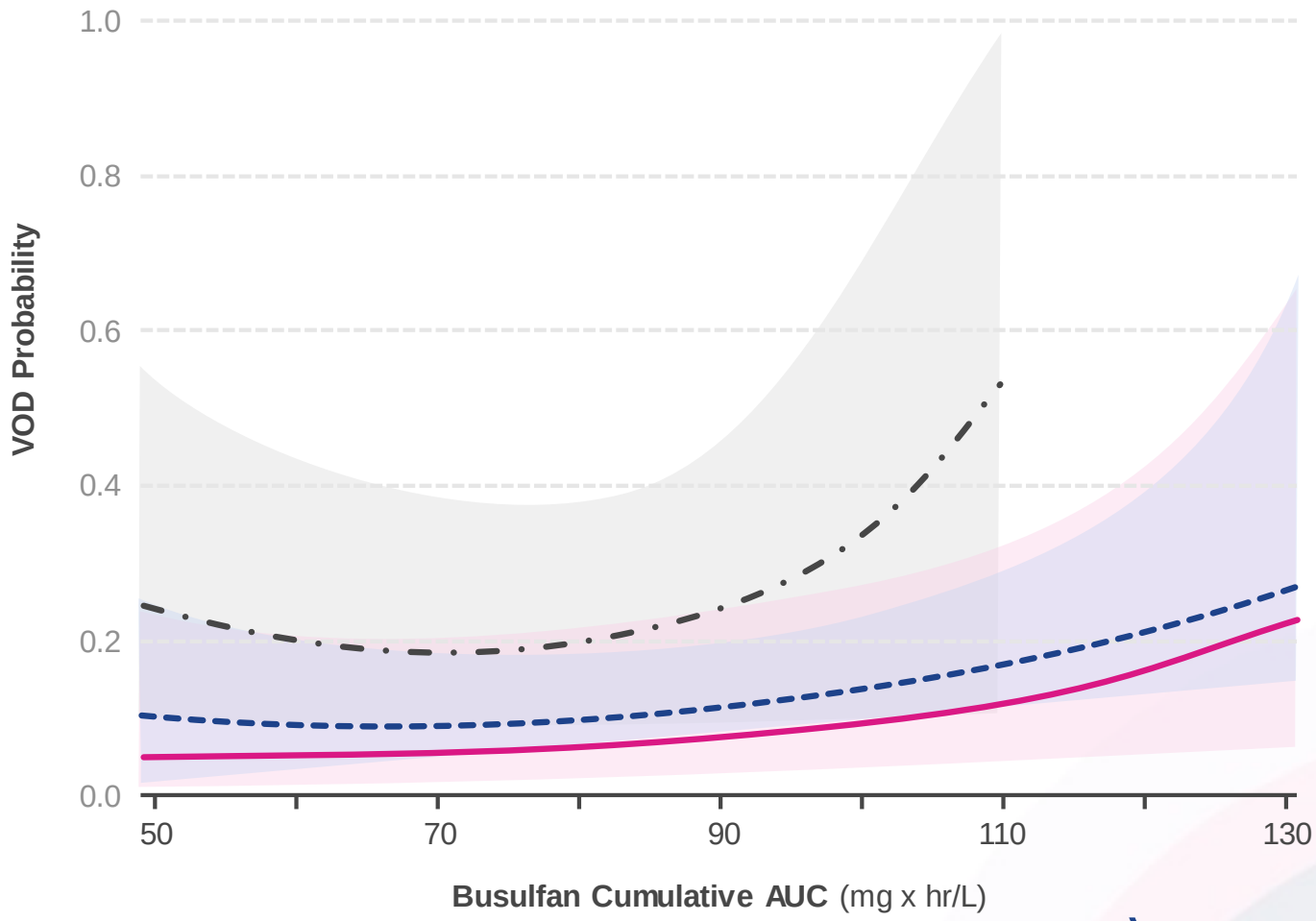
2 : Bu/Cy and Bu/Flu

3 : Bu/Cy/Mel

Shaded regions indicate 95% confidence interval

Cy, Flu and Mel immunodeplete with full immunological recovery typically taking years

Risk of veno-occlusive disease (VOD) decreases with fewer alkylating agents



Source: Bartelink IH et al, Lancet Haematol, 2016, Appendix Figure 5C
Cy: Cyclophosphamide; Flu: Fludarabine; Mel: Melphalan; Bu: Busulfan; AUC: Area Under the Curve

Data suggest favorable long-term safety profile in non-oncology patients

Thousands of non-cancer patients have received Bu, only 1 published report of t-MDS/AML possibly related to Bu…

t-MDS in bluebird bio's HGB-206 trial (NCT02140554)

- Cause unknown but LV-mediated oncogenesis excluded
- NIH still investigating the cause

Potential root causes

- Sickle cell disease (SCD) is associated with increased incidence of leukemia including AML
- Long-term SCD treatment with hydroxyurea pre-/post-transplant
- Family history and environmental cancer risk factors—no information
- Bu at sub-protocol cumulative AUC
- Spontaneous (i.e. not related to prior therapy)

Potential exacerbating factors include

- "Sub-optimal marrow" transplanted—low level of protection against outgrowth of an MDS clone

… AVROBIO's approach

Carefully selected indications

- Lysosomal disorders do not have an increased risk of MDS/leukemias
- Standard of care—ERTs are not associated with malignancy

AVROBIO's commitment to leading on patient safety includes

- Constantly improving our manufacturing and testing to optimize drug product
- Optimizing our conditioning regimen including target concentration intervention (TCI)
- Actively evaluating pre-treatment screening to detect DNA changes associated with increased potential risk of developing MDS/AML

Source: Hsieh et al., Blood Advances, 2020
t-MDS: Treatment-Related Myelodysplastic Syndrome; MDS: Myelodysplastic Syndrome; AML: Acute Myeloid Leukemia; ERT: Enzyme Replacement Therapy; DNA: Deoxyribonucleic Acid; Bu: Busulfan; LV: Lentiviral; AUC: Area Under the Curve; NIH: National Institutes of Health

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Infertility risk from single agent, single cycle busulfan use in gene therapy continues to be studied

Oncology use

Challenging to extrapolate risk from Bu label for CML due to additional risk factors for infertility with CML:

- Combined w/ Cy or Flu
- Weight-based dosing, wide range of AUCs incl. exceeding therapeutic window
- Allogenic GvHD (known impact on fertility)
- Multiple rounds of radiation / drug therapy
- No data on % affected or duration of infertility

Lentiviral gene therapy Bu90-TCI use

Sparse data re: infertility in this setting

- Single agent, single cycle
- TCI—avoiding potential for out-of-range toxicity and high-end Tx range risks
- No GvHD (autologous)
- Non-oncology—no prior radiation / toxic drug treatments

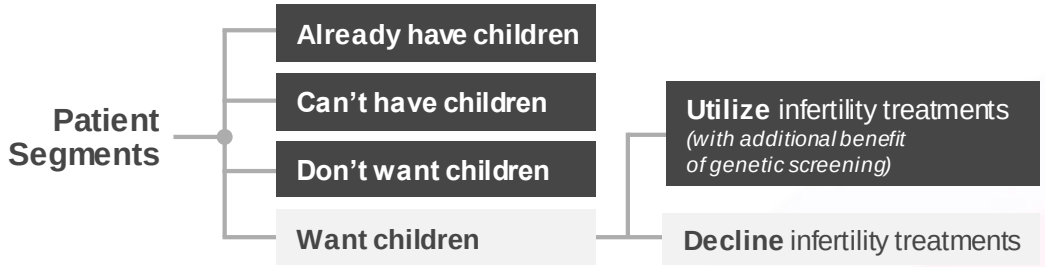
FDA label for busulfan + cyclophosphamide to treat CML

BUSULFEX is an alkylating drug indicated for:

- Use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia (CML)

Infertility
Females: Ovarian suppression and amenorrhea commonly occur in premenopausal women undergoing chronic, low-dose busulfan therapy for chronic myelogenous leukemia.
Males: Sterility, azoospermia, and testicular atrophy have been reported in male patients.

~90%
*of patients do not see risk of infertility as a barrier**



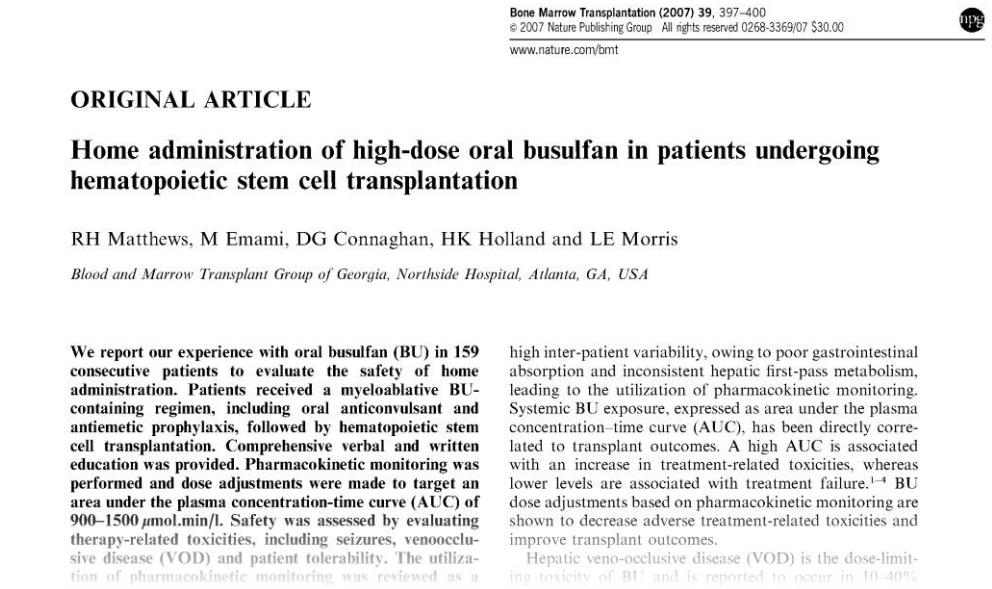
** Results are suggested based on two AVROBIO-commissioned qualitative patient primary market research studies, data on file*
Sources: Busulfex (busulfan) USPI, Bartelink IH et al., Lancet Haematol, 2016; McCune JS et al., Clin. Cancer Res, 2014; AVROBIO market research on file
GvHD: Graft Versus Host Disease; CML: Chronic Myeloid Leukemia; Bu90-TCI: Busulfan 90-Target Concentration Intervention; AUC: Area Under the Curve; Bu: Busulfan; FDA: Food and Drug Administration; TCI: Target Concentration Intervention; Tx: Therapy; Cy: Cyclophosphamide; Flu: Fludarabine

AVROBIO

Busulfan routinely used in outpatient and home settings

Safety profile and efficacy established in thousands of oncology patients

Matthews et al, Bone Marrow Transplant, 2007



Bone Marrow Transplantation (2007) 39, 397–400
© 2007 Nature Publishing Group All rights reserved 0268-3369/07 $30.00
www.nature.com/bmt

ORIGINAL ARTICLE

Home administration of high-dose oral busulfan in patients undergoing hematopoietic stem cell transplantation

RH Matthews, M Emami, DG Connaghan, HK Holland and LE Morris

Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA, USA

We report our experience with oral busulfan (BU) in 159 consecutive patients to evaluate the safety of home administration. Patients received a myeloablative BU-containing regimen, including oral anticonvulsant and antiemetic prophylaxis, followed by hematopoietic stem cell transplantation. Comprehensive verbal and written education was provided. Pharmacokinetic monitoring was performed and dose adjustments were made to target an area under the plasma concentration-time curve (AUC) of 900–1500 μmol.min/l. Safety was assessed by evaluating therapy-related toxicities, including seizures, venoocclusive disease (VOD) and patient tolerability. The utilization of pharmacokinetic monitoring was reviewed as a

high inter-patient variability, owing to poor gastrointestinal absorption and inconsistent hepatic first-pass metabolism, leading to the utilization of pharmacokinetic monitoring. Systemic BU exposure, expressed as area under the plasma concentration–time curve (AUC), has been directly correlated to transplant outcomes. A high AUC is associated with an increase in treatment-related toxicities, whereas lower levels are associated with treatment failure.[1–4] BU dose adjustments based on pharmacokinetic monitoring are shown to decrease adverse treatment-related toxicities and improve transplant outcomes.

Hepatic veno-occlusive disease (VOD) is the dose-limiting toxicity of BU and is reported to occur in 10–40%

High-dose oral busulfan conditioning at home

Busulfan used in home setting

Background	• Busulfan safety profile thoroughly characterized – Thousands of patients treated over 20+ years – Safety—no difference between oral Bu at home relative to oral/IV Bu in hospital
Dosing/PK	• Readily supported
Support for patients	• Comprehensive advice and support provided to patients and caregivers • Anticipatory management with education and pre-supplied medication, e.g. antiemetics • Access to conditioning team – Routine follow-up with patients over 4 weeks from conditioning initiation

Sources: Matthews, RH et al, Bone Marrow Transplantation, 2007; de Lima et al, Bone Marrow Trans, 2019
PK: Pharmacokinetics; Bu: Busulfan; IV: Intravenous

AVROBIO

Patient Experience

Lysosomal disorder patients are often younger with fewer comorbidities compared to oncology patients and other gene therapy indications

Typical characteristics	Cancer patients	Other LV GT patients (e.g. SCD, TDT)	AVROBIO LD patients (Fabry, Gaucher*, cystinosis, Hunter*, Pompe)
Healthy bone marrow	✗	✗	✓
Healthy immune systems	✗	✓	✓
Healthy livers	✗	✗	✓
Fewer comorbidities	✗	✓	✓
Younger	✗	✓	✓

** Healthy livers characteristic potentially excludes treatment-naïve Gaucher disease type 1 and treatment-naïve Hunter syndrome*
LV GT: Lentiviral Gene Therapy; TDT: Transfusion-Dependent β-Thalassemia; LD: Lysosomal Disorder; SCD: Sickle Cell Disease

AVROBIO

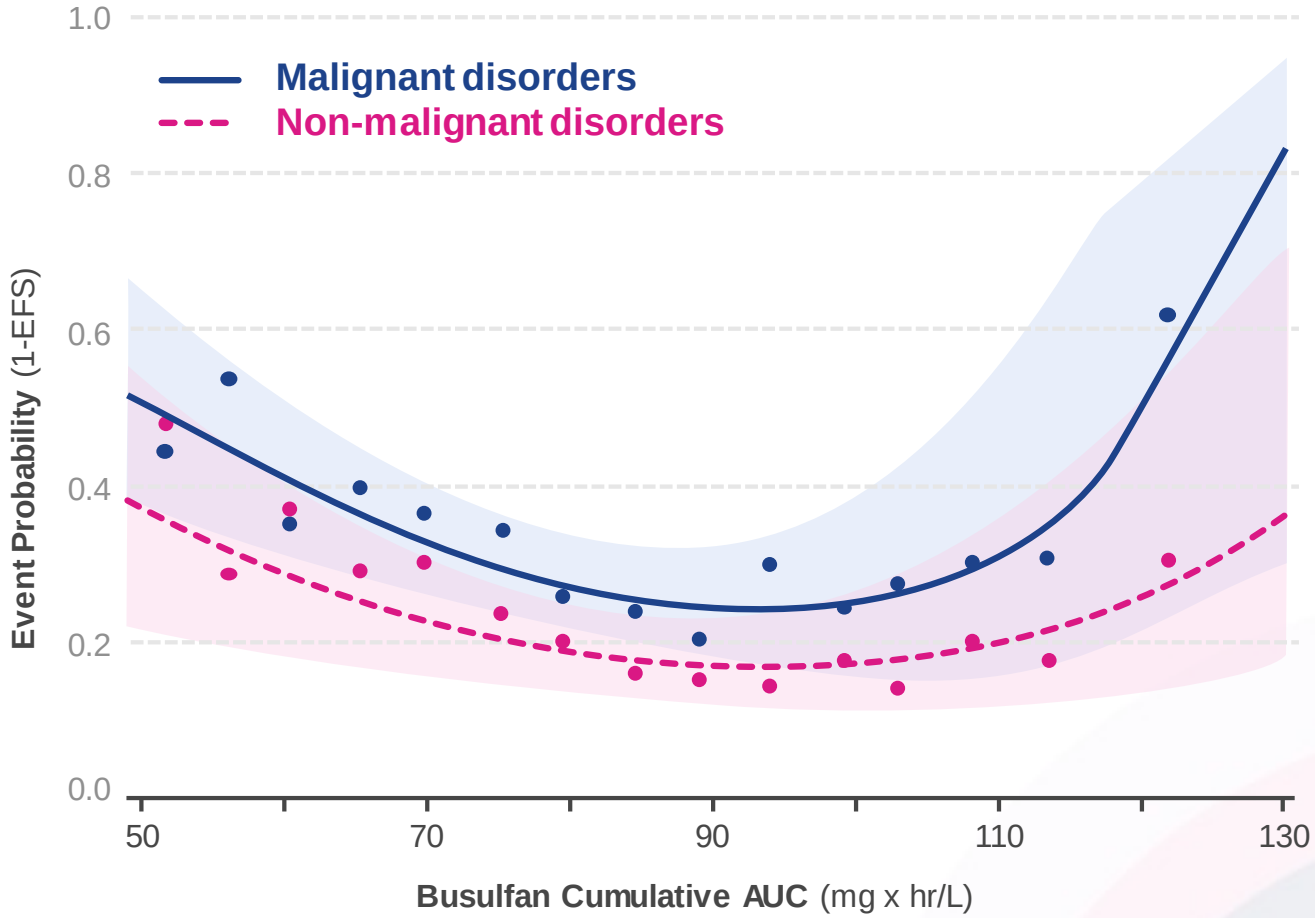
Patients with normal bone marrow typically do better

Patients with lysosomal disorders typically have healthy bone marrow*

Quality of bone marrow impacts speed and durability of engraftment

- Normal bone marrow is associated with:
  - Rapid and predictable engraftment
- Compromised bone marrow (oncology, TDT, SCD) is associated with:
  - Reduced quality apheresis product
  - Process challenged (more contaminants, e.g. immature RBCs)
  - Delayed engraftment

For a given Bu AUC—Increased event-free survival for non-malignant versus malignant disorders



** Potentially excludes treatment-naïve Gaucher type 1 and treatment-naïve Hunter syndrome*
Source: Bartelink IH et al., Lancet Haematol, 2016
EFS: Event-Free Survival; TDT: Transfusion-Dependent β-Thalassemia; RBC: Red Blood Cell; Bu: Busulfan; AUC: Area Under the Curve; SCD: Sickle Cell Disease

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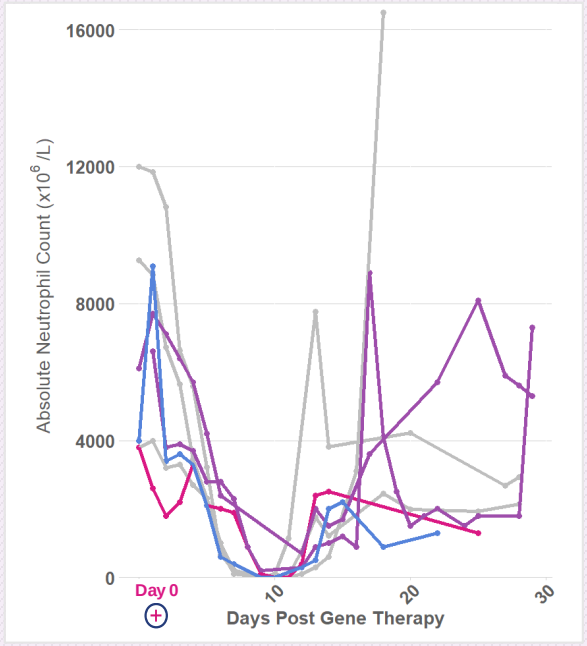
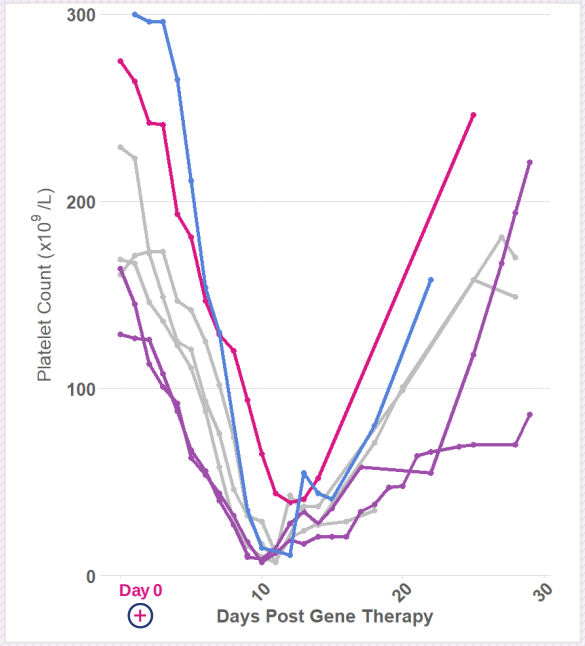
Busulfan is transiently myeloid depleting while sparing lymphocytes

Busulfan has minimal impact on adaptive immune system

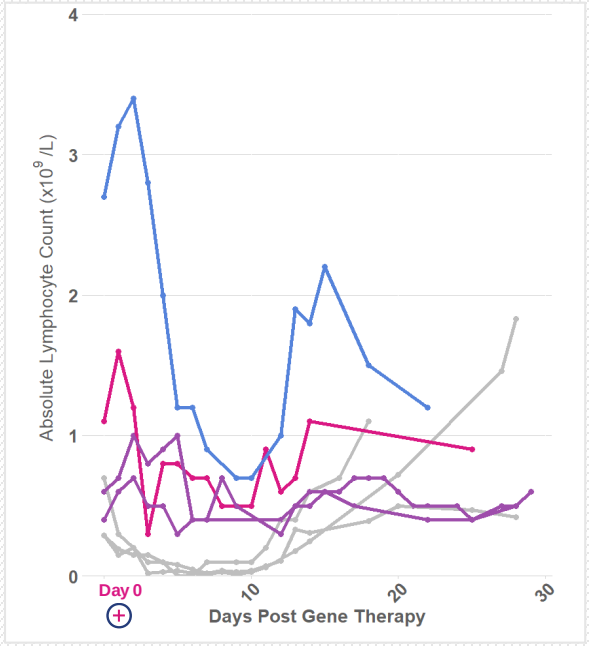
Absolute Neutrophil Count (ANC)



