UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 7, 2022

AVROBIO, INC.

(Exact name of registrant as specified in its charter)

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

100 Technology Square
Sixth Floor
Cambridge, MA 02139
(Address of principal executive offices, including zip code)

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

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

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

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

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

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

Emerging growth company ☒

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

Item 7.01 Regulation FD Disclosure.

On December 7, 2022, AVROBIO, Inc. (the "Company") issued a press release titled "AVROBIO Announces New Positive Clinical Data and Outlines Clinical Development Plan Following Regulatory Discussions for its Gaucher Disease Gene Therapy." A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

On December 7, 2022, the Company updated its corporate presentation for use in meetings with investors, analysts and others. A copy of the slide presentation is filed as Exhibit 99.2 to this Current Report on Form 8-K.

The information in Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.1 and 99.2 attached hereto, shall not be deemed "filed" for purposes of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

99.1	AVROBIO, Inc. press release, dated December 7, 2022.
99.2	AVROBIO, Inc. slide presentation, dated December 7, 2022.
104	The cover page from this Current Report on Form 8-K, formatted in Inline XBRL.

SIGNATURES

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

AVROBIO, INC.

Date: December 7, 2022

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

Exhibit 99.1

AVROBIO Announces New Positive Clinical Data and Outlines Clinical Development Plan Following Regulatory Discussions for its Gaucher Disease Gene Therapy

New compelling clinical data from first-ever Gaucher disease type 3 (GD3) patient and four Gaucher disease type 1 (GD1) patients dosed with investigational AVR-RD-02

Data from first pediatric GD3 patient, the more severe, progressive form of Gaucher disease, show biochemical correction and improvement in major refractory element of disease 15 months post gene therapy

Data from first four adult patients dosed in GD1 clinical trial show important reductions below baseline ERT levels in liver and spleen volume up to two years post gene therapy

Following positive feedback from FDA and MHRA, registrational, global Phase 2/3 clinical trial for GD3 planned for second half 2023

AVROBIO believes plato® gene therapy platform is late-stage ready with no major CMC changes anticipated

Gaucher Disease Program Update to be webcast today starting at 8 a.m. ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)—Dec. 7, 2022-- AVROBIO, Inc. (Nasdaq: AVRO), a leading clinical-stage gene therapy company working to free people from a lifetime of genetic disease, today announced new interim pharmacokinetic, pharmacodynamic and clinical efficacy data, showing stabilization or reversal of multiple clinically relevant measures in five patients with Gaucher disease after they received a single dose of AVR-RD-02, an investigational hematopoietic stem cell (HSC) gene therapy. In addition, following positive discussions with regulators, AVROBIO plans to initiate a global, registrational Phase 2/3 clinical trial in Gaucher disease type 3 (GD3) in the second half of 2023.

Gaucher disease is the largest, most common lysosomal disorder. Even on enzyme replacement therapy (ERT) – the current standard of care – people with Gaucher disease type 1 (GD1) typically have a shortened life expectancy and may experience debilitating symptoms that significantly reduce their quality of life. GD3 is a more severe, progressive form of Gaucher disease, which presents with more widespread systemic manifestations, typically refractory to standard of care treatment, as well as neurological signs and symptoms.

“We are thrilled to share new, compelling data from patients impacted across the spectrum of Gaucher disease, the most common lysosomal disorder. This includes what we believe to be transformational data from the first pediatric GD3 patient treated with an HSC gene therapy, showing complete biochemical correction, which means both enzyme activity and substrate levels have normalized post gene therapy. This pharmacodynamic efficacy equates with improvements in major refractory elements of disease for this patient, something the child has never experienced on current standard of care,” said Essra Ridha, M.D., MRCP, FFPM, chief medical officer at AVROBIO. “Following constructive regulatory conversations, including with FDA, we are now focused on initiating a randomized controlled, Phase 2/3 clinical trial for GD3 next year, the first such trial for a gene therapy, to further evaluate the benefit-risk profile of AVR-RD-02 in a clinical trial setting.”

“Additionally, today’s interim data from the ongoing Guard1 clinical trial, our Phase 1/2 trial for GD1, reinforce the potential clinical impact of HSC gene therapy in this subset of Gaucher disease, with the first patient dosed now two years post gene therapy. In our previous update, we shared favorable data across clinical biomarkers – today, we’re pleased to share new interim data showing not only sustained pharmacodynamic efficacy, but also some clinically significant reductions in liver and spleen volume, demonstrating that our gene therapy is having an impact above and beyond the standard of care baseline measures,” said Ridha. “We believe our current GD1 and planned GD3 clinical trials combined will create a robust data set that will further the development of this investigational gene therapy and move us ever closer to bringing a potential one-time treatment option to people living with Gaucher disease.”

AVR-RD-02 for GD3: First pediatric patient dosed with investigational AVR-RD-02

- An 11-year-old patient was dosed at the University of Manchester, U.K., on a named patient basis
- Fifteen months post gene therapy, the patient has normalized peripheral glucocerebrosidase (GCase) enzyme activity and plasma chitotriosidase, a marker of activated macrophages, and remains off enzyme replacement therapy (ERT) and substrate reduction therapy (SRT)
- Patient’s albumin levels increased 33% eight months post gene therapy, reflecting improvements in lymphadenopathy and enteropathy. This patient was previously refractory to maximal and multimodal medical therapy, including ERT, SRT, enteral steroids, dietary restrictions and intermittent albumin infusions
- Additionally, the patient did not develop any new lesions on MRI assessments post gene therapy, on a background of rapidly developing lesions, and had no clinically detectable change in neurological status or new neurological manifestations 15 months post gene therapy
- Safety data from this patient indicate no adverse events (AEs) related to drug product. All AEs observed were related to myeloablative conditioning, stem cell mobilization, underlying disease or pre-existing conditions

AVR-RD-02 for GD1: Clinically meaningful reductions in organomegaly and improvements from baseline ERT levels in plasma lyso-Gb1 and chitotriosidase activity

- All four adult GD1 patients in the Guard1 clinical trial who have been infused with investigational AVR-RD-02 to date saw sustained engraftment with vector copy numbers (VCN) between 0.54 to 0.86 per diploid genome 14 weeks to two years post gene therapy, and reconstitution of GCase enzyme activity both in plasma and peripheral blood leukocytes within the normal range

- Glucosylsphingosine (lyso-Gb1) decreased 21% to 70% (21%, 21%, 30% and 70%, respectively) below ERT baseline levels for all four patients 12 weeks to two years post gene therapy. A downstream metabolic product of glucocerebroside, lyso-Gb1, is considered a sensitive and specific biomarker used for disease monitoring

- The metabolite chitotriosidase was reduced in the two patients with evaluable samples to date, reflecting a reduction in macrophage activation and inflammation. Patient 1's chitotriosidase level has almost completely normalized, declining from a high of 145.8 μmol/L/h prior to gene therapy treatment to 42.4 μmol/L/h (≤38.1 μmol/L/h is considered normal range) two years post gene therapy. Patient 2, who was in the normal range before gene therapy treatment, still decreased from 24.3 μmol/L/h at baseline to 19.2 μmol/L/h at week 52

- Importantly, three of the four patients dosed demonstrate a reduction in liver and spleen volume below their own ERT baseline. Patient 4 is not yet out far enough post gene therapy to be scanned for liver or spleen volume

    - Patient 1 data showed a clinically significant 24% reduction in liver volume at 104 weeks post gene therapy (patient underwent a splenectomy during childhood)

    - Patient 2 data showed a clinically significant 11% reduction in liver volume and 23% reduction in spleen volume at 52 weeks post gene therapy

    - Patient 3 data showed a 4% reduction in liver volume and a 19% reduction in spleen volume, at 26 weeks post gene therapy

- Safety data from the four patients dosed to date indicate no AEs related to drug product. All AEs observed were related to myeloablative conditioning, stem cell mobilization, underlying disease or pre-existing conditions. The majority of AEs were mild or moderate and resolved without clinical sequelae. Additionally, hemoglobin and platelet levels, a core feature of successful Gaucher disease treatment, remain in normal range following gene therapy

- The ongoing Guard1 clinical trial (NCT04145037) is a multinational, open-label study to assess the safety and efficacy of investigational AVR-RD-02 in approximately eight to 16 participants (male or female) who are ≥18 and ≤50 years of age with a confirmed diagnosis of GD1

Planning first ever, randomized controlled clinical trial for GD3 in 2023

- AVROBIO plans to initiate a Phase 2/3 pediatric clinical trial for investigational AVR-RD-02 in GD3 in the second half of 2023, following constructive meetings with the U.S. Food and Drug Administration (FDA) and U.K. Medicines and Healthcare products Regulatory Agency (MHRA)

- Global, open label, parallel-arm and randomized controlled clinical trial designed to evaluate the efficacy and safety of investigational AVR-RD-02. The trial is expected to include approximately 40 GD3 participants (male or female) who will be randomized 1:1 to receive HSC gene therapy or continue to receive standard of care ERT. Following the observation period, eligible participants who received ERT can cross over into the active arm and receive HSC gene therapy

- Planned primary efficacy endpoint is a novel, multi-domain endpoint to reflect the systemic and heterogeneous nature of Gaucher disease, including ataxia (impaired coordination), breathing ability and liver and spleen volume. A key secondary efficacy measure will examine substrate levels in cerebrospinal fluid (CSF), which reflects the impact of the HSC gene therapy in the central nervous system

- Overall, data from both the Guard1 and planned global Phase 2/3 GD3 clinical trials are expected to further development of this investigational gene therapy, leveraging the similar underlying pathophysiology for both types of Gaucher disease.

“AVROBIO is transitioning into a late-stage company in 2023, targeting indications with large, pre-identified patient populations and with attractive commercial opportunities,” added AVROBIO President and Chief Executive Officer Geoff MacKay. “We look forward to this next stage in our journey, as we continue to work every day toward our shared purpose of freeing patients from a lifetime of genetic disease.”

AVROBIO believes its plato® gene therapy platform is late stage-trial ready, with no major CMC changes anticipated

plato®, AVROBIO’s end-to-end solution covering vector design and production, drug product manufacturing and analytics, has received feedback from multiple regulatory agencies and no major chemistry, manufacturing and controls (CMC) changes are anticipated as the company enters late-stage clinical trials.

New data showed consistent quality attributes across the Gaucher disease drug product, including purity, percent transduction, VCN, as well as potency. Additionally, the company reinforced its commitment to vector safety and showcased favorable data on the combined use of two state-of-the-art assays to evaluate the genotoxicity risk of integrating vectors used in HSC gene therapy prior to clinical use.

Gaucher Disease Program Update webcast information

A live webcast of the Virtual Gaucher Disease Program Update and accompanying slides will be available under “Events and Presentations” in the Investors section of the company’s website at www.avrobio.com. An archived webcast recording of the event will be available on the website for approximately 30 days.

About Gaucher disease

Gaucher disease is a rare, inherited lysosomal disorder characterized by the toxic accumulation of glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph) in macrophages. Macrophages enlarged with these fatty substances are called Gaucher cells which amass primarily in the spleen, liver and bone marrow. This results in a variety of potential symptoms, including grossly enlarged liver and spleen, bone issues, fatigue, low hemoglobin levels and platelet counts and an adjusted lifetime relative risk of developing Parkinson's disease that may be more than 20 times greater than the general population. Even on enzyme replacement therapy (ERT) – the current standard of care – people with Gaucher disease typically have a shortened life expectancy and may experience debilitating symptoms that significantly reduce their quality of life.

