AVROBIO

THE GREAT POTENTIAL TO CURE

October 2018

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Our Mission

Curing rare disease in a single dose.

Just as enzyme replacement therapies (ERTs) revolutionized the past, gene therapy has the potential to revolutionize the future.

Clinical-Stage Company Developing Disruptive Gene Therapies to Cure Rare Diseases

- Developing first-line therapies for lysosomal storage diseases (LSDs)
- Initial programs in Fabry, Gaucher, Pompe, and cystinosis
- Compelling Fabry preliminary Phase 1 and Phase 2 data
- Targeting standard of care therapies with ~$4B ww 2017 net sales
- Optimized platform to be clinic-ready in 2019
- Establishing robust global manufacturing solutions
- World class management team and investors

Cell, Gene and Rare Disease Industry Leaders

Experienced Management Team

Geoff MacKay
President and CEO, Director

Organogenesis Inc. · NOVARTIS

Katina Dorton, MBA, JD
Chief Financial Officer

immatics · Morgan Stanley

Kim Warren, PhD
Head of Operations

Lonza · CCRM

Nerissa Kreher, MD, MS, MBA
Chief Medical Officer

ALEXION · genzyme

Chris Mason, MD, PhD, FRCS
Chief Science Officer

UCL

Kathryn McNaughton, PhD
SVP Portfolio & Program Management

Shire · Synageva

Deanna Petersen, MBA
Chief Business Officer

Shire · agenus

Board of Directors

Bruce Booth, DPhil
Chairman
ATLAS VENTURE

Ian Clark
Genentech
A Member of the Roche Group

Annalisa Jenkins, MBBS, FRCP
MERCK SERONO · DIMENSION THERAPEUTICS

Phillip Donenberg
DEPOMED · avexis

Chris Paige, PhD
UHN

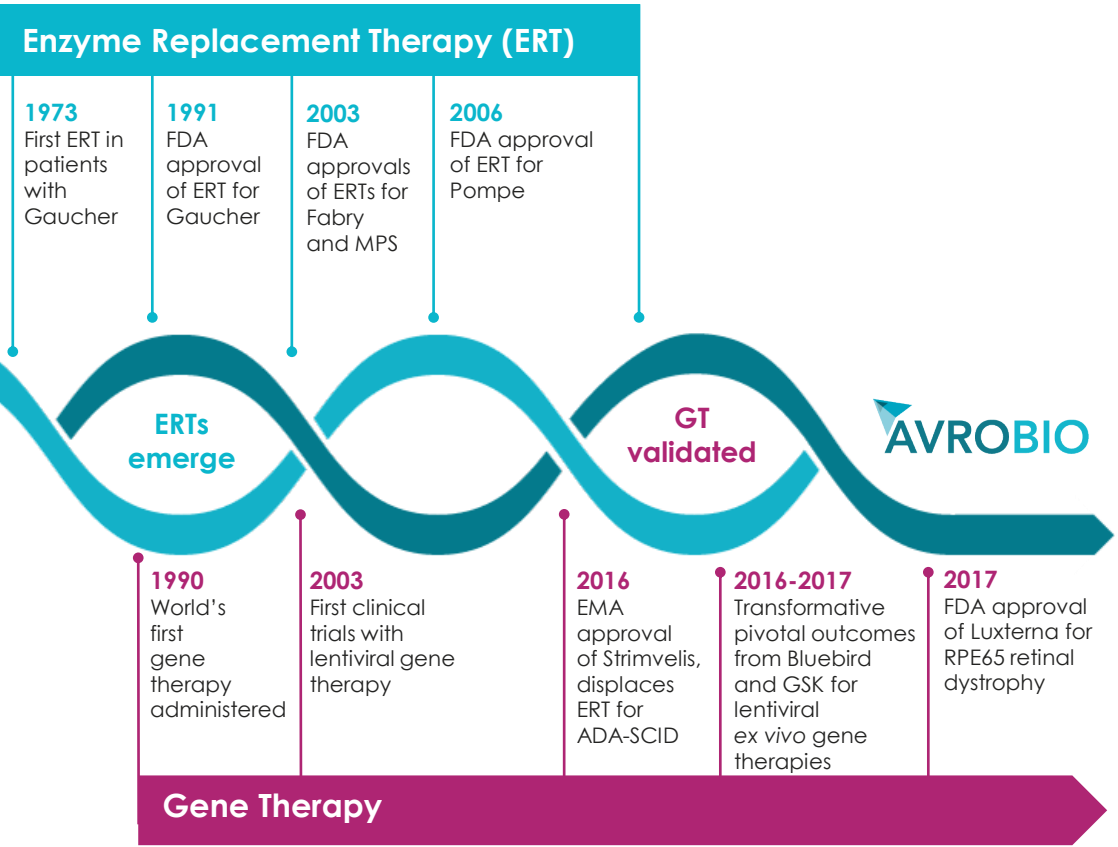
Scott Requadt, JD, MBA
clarus Ventures

Joshua Resnick, MD, MBA
SV HEALTH INVESTORS

AVROBIO

SURVEYOR · BRACE PHARMA CAPITAL · MORNINGSIDE PRIVATE INVESTORS · SV HEALTH INVESTORS · CORMORANT ASSET MANAGEMENT · AISLING CAPITAL · EVENTIDE · ATLAS VENTURE · clarus

