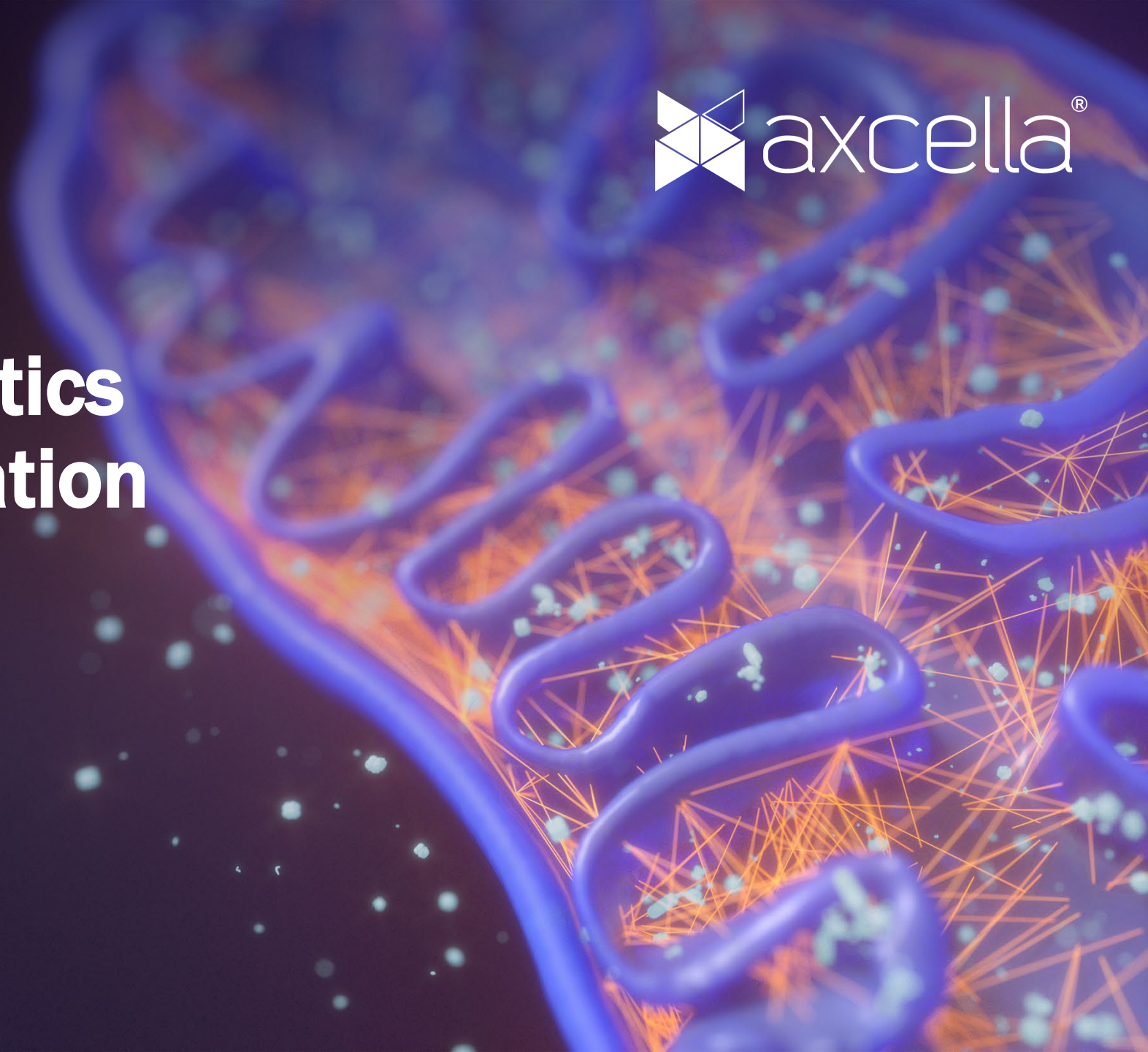
NASDAQ: AXLA

Axcella Therapeutics Investor Presentation



May 2022

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding the characteristics, competitive position and development potential of AXA1125 and potential future EMM compositions, the potential for AXA1125 to serve as a treatment for Long COVID and a first-line NASH monotherapy for adult and pediatric patients and be used in combination with other agents if required, the design, status and timing of the company's Phase 2a and Phase 2b clinical trials of AXA1125, the intended results of the company's strategy and approach, the size and growth potential of the markets for the company's product candidates, the company's intellectual property position, the company's cash runway and the company's ability to address other complex diseases and conditions utilizing EMM compositions. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, those related to the potential impact of COVID-19 or other events on our ability to conduct and complete ongoing or planned clinical studies and clinical trials and planned submissions to FDA or other regulatory authorities in a timely manner or at all due to patient or principal investigator recruitment or availability challenges, clinical trial site shutdowns or other interruptions and potential limitations on the quality, completeness and interpretability of data we are able to collect in our clinical studies and potential delays in disclosure of the same; other potential impacts of COVID-19 or other events on our business and financial results, including with respect to our ability to raise additional capital and operational disruptions or delays, changes in law, regulations, or interpretations and enforcement of regulatory guidance; clinical trial initiation plans and timing, clinical trial design and target indication(s) for AXA1125 the clinical development and safety profile of our product candidates and their health or therapeutic potential; whether and when, if at all, our product candidates will receive approval from the FDA or other comparable regulatory authorities, and for which, if any, indications; competition from other biotechnology companies; past results from clinical studies not being representative of future results and other risks identified in our SEC filings, including Axcella's Annual Report on Form 10-K, Quarterly Report on Form 10-Q and subsequent filings with the SEC. The company cautions you not to place undue reliance on any forward-looking statements, which speak only as of the date they are made. Axcella disclaims any obligation to publicly update or revise any such statements to reflect any change in expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements. Any forward-looking statements contained in this presentation represent our views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date.

Investment Highlights: Unique Approach with Two Near-Term Readouts

1 Q3 ‘22 Ph2a TLD Readout in Long COVID	First-mover to address a large, rapidly growing public health crisis with a strong scientific rationale
2 Q3 ‘22 Ph2b IA Readout in NASH	First-line potential based on the strength of data, a unique multi-targeted MOA and an endogenous, oral approach
3 Large Unserved/Underserved Markets	Tens of millions impacted by Long COVID and NASH with no approved treatments
4 Increased Probability of Success	Prior clinical studies of AXA1125 demonstrated safety/tolerability and strong multifactorial activity based on strong scientific foundation
5 Established Platform and Strong IP	Efficient and informed design platform; wholly-owned oral candidates; growing number of patents with protection ≥2037
6 High-Caliber Leadership and Investors	Strong management and board; majority of shares owned by Flagship Pioneering, Fidelity and Nestle Health Sciences

Abbreviations: IA, Interim Analysis; TLD, Top Line Data

Multi-Targeted Therapeutics to Restore Homeostasis

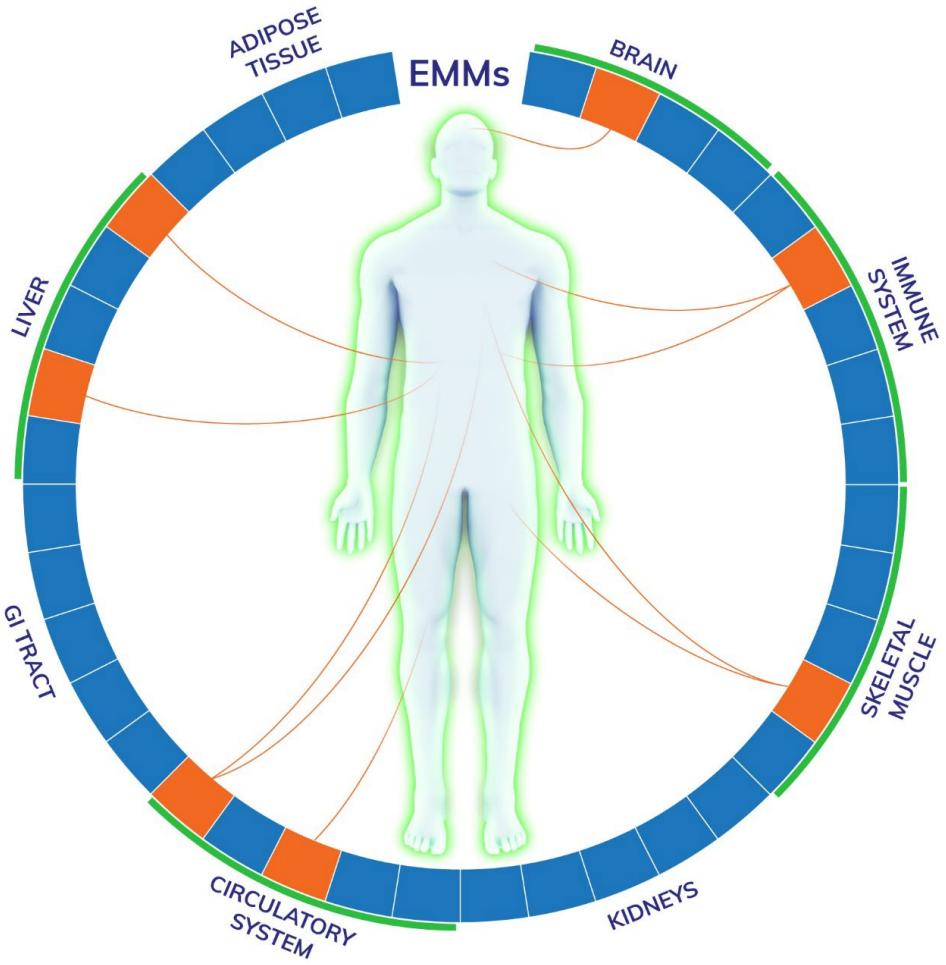
Leveraging Endogenous Metabolic Modulator (EMM) compositions to treat complex medical conditions

