What if ONE GENE can change your entire world?

AVROBIO

Arianna living with Gaucher disease type 3

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Leading hematopoietic stem cell (HSC) gene therapy company

Lysosomal disorder pipeline targeting multi-billion dollar market

- Strong data generated to date across two clinical-stage programs
- Late-stage trials in Gaucher disease and cystinosis planned for 2023
- Unique competitive position with first mover advantage in lead programs
- plato® platform delivers unrivaled CMC & analytics capabilities
- Multiple clinical and regulatory milestones anticipated over next 12 months

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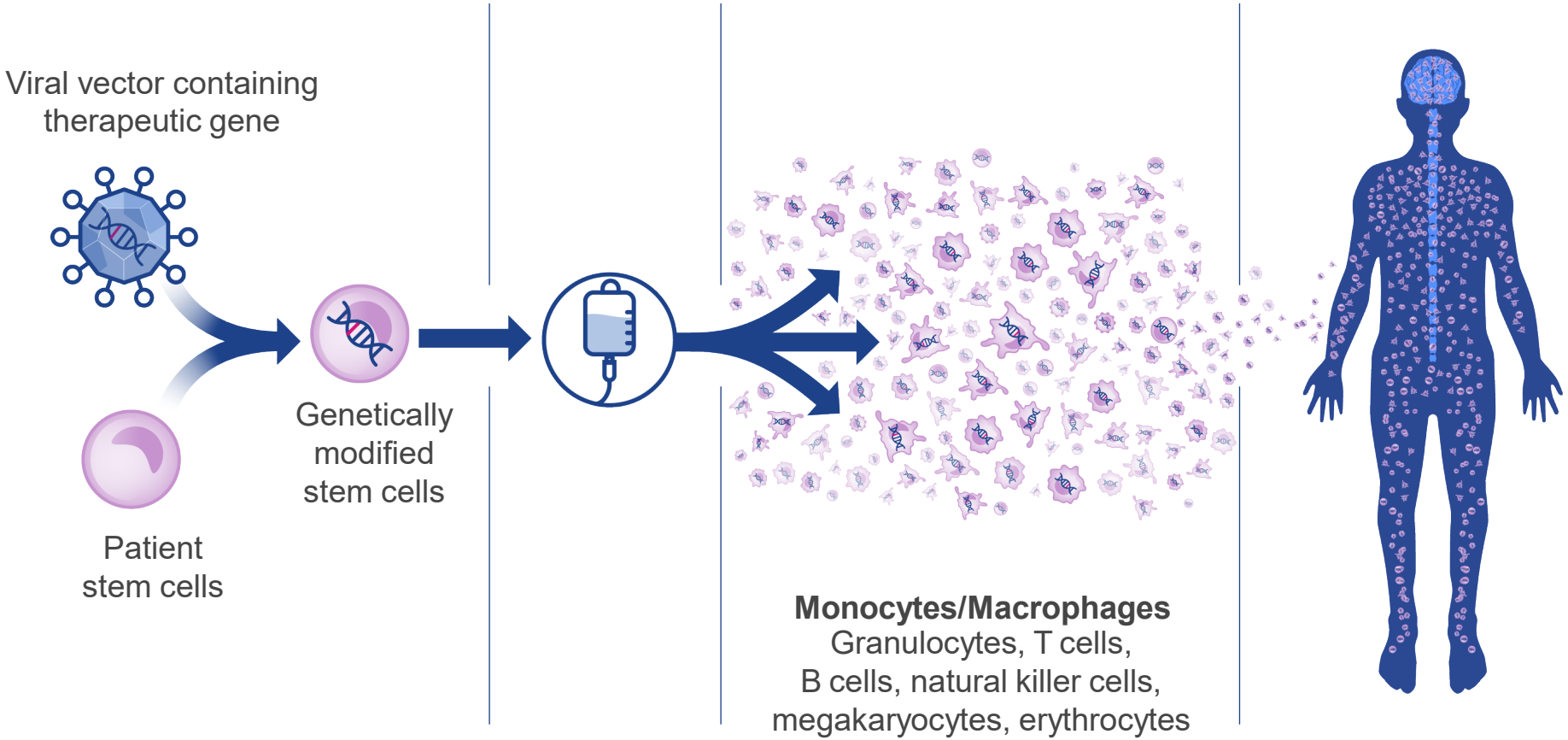
CMC=Chemistry, manufacturing and controls

HSC GT approach delivers durable, systemic distribution

Transduction | **Back into body** | **Proliferation and differentiation** | **Billions of genetically modified cells**



Key advantages

- **Physiological cellular enzyme production**
- **Continuous cellular enzyme expression**
- **Access CNS and periphery**
- **Predicted durability of effect**

Capotondo A. et al. 2012; Gordon, S., Plüddemann, A. 2017; HSC=Hematopoietic stem cell; CNS=Central nervous system; GT=Gene therapy

Established HSC gene therapy approach

Growing body of third-party evidence demonstrating safety, efficacy and durability

3

HSC gene therapies approved[1]

12

HSC gene therapies in clinical development[2]

$2.8 - $3.2

Million price reflects value of these life-changing therapies[3]

380+

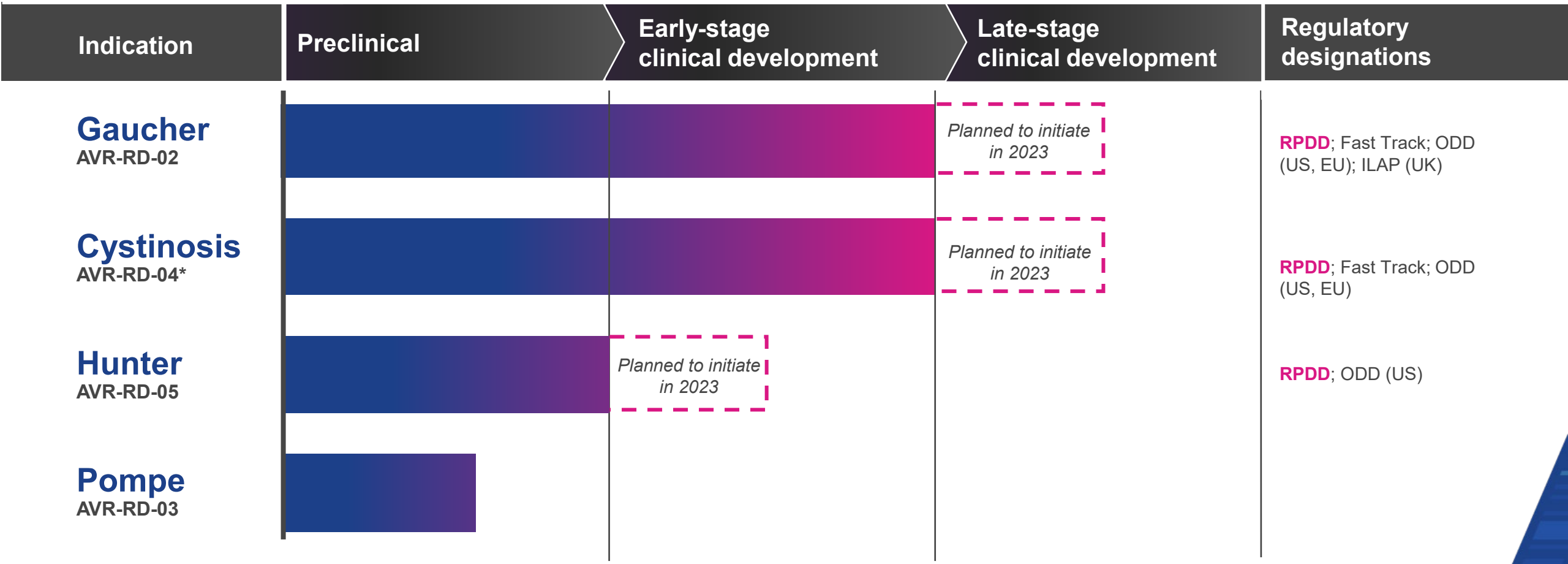
patients treated[4]

700+

patient-years of treatment[4]

1) In U.S., LVGTs from bluebird bio for CALD and beta-thal; In EU, Orchard's Libmeldy. 2) ClinicalTrials.gov, 2022; 3) bluebird bio at $2.8M for Zynteglo (Aug. 2022) and Orchard's Libmeldy at $3.2M (£2.8M, Feb 2022); 4) Tucci *et al*., 2022; HSC=Hematopoietic stem cell

AVROBIO entering late-stage development



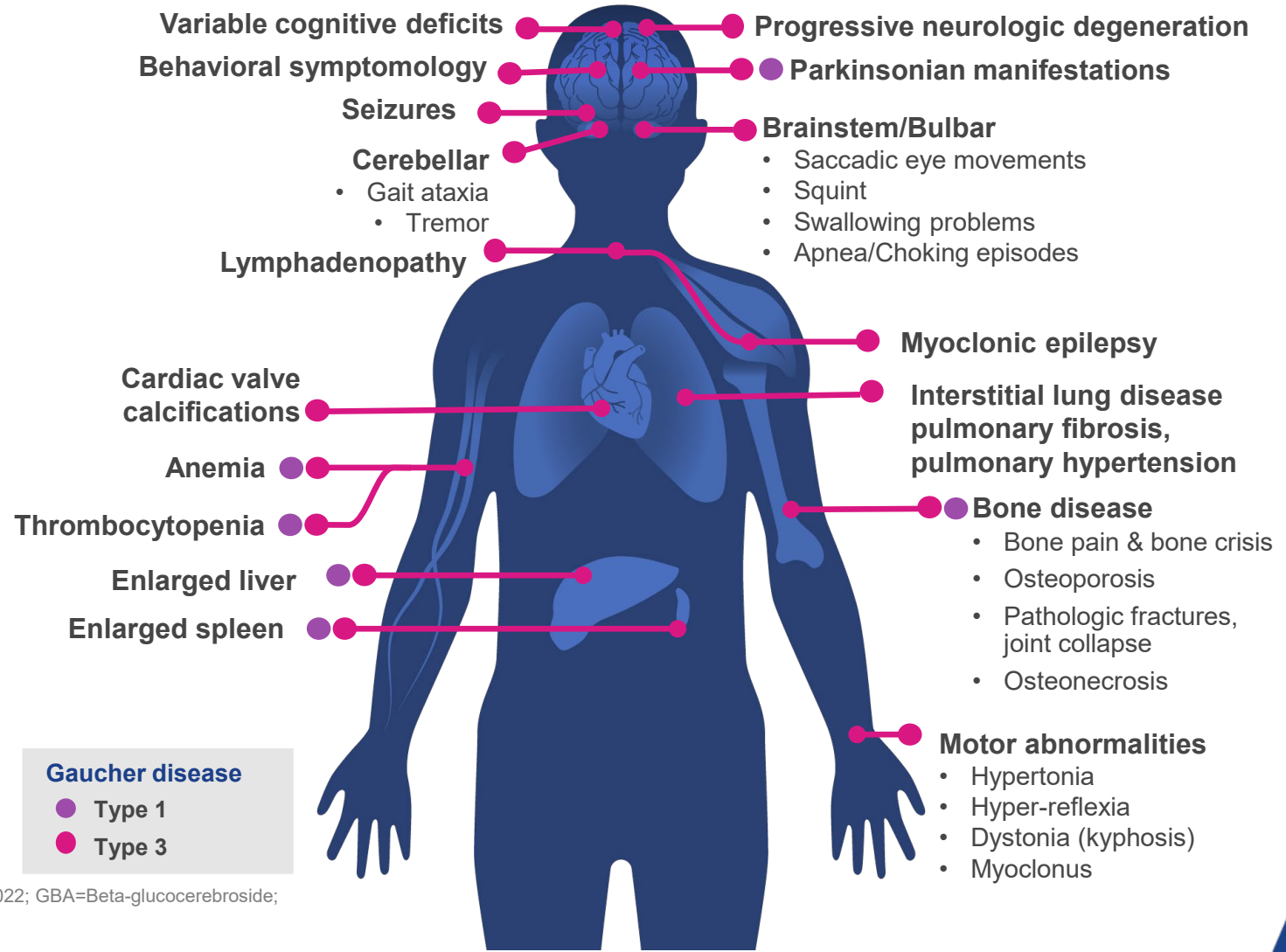
Planned regulatory milestones subject to regulatory agency clearance; *Collaborator-sponsored Phase 1/2 clinical trial of AVR-RD-04 is funded in part by grants to UCSD from the California Institute for Regenerative Medicine (CIRM), Cystinosis Research Foundation (CRF), and National Institutes of Health (NIH); ILAP=Innovative Licensing and Access Pathway; ODD=Orphan drug designation; RPDD=Rare pediatric drug designation

Gaucher is a progressive, debilitating disease

Affects 1:50,000–100,000 people

- More than 300 disease-related mutations identified in the *GBA1* gene
- Autosomal recessive trait affecting lyso somal enzyme β-Glucocerebrosidase (GCase)
- Biallelic mutations impair GCase activity and result in substrate engorged macrophages (“Gaucher cells”)
- Gaucher cells accumulate and trigger proinflammatory cascade in affected organs and tissues

Other disease impacts: ●●
- High burden of illness
- Chronic fatigue and pain
- Failure to thrive, growth retardation
- Decreased life expectancy
- High treatment burden
- Significant unmet need on SOC



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Sidransky, 2004; MedlinePlus: Gaucher disease, 2022; GBA=Beta-glucocerebroside; Gcase=β-Glucocerebrosidase

GD1 patients endure debilitating symptoms even on ERT

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%

Incomplete therapeutic response on ERT

- **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]

* 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; 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. [1] Weinreb *et al.*, 2008; [2] Weinreb *et al.*, 2013; [3] Giraldo *et al.*, 2005; GD1=Gaucher disease type 1; ERT=Enzyme replacement therapy; EOW=Every other week

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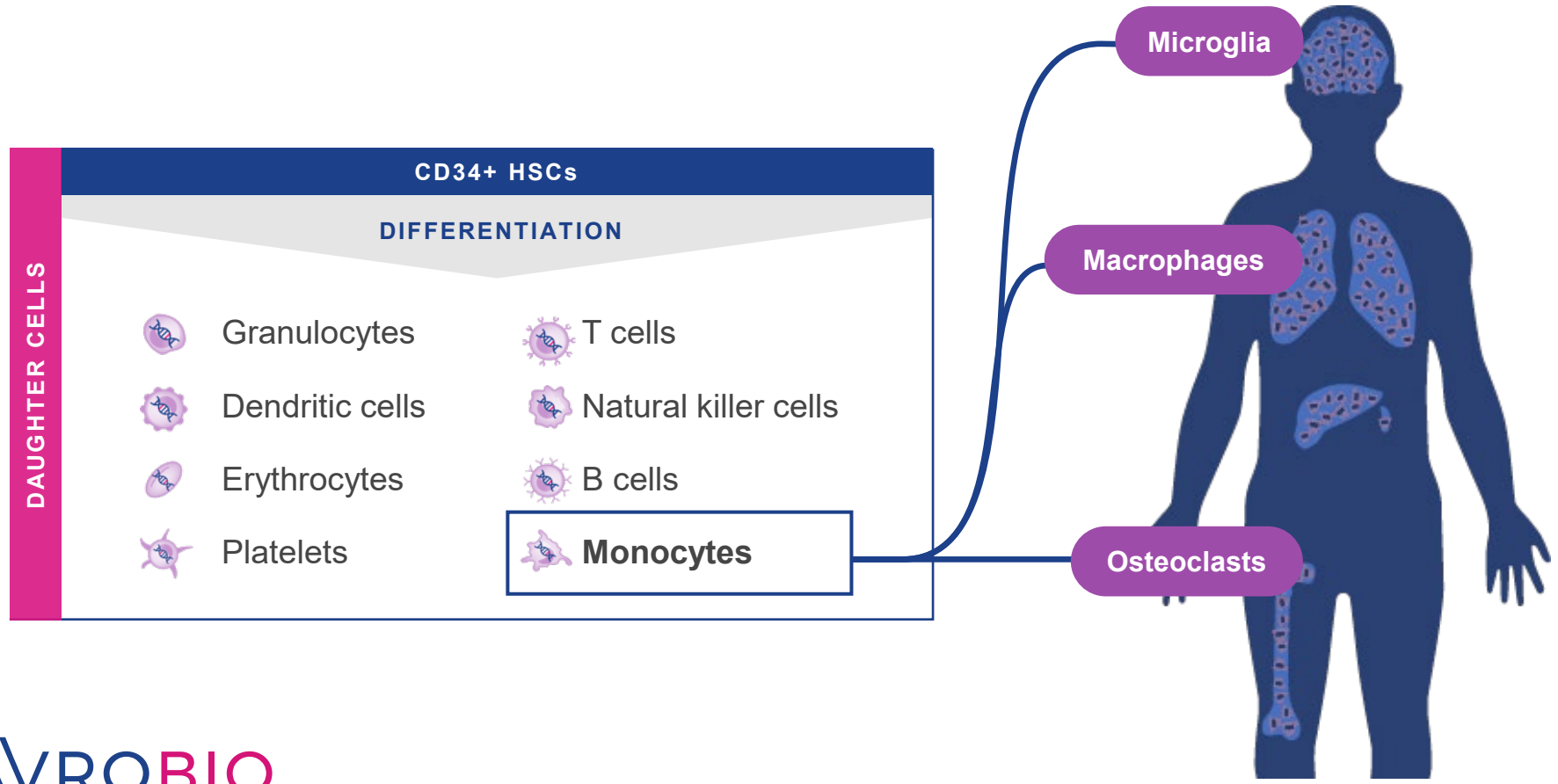
HSC GT approach well-suited for Gaucher disease

Leverages HSC myeloid lineage

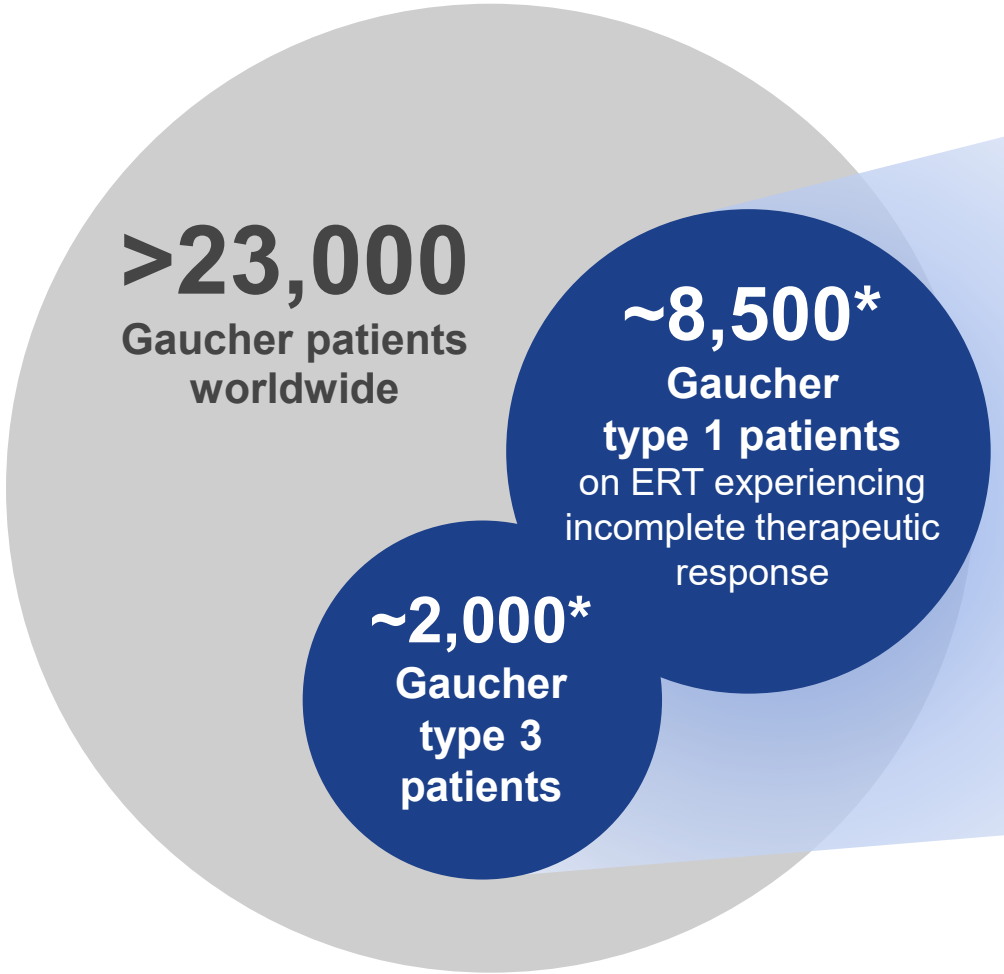


Key potential advantages of HSC gene therapy

- Physiological cellular enzyme production
- Continuous cellular enzyme expression
- Access to CNS and periphery
- Predicted durability of effect

Capotondo *et al.*, 2012; Gordon and Plüddemann, 2017; HSC=Hematopoietic stem cell; GT=Gene therapy; CNS=Central nervous system

Multi-billion revenue potential for Gaucher disease



ILLUSTRATIVE ANALYSIS AND ESTIMATES

Aggregate revenue potential

Potential penetration rate	Number of patients served	Potential price ~$1.3M 3-year U.S. SOC cost	Potential price ~$2.3M 5-year U.S. SOC cost	Potential price ~$3.2M 7-year U.S. SOC cost*
10%	~1,000	**$1.4B**	**$2.3B**	**$3.2B**
25%	~2,600	**$3.6B**	**$6.0B**	**$8.3B**
33%	~3,500	**$4.8B**	**$8.0B**	**$11.2B**

Estimates of patient populations, penetration rates and market size, U.S. SOC costs and aggregate revenue potential are assumptions based on available information and are subject to change. Actual results may differ.

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Market Research 2020, 23k patients excludes patients in China and India; *10.5k includes US, EU, Japan only; Incomplete therapeutic response subgroup based on Weinreb analysis; ERT=Enzyme replacement therapy; SOC=Standard of Care

Clinical and regulatory progress across Gaucher program

Clinical data

100%

GD1 patients infused to date have improved from baseline ERT across multiple measures (n=4)

1st

GD3 named patient data to date show evidence of biochemical correction

Regulatory alignment

Phase 2/3 trial

Pursue one global pediatric Phase 2/3 trial for GD3 following positive feedback from FDA and MHRA

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GD1=Gaucher disease type 1; GD3=Gaucher disease type 3; ERT=Enzyme replacement therapy; FDA=Food and Drug Administration; MHRA=Medicines and Healthcare products Regulatory Agency

Today's agenda

What if one gene could change your life?: The *GBA* gene and Gaucher disease

- Welcome and opening remarks – Geoff MacKay, AVROBIO
- Arianna and Veronica's story: Living with Gaucher disease type 3
- The role of *GBA* in Gaucher Disease – Timothy Cox, M.D., MAE, FRCP, FMedSci, University of Cambridge, UK

Fulfilling the one-gene promise: AVROBIO's Gaucher disease program

- Gaucher disease type 1 data – Essra Ridha, M.D., MRCP, FFPM, AVROBIO
- Gaucher disease type 3 data – Rob Wynn, M.D. (Camb), MB BChir, MRCP, FRCPath, Royal Manchester Children's Hospital, and Simon Jones, M.D., BSc, MRCPCH, Manchester Centre for Genomic Medicine at Saint Mary's Hospital, UK

Paving a clinical path: AVROBIO's strategy for advancing AVR-RD-02

- Development and design of clinical trials for Gaucher disease – Essra Ridha, M.D., MRCP, FFPM, AVROBIO

Delivering for patients: CMC and analytics to execute on the one-gene promise

- Deploying the plato® advantage – Azadeh Golipour, Ph.D., AVROBIO
- Recent advances in vector safety – Azadeh Golipour, Ph.D., AVROBIO

Closing remarks and Q&A

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Perspective from leading KOLs

Timothy M. Cox, M.D., MAE, FRCP, FMedSci

Professor, University of Cambridge; Cambridge University Hospitals UK

Robert Wynn, M.D. (Camb), MB BChir, MRCP, FRCPath

Professor, Pediatric Hematology at Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust

Simon Jones, M.D., BSc, MRCPCH

Professor, Pediatric Inherited Metabolic Diseases at the Manchester Centre for Genomic Medicine at Saint Mary's Hospital, Manchester University NHS Foundation Trust

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Profs. Cox, Wynn and Jones are consultants to AVROBIO; KOL: Key Opinion Leader

An Introduction to Gaucher disease

Timothy M Cox

Department of Medicine

University of Cambridge

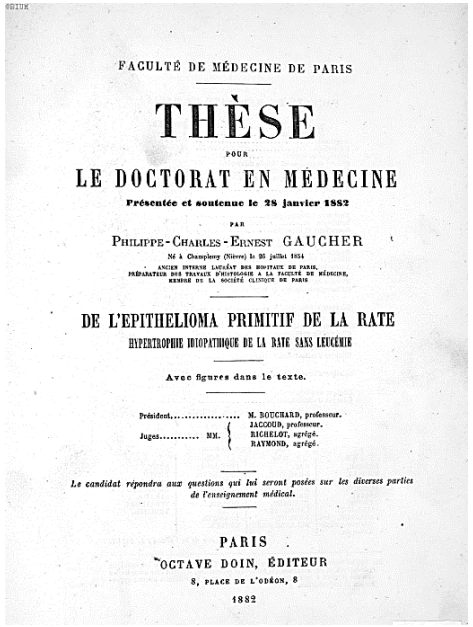
Addenbrooke's Hospital

Cambridge University NHS Hospitals Trust

Dr Gaucher (1854-1918)

S... Victorine, âgée de 32 ans, entrée à l'hôpital Cochin, salle Saint-Jean, service de M. Bucquoy, pour la première fois le 7 février 1879.

