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): **August 2, 2022**

AXCELLA HEALTH INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-38901**	**26-3321056**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

840 Memorial Drive **Cambridge, Massachusetts**	**02139**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(857) 320-2200**

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 (see General Instruction A.2. below):

☐ 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, $0.001 Par Value	**AXLA**	**Nasdaq Global 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 August 2, 2022, Axcella Health Inc. (the "Company" or "Axcella") issued a press release announcing top-line data from its Phase 2a clinical trial of AXA1125 for the treatment of Long COVID entitled "Axcella Announces Results from Phase 2a Clinical Trial for Long COVID." The Company also hosted a conference call to discuss the top-line data results on Tuesday, August 2, 2022 at 8:00 a.m. Eastern Time. Copies of the press release and presentation are attached as Exhibits 99.1 and 99.2, respectively, to this Current Report on Form 8-K and are incorporated herein by reference.

The information in this Item 7.01 and Exhibits 99.1 and 99.2 attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall they 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 filing.

Item 8.01 Other Events.

On August 2, 2022, the Company reported topline results from the Phase 2a randomized, double-blind, placebo-controlled investigation to evaluate the efficacy and safety of AXA1125 in patients with fatigue related to Long COVID.

In the study, 41 subjects were enrolled and randomized to receive either 67.8 grams per day of AXA1125 (N=21) or a matched placebo (N=20) in two divided doses for 28 days, with a one-week safety follow-up period. All 41 subjects who started the study remained in the study to completion. Endpoints included phosphocreatine recovery time (PCrt) following moderate exercise as assessed by 31P-magnetic resonance spectroscopy (MRS), which was included to assess mitochondrial function, and most importantly, clinically relevant endpoints including self-reported mental and physical fatigue as assessed by the Chalder Fatigue Questionnaire (CFQ-11), 6 minute walk test (6MWT) as well as serum lactate levels. The CFQ-11 is a validated patient reported outcome measure of fatigue that has been used in measuring patient impact in fatigue states such as chronic fatigue syndrome.

Subjects who received AXA1125 had improvements in measures of mental and physical fatigue that were both highly statistically significant and clinically relevant compared to those who received placebo. Mean changes in total, physical and mental scores in the CFQ-11 versus placebo were -4.30 ($p=0.0039$), -2.94 ($p=0.0097$) and -1.32 ($p=0.0097$), respectively. Clinically meaningful shifts in the severity of physical and mental fatigue were also noted in subjects who received AXA1125 compared to those who received placebo. There was a statistically significant correlation of improvement in fatigue score and greater distance achieved in the 6MWT ($p=0.0027$), an objective measure of physical ability, only observed in subjects who received AXA1125 when compared to those receiving placebo.

Baseline PCrτ among all subjects was significantly higher and had a higher degree of inter-subject variability (92.46 S + 35.3 S) than previously reported in the literature. These findings support the hypothesis that there is significant mitochondrial dysfunction in these patients but limits the utility of this parameter in a clinical trial. The trial did not meet its exploratory primary endpoint of showing a change from baseline to week four in the PCrτ recovery rate following moderate exercise between subjects receiving AXA1125 and placebo. There was a notable trend toward significant improvement in serum lactate levels after a 6MWT in AXA1125 subjects (p=0.0730). AXA1125 was safe and well tolerated with no significant emergent adverse events or serious adverse events reported by study subjects.

Cautionary Note Regarding Forward-Looking Statements

This Form 8-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding interest that may ensue in the Company's product candidates or securities following announcement of the Company's recent clinical trial results and the timing of the Company's clinical trial data readouts and next steps for its clinical programs, including a potential registration trial of AXA1125 for the treatment of Long COVID. 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 Form 8-K 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 Form 8-K, including, without limitation, those related to the belief that mitochondrial dysfunction is a key driver of Long COVID induced fatigue, potential impact of COVID-19 on the Company's ability to conduct and complete its ongoing or planned clinical studies and clinical trials 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 the Company is able to collect in its clinical trials of AXA1125, other potential impacts of COVID-19 on the Company's business and financial results, including with respect to its ability to raise additional capital and operational disruptions or delays, changes in law, regulations, or interpretations and enforcement of regulatory guidance, whether data readouts support the Company's clinical trial plans and timing, clinical trial design and target indications for AXA1125, the clinical development and safety profile of AXA1125 and its therapeutic potential, whether and when, if at all, the Company's product candidates will receive approval from the FDA or other comparable regulatory authorities, potential competition from other biopharma companies in the Company's target indications, and other risks identified in the company's SEC filings, including Axcella's Annual Report on Form 10-K, Quarterly Reports 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 Form 8-K represent the company's views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date. The Company explicitly disclaims any obligation to update any forward-looking statements.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Press Release dated August 2, 2022 entitled "Axcella Announces Results from Phase 2a Clinical Trial for Long COVID"
99.2	Presentation of Axcella Health, Inc., doing business as "Axcella Therapeutics," dated August 2, 2022
104	Cover Page Interactive Data (embedded within the Inline XBRL document)

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.

AXCELLA HEALTH INC.

Date: August 2, 2022

By: /s/ William R. Hinshaw, Jr.
William R. Hinshaw, Jr.
Chief Executive Officer, President and Director

Exhibit 99.1

Axcella Announces Highly Promising Results from Phase 2a Placebo Controlled Clinical Trial for Long COVID

Subjects with Long COVID receiving AXA1125 experienced a clinically and statistically significant improvement in mental (p=0.0097) and physical (p=0.0097) fatigue scores compared to placebo subjects

Responders to AXA1125 demonstrated significantly improved scores during a 6 minute walk test

No emergent adverse events (AEs) or serious adverse events (SAEs) occurred

Regulatory meetings are planned to discuss a path to registration trial

Axcella to host a conference call today at 8:00 a.m. ET; To register, click here

CAMBRIDGE, Mass. – August 2, 2022 – Axcella Therapeutics (Nasdaq: AXLA), a clinical-stage biotechnology company pioneering novel approaches to treating complex diseases using multi-targeted endogenous metabolic modulator (EMM) compositions, today reported topline results from the Phase 2a randomized, double-blind, placebo-controlled investigation to evaluate the efficacy and safety of AXA1125 in patients with fatigue related to Long COVID.

Long COVID is a persistent and growing challenge of the pandemic, affecting an estimated one hundred million patients worldwide with fatigue as the most common symptom reported. The recent Congressional subcommittee on Long COVID stated that one million Americans have been pushed out of work due to Long COVID. Additionally, it was stated that Long COVID contributed to approximately $1 trillion in lost earnings and $529 billion in increased medical spending.

We believe effective treatment of this complex and often debilitating disease requires addressing the underlying dysregulation of multiple biological pathways. Given the lack of therapeutic options for Long COVID patients and based on our understanding of AXA1125's positive impact on mitochondrial function, bioenergetics, and inflammation, Axcella conducted a placebo-controlled interventional study in collaboration with clinical researchers at University of Oxford as an exploratory trial to test the hypothesis that administration of AXA1125 could ameliorate fatigue symptoms of Long COVID. Bill Hinshaw, CEO of Axcella, remarked "At Axcella, once we understood we had a potential Long COVID intervention we acted rapidly to test the hypothesis that we could address the high and growing need that exists for patients living with debilitating Long COVID fatigue. We are delighted to report that we have meaningful clinical results as well as an increased understanding on the best endpoints for future, potentially registrational studies and look forward to engaging with the regulatory authorities around the next steps in clinical development."

Since established endpoints for Long COVID do not exist, the study incorporated multiple endpoints for prioritization, selection, and use in a future registration trial to assess the effects of AXA1125 compared to placebo in subjects with moderate to severe fatigue. Safety and tolerability were also studied.

In the study, 41 subjects were enrolled and randomized to receive either 67.8 grams per day of AXA1125 (N=21) or a matched placebo (N=20) in two divided doses for 28 days, with a one-week safety follow-up period. All 41 subjects who started the study remained in the study to completion. Endpoints included phosphocreatine recovery time (PCr_τ) following moderate exercise as assessed by 31P-magnetic resonance spectroscopy (MRS), which was included to assess mitochondrial function, and most importantly, clinically relevant endpoints including self-reported mental and physical fatigue as assessed by the Chalder Fatigue Questionnaire (CFQ-11), 6 minute walk test (6MWT) as well as serum lactate levels. The CFQ-11 is a validated patient reported outcome measure of fatigue that has been used in measuring patient impact in fatigue states such as chronic fatigue syndrome.

Subjects who received AXA1125 had improvements in measures of mental and physical fatigue that were both highly statistically significant and clinically relevant compared to those who received placebo. Mean changes in total, physical and mental scores in the CFQ-11 versus placebo were -4.30 (p=0.0039), -2.94 (p=0.0097) and -1.32 (p=0.0097), respectively. Clinically meaningful shifts in the severity of physical and mental fatigue were also noted in subjects who received AXA1125 compared to those who received placebo. There was a statistically significant correlation of improvement in fatigue score and greater distance achieved in the 6MWT (p=0.0027), an objective measure of physical ability, only observed in subjects who received AXA1125.

Baseline PCr_τ among all subjects was significantly higher and had a higher degree of inter-subject variability (92.46 Seconds $\pm$ 35.3 Seconds) than previously reported in the literature. These findings support the hypothesis that there is significant mitochondrial dysfunction in these patients but limits the utility of this parameter in a clinical trial. There was no significant difference on the primary outcome measure of PCr_τ following moderate exercise between subjects receiving AXA1125 and placebo. There was a notable trend toward significant improvement in serum lactate levels after a 6MWT in AXA1125 subjects (p=0.0730). AXA1125 was safe and well tolerated with no significant adverse events reported by study subjects.