Proven Platform, Proven Disease Targets



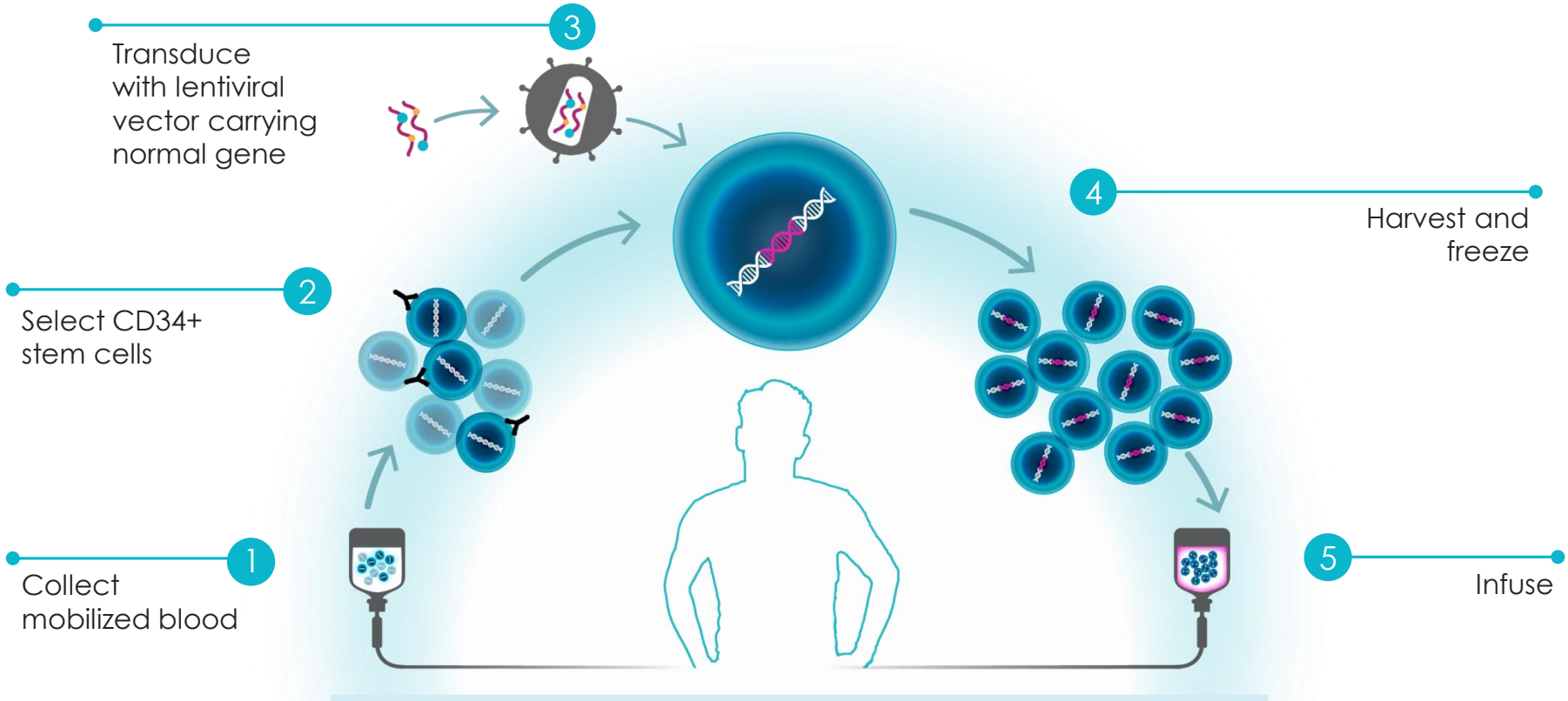
LSDs have well-understood biology

- ✓ ERT validates exogenous enzyme delivery
- ✓ Established regulatory and reimbursement processes

Proven lentiviral gene therapy platform

- ✓ >200 patients treated in rare disease clinical trials
- ✓ 10+ years of promising efficacy and safety

One Optimized Platform Applied Across Our Portfolio

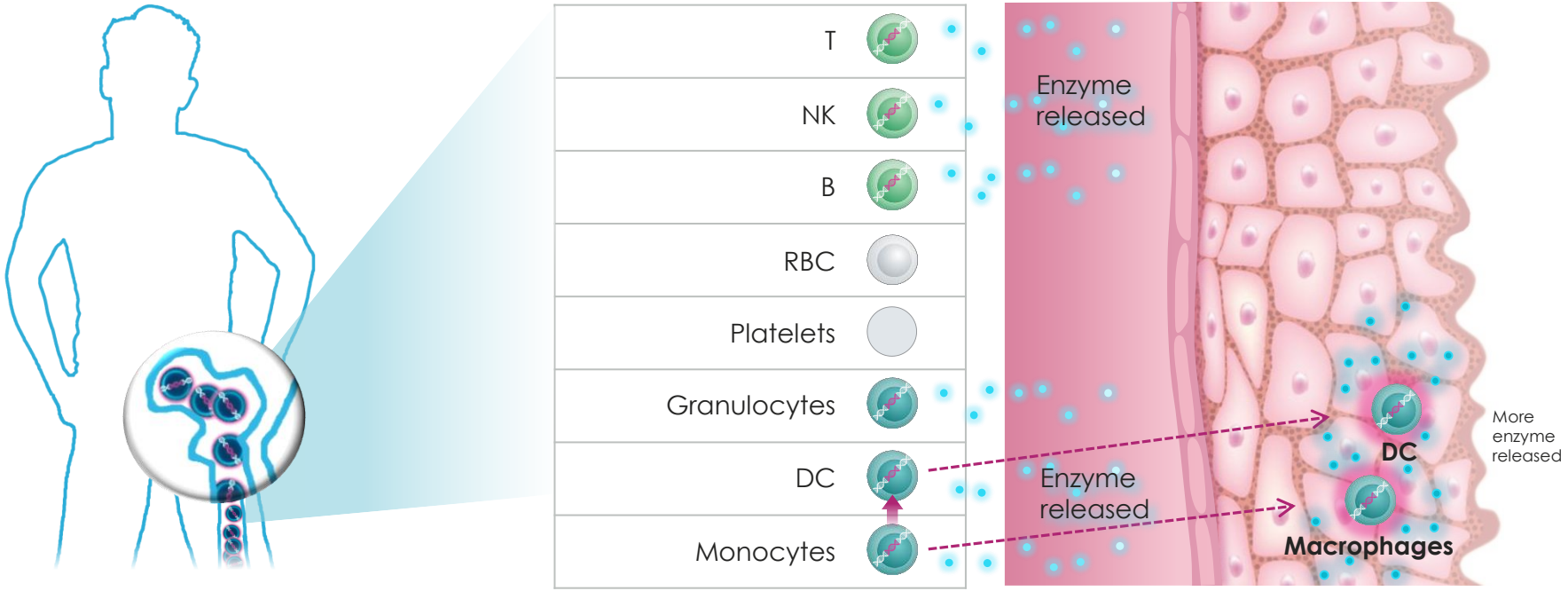


Lentiviral Gene Therapy Enables Durable, Systemic Delivery of Proteins

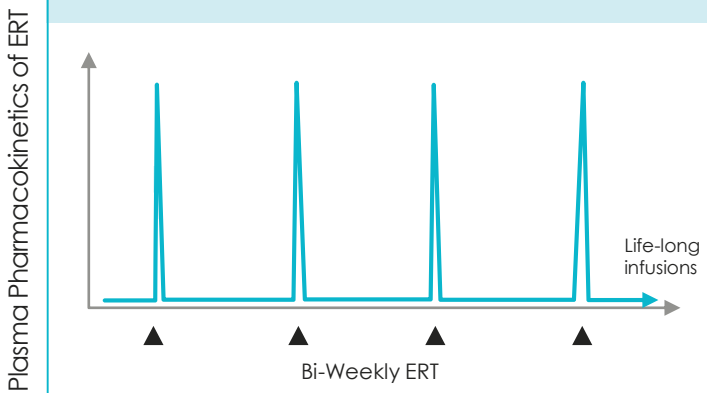
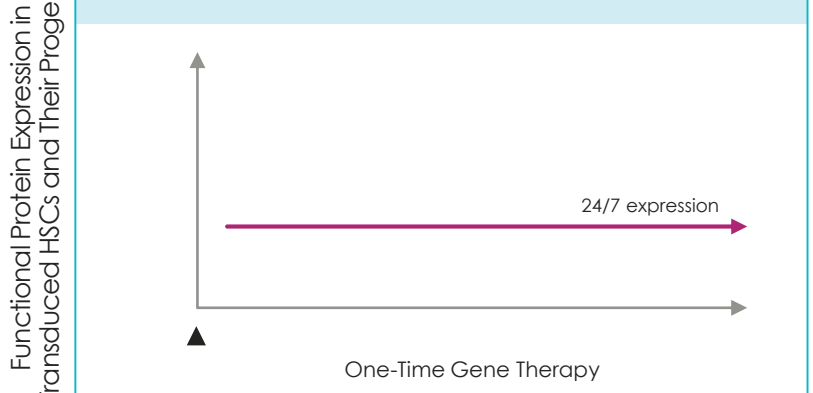
Long-Term Engraftment in Bone Marrow