About AVROBIO

Our vision is to bring personalized gene therapy to the world. We target the root cause of genetic disease by introducing a functional copy of the affected gene into patients' own hematopoietic stem cells (HSCs), with the goal of durably expressing the therapeutic protein throughout the body, including the central nervous system. Our first-in-class pipeline includes clinical programs for Gaucher disease and cystinosis, as well as preclinical programs for Hunter syndrome and Pompe disease. Our proprietary plato® gene therapy platform is scalable for planned global commercialization. We are headquartered in Cambridge, Mass. For additional information, visit avrobio.com, and follow us on Twitter and LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words and phrases such as "aims," "anticipates," "believes," "continue," "could," "designed to," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "predicts," "projects," "seeks," "strives," "should," "will," and variations of these words and phrases or similar expressions that are intended to identify forward-looking statements. These forward-looking statements include, without limitation, statements regarding our business strategy for and the potential therapeutic benefits of our preclinical and clinical product candidates, including AVR-RD-02 for the treatment of Gaucher disease, including its use in a compassionate use or named patient setting, the design, commencement, enrollment and timing of planned clinical trials, our plans and expectations with respect to the development of our clinical and preclinical product candidates, including timing, design, and initiation of our potential clinical and registration trials and anticipated interactions and expectations with regulatory agencies, the timing of anticipated clinical and regulatory updates, the timing of patient recruitment and enrollment activities, preclinical, compassionate use or clinical trial results, product approvals and regulatory pathways, anticipated benefits of our gene therapy platform including potential impact on our commercialization activities, timing and likelihood of success, the expected benefits and results of our implementation of manufacturing technology, including the implementation of our plato® platform in our clinical trials and gene therapy programs including its late-stage readiness, and the expected safety profile of our preclinical and investigational gene therapies. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Results in preclinical or early-stage clinical trials may not be indicative of results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements, or the scientific data presented.

Any forward-looking statements in this press release are based on AVROBIO's 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 AVROBIO's 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 AVROBIO may not successfully recruit or enroll a sufficient number of patients for our clinical trials, the risk that AVROBIO 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 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 AVROBIO's 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 enrollment and development timelines 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 materially and adversely from those contained in the forward-looking statements, see the section entitled "Risk Factors" in AVROBIO's most recent Quarterly Report, 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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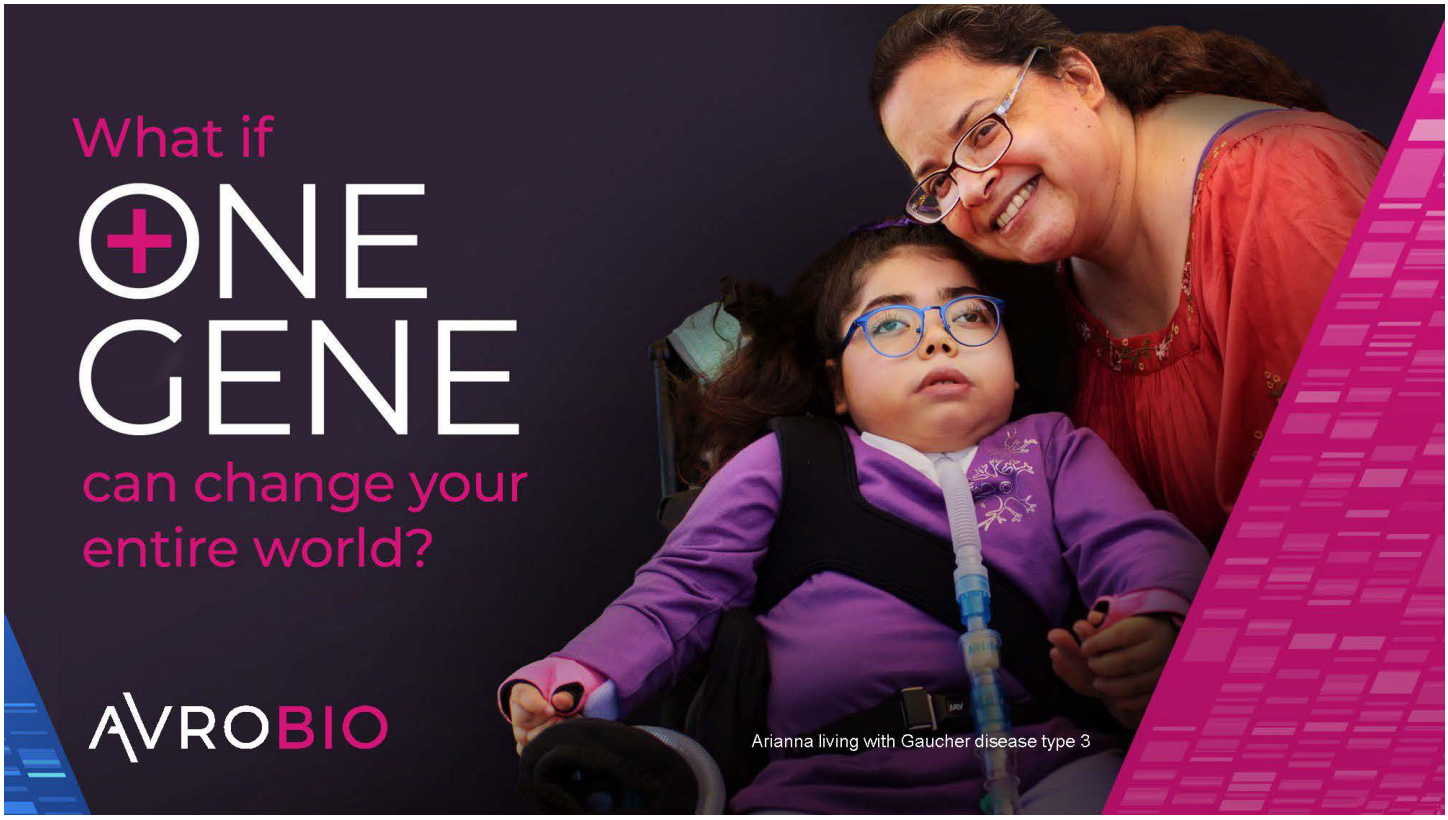
Exhibit 99.2


What if
ONE
GENE
can change your
entire world?
AVROBIO
Arianna living with Gaucher disease type 3

Disclaimer

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

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

Any forward-looking statements in this presentation are based on our current expectations, estimates, and projections about our industry as well as management's current beliefs and expectations of future events only as of today and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that any one or more of our product candidates will not be successfully developed or commercialized; the risk that regulatory agencies may disagree with our anticipated development approach for any one or more of our product candidates; 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 or potential use of monoclonal antibody conditioning agents, 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 ongoing COVID-19 pandemic 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, as well as discussions of potential risks, uncertainties and other important factors in AVROBIO's subsequent filings with the Securities and Exchange Commission. AVROBIO explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

Note regarding trademarks: plato® is a registered trademark of AVROBIO. Other trademarks referenced in this presentation are the property of their respective owners.

AVROBIO

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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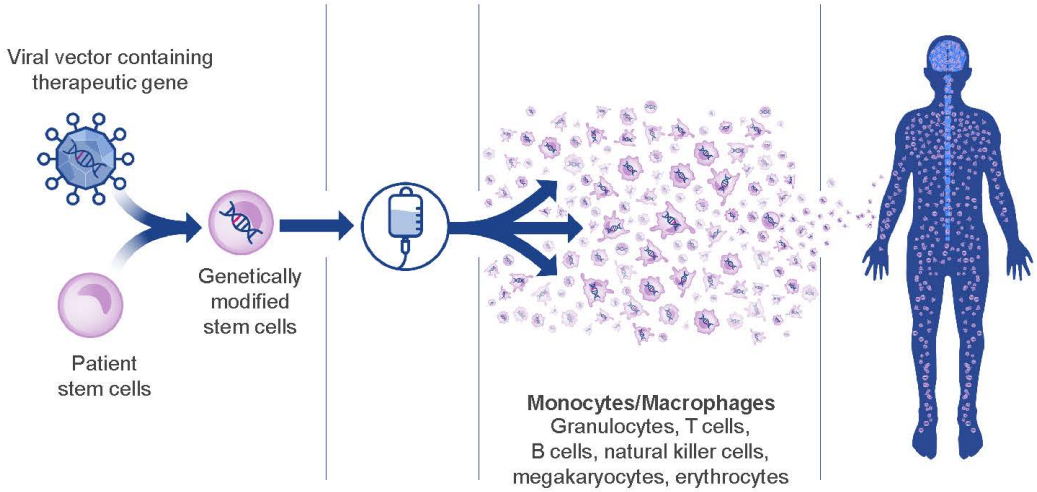
CMC=Chemistry, manufacturing and controls

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

AVROBIO

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]

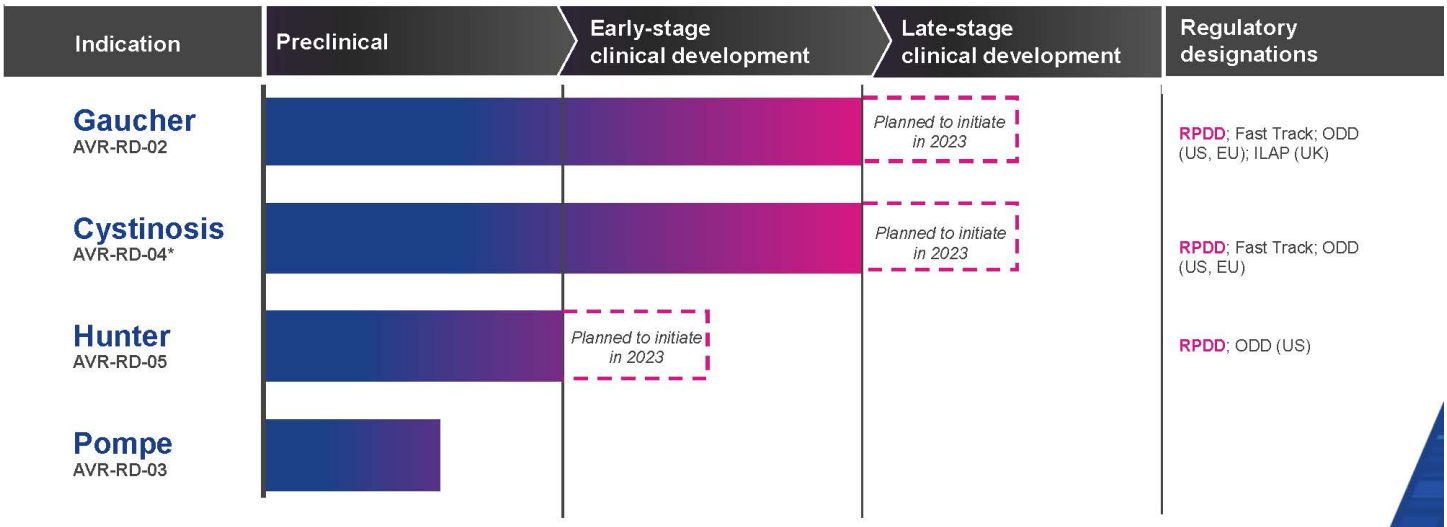
380+
patients treated[4]

700+
patient-years of treatment[4]

AVROBIO

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



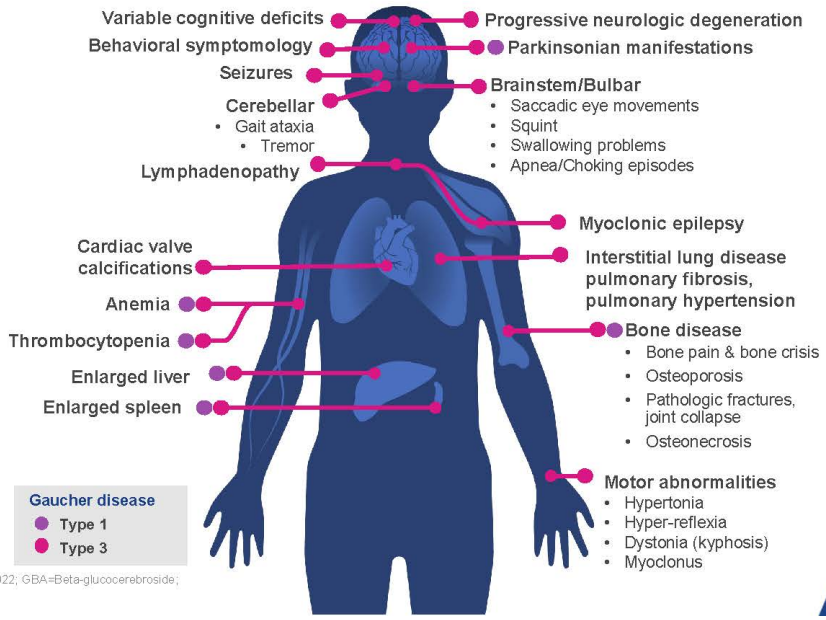
Planned regulatory milestones subject to regulatory agency clearance; *Collaborator-sponsored Phase 1/2 clinical trial of AVR-RD-04 is funded in part by grants to UCSD from the California Institute for Regenerative Medicine (CIRM), Cystinosis Research Foundation (CRF), and National Institutes of Health (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 lysosomal 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