- Complex conditions are driven by dysregulation in multiple biological pathways, limiting the effect of single-targeted therapies

- Amino acid-based therapeutics can be safely used to:
  - Regulate key signaling pathways
  - Restore mitochondrial function
  - Shift substrate/redox balance to restore homeostasis

- Potential therapeutic benefits include:
  - Enhancing muscle function
  - Correcting metabolism
  - Decreasing inflammation
  - Improving neurocognition
  - Rebalancing IEMs
  - Reducing fibrosis

Axcella's clinical data demonstrate the potential to harness the power of EMMs to tackle complex chronic conditions

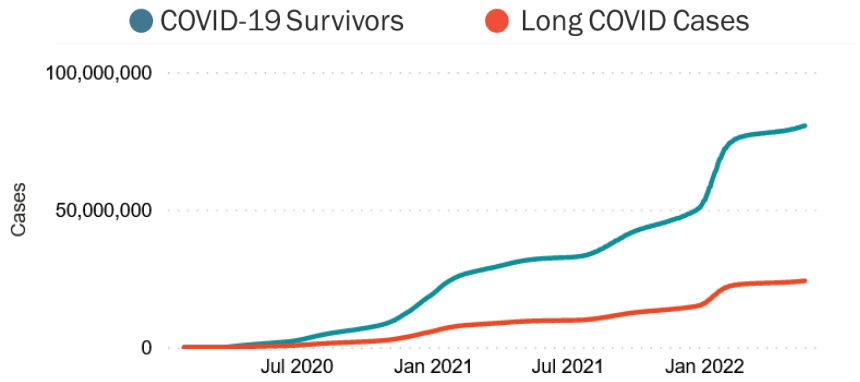


AXA1125 for Long COVID

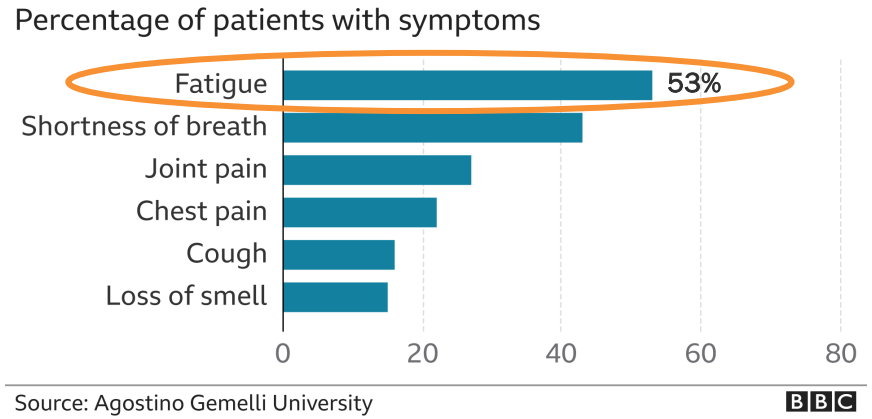
Long COVID: A Large and Still Emerging Public Health Crisis

- ~520M confirmed COVID-19 cases worldwide to date[1]
- ~20-40% of COVID patients report Long COVID conditions and symptoms[2,3,4]
- Long COVID's effects are being felt regardless of vaccination or variants
- Most commonly reported symptom: Chronic fatigue, experienced by **most** Long COVID patients
- Potential to be first to market with no approved Long COVID therapies and few even in clinical development

U.S. COVID Survivals and Long COVID Cases[5]



Most Common Long COVID Symptoms

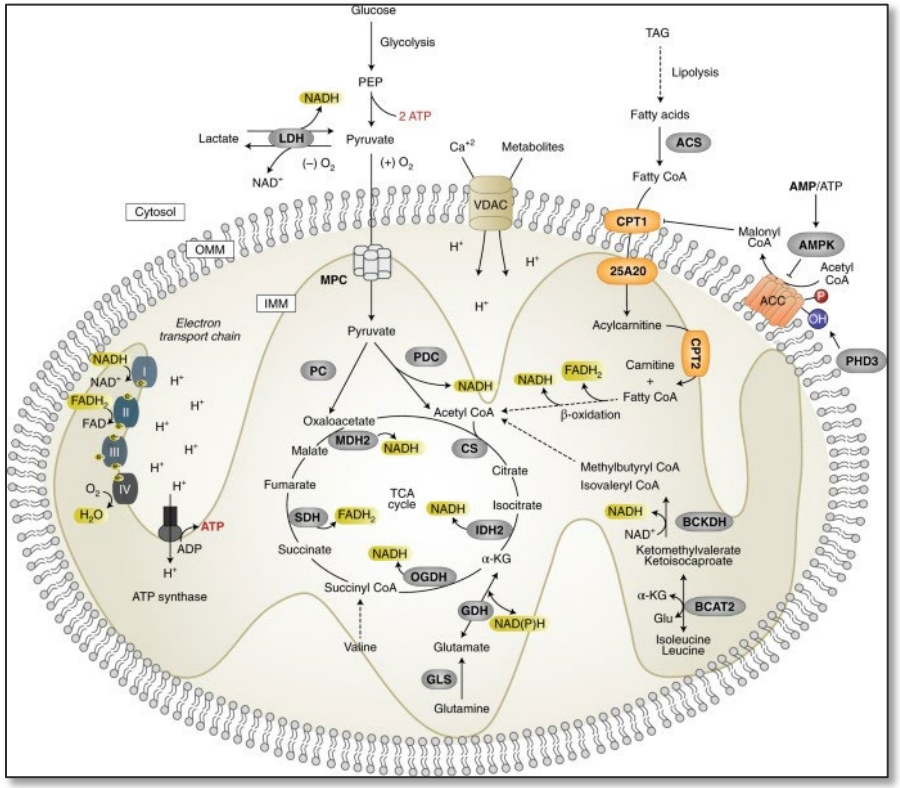


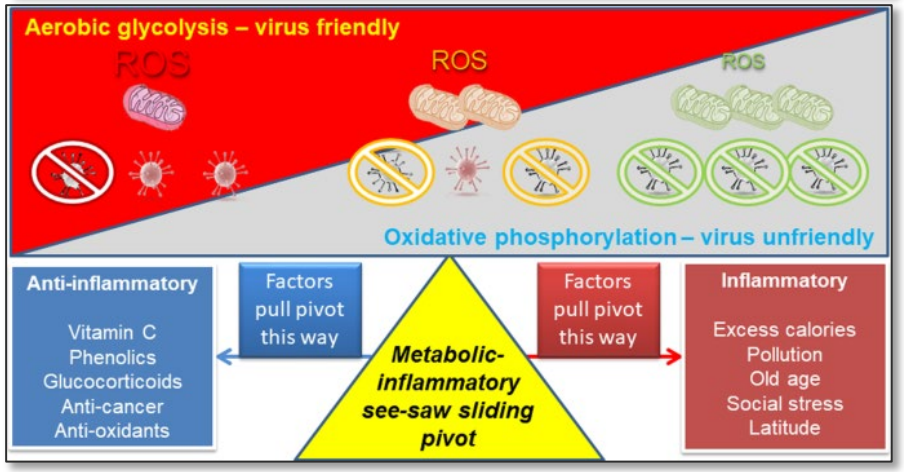
1. WHO Coronavirus (COVID-19) Dashboard: https://covid19.who.int/, accessed 5/18/22; 2. Fair Health "A Detailed Study of Patients with Long-Haul COVID". 6/15/21; 3, Taquet, M., et. Al. (2021). PLoS Med 18(9): e1003773.; 4. Yoo, S.M., et. al. (2022). https://doi.org/10.1007/s11606-022-07523-3.; 5. American Academy of Physical Medicine and Rehabilitation's "PASC Dashboard". PASC = Post-acute Sequelae of COVID-19. https://pascdashboard.aapmr.org/, accessed 5/18/22.