1882



FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MÉDECINE

Présentée et soutenue le 28 janvier 1882

PAR

PHILIPPE-CHARLES-ERNEST GAUCHER

Né à Champigny (Nièvre) le 25 juillet 1854

ANCIEN INTERNE LAURÉAT DES HOPITAUX DE PARIS,
PRÉPARATEUR DES TRAVAUX D'HISTOLOGIE A LA FACULTÉ DE MÉDECINE,
MEMBRE DE LA SOCIÉTÉ CLINIQUE DE PARIS

DE L'EPITHELIOMA PRIMITIF DE LA RATE

HYPERTROPHIE IDIOPATHIQUE DE LA RATE SANS LEUCÉMIE

Avec figures dans le texte.

Président,..... M. BOUCHARD, professeur.

Juges..... MM. { JACCOUD, professeur. / RICHELOT, agrégé. / RAYMOND, agrégé.

Le candidat répondra aux questions qui lui seront posées sur les diverses parties de l'enseignement médical.

PARIS

OCTAVE DOIN, ÉDITEUR

8, PLACE DE L'ODÉON, 8

1882

SV ♀ aged 34 years

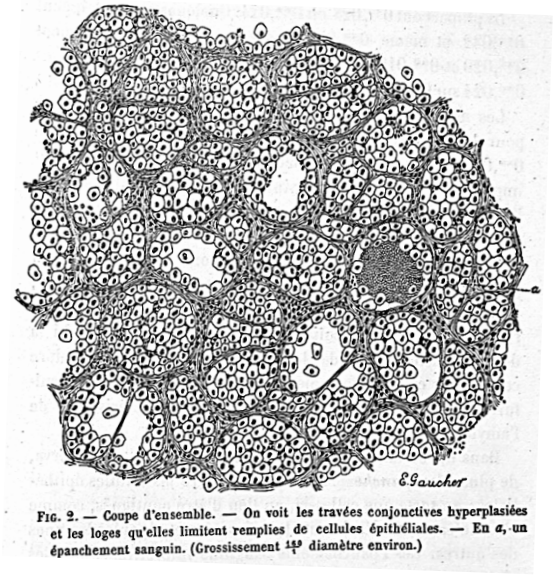
Splenomegaly from 7

Bleeding and pain

Swollen abdomen

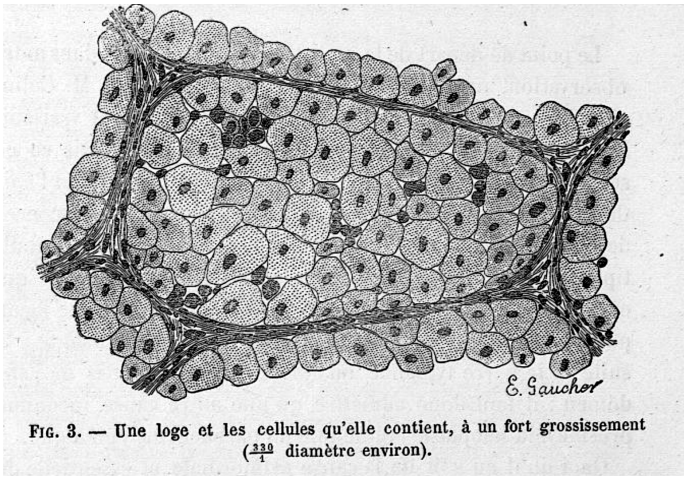
Necropsy (6 April 1881)

- Cachexia (31 Kg)
- Spleen: 4.77 Kg
- Liver: 3.88 Kg



E Gaucher

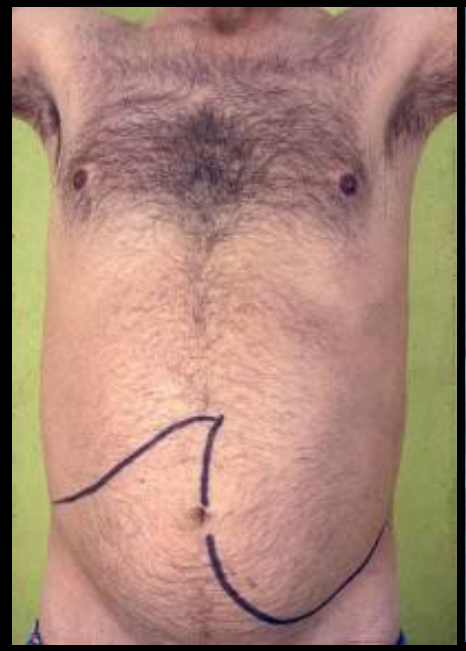
FIG. 2. — Coupe d'ensemble. — On voit les travées conjonctives hyperplasiées et les loges qu'elles limitent remplies de cellules épithéliales. — En *a*, un épanchement sanguin. (Grossissement $\frac{15}{1}$ diamètre environ.)

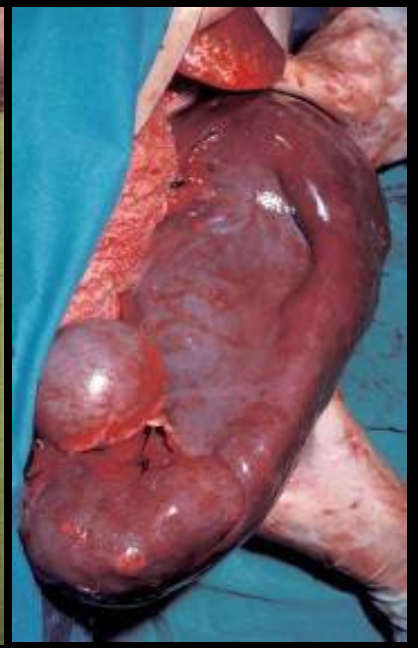


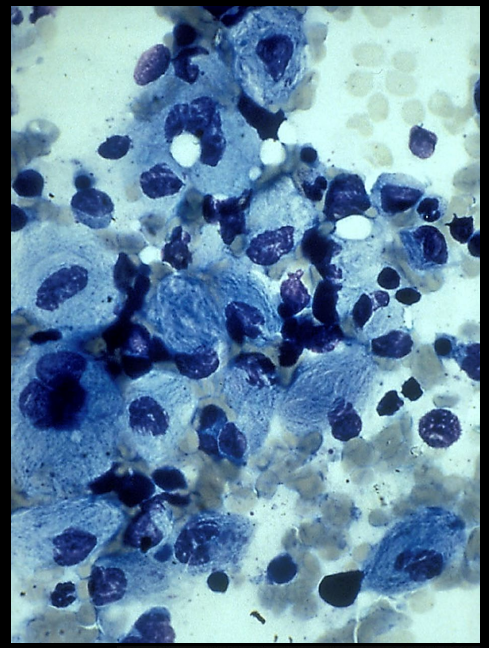
E. Gaucher

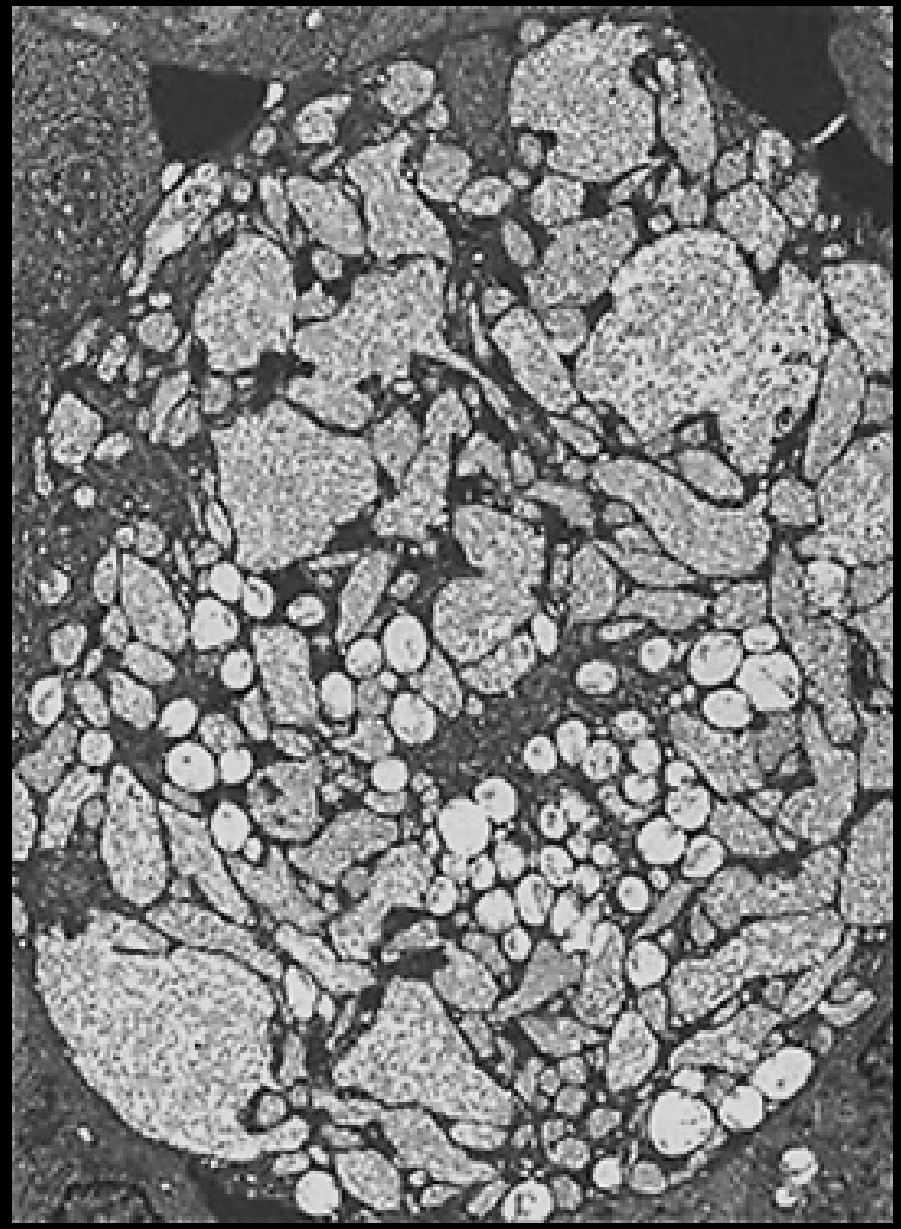
FIG. 3. — Une loge et les cellules qu'elle contient, à un fort grossissement ($\frac{330}{1}$ diamètre environ).

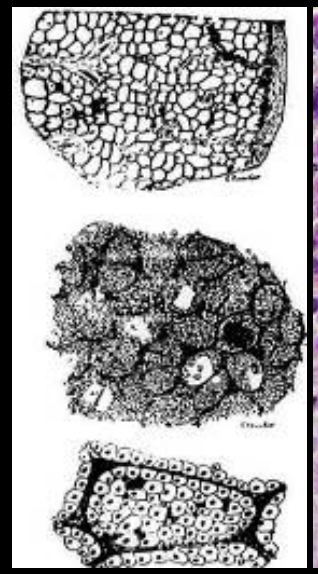
The disease and Dr Gaucher's cells

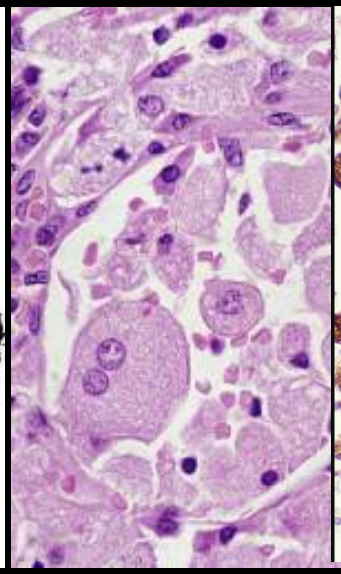


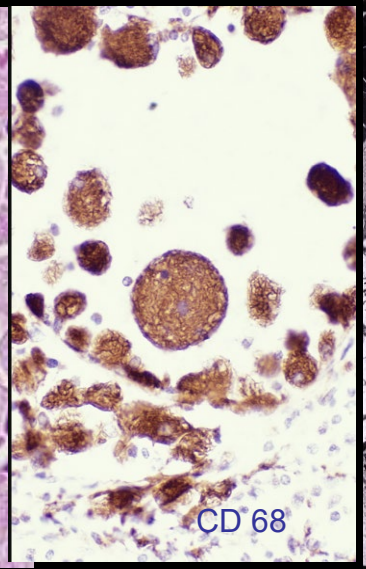


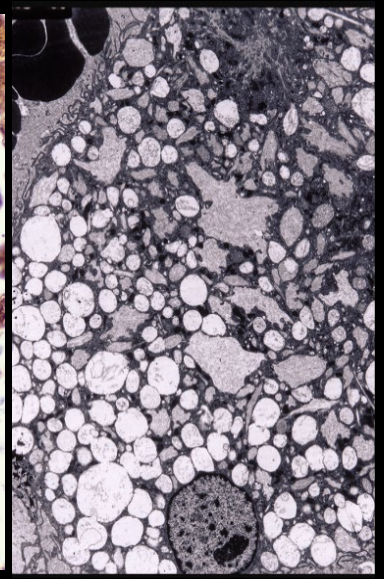












A KEY DISCOVERY - GLUCOSYLCERAMIDE

FACULTÉ DE MÉDECINE DE PARIS

THÈSE 546

POUR

LE DOCTORAT EN MÉDECINE

(Diplôme d'État)

PAR

Henriette AGHION

Ancienne Élève des Hôpitaux de Paris
Ancienne Interne Pr. de l'Hôtel-Dieu de Paris

Née à Paris, le 30 Janvier 1906

LA MALADIE DE GAUCHER
DANS L'ENFANCE
(FORME CARDIO-RÉNALE)

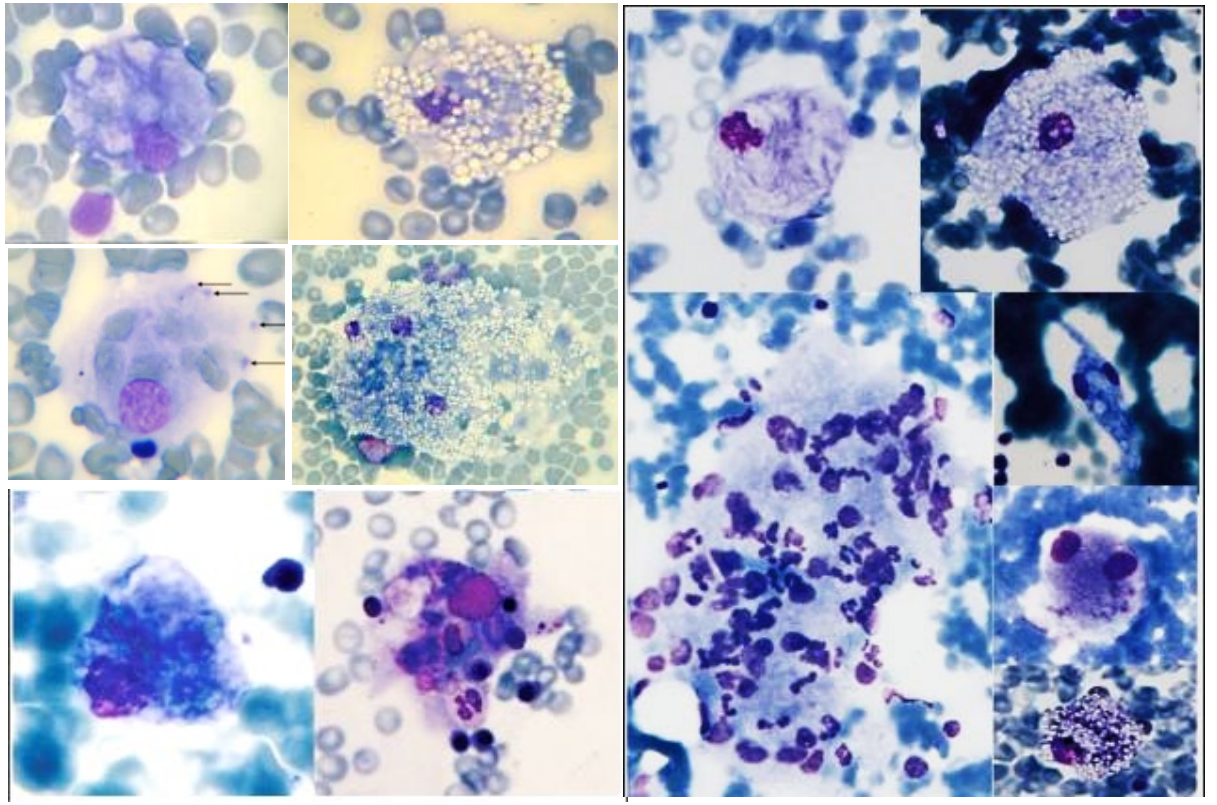
Président de Thèse : M. le Professeur DEBRÉ

IMPRIMERIE DE PERSAN-BEAUMONT
80, Avenue Wilson, 80
PERSAN (S.-et-O.)

Aghion H (1934)
Thèse de Paris

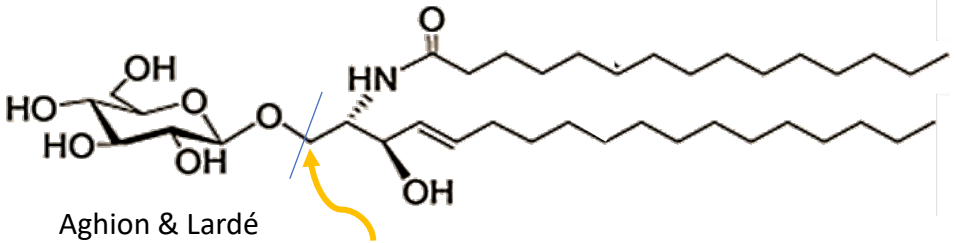
Henriette Aghion

1906-1986



Machaczka M, Klimkowska M, Regenthal S, Hägglund H (2011) Gaucher disease with foamy transformed macrophages and erythrophagocytic activity. J Inherit Metab Dis.34:233-235

β- D-glucosyceramide (C16)

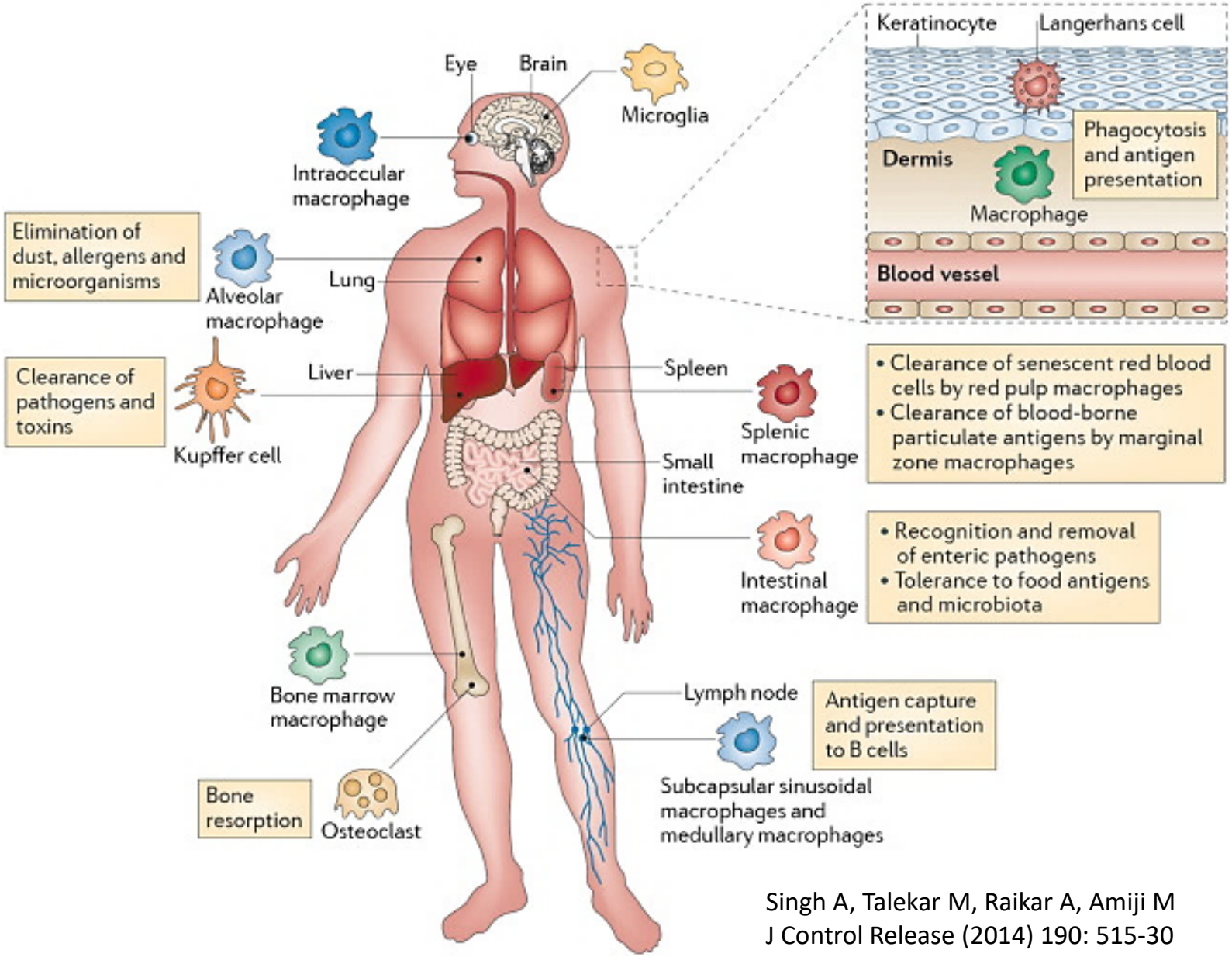


Aghion & Lardé

Glucosylceramidase/glucocerebrosidase

(Brady et al., 1965; Patrick 1965)

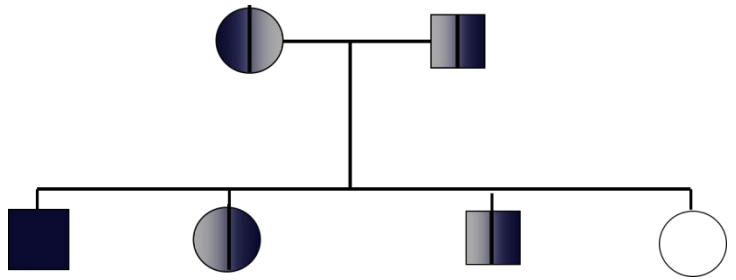
Macrophages – scavengers, recyclers, immune activators