Manufacturing, Transportation and Delivery in Blood

Final Destination in Tissues and Organs



Life-Long Treatments vs. Single Dose Potential Cure

	Disease Progression ***Continues***	*Disease Progression* ***Can Halt***
	Enzyme Replacement Therapy (ERT) Temporary bolus of enzyme, not curative	**AVROBIO Gene Therapy** 24/7 expression of protein, curative potential
		
Enzyme or protein level	Transient, intermittent elevation	Long-term, continuous elevation
Treatment burden	Bi-weekly IV infusions	Single IV infusion

Steady Stream of Clinical-Stage Products

Program	Proof-of-Concept	IND-Enabling	Phase 1	Phase 2	Pivotal	Expected Next Milestone	Worldwide Rights
Fabry AVR-RD-01						Continued patient data Phase 1 and Phase 2	**AVROBIO**
Gaucher AVR-RD-02						Initiate Phase 1/2 clinical trial	**AVROBIO**
Pompe AVR-RD-03						Advance preclinical program	**AVROBIO**
Cystinosis AVR-RD-04						Academic partner file IND	**AVROBIO**

Fabry is a Serious Rare Genetic Disease

Disease

- Mutations in α-galactosidase A (AGA) gene result in deficient enzyme activity
- Leads to accumulation of globotriaosylceramide (Gb3)

Impact

- Premature mortality (life expectancy decreased by 20 years in classic males)
- Cardiac disease, progressive renal failure, stroke, GI distress, acroparesthesias, anhidrosis, debilitating pain, fatigue

Standard of Care – ERT

- Not curative, relentless progression of disease continues
- Burdensome and expensive

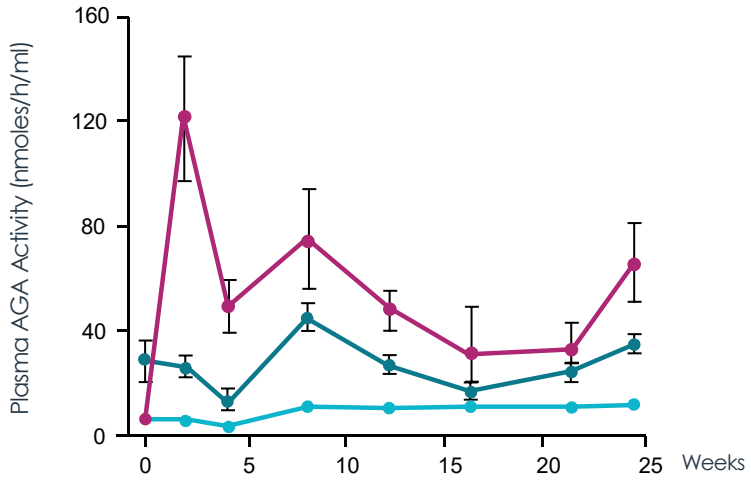
Population Estimates

- 1:40,000 male live births (classic males) and 1:118,000 females

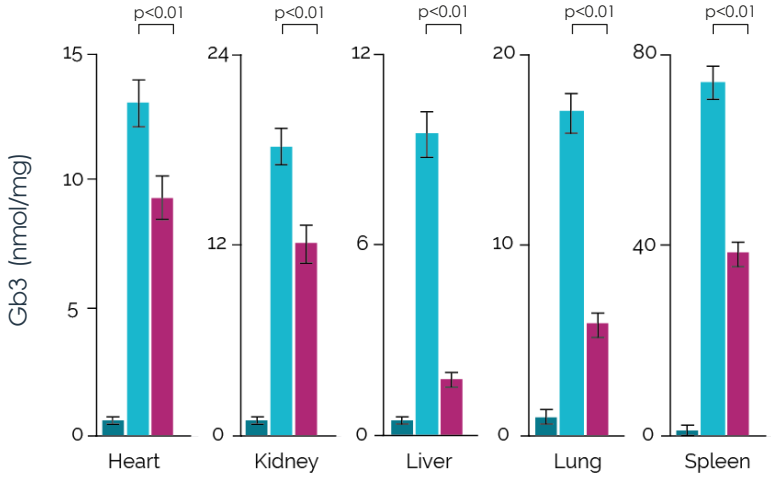
Sources: Meikle PJ et al, JAMA, 1999; Desnick R, J Inherit Metab Dis, 2001

Compelling Pre-Clinical Fabry Data

Increased Enzyme Activity in Fabry Mouse Model After Receiving AVR-RD-01



Significant Reduction in Gb3 Levels in Multiple Tissues in a NOD/SCID/Fabry Mouse Model After Receiving AVR-RD-01



Normal mice Untreated Fabry mice Fabry mice post AVR-RD-01

Sources: Yoshimitsu M et al, Gene Ther, 2007; Pacienza N et al, Mol Ther, 2012

Ongoing Investigator-Sponsored Phase 1 Fabry Study

Fabry Patients

Day -30	Day -1	Day 0	Day 28	Day 30
Stop ERT Mobilize stem cells	Mild conditioning	Infuse AVR-RD-01	Post-treatment assessment	Re-start ERT

Clinical Pilot Study of Autologous Stem Cell Transplantation of CD34+ Cells Engineered to Express AGA in Patients with Fabry Disease

Inclusion Criteria	Objectives	Patients	Assess
• Safety • Preliminary efficacy	• Safety • Preliminary efficacy	• Up to 6 patients • 18-50 year old males • Receiving ERT	• Plasma and leukocyte enzyme activity • Presence of vector in peripheral blood and bone marrow cells • Safety

Fabry Phase 1 Study: Patient Characteristics

Patient #1

- 48 year old male; has been receiving ERT since 2005
- Medical history: Significant for urinary urgency, abdominal pain, proteinuria, angiokeratomas and left ventricular hypertrophy
- **Patient had ERT discontinued in July 2018**