AVROBIO

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

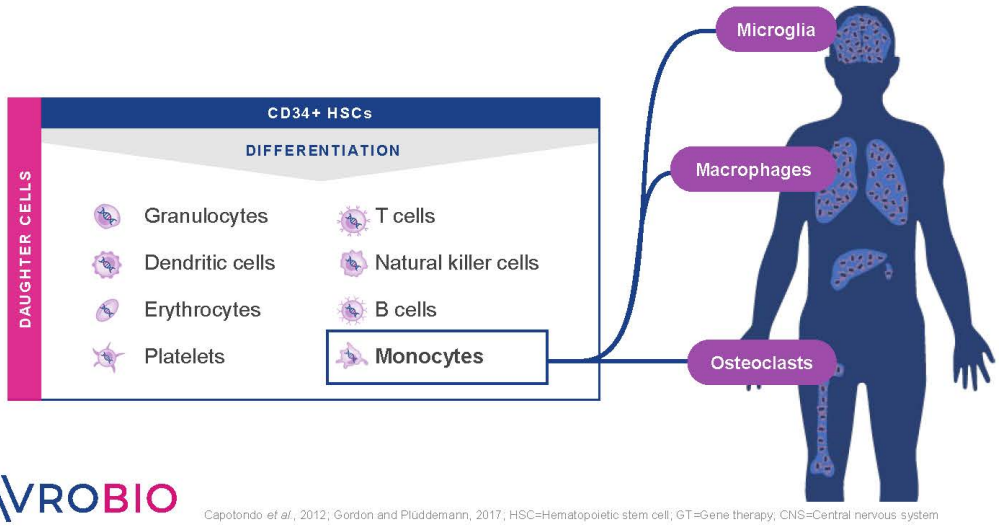
- **60% failed to achieve** at least one of six therapeutic goals after 4+ yrs of ERT[1]
- Many continue to exhibit **bone pain, organomegaly and cytopenia** after 10 yrs of ERT[2]
- **25% have physical limitations** after 2 yrs of ERT, primarily due to bone disease[3]

* 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

AVROBIO

HSC GT approach well-suited for Gaucher disease

Leverages HSC myeloid lineage



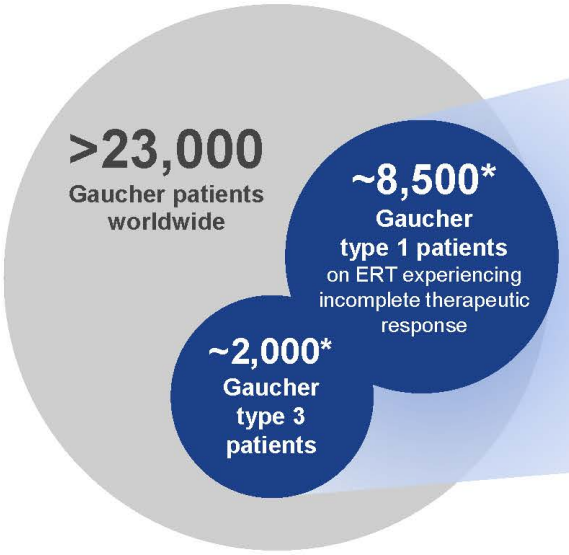
Key potential advantages of HSC gene therapy

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

AVROBIO

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

Potential penetration rate	Number of patients served	Aggregate revenue potential — Potential price ~$1.3M 3-year U.S. SOC cost	~$2.3M 5-year U.S. SOC cost	~$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.

AVROBIO

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

AVROBIO

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

AVROBIO

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

AVROBIO

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

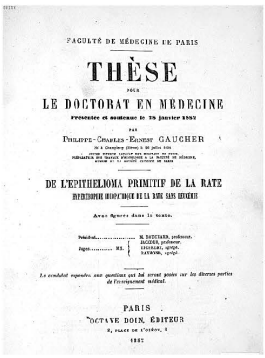
Addenbrooke's Hospital

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 25 JANVIER 1882

PAR

PHILIPPE-CHARLES-ERNEST GAUCHER

DE L'ÉPITHÉLIOMA PRIMITIF DE LA RATE

HYPERTROPHIE IDIOPATHIQUE DE LA RATE SANS LEUCÉMIE

Avec figures dans le texte.

PARIS

OCTAVE DOIN, ÉDITEUR

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

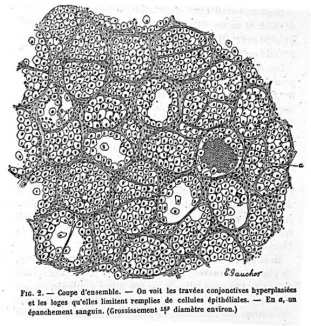


FIG. 2. — Coupe d'ensemble. — On voit les travées conjonctives hyperplasiées et les loges qu'elles limitent remplies de cellules épithéliales. — En a, un épanchement sanguin. (Grossissement $\frac{1}{10}$ diamètre environ.)

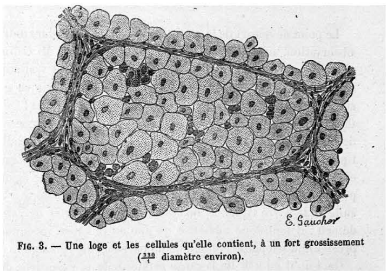
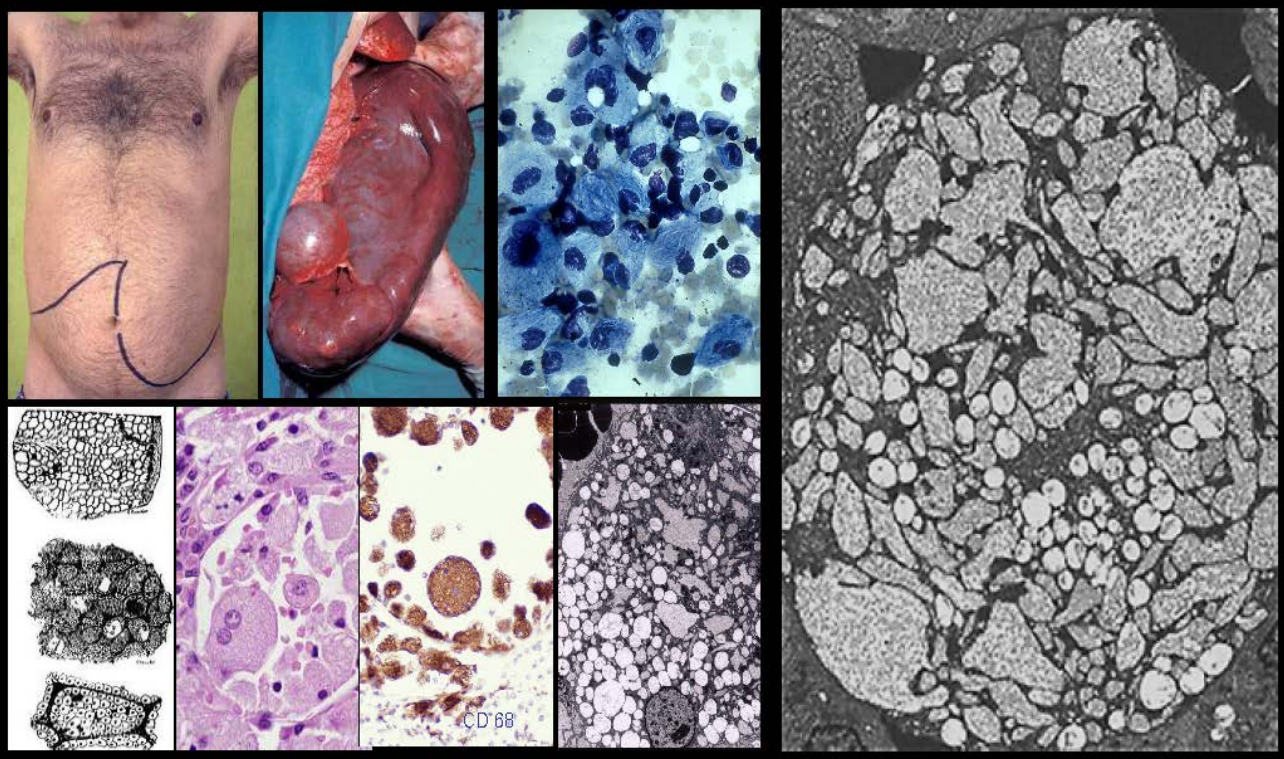


FIG. 3. — Une loge et les cellules qu'elle contient, à un fort grossissement ($\frac{1}{1}$ diamètre environ).

The disease and Dr Gaucher's cells



A KEY DISCOVERY - GLUCOSYLCERAMIDE


FACULTÉ DE MÉDECINE DE PARIS

THÈSE 516

POUR

LE DOCTORAT EN MÉDECINE

(Diplôme d'État)

PAR

Henriette AGHION

LA MALADIE DE GAUCHER DANS L'ENFANCE

(FORME CARDIO-RÉNALE)

Président de Thèse : M. le Professeur DEBRÉ

IMPRIMERIE DE PERSAN-BEAUMONT

Ve Auguste MOREL Fils

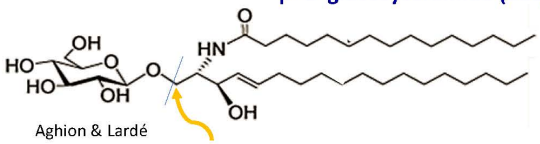
PERSAN (S.-et-O.)

Henriette Aghion

1906-1986

Aghion H (1934)
Thèse de Paris

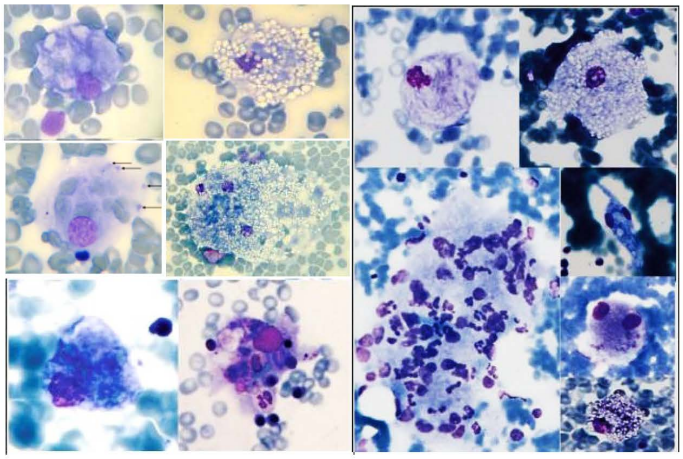
β- D-glucosyceramide (C16)



Aghion & Lardé

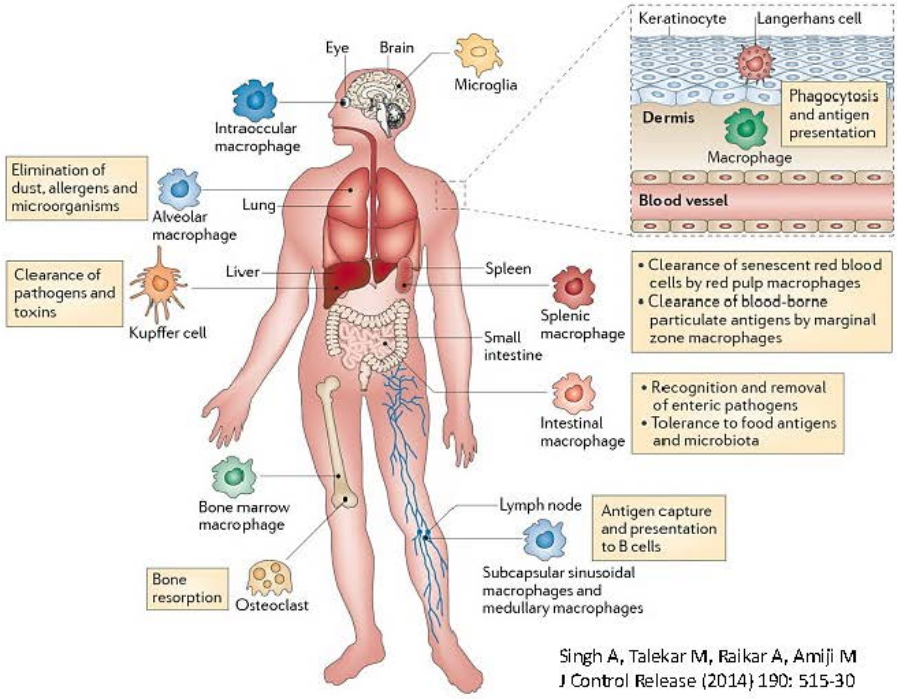
Glucosylceramidase/glucocerebrosidase

(Brady et al., 1965; Patrick 1965)