Platelet Count



Absolute Lymphocyte Count



Cystinosis
Patient 1 & 2: Busulfan

Fabry Ph2
Patients 1-3: Mel

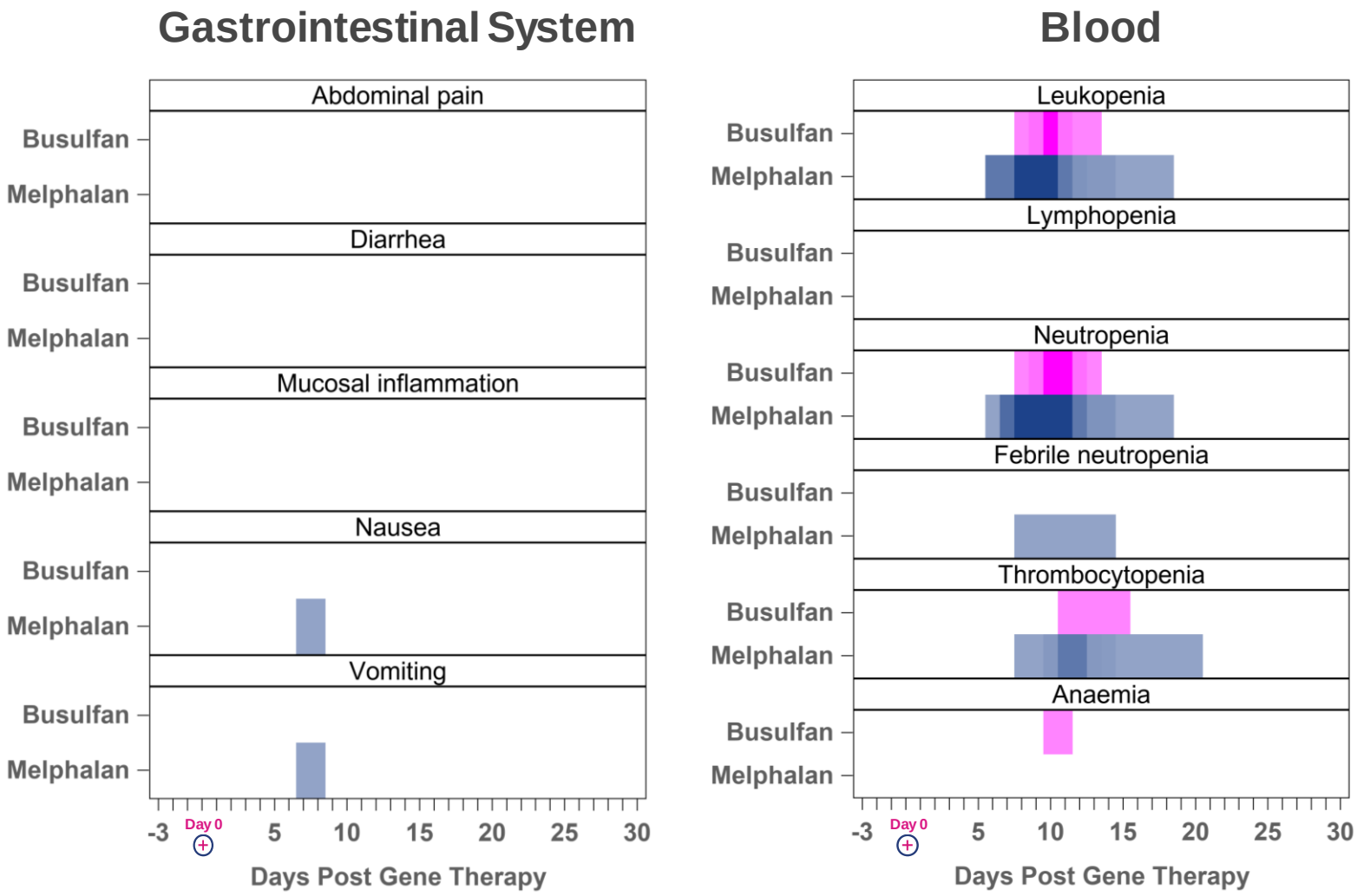
Fabry Ph2
Patient 4: Bu90-TCI

Gaucher
Patient 1: Bu90-TCI

Fabry: Patients 1-3 melphalan 100mg/m^2; all other patients busulfan 'AUC 90'; threshold levels for prophylaxis; ANC <0.5 x 10e9/L (AABB); platelets <10e9/L (AABB)
G-CSF administration post-gene therapy: Pt 1: 7 doses, day 7–14, Pt 2: 11 doses, day 7–17, Pt 3: 6 doses, day 7–12, Pt 4: 5 doses, day 8–12
Platelet transfusion: Pt 1: day 10; Pt 2, 3: day 11, Pt 4: no transfusion
G-CSF: Granulocyte-Colony Stimulating Factor; Mel: Melphalan; AUC: Area Under the Curve; ANC: Absolute Neutrophil Count; Pt: Patient;
Bu90-TCI: Busulfan 90-Target Concentration Intervention; AABB: American Association of Blood Banks

AVROBIO

Emerging tolerability profile has been predictable and manageable

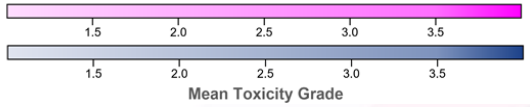


Observations to date

Short-term side effects start ~1 week after conditioning, peak over the next 3-5 days with patients typically discharged 1-2 days later

Charts show transient grade 3 and 4 side effects (n=2 Bu, n=3 Mel)

Grade 1 - mild
Grade 2 - moderate
Grade 3 - severe
Grade 4 - life-threatening
Grade 5 - death



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AE: Adverse Event; Bu: Busulfan; Mel: Melphalan

Supportive care can help prevent or diminish side effects

Elevated focus on preventing or mitigating side effects

Proactive approach toward management of side effects

Common side effects

- Mucositis = magic mouthwash, drugs that accelerate mucosal healing, pain relievers as necessary
- Nausea = anti-nausea drugs, hydration
- Risk of infection = improved preventative antimicrobials and rapid neutrophil recovery (can be further enhanced by G-CSF)
- Risk of bleeding = rapid platelet recovery (can be further enhanced by platelet transfusion)
- Hair thinning/loss = cold caps

AVROBIO is developing guidelines

- To further enhance patient experience

Source: Matthews, RH et al., Bone Marrow Transplantation, 2007
G-CSF: Granulocyte Colony Stimulating Factor

AVROBIO

Enhancing the patient experience to develop first-line therapies

AVROBIO is harnessing the proven record of busulfan…

- Single agent, single cycle
- Optimized and precisely targeted exposure / 4-day AUC monitoring
- Elevated focus on supportive care aims to prevent or mitigate side effects
- Access across multiple sites of care
- Potential to treat both body and brain

…and is applying primarily to patient populations with favorable characteristics for lentiviral gene therapy

- Typically normal marrow* / immune systems / livers

** Potentially excludes treatment-naïve Gaucher type 1 and treatment-naïve Hunter syndrome*
AUC: Area Under the Curve

Today's agenda

	Time
Clinical updates New data and update on future regulatory plans	9:15
Precision conditioning designed to enable durability and head-to-toe reach The Bu90-TCI advantage	10:00
Addressing industry manufacturing challenges with advanced CMC and analytic solutions AVROBIO's platform for global gene therapy commercialization	10:35
The second wave Working to prevent irreversible damage to body and brain	11:30

Bu90-TCI: Busulfan 90-Target Concentration Intervention; CMC: Chemistry, Manufacturing, and Controls

CMC challenges for gene therapy

Anthony Davies, Ph.D.

Nov. 17, 2020

State of the Nation

BLAs in the cell therapy field are being rejected and delayed

IOVANCE BIOTHERAPEUTICS

IOVA delayed its BLA filing for lifileucel until 2021:

- The cytokine release potency assay, despite being used for tisagenleucel (Kymriah) shows too great lot variability (*per* FDA ODAC)
- Other methods in development are not yet validated

mesoblast

MESO received a Complete Response Letter (CRL) for remestemcel-L:

- Numerous failed placebo-controlled trials were followed with a single arm trial
- The TNFR1 potency assay was not considered to relate to either clinical effectiveness or mechanism of action
- Neither the potency nor identity assays captured batch heterogeneity or up-scaled batch comparability

DHC DARK HORSE CONSULTING

State of the Nation

BLAs in the gene therapy field are being rejected and delayed

AXGT: delayed AXO-Lenti-PD Phase II Parkinson's disease enrollment until 2022:

- CMO Oxford BioMedica was unable to complete scale-up of their manufacturing process into suspension culture
- This should not have been difficult: Oxford has advertised 200L cabability since 2016

BMRN: received a Complete Response Letter (CRL) for valoctocogene roxaparvovec:

- Represented as a 'one and done' therapy, but clinical data accepted was not long-term
- Possible that process scale-up and Factor VIII assay comparability issues invalidated long-term clinical data from earlier trials

SRPT: delayed initiation of Phase III study of SRP-9001 in Duchenne Muscular Dystrophy

- The single potency assay assay chosen by the sponsor was not considered adequate by the FDA
- Additional assays exist, but are not yet validated or submitted to the FDA

ORTX was notified that a patient treated with Strimvelis®, a gammaretrovirus-based product, was diagnosed with lymphoid T cell leukemia:

- Lentivirus next-generation version of this product OTL-101 was recently de-prioritized

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Is the FDA Changing Its Approach?

Clinical data must meet the intent of the product sponsor, at both early and late stage development, but has recently masked some significant CMC issues in the field:

- valoctocogene roxaparvovec scale-up and bioanalytical changes likely invalidated critical long-term clinical outcome data
- Failure to replace Strimvelis with OTL-101 looking regrettable in hindsight
- Multiple companies' adoption of inadequate potency assays has delayed clinical progress

- The FDA is NOT tightening up its enforcement of CMC guidance, but rather is reverting to a more 'originalist' interpretation as the field matures
- The FDA is over-burdened, but this is not affecting the progress of well sponsored drugs
- More products are approaching the stage when the process has always been tightly regulated

- Cell and gene therapies with strategically planned CMC programs which adhere to existing, clear guidance will receive timely review and material technical dialogue

DARK HORSE CONSULTING

Manufacturing Scalability Requires Process Robustness and Analytical Depth

Process robustness is required for:

- Scaling to larger patient numbers, especially post-approval
- Scaling to new global geographies

Robustness has many flavours:

- Raw materials provenance
- Facility:Facility manufacturing comparability
- Facility:Facility analytical comparability

Demonstration of robustness requires validated analytics

- It's all about the potency assays
- They need to be both RELEVANT
- And VALIDATED

IT'S THE COGS, STUPID!

DARK HORSE CONSULTING

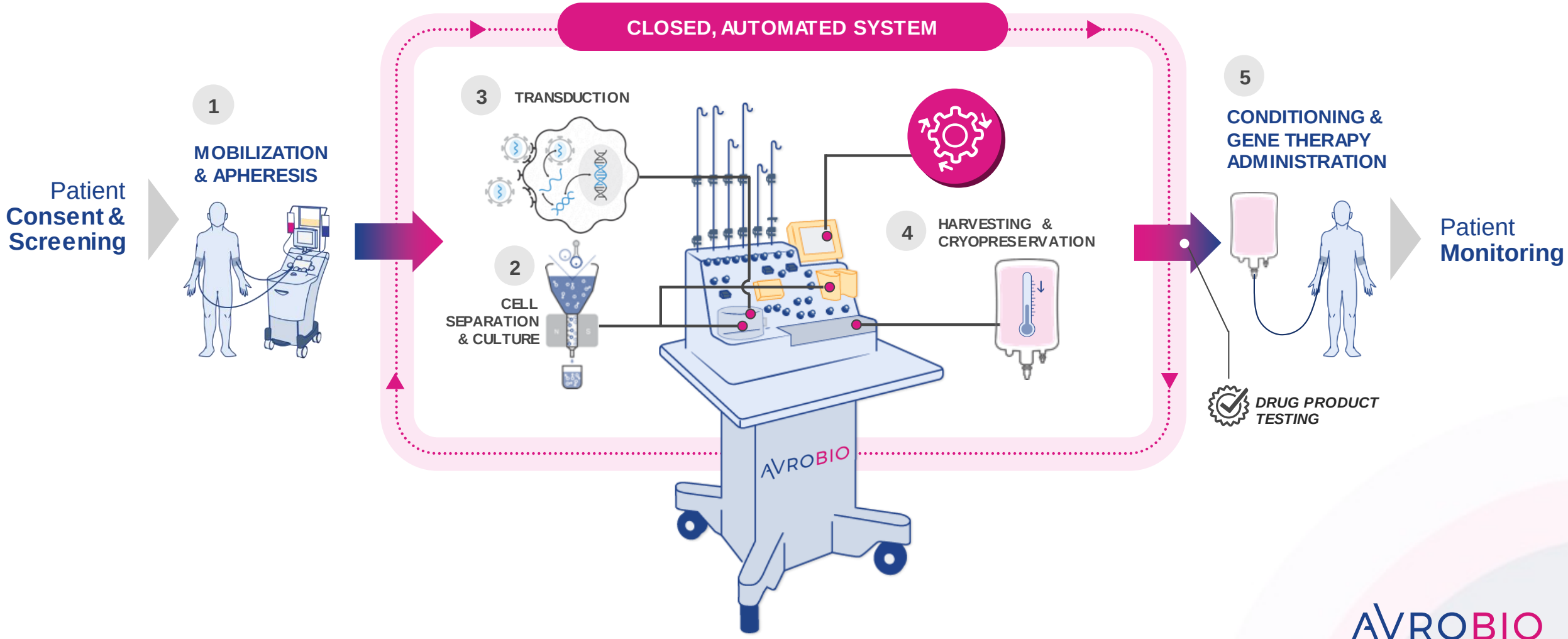
plato®

AVROBIO's platform for global gene therapy commercialization

- Redefines manufacturing best practices
- Solves key industry challenges

Industry-leading platform across our entire portfolio

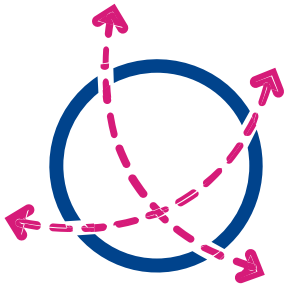
Designed for the future, delivering today



plato® is built to solve key industry challenges

PROCESS ROBUSTNESS

SCALE



GLOBALIZATION

COST EFFECTIVENESS

ANALYTICS

AVROBIO

Process Robustness

Process Robustness

Best-in-class lentiviral vector manufacturing

Robust platform for the pipeline

Commercial ready

- 200L serum free, suspension culture
- Optimized downstream, fill, and finish
- Minimal process variability

Strong quality and safety profile

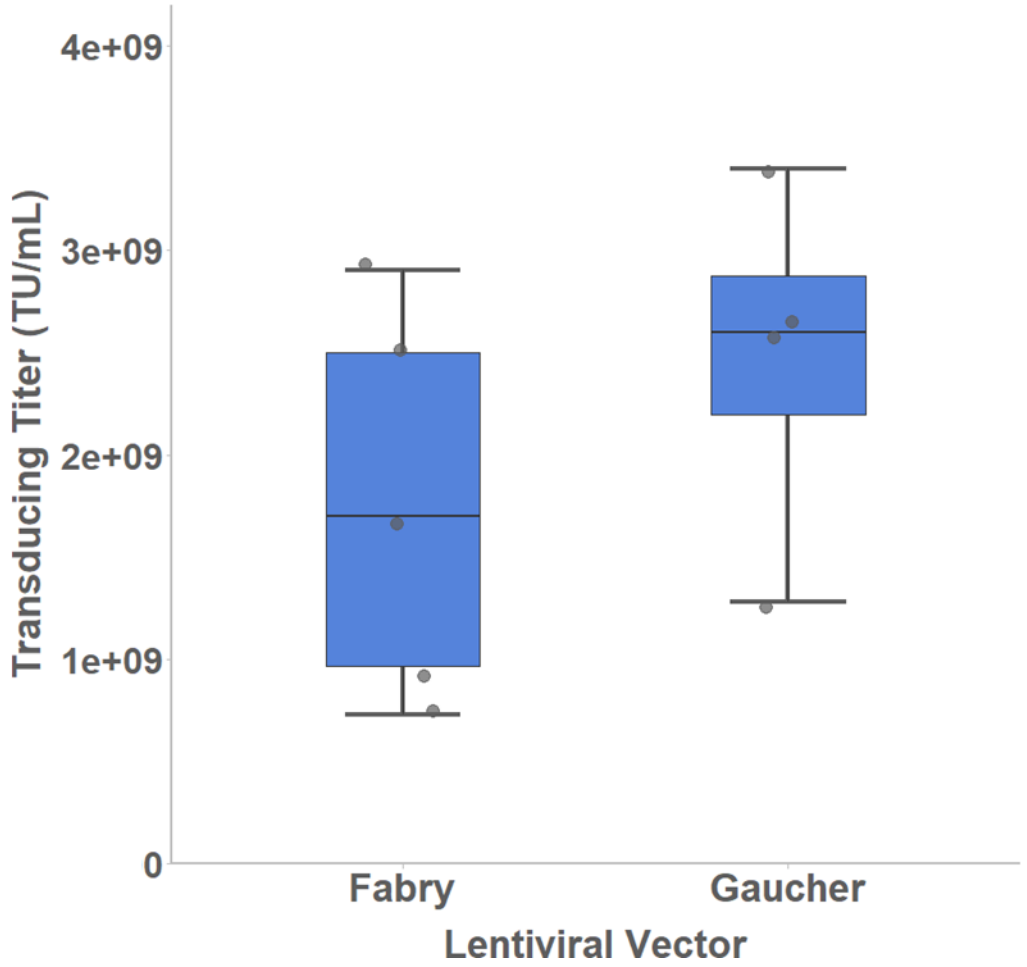
- Low impurities
- No empty capsids with lentivirus

Consistent, high titer

AVROBIO

Process Robustness

Reliably high titers outperforming industry standards



- Titer consistently above industry standard of 1e08
- Higher titers mean fewer batches required to fulfill demand
- Manufacturing process applied across the pipeline

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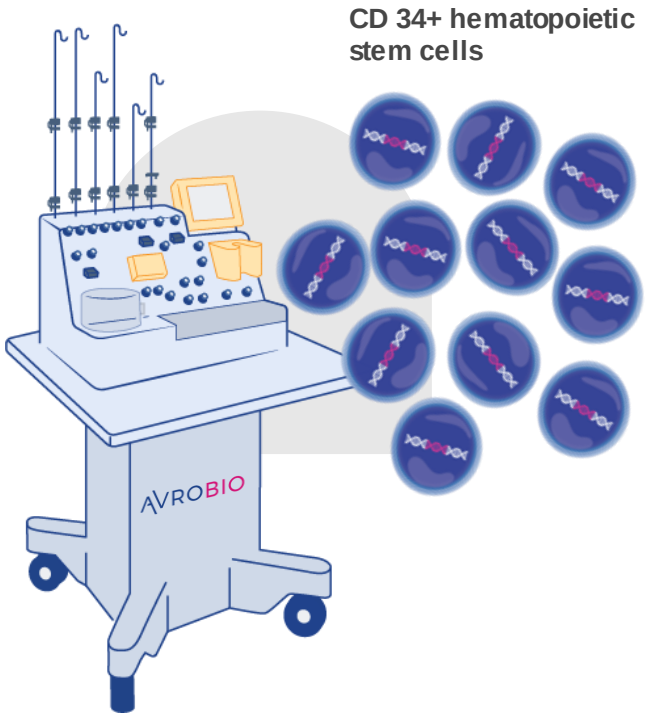
Automation enables robust global processes

Empowers consistency, quality control, and transferability



Closed system from apheresis to drug product

- Reduces contamination risk
- Reduces clean room requirements

Automation designed to work across the pipeline

- Improves process consistency and quality
- Reduces human error, inter-operator variability and training burden
- Enables easy technology transfer and scale out