Patient #2

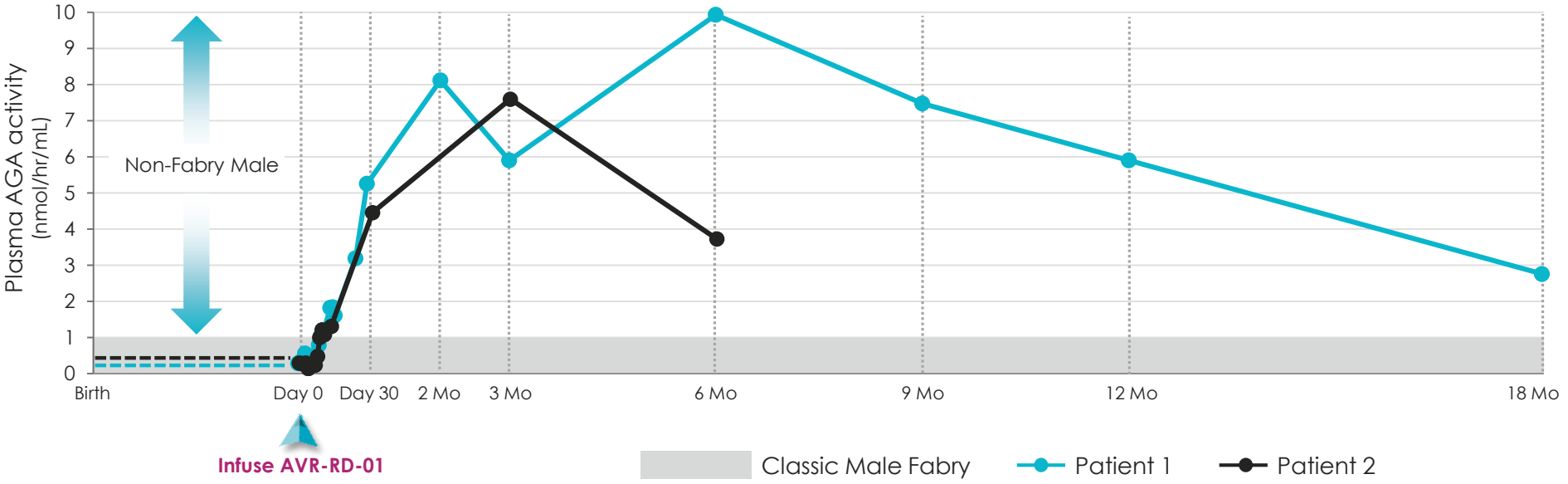
- 39 year old male; has been receiving ERT since 2011
- Medical history: Significant for peripheral sensory neuropathy, cold and heat intolerance, hypohidrosis, angiokeratomas, gastrointestinal issues, increased albumin to creatinine ratio, limb edema, corneal whorls, chronic kidney disease and proteinuria and cysts

Patient #3

- 39 year old male; has been receiving ERT since 2014
- Medical history: Significant for acroparesthesias, tinnitus, sinus bradycardia, type 1 Chiari malformation, left ventricular hypertrophy, dizziness, corneal verticillata, headache, atrial fibrillation, and palpitations

Fabry Phase 1 Study: Significant Enzyme Activity Elevation After Single Dose

Level of AGA Enzyme Activity Rose from Nearly Undetectable Levels to Levels Above the Range for Males with Classic Fabry Disease



Fabry Phase 1 Study: VCN Data

Drug Product VCN	
Patient 1	0.7
Patient 2	1.4
Patient 3	0.8

Peripheral blood average VCN	Patient 1	Patient 2	Patient 3
1 Month	0.4	0.8	0.2
3 Months	0.6	1.1	
6 Months	0.4	0.4	
9 Months	0.3		
12 Months	0.2		
18 Months	0.1		

Patient #1 Bone marrow aspirate data at 14 months continues to support engraftment with a colony forming unit assay result of 13%

FAB-201: First Patient Dosed June 7

Phase 2 Open-Label, Multinational Study of the Efficacy and Safety of *Ex Vivo* Lentiviral-Based Vector Gene Therapy AVR-RD-01 for Treatment-Naïve Subjects with Classic Fabry Disease

Objectives	Patients	Assess
• Efficacy (biomarkers and functional endpoints) • Safety	• 8-12 patients • Adult males (age ≥ 16 years) • Treatment-naïve	• Primary efficacy endpoint: reduction of substrate in kidney biopsy • Substrate reduction (Gb_3 and/or lyso-Gb3) in urine, plasma, skin • Enzyme (AGA) activity • Kidney function • Cardiac size • GI symptoms • Pain and quality of life • Vector Copy Number (VCN) and chimerism • Safety

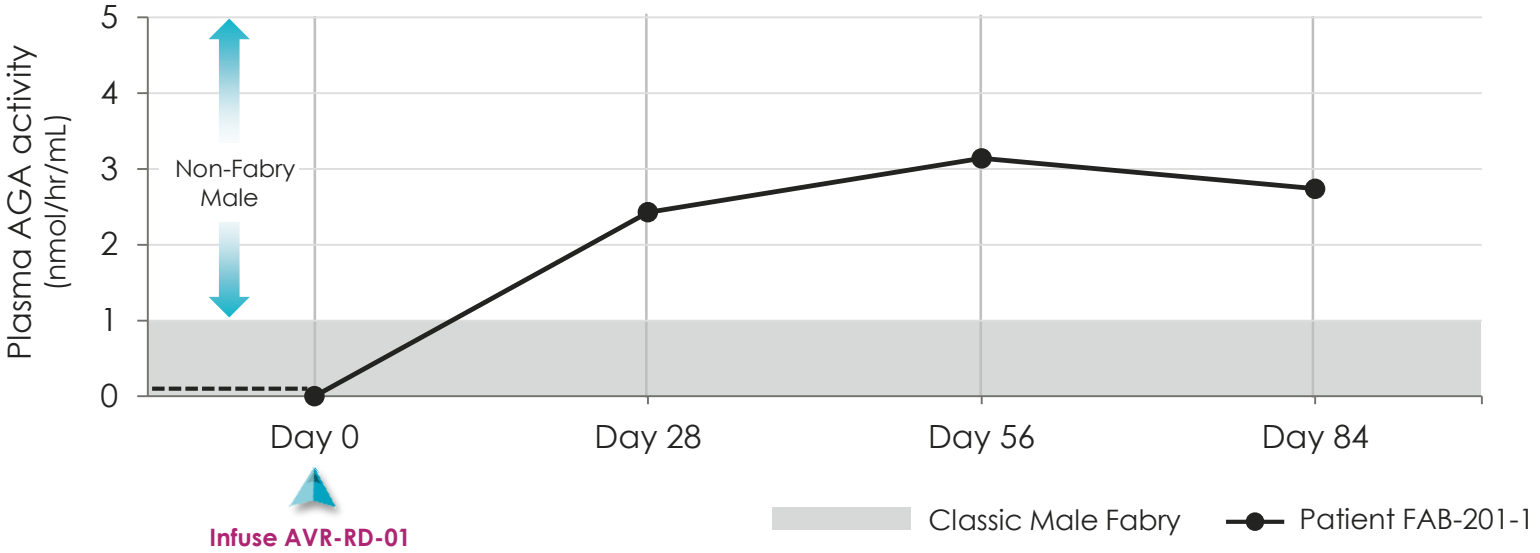
FAB-201: Patient Characteristics

Patient FAB-201-1

- 21 year old male
- Has not received any prior treatment with ERT
- Medical history: Significant for chronic acral pain, knee pain, intermittent diarrhea, traumatic eye injury, pansinusitis, umbilical keratoma, chronic obstructive pulmonary disease, decreased cold sensation, and epilepsy

FAB-201: Significant Enzyme Activity Elevation After Single Dose

Level of AGA Enzyme Activity Rose from Nearly Undetectable Levels to Levels Above the Range for Males with Classic Fabry Disease



FAB-201: FAB-201-1 VCN Data

Drug Product VCN	
Patient FAB-201-1	0.7

Peripheral blood average VCN	Patient FAB-201-1
1 Month	0.2
2 Months	0.2
3 Months	0.5