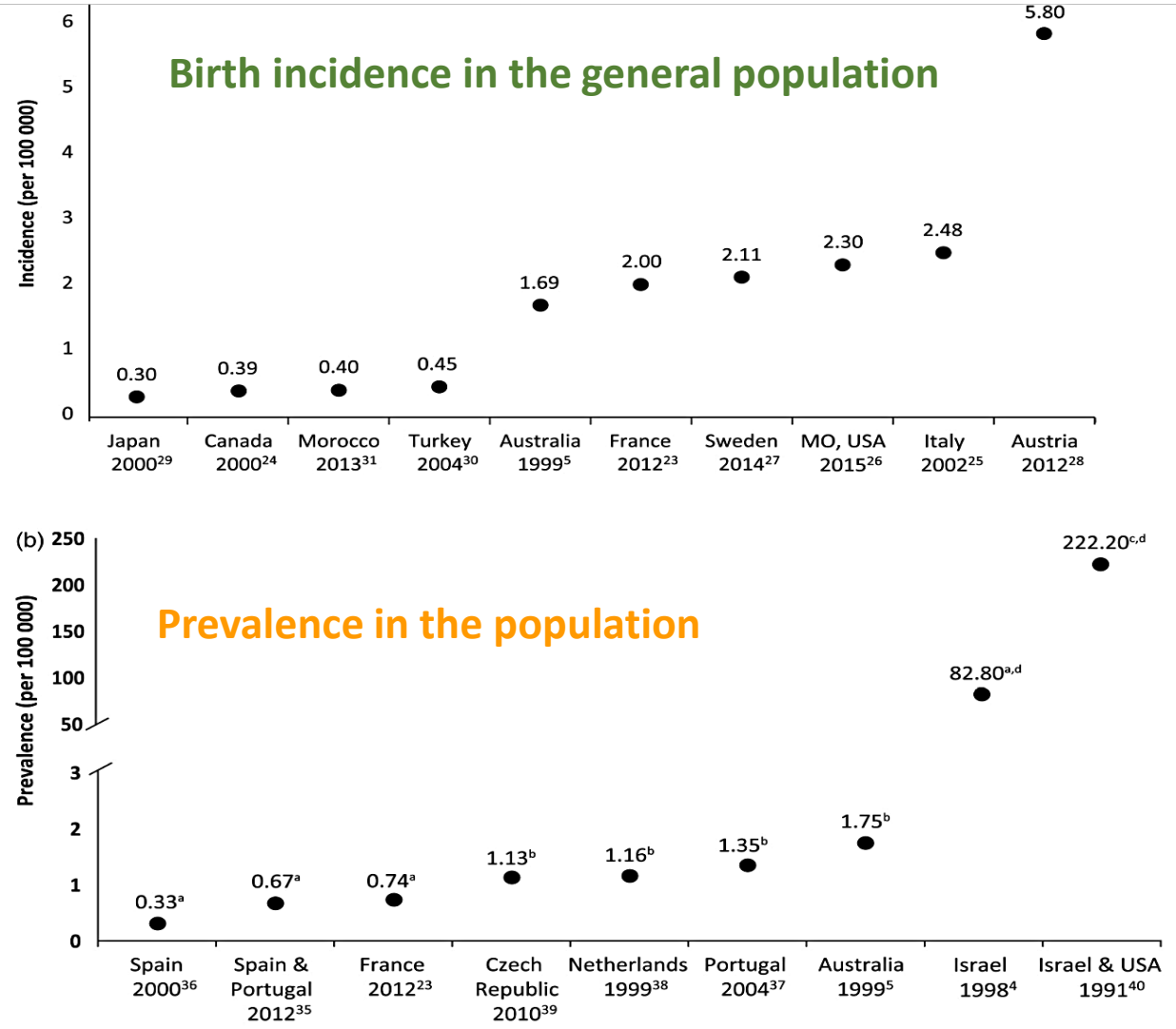
Singh A, Talekar M, Raikar A, Amiji M
J Control Release (2014) 190: 515-30

Gaucher disease

- Acid β-glucosidase (β-glucocerebrosidase) deficiency
- A lysosomal enzyme
- Chromosome 1
- Autosomal recessive inheritance
- One of the most frequent lysosomal diseases ≈1/60,000 births …
- Progressive, multisystem disorder



Epidemiology of Gaucher disease

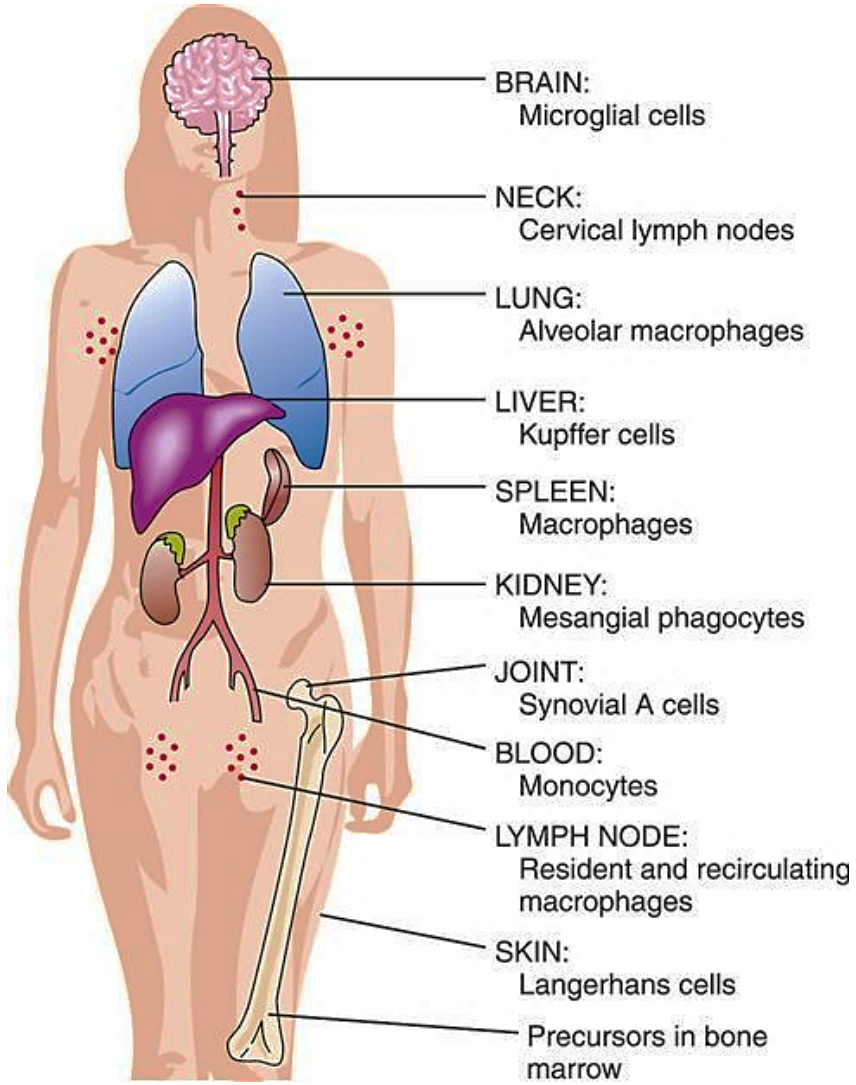


Nalysnyk L, Rotella P, Simeone JC, Hamed A, Weinreb N 2017. Gaucher disease: Epidemiology and natural history, a comprehensive review of the literature. Hematology 22: 65-73

Gaucher disease - a multisystem and protean disorder

SYMPTOMS

- Growth retardation
- Fatigue
- Poor apetiite
- Bruising/bleeding
- Menorrhagia
- Abdominal pain
- Bone pain
- Breathlessness
- Poor visual fixation
- Clumsiness & tremor
- Speech defects
- Deafness
- Swallowing difficulties
- Impaired cognition
- Behavioural difficulties
- Seizures



Redrawn from Schindler LW: Understanding the immune system, NIH Pub No. 92-529, Bethesda, MD, 1991, U.S. Department of Health and Human Services, p 9.

CLINICAL & RADIOLOGICAL FEATURES

Enlarged spleen* (87%)

Enlarged liver (79%)

Marrow infiltration (40%)

Anemia (64%)

Thrombocytopenia (56%)

*Splenectomy (32%)

Osteonecrosis (50%)

Erlenmeyer deformity (46%)

Fragility fracture (15%)

Osteolytic lesions (8%)

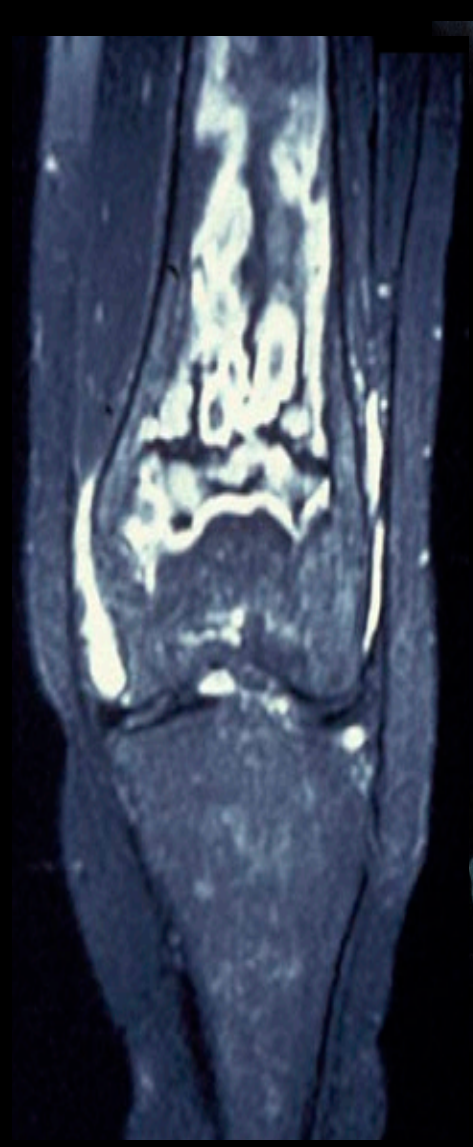
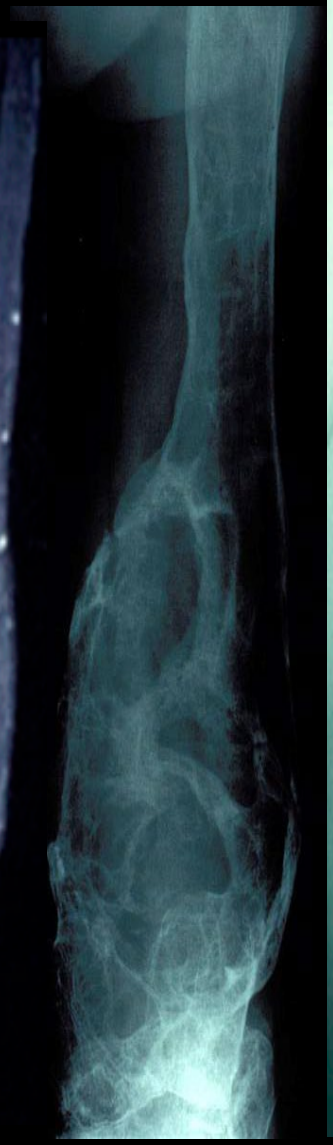
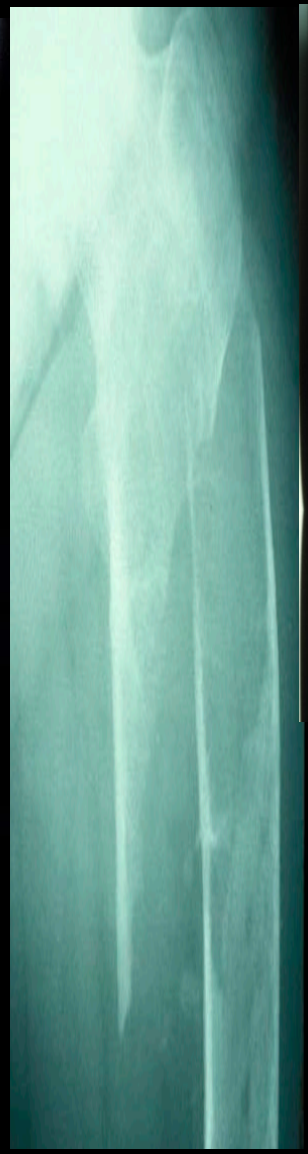
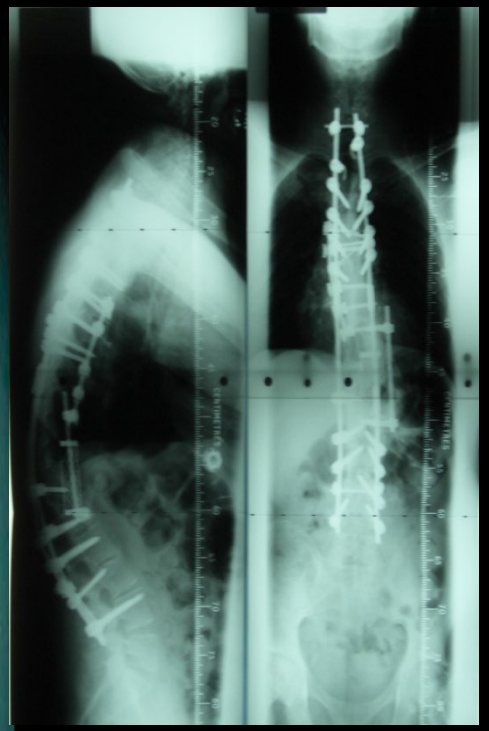
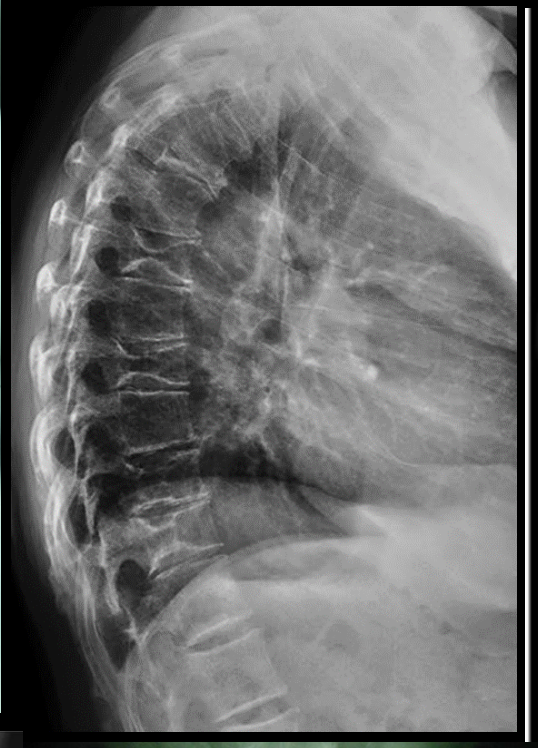
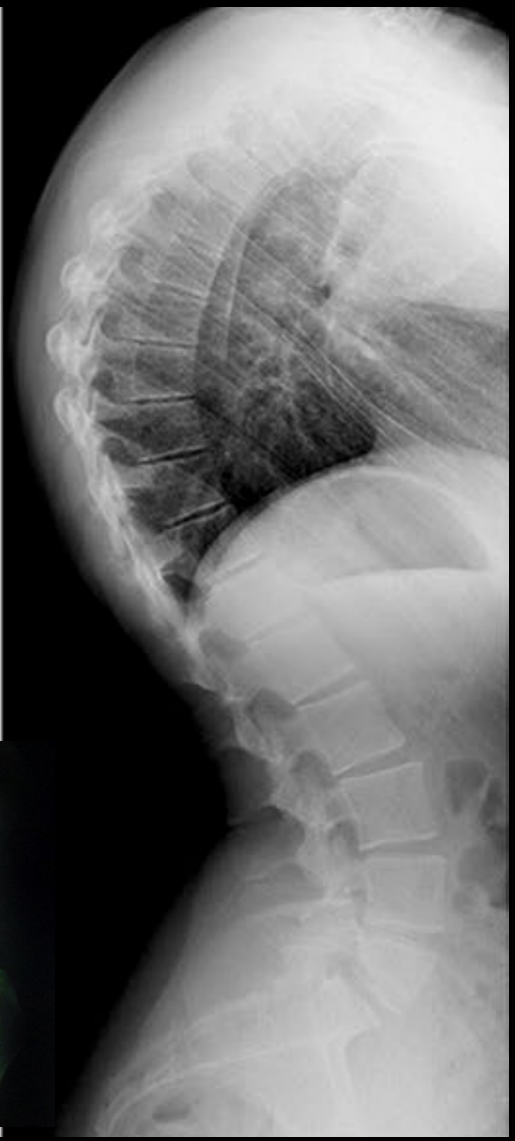
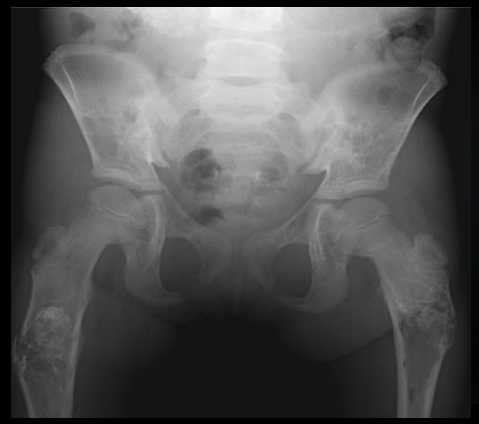
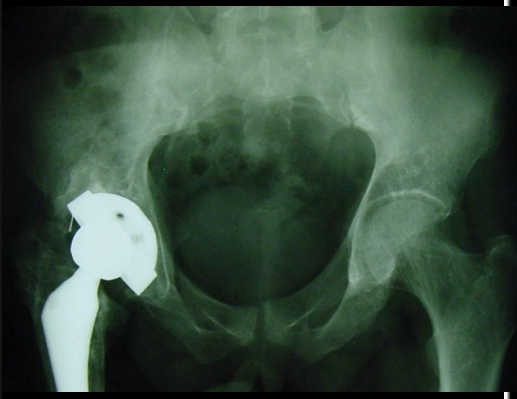
Lung infiltration

Neurological disease

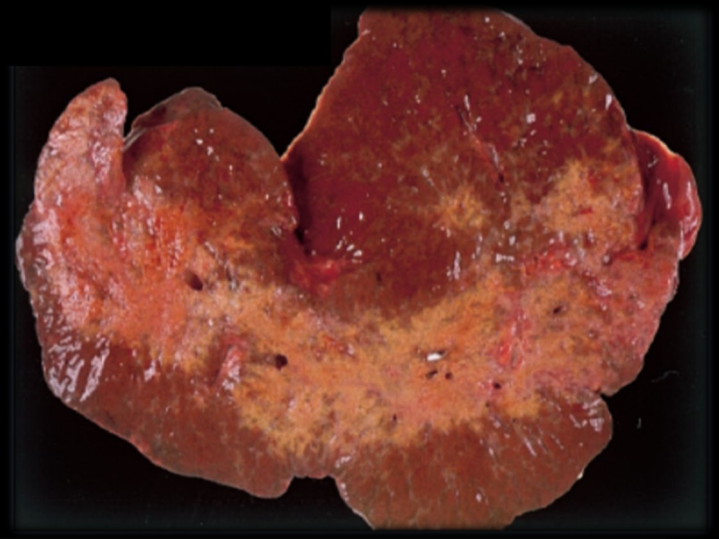
Cancers

Charrow J, et al. Arch Intern Med. 2000;160:2835-2843
The Gaucher Registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. Baseline study - 38 countries collected – 45% US, 17% Israel

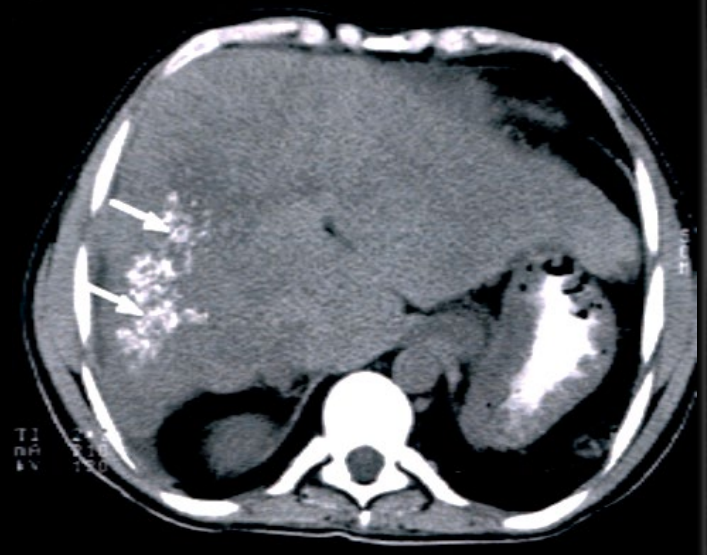
Late sequelae of Gaucher disease in the skeleton

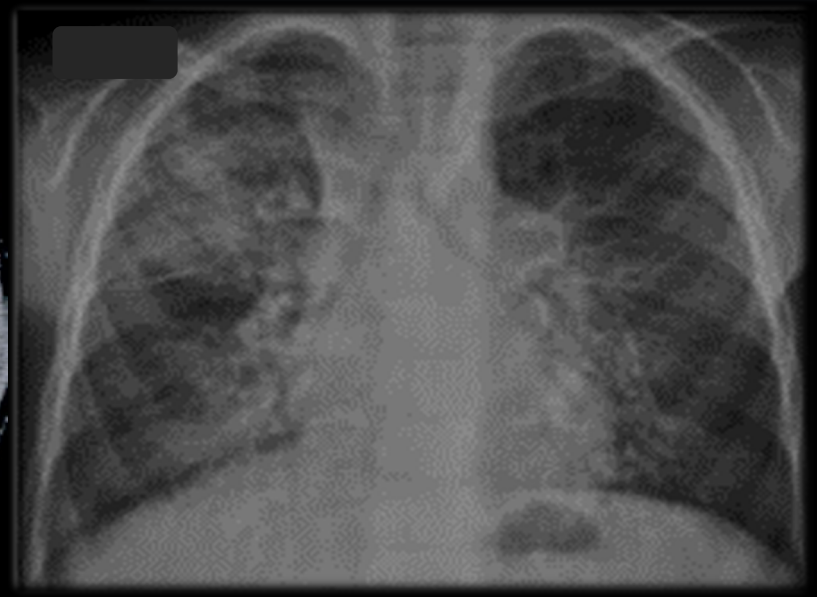









Gaucher disease: severe involvement of macrophage-rich organs



The Liver

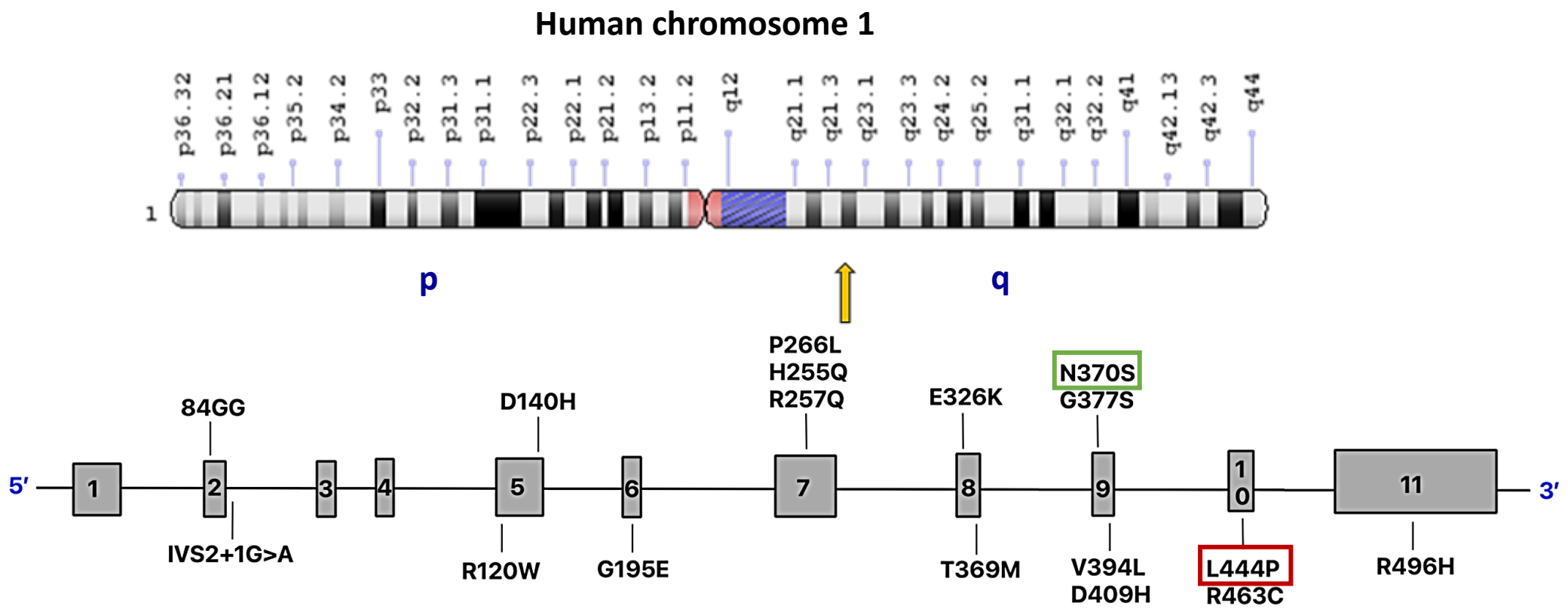




The Lung

Lachmann RH, Wight DGJ, Lomas DJ, Fisher NC, Schofield JP, Elias E & Cox TM (2000) Massive hepatic fibrosis in Gaucher's disease: clinicopathological and radiological features. *Quart J Med* **93:** 237-44
Lee FS, Yen HJ, Niu DM, Hung GY, Lee CY, Yeh YC, Chen PC, Chang SK, Yang CF. (2020) Allogeneic hematopoietic stem cell transplantation for treating severe lung involvement in Gaucher disease.
Mol Genet Metab Rep. 2020 Oct 20;25:100652.