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

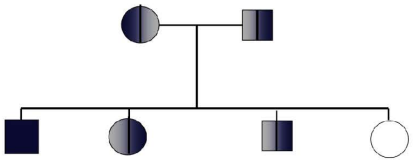
Macrophages – scavengers, recyclers, immune activators



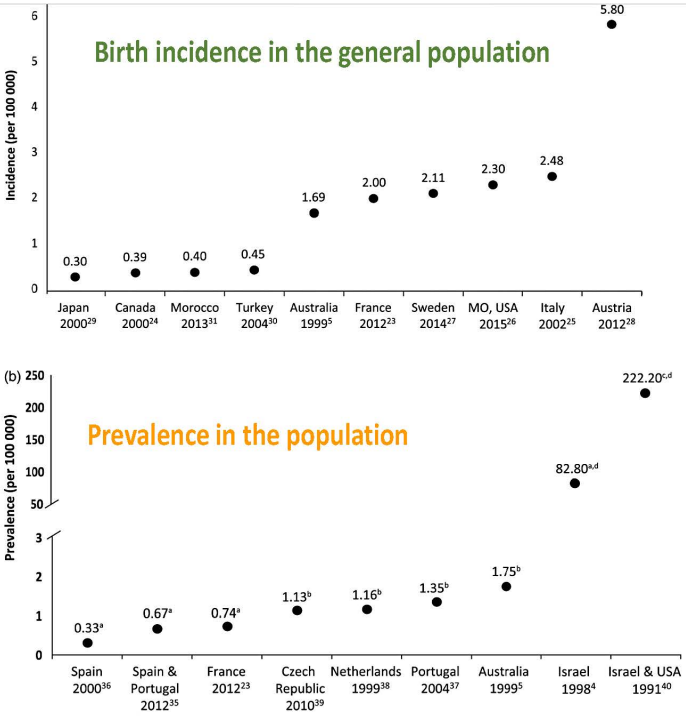
Singh A, Talekar M, Raikar A, Amiji M
J Control Release (2014) 190: 515-30

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

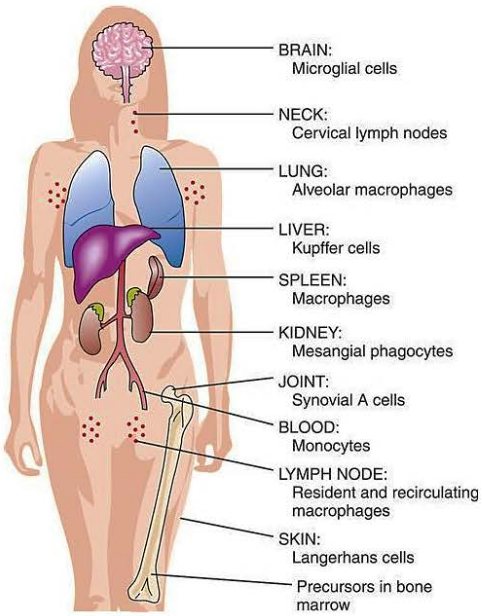


Nalysnyk L, Rotella P, Simeone JC, Hamed A, Weinreb N 2017. Gaucher disease: Epidemiology and natural history, a comprehensive review of the literature. Hematology 22: 65-73

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



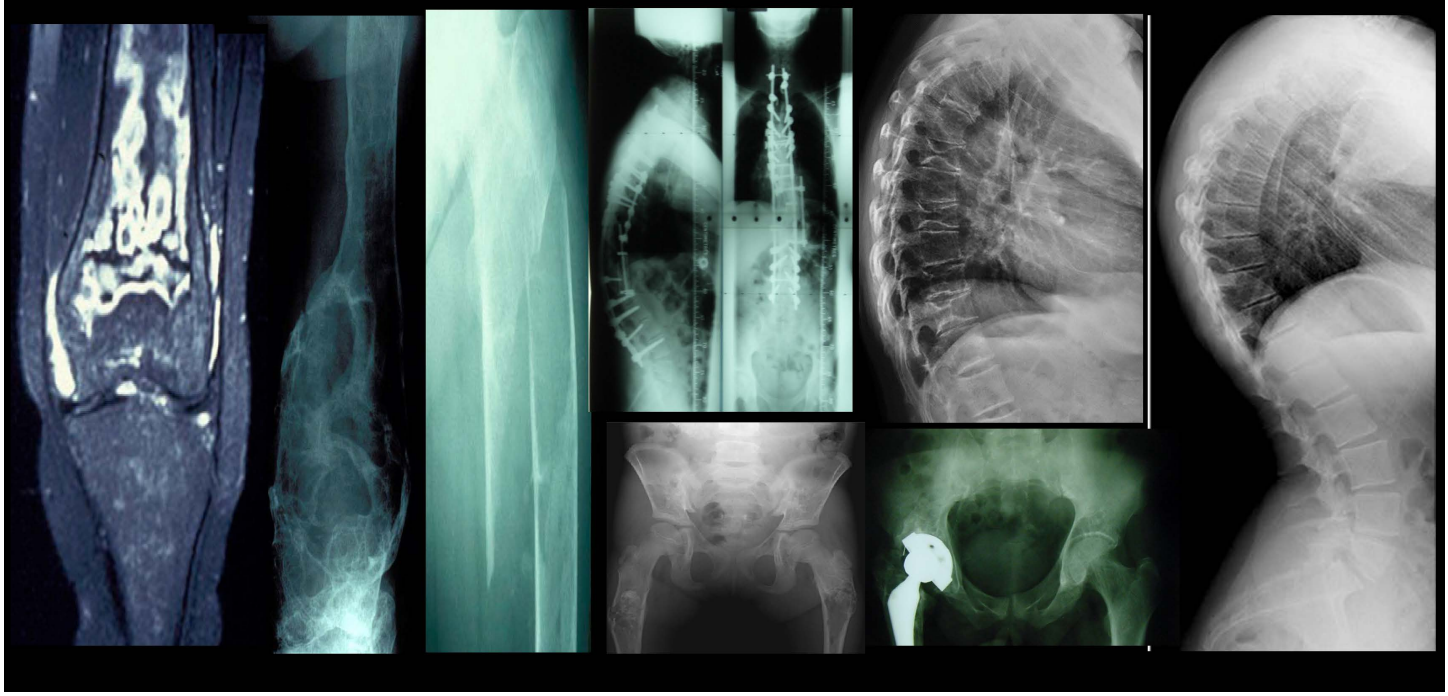
Redrawn from Schindler LW: Understanding the immune system, NIH Pub No. 92-529, Bethesda, MD, 1991, U.S. Department of Health and Human Services, p 9.

CLINICAL & RADIOLOGICAL FEATURES

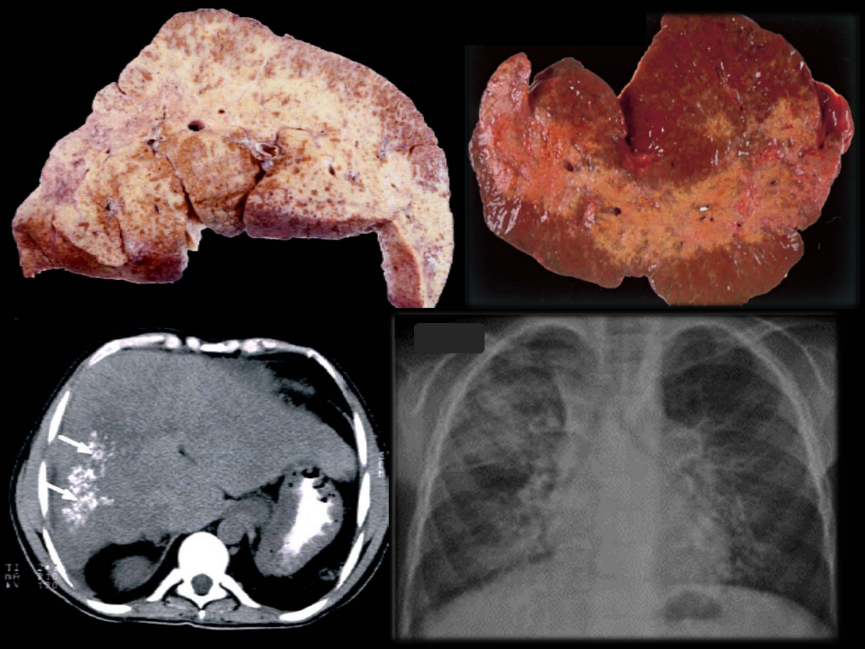
Enlarged spleen* (87%)
Enlarged liver (79%)
Marrow infiltration (40%)
Anemia (64%)
Thrombocytopenia (56%)
*Splenectomy (32%)
Osteonecrosis (50%)
Erlenmeyer deformity (46%)
Fragility fracture (15%)
Osteolytic lesions (8%)
Lung infiltration
Neurological disease
Cancers