Mitochondrial Cascade in Long COVID

Cascade of effects on the mitochondria, including:

1. Switch to inefficient glycolysis, compromising bioenergetics
2. Increased oxidative stress and compounding inflammation
3. Impaired immune response and muscle function



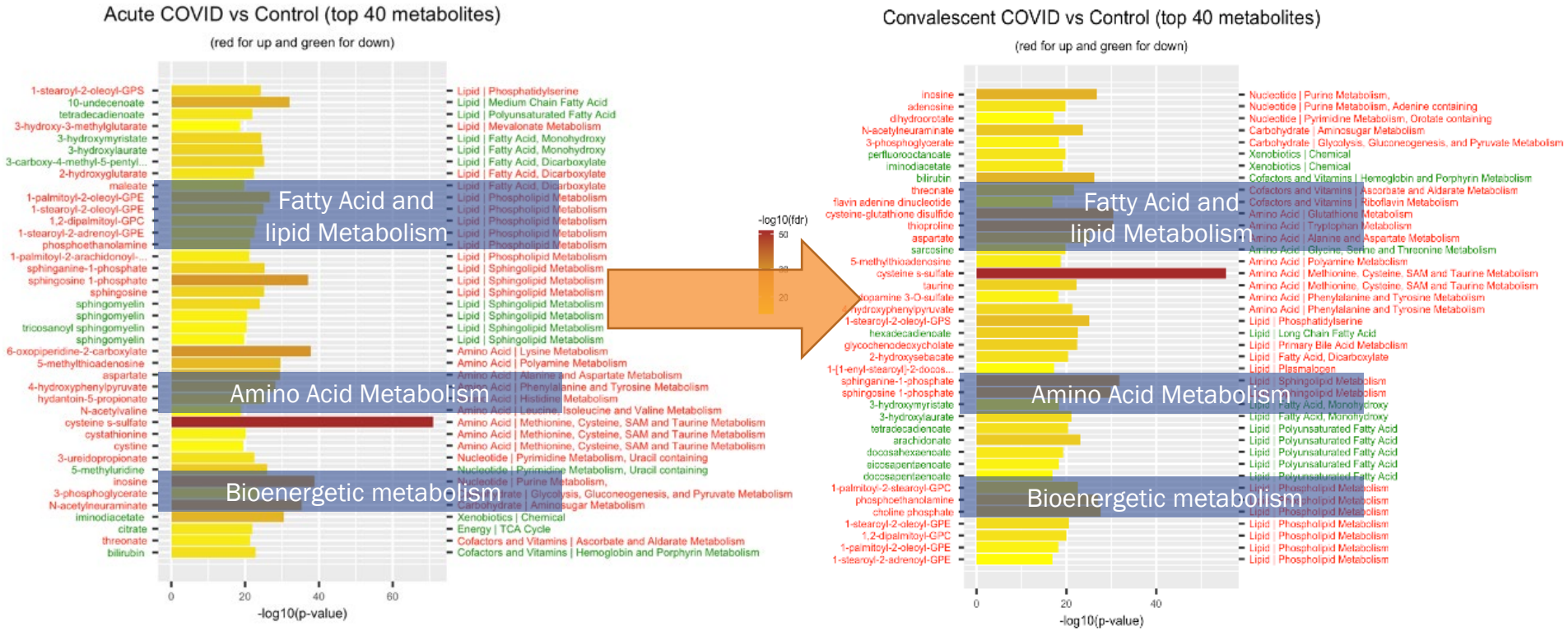


Top right: Nat Cell Biol. 2018 July, 20(7): 745–754; Bottom right: Immunity & Ageing (2020) 17:33 Cell Metabolism 32, 437–446

Long COVID Patient Data Demonstrate Dysregulation of Energetics, Amino Acids and Lipid Metabolism

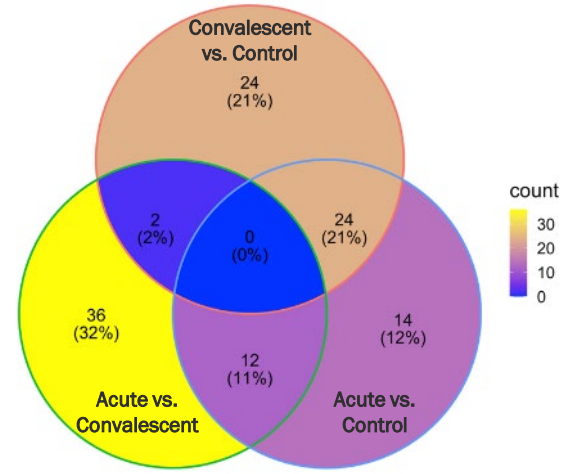
Emerging data from Institute for Systems Biology

Acute vs. Control → Convalescent vs. Control



Biological changes that are initiated in Acute COVID persist into Long COVID

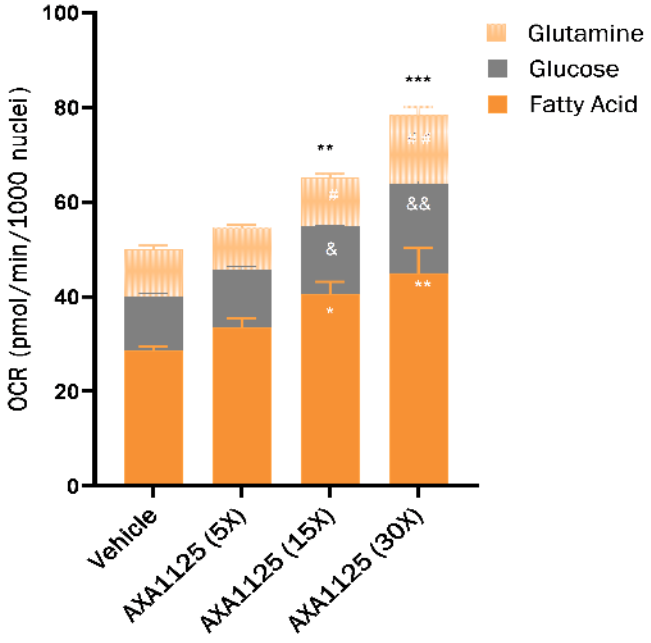
Top 50 Metabolites in Each Comparison



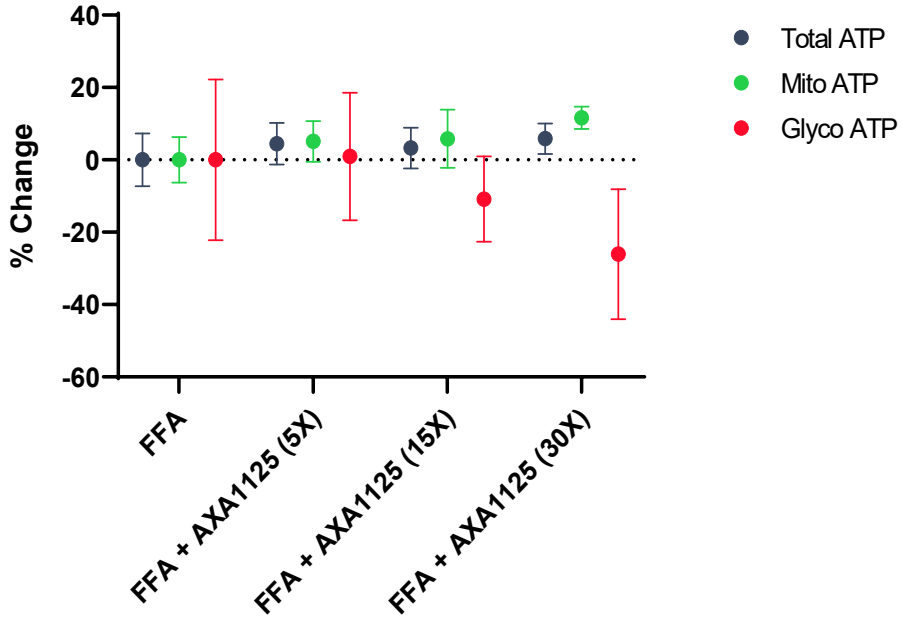
AXA1125 Drives Improvement in Mitochondrial Respiration

Treatment of hepatocytes induces substrate mobilization for mitochondrial respiration