Genetics of Gaucher disease – *GBA1* encodes human acid β-glucosidase



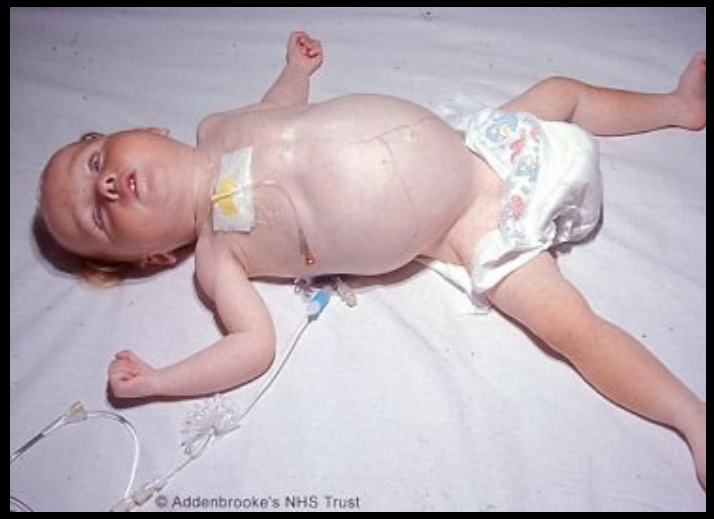
Most frequent mutations of ≈ 380 described L444P, N370S, RecNciI, R496H, R463C, IVS2+1, D409H (>95%)…

Deegan PB, Cox TM. *Drug Des Devel Ther*. 2012;6:81-106. Hruska KS, et al. *Hum Mutat*. 2008;29(5):567-583. Grabowski GA. *Lancet*. 2008;372(9645):1263-1271.

Gaucher disease in the UK with untreatable neurological manifestations

Acute
Type 2

Type 3

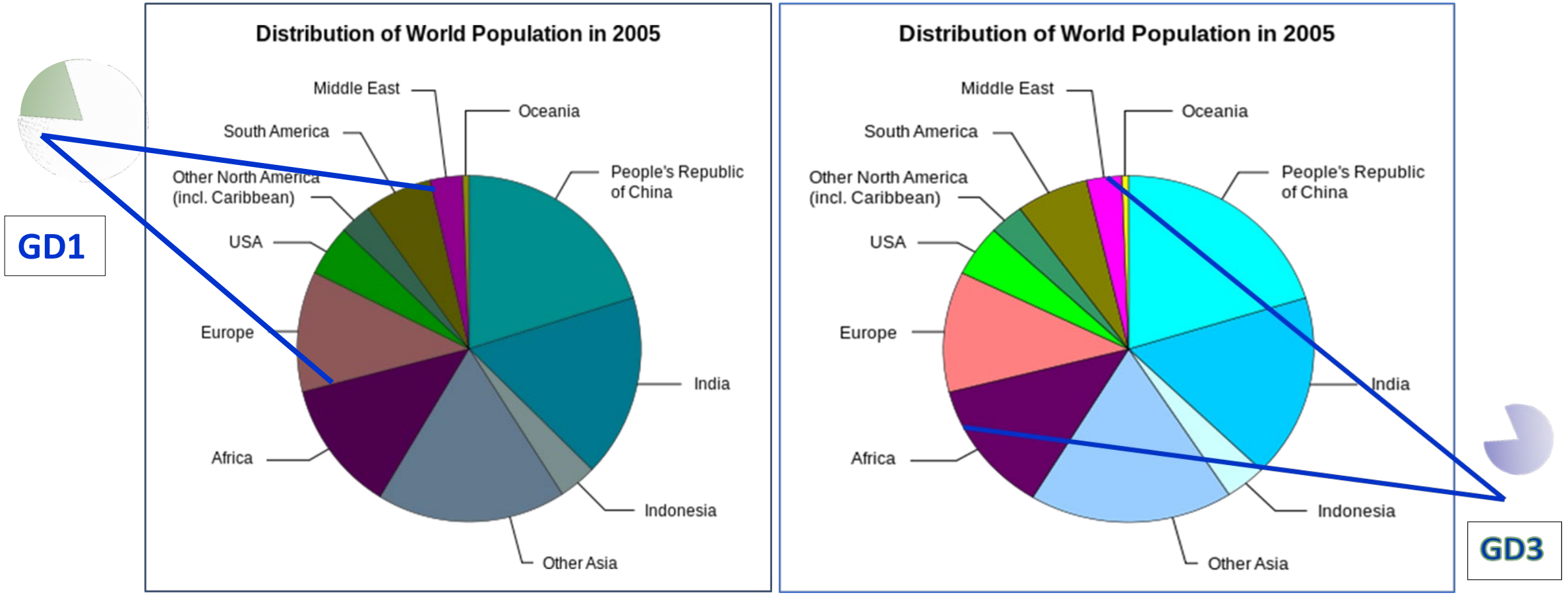


Subacute
Type 2/3

Speaker's own images and/or used with appropriate permission from the patients and/or their principal carers

5710 Gaucher disease patients in regions proportional to global population

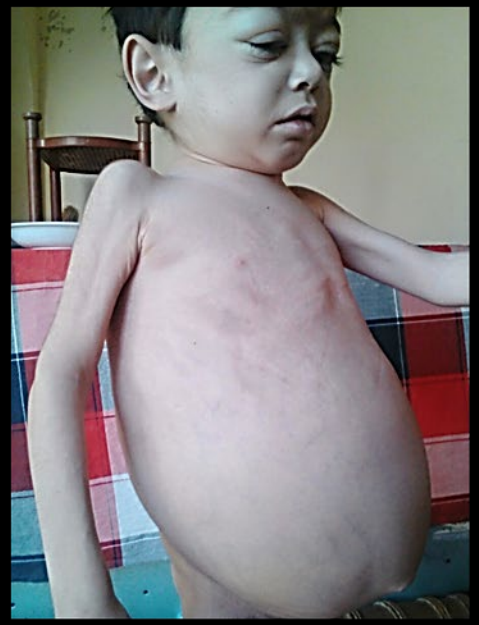
North America (2108); Europe (1477); Middle East/Africa (986); Latin America (901); Asia-Pacific (238)

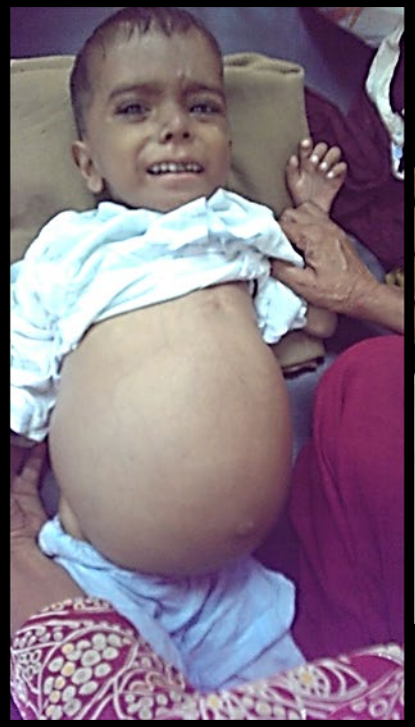


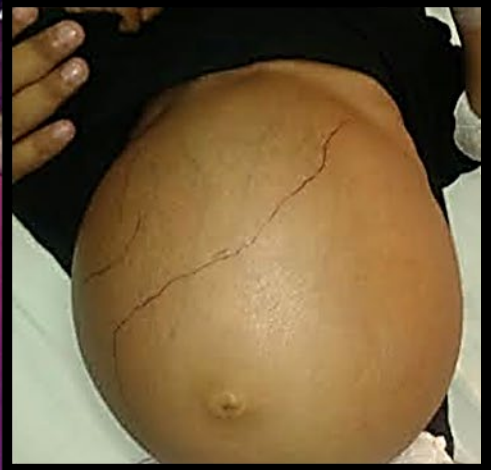
1. Kim H, et al. *Haematologia*. 2010;95(Suppl2):743.
2. WIKIMEDIA. 2022. https://commons.wikimedia.org/wiki/File:World_population_distribution.svg.

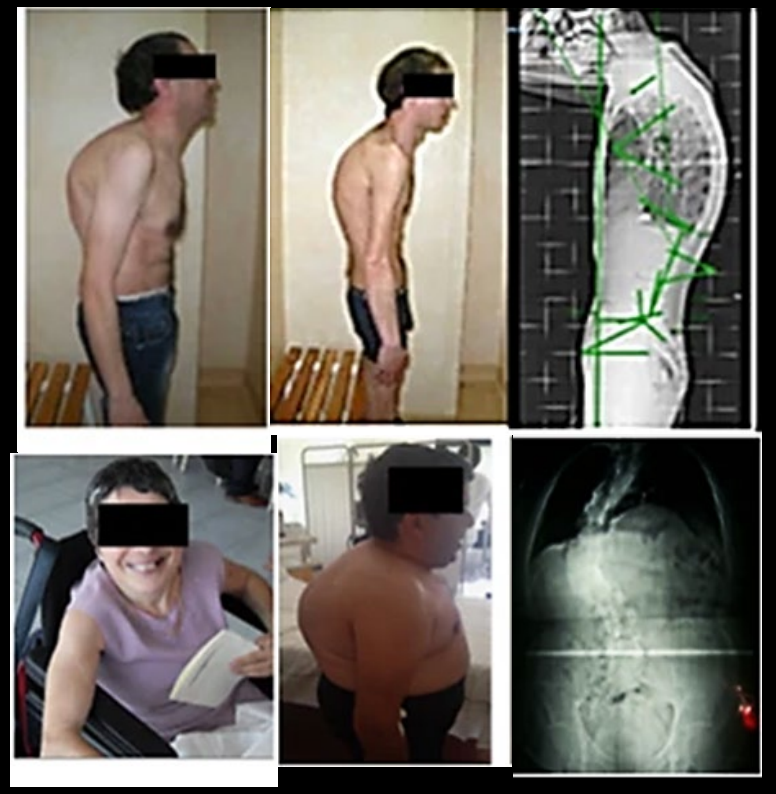
Clinical diversity in neuronopathic Gaucher disease (type 3)

All patients assigned the L444P *GBA1* genotype







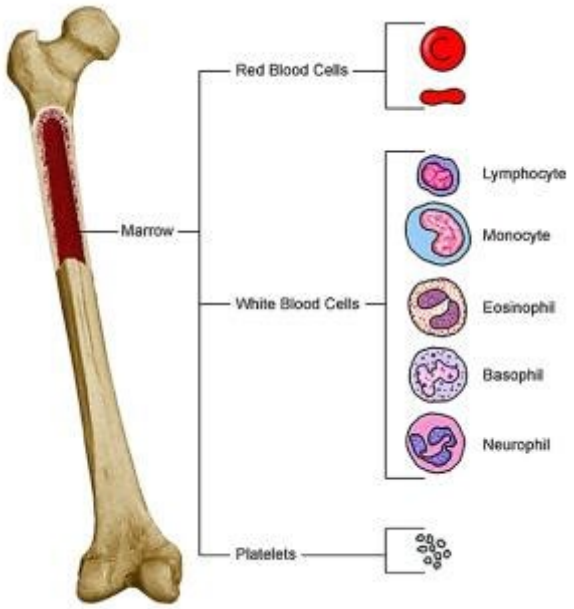


Images kindly supplied and shown by permission of Professor Huma Cheema
The Children's Hospital and the Institute of Child Health, Lahore

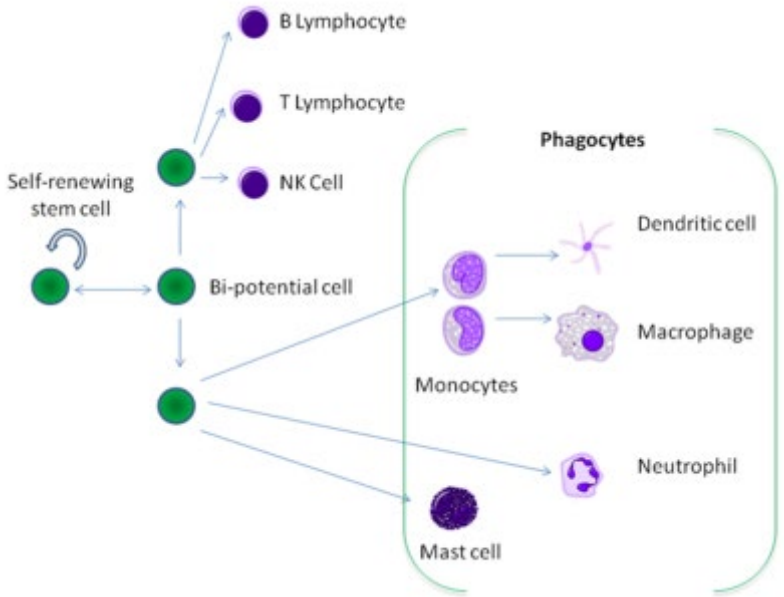
Sestito S, Filocamo M, Ceravolo F, Falvo F, Grisolia M, Moricca MT, Cantaffa R, Grossi S, Strisciuglio P, Concolino D. Norrbottnian clinical variant of Gaucher disease in Southern Italy. J Hum Genet. 2017 Apr;62(4):507-511.

Origin of tissue macrophages

Marrow transplant in Gaucher disease
Born 1973 Transplant 1982 aged 9y



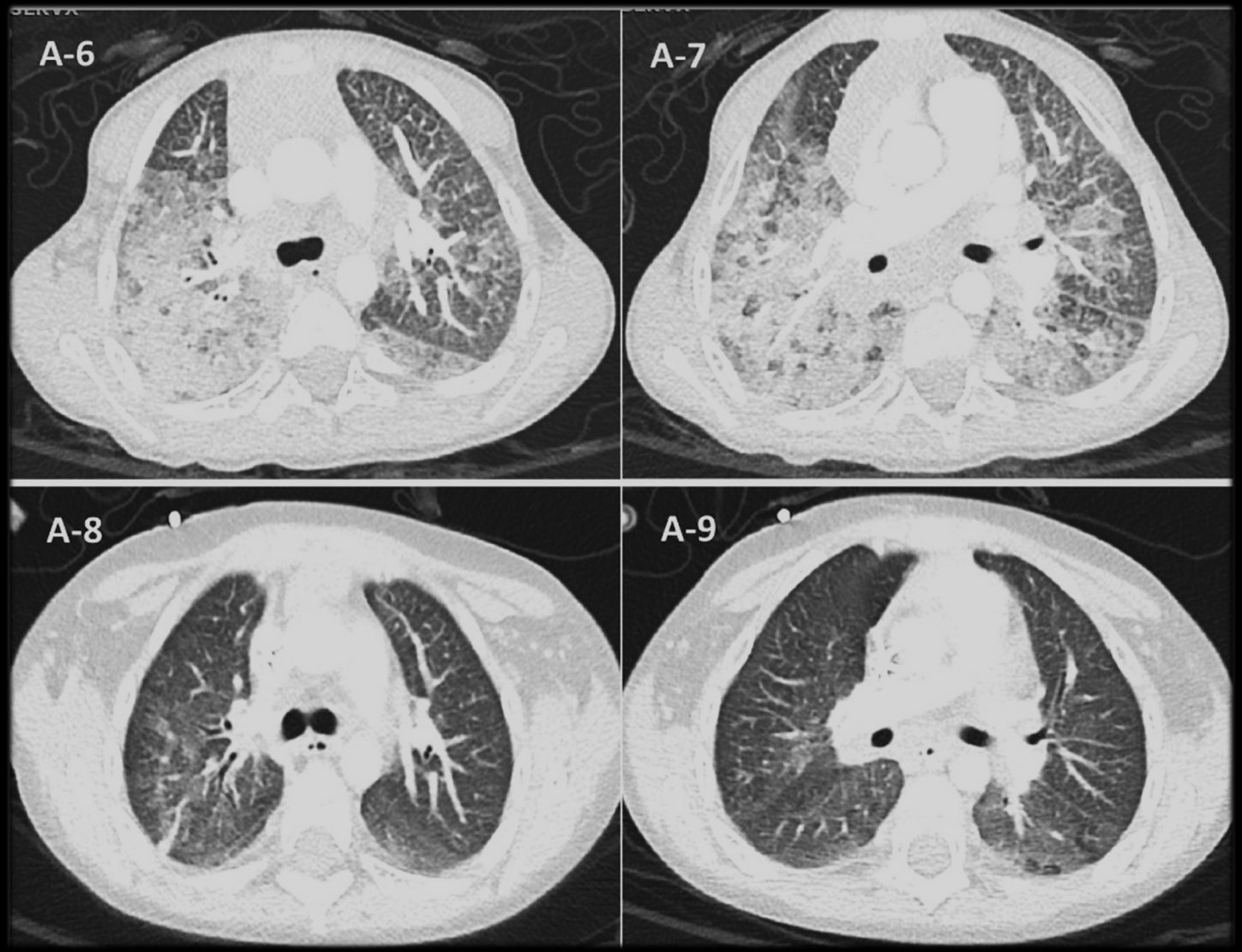
Cellular and Molecular Immunology AK Abbas, AHH Lichtman and S Pillai - Elsevier, N Holland Eighth Edition 2015, 544 pp



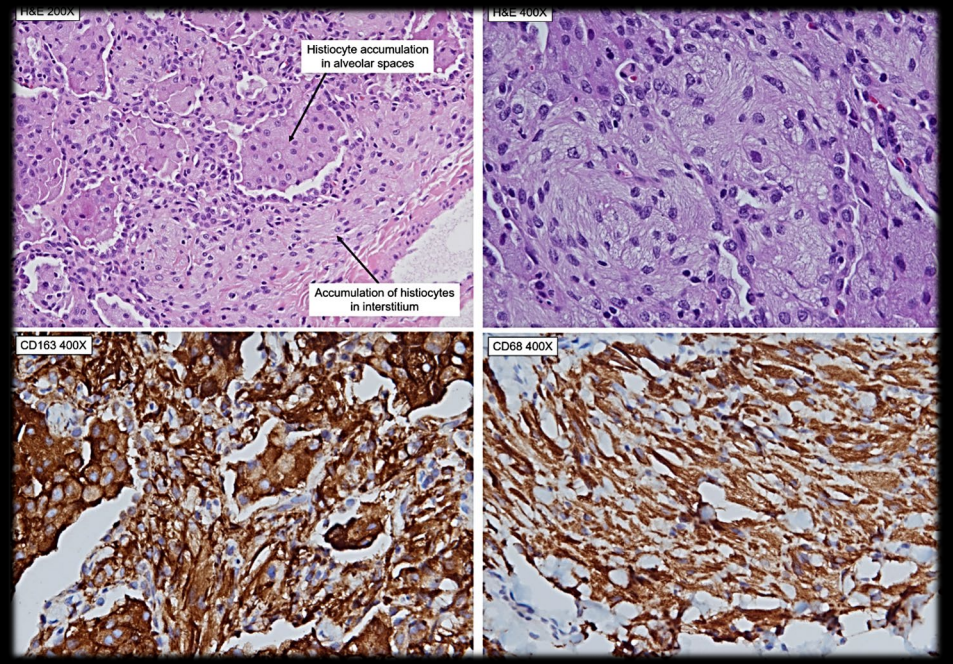
Open Textbook Pilot Project,Office of the Provost, UC Davis Library, California State University

Ringdén O, Groth CG, Erikson A et al Transplantation. 1988 Jul;46(1):66-70

Gaucher disease: severe pulmonary involvement



Lee FS, Yen HJ, Niu DM, Hung GY, Lee CY, Yeh YC, Chen PC, Chang SK, Yang CF. (2020) Allogeneic hematopoietic stem cell transplantation for treating severe lung involvement in Gaucher disease. Mol Genet Metab Rep. 2020 Oct 20;25:100652.



FS Lee et al., Mol Genet Metab Rep. 2020 Oct 20;25:100652

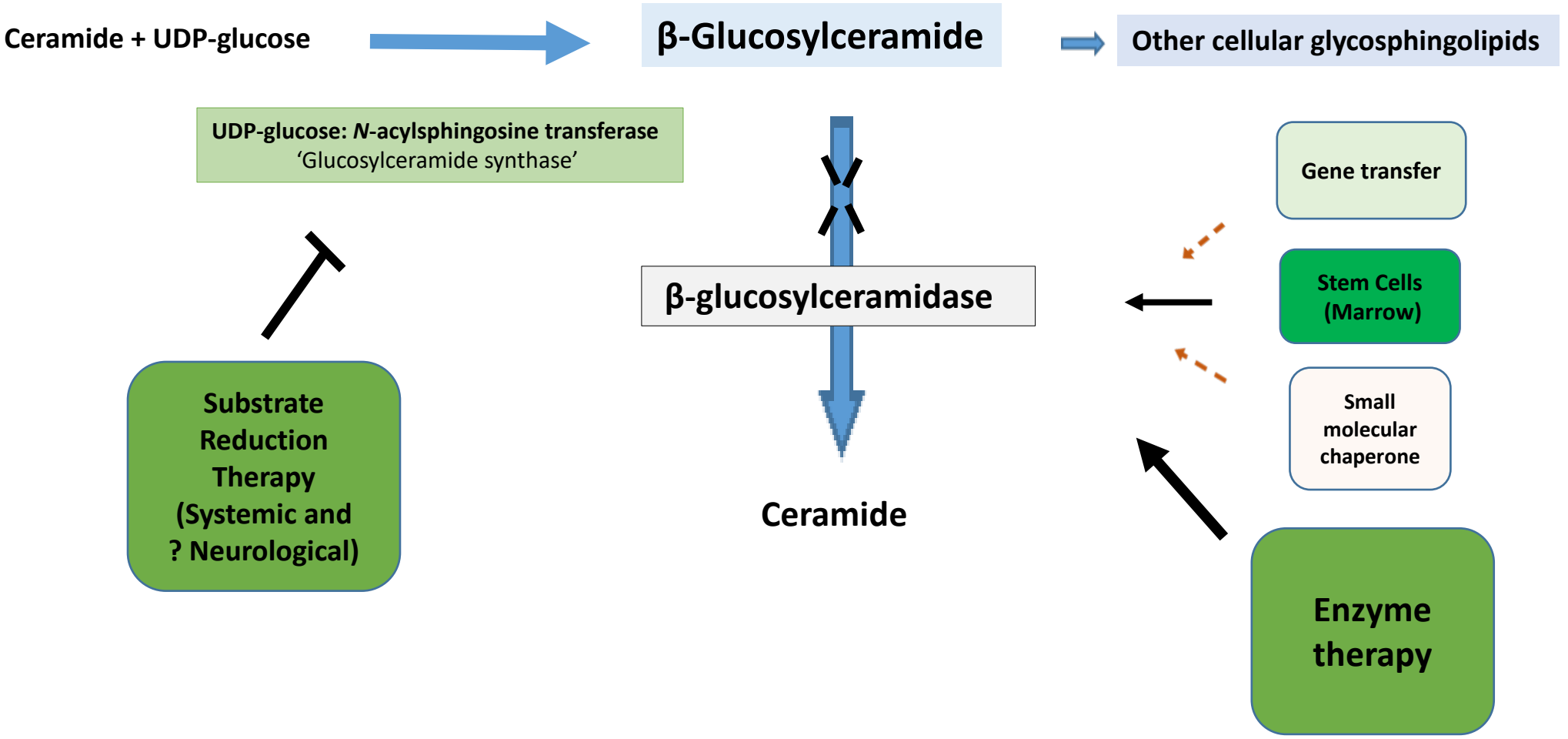
♂ **Gaucher disease - L444P homozygote (p.L483P)**

Hepatosplenomegaly, cytopenias developmental delay
Started enzyme therapy aged 17 months (60u/kg/2w)
Respiratory distress by 5 year 2 mths (Rx 120u/kg/2w)
Bilateral interstitial infiltration & R lung consolidation

Allogeneic HSCT Matched unrelated donor

1/12 Respiratory symptoms subsided
3/12 white-cell β-glucosylceramidase healthy range
4/12 Improved chest imaging & lung function

Possible ways to treat Gaucher disease



Based on - JA Shayman (2015) Developing novel chemical entities for the treatment of lysosomal storage disorders: an academic perspective Am J Physiol Renal Physiol 309: F996-F999

Today's agenda

What if one gene could change your life?: The *GBA* gene and Gaucher disease

- Welcome and opening remarks – Geoff MacKay, AVROBIO
- Arianna and Veronica's story: Living with Gaucher disease type 3
- The role of *GBA* in Gaucher Disease – Timothy Cox, M.D., MAE, FRCP, FMedSci, University of Cambridge, UK

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- Development and design of clinical trials for Gaucher disease – Essra Ridha, M.D., MRCP, FFPM, AVROBIO

Delivering for patients: CMC and analytics to execute on the one-gene promise

- Deploying the plato® advantage – Azadeh Golipour, Ph.D., AVROBIO
- Recent advances in vector safety – Azadeh Golipour, Ph.D., AVROBIO