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

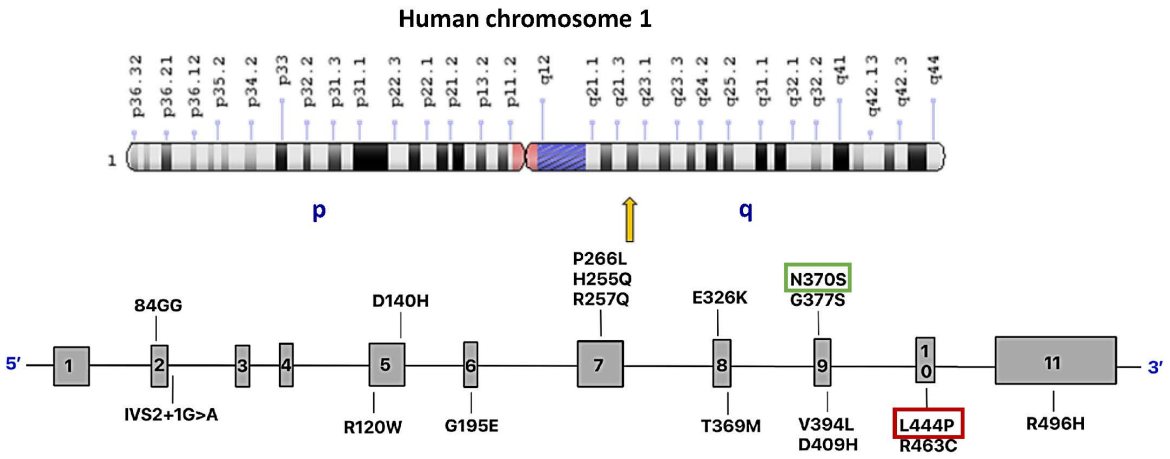


The Liver

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

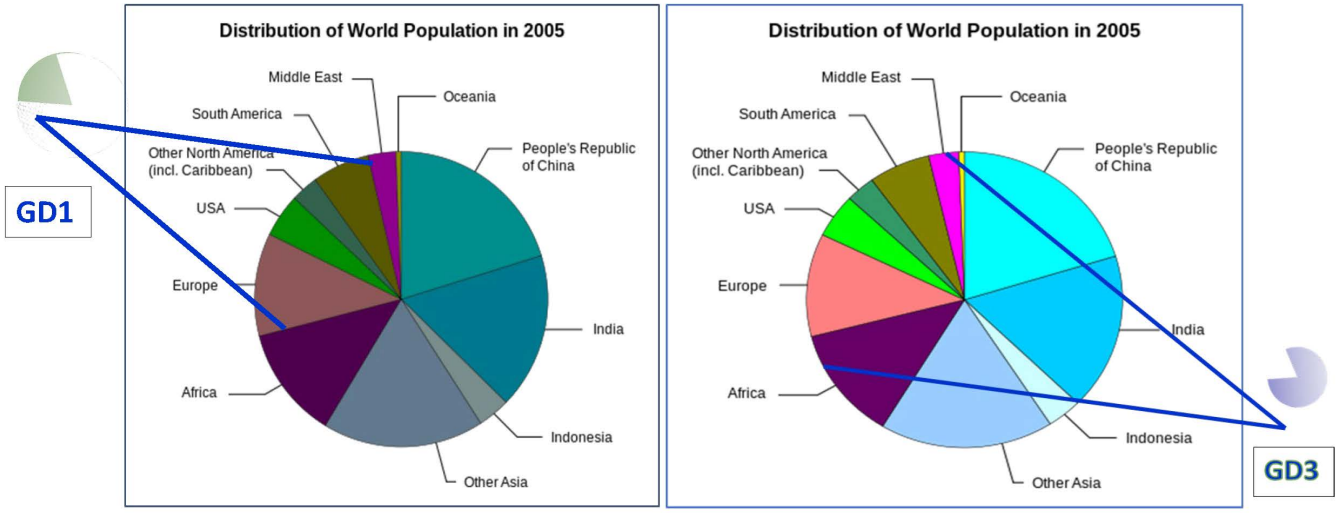
Subacute
Type 2/3

Type 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

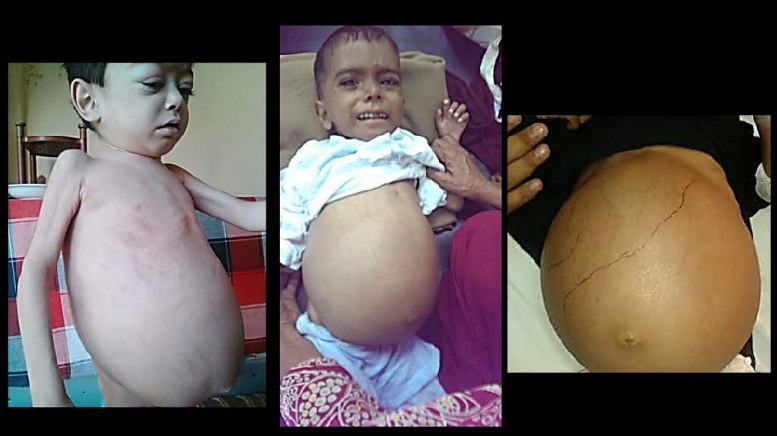
North America (2108); Europe (1477); Middle East/Africa (986); Latin America (901); Asia-Pacific (238)



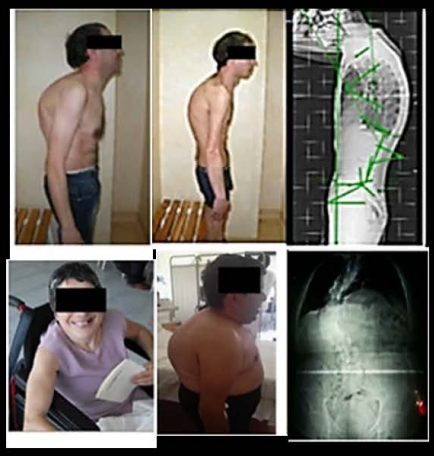
1. Kim H, et al. *Haematologia*. 2010;95(Suppl2):743.
2. WIKIMEDIA. 2022. https://commons.wikimedia.org/wiki/File:World_population_distribution.svg.

Clinical diversity in neuronopathic Gaucher disease (type 3)

All patients assigned the L444P *GBA1* genotype



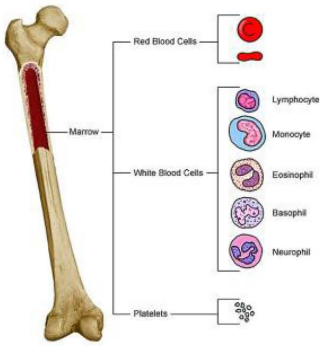
Images kindly supplied and shown by permission of Professor Huma Cheema
The Children's Hospital and the Institute of Child Health, Lahore



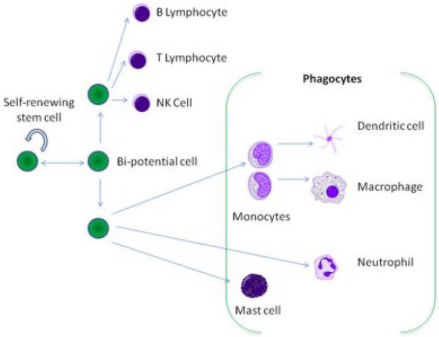
Sestito S, Filocamo M, Ceravolo F, Falvo F, Grisolia M, Moricca MT, Cantaffa R, Grossi S, Strisciuglio P, Concolino D. Norrbottnian clinical variant of Gaucher disease in Southern Italy. J Hum Genet. 2017 Apr;62(4):507-511.

Origin of tissue macrophages

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



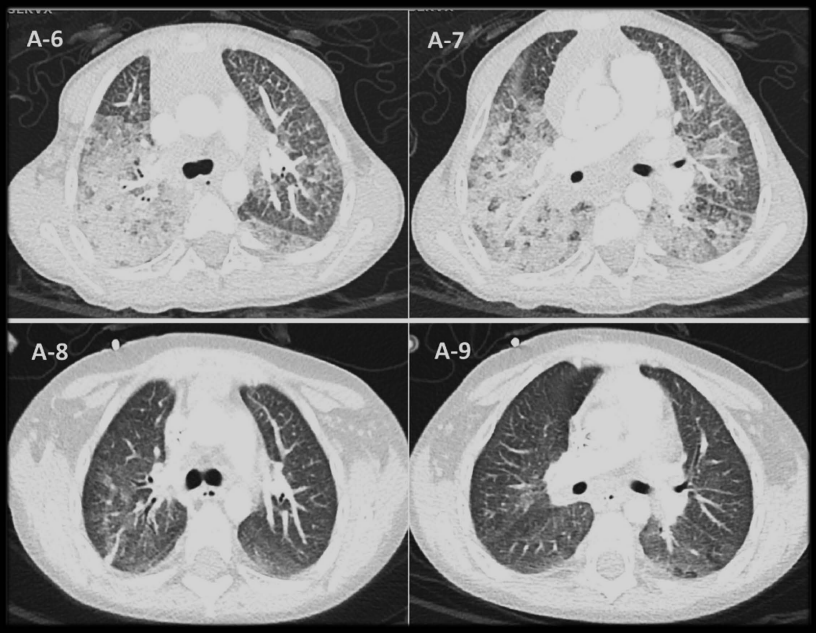
Cellular and Molecular Immunology AK Abbas, AHH Lichtman and S Pillai - Elsevier, N Holland Eighth Edition 2015, 544 pp



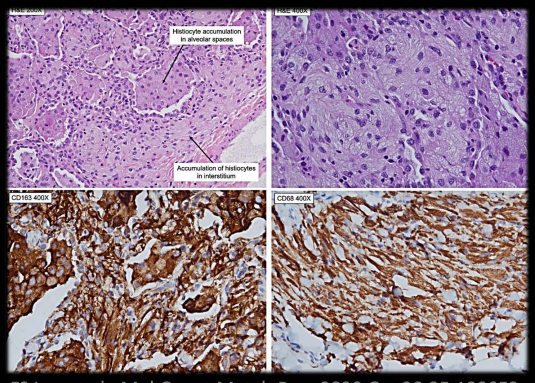
Open Textbook Pilot Project,Office of the Provost, UC Davis Library, California State University

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

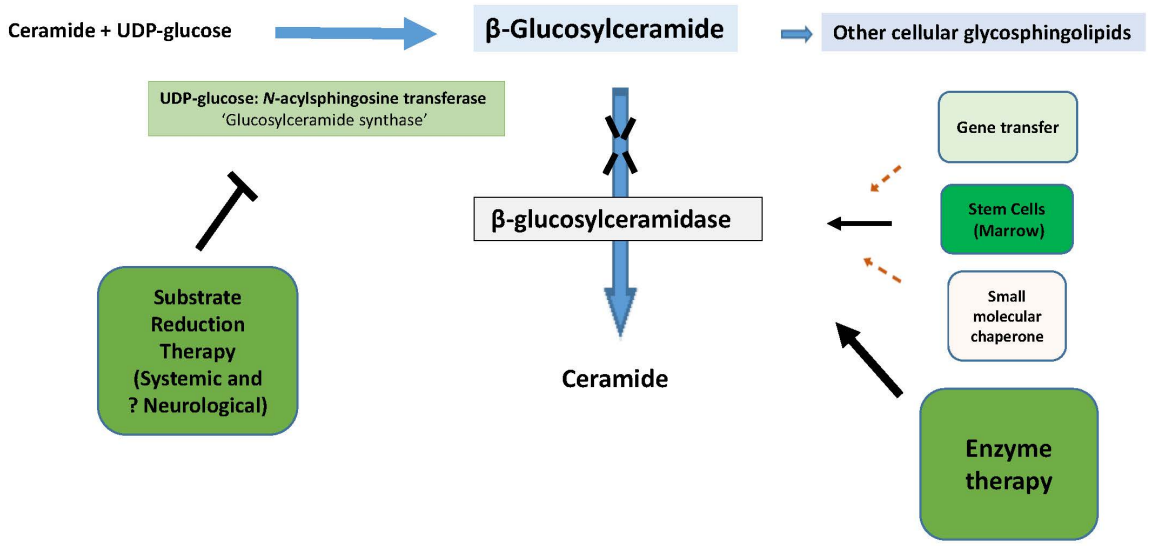
♂ **Gaucher disease - L444P homozygote (p.L483P)**

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

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- 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
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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

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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

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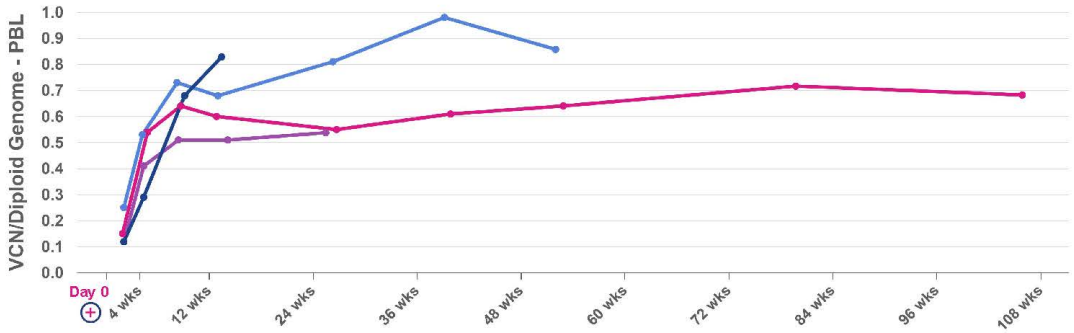
VCN trending as expected, indicating sustained engraftment