↑ Fatty Acid Oxidation, Basal Respiration



↑ ATP Production



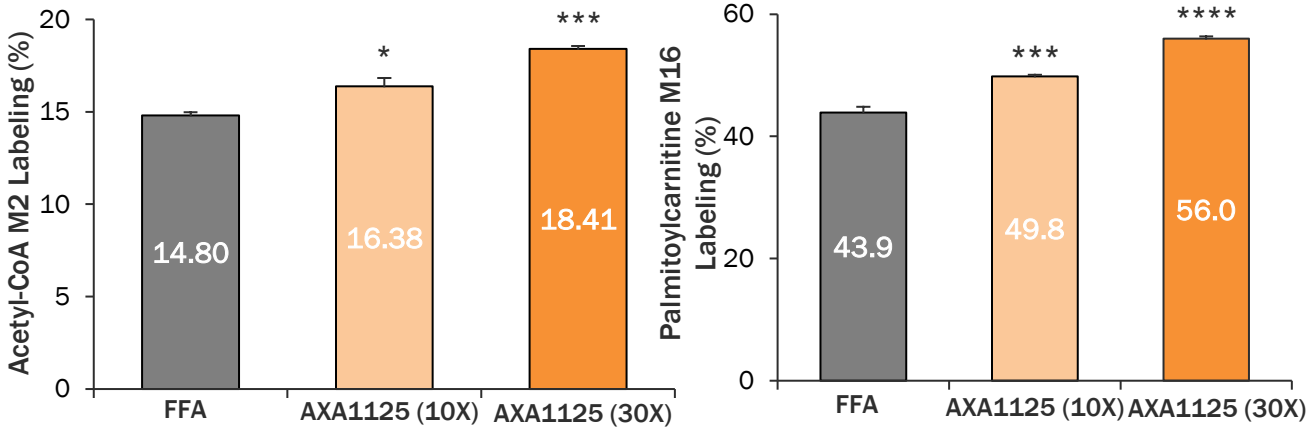
*: p<0.05
**: p<0.01,
***: p<0.001

Data shown above were generated in vitro with the same AA constituents of AXA1125, i.e. LIVRQNac, at a multiple of their baseline concentrations as found in the Human Metabolome Database.

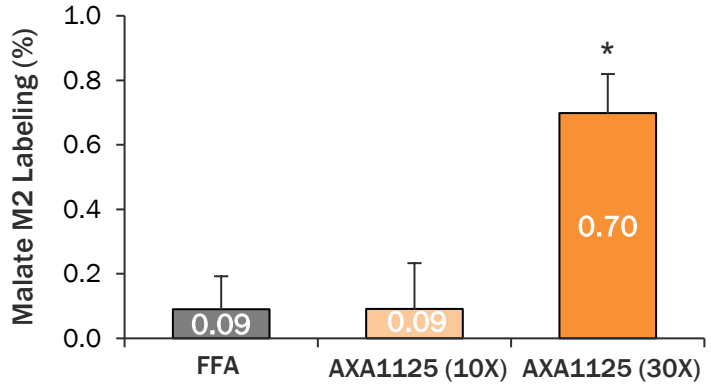
Increased Fatty Acid Oxidation with AXA1125 Provides Further Mechanistic Support for Mitochondrial Bioenergetic Improvement

Treatment induces substrate mobilization to meet energetic demands and prevent FA accumulation

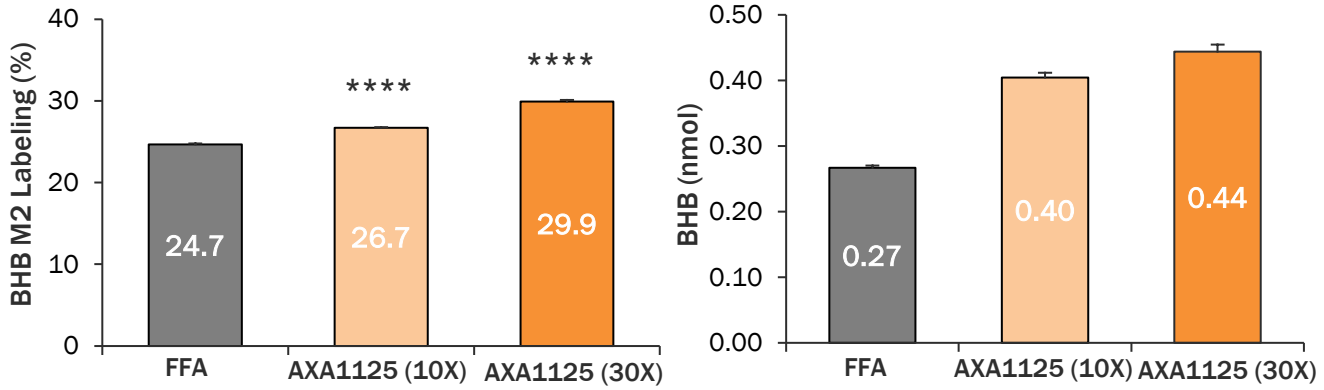
Increase in Acetyl-CoA M2 and Palmitoylcarnitine M16 demonstrate engagement of beta oxidation pathway



Increase in Malate M2 demonstrates engagement of TCA cycle



Increase in BHB M2 demonstrates roughly a doubling of cellular metabolism



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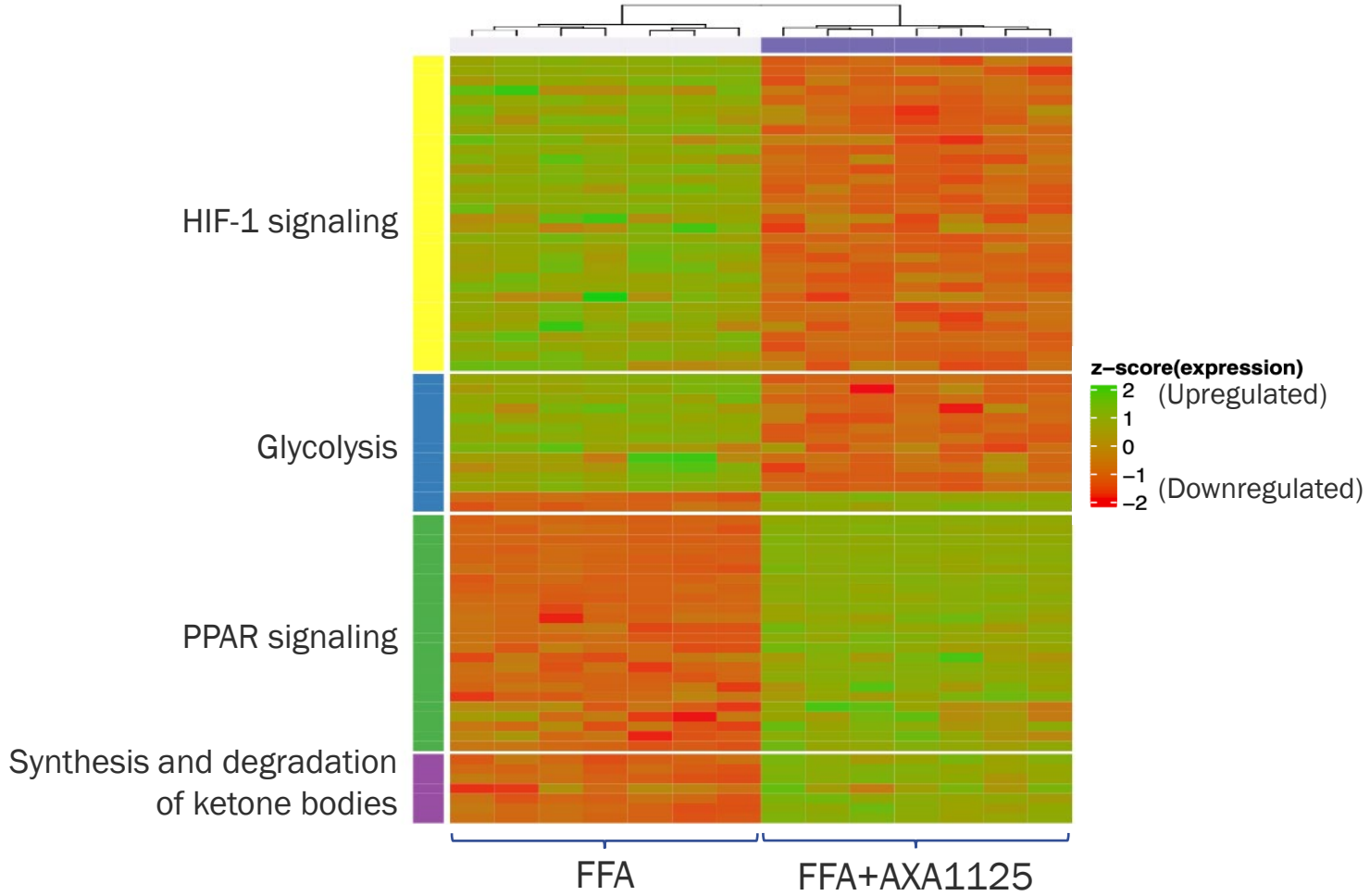
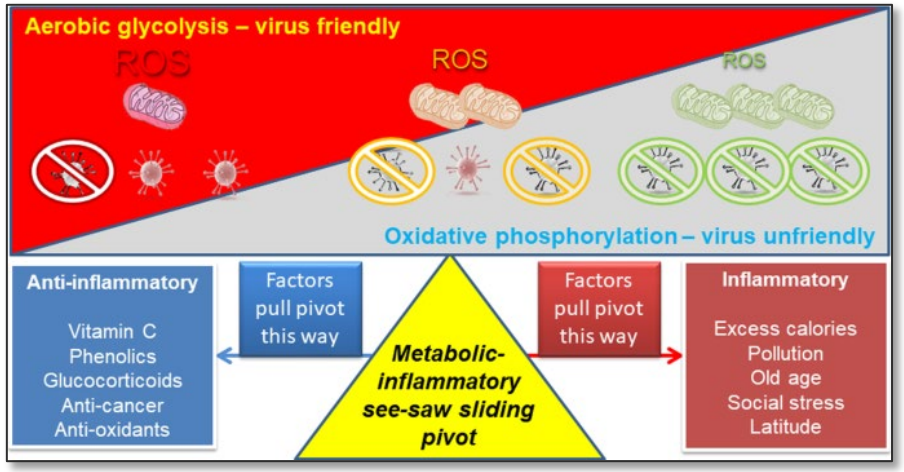
**: p<0.01
***: p<0.001
****: p<0.0001