Closing remarks and Q&A

AVROBIO

Fulfilling the one-gene promise: AVROBIO's Gaucher disease program

Key takeaways

- GD1 patient data to date has improved from baseline ERT with some clinically significant reductions in liver (n=3) and spleen volume (n=2)
- GD3 named patient data to date show evidence of biochemical correction, with lymphadenopathy and enteropathy improvements and neurological stabilization
- Continued favorable safety profile to date

AVROBIO

Arianna living with Gaucher disease type 3

Gaucher type 1 Phase 1/2 has 6 patients enrolled to date

Guard1 - Phase 1/2

AVR-RD-02

Actively recruiting

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: – GBA biallelic mutations on genetic sequencing – Deficient glucocerebrosidase enzyme activity

Gaucher disease type 1 patients who are:

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

AVROBIO

GD1=Gaucher disease type 1; ERT=Enzyme replacement therapy; SRT=Substrate reduction therapy

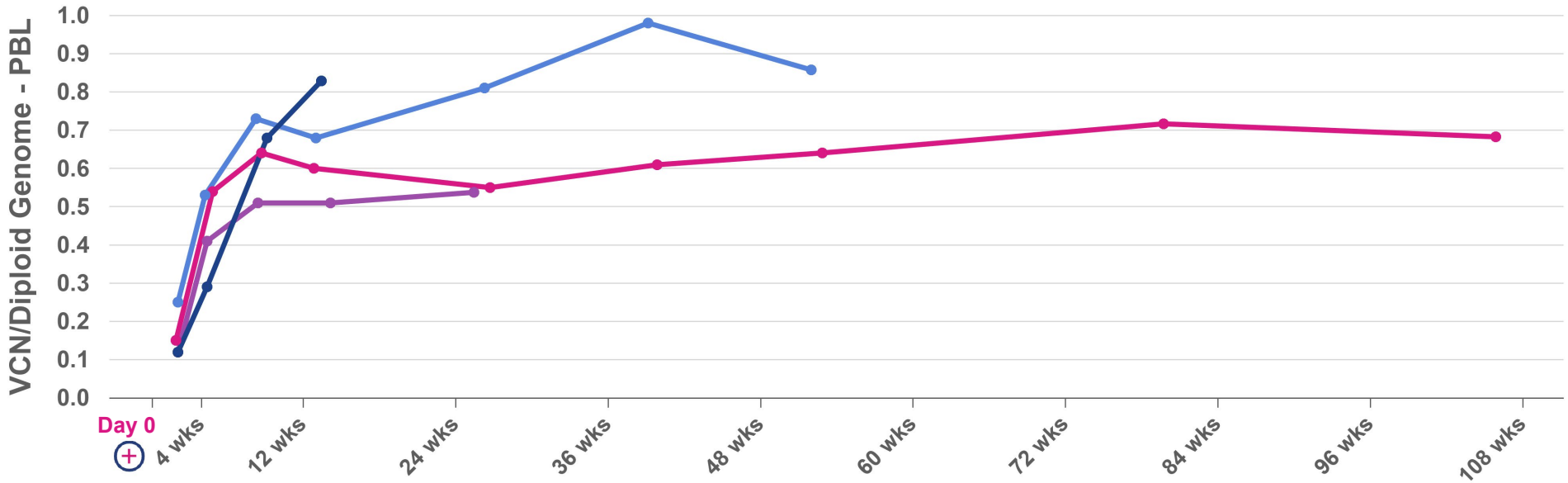
Guard1 patient baseline characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age of symptom onset/diagnosis	1 year / 20 months	5 years / 5 years	3 years / 3 years	5 years / 5 years
Age dosed	31 years	44 years	24 years	34 years
Gender	Female (white)	Female (white)	Male (white)	Male (white)
Mutation	**L444P/L444P Homozygous** *C_Position c.1448T>C* *P_Position p.(Leu483Pro)*	**N370S/L444P Heterozygous** *C_Position c.1226A>G/ c.1448T>C* *P_Position* *p.(Asn409Ser)/ p.(Leu483Pro)*	**N370S/del E02 to E10 Hemizygous** *C_Position c.1226A>G/ deletion encompassing E02 to E10* *P_Position p.(Asn409Ser)*	**L444P/ N501K Heterozygous** *C_Position c.1226A>G/ c.1503C>G* *P_Position p.(Asn409Ser) /p.(Asn501Lys)*
Spleen status	splenectomized	non-splenectomized	non-splenectomized	non-splenectomized
DP dose	3 x10^6 CD34+ cells/kg	6.6 x10 ^6/L cells/kg	7.0 x10 ^6/L cells/kg	4.1 x10 ^6/L cells/kg

AVROBIO

VCN trending as expected, indicating sustained engraftment

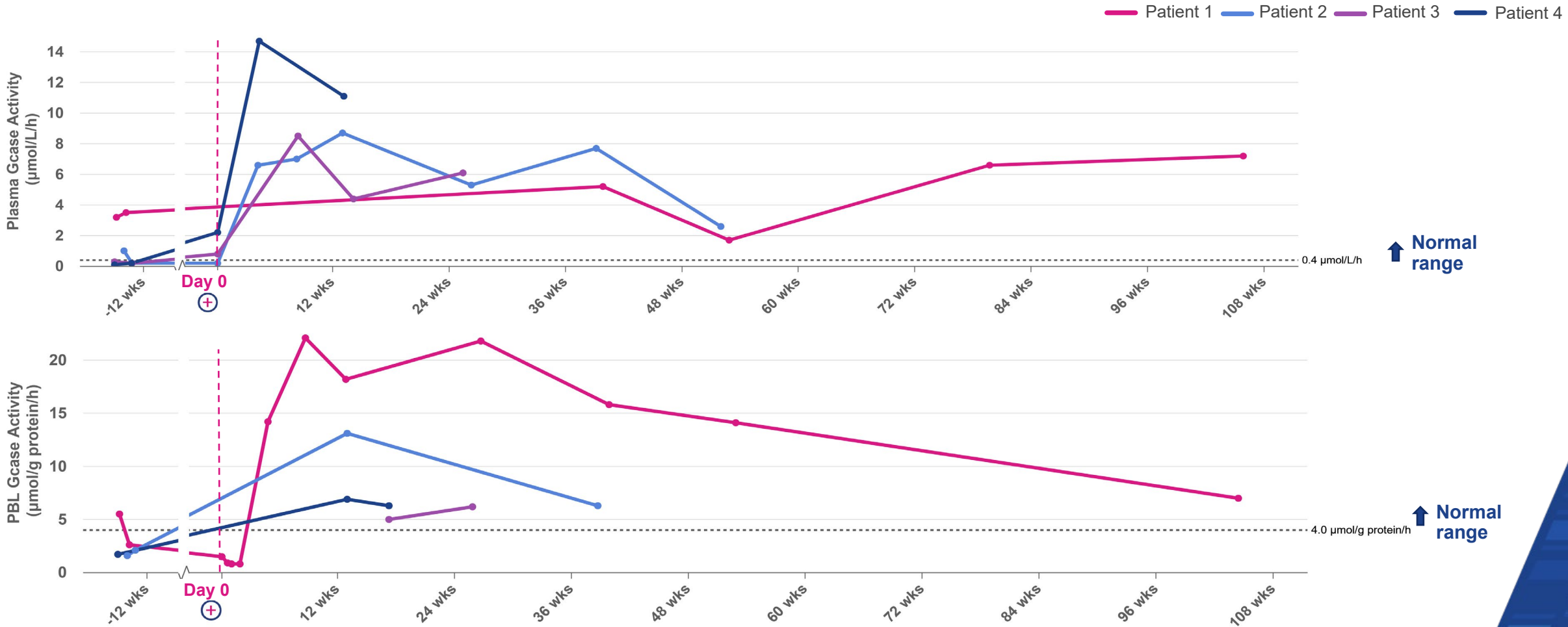
Drug product VCN/transduced cell	
Patient 1	4.2
Patient 2	2.0
Patient 3	2.0
Patient 4	1.8



Data as of Nov. 22, 2022; VCN=Vector copy number; PBL=Peripheral blood leukocytes; wks=Weeks

Plasma and PBL GCase enzyme activity normalized

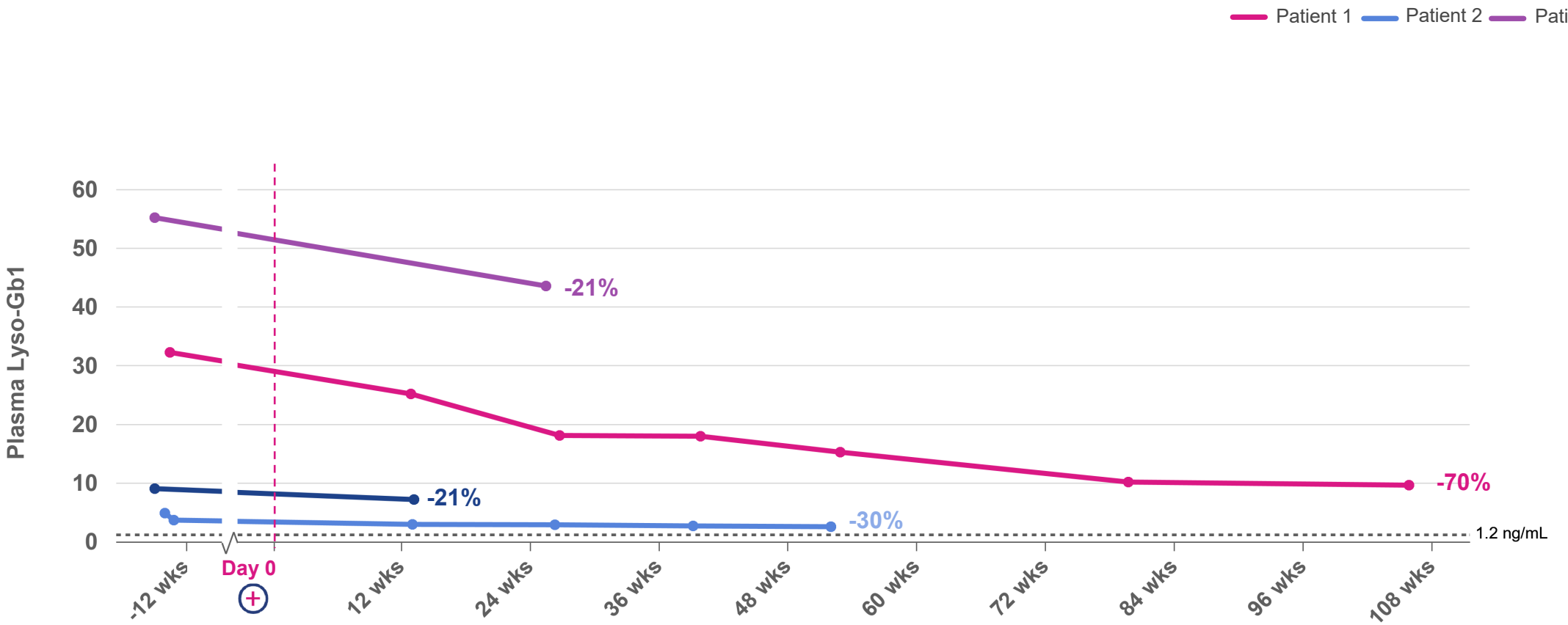
Guard1: PATIENT 1-4



Data as of Nov. 22, 2022; GCase=β-Glucocerebrosidase; ERT=Enzyme replacement therapy; PBL=Peripheral blood leukocytes; wks=Weeks; Normal Range: ≥ 0.4 µmol/L/h

Lyso-Gb1 stable or reduction below ERT baseline

Guard1: PATIENT 1-4

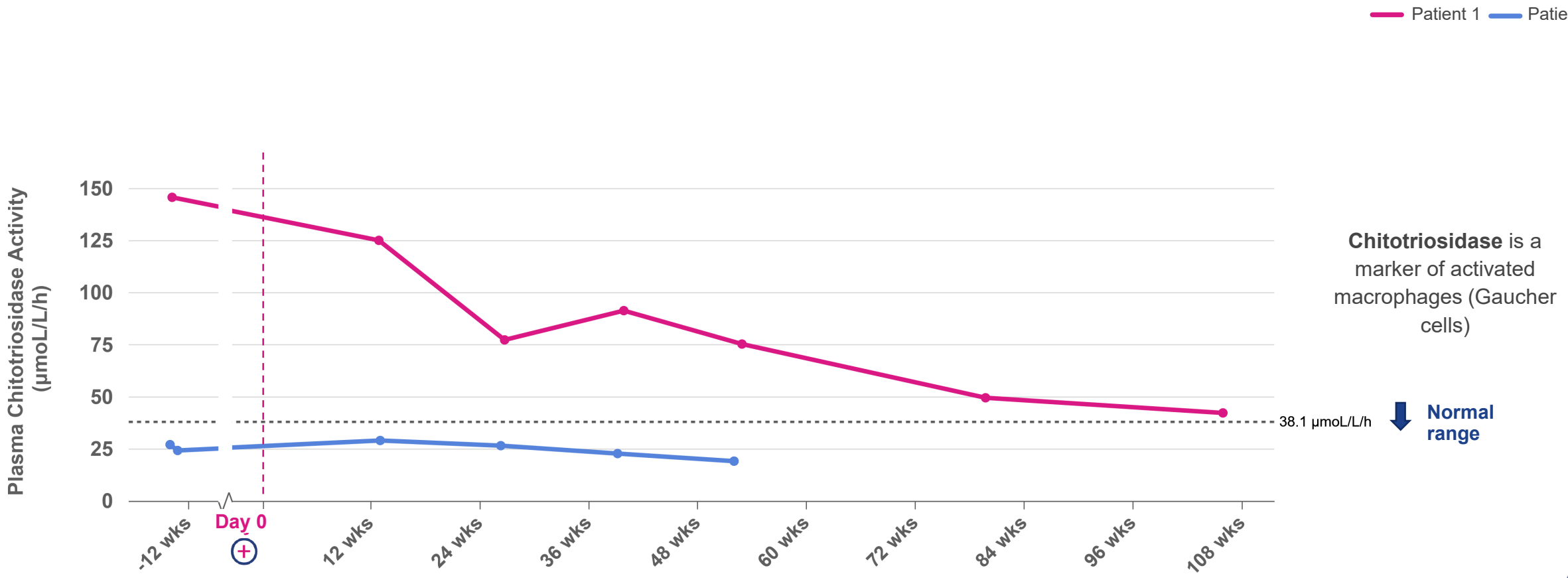


Lyso-Gb1 is a sensitive and specific marker of metabolite accumulation

Data as of Nov. 22, 2022; Lyso-Gb1=Glucosylsphingosine, ERT=Enzyme replacement therapy; wks=Weeks; Normal Range: ≤ 1.2 ng/mL; Baseline for % calculation is defined as the last non-missing value prior to AVR-RD-02 Infusion

Toxic metabolite chitotriosidase stable or reduced below ERT baseline in 2 evaluable patients

Guard1: PATIENT 1-2



Chitotriosidase is a marker of activated macrophages (Gaucher cells)

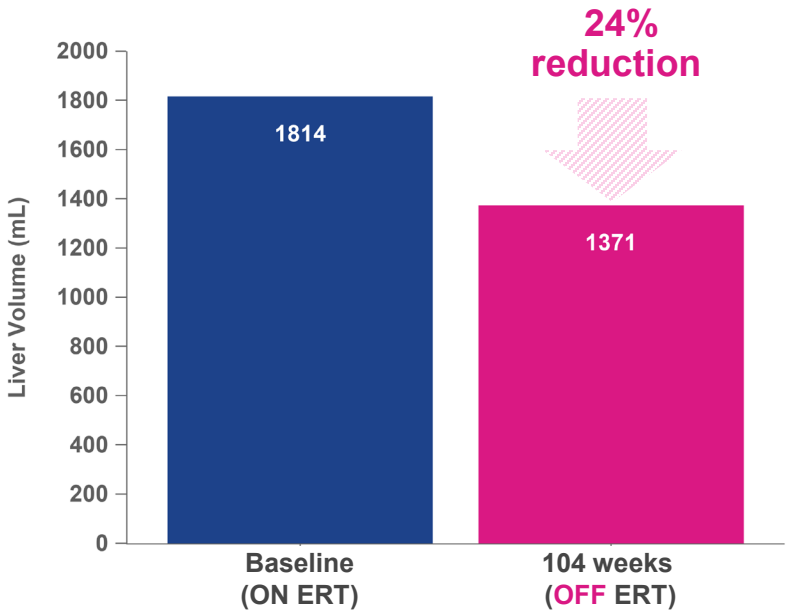
Data as of Nov. 22, 2022; Normal Range: ≤ 38.1 µmol/L/h; Patient 3 and 4 screening, baseline, day 90 (Patient 3, 4) and day 180 (Patient 3) samples are not reported as they are above the upper limit of assay quantitation (150+) and are currently under quality investigation.

Clinically meaningful reduction in liver below ERT baseline

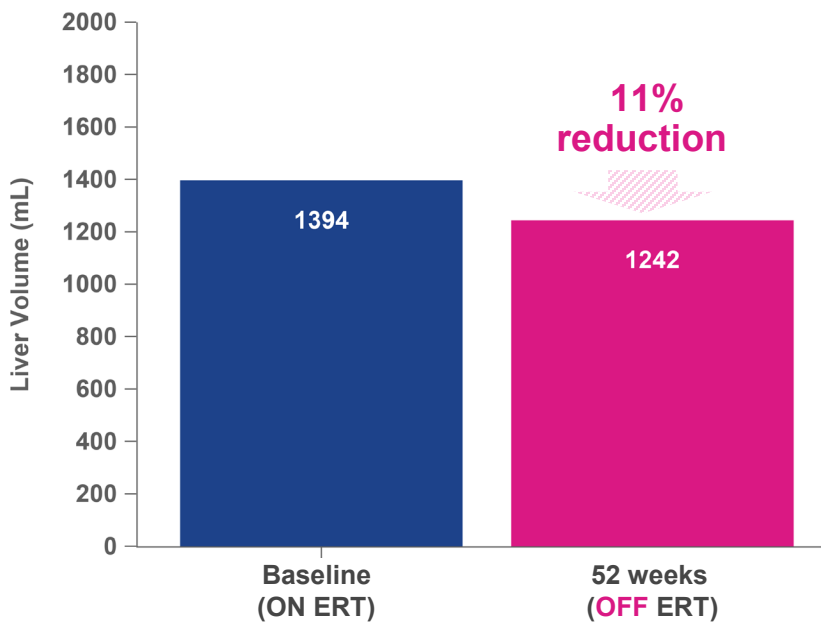
Decreased liver volume sustained out to 104 weeks for first patient

Guard1: PATIENT 1-3

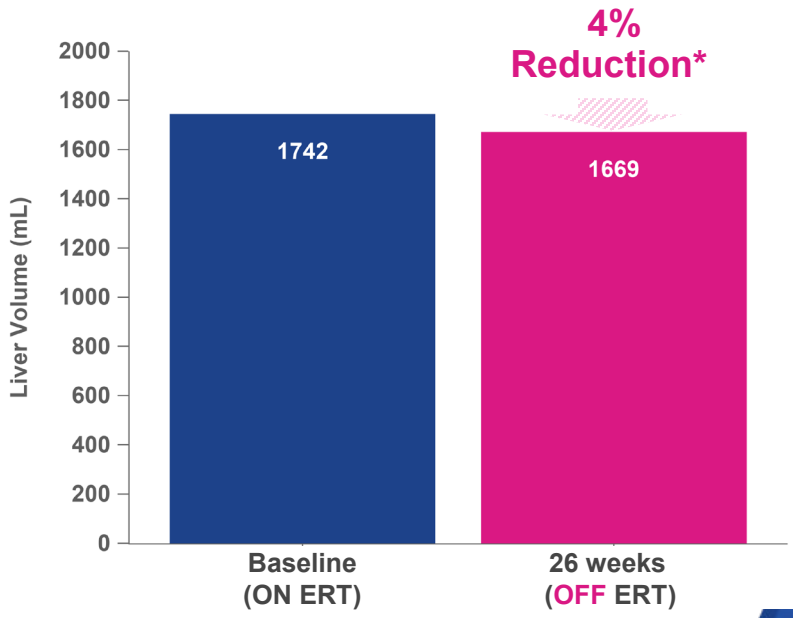
Patient 1



Patient 2



Patient 3



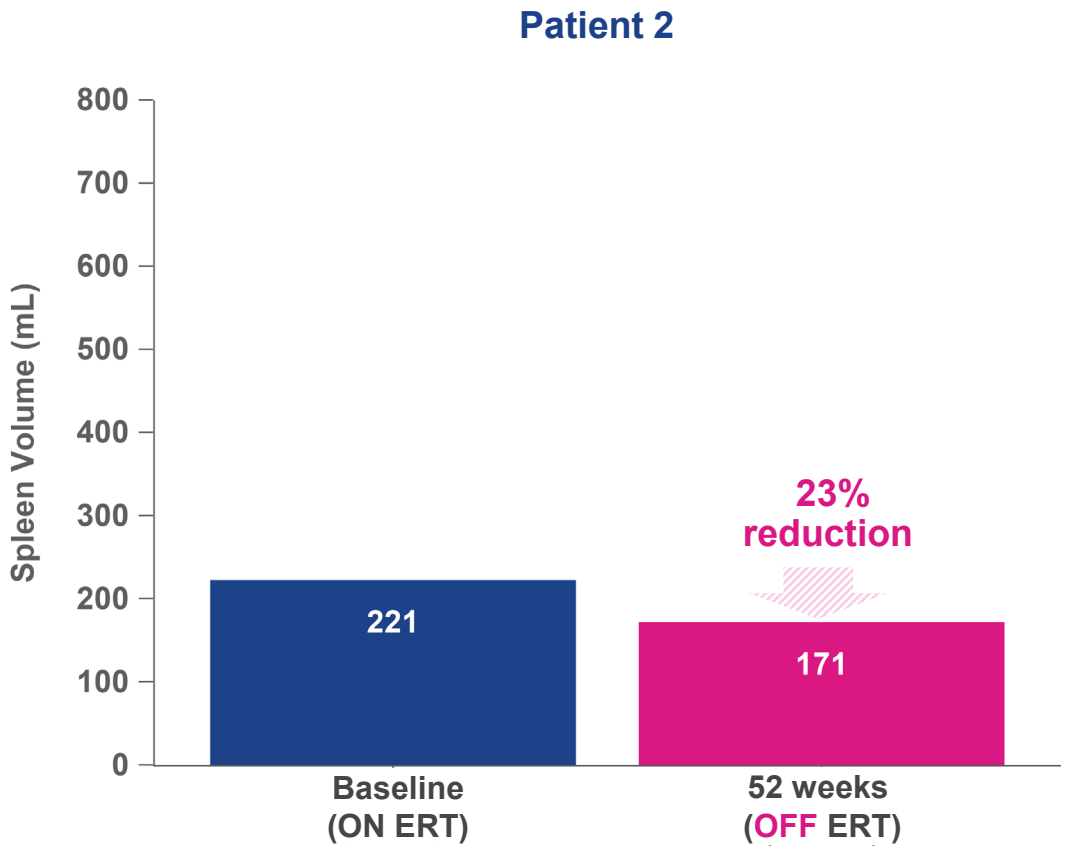
AVROBIO

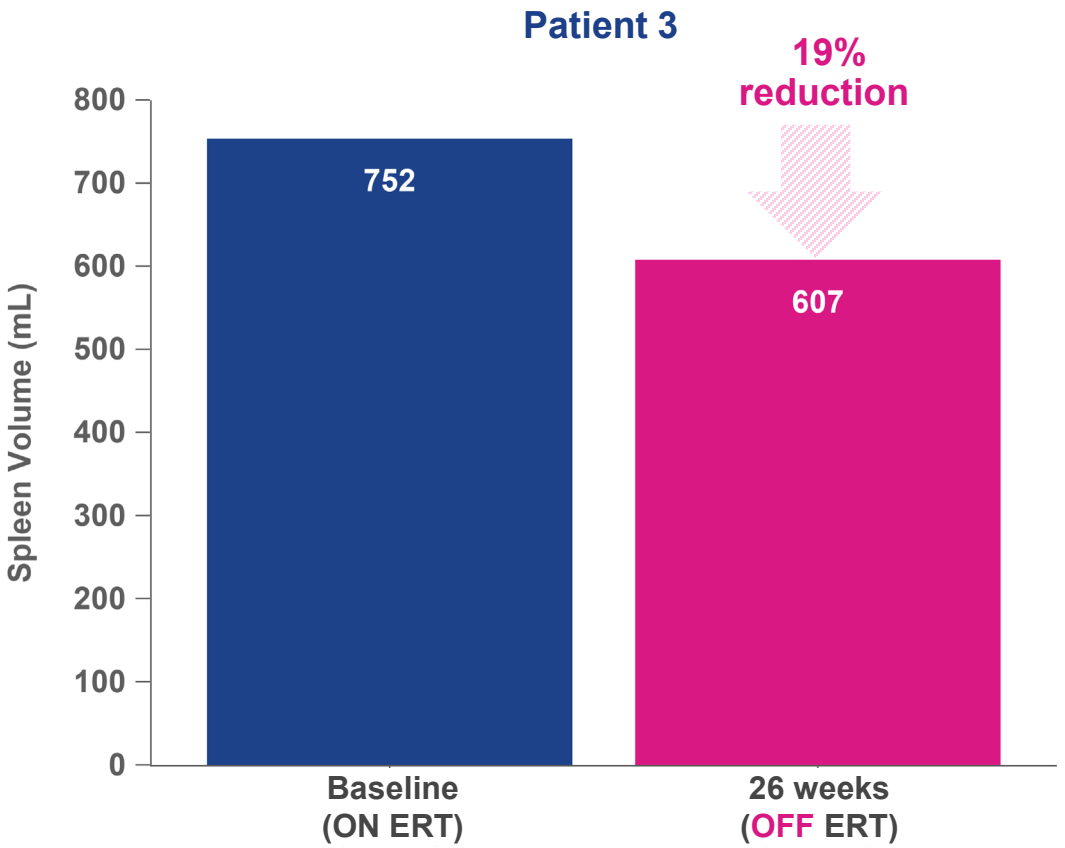
Data as of Nov. 22, 2022; Liver volume assessments from central reader; Patient 4 data not yet available; ERT=Enzyme replacement therapy; ≥10% reduction in liver volume is considered clinically meaningful per Taliglucerase alfa PI (product insert); Taliglucerase alfa approval - FDA Clinical and Statistical Review Imiglucerase (Cerezyme®) as SOC - PB-06-002 - switch study to Taliglucerase alfa;* Patient 3 liver volume reduction not clinically significant at 24 weeks