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

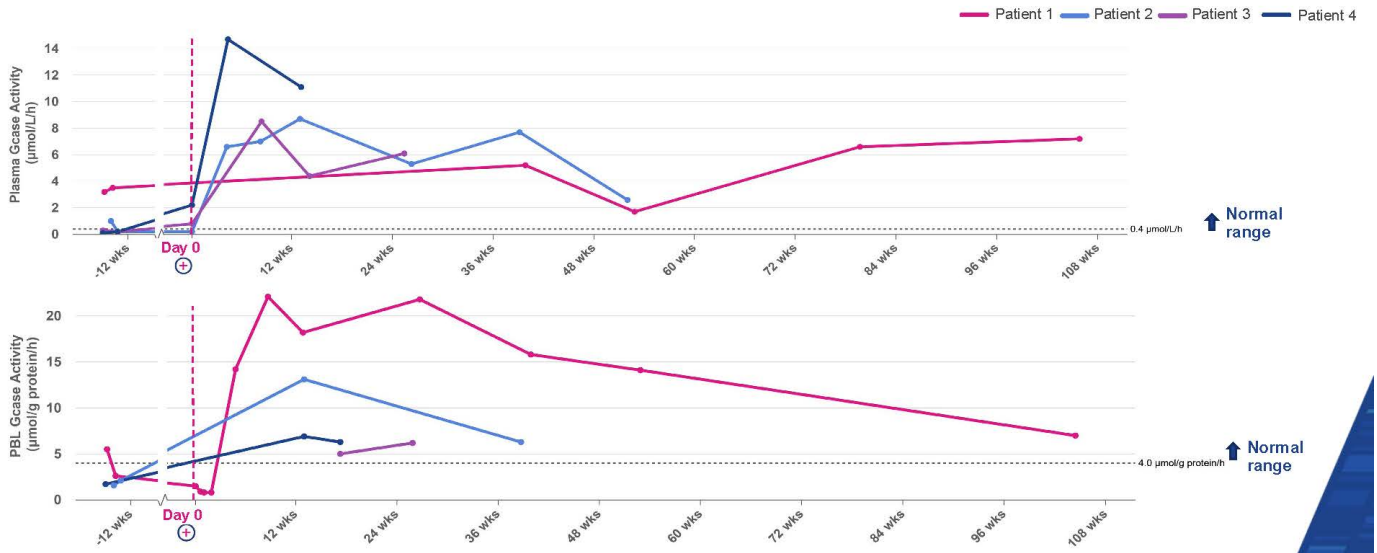


AVROBIO

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

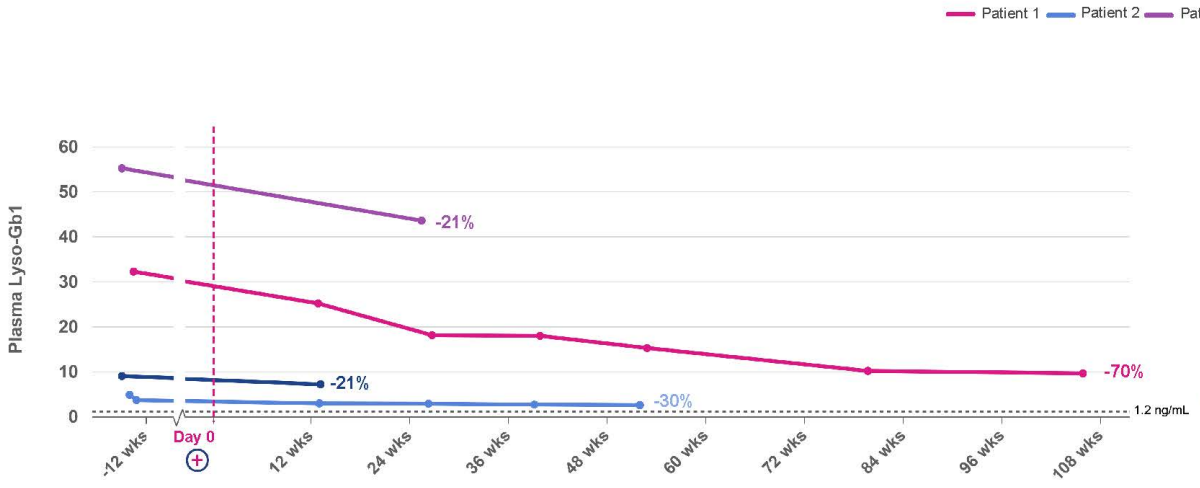


AVROBIO

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



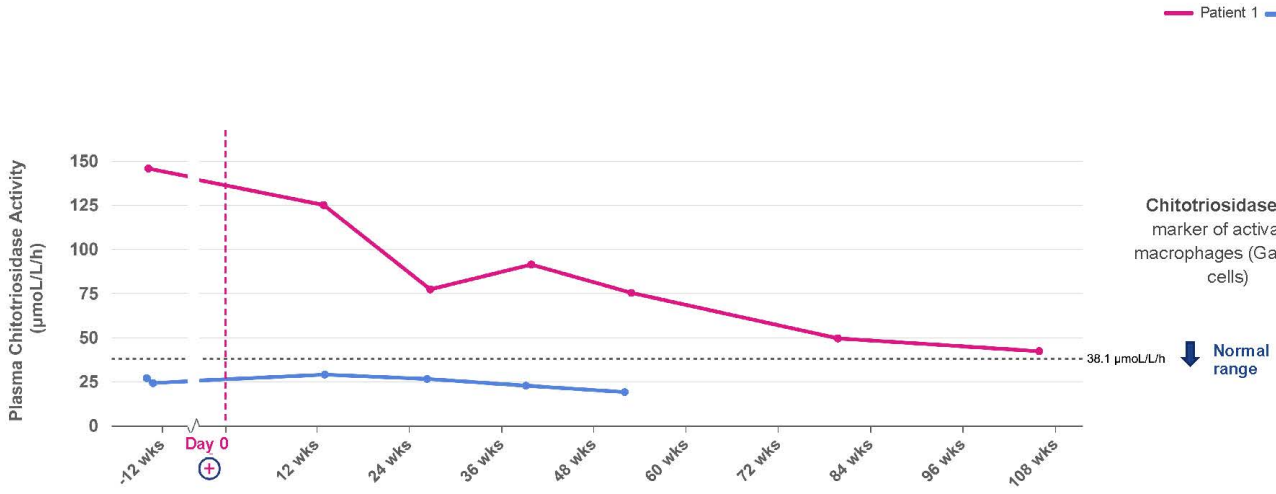
Lyso-Gb1 is a sensitive and specific marker of metabolite accumulation

AVROBIO

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)

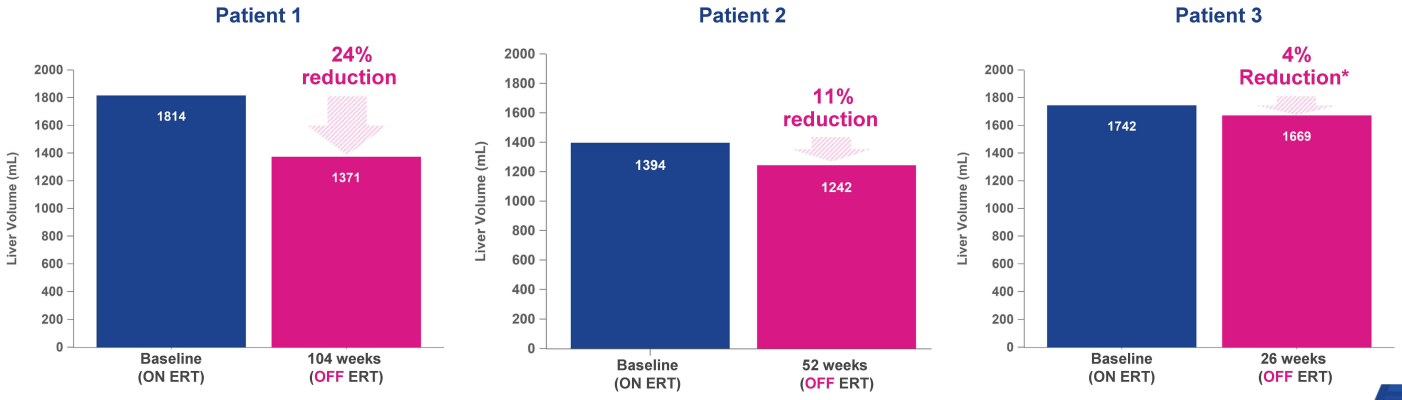
AVROBIO

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



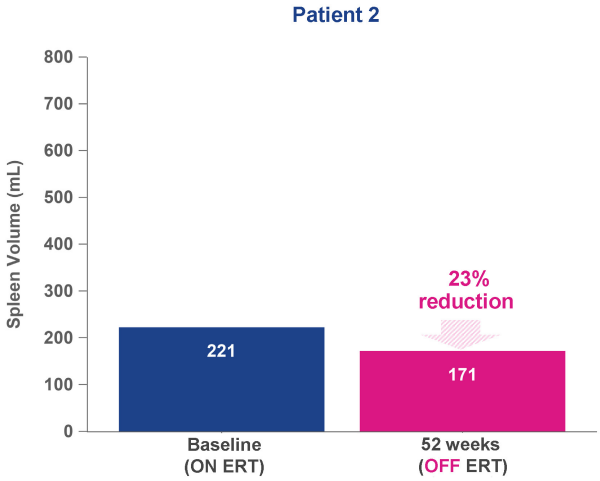
AVROBIO

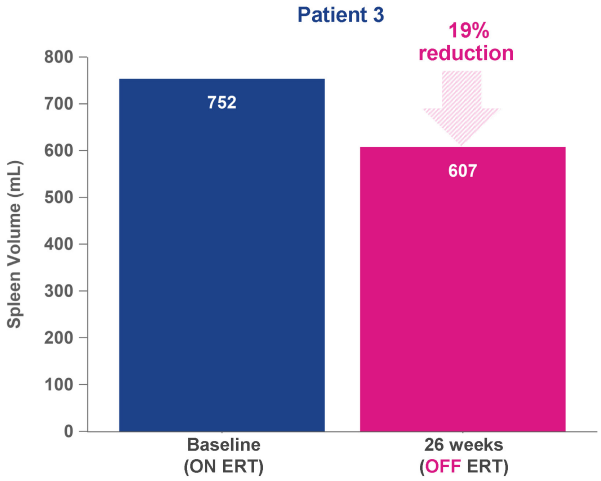
Data as of Nov. 22, 2022; Liver volume assessments from central reader; Patient 4 data not yet available; ERT=Enzyme replacement therapy; ≥10% reduction in liver volume is considered clinically meaningful per Taliglucerase alfa PI (product insert); Taliglucerase alfa approval - FDA Clinical and Statistical 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





AVROBIO

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

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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

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* 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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- The role of *GBA* in Gaucher Disease – Timothy Cox, M.D., MAE, FRCP, FMedSci, University of Cambridge, UK

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Closing remarks and Q&A

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)

AVROBIO

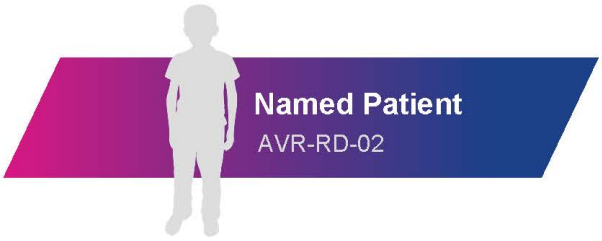
ERT=Enzyme replacement therapy; SRT=Substrate reduction therapy; AEs=Adverse events; FSIQ=Full-scale intelligence quotient; Bu90=Cumulative busulfan AUC of 90mg.hr/L; GT=Gene therapy; GD3=Gaucher disease type 3

"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

AVROBIO

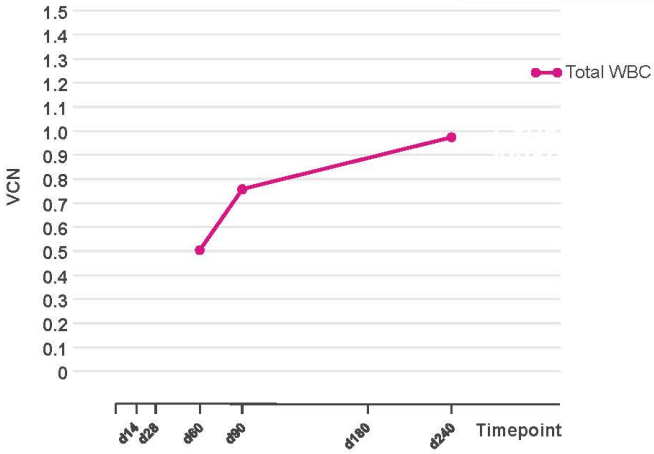
Data as of June 2022; HSC=Hematopoietic stem cell; AEs=Adverse events; Bu90=Cumulative busulfan AUC of 90mg.hr/L; GT=Gene therapy; GD3=Gaucher disease type 3