Data shown above were generated in vitro with the same AA constituents of AXA1125, i.e. LIVRQNac, at a multiple of their baseline concentrations as found in the Human Metabolome Database.

AXA1125 Improves Mitochondrial Energetics, Immune Regulation and Anti-Inflammatory Profile Through Canonical Biochemical Pathways

Pathway Enrichment Reveals Key Drivers of Improvement in Mitochondrial Function





Data shown above were generated in vitro with the same AA constituents of AXA1125, i.e. LIVRQNac, at a multiple of their baseline concentrations as found in the Human Metabolome Database. FFA, free fatty acid; HIF-1, hypoxia-inducible factor 1; LIVRQNac, 5 amino acids and N-acetylcysteine; PPAR, peroxisome proliferator-activated receptors.

Impact of AXA1125 on Mitochondrial Function Matches Key Science and Clinical Need in Long COVID

Evidence of mitochondrial dysfunction in NASH and Long COVID

Result of Mitochondrial Dysfunction and Inflammation in Long Covid

Cascade of effects, including:

- Switch to inefficient glycolysis energetics
- Compromised bioenergetics
- Increased oxidative stress and compounding inflammation
- Impaired immune response and muscle function

AXA1125: Impact Demonstrated on Mitochondrial Function and Inflammation Thus Far

- Increase preferential fatty acid oxidation, improve cellular respiration
- Increase ATP generation
- Reduce inflammation, improve anti-oxidant response
- Initial clinical translation in NASH; Long COVID trial now underway

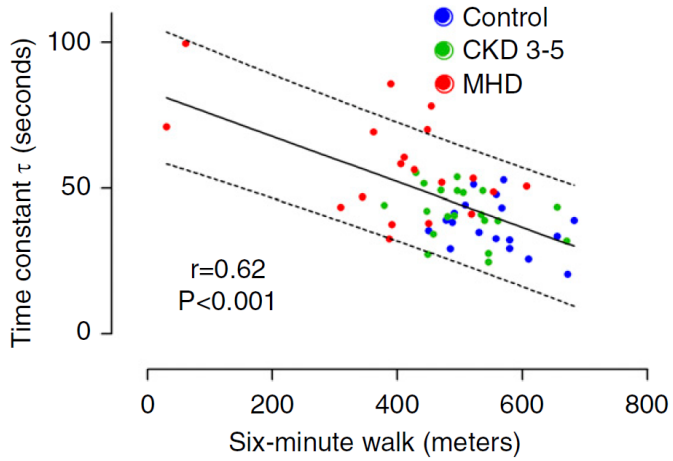
Reduction in Skeletal Muscle PCr Leads to Improved Muscle Function

PCr recovery time after exercise reflects skeletal muscle mitochondrial function *in vivo*

Phosphocreatine (PCr) Recovery Time:

- PCr post exercise time is a ^{31}P-MRS validated and direct measure of skeletal muscle mitochondrial oxidative capacity
- Used to evaluate muscle function in a wide range of other conditions including amyotrophic lateral sclerosis (ALS), Duchenne, chronic kidney disease (CKD), etc.
- Normal PCr tends to be ~24±5 seconds[2]

PCr → 6-Minute Walk in CKD[1]



Improvement in PCr recovery time has been correlated to improved muscle function and outcomes[3]

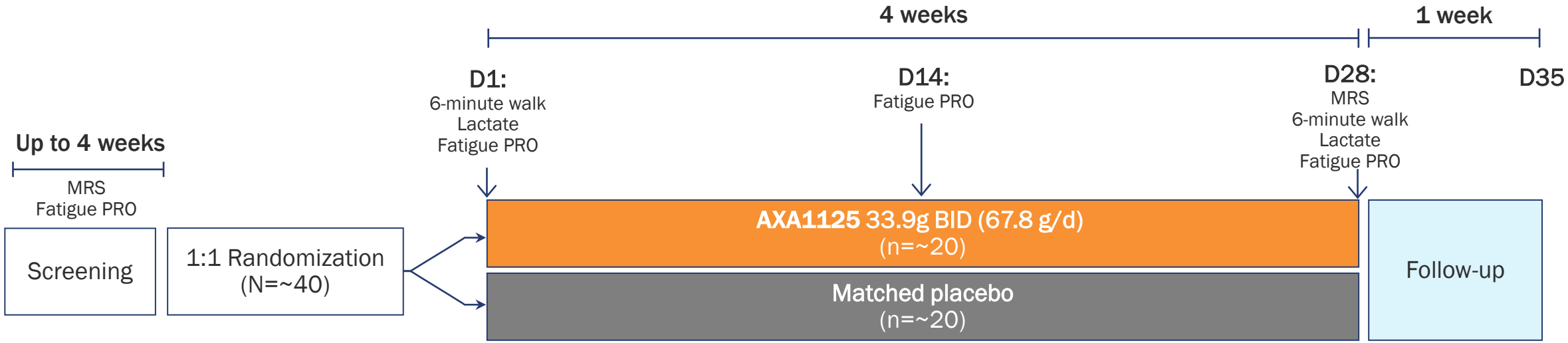
PCr (mitochondrial function) → Muscle function → Walking distance

1. Gamboa et al. CJASN (July 2020) Vol 15
2. Oorschot et al. PLOS ONE (Sept. 2013) Vol 8 Issue 9
3. Zane et al. Aging Cell (2017) 16, pp461–468

P-MRS: Phosphorus Magnetic Resonance Spectroscopy

Phase 2a Long COVID Clinical Trial Now Underway

Top-line data anticipated in Q3 2022



Core elements	Description
Design	• Randomized double blind, placebo-controlled study over 28 days
Study population	• Including Long COVID patients (>12 weeks post PCR+) with fatigue-predominant symptoms/abnormalities: – PCr recovery time of ≥50 sec. – Chalder Fatigue score of >8 • Excluding patients with other potential drivers of fatigue and MRS abnormalities (vascular disease, diabetes, etc.)
Endpoints include	• Primary: PCr recovery time • Lactate levels • 6-minute walk test • Fatigue scores • Safety and tolerability

BID, twice daily; MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; PRO, patient reported outcomes

AXA1125 for Nonalcoholic Steatohepatitis (NASH)

Nonalcoholic Steatohepatitis (NASH)

A complex, chronic disease impacting up to 40 million Americans with no approved therapies

The Disease and Standard of Care:

- Progressive, chronic liver disease involving multiple drivers and pathways
- No NASH therapies approved in U.S.
- Comorbid population (T2D, heart disease, etc.) that already is on ~7 medications[1]
- Most drug candidates have single targets, leading to combination therapy development
  - Administration, safety tolerability challenges (injectables, lipids, pruritis, DDI, etc.)
  - Very limited pediatric development activity