Clinically meaningful reduction in spleen below ERT baseline

Decreased spleen volume sustained out to 52 weeks for first patient

Guard1: PATIENT 2-3





Data as of Nov. 22, 2022; Patient 1 had spleen removed as child; Patient 4 data not yet available; ERT=enzyme replacement therapy; ≥20% reduction in spleen volume is considered clinically meaningful per Taliglucerase alfa PI (product insert); Taliglucerase alfa approval - FDA Clinical and Statistical Review Imiglucerase (Cerezyme®) as SOC - PB-06-002 - switch study to Taliglucerase alfa

Hemoglobin levels, platelets counts remain in normal range

Guard1: PATIENT 1-4

Data as of Nov. 22, 2022. Platelet count data beyond 60 weeks in process and not available as of cut-off date

No adverse events related to AVR-RD-02 drug product

Guard1: PATIENTS 1-4

DATA AS OF SEPT. 27, 2022

0 SAEs or AEs related to AVR-RD-02 drug product

All AEs and SAEs related* to:

- Myeloablative conditioning
- Drugs mandated by protocol or study procedures
- Underlying disease
- Pre-existing conditions

* AEs/SAEs as determined by investigator. Of the non-AVR-RD-02 drug product AEs/SAEs observed, 71 are AEs and 2 are SAEs, including anemia, leukopenia, neutropenia, thrombocytopenia, eye pain, decreased appetite, dehydration, headache, hypophosphatemia, amenorrhea (unresolved and ongoing as of safety database cut date). AVR-RD-02 has not been approved by FDA or by any other regulatory body and its safety and efficacy has not been established; SAE=serious adverse event; AE=adverse event

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- Recent advances in vector safety – Azadeh Golipour, Ph.D., AVROBIO

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AVROBIO

First pediatric patient with GD3 dosed

Named Patient

AVR-RD-02

Manchester University NHS Foundation Trust, UK

Patient

- 12-year-old male with GD3
- Diagnosed at 10 months –lymphadenopathy; hepatosplenomegaly
- Commenced ERT at 17 months
- Seizures developed age 10 years
- Biomarkers and clinical signs of Gaucher disease have never normalized despite maximal multimodal therapies

Primary disease complications

Primary disease complications:

Mesenteric lymphadenopathy

- Protein-losing enteropathy
- Commenced compassionate use SRT at 4.5 years

Neurology

- Saccadic eye movement defect
- Intellectual impairment (FSIQ 66 – Low)
- Seizures (2 x antiepileptic medications)
- Modified Severity Scoring Tool*: 1.5-12.5 (2016-2021)

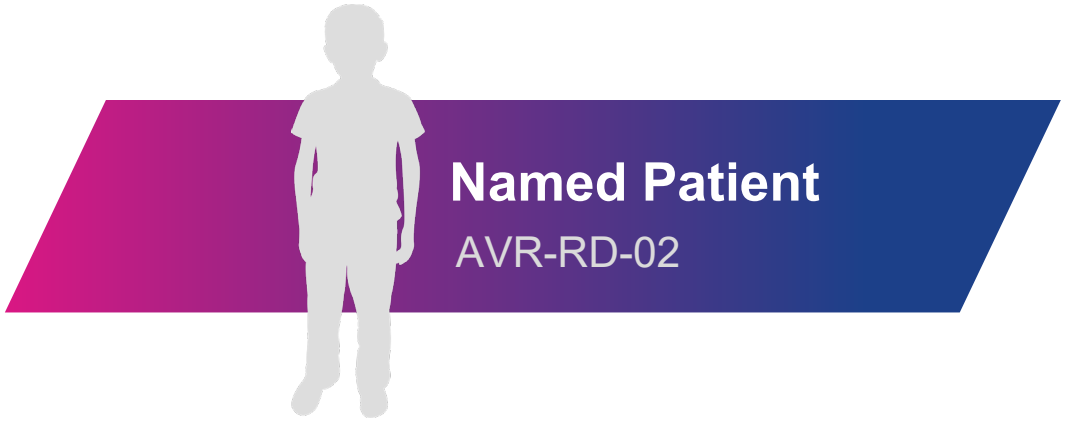
ERT=Enzyme replacement therapy; SRT=Substrate reduction therapy; AEs=Adverse events, FSIQ=Full-scale intelligence quotient; Bu90=Cumulative busulfan AUC of 90mg.hr/L; GT=Gene therapy; GD3=Gaucher disease type 3

"Having a child with Gaucher type 3 disease can, at times, feel hopeless and helpless. Our son was on ERT and developed seizures and protein-losing enteropathy (PLE) which required additional steroids and medications. I was always worried about the long-term use of the steroids specifically as he is still growing. The process to receive his medications was overwhelming and time consuming.

He was declining cognitively, and he developed seizures that kept getting worse despite anti-epileptic medications. Our son's cognitive decline and seizures were very scary and devastating to all of us, and I was looking for new treatment options online when I found gene therapy. We finally had a glimpse of hope."

Parent of Named Patient

HSC gene therapy well tolerated to date



- Age at treatment: 11 years
- Underwent mobilization and apheresis of HSCs which were then transduced *ex-vivo* with LV-containing *GBA* gene to produce AVR-RD-02 drug product
- Received conditioning with busulfan (Bu90-TCI) which was uncomplicated
- Engraftment achieved at Day 9 (neutrophils > 1× 109/L and platelets > 50 × 109/L)
- Required no blood products
- No AEs related to drug product
- Minimal AEs of low grade/severity
    - Single episode of febrile neutropenia which was culture negative and resolved within 48 hours without sequalae

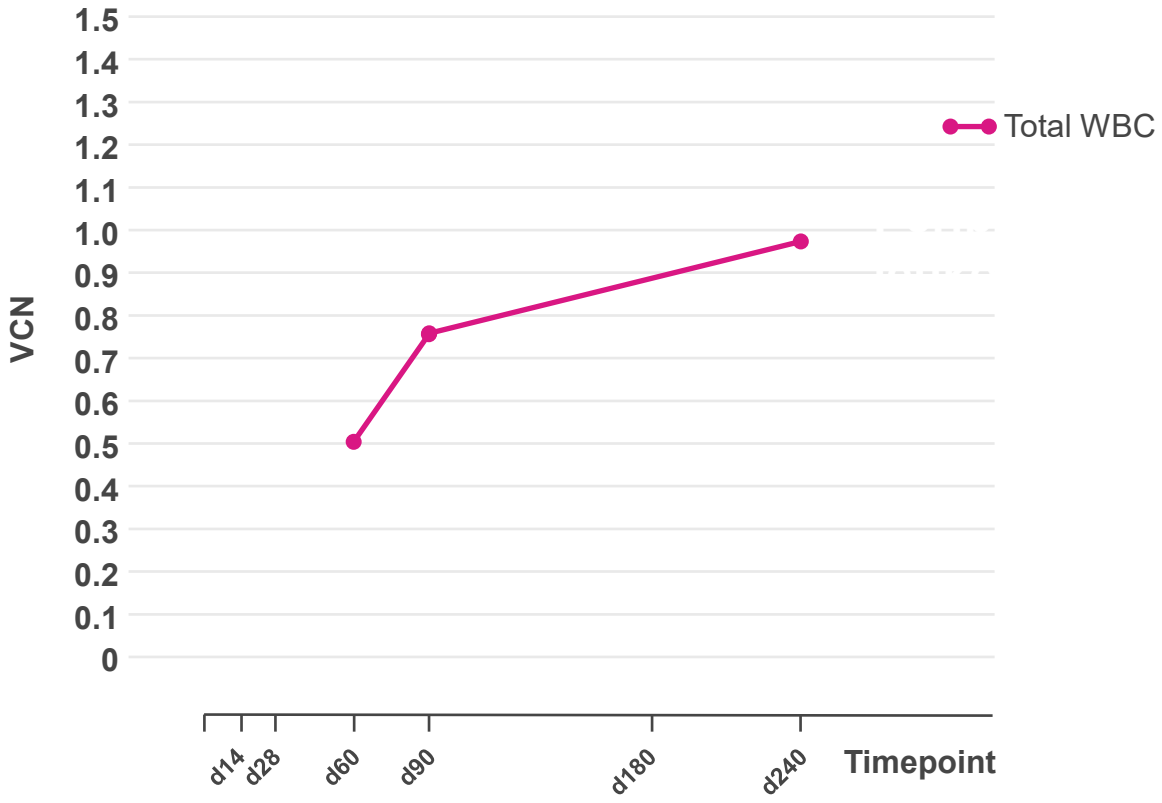
Data as of June 2022; HSC=Hematopoietic stem cell; AEs=Adverse events, Bu90=Cumulative busulfan AUC of 90mg.hr/L; GT=Gene therapy; GD3=Gaucher disease type 3

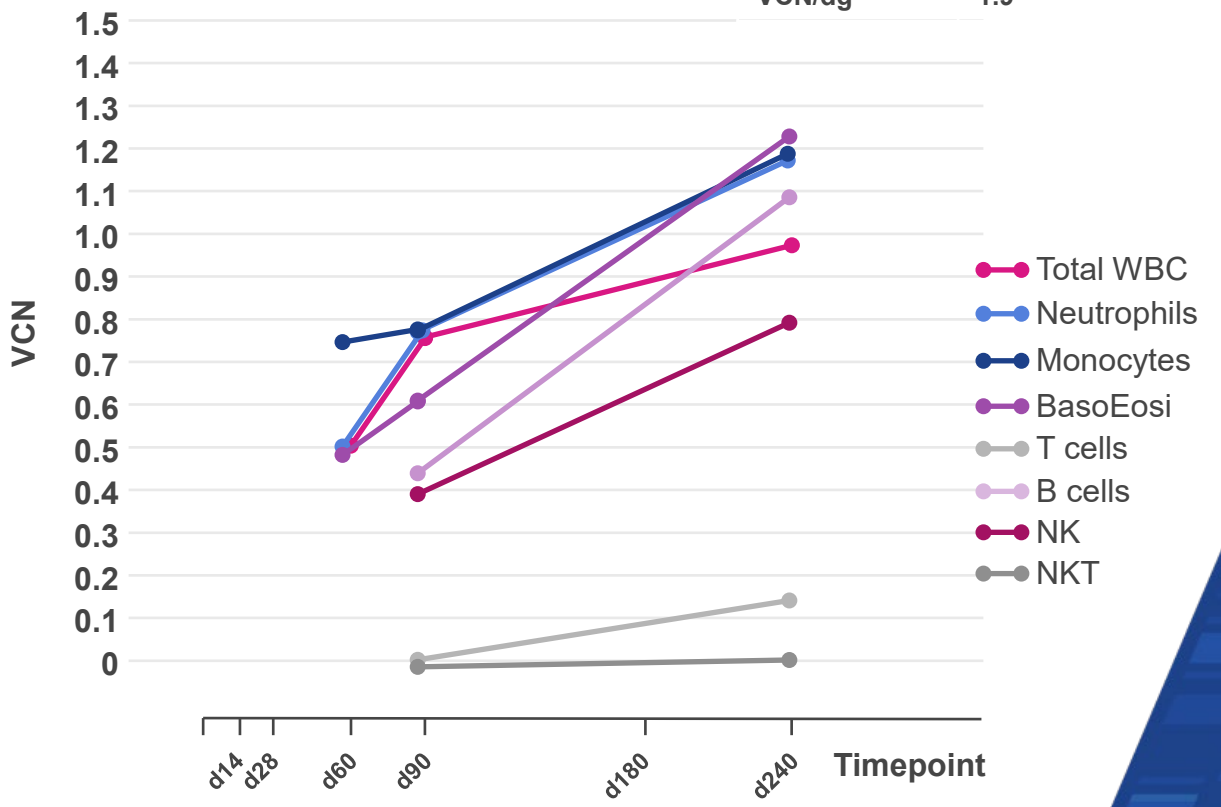
VCN trending as expected, indicates sustained engraftment

GD3: Named Patient

Drug product characteristics	
Total CD34+ cell dose	14.3x10^6 cells/kg
VCN/dg*	1.9

Peripheral blood leukocytes

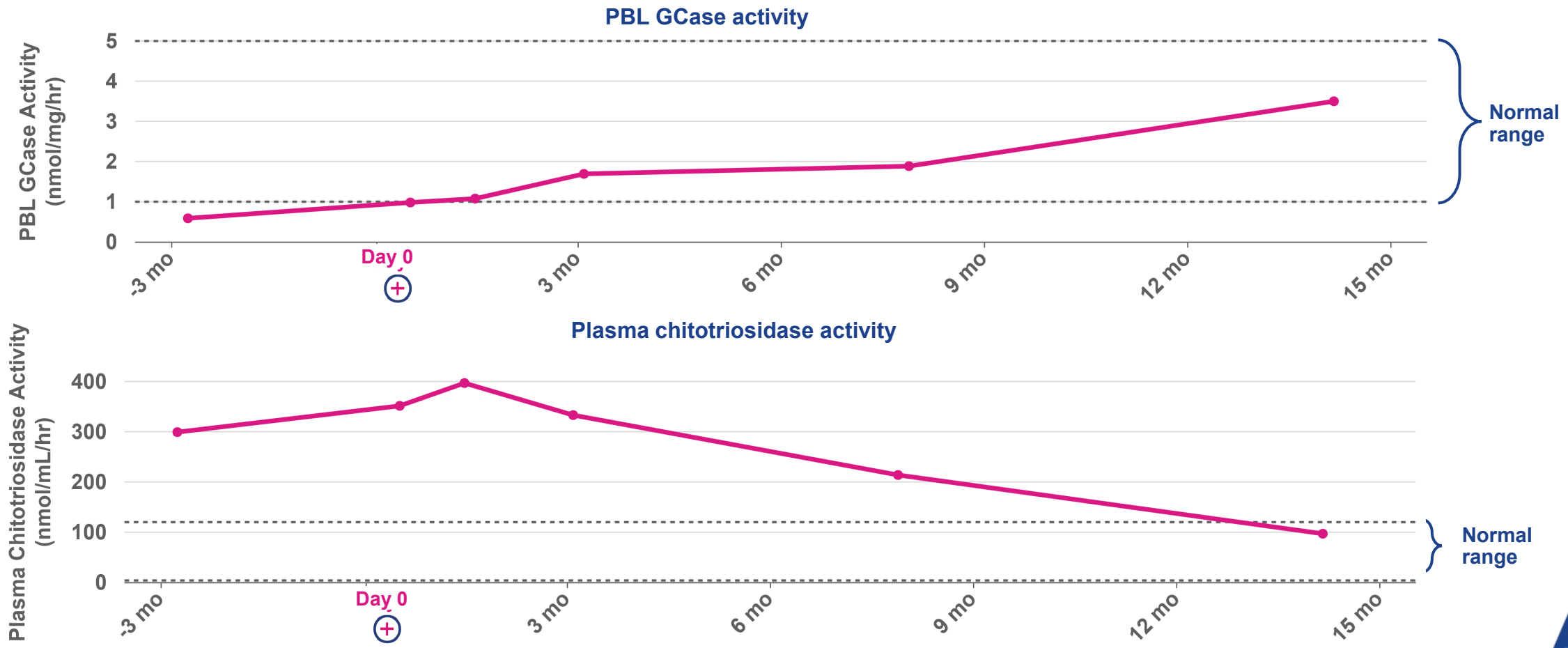




Data as of June 2022; AVROBIO Translational Research Group analysis; *Average of two VCN/transduced cell measures across 2 DPs; VCN=vector copy number; dg=Diploid genomes; d=Day

Normalization of chitotriosidase activity and sustained increase in PBL GCase

GD3: Named Patient



Data as of June 2022; lasma chitotriosidase activity (nmol/mL/hr) normal range: 4 nmol/mL/hr to 120 nmol/mL/hr.; PBL Gcase (nmol/mg/hr) normal range for non-Gaucher healthy individual: 1.0 nmol/mh/hr to 5.0 nmol/mg/hr.; The patient received treatment with AVR-RD-02 on Day 1; ERT = enzyme replacement therapy; GCase = β-glucocerebrosidase; mo=Month; PBL = Peripheral blood leukocytes.

Increase in albumin levels post treatment reflects improvement in lymphadenopathy and enteropathy

Previously refractory to maximal quadruple medical therapy

GD3: Named Patient

Timepoint (post infusion)	Albumin (g/L)
Baseline	15
Month 1	18
Month 2	18
Month 2	16
Month 3	19
Month 8	20

In the 6 years prior to gene therapy this patient never achieved an albumin greater than 18g/L, despite maximal and multimodal medical therapy

Data as of June 2022; Albumin reference range: 30-45g/L

Biomarkers normalized 15 months post gene therapy

GD3: Named Patient

DATA AS OF JUNE, 2022

Patient remains OFF ERT, SRT, enteral steroids, dietary restrictions and intermittent albumin infusions

- Normalized peripheral GCase enzyme activity and plasma chitotriosidase (ERT and SRT free)
- Lymphadenopathy – reduction on MRI, with highest albumin levels achieved in parallel with stopping enteropathy-oriented therapy
- MRI brain – no new lesions post-gene therapy when previously they were developing rapidly
- No clinically detectable change in neurological status (mSST)
- No new neurological manifestations post gene therapy
- No adverse events related to AVR-RD-02 drug product
  - Reported AEs and SAEs consistent with myeloablative conditioning, drugs mandated by protocol or study procedures, underlying disease or pre-existing conditions

AVROBIO

GD3=Gaucher disease type 3; GCase=β-Glucocerebrosidase, ERT=Enzyme replacement therapy; SRT=Substrate reduction therapy; MRI=Magnetic resonance imaging; mSST=Modified severity scoring tool

“Following gene therapy, we have seen real changes in our life and our son's life. The first few weeks were a bit rough in terms of mucosal inflammation, hair loss and skin changes, but overall, he appeared to respond to the treatment very well. He is off ERT, steroids and SRT completely, with no return of PLE symptoms, such as edema and GI distress.

He still has seizures but no further change in cognitive abilities. My son now is sleeping throughout the night, while he used to wake up often.

Our family gained freedom as we are no longer tied to a challenging medication schedule and many hospital visits.”

Parent of Named Patient

Today's agenda

What if one gene could change your life?: The *GBA* gene and Gaucher disease

- Welcome and opening remarks – Geoff MacKay, AVROBIO
- Arianna and Veronica's story: Living with Gaucher disease type 3
- The role of *GBA* in Gaucher Disease – Timothy Cox, M.D., MAE, FRCP, FMedSci, University of Cambridge, UK

Fulfilling the one-gene promise: AVROBIO's Gaucher disease program

- Gaucher disease type 1 data – Essra Ridha, M.D., MRCP, FFPM, AVROBIO
- Gaucher disease type 3 data – Rob Wynn, M.D. (Camb), MB BChir, MRCP, FRCPath, Royal Manchester Children's Hospital, and Simon Jones, M.D., BSc, MRCPCH, Manchester Centre for Genomic Medicine at Saint Mary's Hospital, UK

Paving a clinical path: AVROBIO's strategy for advancing AVR-RD-02

- Development and design of clinical trials for Gaucher disease – Essra Ridha, M.D., MRCP, FFPM, AVROBIO

Delivering for patients: CMC and analytics to execute on the one-gene promise

- Deploying the plato® advantage – Azadeh Golipour, Ph.D., AVROBIO
- Recent advances in vector safety – Azadeh Golipour, Ph.D., AVROBIO

Closing remarks and Q&A

AVROBIO

Development and design of clinical trials for Gaucher disease

Key takeaways

- Pursue one global Phase 2/3 trial for GD3 following positive feedback from FDA and MHRA
- Clinical development approach intends to use combined data set for GD1 and GD3 based on common underlying pathology of disease

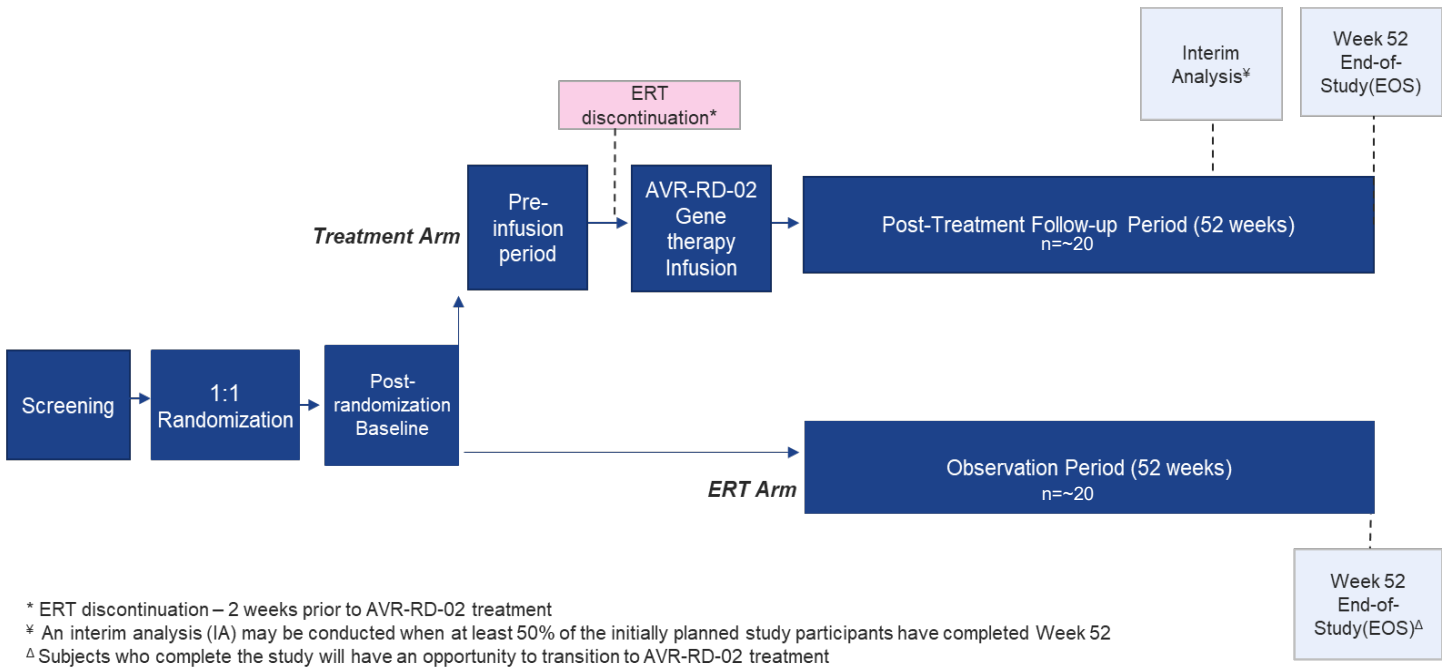
Arianna living with Gaucher disease type 3

AVROBIO

Planned GD3 Phase 2/3 registrational clinical trial design

- First RCT in HSC gene therapy
- Open-label, parallel-arm, randomized controlled, pediatric Phase 2/3 study evaluating efficacy and safety of AVR-RD-02

GD3 study design



* ERT discontinuation – 2 weeks prior to AVR-RD-02 treatment
¥ An interim analysis (IA) may be conducted when at least 50% of the initially planned study participants have completed Week 52
Δ Subjects who complete the study will have an opportunity to transition to AVR-RD-02 treatment