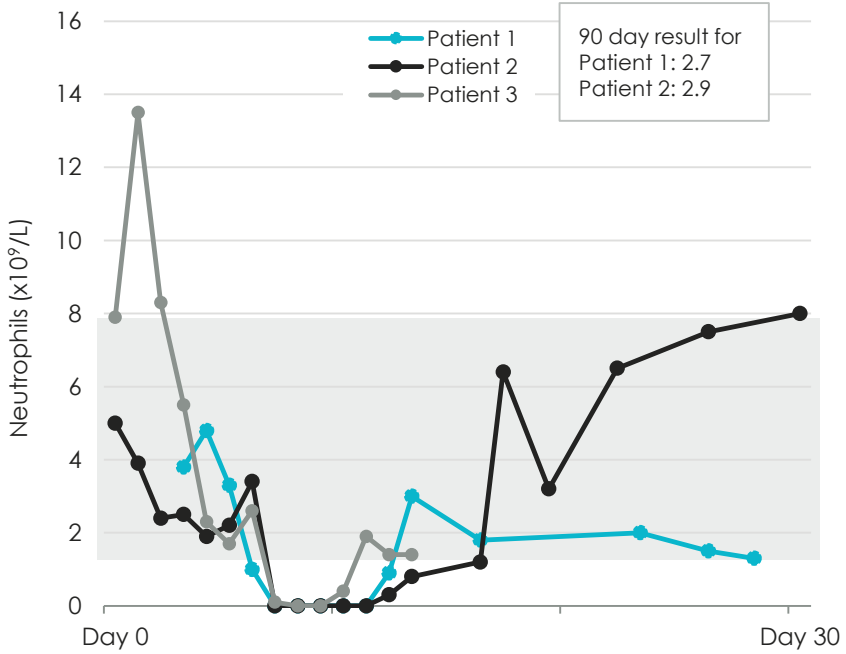
Safety and Tolerability of AVR-RD-01

- First three enrolled subjects in Phase 1 investigator-sponsored study*
  - AVR-RD-01 was generally well tolerated
  - No serious adverse events related to AVR-RD-01
- FAB-201-1 (first patient in FAB-201)**
  - AVR-RD-01 was generally well tolerated
  - Two serious adverse events reported, one pre-treatment and one post-treatment (dehydration, nausea and vomiting), neither was considered related to AVR-RD-01

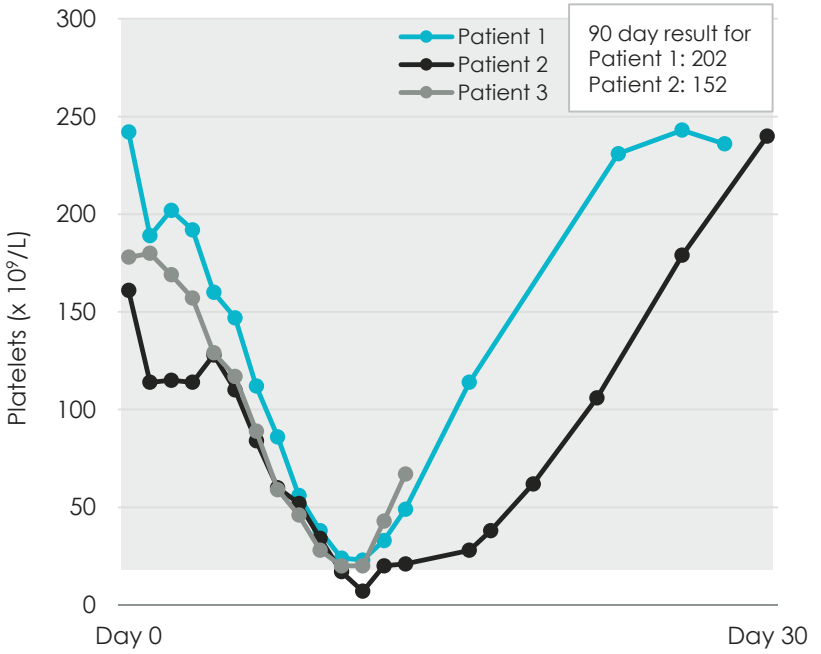
*data cutoff date: August 24, 2018
**data cutoff date: August 28, 2018

Conditioning to Develop First-Line Therapies: Fabry Phase 1

Neutrophil Count Recovery



Platelet Count Recovery

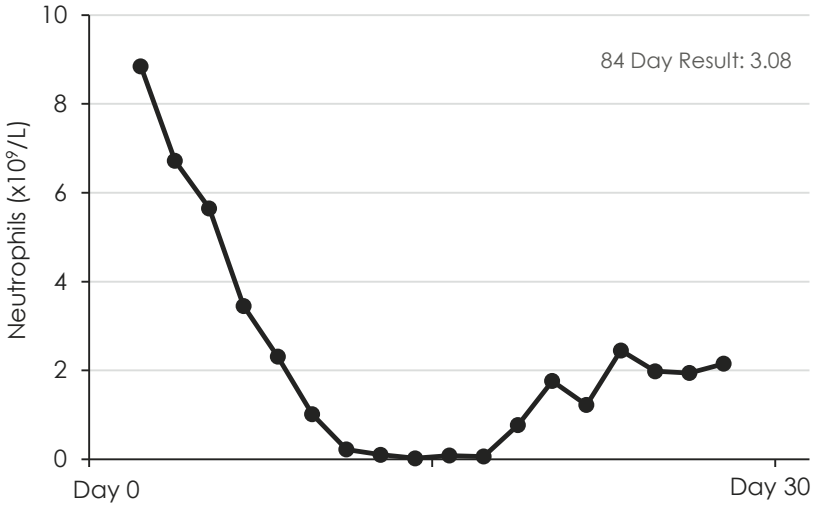


Melphalan 100mg/m^2 IV on Day -1

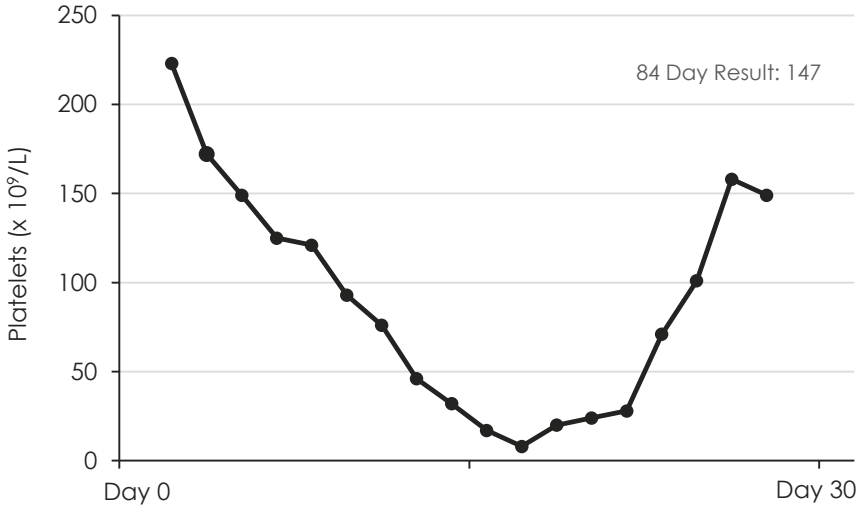
Note: Neutrophil count lower range defined as when patients no longer require GCSF support per OZM-074 protocol
Note: Platelet count lower range defined as when platelet transfusion support would be considered clinically given increased risk of spontaneous bleeding