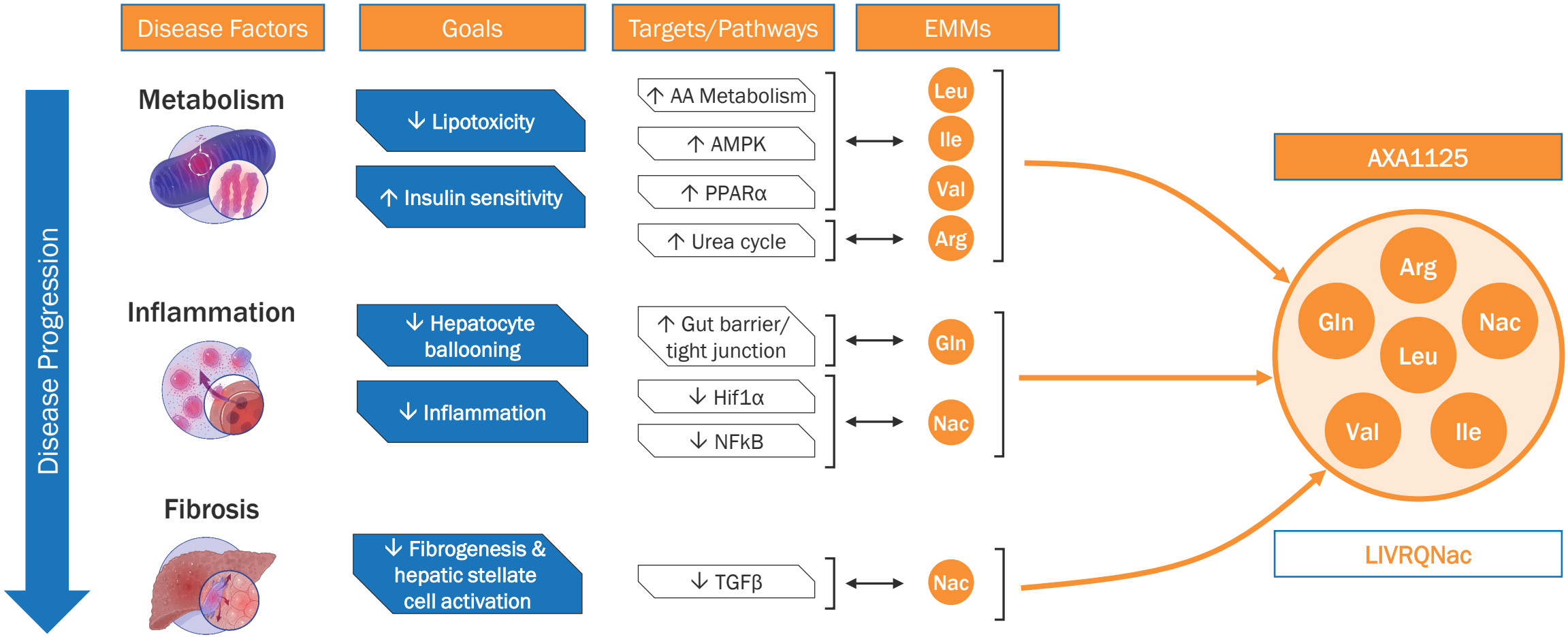
State of the Market:

- Up to 40 million NASH patients in the U.S. alone and growing rapidly[2]
- Approximately 10% of U.S. children are estimated to have NASH[2]
- >40% of NASH patients also have type 2 diabetes (T2D)[3]
- Lifetime costs for all U.S. NASH patients exceeds $300 billion[2]

1. Desai, R. et al. Characterization of Polypharmacy in Patients with NAFLD. AASLD 2018
2. Global Liver Institute U.S. NASH Action Plan (Dec. 2020).
3. Younossi, Z. et al. Hepatology. Vol. 64, No. 1, 2016.

AXA1125 - Designed to Target Multiple Metabolic Pathways

Potential for multifactorial activity in NASH and compounding benefits over time



Hypothesized mechanisms depicted above.

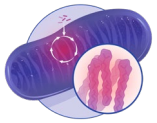
AAs, amino acids; AMPK, AMP-activated protein kinase; Arg, arginine; Gln, glutamine; GSH, glutathione; Hif1α, hypoxia-inducible factor 1 alpha; GSH, glutathione; Ile, isoleucine; Leu, leucine; Nac, N-acetylcysteine; NASH, nonalcoholic steatohepatitis; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NH3, ammonia; NO, nitric oxide; PPARα, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; TGFβ, transforming growth factor beta; Val, valine.

Reductions Noted in Key Biomarkers with AXA1125

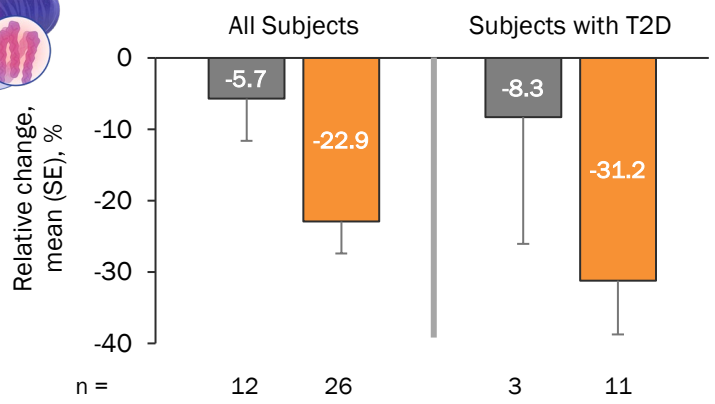
Changes from baseline at week 16

EASL THE DIGITAL INTERNATIONAL LIVER CONGRESS™ 27–29 August 2020 www.ilc-congress.eu