“The statistically significant improvement in reported mental and physical fatigue among study participants receiving AXA1125 is a very encouraging finding for Long COVID patients, who often experience extreme and constant fatigue throughout their day,” said study leader, Dr. Betty Raman, Associate Professor of Cardiovascular Medicine at the Radcliffe Department of Medicine, University of Oxford.

Karim Azer PhD, Axcella’s VP, Platform and Discovery stated, “The results of this trial encourage us to further evaluate the multi-targeted effects of AXA1125 on mitochondrial and related biomarkers to advance our understanding of the benefits AXA1125 delivers to Long COVID patients. Preliminary analysis including mitochondrial, inflammatory, and endothelial environment biomarker work provides additional data strengthening the core rationale for AXA-1125’s compelling clinical benefits.”

Dr. Jason Maley, Director of Beth Israel Deaconess Medical Center Critical Illness and COVID-19 Survivorship Program, remarked that “This is the first pharmaceutical agent to demonstrate improved outcomes for patients with Long COVID in a randomized controlled trial and suggests that AXA1125 may play an important part in the long-term treatment of these patients as they seek to return to the life they had before the infection. On behalf of the innumerable patients urgently seeking therapies for the debilitating symptoms of Long COVID, I am excited to see the continued development of AXA1125.”

Conference Call Information
Register for the call by clicking here.
A live webcast of the call, as well as a replay, will be available on the Events and Presentations section on the Company’s website: https://ir.axcellatx.com/events-and-presentations.

Internet Posting of Information
Axcella uses the “Investors and News” section of its website, www.axcellatx.com, as a means of disclosing material nonpublic information, to communicate with investors and the public, and for complying with its disclosure obligations under Regulation FD. Such disclosures include, but may not be limited to, investor presentations and FAQs, Securities and Exchange Commission filings, press releases, and public conference calls and webcasts. The information that we post on our website could be deemed to be material information. As a result, we encourage investors, the media and others interested to review the information that we post there on a regular basis. The contents of our website shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended.

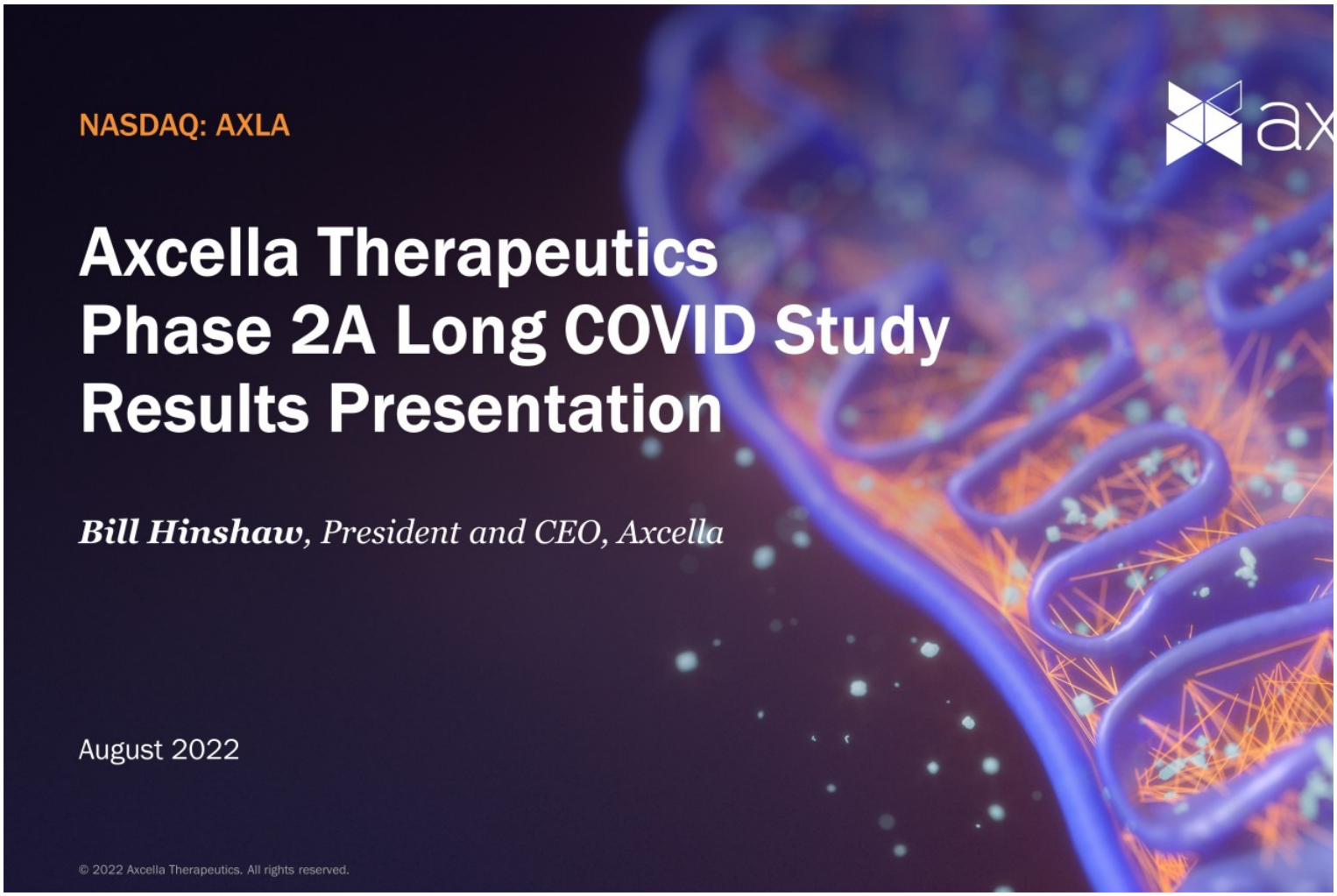
About Axcella Therapeutics (Nasdaq: AXLA)
Axcella is a clinical-stage biotechnology company pioneering a new approach to treat complex diseases using compositions of endogenous metabolic modulators (EMMs). The company’s product candidates are comprised of EMMs and derivatives that are engineered in distinct combinations and ratios to restore cellular homeostasis in multiple key biological pathways and improve cellular energetic efficiency. Axcella’s pipeline includes lead therapeutic candidates in Phase 2 development for the treatment of Long COVID and non-alcoholic steatohepatitis (NASH). The company’s unique model allows for the evaluation of its EMM compositions through non-IND clinical studies or IND clinical trials. For more information, please visit www.axcellatx.com.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding interest that may ensue in the Company’s product candidates or securities following announcement of the Company’s recent clinical trial results and the timing of the Company’s clinical trial data readouts and next steps for its clinical programs, including a potential registration trial of AXA1125 for the treatment of Long COVID. 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 press release 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 press release, including, without limitation, those related to the belief that mitochondrial dysfunction is a key driver of Long COVID induced fatigue, potential impact of COVID-19 on the Company’s ability to conduct and complete its ongoing or planned clinical studies and clinical trials 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 the Company is able to collect in its clinical trials of AXA1125, other potential impacts of COVID-19 on the Company’s business and financial results, including with respect to its ability to raise additional capital and operational disruptions or delays, changes in law, regulations, or interpretations and enforcement of regulatory guidance, whether data readouts support the Company’s clinical trial plans and timing, clinical trial design and target indications for AXA1125, the clinical development and safety profile of AXA1125 and its therapeutic potential, whether and when, if at all, the Company’s product candidates will receive approval from the FDA or other comparable regulatory authorities, potential competition from other biopharma companies in the Company’s target indications, and other risks identified in the company’s SEC filings, including Axcella’s Annual Report on Form 10-K, Quarterly Reports 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 press release represent the company’s views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date. The Company explicitly disclaims any obligation to update any forward-looking statements.

Dr. Maley receives compensation as a consultant for the Company.

# # #

Company Contact
Ashley Robinson
arr@lifesciadvisors.com
(617) 430-7577


NASDAQ: AXLA
Axcella Therapeutics
Phase 2A Long COVID Study
Results Presentation
Bill Hinshaw, President and CEO, Axcella
August 2022
© 2022 Axcella Therapeutics. All rights reserved.

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, inclu limitation, statements regarding the characteristics, competitive position and development potential of AXA1665, AXA1125 and potential future EMM 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 com 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 compa approach, the size and growth potential of the markets for the company's product candidates, the company's intellectual property position, the comp the company's ability to address other complex diseases and conditions utilizing EMM compositions. The words "may," "will," "could," "would," "shou "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify for statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this presentation are ba current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to d those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, those related to the poter 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 oth authorities in a timely manner or at all due to patient or principal investigator recruitment or availability challenges, clinical trial site shutdowns or ot potential limitations on the quality, completeness and interpretability of data we are able to collect in our clinical studies and potential delays in discl other potential impacts of COVID-19 or other events on our business and financial results, including with respect to our ability to raise additional capi disruptions or delays, changes in law, regulations, or interpretations and enforcement of regulatory guidance; clinical trial initiation plans and timing and target indication(s) for AXA1125, the clinical development and safety profile of our product candidates and their health or therapeutic potential; at all, our product candidates will receive approval from the FDA or other comparable regulatory authorities, and for which, if any, indications; compe biotechnology companies; past results from clinical studies not being representative of future results and other risks identified in our SEC filings, inclu 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 statements, which speak only as of the date they are made. Axcella disclaims any obligation to publicly update or revise any such statements to reflec expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual resu those set forth in the forward-looking statements. Any forward-looking statements contained in this presentation represent our views only as of the d not be relied upon as representing its views as of any subsequent date.