FAB-201-1: Conditioning to Develop First-Line Therapies

Neutrophil Count Recovery



Platelet Count Recovery



Patient FAB-201-1

Melphalan 100mg/m^2 IV on Day -1

Gaucher Type 1 is a Serious Rare Genetic Disease

Disease

- Mutations in glucocerebrosidase (GCase) gene result in deficient enzyme activity
- Leads to infiltration of glucocerebroside (GluCer) in macrophages (Gaucher cells) and accumulation in multiple tissues/organs

Impact

- Splenomegaly, hepatomegaly, bone pain, bone crises, fractures, osteoporosis, anemia, thrombocytopenia, fatigue

Standard of Care – ERT

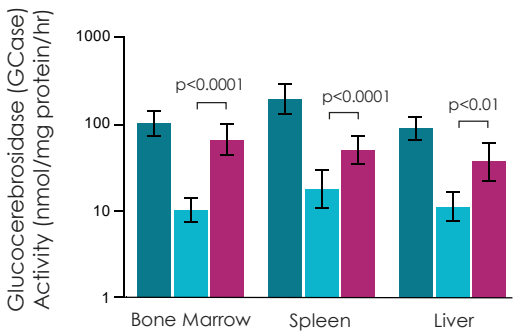
- Not curative, relentless progression of disease continues
- Burdensome and expensive

Population Estimates

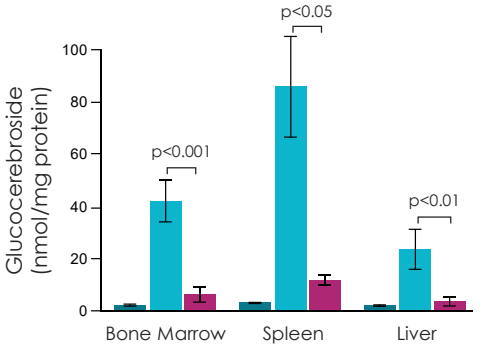
- 1:44,000 live births (Types 1 (90% in Western countries),2,3)

Sources: Burton B et al, J Pediatr, 2017; Hopkins P et al, J Pediatr, 2015; Nalysnyk L et al, Hematology, 2016; Dahl M et al, Mol Ther, 2015

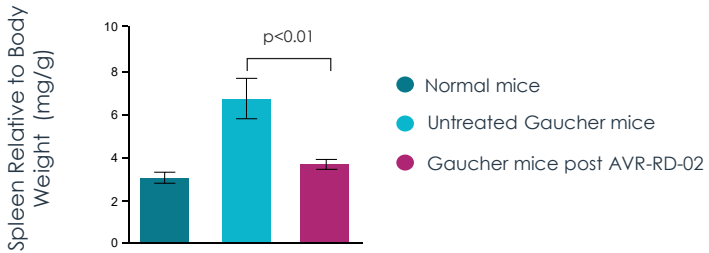
AVR-RD-02 Leads to Significant Elevation of GCase Activity Across Multiple Clinically Relevant Tissues



AVR-RD-02 Leads to Significant Reduction in Glucocerebroside Levels Across Multiple Clinically Relevant Tissues



Ex Vivo Lentiviral-Based Gene Therapy Leads to Significant Reduction in Spleen Volume in a Mouse Model of Gaucher Disease



GAU-201: No Objection to CTA Received from Health Canada

Open-Label, Multinational Study of the Efficacy and Safety of *Ex Vivo* Lentiviral-Based Vector-mediated Gene Therapy AVR-RD-02 for Subjects with Type 1 Gaucher Disease

Objectives	Patients	Assess
• Efficacy (biomarkers and functional endpoints) • Safety	• 8-16 patients • Males and females (≥ 16 years, ≤ 35 years of age) • Both switch-stable and treatment-naïve	• Hemoglobin concentration • Platelet count • Liver volume • Spleen volume • Vector Copy Number (VCN) and chimerism • GCase activity • Bone mineral density • Biomarkers (e.g. chitotriosidase, CCL18, BMB) • Quality of life • Safety

Pompe is a Serious Rare Genetic Disease

Disease

- Mutations in the acid alpha-glucosidase (GAA) gene resulting in deficient enzyme activity
- Leads to accumulation of glycogen in tissues and organs, especially in muscles

Impact

- Premature mortality
- Proximal myopathy (eventually wheelchair bound), respiratory insufficiency (often requiring ventilation), chronic respiratory infections, sleep apnea, fatigue

Standard of Care – ERT

- Not curative, relentless progression of disease continues
- Burdensome and expensive

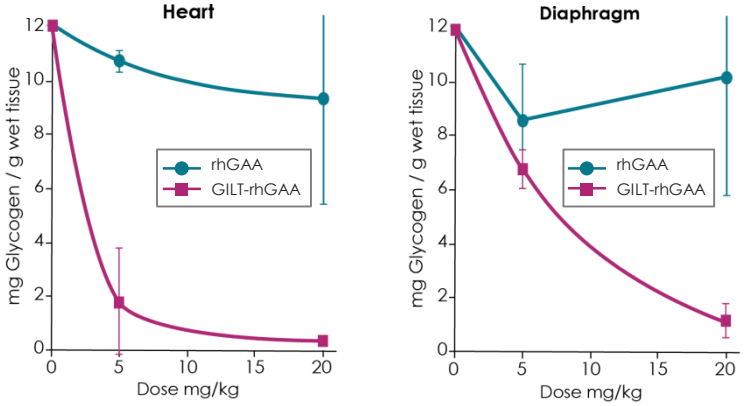
Population Estimates

- 1:58,000 live births, detection projected to increase to 1:22,000 due to newborn screening

The Challenge

- Pompe requires 20x more ERT than Fabry or Gaucher
- Distribution of enzyme into muscle is limited

GILT-Tag Version of Recombinant Human (rh)GAA Impact on Levels of Stored Glycogen Compared to Non GILT-Tagged Recombinant Human (rh)GAA



Sources:
Burton B et al, J Pediatr, 2017; Ausems M et al, Eur J Hum Genet, 1999; Gungor D et al, Orphanet J Rare Dis, 2011; Maga JA et al, J of Bio Chem 2013

Cystinosis is a Serious Rare Genetic Disease

Disease

- Mutations in the CTNS gene resulting in deficiency in a lysosomal exporter protein, cystinosin
- Leads to accumulation of cystine in tissues and organs

Impact

- Premature mortality
- Renal Fanconi syndrome, kidney failure requiring transplant, corneal cysteine crystals, visual impairment, myopathy, hypothyroidism, rickets

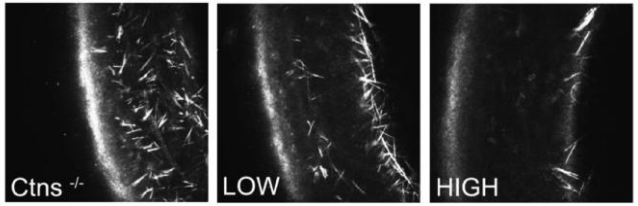
Standard of Care – Cysteamine

- Not curative, relentless progression of disease continues
- Burdensome and expensive