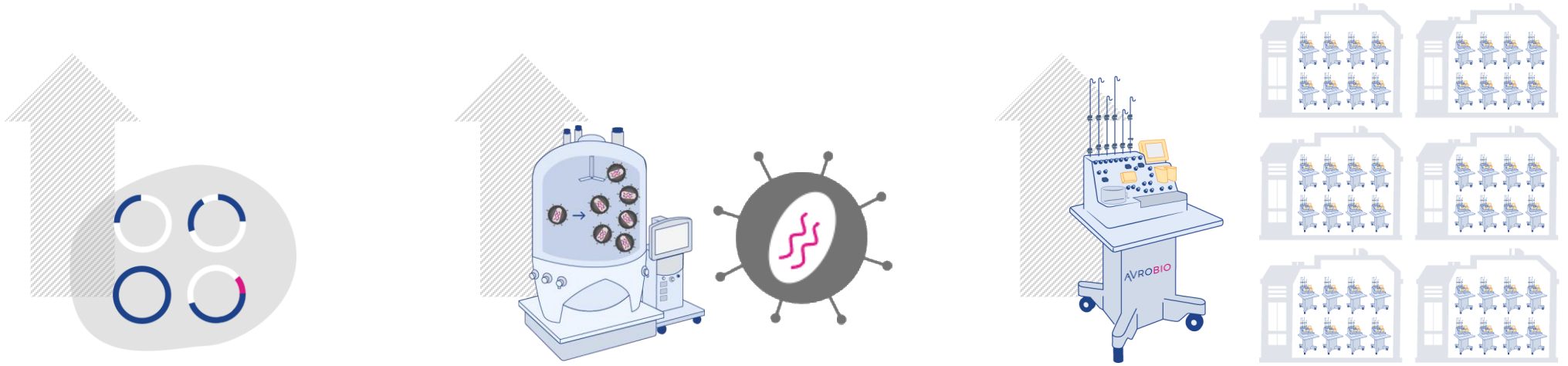
AVROBIO

Scale

Scale

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

Scale

Scalable platform for commercial supply

Global infrastructure already in place, poised to manufacture at scale

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

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Globalization

Globalized production capabilities

Drug product manufacturing on three continents

Shading indicates patient reach; Maastricht facility expected to open by 1H 2021

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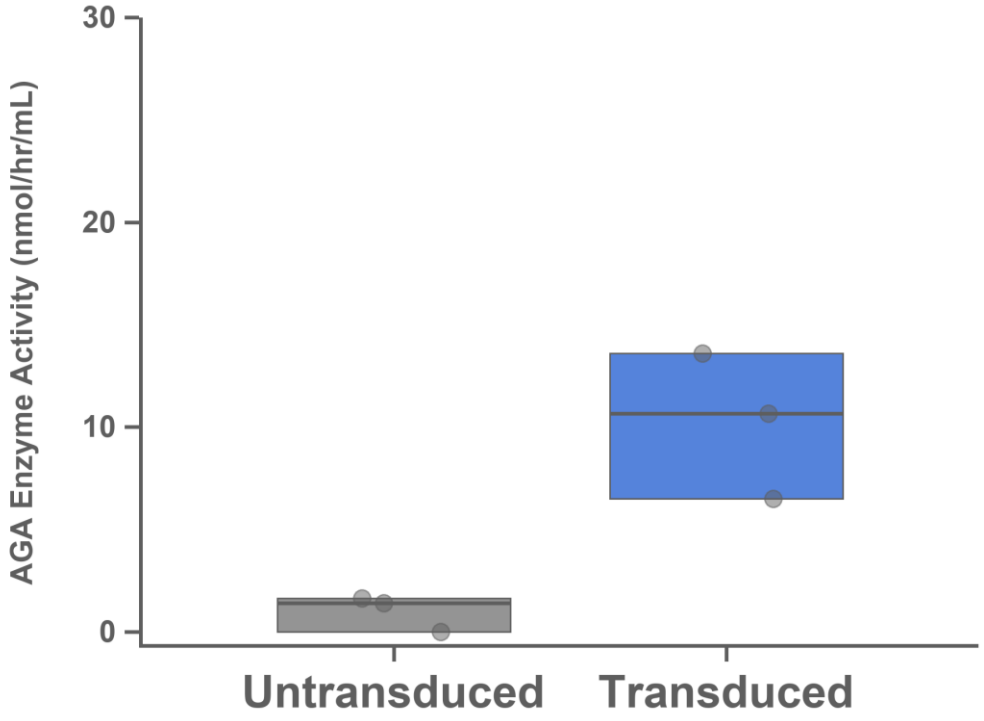
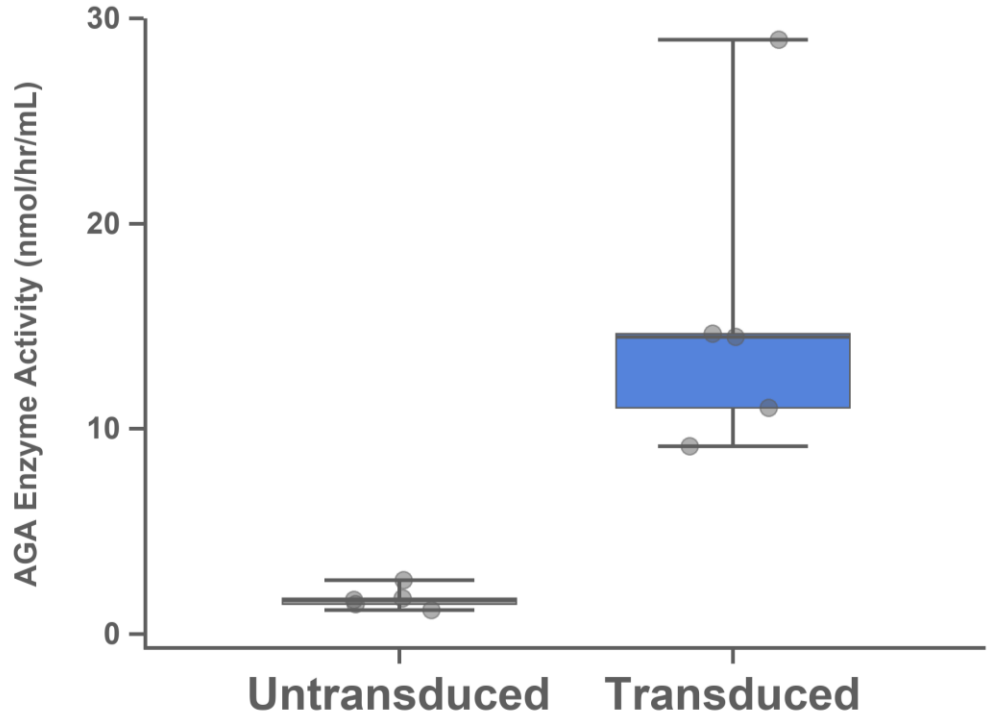
Fabry potency data globally consistent

AGA enzyme activity by contract manufacturer

Asia-Pacific



U.S.

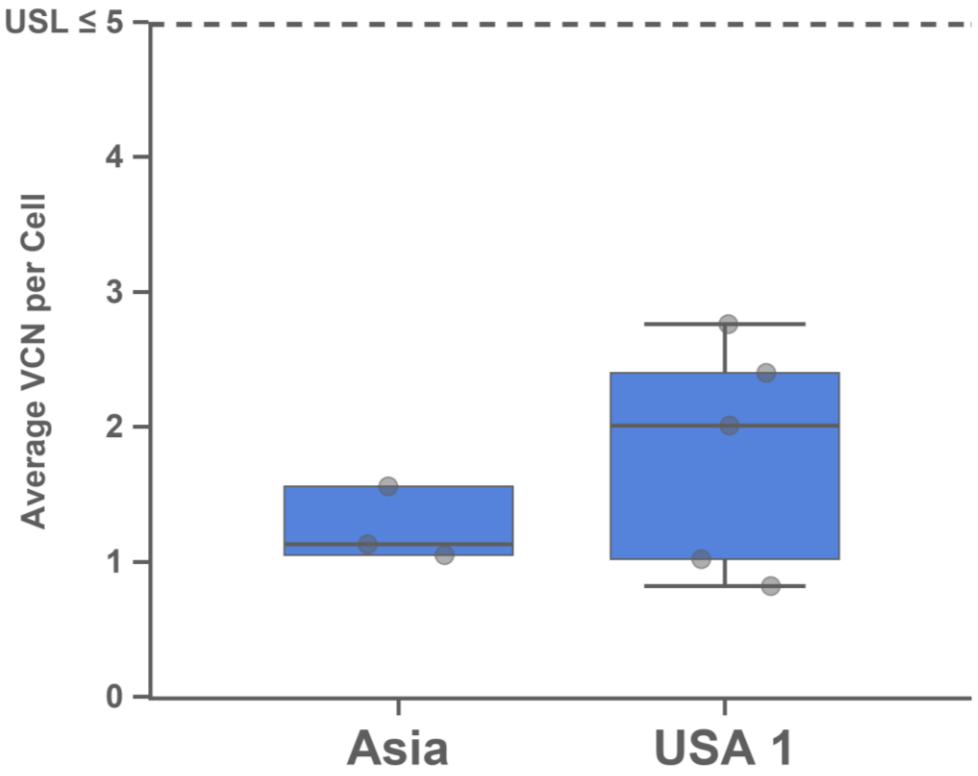


AGA: Aspartylglucosaminidase

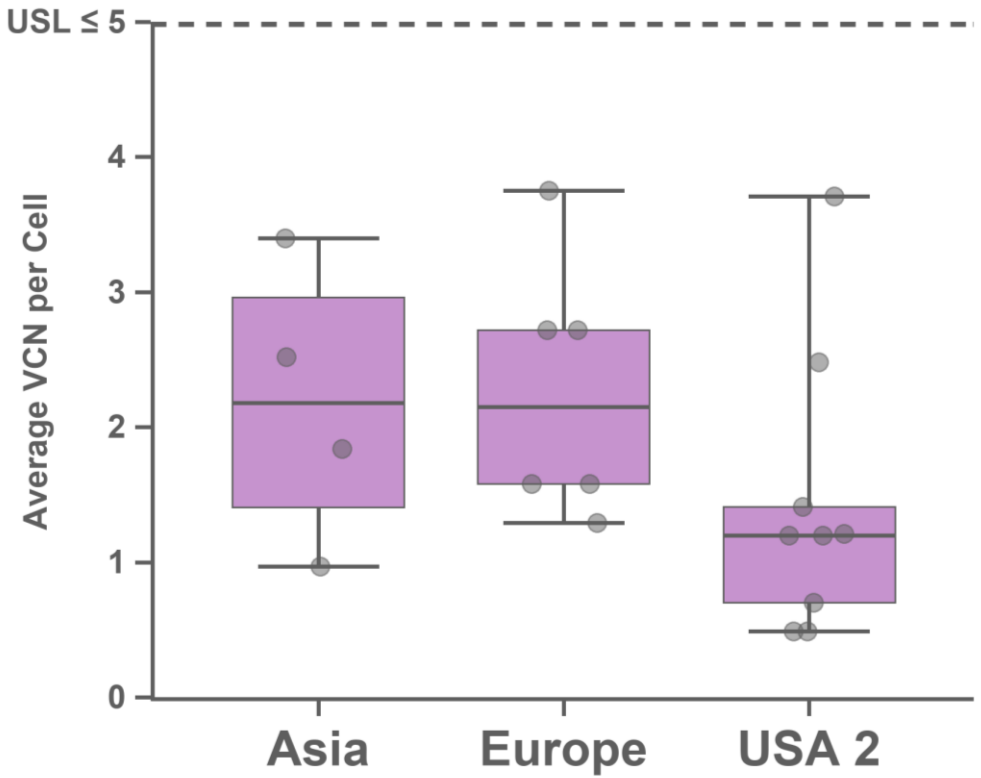
plato® VCN assay globally consistent

Global CMOs produce highly comparable drug product

Fabry

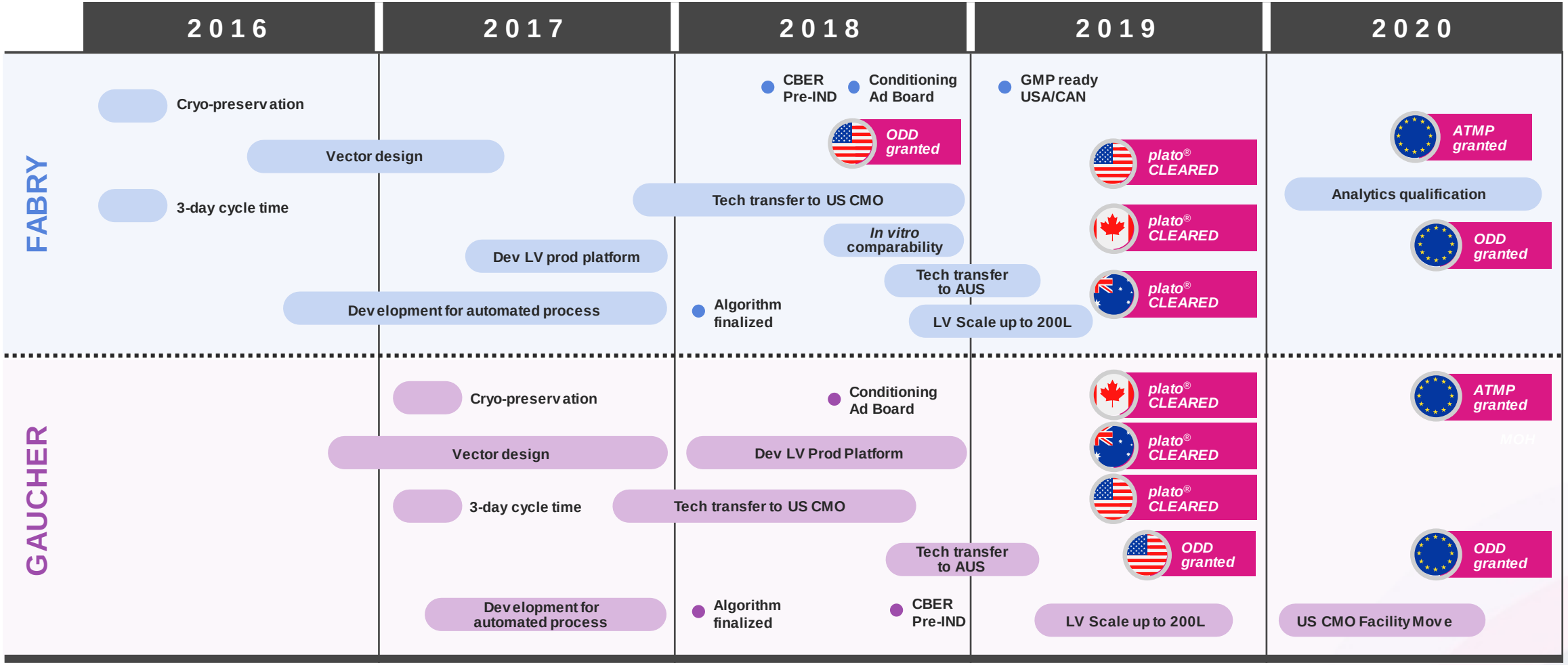


Gaucher



USL: Upper Specification Limit; VCN: Vector Copy Number; CMO: Contract Manufacturing Organization

Five years and hundreds of thousands of hours of development work to create plato®



Note: plato® in Fabry cleared for use in US via IND, in Canada via protocol and CMC CTA amendment, and in AUS via CTN and HREC clearance; plato® in Gaucher cleared for use in Canada via CTA and protocol CTA amendment

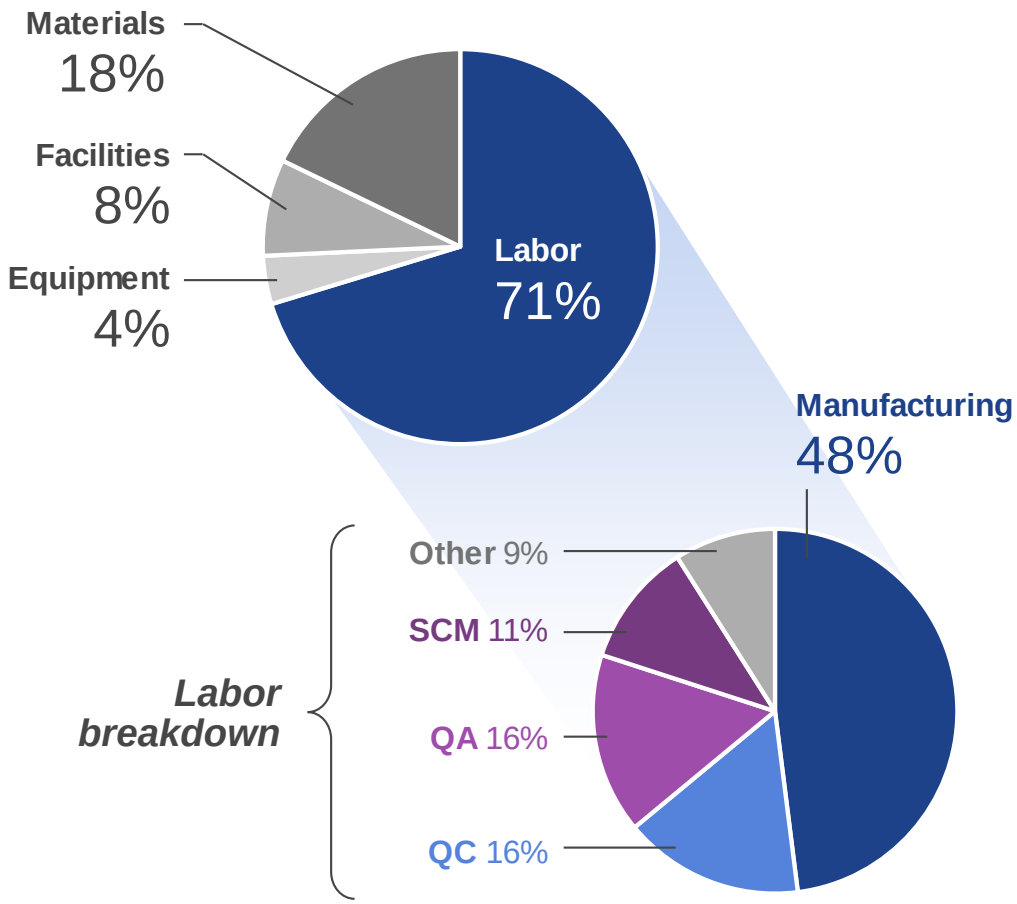
IND: Investigational New Drug; CMC: Chemistry, Manufacturing, and Controls; CTA: Clinical Trial Application; CTN: Clinical Trial Notification; HREC: Human Research Ethics Committee; LV: Lentiviral; CBER: Center for Biologics Evaluation and Research; GMP: Good Manufacturing Practices; ODD: Orphan Drug Designation; CMO: Contract Manufacturing Organization; ATMP: Advanced Therapy Medicinal Products

Cost Effectiveness

plato®'s significant COGs advantages

Automation drives major savings

COGs breakdown of example CAR-T product[1]:



plato® drives down COGs

- Automated, short manufacturing process can reduce labor costs by up to 60%
- Economies of scale with plasmids and large-scale vector manufacturing can reduce material costs
- Low vector quantity required per patient
- Closed system manufacturing can reduce facility and overhead costs by up to 50%
- Next-generation, automated analytics can reduce QC labor and testing costs

Source: [1]The long road to affordability: a cost of goods analysis for an autologous CAR-T process Katy Spink & Andrew Steinsapir (Dark Horse Consulting), Cell Gene Therapy Insights 2018; 4(11), 1105-1116
COGs: Cost Of Goods; CAR-T: Chimeric Antigen Receptor T Cell; SCM: Supply Chain Management; QA: Quality Assurance; QC: Quality Control

AVROBIO

Analytics

Innovation aiming to accelerate regulatory approvals

Our mantra is “BLAs without delays”

FDA

“…product characterization testing,… are used to establish that a consistently manufactured product is administered during all phases of clinical investigation.”

In other words, regulators require high quality CMC & analytics with no corners cut.

CHALLENGE

Accelerated development requires companies combine data sets:

- All phases of clinical development
- Different manufacturing sites
- Pre- and post-process changes

OUR SOLUTION

1. **Robust platform analytics**
2. **Deep product characterization**
3. **Potency assay matrix**

Sources: U.S. Food and Drug Administration/Center for Biologics Evaluation and Research (2011); Guidance for Industry Potency Tests for Cellular and Gene Therapy Products
BLA: Biologics License Application; FDA: Food and Drug Administration; CMC: Chemistry, Manufacturing, and Controls

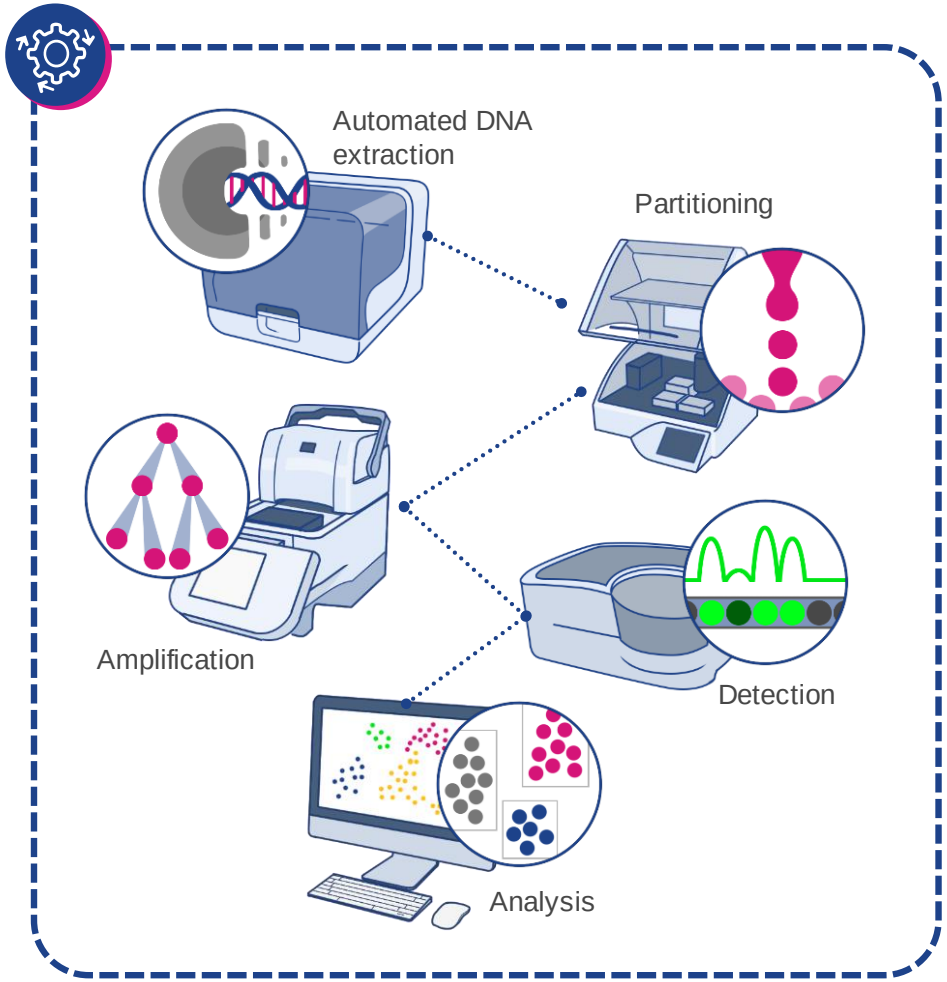
AVROBIO

1

Robust Platform Analytics

Enabling VCN comparison through development

State-of-the-art assay across the portfolio



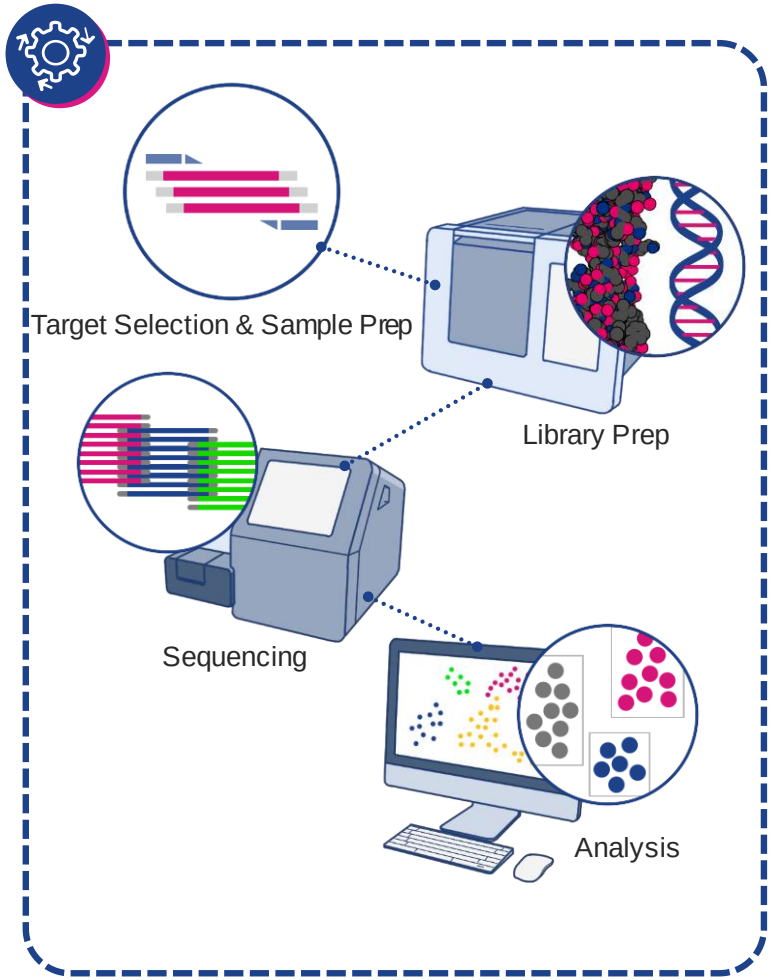
- Reproducible
- Validatable
- Automated
- Transferable to multiple jurisdictions
- Leverageable across manufacturing, clinical and non-clinical