Today's Agenda

Agenda	Length	Time	Speaker
Introductory Remarks	5 min	8:00 am – 8:05 am	Bill Hinshaw
Clinical Trial Design and Protocol	10 min	8:05 am – 8:15 am	Dr. Raman
Clinical Trial Results	20 min	8:15 am – 8:35 am	Margaret Koziel
Patient Experience	5 min	8:35 am – 8:40 am	Dr. Raman
Mechanism of Disease & AXA1125	10 min	8:40 am – 8:50 am	Karim Azer
Independent 3rd Party Perspective	15 min	8:50 am – 9:05 am	Dr. Maley
Conclusion and Next Steps	5 min	9:05 am – 9:10 am	Bill Hinshaw
Q&A	20 min	9:10 am – 9:30 am	Bill, Margaret, Karim, Dr. Raman, Dr. Maley, Bob

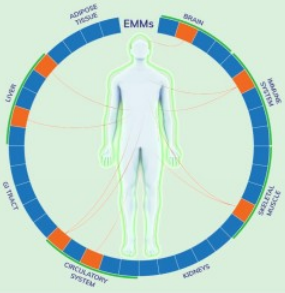
Dr. Betty Raman
Radcliffe Department of
Associate Professor of Ca

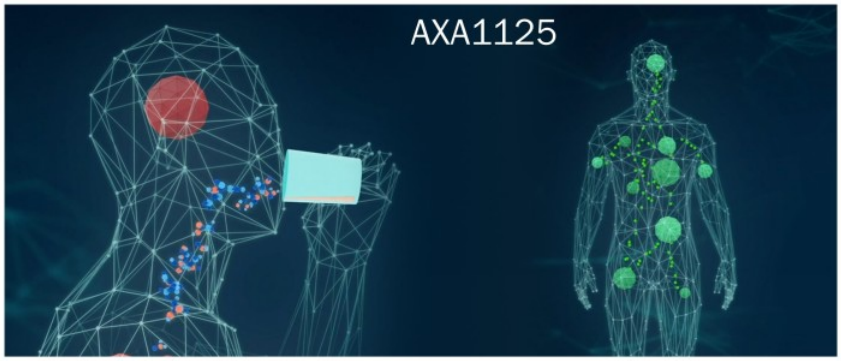
Dr. Jason Maley
Beth Israel Deaconess M
Director, BIDMC Critical
Survivorship Program
Director of Quality, Pulm
Sleep Medicine
Core Faculty, Center for

World leader of multi-targeted therapies in complex disea

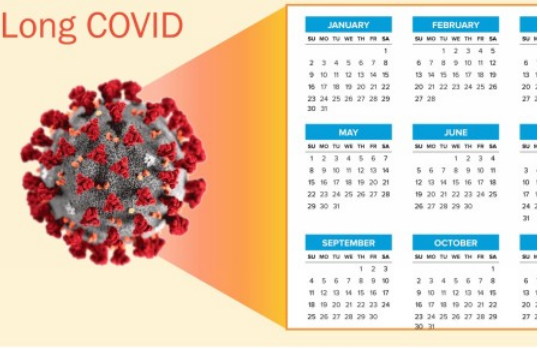
axcella®

Endogenous Metabolic Modulators



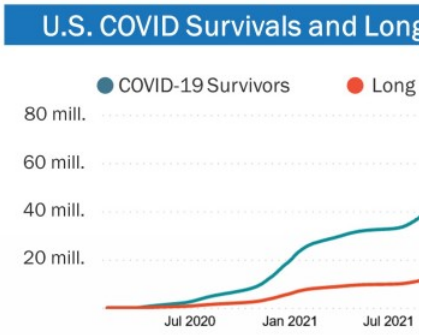


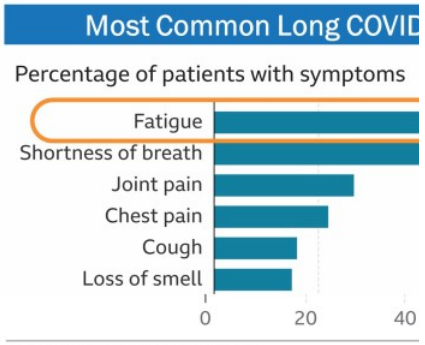
Long COVID



Long COVID: A Large and Still Emerging Public Health Cris

- ~500M confirmed COVID-19 cases worldwide to date[1]
- 20-30% (100M-167M) of COVID patients report Long COVID symptoms[4]
- Susceptibility to Long COVID is not related to vaccination status, variant type, or severity of acute infection[5,6]
- Commonly reported symptoms include fatigue
- Estimated healthcare burden up to $40+ billion
- Growing Impact on the population:
  - 1 million Americans already out of work[3]
  - ~22% of UK work absences due to Long COVID





1. WHO Coronavirus (COVID-19) Dashboard: https://covid19.who.int/
2. American Academy of Physical Medicine and Rehabilitation's "PASC Dashboard". PASC = Post-acute Sequelae of COVID-19. https://pascdashboa
3. Science & Tech Spotlight: Long COVID. (2022). Retrieved 29 July 2022, from https://www.gao.gov/products/gao-22-105666
4. Assessing the Global Burden of Post-COVID-19 Conditions. (2022). Retrieved 29 July 2022, from https://www.iqvia.com/insights/the-iqvia-institute/reports/assessing-the-global-burden-of-post-covid-19-c
5. Ayoubkhani D. (2022, May 6). Self-reported long COVID after infection with the Omicron variant in the UK. ONS.Gov.UK. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/con
edlongcovidafterinfectionwiththeomicronvariant/6may2022#prevalence-of-self-reported-long-covid-between-variants.
6. Penfold, R., Merino, J., Sudre, C., Molteni, E., Berry, S., Canas, L., Graham, M., Kl hen, L., Deng, J., Österdahl, M., Cheetham, N., Drew, D., Nguyen,
Polidori, L., May, A., Wolf, J., Chan, A., Hammers, A., Duncan, E., Spector, T., Ourselin, S. and Steves, C., 2022. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the C

Very Limited Development and Axcella Leadership Oppor

Very Few Trials in Long COVID and almost none in Fatigue
And
Growing Attention to this Public Health Crisis

THE WHITE HOUSE

BRIEFING ROOM

Memorandum on Addressing the Long-Term Effects of COVID-19

APRIL 05, 2022 • PRESIDENTIAL ACTIONS

MEMORANDUM FOR THE HEADS OF EXECUTIVE DEPARTMENTS AND AGENCIES

Axcella Leadership Opp

- Differentiated Profile
- Most Advanced Prog
- Leadership Opportur

*** Confidential ***

Long COVID Overview

Betty Raman

British Heart Foundation Oxford Centre for Research Excellence Intermediate Transition Clinical Review Fellow

Associate Professor of Cardiovascular Medicine
Radcliffe Department of Medicine
University of Oxford

axcella

Long COVID/Post-Acute Sequelae of COVI

Betty Raman MBBS FRACP DPhil
Associate Professor of Cardiovascular Medicine
Radcliffe Department of Medicine
University of Oxford, United Kingdom
British Heart Foundation Oxford Centre of Research Excellence
Transition Intermediate Research Fellow
NIHR OXFORD BRC

Long COVID Overview

Betty Raman

British Heart Foundation Oxford Centre for Research Excellence Intermediate Transition Clinical Research Fellow

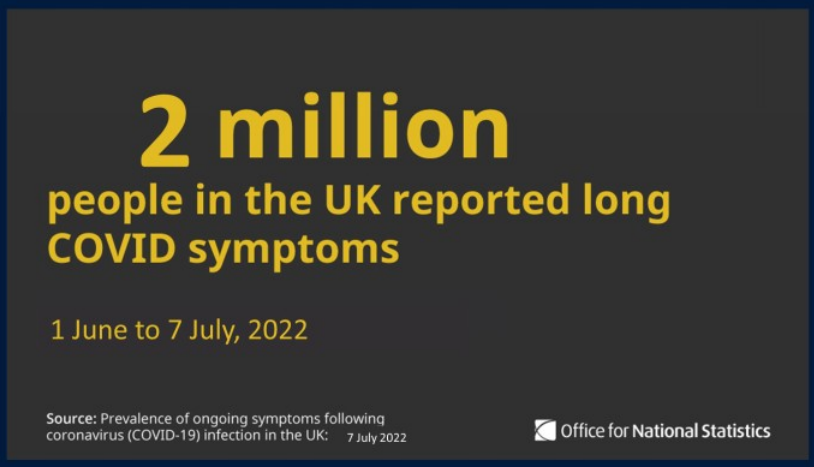
Associate Professor of Cardiovascular Medicine

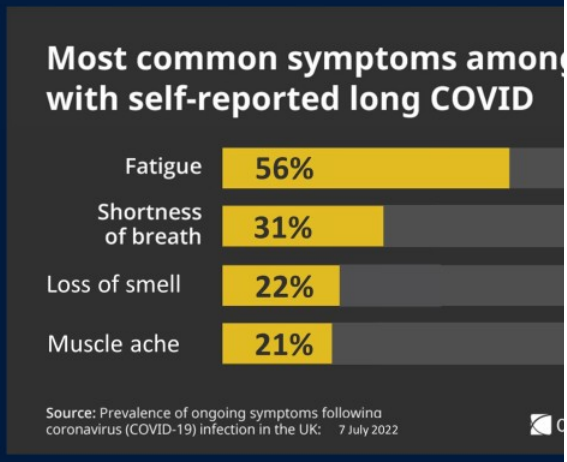
Radcliffe Department of Medicine

University of Oxford

axcella

Long COVID: UK Prevalence





Source: https://www.on

Long COVID: Patient Journey

- "I have lost everything – my job, my life, my partner. Most of all lost myself. I want the old me back." – P.L

LONG COVID SOS

Source:https://www.youtube.com/wat
Long COVID SOS support

Post-viral fatigue syndrome and myalgic encephali

- 1918 Spanish influenza
- 2003 SARS
- 2009 H1N1
- Ebola virus
- Ebstein Barr Virus
- Human Herpes Virus

CFS

No approved treatment for Long COVID or relate
disorders.....