Primary efficacy endpoint – Multi-domain endpoint

- Primary endpoint includes:
  1. Scale for the assessment and rating of ataxia (SARA)
  2. Diffusing capacity of the lung for carbon monoxide (DLCO)
  3. Liver volume
  4. Spleen volume
- Key secondary endpoint: Lyso-Gb1 level in CSF
- Change from Baseline to Week 52 (length TBC) in multi-domain endpoint
- Primary inference based on treatment comparison at Week 52

Regulatory alignment based on guidance received during MHRA advice meeting and FDA type C meeting; CTA and IND amendments to follow in 2023; Multi-component endpoint: Weighting on liver and spleen endpoints and 52 weeks trial length subject to regulatory alignment; GT=Gene therapy; LTFU=Long term follow-up; pts=Patients; CSF=Cerebrospinal fluid

GD3 Phase 2/3 clinical trial recruitment strategy

Strong interest anticipated given high unmet need and data generated to date

Education to increase awareness among global patient advocacy groups and other stakeholders

- **Plan 8-12 trial sites in U.S., EU and U.K.**
- **Includes GD treatment centers, satellite centers and referral centers**

Digital advertising to increase awareness

AVROBIO

GD3 clinical development strategy is substantially de-risked

Strong GD preclinical and clinical data package

Input from FDA Type C and MHRA Scientific Advice meetings in fall 2022

Initial NICE feedback

AVR-RD-02 regulatory designations: RPDD; Fast Track; ODD (US and EU); ILAP (UK)

AVROBIO

NICE= National Institute for Health and Care Excellence (UK)

Gaucher disease clinical development approach intends to use combined data set for GD1 and GD3

Intend to broaden applicability for all Gaucher disease based on common underlying pathophysiology

GD3 Phase 2/3	GD1 Phase 1/2	Combined data set
RCT to be initiated in 2023 **n= ~20:20** **Submit BLA upon study completion**	**Within: ongoing patient control trial** • ERT-switch • ERT-naïve • Splenectomized and non-splenectomized patients **n= ~12 to 16** (6 enrolled)	**n = ~52-56 patients** • Efficacy data • Durability data • Safety data

RCT=Randomized controlled clinical trial; BLA=Biologics license application; ERT=Enzyme replacement therapy

Gaucher disease - AVR-RD-02

Anticipated next steps

- Initiate global GD3 registrational trial in 2H 2023
- Complete GD1 Phase 1/2 patient enrollment in YE 2023

GD3=Gaucher disease type 3; GD1=Gaucher disease type 1

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Closing remarks and Q&A

AVROBIO

plato®

AVROBIO's platform for global gene therapy commercialization and pipeline expansion

- **Reinvents manufacturing best practices**
- **Redefines safety best practices**

Photo depicts multiple Miltenyi Biotec Prodigy® units in a cleanroom; Photo courtesy of Miltenyi Biotec

Deploying the plato® advantage

Key takeaways

- Late-stage ready with no major CMC changes anticipated
- Scalable to support commercialization globally
- Designed to reduce COGs

Arianna living with Gaucher disease type 3

AVROBIO

Path through BLA is well understood

Oct 20, 2022

- Positive FDA Type C meeting on proposed GD3 Phase 2/3 Trial
- No major CMC changes anticipated for Phase 2/3 trial

Clarity on regulators' expectations regarding

- Potency assay
- Product release and characterization (LV and DP)
- Comparability
- Traceability
- Stability

AVROBIO has obtained feedback from multiple regulatory agencies and is working to incorporate it

- US
- Canada
- Japan
- Israel
- Brazil
- UK

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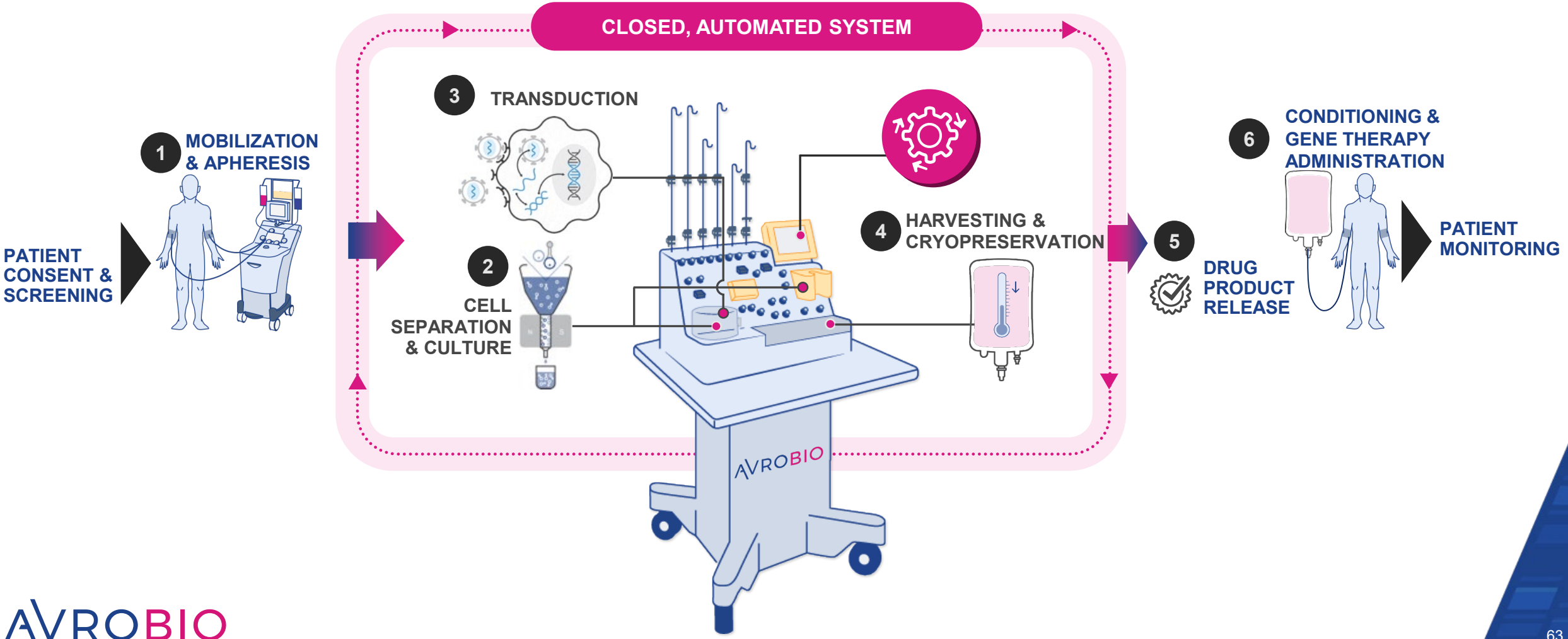
BLA=Biologics license application; LV=Lentiviral; DP=Drug product; FDA=Food and Drug Administration; CMC=Chemistry, manufacturing and controls

Unrivaled manufacturing platform for HSC gene therapy



Drug product manufacturing is automated

Enables consistency, product quality and transferability

Miltenyi Prodigy with
AVROBIO process algorithm

Automation designed to work across the pipeline

- Improves process consistency and product quality
- Enhanced transduction efficiency
- Reduces human error, inter-operator variability and training burden
- Enables easy technology transfer and scale out
- Drives COGs down

Closed system from apheresis to final drug product

- Reduces contamination risk
- Reduces clean room requirements (significant cost savings and increasing space options)
- Different disease products for different patients made in same room

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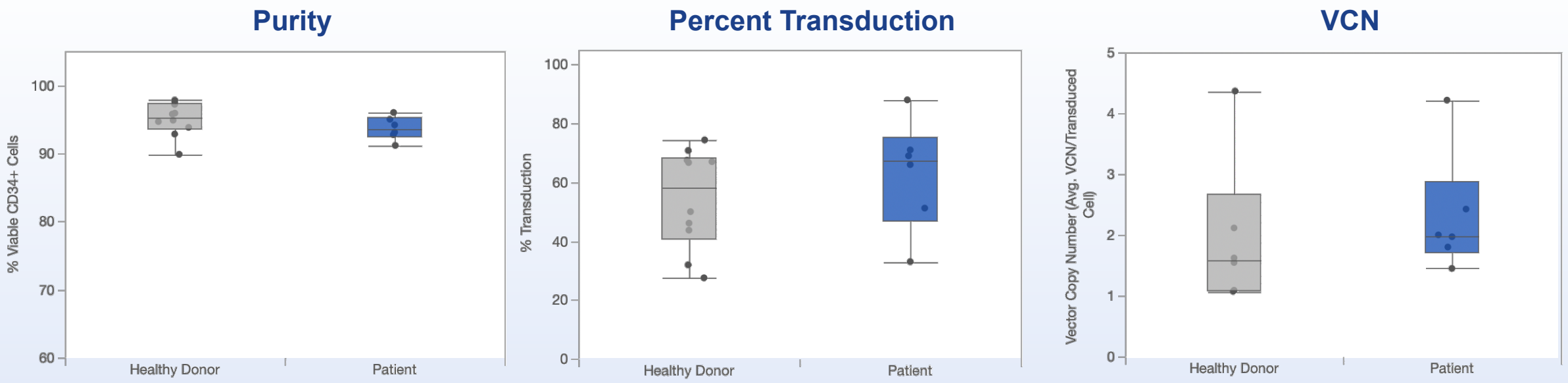
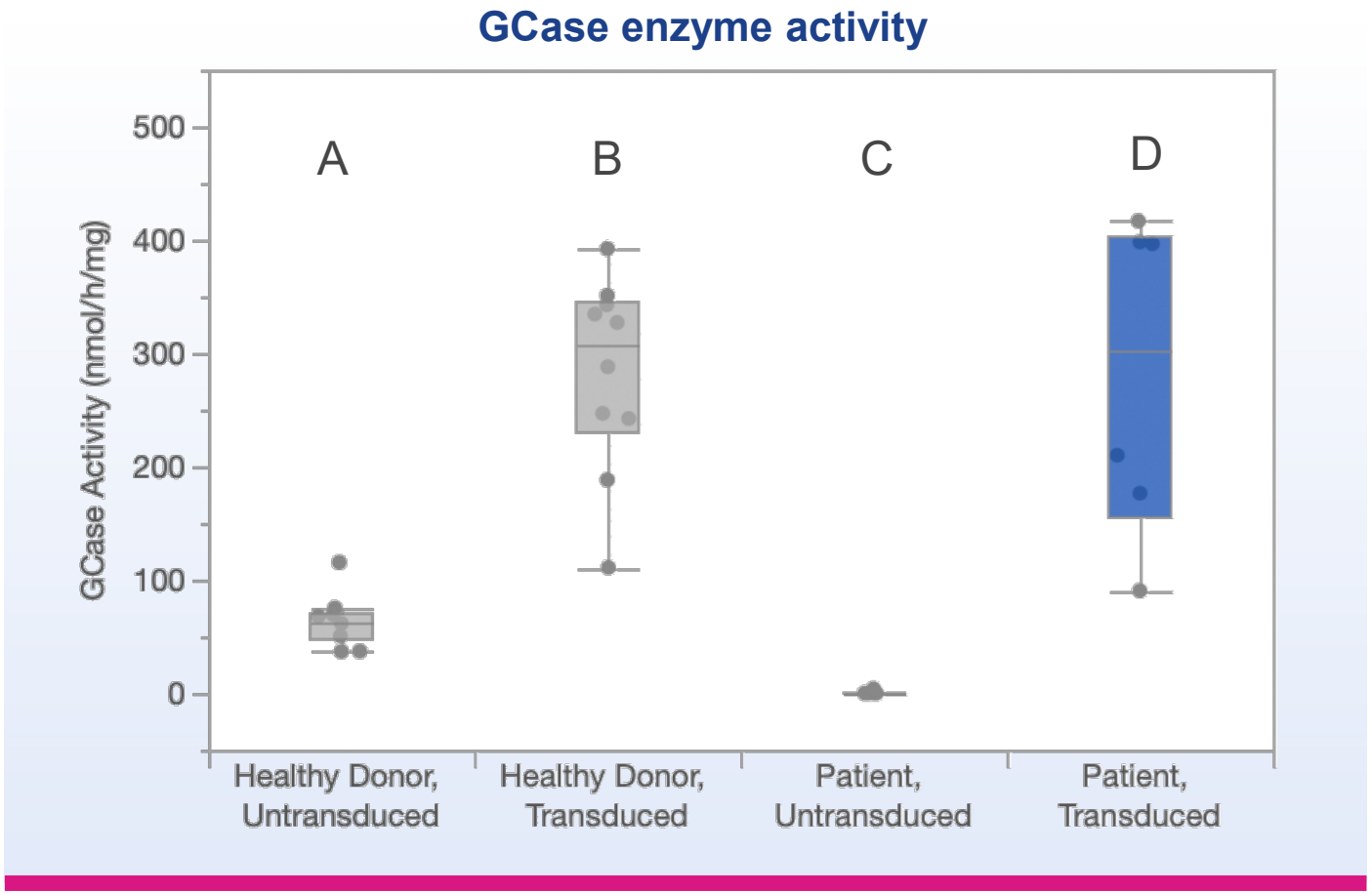
COGs=Cost of goods

Demonstrated manufacturing capability and consistency indicative of high-quality drug product



VCN=Vector copy number; DP=Drug product

Gaucher drug product GCase enzyme activity comparable to healthy donor cells



Commercial scale lentiviral vector manufacturing

Robust vector production platform for the pipeline

Biostat STR Bioreactor

Commercial scale

- 200L serum free, suspension culture
- 50 patient doses per batch
- Optimized process, including fill/finish
- Minimal lot to lot variability
- Validated analytics

Strong quality profile

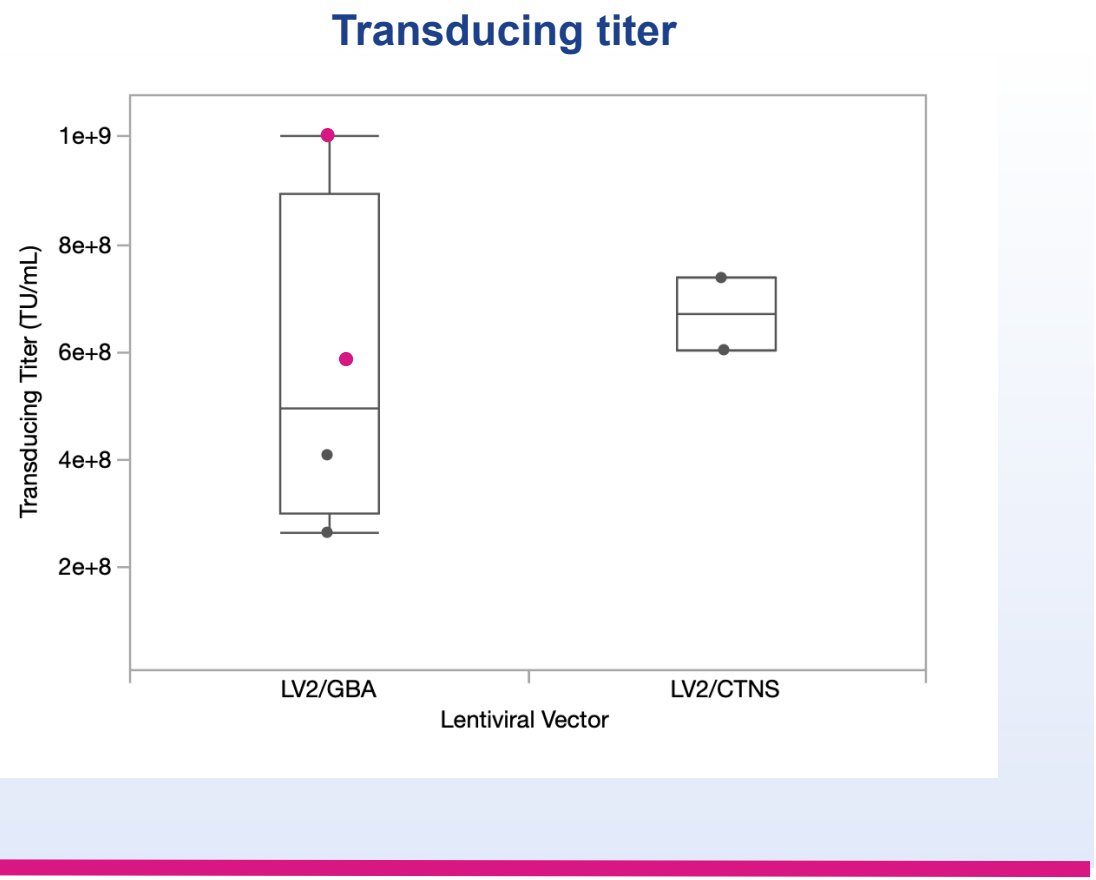
- Low impurities
- No “empty” capsids with lentiviral vectors

Consistent, high titer

AVROBIO

STR=Stirred tank bioreactor

Reliably high titers outperforming industry standards

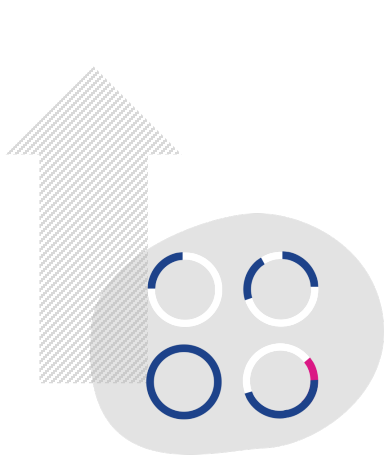


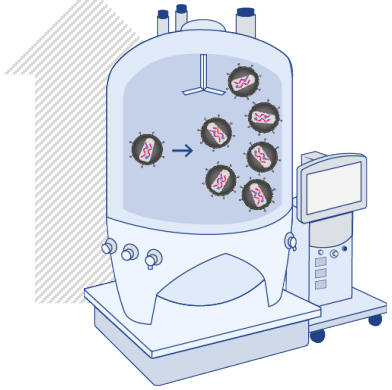
- Titer consistently above industry standard
- Higher titers mean fewer batches required to fulfill demand
- Manufacturing process applied across entire pipeline

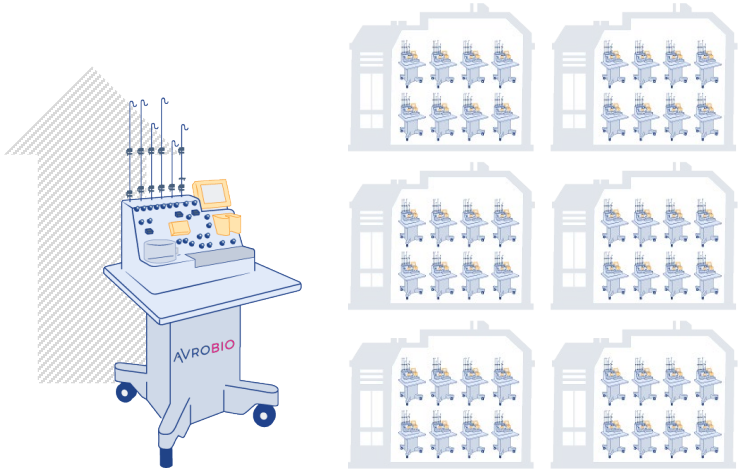
LV=Lentiviral; GBA=Beta-Glucosylceramidase; CTNS=Cystinosin, Lysosomal Cystine Transporter

Manufacturing platform is scalable

Common components and automation leveraged across manufacturing







OPTIMIZED VECTOR → **VECTOR SCALE UP** → **DRUG PRODUCT SCALE OUT**

Designed for safety, efficacy and manufacturability

Optimized plasmid concentration, transfection reagent concentration as well as packaging cell concentration for high titer vector production

State of the art, largest commercial scale vector production

Designed to achieve commercial demand through scale up. Vector can be manufactured at 200L scale, frozen, and stored for use in drug product production

Closed system automated platform

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

AVROBIO

Innovation drives scale

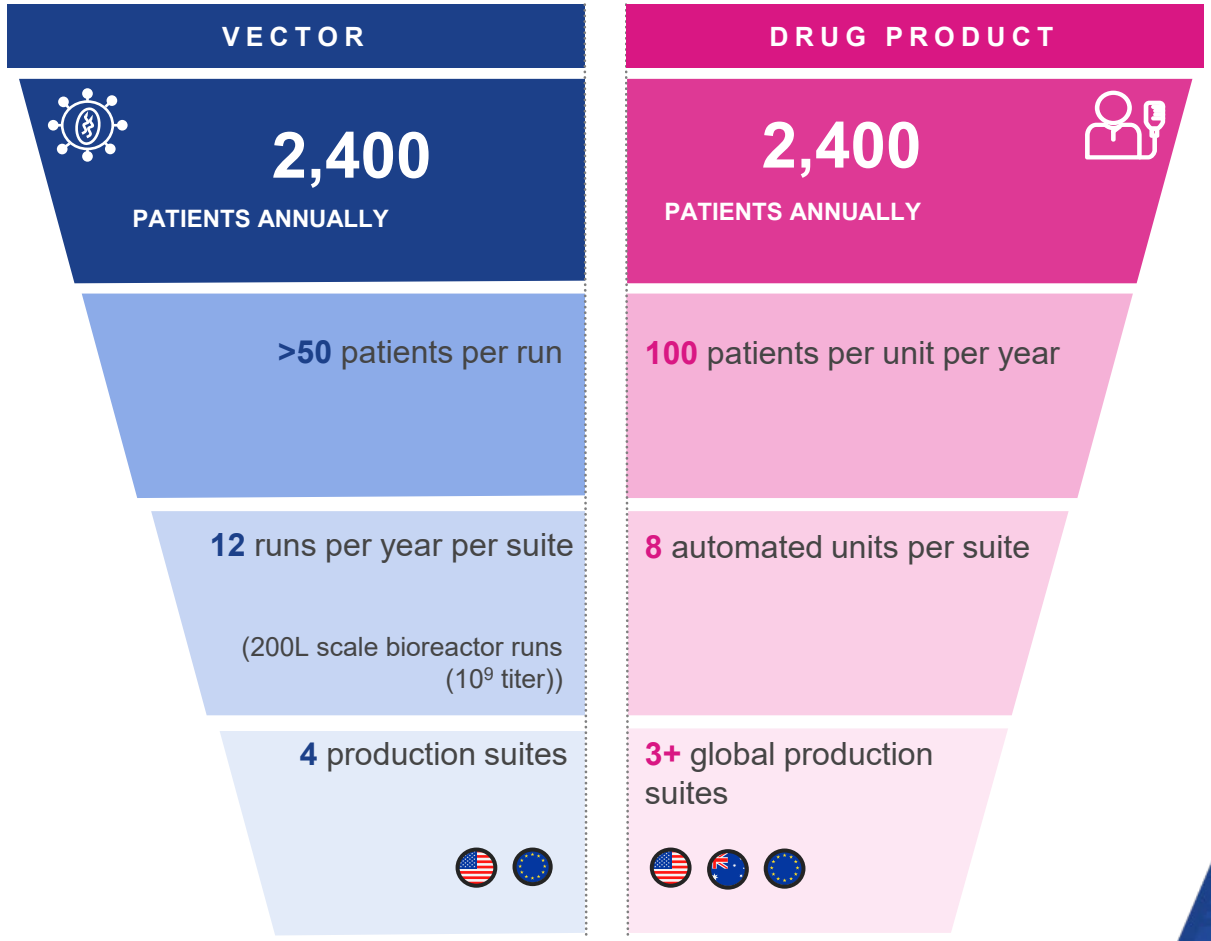
Transferability between production facilities established

Innovations:

Vector manufacturing
- 200L scale
- High titer
- 50 patients per single run

Drug product manufacturing
- Automated
- Closed
- Short process

This diagram is for illustrative purposes only



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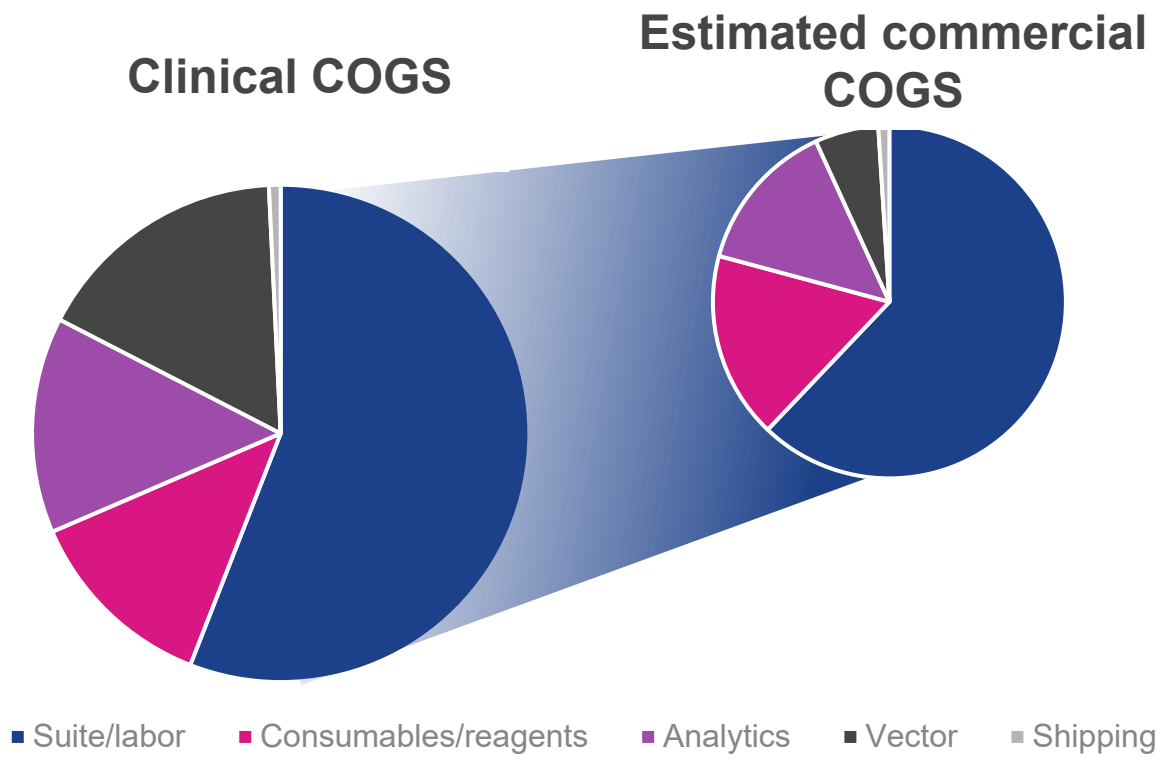
Attractive COGS profile

Estimated gross margin exceeds 90%



COGS breakdown

plato® designed to reduce COGs

- Economies of scale with plasmids and large-scale vector manufacturing can reduce material costs
- Low vector quantity required per patient due to high titer
- Automated, short manufacturing process reduces labor costs
- Closed system manufacturing reduces facility and overhead costs
- Next-generation, automated analytics can reduce QC labor and testing costs

AVROBIO

COG=Cost of goods, QC=Quality control

Strategic investment in technology laid foundation for our manufacturing platform

Manufacturing

Robust production platform

- Unrivalled 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

VCN=Vector copy number; LV-Lentiviral; COGs=Cost of goods

Recent Advances in Vector Safety

Key takeaways

- No reported cases of insertional oncogenesis in AVROBIO clinical trials
- No evidence of persistent dominant clonal expansion in any AVROBIO clinical trials
- AVROBIO used state-of-the-art vectors and assessed vector safety before entering clinic

Arianna living with Gaucher disease type 3

No reported cases of insertional oncogenesis across lentiviral HSC gene therapy programs outside of CALD

3 insertional oncogenic events	**0** insertional oncogenic events
LVV-MND-ABCD1 for CALD …	**All other gene therapies using lentiviral vectors …**
1 vector construct + indication	**16** vector constructs + indications
67 patients	**55** clinical trials
	314 patients

72nd Cellular, Tissue and Gene Therapies Advisory Committee June 9-10, 2022; Tucci *et al.*, 2022 (updated manually for the last two years with publicly available patient numbers from bluebird, Orchard Therapeutics, Rocket Pharma, and AVROBIO)
CALD=Cerebral adrenoleukodystrophy; LVV=Lentiviral vector

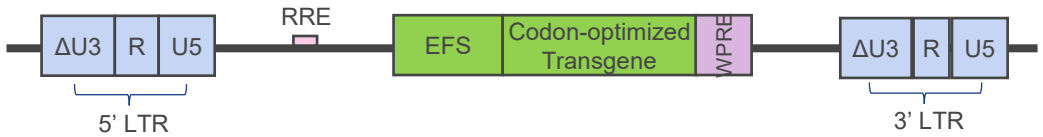
AVROBIO state-of-the-art vector

Designed with the highest safety standards and tested extensively

Vector design elements

- Replication incompetent
- SIN modified to abolish viral LTR promoter/enhancer activity
- EF1α/EFS nonviral promoter with greatly reduced enhancer activity
  - Used in at least 6 indications with 75 patients, out up to 10 years
- Kozak sequence to direct correct start of translation
- Codon optimization to optimize expression and remove cryptic splice sites
- WPRE
  - Increase transgene expression and reduce readthrough to neighboring genes
  - Modified to reduce potential toxicity of regulatory element caused by WHV X protein

AVROBIO's plato® vector



Tucci *et al.*, 2022; SIN=Self inactivated; LTR=Long terminal repeat; EFS=Factor 1alpha binding sequence; WPRE=Woodchuck Hepatitis Virus (WHP) posttranscriptional regulatory element

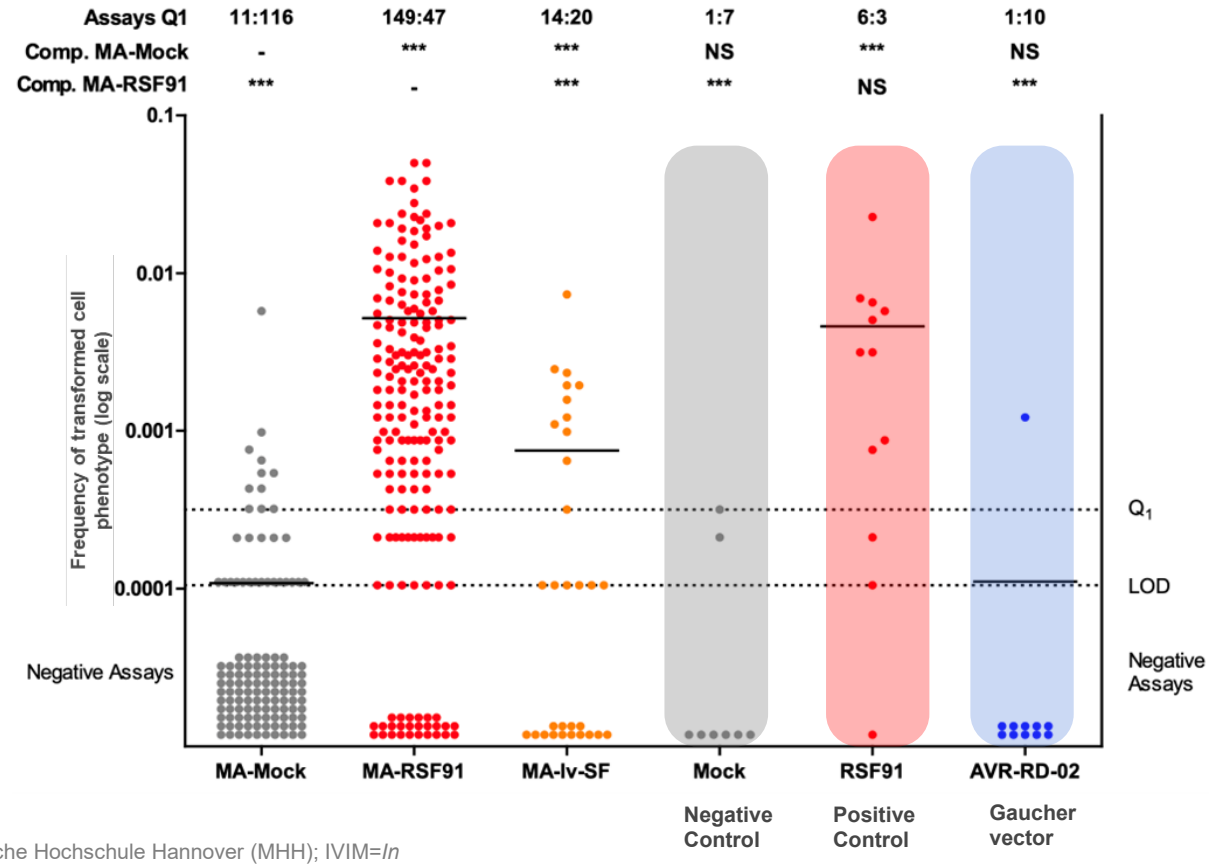
Favorable Gaucher vector safety profile via IVIM

Evaluated with IVIM before clinical use

Gaucher vector IVIM results

- No effects on cell proliferation
- No statistical difference compared to the non-transduced (Mock negative control)
- Significantly lower frequency of cellular transformation compared to gamma retroviral vector (RSF91 positive control)

Assessment of Gaucher vector



Data courtesy of Dr. Michael Rothe and Prof. Axel Schambach, Medizinische Hochschule Hannover (MHH); IVIM=*In vitro* immortalization; RSF 91=non-SIN gamma-retroviral vector

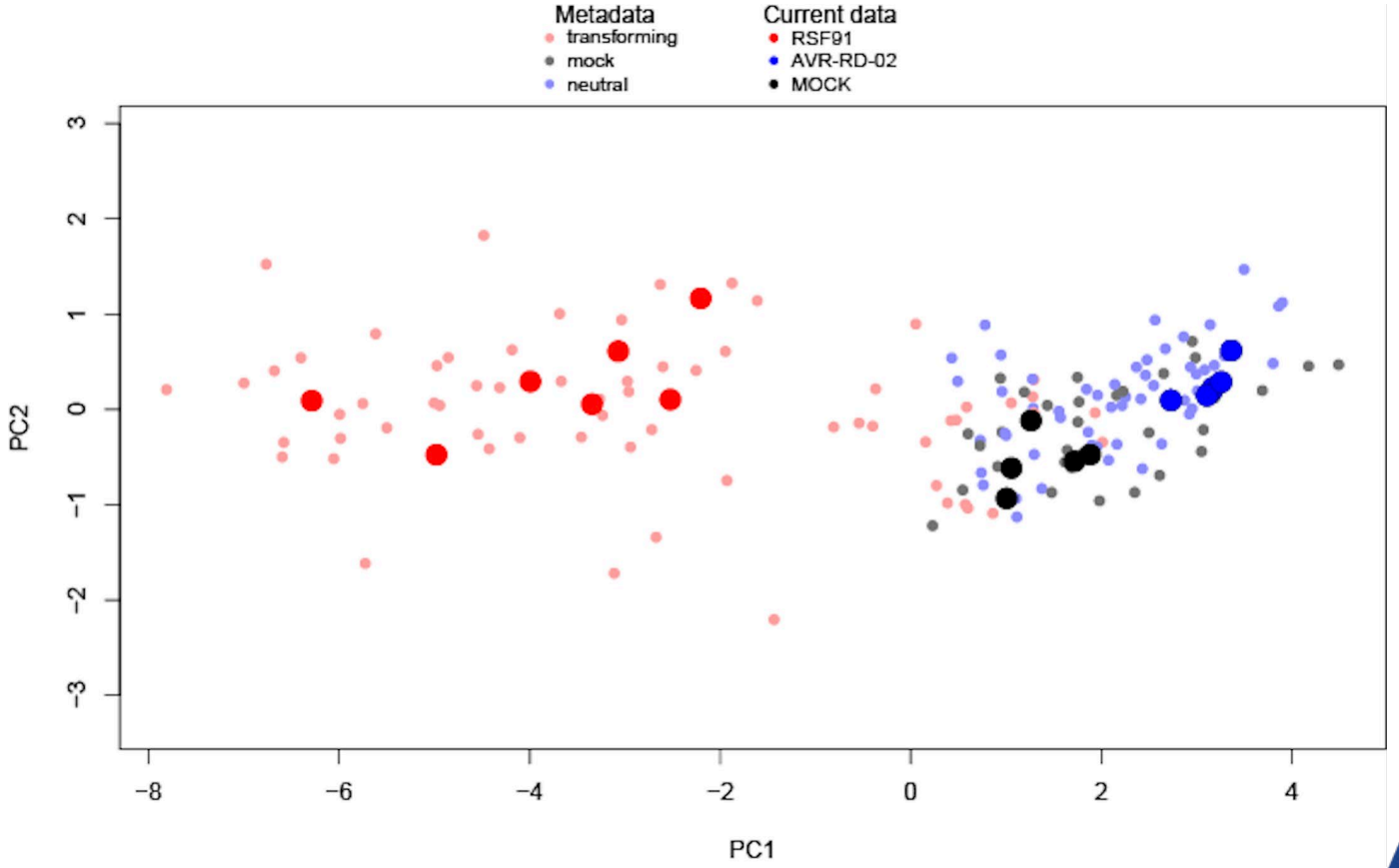
Favorable Gaucher vector safety profile via SAGA

Evaluated with SAGA before clinical use

Gaucher vector SAGA results

- Significantly lower risk to dysregulate a gene expression signature linked to vector-induced transformation compared to gamma retroviral vector (RSF91 positive control)

Assessment of Gaucher vector



principal component (PC) analysis

Data courtesy of Dr. Michael Rothe and Prof. Axel Schambach, Medizinische Hochschule Hannover (MHH); SAGA=Surrogate assay for genotoxicity assessment

Commitment to vector safety across platform

- No reported cases of insertional oncogenesis in AVROBIO clinical trials
- No evidence of persistent dominant clonal expansion in AVROBIO clinical trials
- Developed and used state-of-the-art vector designed with safety features
- Rigorously test using state-of-the-art vector safety assays to assess risk of insertional oncogenesis before entering clinic

AVROBIO

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- Deploying the plato® advantage – Azadeh Golipour, Ph.D., AVROBIO
- Recent advances in vector safety – Azadeh Golipour, Ph.D., AVROBIO

Closing remarks and Q&A

AVROBIO

Closing remarks

Arianna living with Gaucher disease type 3

Building a leading Gaucher disease program

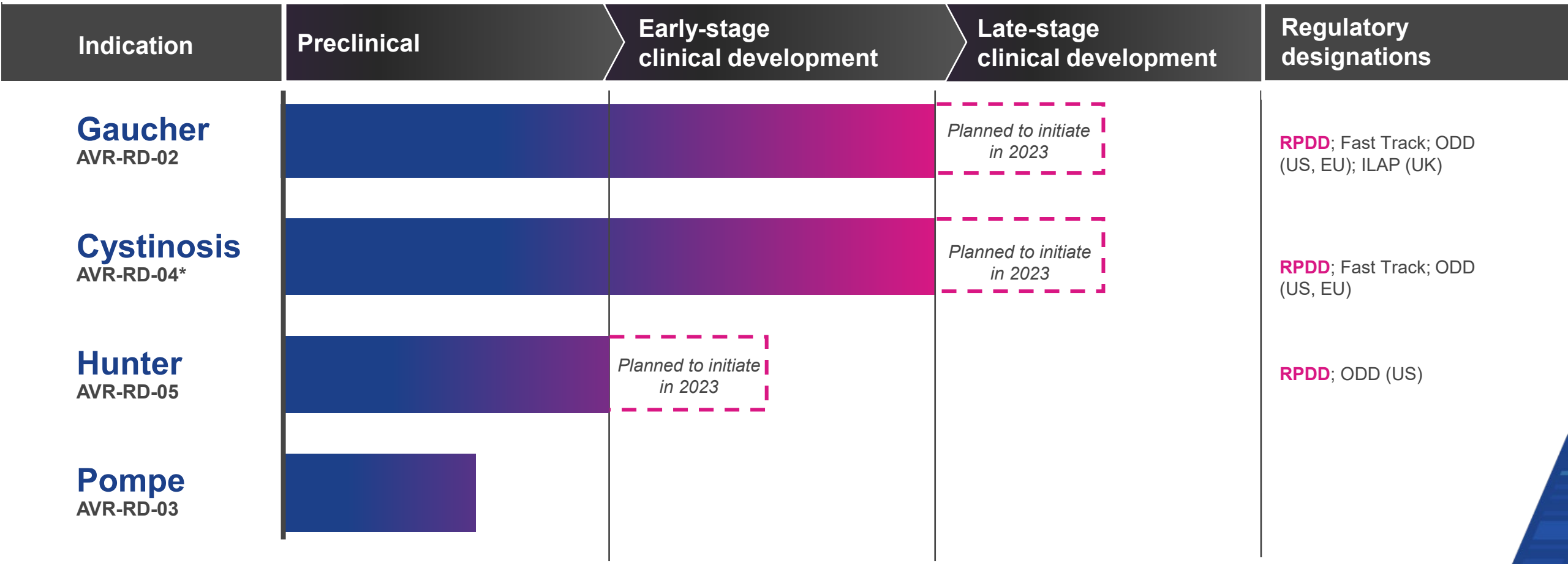
First mover advantage

Program targeting multi-billion dollar market opportunity

- AVROBIO transitioning into a late-stage company in 2023
- Key takeaways from today:
  - GD1 – expanding positive data set
  - GD3 – initial data with early signs of clinical activity
  - GD3 – pursue one global pediatric Phase 2/3 trial
  - Plan to utilize combined data set for GD1 and GD3 for Gaucher program development approach
- Manufacturing late-stage trial ready, no CMC changes anticipated
- Attractive commercial opportunity with large, pre-identified patient population

AVROBIO

AVROBIO entering late-stage development



Planned regulatory milestones subject to regulatory agency clearance; *Collaborator-sponsored Phase 1/2 clinical trial of AVR-RD-04 is funded in part by grants to UCSD from the California Institute for Regenerative Medicine (CIRM), Cystinosis Research Foundation (CRF), and National Institutes of Health (NIH); ILAP=Innovative Licensing and Access Pathway; ODD=Orphan drug designation; RPDD=Rare pediatric drug designation

Multiple billion-dollar markets

	High unmet need	First to initiate clinical trials	Strong premium price rationale	Substantial patient numbers	
	Relative to SOC	Gene therapy timing	5-year SoC cost per US patient[1]	Global[2]	Initial markets US, EU, JA[2]
Gaucher	↑ Very high for GD3 High for GD1 segments	1st	$2.3M	23,000	16,300
Cystinosis	↑ Very high	1st	$4.3M	3,500	1,600
Hunter	↑ Very high	1st HSC GT	$2.4M	2,000	1,400
Pompe	↑ Very high	Potential to be 1st HSC GT	$3.2M	15,000	9,600
				43,500	**28,900**

AVROBIO

1) WAC pricing from Redbook using standard dosing assumptions; Horizon's Procysbi oral therapy (delayed release cysteamine bitartrate) mid point between avg. adult and pediatric; 2) Market Research 2018 and 2019, excludes China and India; GD1=Gaucher disease type 1; GD3=Gaucher disease type 3; HSC GT=Hematopoietic stem cell gene therapy; SOC=Standard of care

Key anticipated 2023 milestones

Gaucher **AVR-RD-02**	Initiate Phase 2/3 clinical trial for GD3 in 2H 2023 Complete enrollment in Guard1 by year end 2023
Cystinosis **AVR-RD-04**	Engage with MHRA on clinical trial design in 1Q 2023 Initiate late-stage clinical trial activities in 2H 2023
Hunter **AVR-RD-05**	Dose first patient in collaborator-sponsored Phase 1/2 trial early 2023 Share initial patient data in 2H 2023

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FDA=Food and Drug Administration; 2H=Second Half; MHRA=Medicines and Healthcare products Regulatory Agency


THANK YOU

Appendix

Jaxon living with cystinosis

Cystinosis

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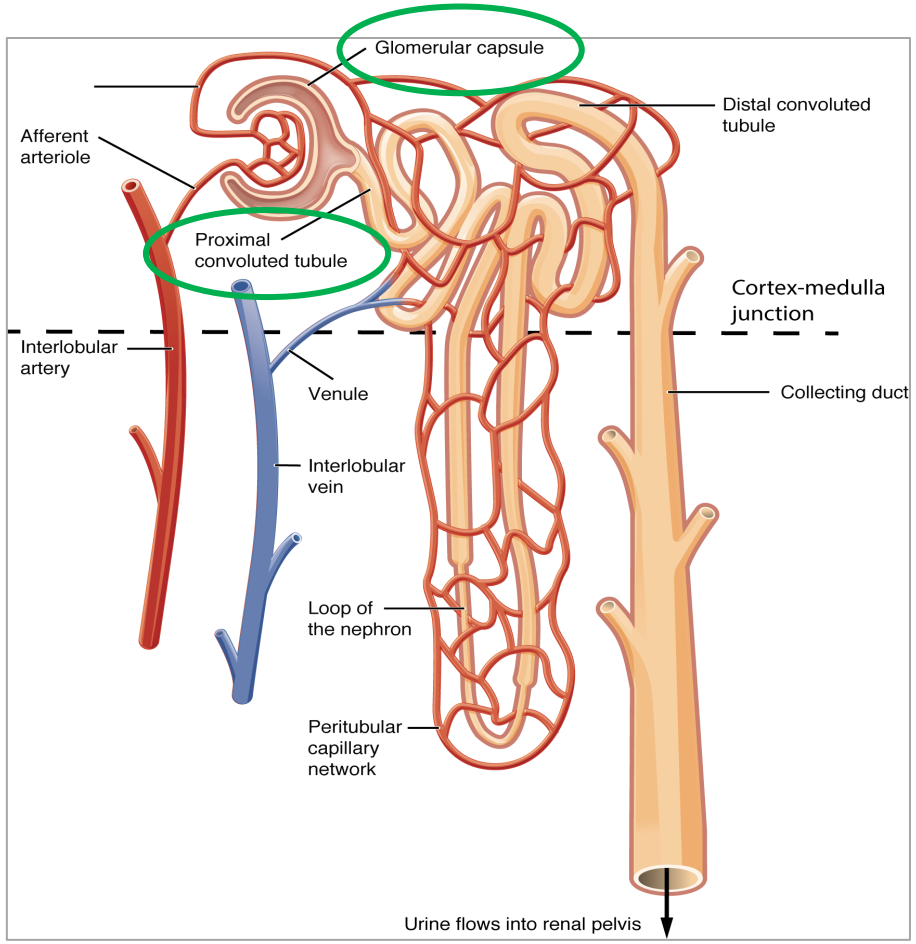
Jaxon living with cystinosis

Planned RFS endpoint captures complexity of disease

Potential to *reverse* RFS by providing functional cystinosin

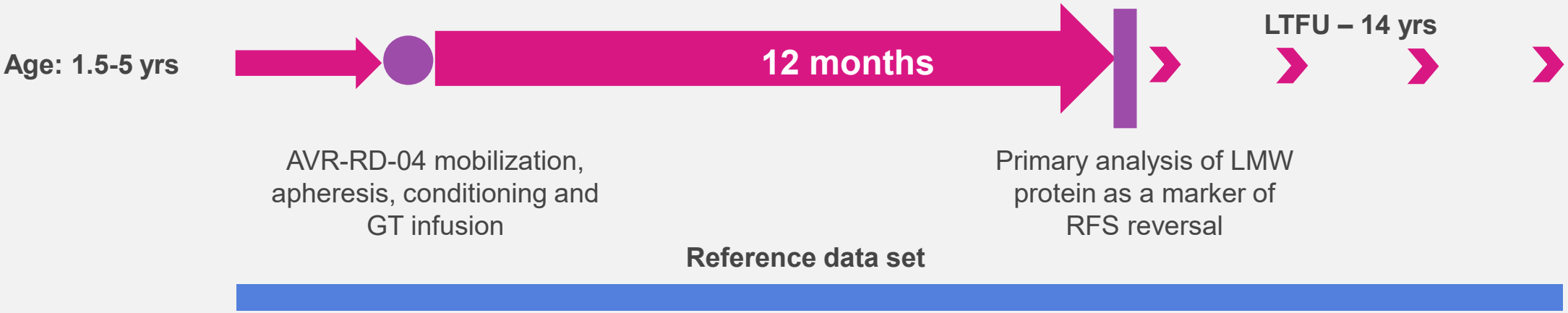
- RFS is hallmark of nephropathic cystinosis
  - Dysfunction of proximal tubules
  - Causes urinary losses of amino acids, LMW proteins and electrolytes
  - Cysteamine MOA does not address RFS
- Progressive loss of glomerular function leads to ESRD
  - Glomerulopathy manifests clinically with reductions in GFR
- Providing functional cystinosin reverses RFS and preserves renal function in CTNS -/- mice with syngeneic BM-derived stem cells
- AVR-RD-04 may partially or completely restore the proximal tubule physiology and *reverse* RFS



Syres 2009; Yeagy 2011, Gabriel 2017; RFS=Renal Fanconi Syndrome; LMW=Low molecular weight; ESRD=End-stage renal disease; BM=Bone marrow: MOA=Method of action; GFR=Glomerular filtration rate

Planned cystinosis Phase 1/2 clinical trial design

Single-arm trial designed to be registration-enabling, subject to regulatory alignment



PRIMARY EFFICACY ENDPOINT: Change from baseline to 12 months after DP administration in uptake of ^{99m}Tc-DMSA

TWO-STAGE CLINICAL STRATEGY:

- Pre-renal transplant population planned for initiation in 2H 2023
- Post-renal transplant population as second stage

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DP=Drug product; GT=Gene therapy; LMW=Low molecular weight