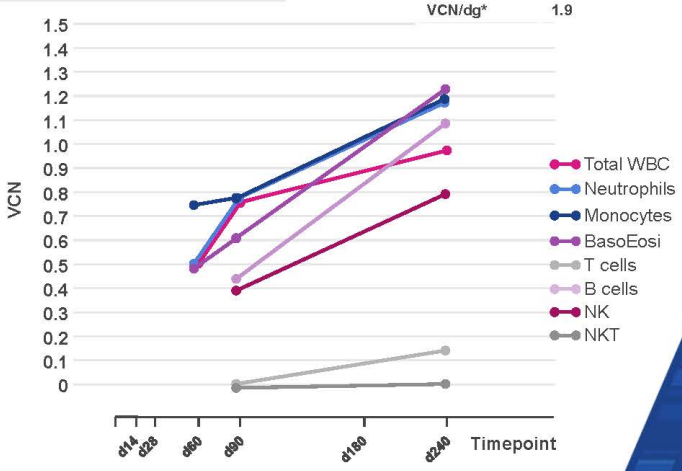
VCN trending as expected, indicates sustained engraftment

GD3: Named Patient

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

Peripheral blood leukocytes





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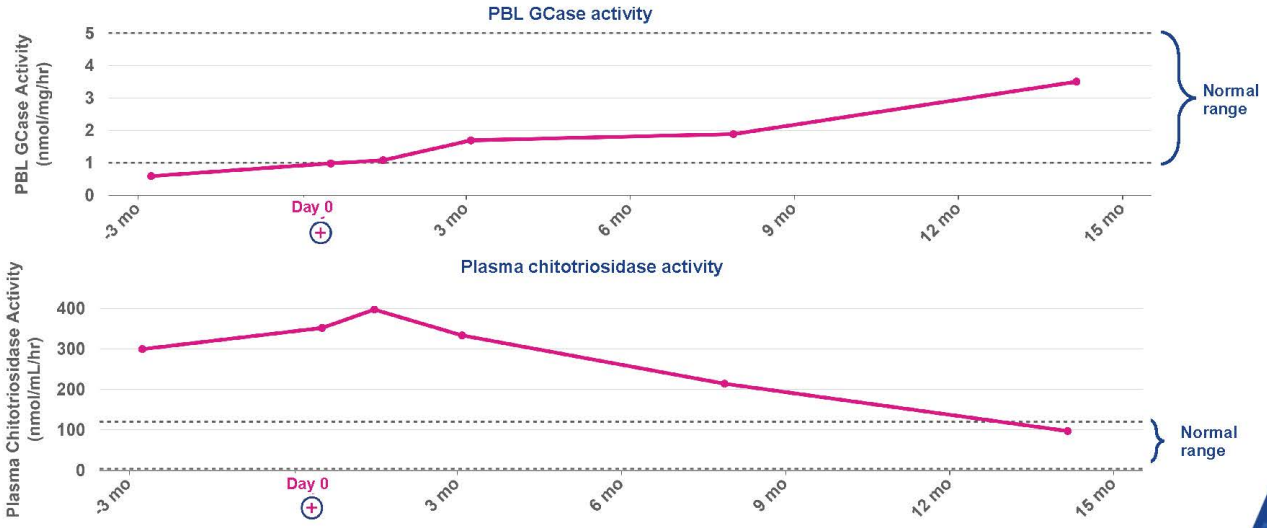
Data as of June 2022; AVROBIO Translational Research Group analysis; *Average of two VCN/transduced cell measures across 2 DPs; VCN=vector copy number; dg=Diploid genomes; d=Day

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

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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

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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

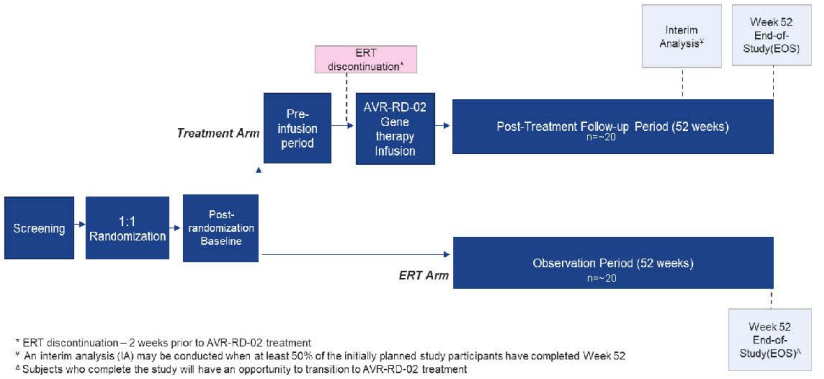
AVROBIO

Arianna living with Gaucher disease type 3

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
^ 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

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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

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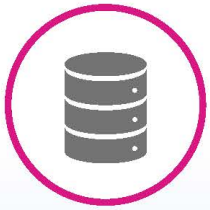
GD3 clinical development strategy is substantially de-risked



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)

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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

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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

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

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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

AVROBIO

Arianna living with Gaucher disease type 3

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

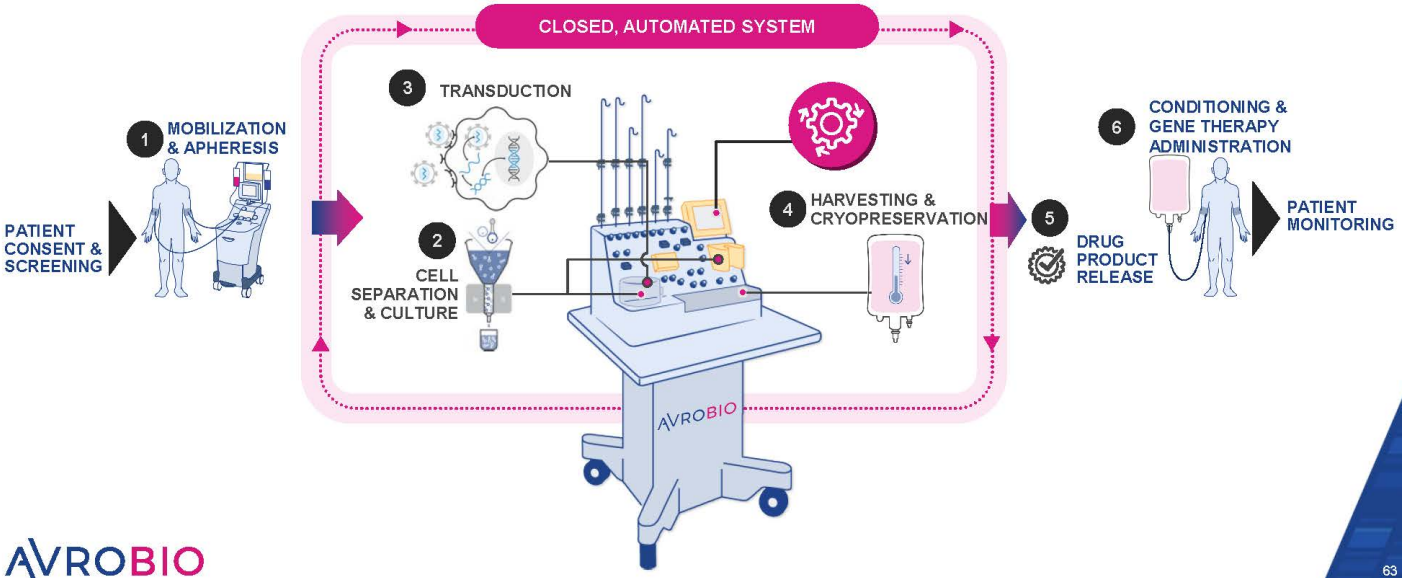
AVROBIO has obtained feedback from multiple regulatory agencies and is working to incorporate it

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

AVROBIO

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



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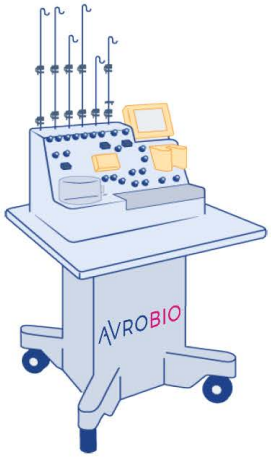
Drug product manufacturing is automated

Enables consistency, product quality and transferability

Miltenyi Prodigy with
AVROBIO process algorithm



AVROBIO

COGs=Cost of goods

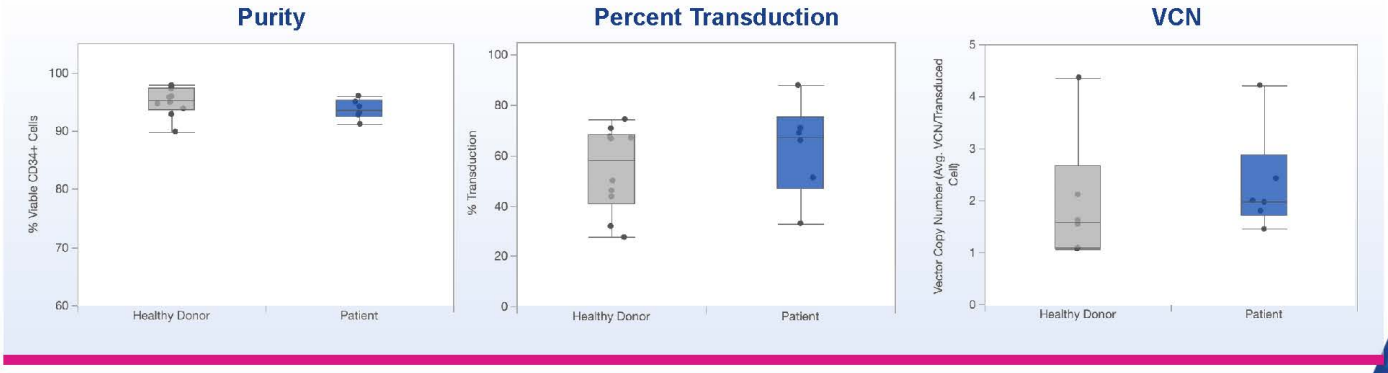
Automation designed to work across the pipeline

- 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

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



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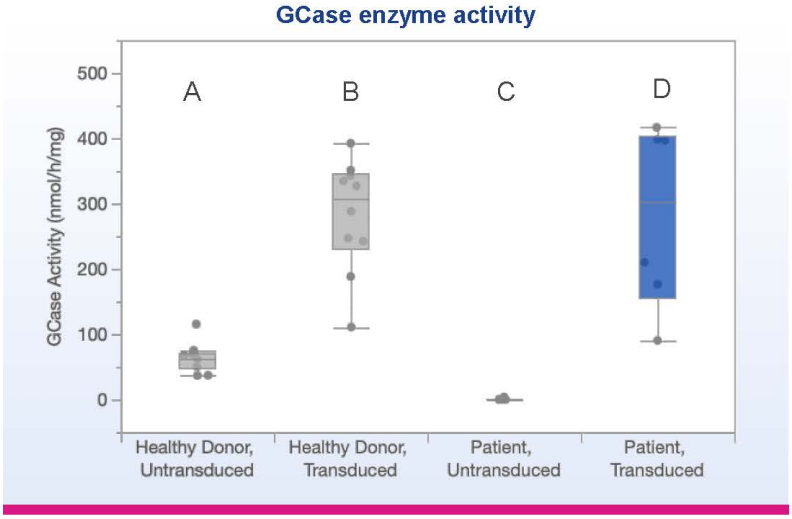
VCN=Vector copy number; DP=Drug product

Gaucher drug product GCase enzyme activity comparable to healthy donor cells



AVROBIO

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

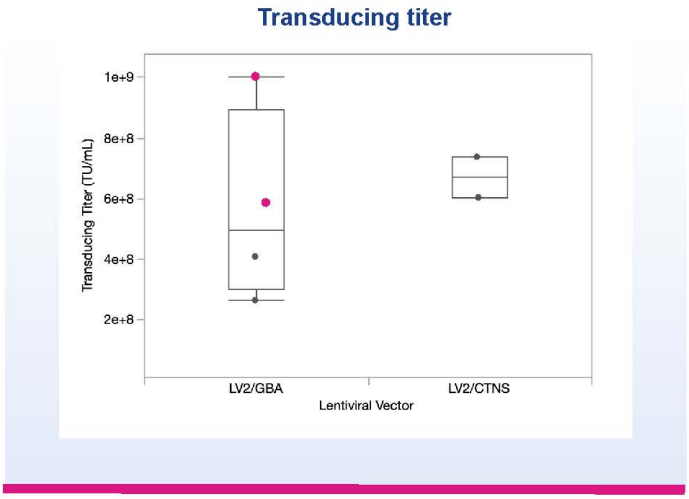
- Low impurities
- No “empty” capsids with lentiviral vectors