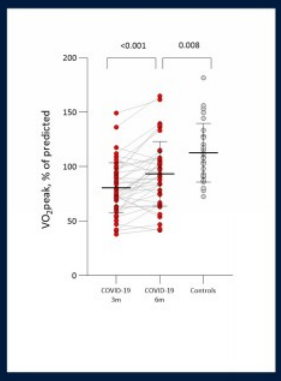
Long COVID: Research in Oxford

- C-MORE study – holistic multisystem study (Raman & Neubauer)
- Urgent Public Health Badging, NIHR-BHF COVID-19 Flagship status
- Impact on individuals
- 3 UK National post-COVID-19 studies – PHOSP-COVID, CONVALESCENCE, EXPLA

Raman B et al, EClinicalMedicine, 2

Long COVID: Insights from Oxford

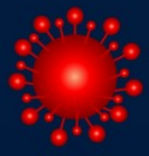
- Fatigue – most challenging and debilitating symptom expe by patients
- Mitochondrial dysfunction highly likely – insights from CPE



Preserved breathing reserve
Normal O2 pulse
Normal cardiac function and volur
Early Anaerobic threshold[3]

Cassar. M et al, EClinicalMedic

Mitochondrial dysfunction – COVID-19



SARS-CoV-2

Direct effects

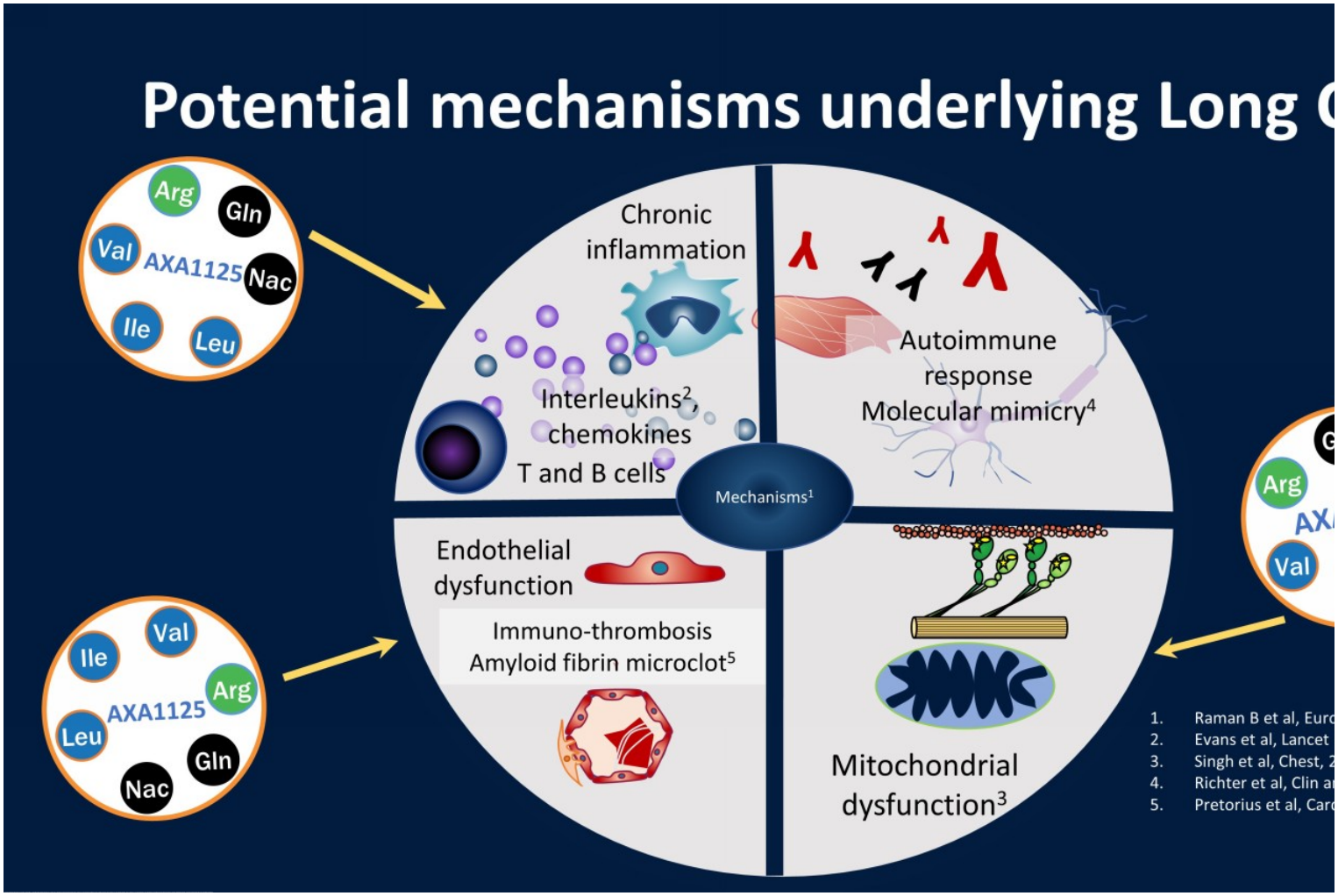
Inhibit mitochondrial anti-viral signaling proteins (MAVS)[1]
Increased ROS[1,2,3]
Activation of inflammasomes → inflammation[1,2]
Muted interferon signaling
Release of mitokines[1]

Indirect effects

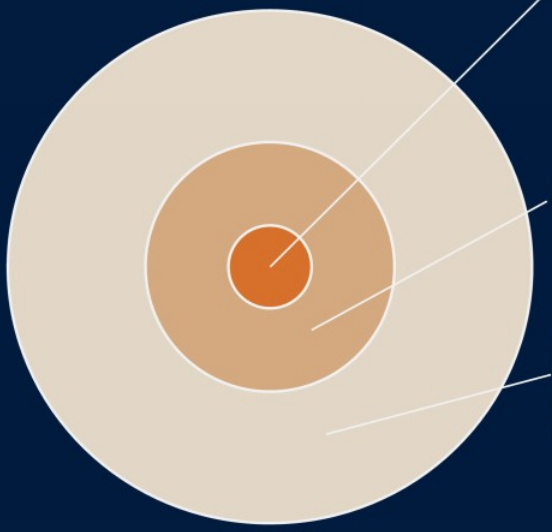
ACE2 – activation of RAA[1]
Chronic inflammatory signalling

Chronic fatigue syndrome – **mitochondrial dysfunction**

1. Singh et al, Am J Physiol Cell Phys
2. Ajaz et al, Am J Physiol, 2020
3. Gibellini et al, EMBO Molecular M
4. Cassar M et al, EClinicalMedicine


Potential mechanisms underlying Long C
Arg
Gln
Val
AXA1125
Nac
Ile
Leu
Chronic inflammation
Interleukins[2], chemokines
T and B cells
Autoimmune response
Molecular mimicry[4]
Mechanisms[1]
Endothelial dysfunction
Immuno-thrombosis
Amyloid fibrin microclot[5]
Mitochondrial dysfunction[3]
Ile
Val
Arg
AXA1125
Leu
Gln
Nac
Arg
Val
1. Raman B et al, Eurc
2. Evans et al, Lancet
3. Singh et al, Chest, 2
4. Richter et al, Clin a
5. Pretorius et al, Carc

Outcome measures of Clinical Efficacy



- **Chalder Fatigue Scale (CFQ-11): Validated in c**
  fatigue score
- **Includes both physical and mental subscales**
- **Six Minute Walk Test (6MWT)**

- Lactate Levels: used as measure of metabolic s
- Biomarkers of inflammation

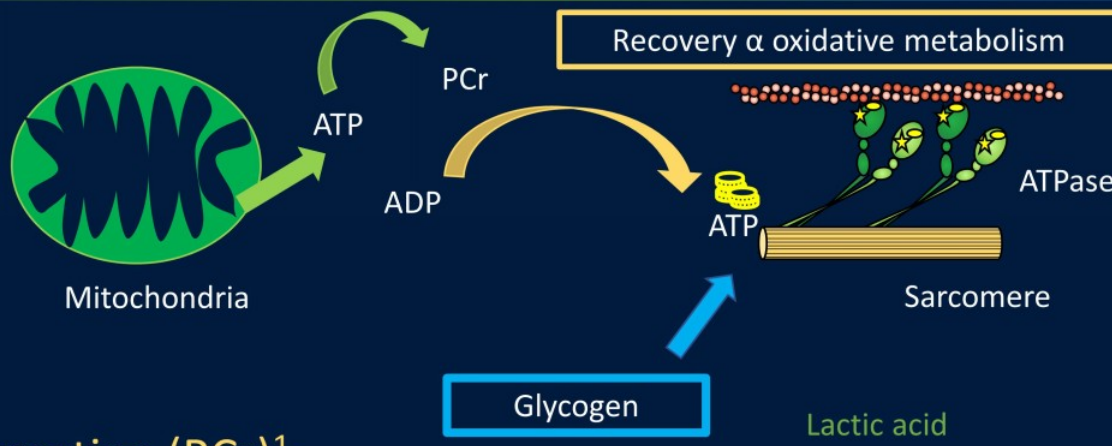
- Phosphocreatine Recovery Time (PCr, primary
  endpoint): measure of mitochondrial oxidative
- Other measures in magnetic resonance spectr
  mitochondrial function

Chalder Fatigue Questionnaire

- Developed and validated for use in chronic fatigue syndrome/myalgic encephalomyelitis
- Assesses both physical and mental components of fatigue
- Standardized definitions to assess fatigue
- Two different scoring systems in use for the 11 questions
  - Bimodal (total 0-11)
  - Likert (total 0-33) (graded scoring for each question –0,1,2,3)

Do you have problems with tiredness
Do you need to rest more?
Do you feel sleepy or drowsy?
Do you have problems starting things?
Do you lack energy?
Do you have less strength in your mus
Do you feel weak?
Do you have difficulty concentrating?
Do you make slips of the tongue wher
Do you find it more difficult to find th
How is your memory?