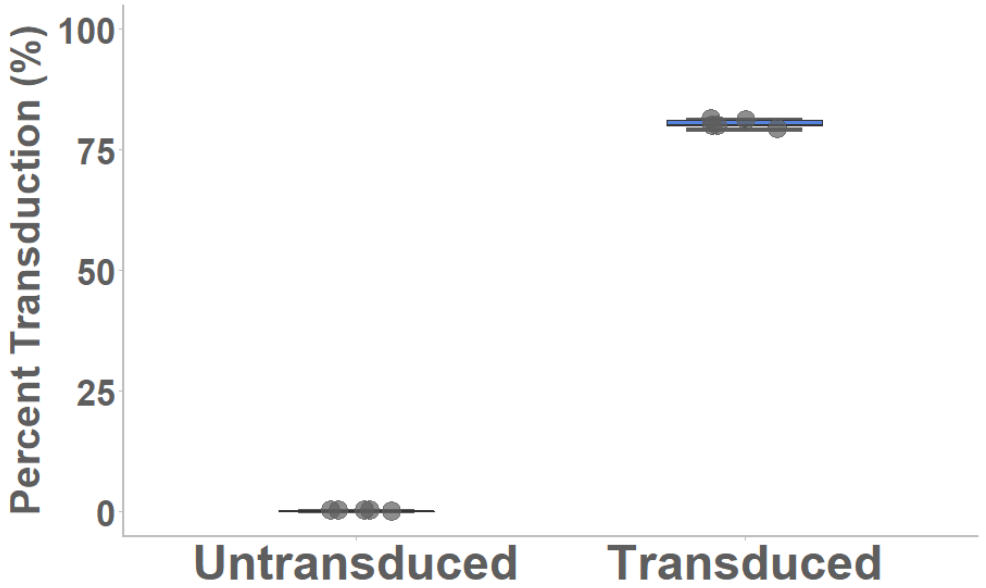
VCN: Vector Copy Number

Robust Platform Analytics

Enabling drug product release in days – not months

First-in-class rapid transduction assay





- One transduction assay across portfolio
- Automated, high throughput, scalable
- Reproducible, reliable, validatable
- Transferable to multiple jurisdictions

Developed in collaboration with Mission Bio

AVROBIO

2

Deep Product Characterization

Cutting edge product characterization

Next-gen analytics set new standard for process knowledge and control

Enables product understanding, process know-how and identifies process drifts

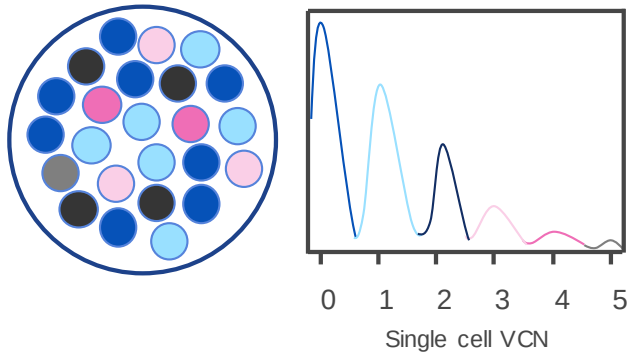
Allows comparability to be established if process improvements are made

Facilitates **appropriate data sets** to be included

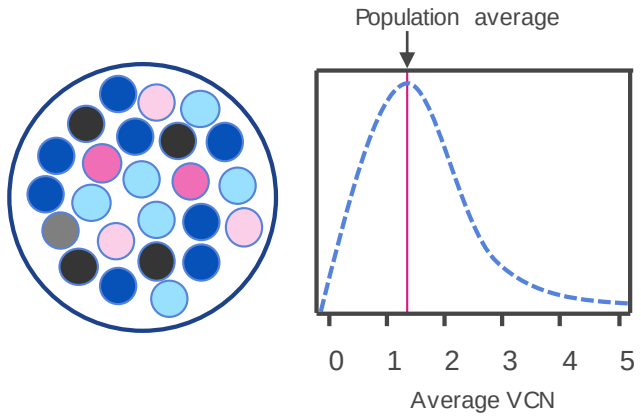
Advanced control over manufacturing consistency

Enhanced characterization and quality via single cell analytics

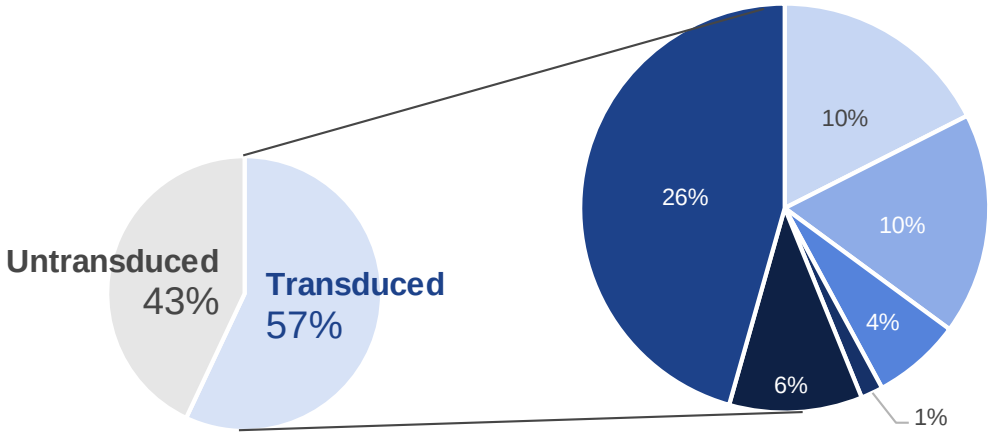
Single cell VCN



Average VCN



Proportion of single cells with predicted VCN



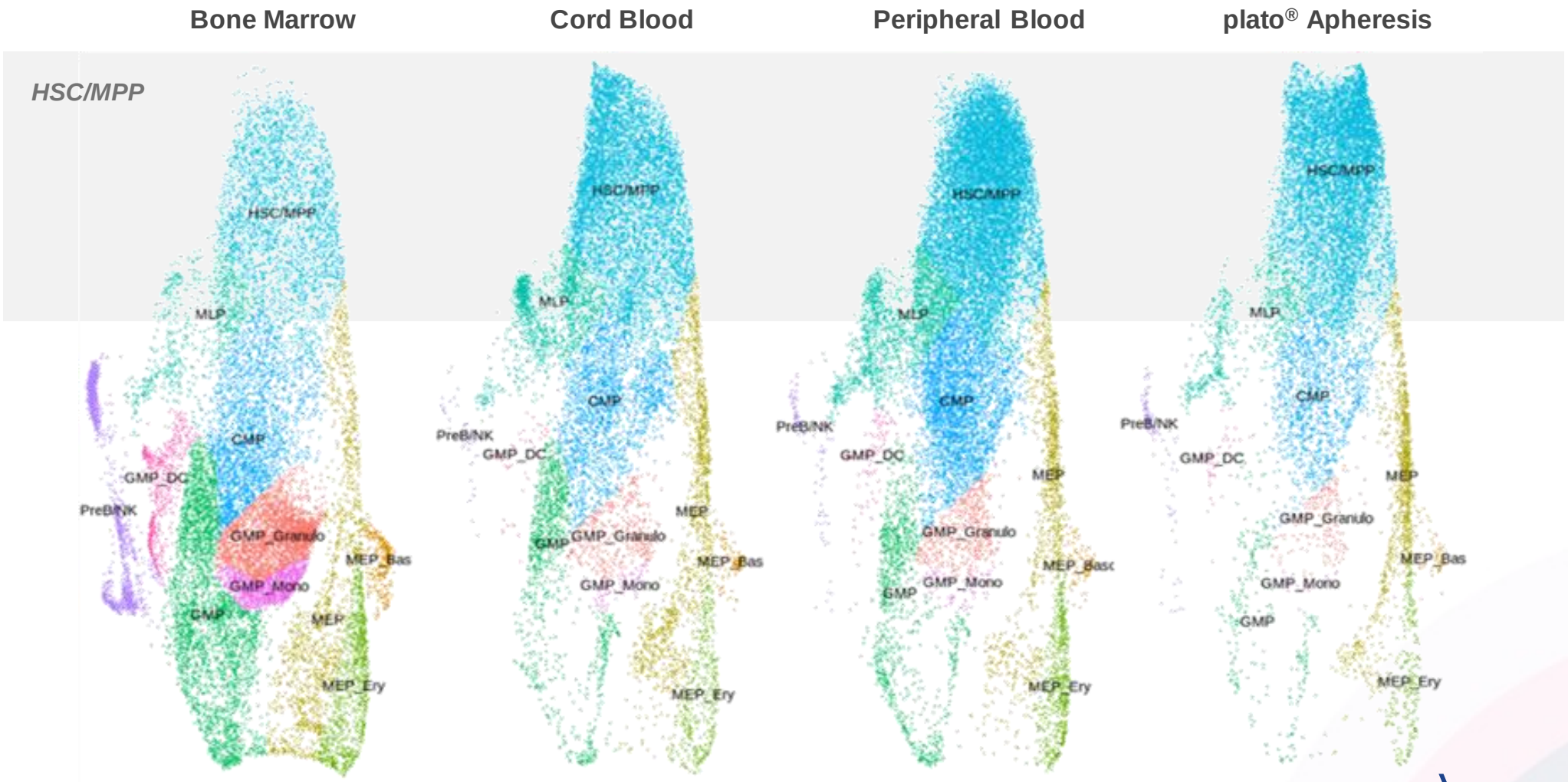
- Enables a new level of resolution
- Designed to ensure quality
- Highly informative for process optimization

Developed in collaboration with Catapult
VCN: Vector Copy Number

AVROBIO

Tracking long-term engrafting cells to predict durability

Industry-first method shows HSCs preserved by plato® apheresis



HSC: Hematopoietic Stem Cell; MPP: Multipotent Progenitor

AVROBIO

3

Potency Assay Matrix

Prioritizing alignment with regulators on potency approach is key

FDA

"All attempts should be made to develop potency measurements that reflect the products' relevant biological properties."

In other words, potency assay is product specific and ideally represents the mechanism of action (MOA).

CHALLENGE

CGT products have complex and/or not fully understood MOAs:

- Rely on multiple biological activities
- Difficult to determine the attributes most relevant to potency

OUR SOLUTION

Establish potency assay matrix (multiple assays) early in development

- Multiple complementary assays that measure different product attributes are employed
- Data is combined and correlated with available relevant clinical data
- Seek early FDA agreement

Source: U.S. Food and Drug Administration/Center for Biologics Evaluation and Research (2011); Guidance for Industry Potency Tests for Cellular and Gene Therapy Products
FDA: Food and Drug Administration; MOA: Mechanism Of Action; CGT: Cell and Gene Therapy

WORKING TO DELIVER ON:

‘BLAs without delays’

Our strategy:

- A ‘future-ready’ AVROBIO empowered by a suite of next-generation platform analytics leveraged across programs

Target outcomes:

- Minimized risk of regulatory delays on CMC
- Multiple synergies within and across programs

BLA: Biologics License Application; CMC: Chemistry, Manufacturing, and Controls

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

AVROBIO

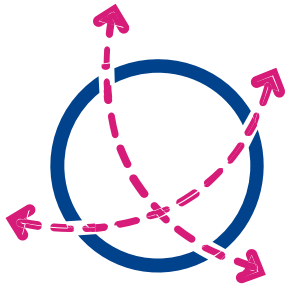
CMC: Chemistry, Manufacturing, and Controls; VCN: Vector Copy Number; LV: Lentiviral; COGs: Cost Of Goods

Designed for the future, delivering today

plato® is an end-to-end solution for the industry's key challenges

PROCESS ROBUSTNESS

SCALE



GLOBALIZATION

COST EFFECTIVENESS

ANALYTICS

AVROBIO

Today's agenda

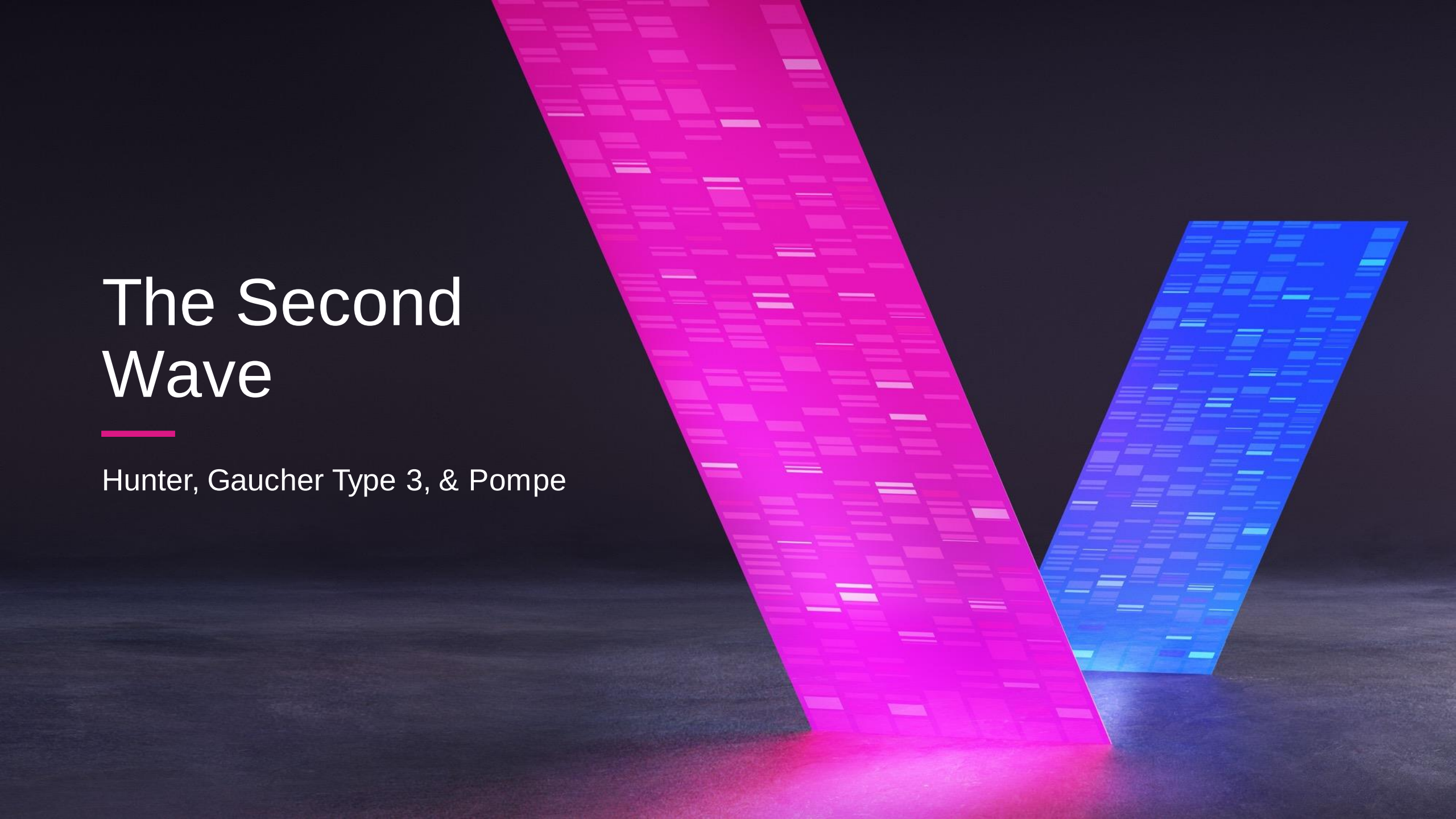
	Time
Clinical updates New data and update on future regulatory plans	9:15
Precision conditioning designed to enable durability and head-to-toe reach The Bu90-TCI advantage	10:00
Addressing industry manufacturing challenges with advanced CMC and analytic solutions AVROBIO's platform for global gene therapy commercialization	10:35
The second wave Working to prevent irreversible damage to body and brain	11:30

AVROBIO

Bu90-TCI: Busulfan 90-Target Concentration Intervention; CMC: Chemistry, Manufacturing, and Controls

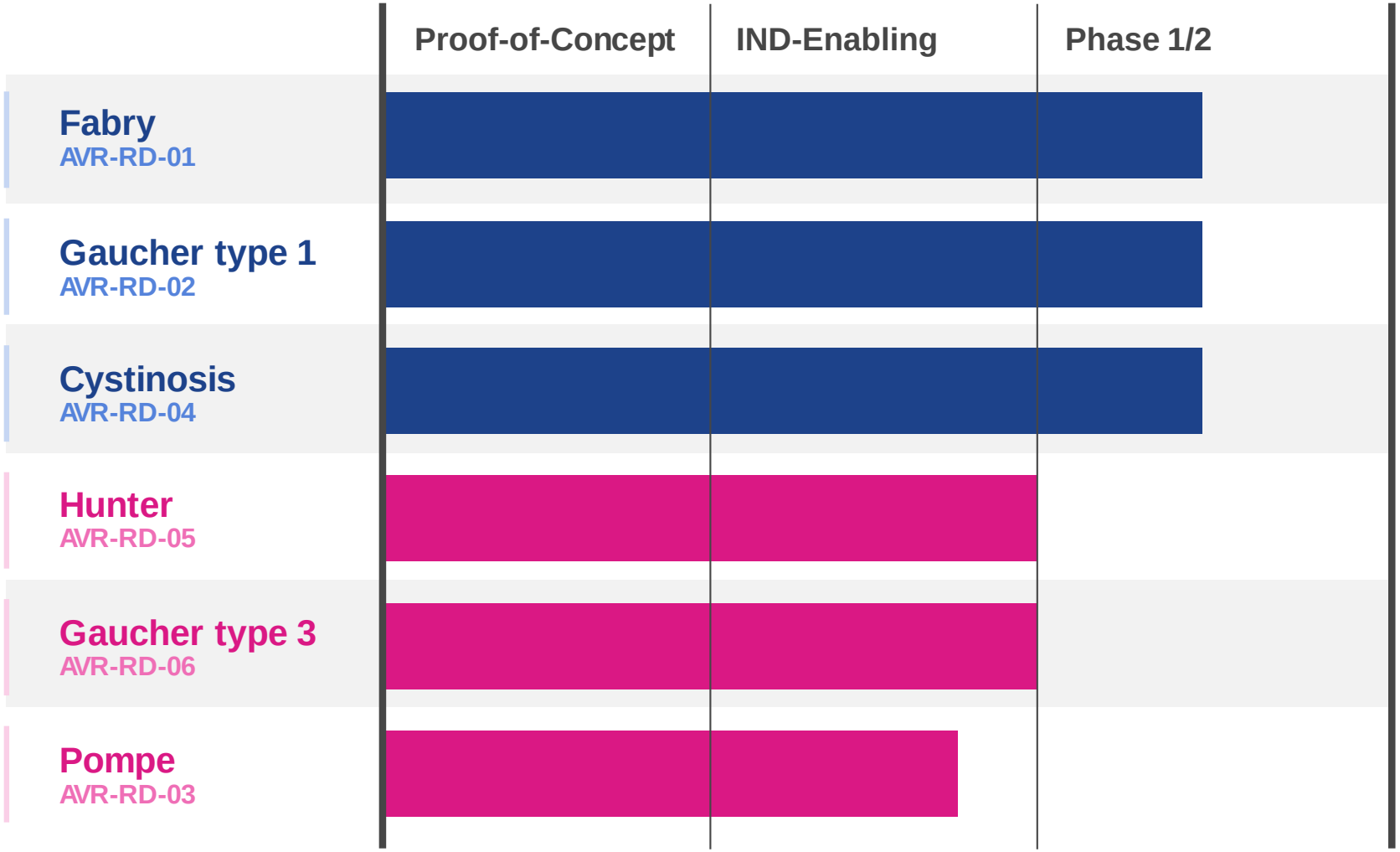
The Second Wave

Hunter, Gaucher Type 3, & Pompe



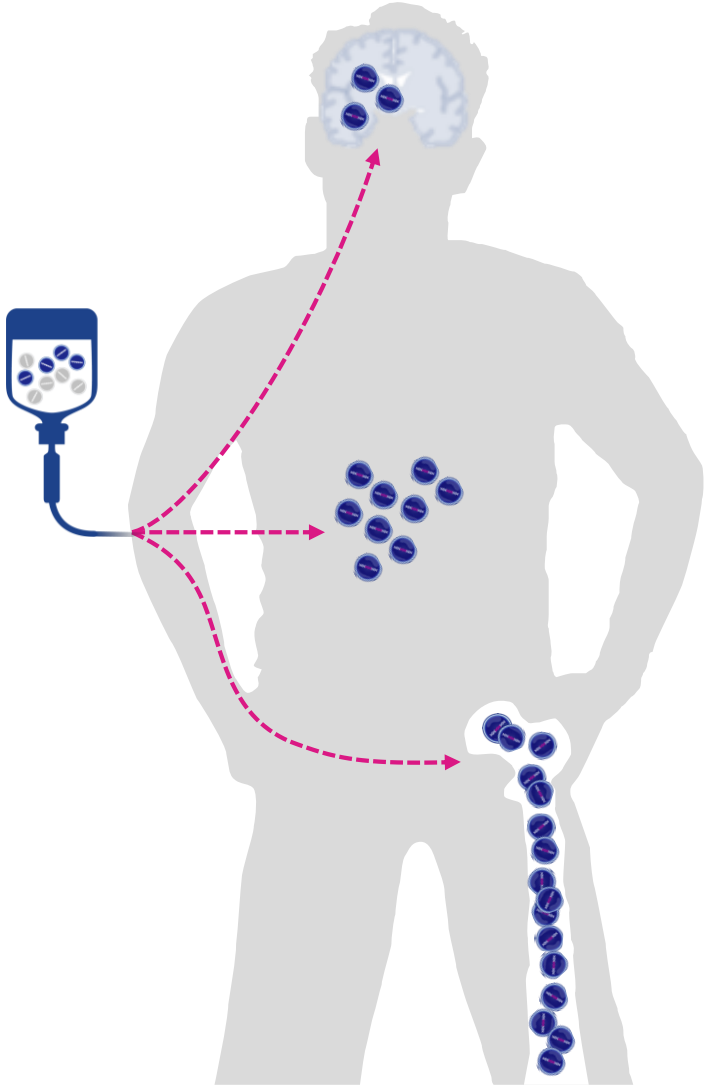
Bold expansion of our leadership in lysosomal disorders