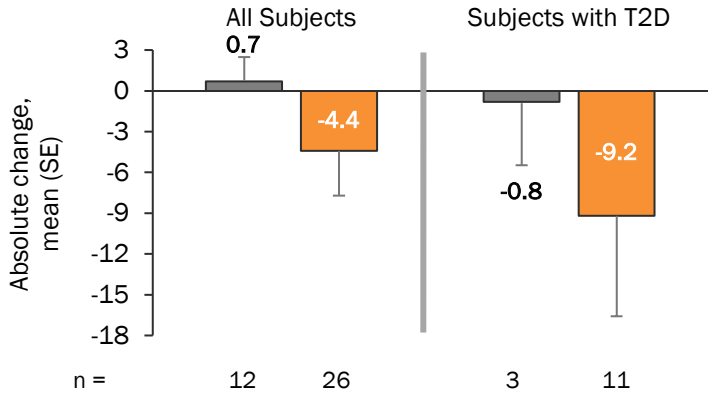
Metabolism



MRI-PDFF

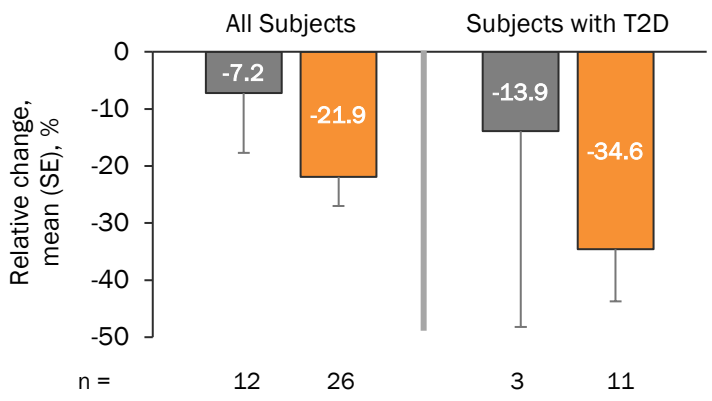


HOMA-IR

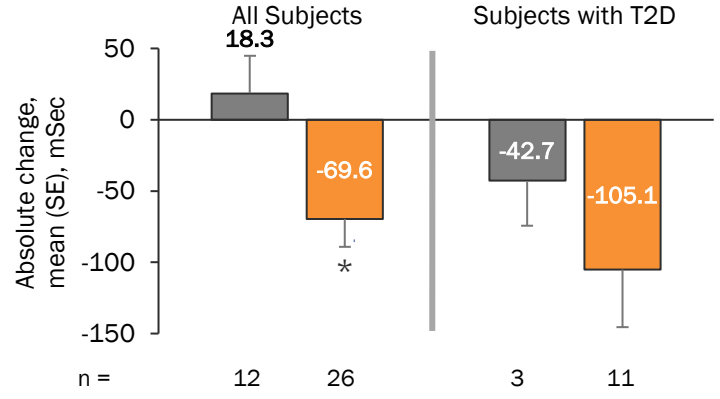


Inflammation

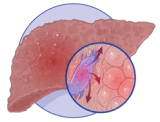
ALT



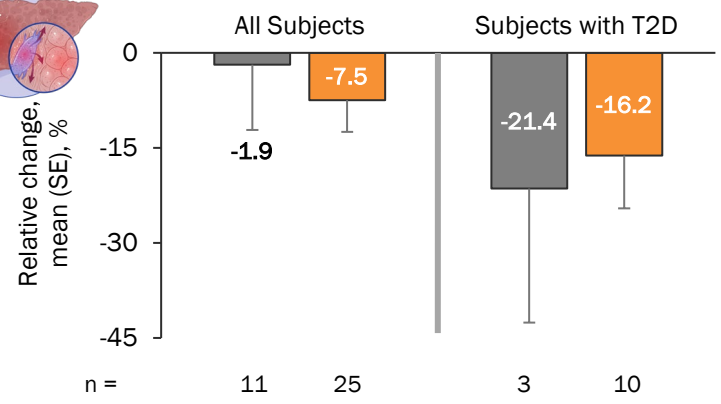
cT1



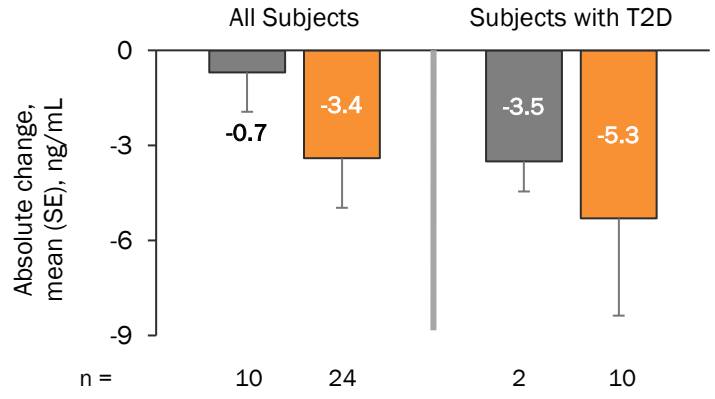
Fibrosis



FIB-4



ProC3



Placebo AXA1125

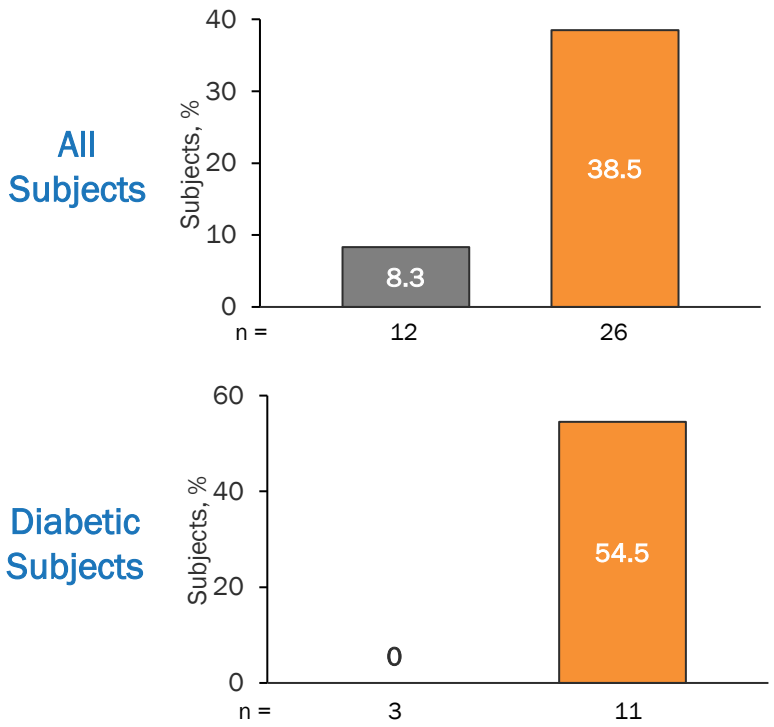
*p<0.05 versus placebo.

ALT, alanine aminotransferase; cT1, corrected T1; FIB-4, fibrosis 4; HOMA-IR, homeostasis model assessment of insulin resistance; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ProC3, propeptide of type III collagen; SE, standard error; T2D, type 2 diabetes.

AXA1125: Meaningful Thresholds of Activity Achieved

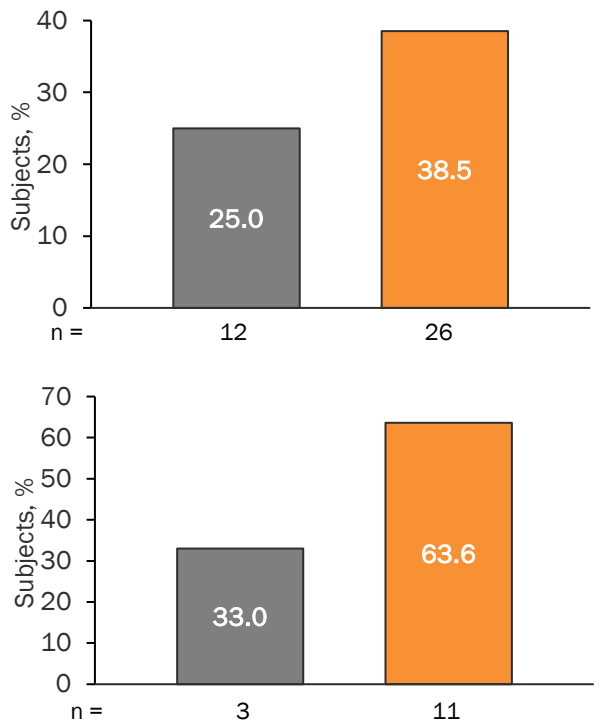
Increasing evidence linking PDFF, ALT and cT1 with improved histological outcomes

≥30% Reduction in MRI-PDFF



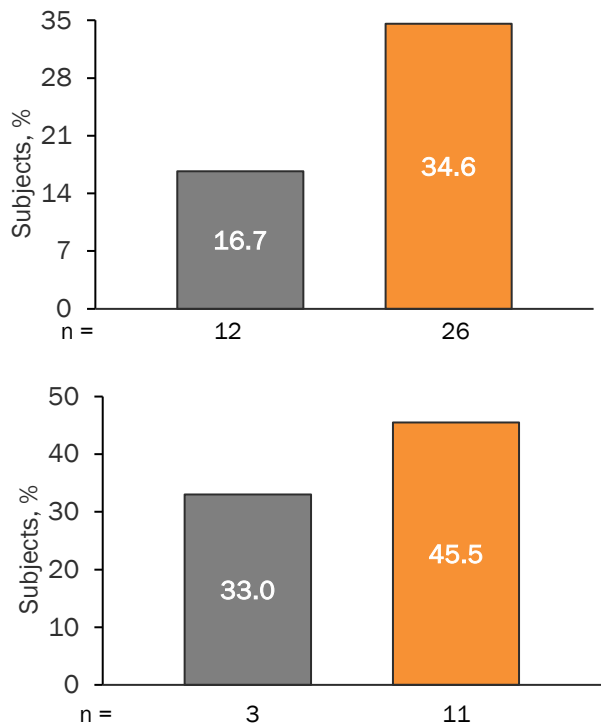
≥30% reduction associated with histologic response in NASH[1]

≥17 U/L Reduction in ALT



≥17 U/L reduction associated with histologic response in NASH[2]

≥80 mSec Reduction in cT1



>80 mSec reduction may correlate with a 2 pt. NAFLD score improvement[3]

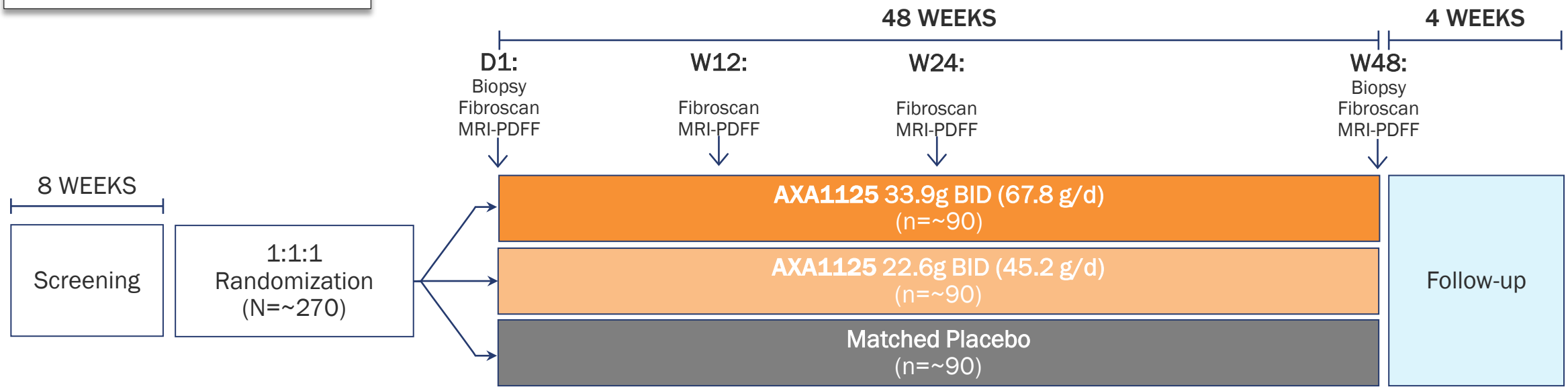
Placebo AXA1125

1. Loomba, R. et al. Hepatology (January 2020). 2. Loomba, R. et al. Gastroenterology (January 2019). 3. Dennis, A. et al. Frontiers in Endocrinology (November 2020).
ALT, alanine aminotransferase; cT1, corrected T1; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NASH, nonalcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; SE, standard error.