Mitochondrial metabolism



- Phosphocreatine (PCr)[1]
- Anaerobic metabolism (glycolytic)
- Aerobic metabolism

PCr = Phosphocreatine

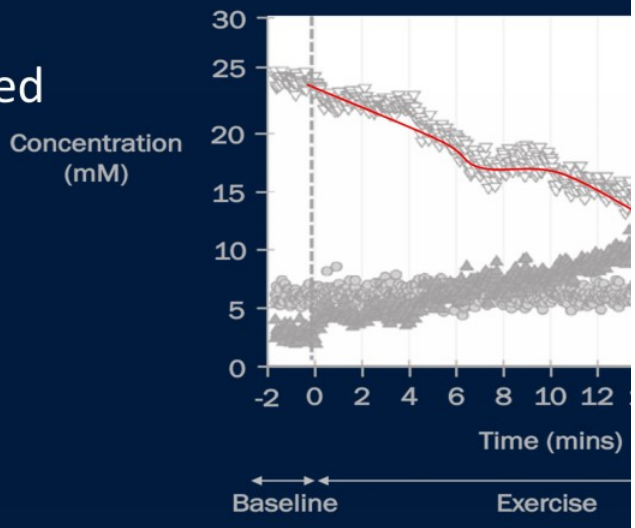
1. Chance et al,PNAS, 1981

PCr recovery time constant

- Normal recovery time constant

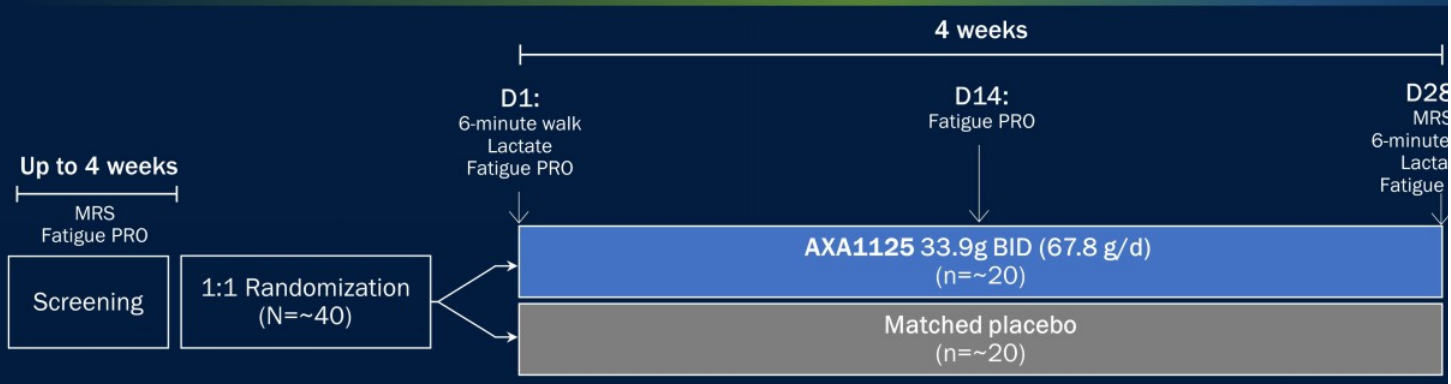
27±7 sec[1]; 31±7sec[2]; 32±3sec[3]

- > 50s is prolonged (>2SD of published norms)
- CFS studies – MRS abnormalities in fatigued patients[4]



1. Yoshida et al, Scand J Med Sci Sports.,
2. Šedivý et al, Med Phys, 2015
3. Scheuermann-Freestone et al, Circulat
4. McCully et al, Muscle & Nerve, 1996

Clinical Trial Study Design

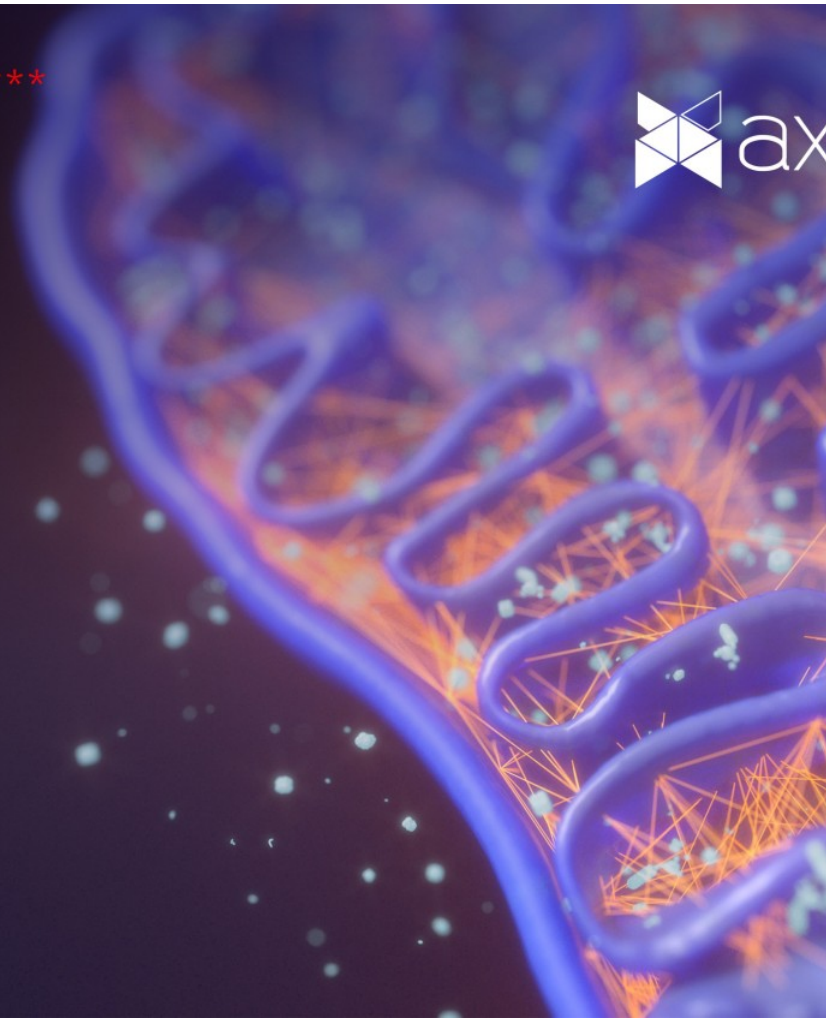


Core elements	Description
Design	• Randomized **double blind**, placebo-controlled study over 28 days
Study population	• Including Long COVID patients (>12 weeks post PCR+) with fatigue-predominant symptoms/abnormalitie – PCr recovery time constant of >50 sec. – Chalder Fatigue bimodal score of >8 (very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

BID = twice daily; MRS = magnetic resonance spectroscopy; PCr = phosphocreatine; PRO = Patient Reported Outcomes

*** Confidential ***

NASDAQ: AXLA



AXA1125 - 201 Top Line Data

Dr. Margaret Koziel

2 August 2022

Executive Summary

- AXA1125, compared to placebo, resulted in
  - Statistically significant improvements in fatigue as measured by CFQ-11
  - Improvements in both the physical and mental components of the fatigue scoring
  - Impressive clinical improvements in most patients treated
- AXA1125 responders had a statistically significant improvement in 6MWT
- In terms of measurement of PCr_{τ}, no differences at end of treatment
  - High variability means statistical demonstration of the difference very unlikely in this s
  - Now shown as nonviable as a clinical trial endpoint
- There was a trend toward a reduction in peak lactate in those subjects who received AXA
- AXA1125 was safe and well tolerated in this study

CFQ-11, Chalder Fatigue Questionnaire 11 item scale; PCr_{τ}, phosphocreatine recovery rate time constant