Consistent, high titer

AVROBIO

STR=Stirred tank bioreactor

Reliably high titers outperforming industry standards



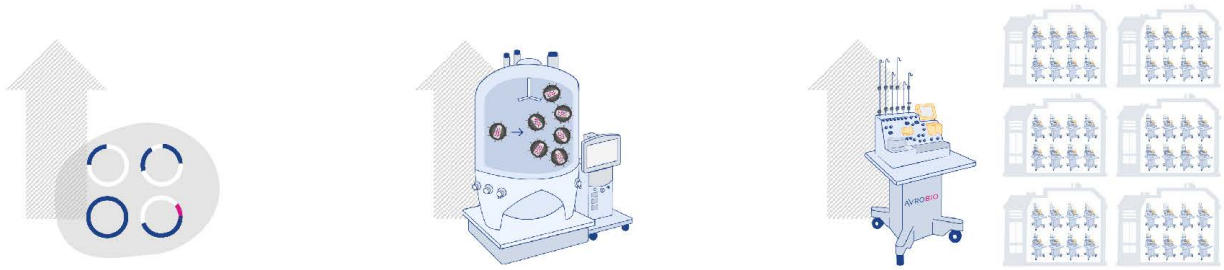
- Titer consistently above industry standard
- Higher titers mean fewer batches required to fulfill demand
- Manufacturing process applied across entire pipeline

AVROBIO

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

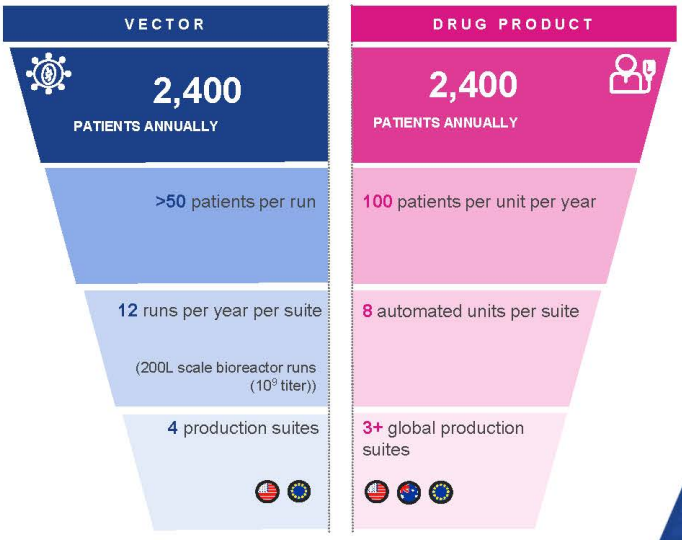
Transferability between production facilities established

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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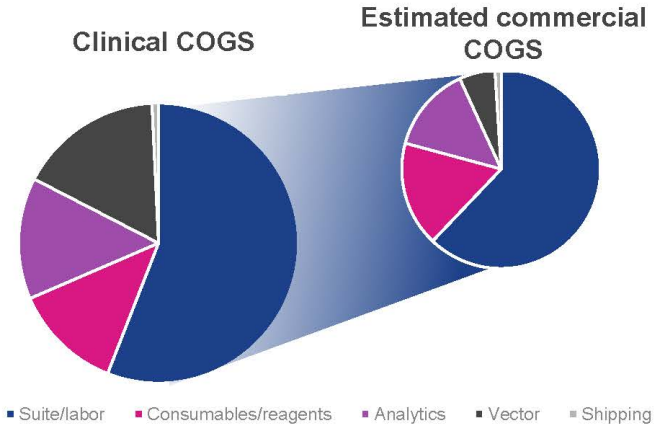
Attractive COGS profile

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

AVROBIO

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

AVROBIO

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

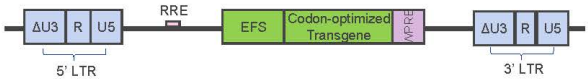
AVROBIO state-of-the-art vector

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

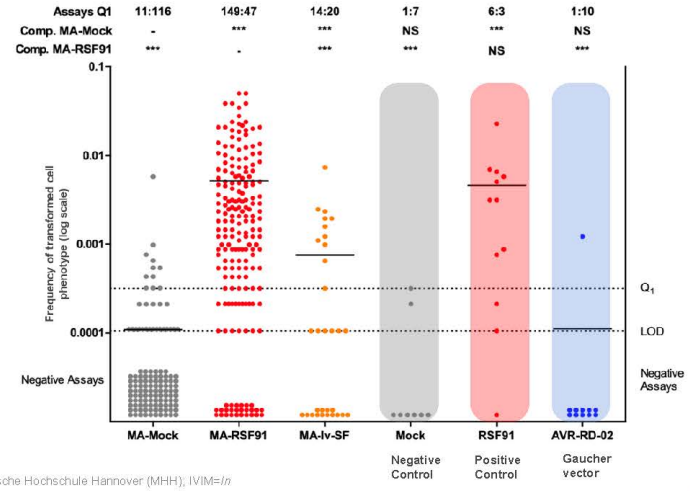
Favorable Gaucher vector safety profile via IVIM

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

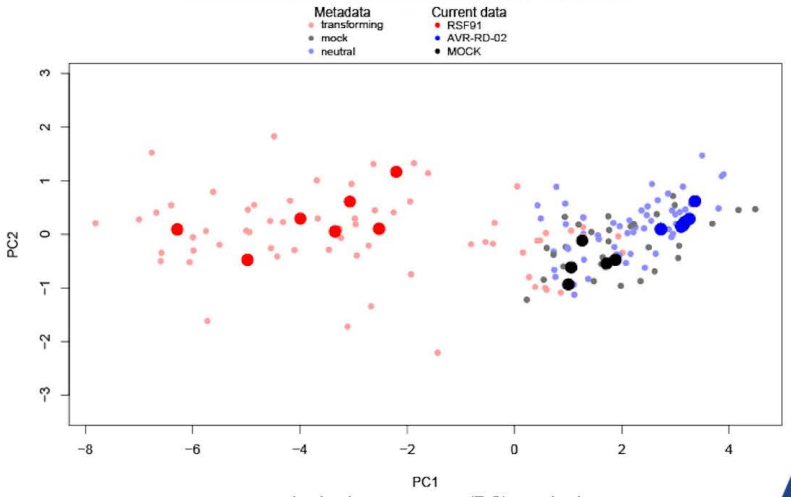
Favorable Gaucher vector safety profile via SAGA

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

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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

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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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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

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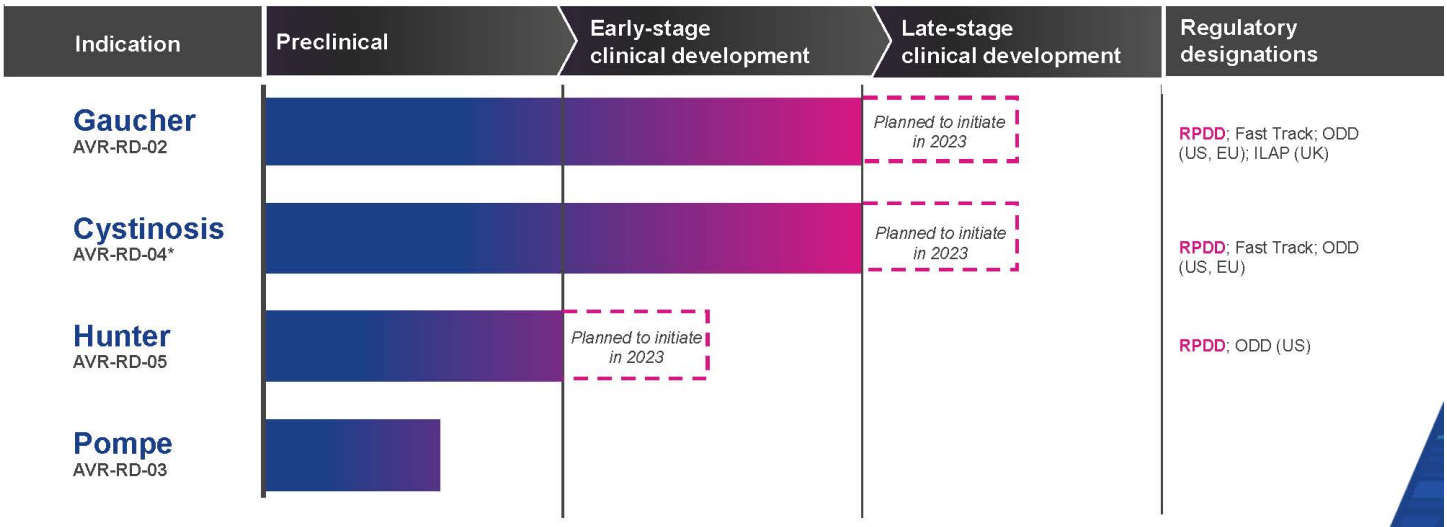
AVROBIO entering late-stage development



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**

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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

Cystinosis

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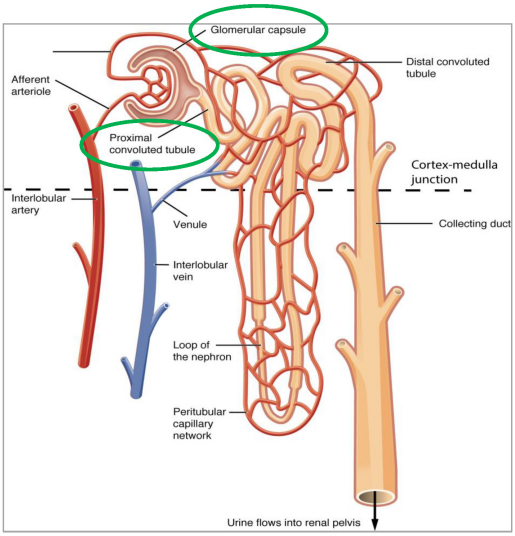
Planned RFS endpoint captures complexity of disease

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



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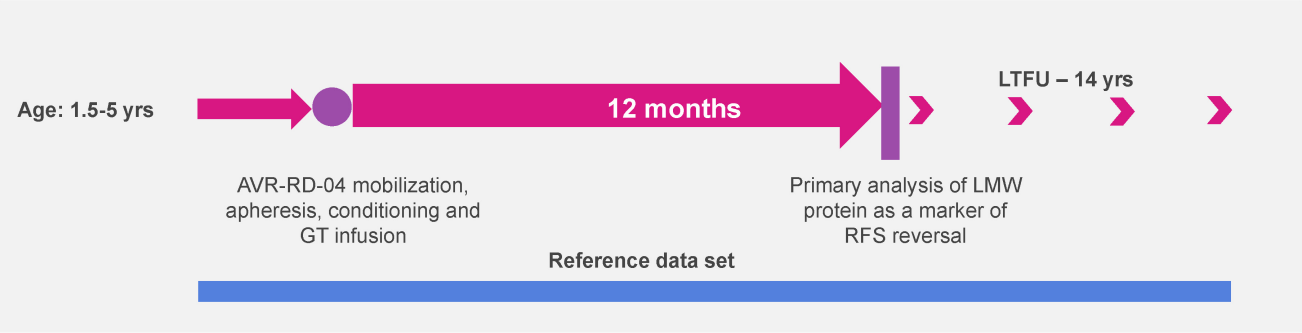
Syres 2009; Yeagy 2011, Gabriel 2017; RFS=Renal Fanconi Syndrome; LMW=Low molecular weight; ESRD=End-stage renal disease; BM=Bone marrow: MOA=Method of action; GFR=Glomerular filtration rate

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