Significant patient population and market opportunity



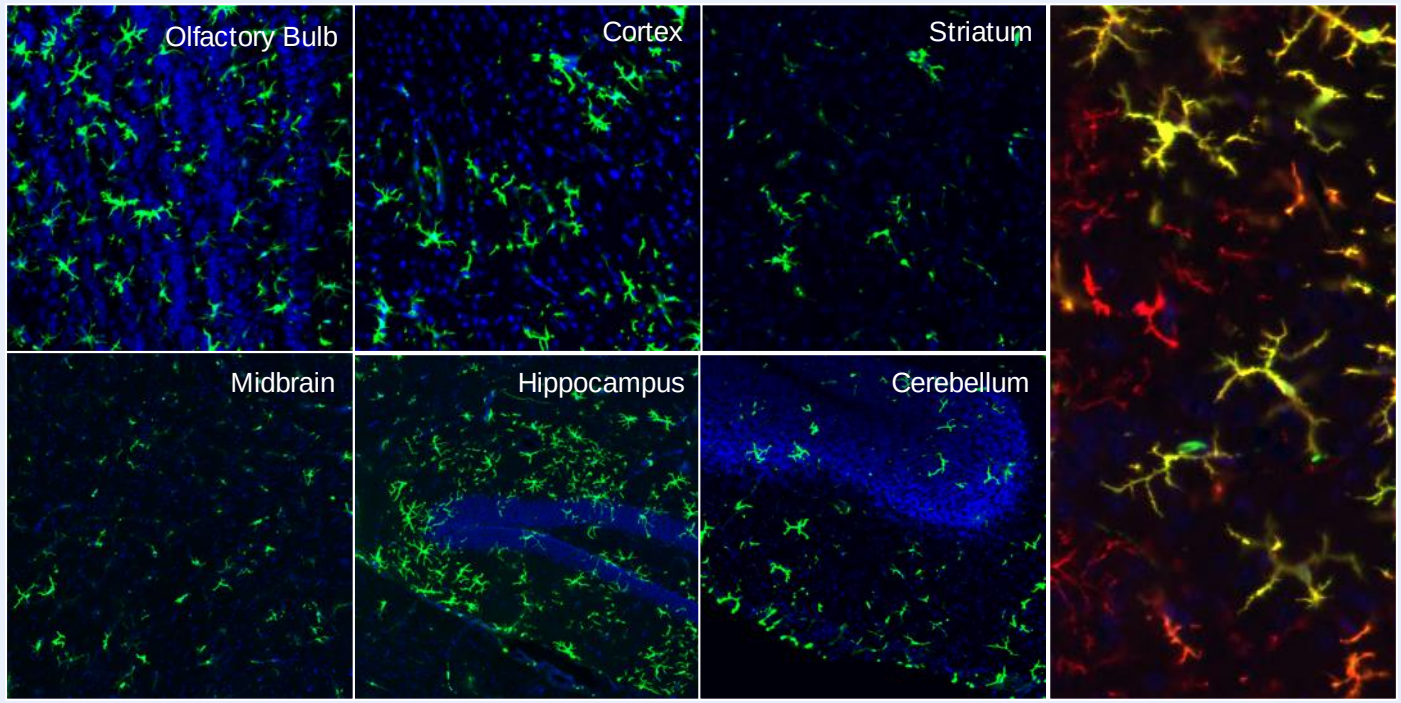
IND: Investigational New Drug

Global distribution in body and brain



Widespread distribution of GFP+ cells in the brain

Colocalization with microglia marker

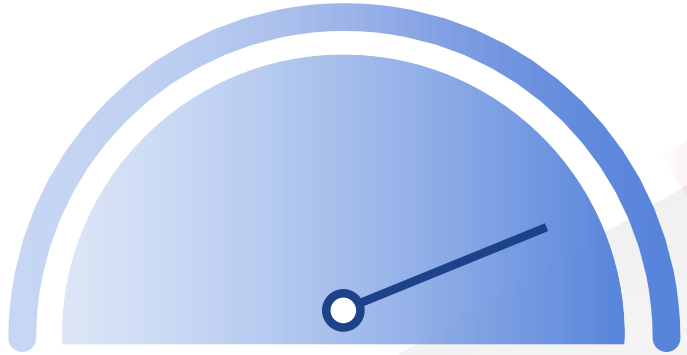


IV-dosed animal

GFP+ Engrafted Cells DAPI Iba1

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

plato® is designed to de-risk and accelerate second wave



plato® tool box

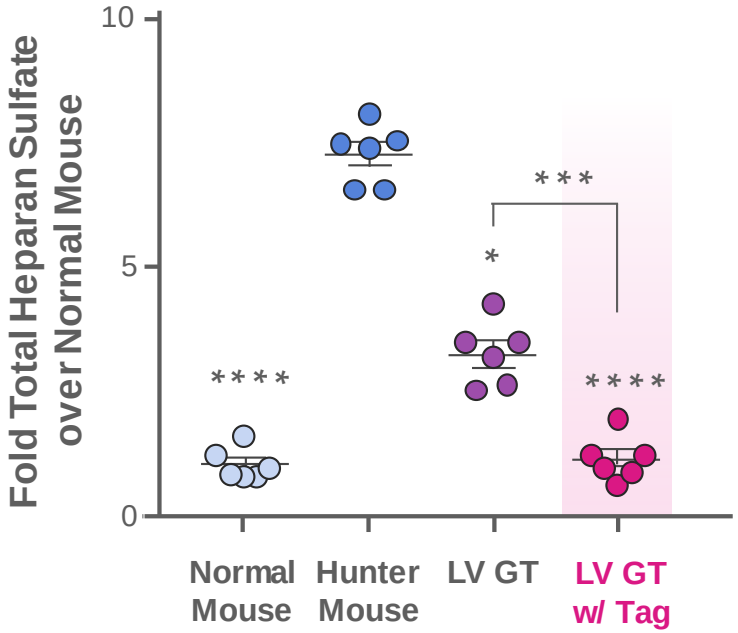
- Four-plasmid vector system
- Automated, closed manufacturing
- Advanced tagging technology
- Bu90-TCI conditioning

Bu90-TCI: Busulfan 90-Target Concentration Intervention

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

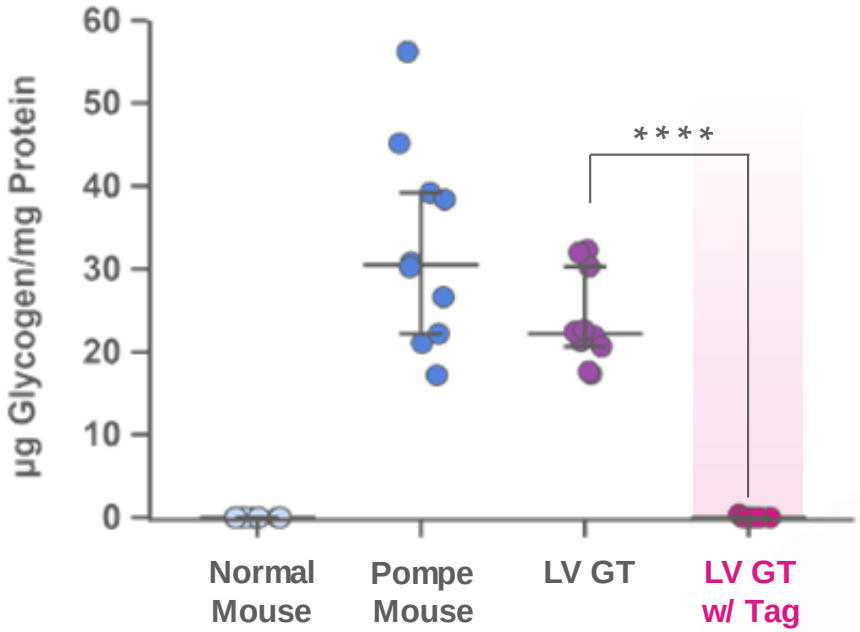


*Figure adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 3A; *P<0.05, ***P<0.001, ****P<0.0001; LV GT: Lentiviral Gene Therapy*

Hunter Syndrome

Young boy from Brazil, living with Hunter syndrome

DIFFERENTIATED TARGET PRODUCT PROFILE *for*

Hunter Syndrome

First-Line Therapy and Functional Cure

Prevents, halts or reverses disease; normalizes lifespan

- CNS: neurologic deterioration, seizures, aggressive behavior
- Delayed development, speech impairment
- Respiratory issues, cardiac valve disease
- Hearing and vision loss
- Compromised stature, stunted growth, coarse facial features
- Hepatosplenomegaly, chronic diarrhea

Lifelong durability

- No waning of efficacy
- Single infusion for life
- Off ERT
- Off concomitant medications
- Save millions in healthcare costs per patient

Addresses all patient segments

- All genetic mutations, neuronopathic and non-neuronopathic
- All age groups
- No AAV or ERT neutralizing antibody limitations

Impacts hard-to-reach organs

- Brain: global distribution of genetically modified microglia
- Global distribution throughout all tissues and organs of genetically modified macrophages

Well-tolerated

- No ERT-related side effects
- Mild-to-moderate, transient side effect profile consistent with Bu90-TCI
- No liver toxicity or adverse immunogenicity

Note: These are target attributes for a first-line therapy

AAV: Adeno-Associated Virus; Bu90-TCI: Busulfan 90-Target Concentration Intervention; CNS: Central Nervous System; ERT: Enzyme Replacement Therapy

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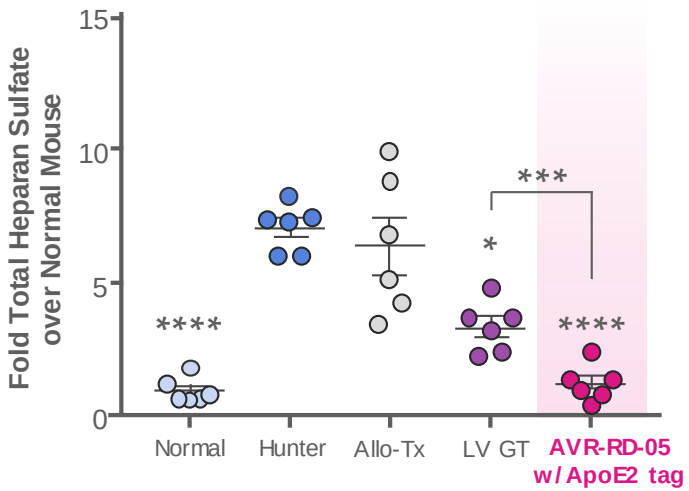
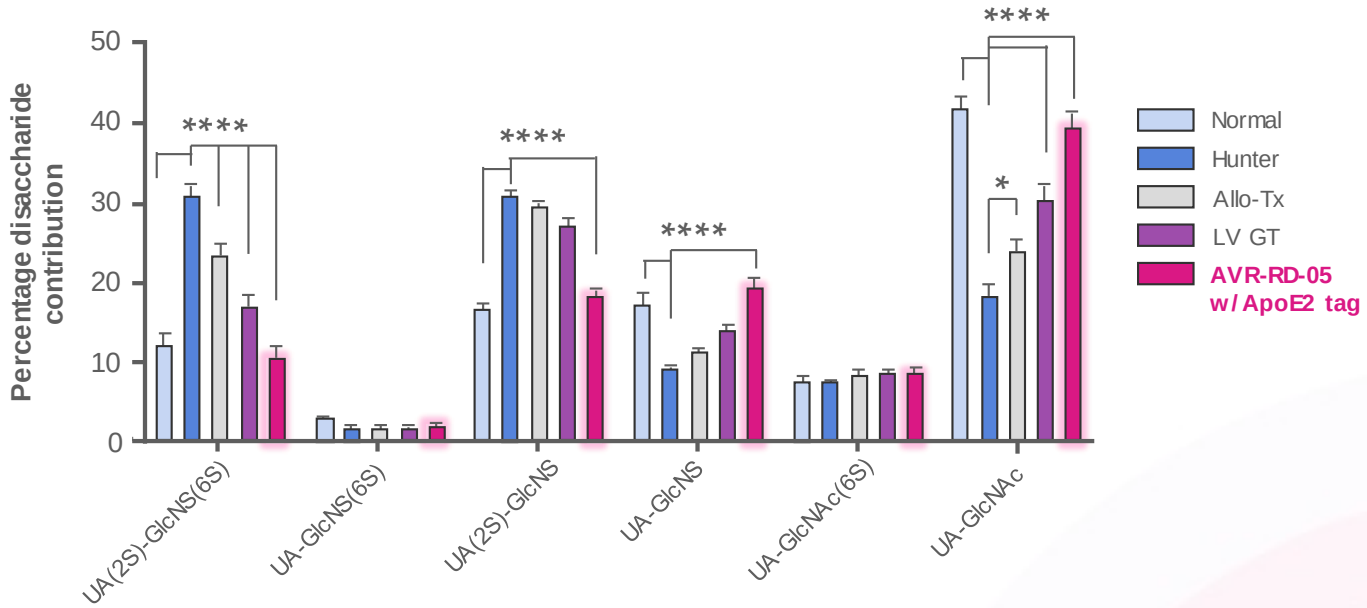
Normalization of substrate in body and brain

Tag enhances physiological normalization of quantity and composition of heparan sulfate in Hunter mice brains

Brain heparan sulfate quantity



Brain heparan sulfate composition



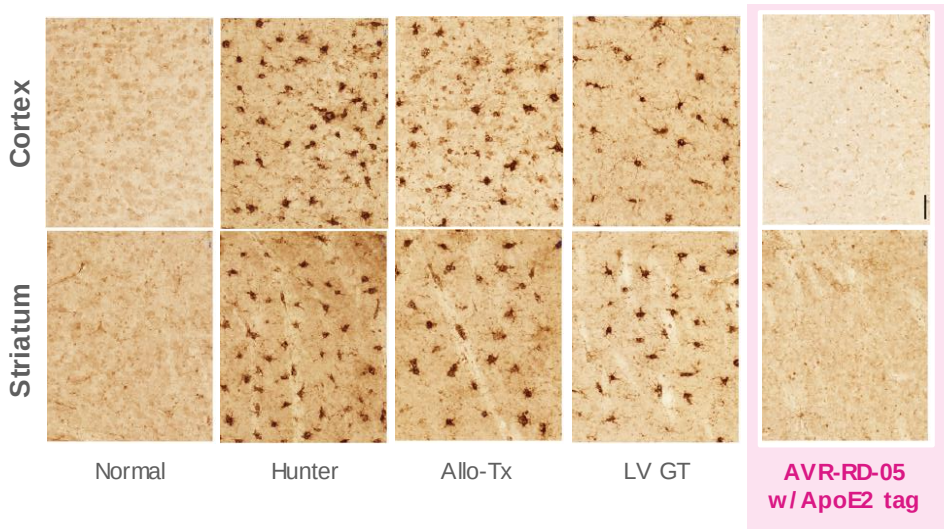
*Figures adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 3, *P<0.05, ***P<0.001, ****P<0.0001, vs. Hunter*
Allo-Tx: Allogeneic Hematopoietic Stem Cell Therapy; LV GT: Lentiviral Gene Therapy; ApoE2: Apolipoprotein E; UA(2S): 2-O-Sulfo Unsaturated Uronic Acid; UA: Uronic Acid; GlcNS(6S): N-Sulfo-D-Glucosamine 6-Sulfate; GlcNS: N-Sulfo-D-Glucosamine; GlcNAc(6S): N-Acetyl-D-Glucosamine 6-Sulfate; GlcNAc: N-Acetyl-D-Glucosamine

Normalization of neuro-inflammation

Tag enables widespread correction of pathological microgliosis and astrogliosis in Hunter mice brains

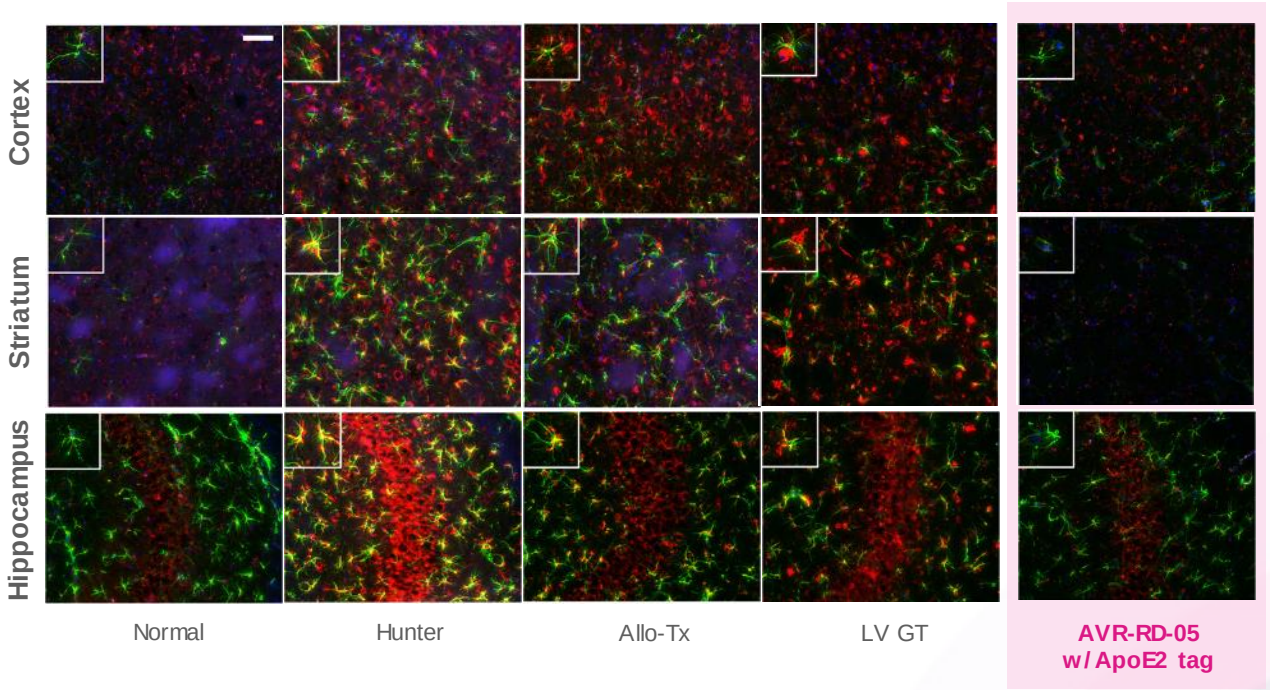
Complete normalization of activated microglia

ILB4 – activated microglia



Elimination of astrogliosis

DAPI – DNA/nucleus
LAMP2 – lysosomes
GFAP – astrocytes

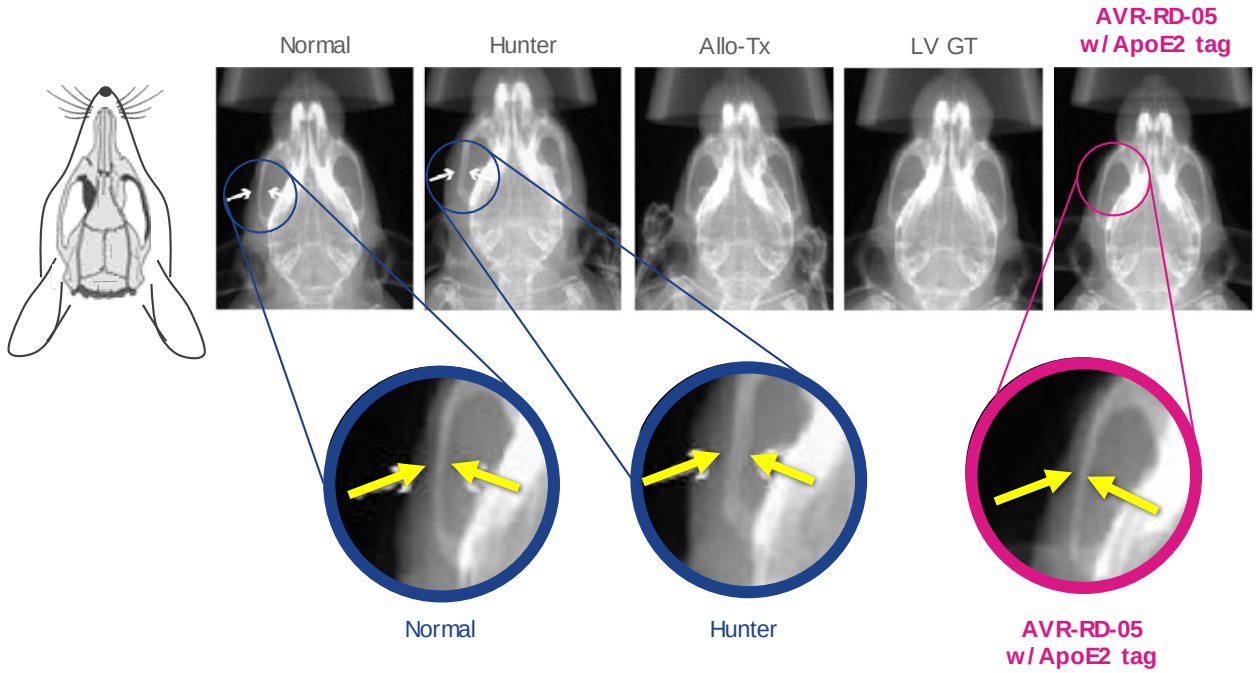


Figures adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 5A, 6E
Allo-Tx: Allogeneic Hematopoietic Stem Cell Therapy; LV GT: Lentiviral Gene Therapy; ApoE2: Apolipoprotein E; ILB4: Isolectin B4; DAPI: 4',6-diamidino-2-phenylindole; LAMP2: Lysosomal Associated Membrane Protein 2; GFAP: Glial Fibrillary Acidic Protein

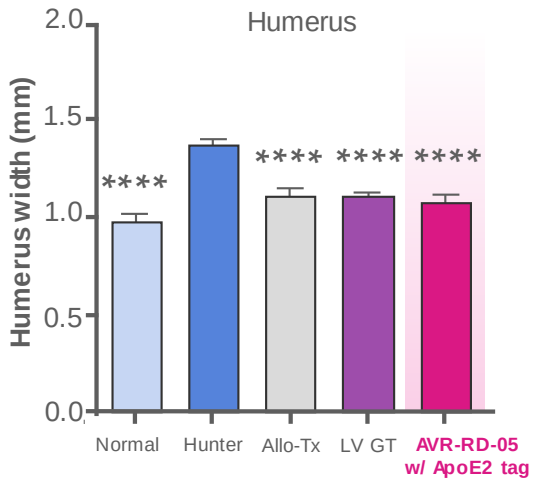
Normalization of facial and skeletal abnormalities