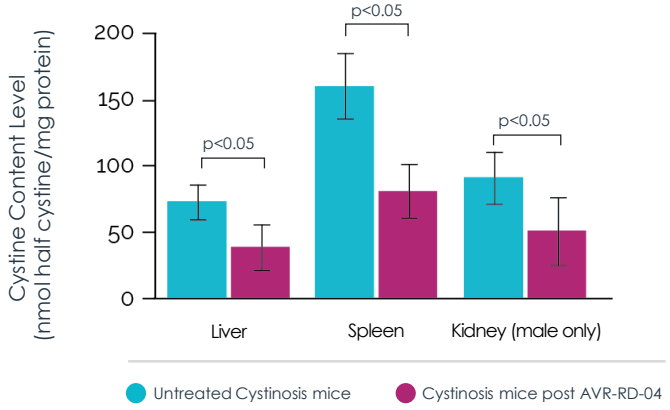
Population Estimates

- 1:170,000 live births

Transplantation of Allogeneic Hematopoietic Stems Cells Results in Reduction of Cystine Crystals in Corneas of Cystinosis Mice



AVR-RD-04 Leads to Lower Cystine Levels in Multiple Tissues in a Mouse Model of Cystinosis



Sources: Gahl et al, NEJM, 2002; Bois et al, J Med Genet, 1976
Harrison F et al, Mol Ther, 2013; Rocca C et al, J Invest Ophthalmol Vis Sci, 2015

Regulatory Strategy Drives Speed-to-Market

Global Solutions to Accelerate Every Step of Development

1. Speed to Start

- Initiate phase 1/2 studies in countries with most efficient CTA approvals
  - Canada
  - Australia
- Leverage Fabry clinical trial approvals for fast Gaucher start

2. Speed to Recruit

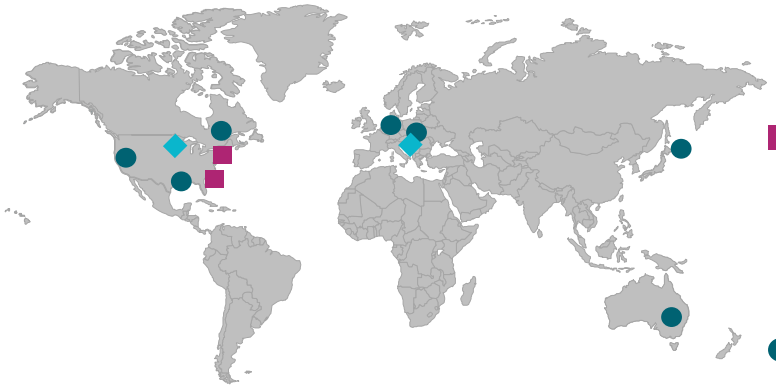
- Planned patient enrollment via clinical trials across 4 continents
  - Canada
  - Australia
  - USA (2019)
  - Japan (2019)
  - EU (2019)
  - Israel (2019)

3. Speed to Market

- Navigate accelerated approval pathways
  - FDA Draft Guidelines for Cell & Gene Therapy
  - FDA Regenerative Medicine Advanced Therapies (RMAT)
  - EMA Priority Medicines (PRIME)
  - PMDA Conditional Time-Based Approval for Cell & Gene Therapy

Global Manufacturing Solutions in Place

Infrastructure Ready to Run Global Clinical Programs



Plasmid CMOs

- Completed GMP-source plasmid production for 3 common plasmids and 3 transgene plasmids (Fabry, Gaucher and cystinosis)
- Discussions initiated for research plasmids (Pompe)

Vector CMOs

- Completed GMP production for Fabry, Gaucher and cystinosis
- 2nd source vendor in place
- Discussions initiated for vector development

Drug Product CMOs

- GMP-ready
- GMP-ready
- Process development of Prodigy and optimized vector GMP-readiness in progress for Fabry
- Process development of Prodigy and optimized vector GMP-readiness in progress for Gaucher
- Additional global sites under evaluation

Industry-Leading Technology Platform

Potent, Scalable, Cost-Effective

		2015-2017	2018	2019
Cells	Production time	3 days	3 days	3 days
	Closed system	No	PD*	Yes
	Automated platform	No	PD	Yes
	Cryopreserved	Yes	Yes	3 of 4
Vector	Plasmid system	3 plasmid	4 plasmid	4 plasmid
	Scalable serum-free suspension process	No	Yes 50 liter	Yes 50 liter
	Transduction efficiency	25%-40%	30%-60%	60%+
	Drug Product VCN	0.7-1.4	1-2	1-3
	Stable producer cell line	No	R&D	R&D
Enhanced Uptake	GILT tag	No	R&D	PD

* PD = Process Development

Key 2019 Platform Optimization Levers

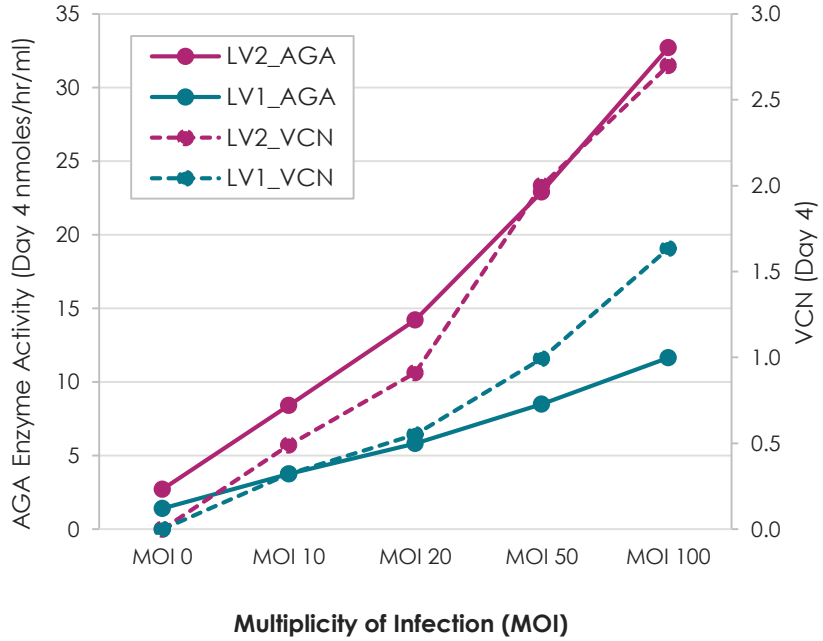
Process changes	VCN	Transduction efficiency	Decreased patient to patient variability	Increase marrow space/ engraftment	Durability of AVR-RD-01
Vector LV2	+	+			+
Automation CP2			+		
Conditioning			+ (TDM*)	+	+