AXA1125-201: Demographics

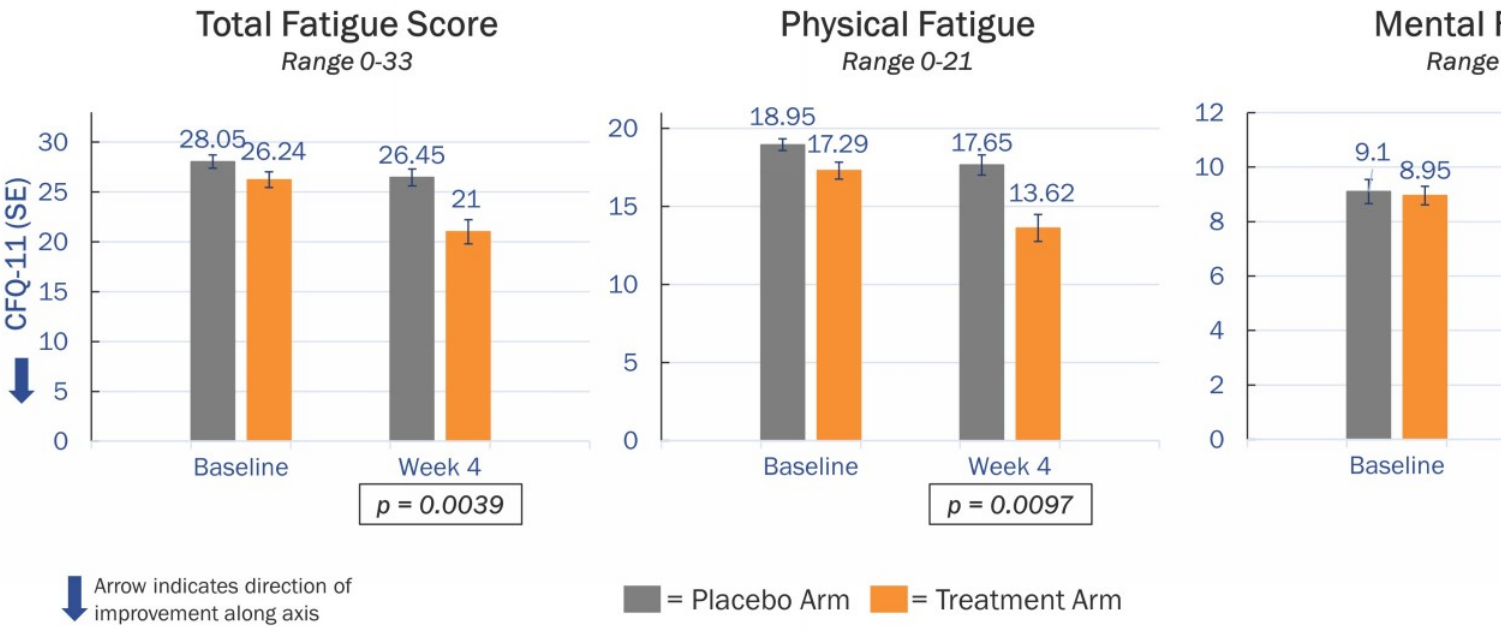
Demographics	Placebo (n=20)	AXA1125 (n=21)
Age, mean, years (SD)	43.6 (7.8)	43.6 (10.1)
Sex (% female)	15 (71.4)	13 (65.0)
Race	19/2 (90.5%) Caucasian 2/20 (9.5%) Asian	18/21 (90%) Cauc 1/21 Asian (5%) Asia 1/21 (5%) Othe
BMI, mean (SE)	26.42 (4.25)	26.38 (4.32
CFQ-11, Total using bimodal (SE) (range 0-11)	10.50 (0.199)	10.48 (0.26
CFQ-11, Total using Likert (SE) (range 0-33)	28.05 (0.663)	26.24 (0.78
Percent predicted 6 minute walk test* (mean, SE)	86.82 (3.86)	82.41 (4.27

All subjects completed all key assessments in the trial

*Based on calculated norm for age, gender, BMI; SD, standard error

There is a Statistically Significant Change in Fatigue Scor

Improvements seen in all scores using Likert scoring of CFQ-11



p-values from ANCOVA and represent LSM adjusting for differences in baseline

Subjects Taking AXA1125 Results in Greater Movement from Moderate/Severe to Mild in BOTH Physical & Mental Scales

Following tables map how patients shift from baseline to week 4

Physical Domain

Visit	Baseline Category	Post-Baseline Category	Placebo BID (n=20)	AXA1125 33.9g BID (n=21)
Baseline	Normal		0	0
	Mild		1 (5.0)	2 (9.5)
	Moderate/Severe		19 (95.0)	19 (90.5)
Week 4	Normal	Normal	0	0
		Mild	0	0
		Moderate/Severe	0	0
	Mild	Normal	0	2 (9.5)
		Mild	0	0
		Moderate/Severe	1 (5.0)	0
	Moderate/Severe	Normal	0	1 (4.8)
		Mild	4 (20.0)	12 (57.1)
		Moderate/Severe	15 (75.0)	6 (28.6)

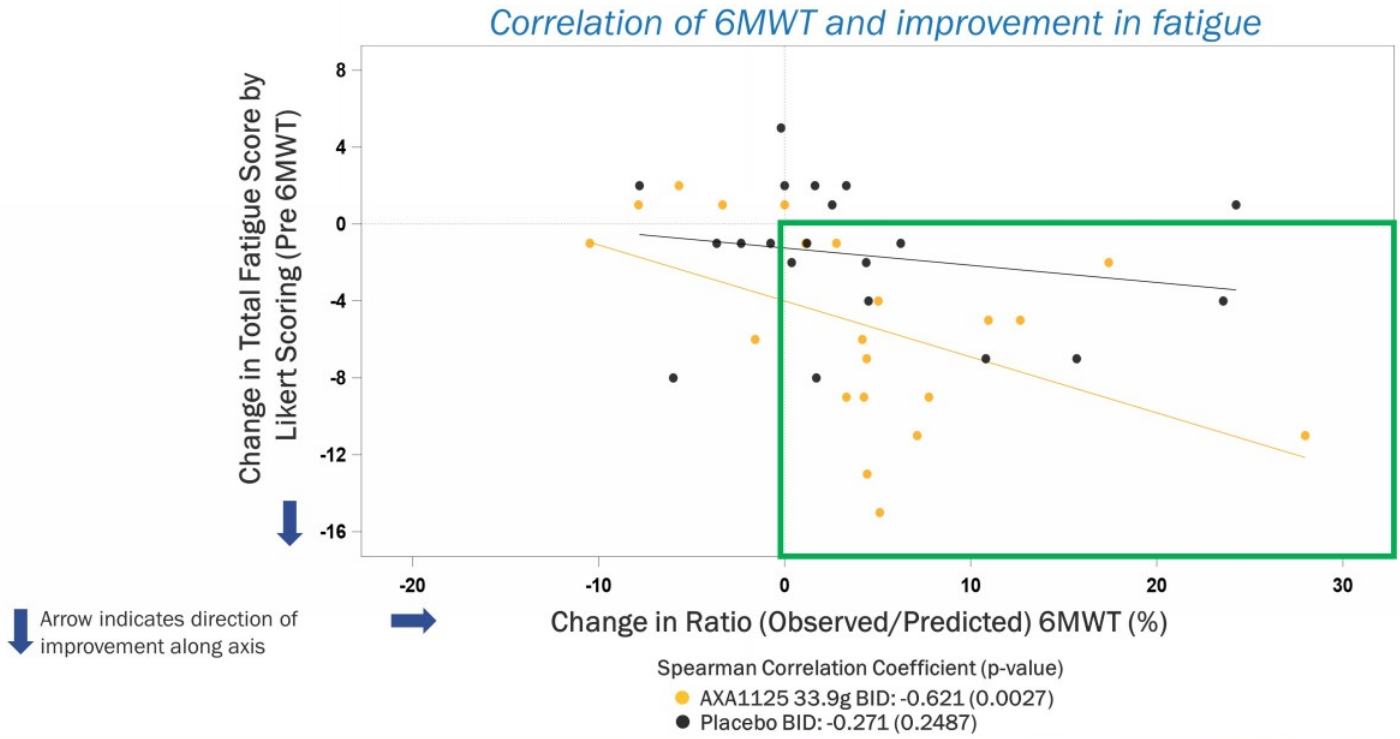
Mental Domain

Visit	Baseline Category	Post-Baseline Category	Placeb (n=2
Baseline	Normal		0
	Mild		4 (20
	Moderate/Severe		16 (8
Week 4	Normal	Normal	0
		Mild	0
		Moderate/Severe	0
	Mild	Normal	0
		Mild	3 (15
		Moderate/Severe	1 (5.
	Moderate/Severe	Normal	0
		Mild	1 (5.
		Moderate/Severe	15 (7

Physical scale: Normal, 0-9; Mild, 10-15; Moderate severe, ≥16 Mental scale: Normal, 0-3; Mild, 4-7; Moderate/severe, ≥8 Note denominator based on total in arm for percent

AXA1125 responders had statistically significant improvements were able to walk farther

This effect only seen in subjects who received AXA1125



No Change in Phosphocreatine recovery rate time consta

Much greater than expected variation in baseline – makes PCr_τ not useful as a clinical trial

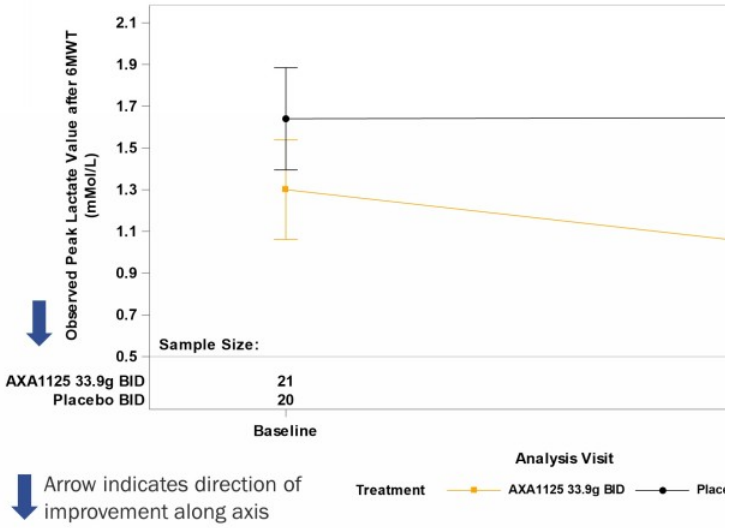
- Unexpected large variation at baseline
  - Overall mean 92.46 S (SD 35.3)
  - Higher degree of variability than seen in other diseases
- No difference in change from baseline in PCr_τ between AXA and placebo
  - Statistical difference would require large sample size to detect planned 10S delta (250-5 or large delta (30S) between groups
- There was a correlation between improvements in fatigue and improvement

PCR_τ, phosphocreatine recovery rate time constant. Rousell et al Biochimica Biophysica Acta 2000

AXA1125 Patients Showed A Trend Toward Improving Lactate L

- Baseline assumption that peak lactate would be high (> 3 mMol/L)
- Trend toward difference in model estimated mean (LSM) when accounting for difference in baseline –0.42 (p = 0.073, 2-sided)
- No correlation of change in lactate with measures of fatigue

Peak lactate



AUC, area under the curve.