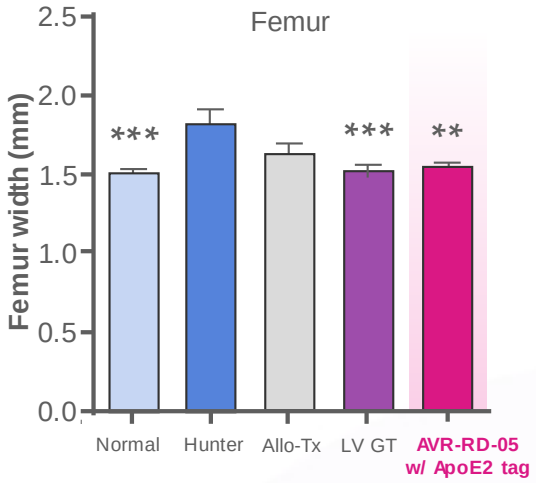
Tag enables widespread normalization of clinically-important skeletal measures in Hunter mouse

Complete normalization of width of zygomatic arch (*cheek bone*)



Complete normalization of width of long bones



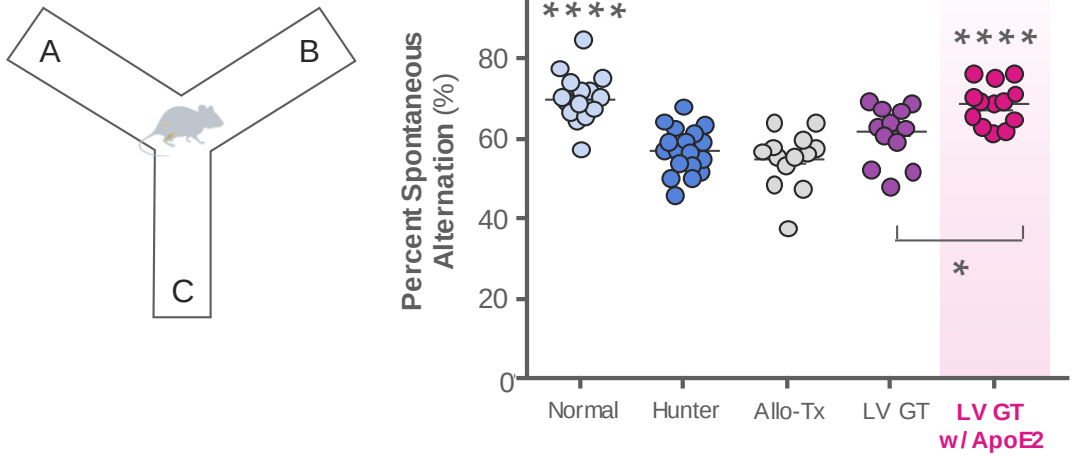


*Figures adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 7A, 7C, 7D. **P<0.01, ***P<0.001, ****P<0.0001, vs. Hunter*
Allo-Tx: Allogeneic Hematopoietic Stem Cell Therapy; LV GT: Lentiviral Gene Therapy; ApoE2: Apolipoprotein E

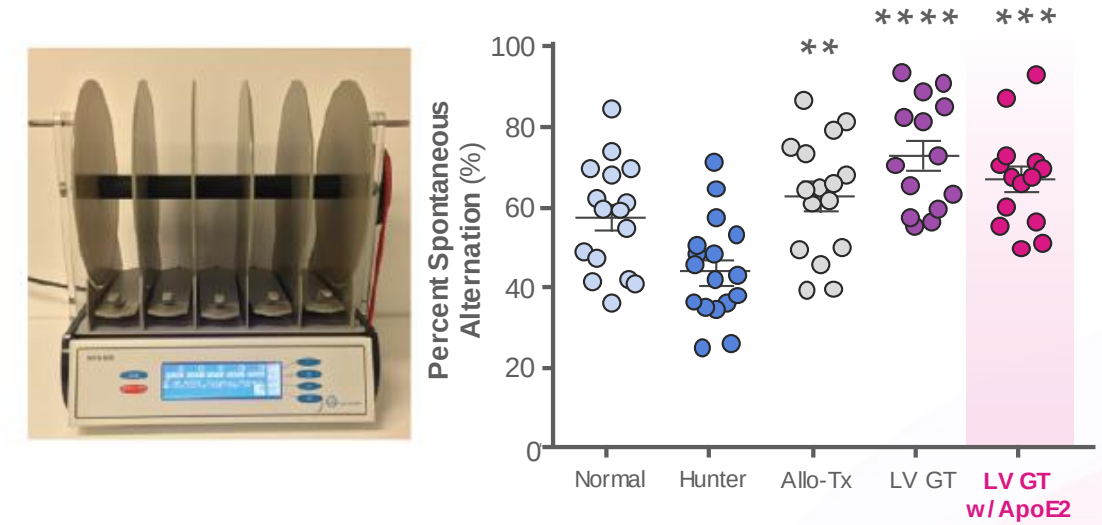
Normalization of cognition and performance

Tag enables complete rescue of clinically important neurological measures in Hunter mouse

Y-maze test (spatial working memory): complete rescue of cognitive symptoms



Accelerating rotarod (sensorimotor coordination and balance): complete rescue of performance



*Figures adapted from Gleitz H et al., EMBO Mol Med, 2018 Fig 6H, 6I, 7E, 7I. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001, vs. Hunter*
Allo-Tx: Allogeneic Hematopoietic Stem Cell Therapy; LV GT: Lentiviral Gene Therapy; ApoE2: Apolipoprotein E

Planned investigator-sponsored Phase 1/2 trial in neuronopathic Hunter syndrome

PHASE 1/2

AVR-RD-05 *n=5*

FIRST PATIENT EXPECTED TO BE DOSED 2H ’21:

OBJECTIVES		PATIENTS
• Safety • Tolerability • Engraftment	• Efficacy • Enzyme and substrate biomarker response	• Early progressive form • Treatment-naïve or on ERT • >3 to <24 months • Male

ERT: Enzyme Replacement Therapy; 2H: Second Half

Planned global regulatory strategy for Hunter syndrome

Planned

POTENTIAL REGISTRATION

- All age groups and genetic mutations
- Treatment-naïve and/or on ERT
- Safety, durability, efficacy
- Cognition and CNS imaging
- Vision, hearing, hepatosplenomegaly
- Quality of life
- Biomarker data

Expect to Dose 1ST Patient 2H 2021

PHASE 1/2 – INVESTIGATOR SPONSORED TRIAL

- n=5, >3 to <24 months, males
- Treatment-naïve and/or on ERT
- Safety, durability, preliminary efficacy
- Cognition
- Multiple clinical metrics
- Quality of life
- Biomarker data

ERT: Enzyme Replacement Therapy; CNS: Central Nervous System; 2H: Second Half

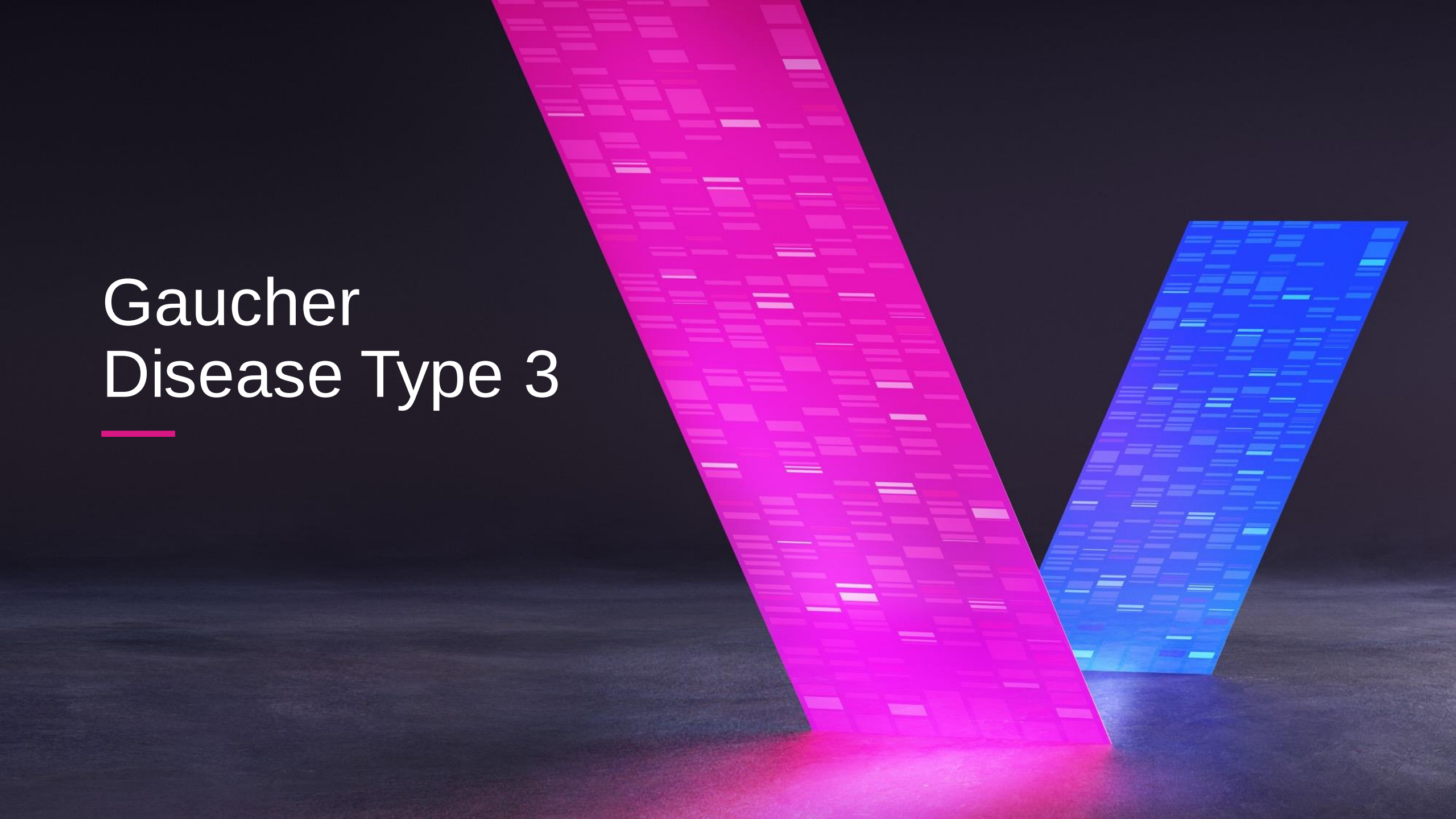
AVR-RD-05

Anticipated Next Steps

- Dose first patient 2H 2021
- Early FDA dialogue on regulatory pathway
- Prepare plato® CMC / analytics requirements

2H: Second Half; FDA: Food and Drug Administration; CMC: Chemistry, Manufacturing, and Controls

Gaucher Disease Type 3



DIFFERENTIATED TARGET PRODUCT PROFILE *for*

Gaucher Disease Type 3

First-Line Therapy and Functional Cure

Prevents, halts or reverses disease; normalizes lifespan

- CNS: Neurologic deterioration, seizures, risk of GBA-Parkinson's
- Bone-related manifestations, physical deformity, bone crises, bone pain, avascular necrosis
- Low hemoglobin levels and platelet counts
- Hepatosplenomegaly, risk of cirrhosis and splenectomy
- Fatigue
- Risk of multiple myeloma

Lifelong durability

- Single infusion for life
- Off ERT/SRT
- No waning of efficacy
- Off concomitant medication
- Save millions in healthcare costs per patient

Addresses all patient segments

- All genetic mutations
- All age groups
- Male and female
- No AAV or ERT neutralizing antibody limitations

Impacts hard-to-reach organs

- Brain: global distribution of genetically modified microglia
- Diseased macrophages (Gaucher cells) replaced by functional macrophages
- Bone and bone marrow: global distribution of genetically modified macrophages and osteoclasts

Well-tolerated

- No ERT-related side effects
- Mild-to-moderate, transient side effect profile consistent with Bu90-TCI
- No liver toxicity or adverse immunogenicity

"My neurological issues are definitely the thing that impacts my life the most… I struggle daily with normal activities or what a healthy person would consider normal… I also have issues with short-term memory loss."

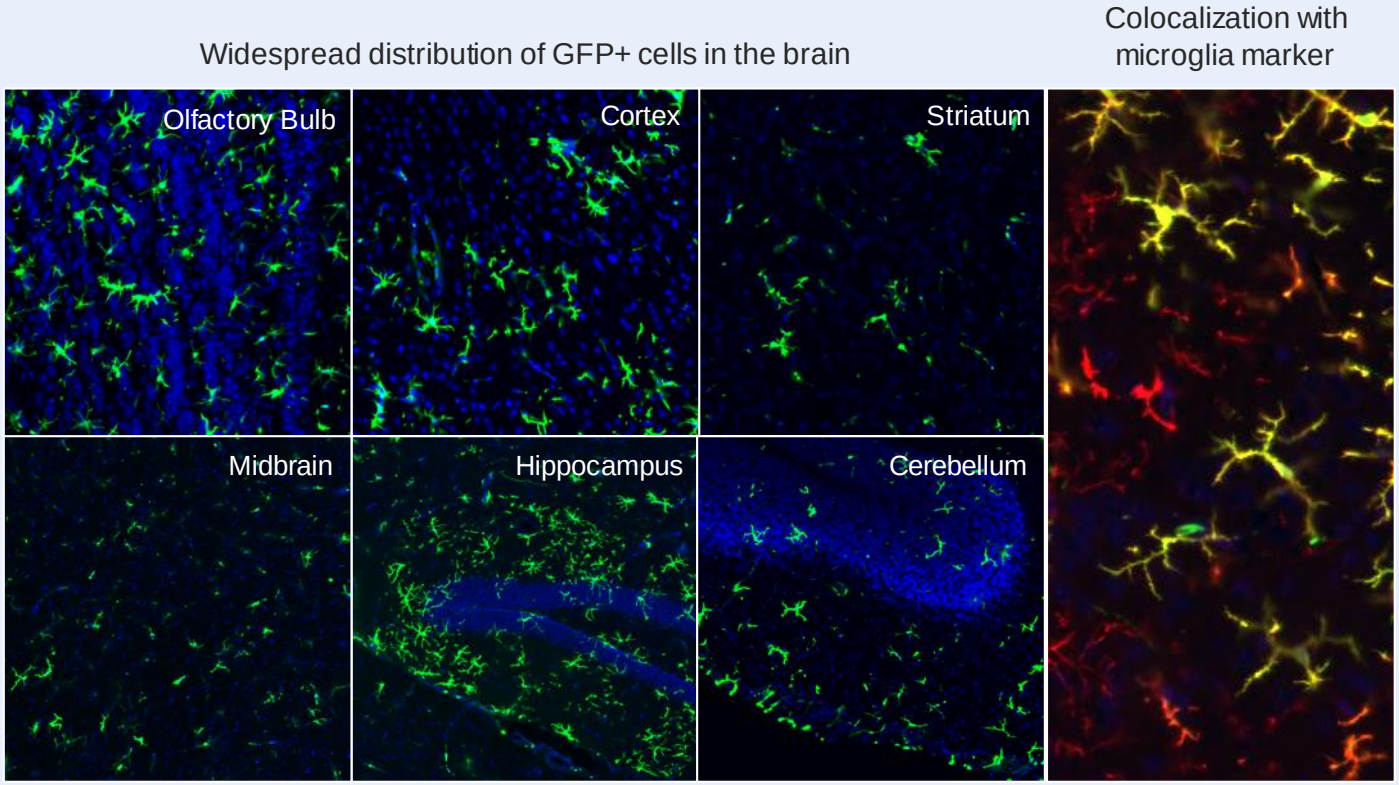
– Maddie, living with Gaucher disease type 3

Note: These are target attributes for a first-line therapy

AAV: Adeno-Associated Virus; Bu90-TCI: Busulfan 90-Target Concentration Intervention; CNS: Central Nervous System; ERT: Enzyme Replacement Therapy; SRT: Substrate Reduction Therapy; GBA: Glucocerebrosidase

AVROBIO

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

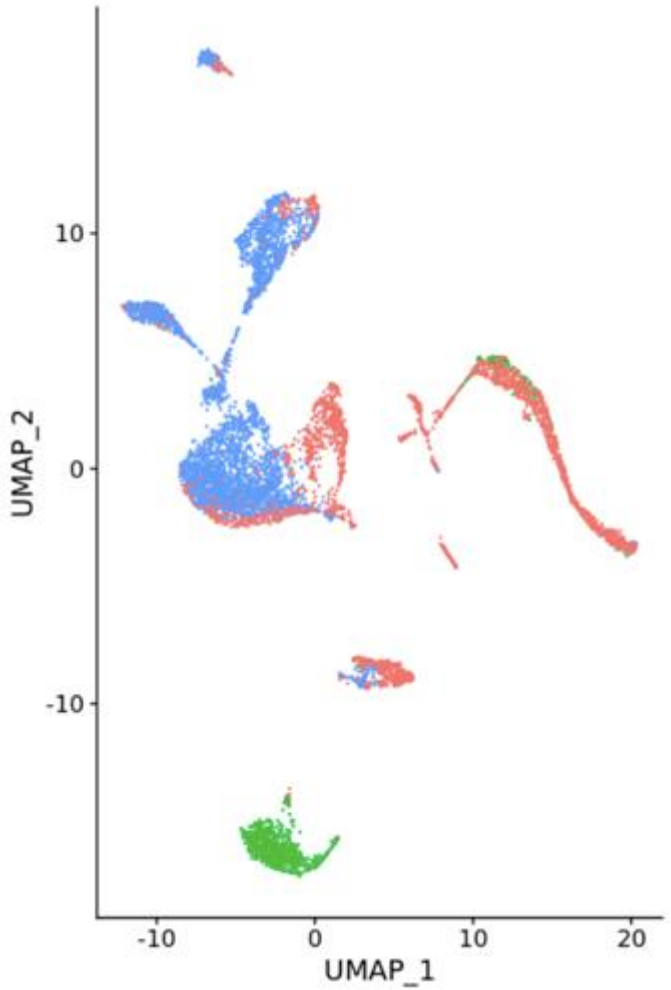


GFP: Green Fluorescent Protein; DAPI: 4',6-diamidino-2-phenylindole; Iba1: Ionized Calcium-Binding Adaptor Molecule 1 antibody; IV: Intravenous