EMMPACT℠ NASH CLINICAL TRIAL

Phase 2b Clinical Trial Underway

Interim analysis expected in Q3 2022



Core elements	Description
Design	• Randomized, double-blind, placebo-controlled, dose-ranging study over 48 weeks
Study population	• Biopsy-proven F2/F3 NASH with NAS>4 • Stratification by type 2 diabetic status
Primary endpoint	• Biopsy-confirmed ≥2 point improvement in NAS
Secondary endpoints	• Biopsy-confirmed resolution of NASH without worsening of fibrosis • Biopsy-confirmed ≥1 stage improvement in fibrosis without worsening of NASH
Other endpoints	• Improvement in non-invasive markers, including MRI-PDFF, ALT and Fibroscan

Summary

Strategy Intended to Protect Axcella's First-Mover Advantages

PATENTING AREAS

Composition/Method of Use

- Liver
- Muscle
- Blood
- CNS

Platform-Focused

- Mechanistic and biological pathway uses

Formulation/Manufacturing

- Pharmaceutical-grade manufacturing
- Low volume and stability formulations
- Taste formulations

LEAD CANDIDATES

Compositions and methods of use patents granted and pending for AXA1125 in NASH and Long COVID; expirations in 2037 and 2042, respectively

TRADE SECRETS

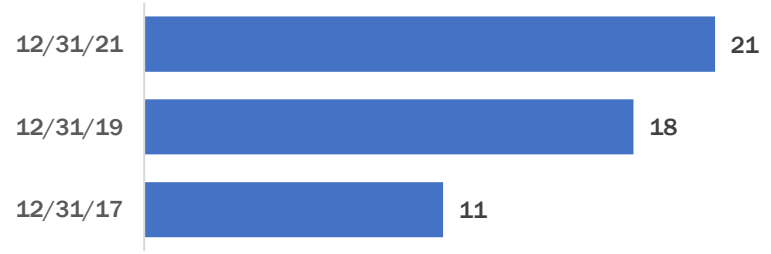
Leveraging extensive know how underlying research platform, EMM composition design and manufacturing

REGULATORY EXCLUSIVITY

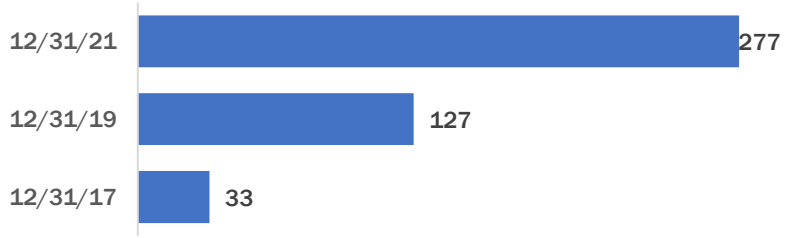
Plans to pursue regulatory exclusivity where available, particularly in U.S., Europe, Japan

PATENTS & APPLICATIONS

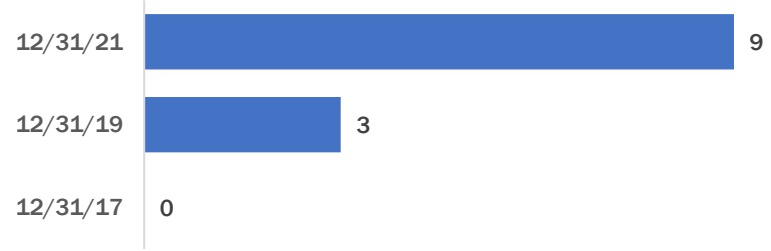
WORLDWIDE PATENT FAMILIES



WORLDWIDE PATENTS PENDING



U.S. PATENTS GRANTED



Axcella Financials

Year end 2021 cash balance bolstered further by $25 million registered direct financing in March 2022

(in thousands)	March 31, 2022
Assets:	
Cash and cash equivalents	$45,190
Marketable securities	18,029
Other assets	5,161
Total assets	**$68,380**
Liabilities and stockholders' equity:	
Liabilities	$38,488
Stockholders' equity	29,892
Total liabilities and stockholders' equity	**$68,380**

(in thousands, except share and per share data)	Three Months Ended March 31, 2022	Year Ended December 31, 2021
Operating expenses:		
Research and development	$13,544	$43,135
General and administrative	4,786	18,711
Total operating expenses	18,330	61,846
Loss from operations	(18,330)	(61,846)
Other income (expense), net	(709)	(2,782)
Net loss	$(19,039)	$(64,628)
Net loss per share, basic and diluted	$(0.46)	$(1.70)
Weighted average common shares outstanding, basic and diluted	**41,426,107**	**38,110,420**

Axcella's Experienced Leadership

Bill Hinshaw
President and CEO
NOVARTIS
Schering-Plough

Margaret Koziel, MD
SVP, Chief Medical Officer
VERTEX Kaleido

Dan Kirby
SVP, Strategic Operations
amag PHARMACEUTICALS Seqirus

Bob Crane
SVP, Chief Financial Officer
sirtris PHARMACEUTICALS PYXIS ONCOLOGY

Paul Fehlner, PhD, JD
SVP, Chief Legal Officer
NOVARTIS
BAKER BOTTS L.L.P.

Virginia Dean
SVP, Chief People Officer
ARIAD TESARO

BOARD OF DIRECTORS

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Executive Partner
Flagship Pioneering

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CFO
2seventy bio

Martin Hendrix, PhD
Head of Global Business Development and M&A ·
Nestlé Health Science

Bill Hinshaw
President and CEO
Axcella Therapeutics

Gary Pisano, PhD
Professor of Business
Harvard Business School

Cristina Rondinone, PhD
Founder
CMR Pharma Consulting

Michael Rosenblatt, MD
Senior Partner
Flagship Pioneering

Paul Sekhri
Former President and CEO
eGenesis

Catherine A. Sohn, PharmD
Adjunct Professor
University of California San Francisco

Expected 2022 Milestones

Program	Update	Timing
AXA1125 for Long COVID	Phase 2a Enrollment	Q2 2022 - Completed
	Phase 2a Top-Line Data	Q3 2022
	Regulatory Engagement*	2H 2022
	Exploration of Other Mitochondrial Opportunities*	2H 2022
AXA1125 for NASH	Phase 2b Interim Data	Q3 2022
	Phase 2b Enrollment Completion	2H 2022

Milestone timing based on current expectations and subject to change.
* Assumes positive Phase 2a data readout.

NASDAQ: AXLA

Thank You

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Cambridge, MA 02139

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Reference Materials

AXA1125 for Long COVID

- Phase 2a Clinical Trial Design and Initiation
- Phase 2a on Clinicaltrials.gov
- Background: Mitochondrial Dysfunction in Long COVID

AXA1125 for NASH

- Mechanism of Action (NASH-TAG 2021)
- Nonclinical Findings (Nature's *Scientific Reports*)
- AXA1125-003 Data (*American Journal of Gastroenterology*)
- EMMPACT Trial in Clinicaltrials.gov

Axcella's EMM Platform and Therapeutic Approach

- Use of Amino Acids as Therapeutics (*iScience*)
- Combinatorial approach to EMMs (ICFSR)

About Axcella's Development Model and Clinical Approach

EMMs have a fundamental role in biology and biological function. Using the Axcella Knowledge Base, Axcella designs and develops novel EMM compositions to engage identified biologies and pathways. Axcella then selects whether to evaluate a product candidate in a non-investigational new drug application (non-IND) clinical study under U.S. Food and Drug Administration regulations and guidance supporting research with food, or under an IND clinical trial. Axcella's non-IND clinical studies evaluate product candidates for safety, tolerability and effects on the normal structures and functions in humans, including in individuals with disease. The company's non-IND clinical studies include a substantial number of biomarkers that may inform biologies relevant to health but are not designed or intended to evaluate a product candidate's ability to diagnose, cure, mitigate, treat or prevent a disease or other health condition. These clinical studies are conducted at reputable medical centers following Good Clinical Practices (GCPs), including Institutional Review Board (IRB) approval, and utilize qualified investigators. Using a combination of data from these studies and/or other relevant information, the company decides whether to advance a product candidate's development as a therapeutic or supplement (independently or in partnership), or to terminate its development.

To date, Axcella has initially evaluated its product candidates as investigational food products in non-IND clinical studies. More recently, Axcella determined its lead compound – AXA1125 – to be a therapeutic product candidate, meaning that its ongoing development will be conducted under IND to investigate its ability to treat diseases. As a result, the company will investigate the treatment of NASH and the treatment of Long COVID with AXA1125.

This presentation refers to Axcella's non-IND clinical studies as "clinical studies" and its IND clinical trials as "clinical trials."