AXA1125 was safe and well tolerated in this study

TEAE s (Treatment Emergent Adverse Events)	Placebo (n=20)	AXA112 (n=21)
Subjects with at least one TEAE	4 (20.0%)	11 (52.4%)
Subjects with at least one serious TEAE	0 (0.0%)	0 (0.0%)
Subjects with TEAE leading to withdrawal of study drug	0 (0.0%)	0 (0.0%)
Subjects with TEAE leading to death	0 (0.0%)	0 (0.0%)
Subjects with TEAE by worst severity grade		
– Grade 1	2 (10.0%)	10 (47.6%)
– Grade 2	2 (10.0%)	0 (0.0%)
– Grade 3	0 (0.0%)	1 (4.8%) (Sync
Subjects with TEAE by worst relationship to study drug		
– Related	2 (10.0%)	6 (28.6%)
– Not related	2 (10.0%)	5 (23.8%)
TEAE seen in 2 or more subjects in either arm		
– Diarrhea	0 (0.0%)	3 (14.3%) (1 rel
– Abdominal distension	2 (10.0%)	0 (0.0%)
– Nausea	0 (0.0%)	2 (9.5%) (1 rel

. TEAE, treatment emergent adverse events.

Conclusion

- AXA1125, compared to placebo, resulted in:
  - Statistically significant improvements in fatigue as measured by CFQ-11
  - Improvements in both the physical and mental components of the fatigue scoring
  - Impressive improvements in Fatigue
- AXA1125 responders had a statistically significant improvement in 6MWT
- In terms of measurement of PCr_{τ}, no differences at end of treatment
  - High variability means statistical demonstration of the difference very unlikely in this stu
- There was a trend toward a reduction in peak lactate in those subjects who AXA1125
- AXA1125 was safe and well tolerated in this study

CFQ-11, Chalder Fatigue Questionnaire 11 item scale; PCr_{τ}, phosphocreatine recovery rate time constant

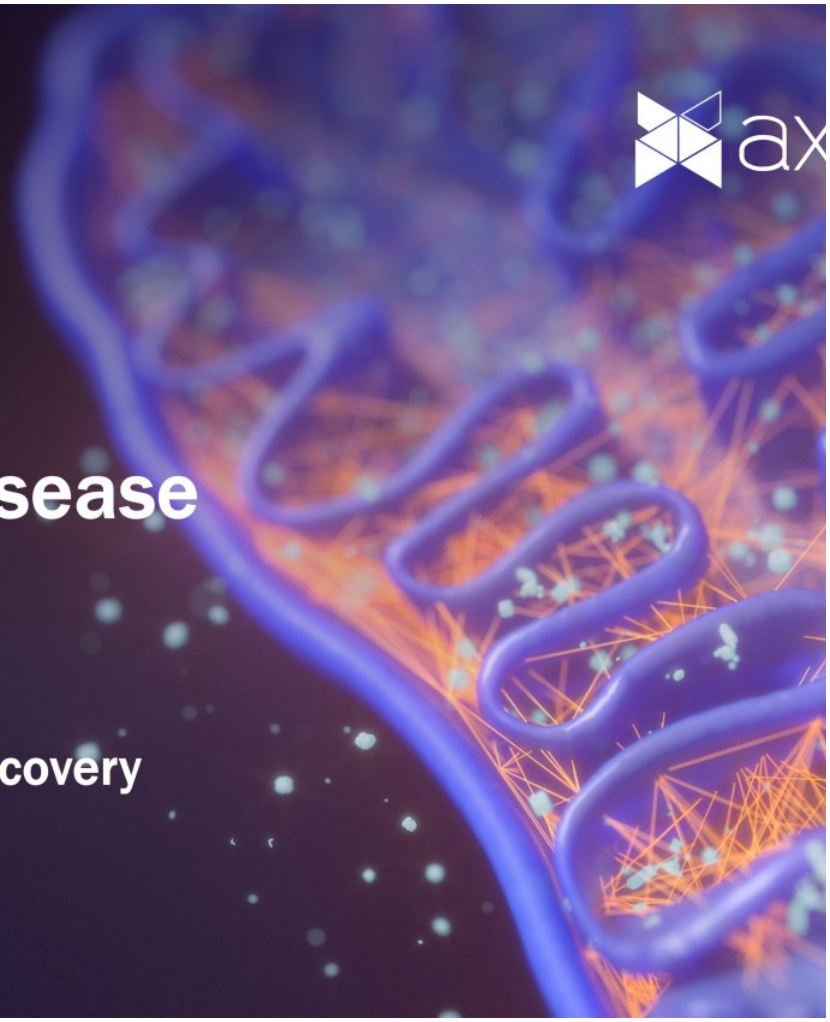
Long COVID: Patient Journey

- "I have lost everything – my job, my life, my partner. Most of all lost myself. I want the old me back." – P.L

LONG COVID SOS

Source:https://www.youtube.com/wat
Long COVID SOS support

NASDAQ: AXLA



Mechanism of Disease & AXA1125

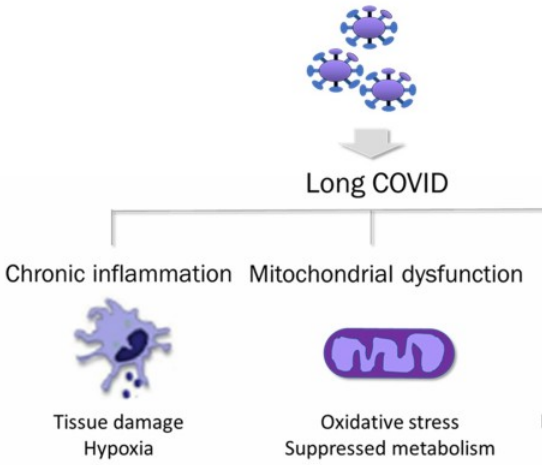
Karim Azer, PhD
VP, Head of Platform & Discovery

2 August, 2022

COVID-19 Hijacks Mitochondrial Metabolism, Dysregulates Vasc System and Leads to Chronic Inflammation in Long Covid

Building on a Foundation of AXA1125 Multi-Targeted Activity

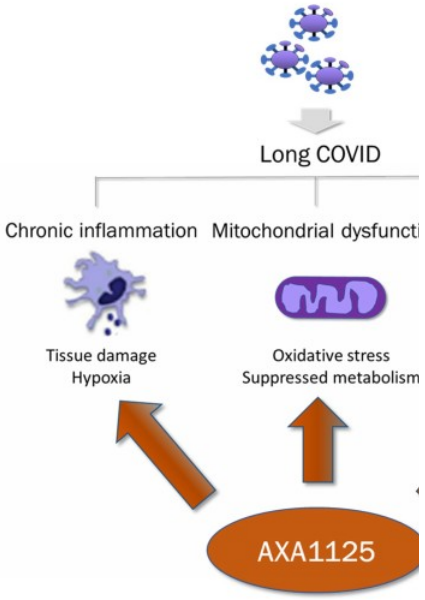
- Vascular environment dysfunction, pro-inflammatory state, and suppressed mitochondrial metabolism are implicated in LC
  - Data supported through clinical registries and long covid literature
- AXA1125's multi-targeted MOA in NASH has
  - shown improvements in mitochondrial metabolism and inflammation
  - Provided the rationale and data to study its potential in Long Covid



AXA1125 Targets Key Environment, Inflammation and Metabol Biologies in Long Covid

Key Hypotheses for Multi-Targeted Effect of AXA1125 Use in Long COVID

- AXA1125 multi-targeted MOA is proposed to improve vascular environment, inflammation, and mitochondrial metabolism.
- Improvement in markers of vascular environment
  - Dysregulated tissue environment in LC
- Improvement in oxidative stress and inflammation
  - Pro-inflammatory state persists from acute setting
  - Increased oxidative stress and reduced antioxidant availability
- Improvement in markers of metabolism and mitochondrial function
  - Dysregulated environment impacts high energy demand organs and limits function



Key MOA Takeaways from AXA1125 in Long Covid Fatigue

Multi-Targeted Impact on Improving Vascular Environment, Inflammation, and Mitochondrial

Disease MOA	Biological Impact	Improved Clinical Treatment Response Biomarker(s) in LC	MOA Concordance from NASH Studies	Pre in F
Vascular Environment Dysfunction	Dysregulated endothelial function, coagulation, reduced micro-vascular perfusion, reduced inflammation	✓ Biomarkers of vascular function	✓ Improved vascular marker	✓
Oxidative Stress, pro-inflammatory state	Reduced antioxidant availability, increased ROS and inflammation	✓ Biomarkers of inflammation and oxidative stress	✓ Reduced inflammation	
Mitochondrial Metabolism & Bioenergetics	Dysregulated lipid oxidation, insulin resistance, Increased glycolysis	✓ Mitochondrial metabolism and inflammation biomarkers e.g. **Lactate, FGF21**	✓ Improved fatty acid oxidation, lipid metabolism	✓

AXA1125 Multi-Targeted MOA Restores Key Biologies Implicate Fatigue Patients

- Vascular environment dysfunction, inflammation and suppressed metabolis implicated in LC patients and reported in clinical registries
  - suppressed mitochondrial metabolism impacts high demand organs e.g. skeletal muscle
- AXA1125 restores key markers of vascular environment function, inflammat metabolism, as supported by Phase2a clinical and biomarker data
  - Building on a foundation of MOA from our NASH studies and pre-clinical models
- The proposed multi-targeted MOA of AXA1125 on both the tissue environme cell metabolism and energetics addresses key reported dysregulated biolog patients suffering from LC fatigue

Long COVID Fatigue: Background and Trial Discussion

Jason H Maley, MD, MS

Assistant Professor of Medicine, Harvard Medical School

Director, Critical Illness and COVID-19 Survivorship Program

Co-Chair, American Academy of PM&R Long COVID Clinic Collaborative

Co-Investigator, NIH Researching COVID to Enhance Recovery (RECOVER) Initia

Director of Quality, Division of Pulmonary, Critical Care, and Sleep Medicine

Beth Israel Deaconess Medical Center, Boston, MA

BIDMC CRITICAL ILLNESS AND COVID-19 SURVIVORSHIP PROGRAM

HARVARD MEDICAL SCHOOL

Beth Israel Lahey Health

Beth Israel Deaconess M

Conflicts of Interest

I was not involved in the design, conduct, or reporting of this Ph 2a clinical trial. Following this trial, I began work as a scientific advisor on the topic of long COVID for Axcella.