Single cell RNA-Seq of HSC-derived lineages can assess fate of engrafted cells

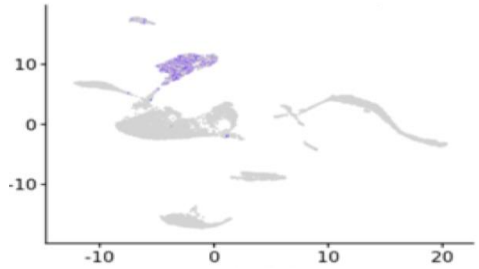
C57BL/6J mouse single cell RNA-Seq

- Bone marrow
- Peripheral blood
- Microglia



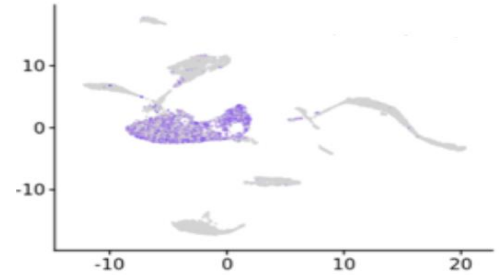
Cd3

T-Cell marker



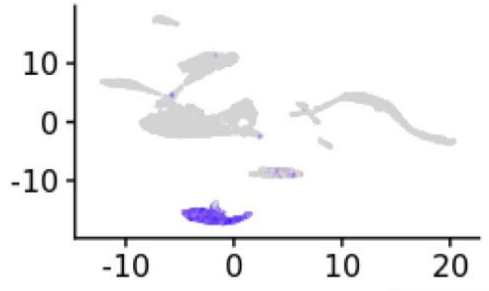
Cd19

B-Cell marker



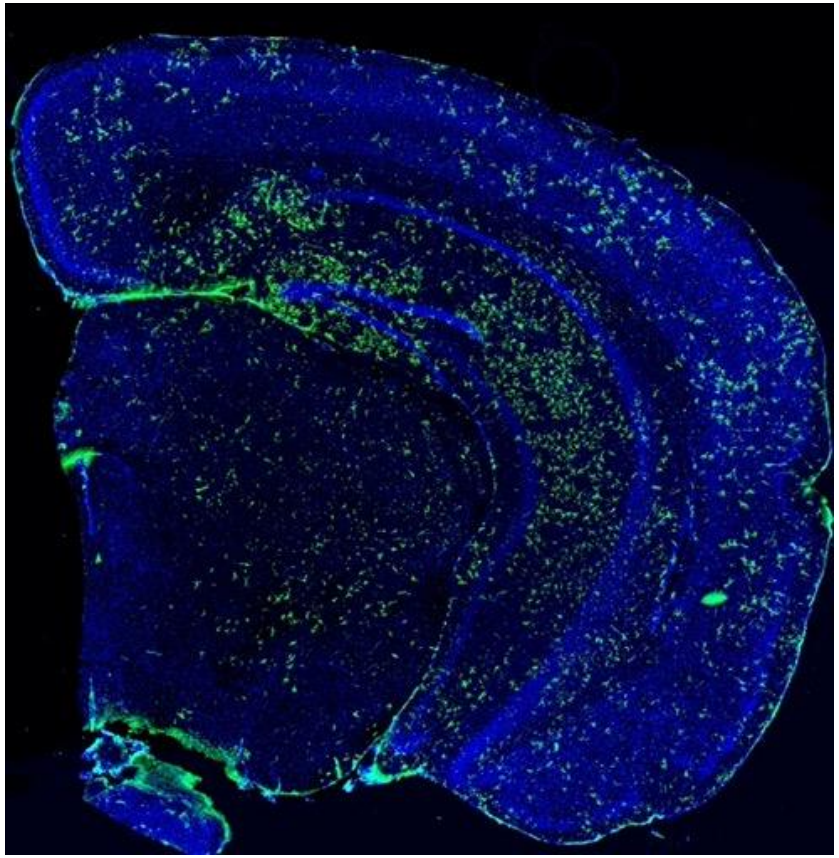
Trem2

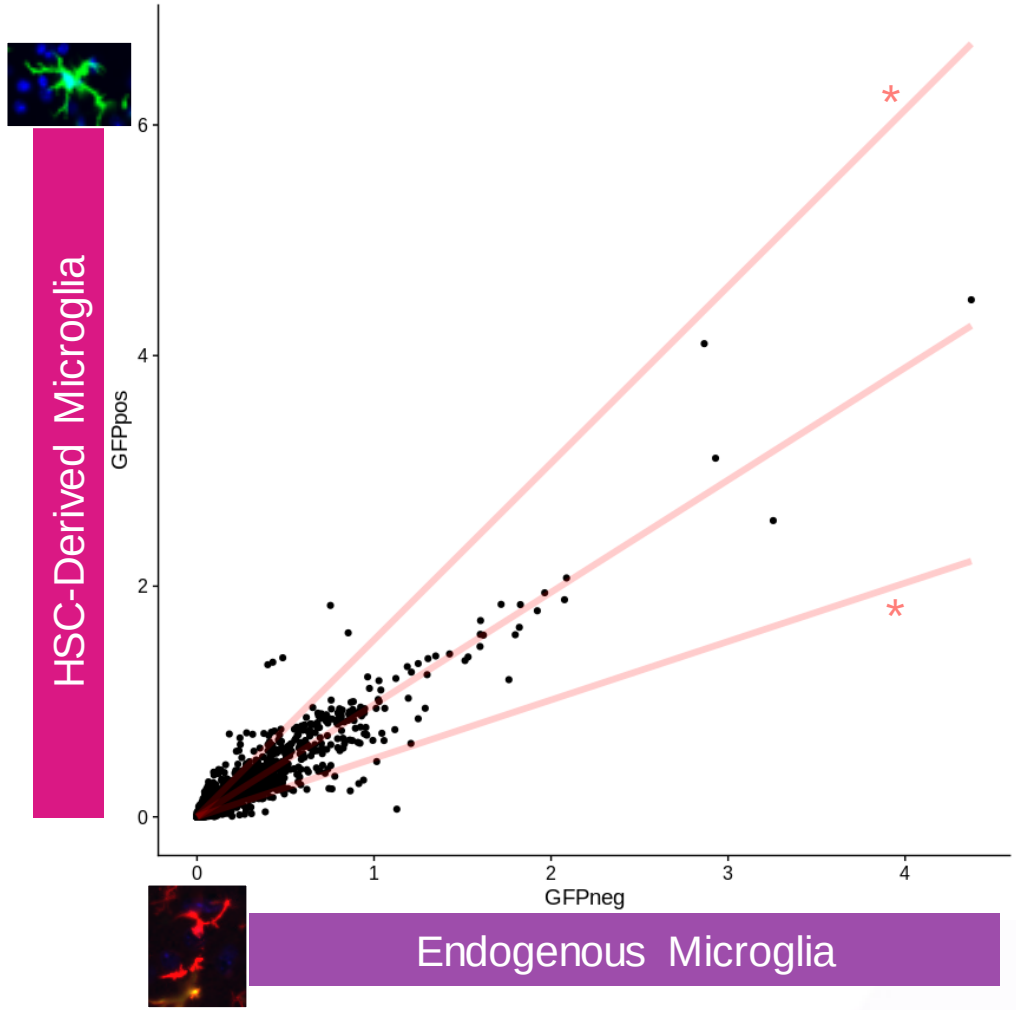
Microglial marker



HSC: Hematopoietic Stem Cell; RNA-Seq: Ribonucleic Acid Sequencing; UMAP: Uniform Manifold Approximation and Projection; Cd3: Cluster of Differentiation 3; Cd19: Cluster of Differentiation 19; Trem2: Triggering Receptor Expressed On Myeloid Cells 2

Engrafted and endogenous microglia show limited transcriptional differences

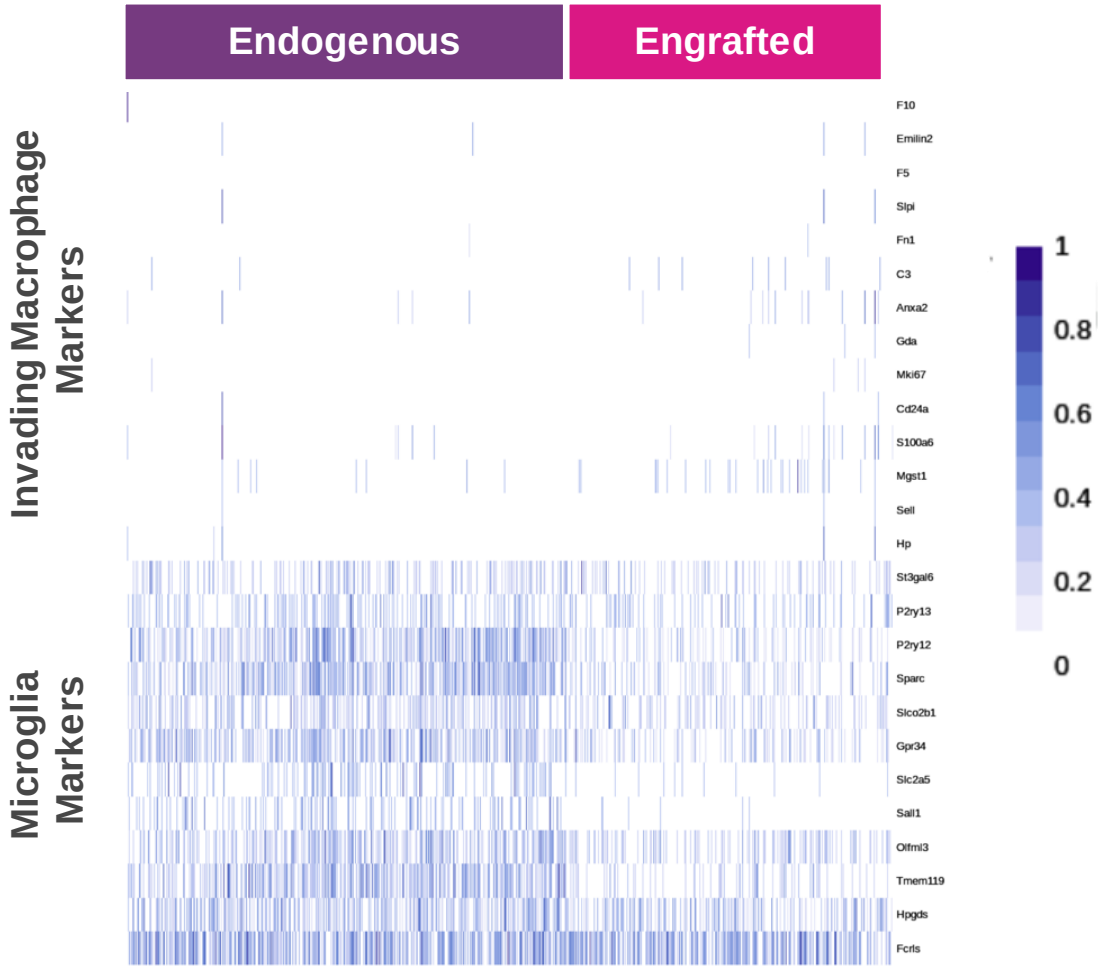




*-95% Quartile

GFP: Green Fluorescent Protein; HSC: Hematopoietic Stem Cell

HSC-derived myeloid cells in brain express bona fide microglia markers



HSC: Hematopoietic Stem Cell

AVR-RD-06

Anticipated Next Steps

- Leverage synergies with Gaucher disease type 1
  - Clinical and safety data
  - plato® CMC, analytics, preclinical package
- FDA dialogue on path to clinic

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

Pompe Disease

Wayne, living with Pompe disease

DIFFERENTIATED TARGET PRODUCT PROFILE *for*

Pompe Disease

First-Line Therapy and Functional Cure

Prevents, halts or reverses disease; normalizes lifespan

- Progressive muscle weakness, loss of mobility
- Breathing difficulties, respiratory failure, respiratory infections
- CNS: Neuromuscular deterioration
- Cardiomyopathy, heart failure
- GI complications, hepatomegaly
- Failure to thrive, delayed motor milestones
- Hearing loss, speech difficulties

Lifelong durability

- Single infusion for life
- No waning of efficacy
- Off ERT
- Save millions in healthcare costs per patient

Addresses all patient segments

- All genetic mutations (classic infantile-onset, non-classic infantile-onset, and late-onset)
- All age groups
- Male and female
- Antibody-status independent (CRIM+ and CRIM-)
- No AAV or ERT neutralizing antibody limitations

Impacts hard-to-reach organs

- Brain, spinal cord, PNS: global distribution of genetically modified microglia
- Skeletal and cardiac muscle: tag-directed enzyme and global distribution of genetically modified macrophages

Well-tolerated

- No ERT-related side effects
- Mild-to-moderate, transient side effect profile consistent with Bu90-TCI
- No liver toxicity or adverse immunogenicity

Note: These are target attributes for a first-line therapy

AAV: Adeno-Associated Virus; Bu90-TCI: Busulfan 90-Target Concentration Intervention; CNS: Central Nervous System; GI: Gastrointestinal; ERT: Enzyme Replacement Therapy; CRIM: Cross-Reactive Immunologic Material; PNS: Peripheral Nervous System

AVROBIO

Classic infantile-onset Pompe has high unmet medical need

Potential opportunity for rapid pathway to approval

Unique challenge of CIOP

Correlation residual GAA activity and clinical onset

- <1% activity with rapid progression in first few months with death at <2 yrs
- Poor/negligible response to ERT
- No GAA activity associated with strong antibody response to ERT [CRIM-ve]
- CNS manifestations

Potential prevention with *ex vivo* LV gene therapy

- 10% activity required for functional cure
- Auto-tolerance to therapeutic protein
- Head-to-toe solution
- No growing-related washout
- Treat in first few months of life—potential for life-long prevention

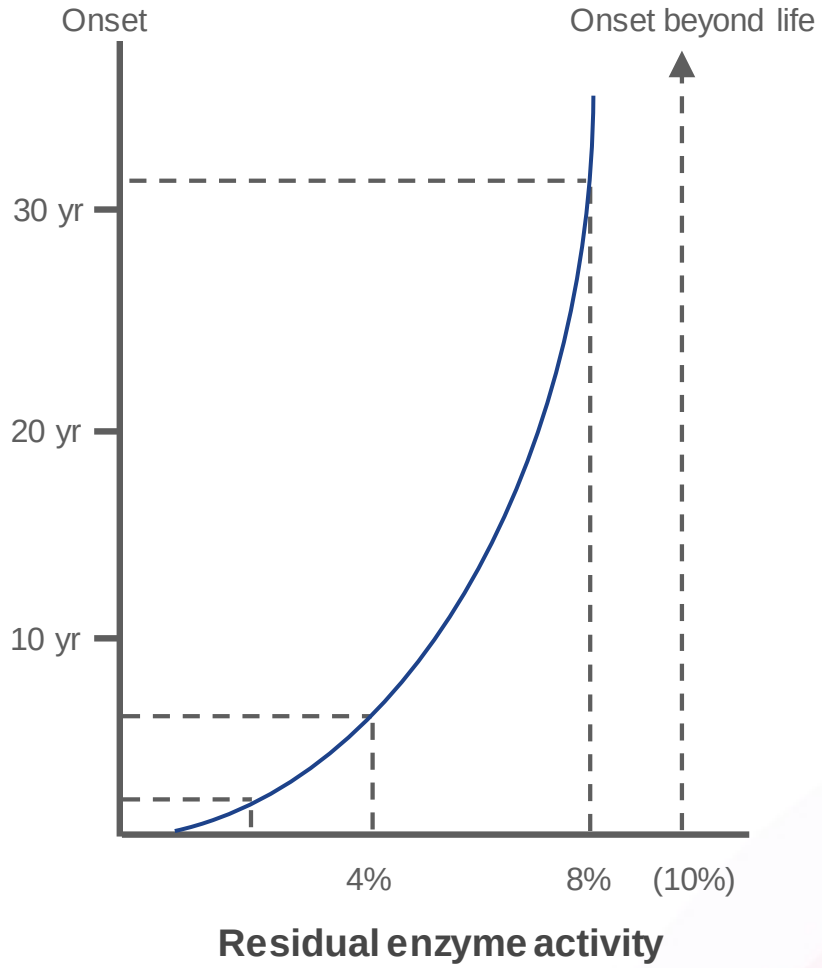
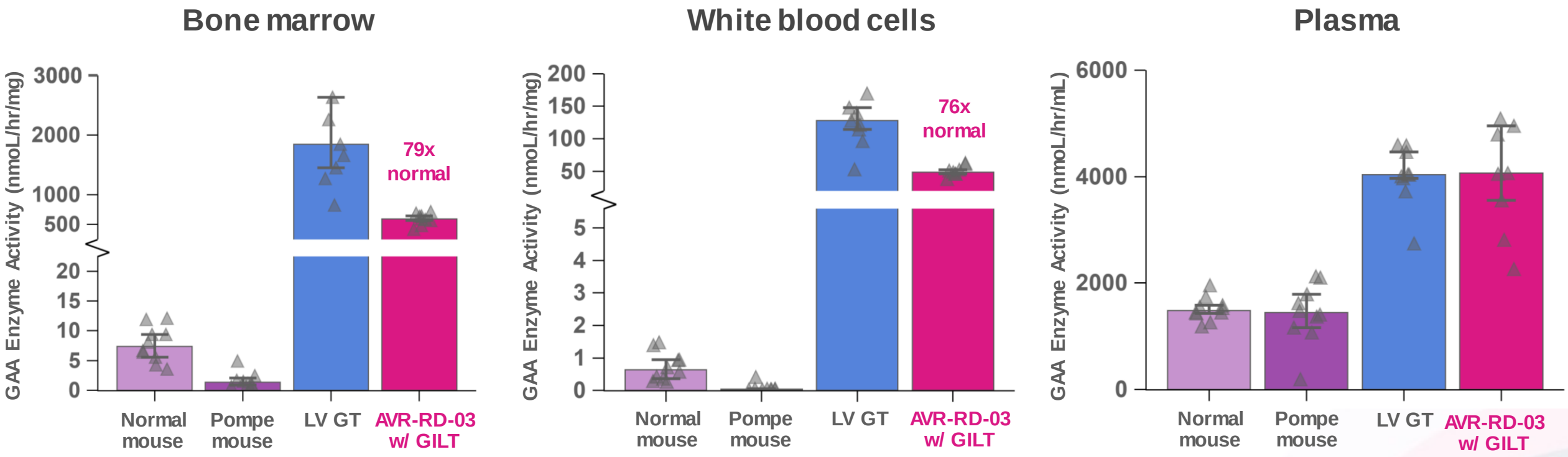


Figure adapted from Suzuki et al., Perspectives in Medicinal Chemistry, 2009 Fig 3
GAA: Acid Alpha-Glucosidase; ERT: Enzyme Replacement Therapy; CNS: Central Nervous System; LV: Lentiviral; CRIM-ve: Cross-Reactive Immunologic Material Negative; CIOP: Classic Infantile-Onset Pompe

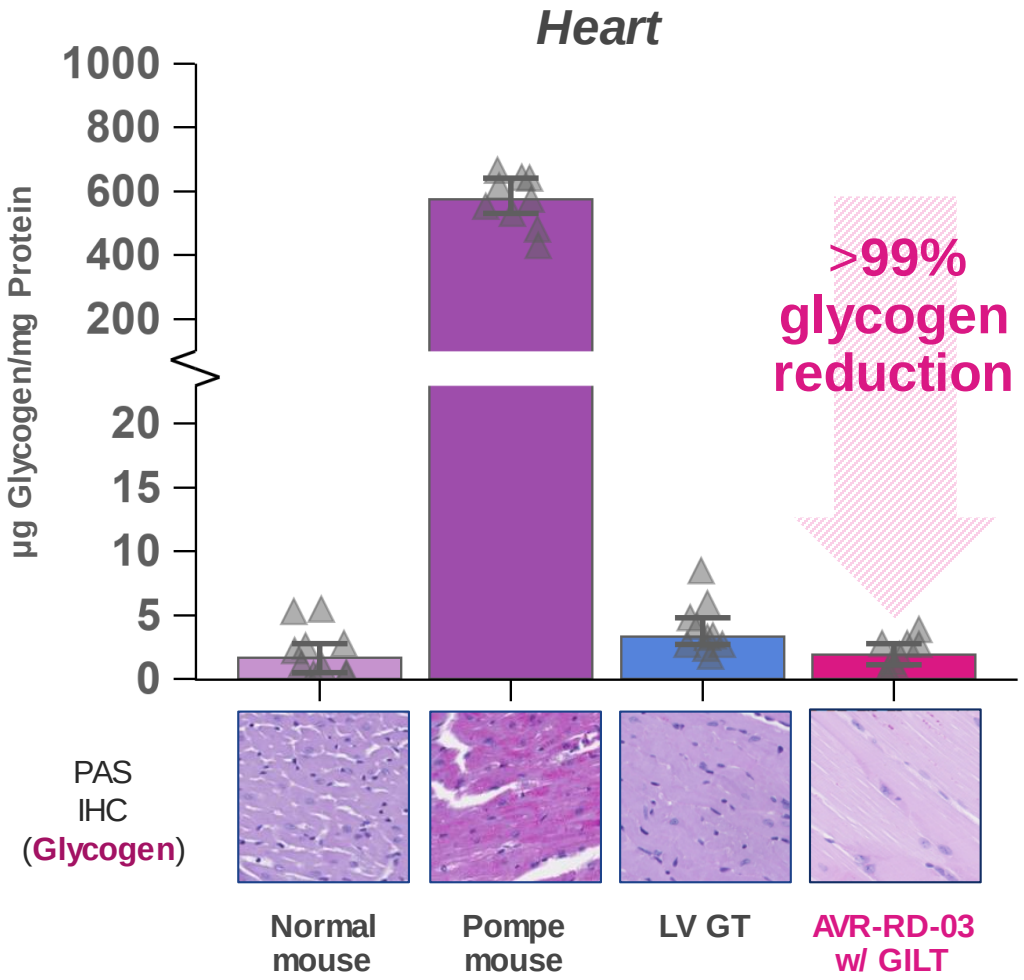
Durable enzyme production in infantile-onset Pompe mice post-therapy

16 weeks after infusion

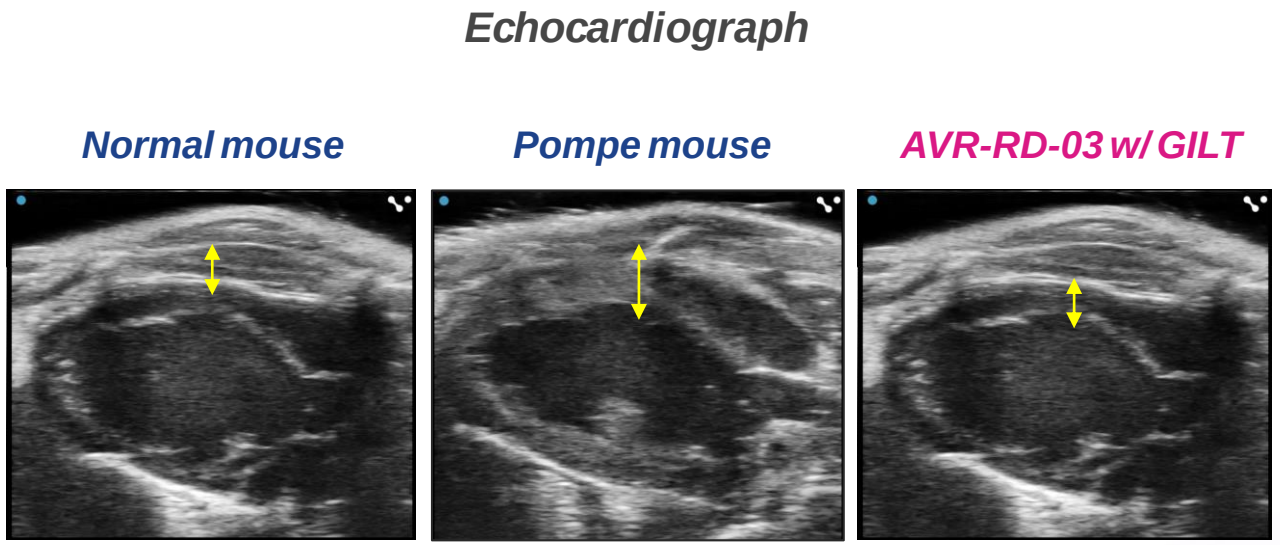


LV GT: Lentiviral Gene Therapy; GILT: Glycosylation-Independent Lysosomal Targeting; GAA: Acid Alpha-Glucosidase

>99% glycogen reduction, reversal of heart remodeling in classic infantile-onset mice treated with GILT-tagged therapy



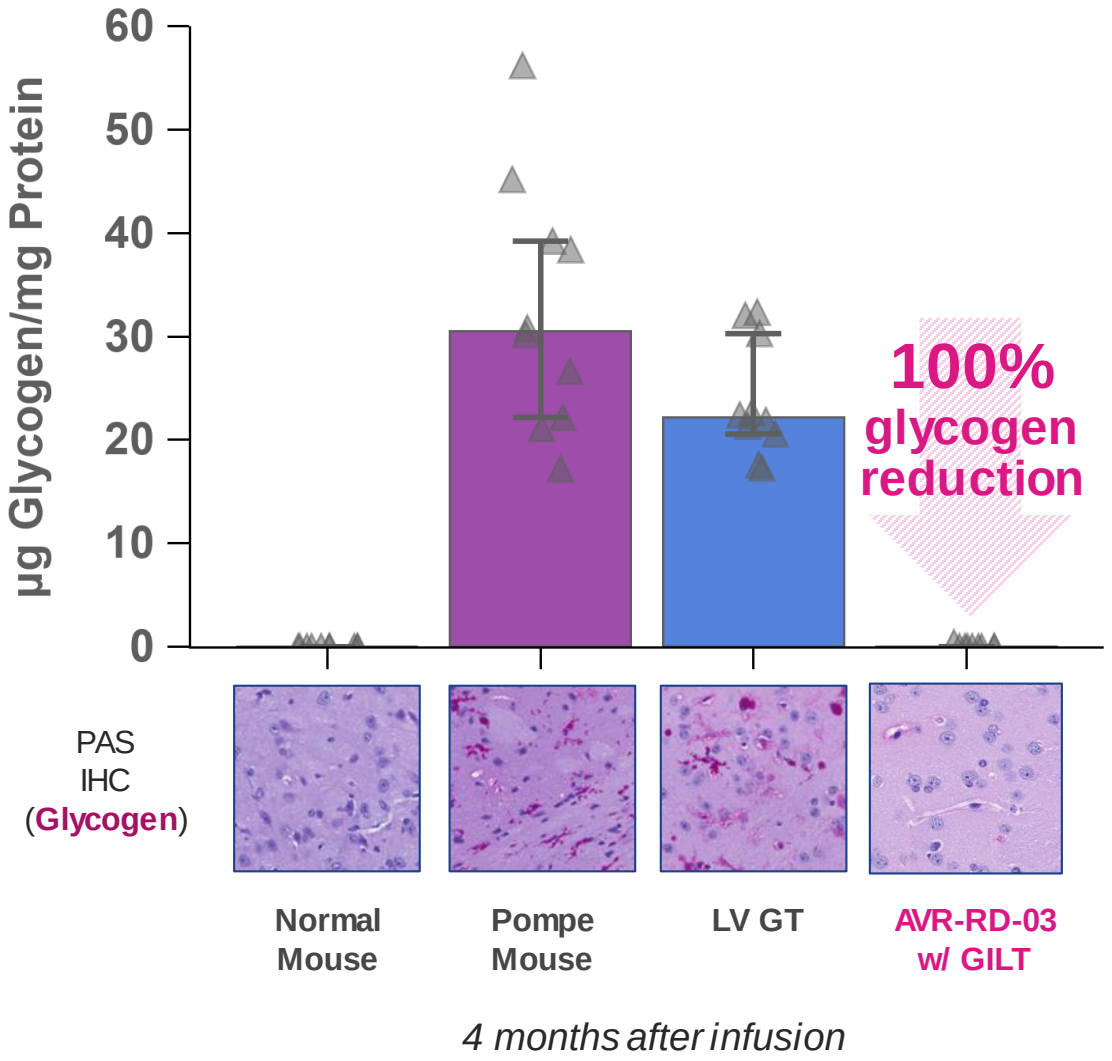
4 months after infusion



7 months after infusion

LV GT: Lentiviral Gene Therapy; GILT: Glycosylation-Independent Lysosomal Targeting; PAS: Periodic Acid-Schiff; IHC: Immunohistochemistry