Long term engraftment and durability

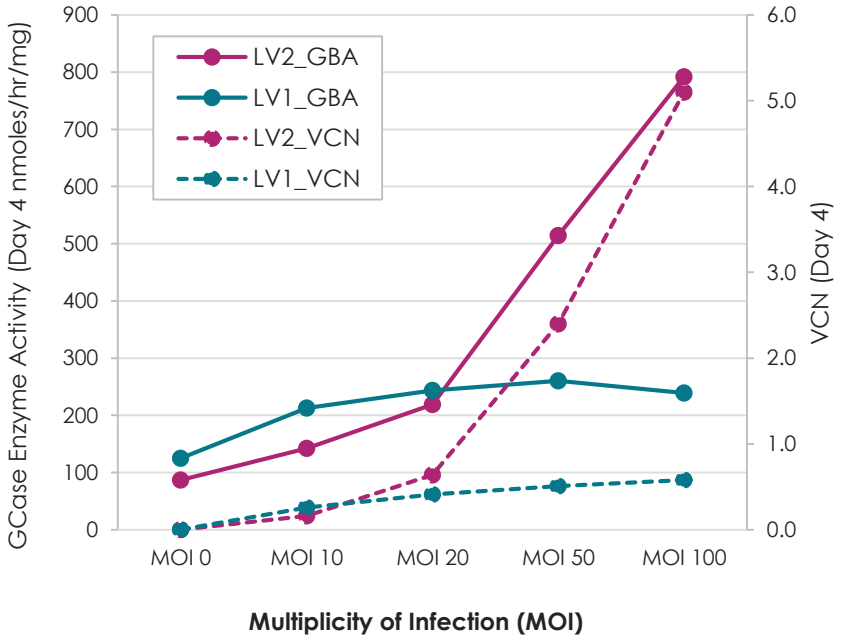
*TDM=therapeutic drug monitoring

Ongoing Vector Optimization Enhances Efficiency

LV2 v. LV1 Fabry Efficiency*



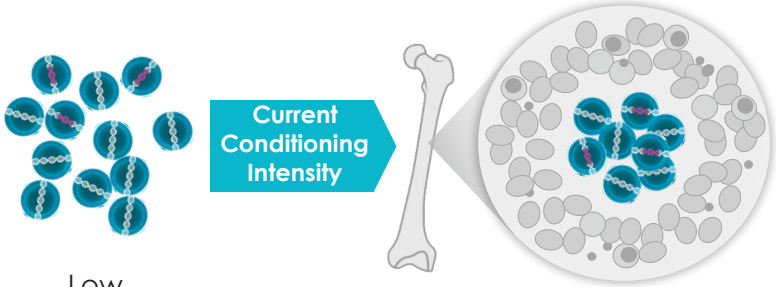
LV2 v. LV1 Gaucher Efficiency*



* CMC data

Platform Optimization to Improve Engraftment of AVR-RD-01

Engraftment of Transduced CD34+ Cells



Low Transduction Efficiency and Low VCN

Engraftment

Enhanced Engraftment of Transduced CD34+ Cells

Increased Transduction Efficiency and Increased VCN

LV1 → LV2

Enhanced Engraftment and Durability

Addressing Multi-Billion Dollar Markets

Current Standard of Care Costs

Disease	Est. Cost Per Year	Approx. 2017 Net Sales
Fabry	$320K	$1.4B
Gaucher	$325-400K	$1.4B
Pompe	$500K	$1B
Cystinosis	$625-750K	n/a

Single-dose

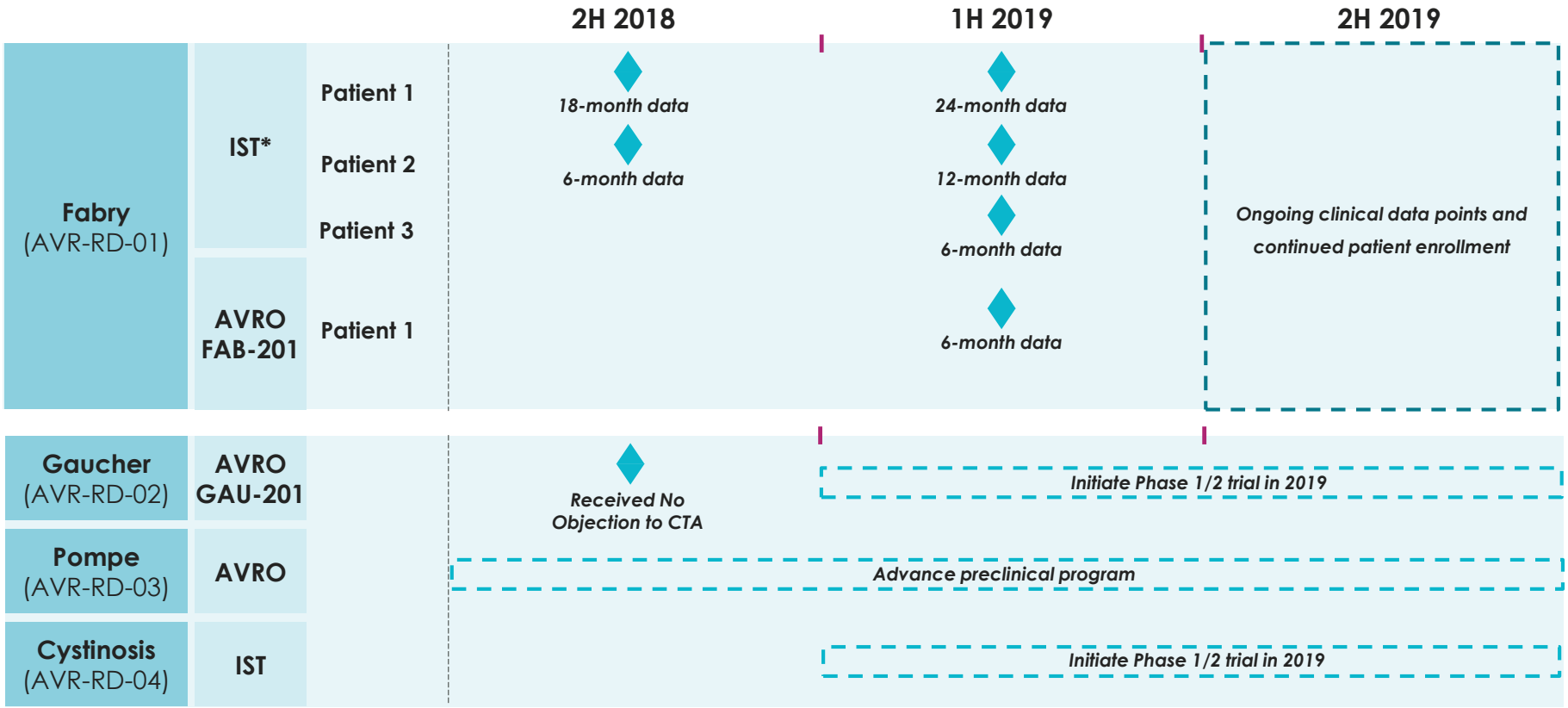
AVROBIO Gene Therapy

Sources: Rombach S et al, Orphanet J Rare Dis, 2013; van Dussen L et al, Orphanet J Rare Dis, 2014; WAC pricing from Redbook; 2017 Net Sales from company annual reports

Well Capitalized via Strong Investor Base

Capital Raised	
IPO (June 2018)	$114.7M
Series B	$60.5M (co-led) CORMORANT ASSET MANAGEMENT SURVEYOR
Series A	$25M ATLAS VENTURE clarus SV HEALTH INVESTORS
Seed	$1.5M ATLAS VENTURE
Cash Available (as of 6/30/18)	Approx. $155M
Credit Facility - Silicon Valley Bank	$10M facility, not drawn down to-date

Steady Stream of Important Data and Milestones



* IST = Investigator-Sponsored Trial

THE GREAT POTENTIAL TO CURE

- Potential to cure rare diseases in a single dose
- FAB-201, Phase 2 clinical trial initiated
- Broad pipeline of first-in-class clinical-stage assets
- Targeting diseases with ~$4B ww 2017 net sales