38-year-old man, engineer, triathlete, COVID-19 in December

- Initial illness managed at home, felt it was a "mild cold," did not require hos and symptoms resolved by day 4 of illness
- 8 weeks later: severe physical and mental exhaustion after an average day o to stop working, can not walk around for more than 15 mins without having down for hours
- "I keep making errors at work that are scary, completely lose train of thoug napping constantly"
- 6 months later, with supportive care and cognitive rehabilitation, remains o due to fatigue impacting physical and cognitive function

38-year-old man, engineer, triathlete, COVID-19 in December 2

- Initial illness managed at home, felt it was a "mild cold," did not require hos and symptoms resolved by day 4 of illness
- 8 weeks later: severe physical and mental exhaustion after an average day o to stop working, can not walk around for more than 15 mins without having down for hours
- "I keep making errors at work that are scary, completely lose train of thoug napping constantly"
- 6 months later, with supportive care and cognitive rehabilitation, remains o due to fatigue impacting physical and cognitive function

- 6-8 month wait list, over 1000 patients seen at our clinic, sa longer wait around the country at 100+ long COVID clinics
- No existing physical or cognitive fatigue treatments targetir of long COVID
- Continue to see new patients with severe long COVID symp were infected in 2020
- Daily messages from around the country from patients des treatment

- Measure progress in small steps every 4-6 months, with ma
  patients experiencing ongoing symptoms 2+ years from inf
- Recovery from prolonged, severe fatigue in 1 month is excep
  seen in the setting of our clinics
- Anticipate ongoing pressing need for treatment indefinitely
  COVID continues to occur in fully vaccinated people
- Patients with chronic post-viral fatigue (ME/CFS) from other
  now contacting our clinic for help as well

Characterizing Long COVID Fatigue

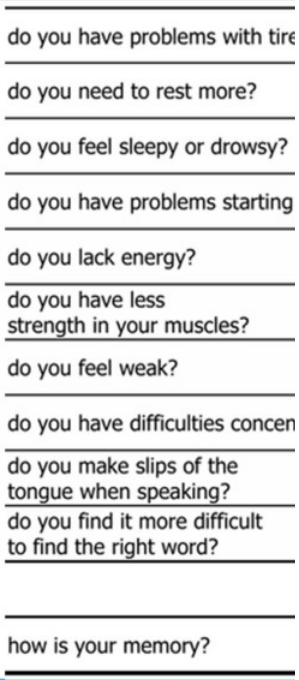
EMERGING EVIDENCE	CLINICAL CHARACTERISTICS
Impaired oxygen extraction during exercise	Exhaustion after minimal physical acti
Prolonged post-infectious inflammation	Post-exertional malaise
Immune Dysregulation	Impairs function at work and hom
Mitochondrial Impairment	Accompanying cognitive impairmer
	Non-restorative sleep

Characterizing Long COVID Fatigue

EMERGING EVIDENCE	CLINICAL CHARACTERISTICS
Impaired oxygen extraction during exercise	Exhaustion after minimal physical acti
Prolonged post-infectious inflammation	Post-exertional malaise
Immune Dysregulation	Impairs function at work and hom
Mitochondrial Impairment	Accompanying cognitive impairmer
	Non-restorative sleep

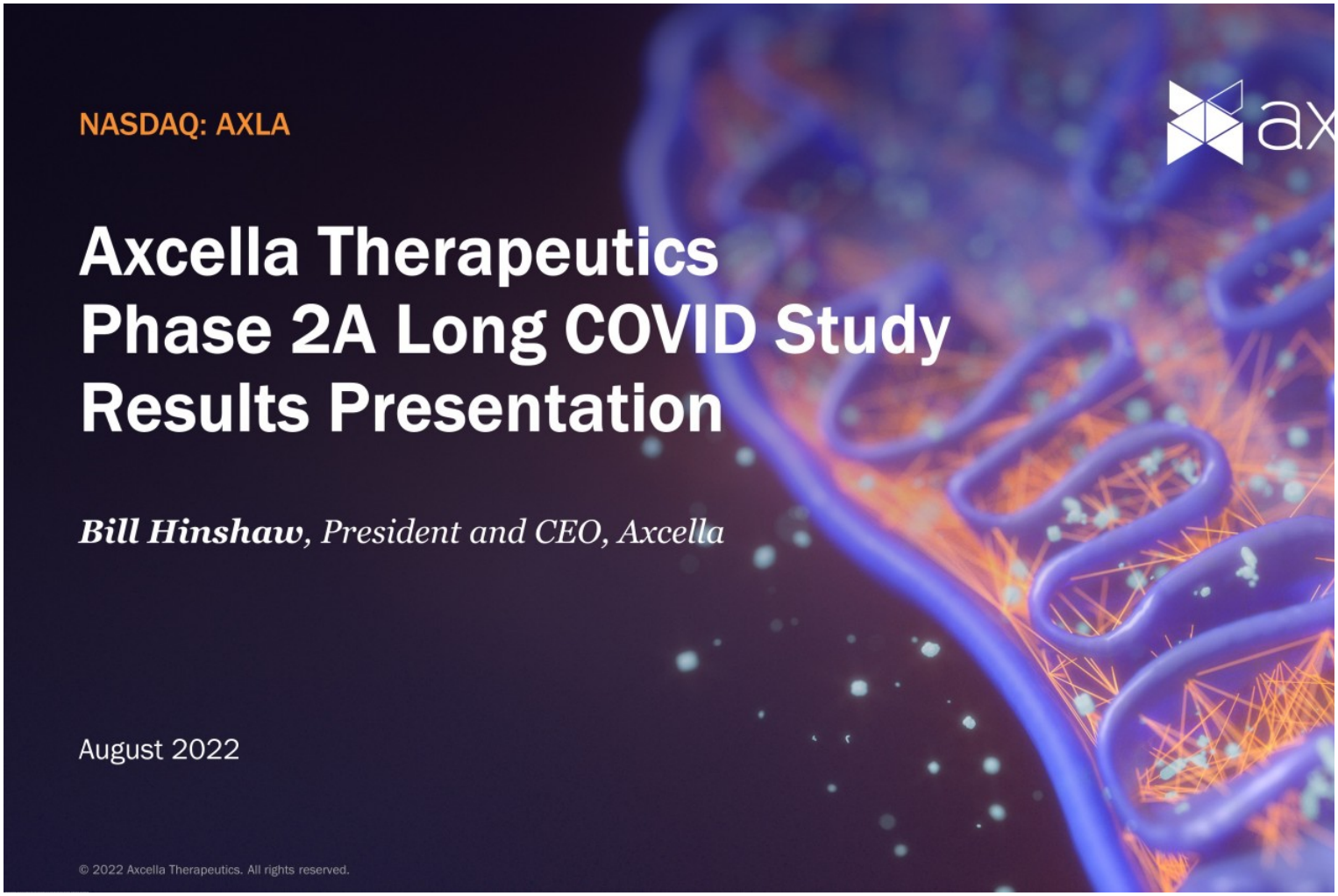
My Key Takeaways from Trial

- Patient-reported outcome – Chalder Fatigue Scale (CFQ-11) – is the outcome that matters to patients and clinicians
- Clinically significant improvement in physical and cognitive domains
- Physical performance (6MWT) improved among those responsive to treatment



What would this mean to patients and to me

- First fatigue therapy addressing underlying biology – no cur
  treatment for fatigue
- Cannot overstate urgency for treatments among patients a
  clinicians
- Ability to return to work, maintain income, participate in hc
- Return of cognitive function: memory, thinking, concentrat
  speech



Milestone Rich Time

Program	Update	Timing
AXA1125 for Long COVID	Phase 2a Enrollment Completion	Q2 2022
	Phase 2a Top-Line Data	Q3 2022
	Regulatory Engagement*	2H 2022
	Scientific Communication	2H 2022
AXA1125 for NASH	Phase 2b Interim Data	Q3 2022
	Scientific Communication	2H 2022

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

In Summary

- AXA1125 Demonstrated Highly Statistically Significant and Clinically Releva
- COVID infections are continuing
- Long COVID will continue to be a major public health crisis
- Patients need options and treatment, not just observation
- Next Steps including Regulatory Engagement and Clinical Plans
- Axcella is leading in Long COVID therapeutics

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

Q&A

Dr. Betty Raman
Radcliffe Department of Medicine, Oxford University

Dr. Jason Maley
Beth Israel Deaconess Medical Center

Bill Hinshaw
President & Chief Executive Off
Axcella

Dr. Margaret Koziel
Chief Medical Officer, Axcella

Dr. Karim Azer
Head of Platform and Discovery,
Axcella

Bob Crane
Chief Financial Officer, Axcella