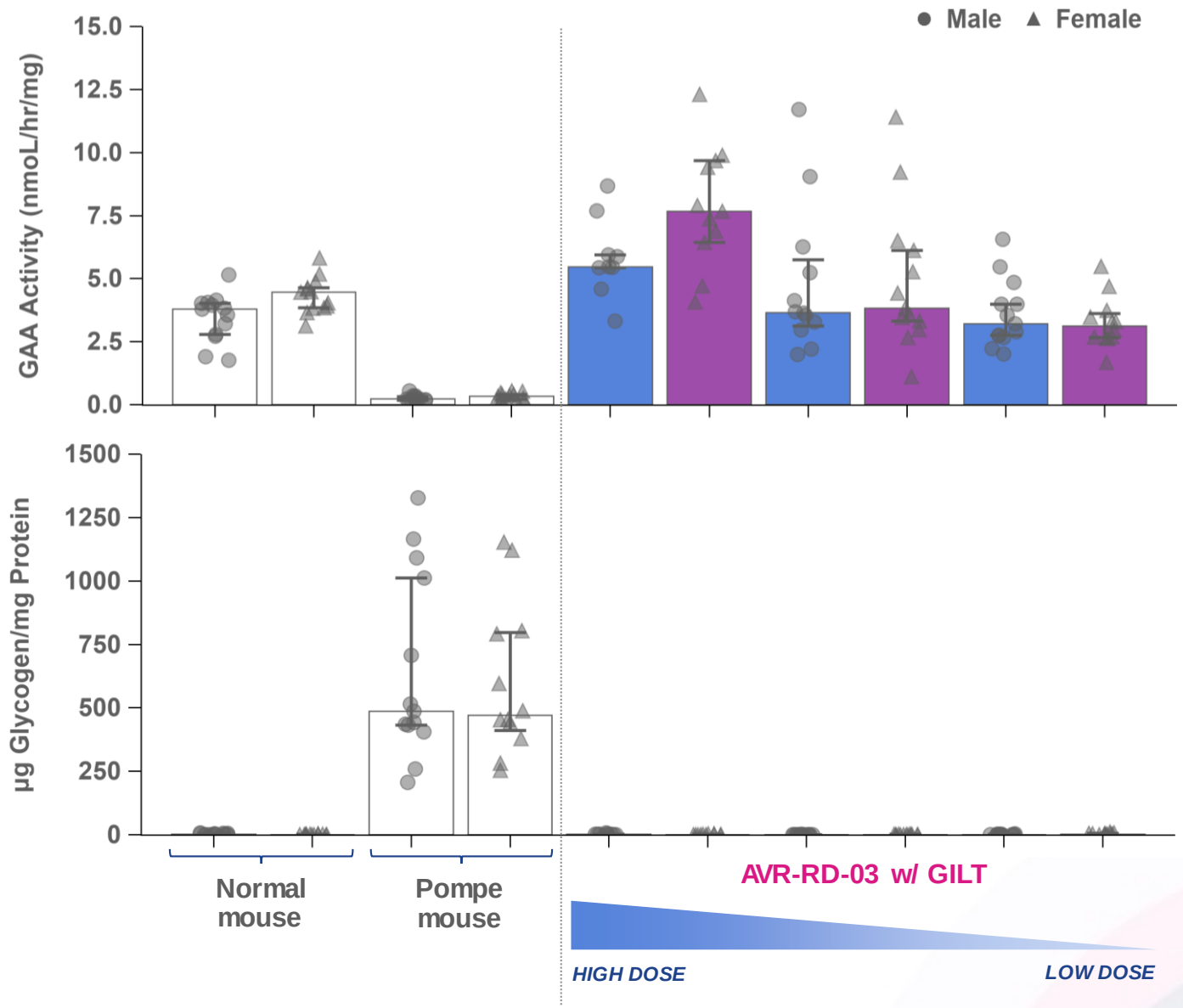
Brain



LV GT: Lentiviral Gene Therapy; GILT: Glycosylation-Independent Lysosomal Targeting; PAS: Periodic Acid-Schiff; IHC: Immunohistochemistry

Heart

>99% glycogen reduction

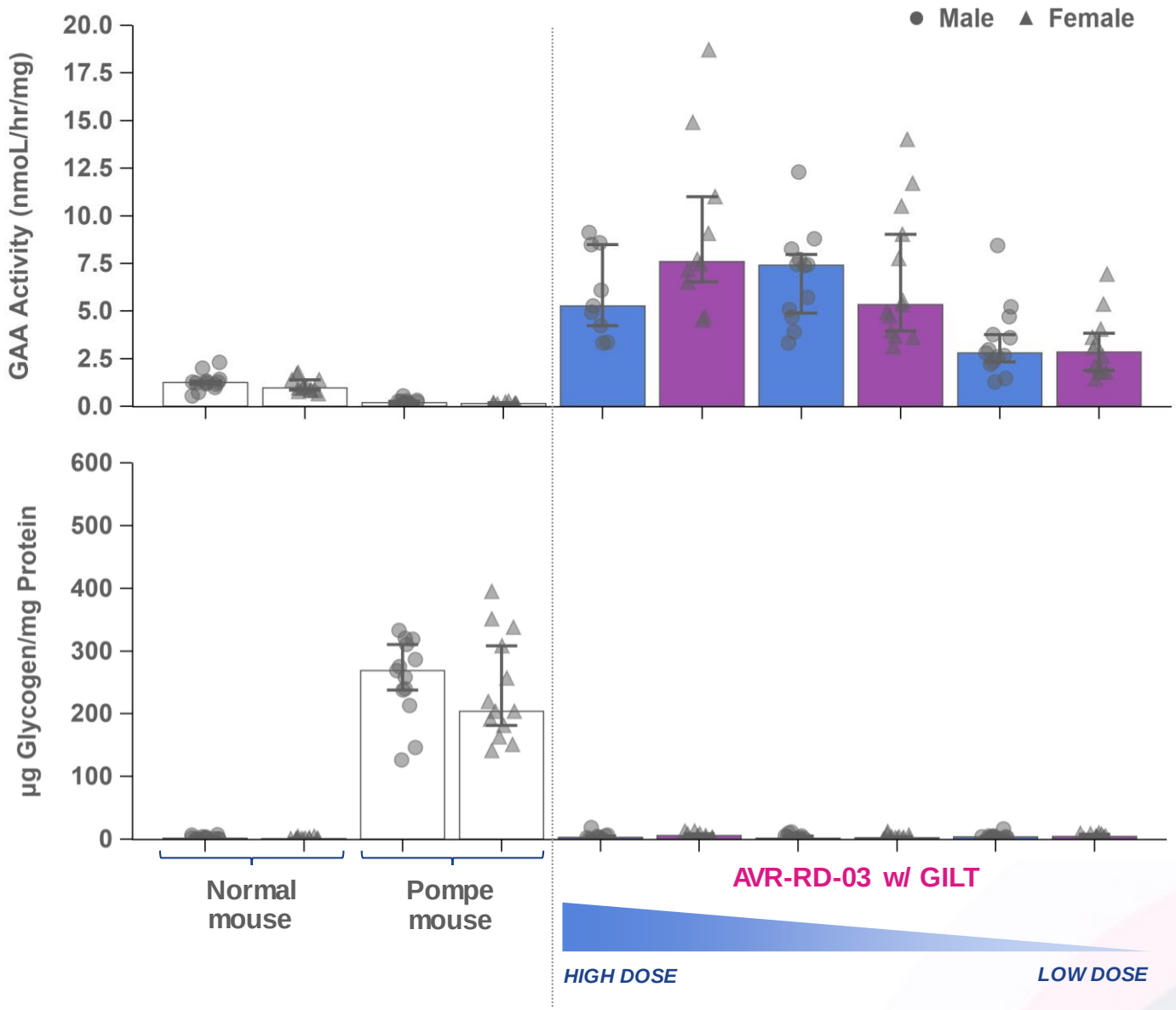


8 months after infusion

GAA: Acid Alpha-Glucosidase; GILT: Glycosylation-Independent Lysosomal Targeting

Diaphragm

>97% glycogen reduction

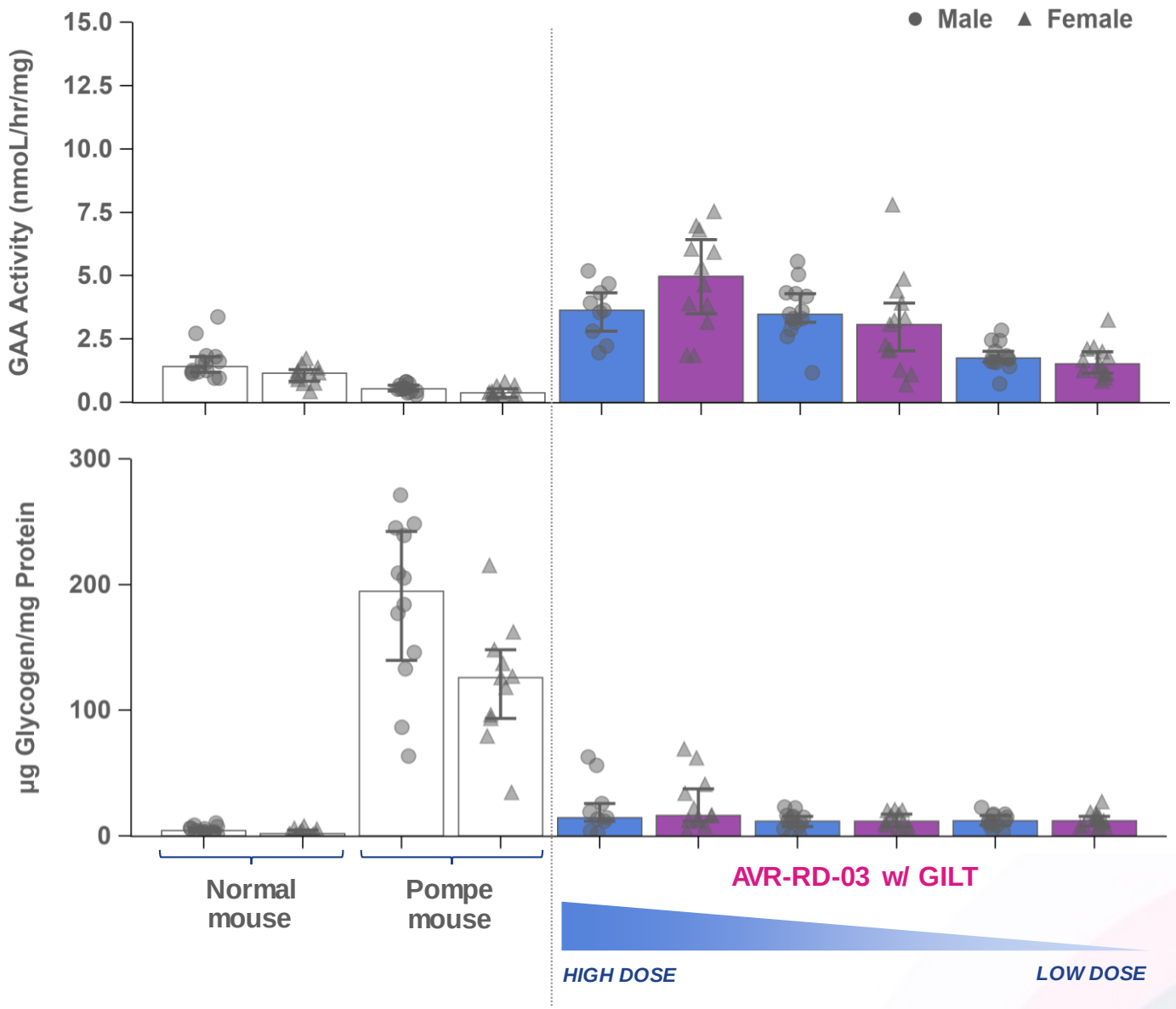


8 months after infusion

GAA: Acid Alpha-Glucosidase; GILT: Glycosylation-Independent Lysosomal Targeting

Skeletal Muscle

>85% glycogen reduction

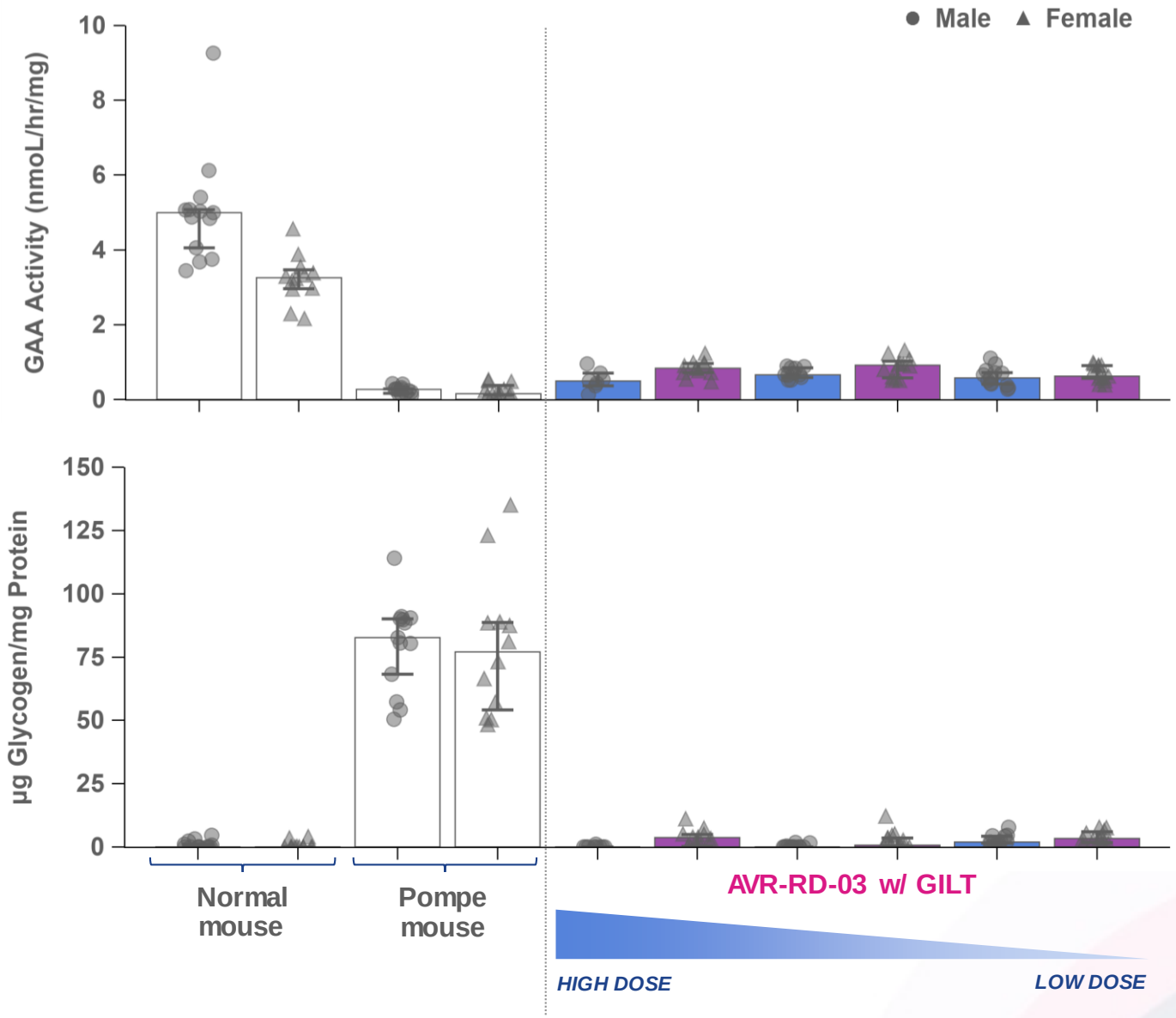


8 months after infusion

GAA: Acid Alpha-Glucosidase; GILT: Glycosylation-Independent Lysosomal Targeting

Brain

>95% glycogen reduction

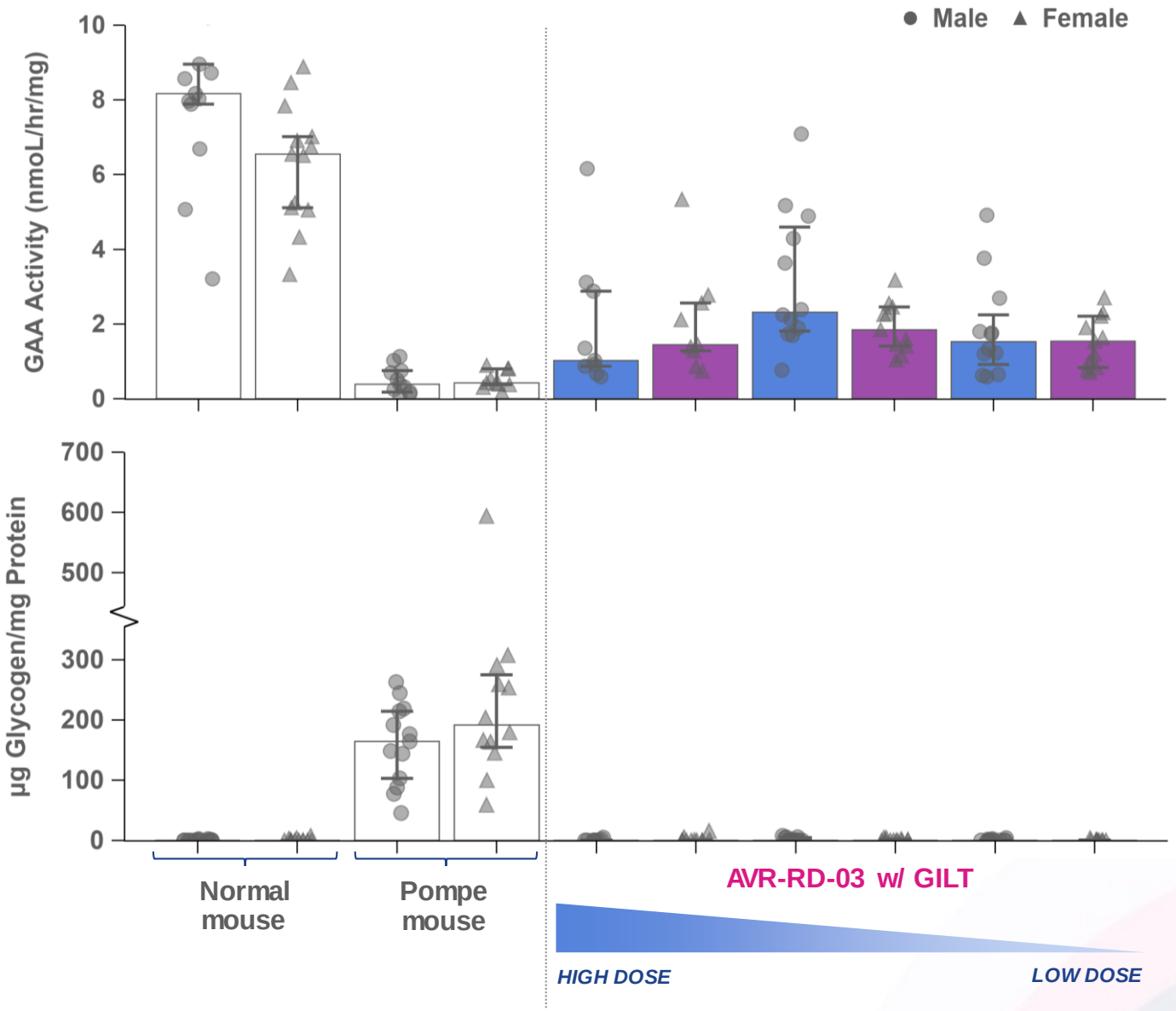


8 months after infusion

GAA: Acid Alpha-Glucosidase; GILT: Glycosylation-Independent Lysosomal Targeting

Spinal Cord

>99% glycogen reduction



8 months after infusion

AVROBIO

GAA: Acid Alpha-Glucosidase; GILT: Glycosylation-Independent Lysosomal Targeting

AVR-RD-03

Anticipated Next Steps

- Secure FDA alignment on classic infantile-onset trial design
- Finalize broad approval development strategy
- Prepare plato® CMC / analytics requirements

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

Closing Remarks

Strong momentum heading into 2021

- Exciting data to date showing **durability** and a favorable **safety** profile across the pipeline
- Advancing toward potential **registration trials** in three indications with additional trials to start next year
- Patient **recruitment accelerating**
- plato® positioned to deliver **"BLAs without delays"**
- Potential clinical advantages of **Bu90-TCI**
- **Leading gene therapy franchise** in lysosomal disorders

CMC: Chemistry, Manufacturing, and Controls; Bu90-TCI: Busulfan 90-Target Concentration Intervention; BLA: Biologics License Application

Key anticipated 2021 milestones

Dose 30 patients cumulatively across trials 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

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


AVROBIO
FOUNDED 2015
Thank you