Targeting the powerhouse of cells to improve the lives of primary mitochondrial disease patients

February 24, 2022

Mitochondria-Targeted Drug Development

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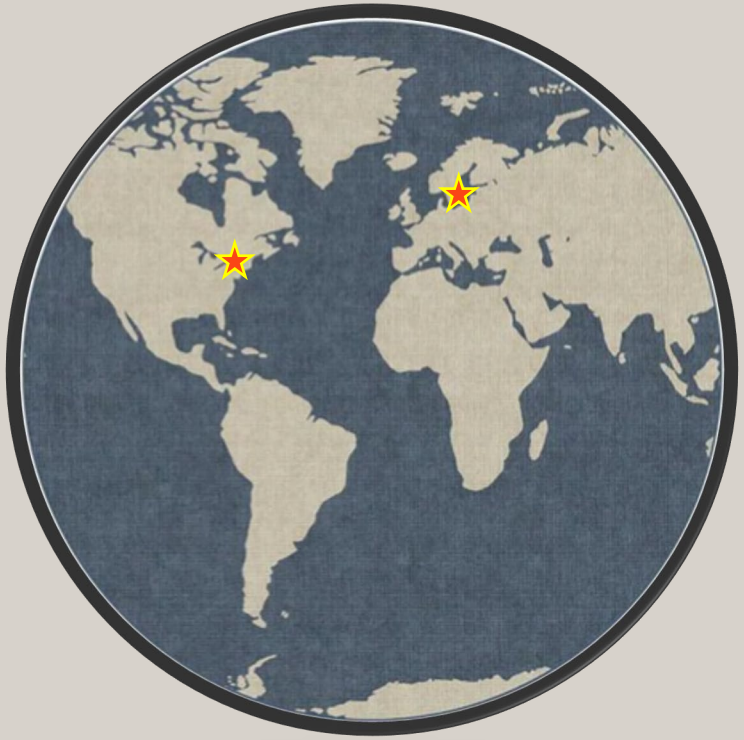
Introducing Abliva



- **Our goal is to become a global leader in mitochondrial medicine.**
- **Our Focus is PMD.** Portfolio of **first-in-class, clinical assets** addressing the rare disease Primary Mitochondrial Disease
- **We Know Mitochondria.** **Experienced team with 20+ years in mitochondrial research**
- **We Put the Patient First.**

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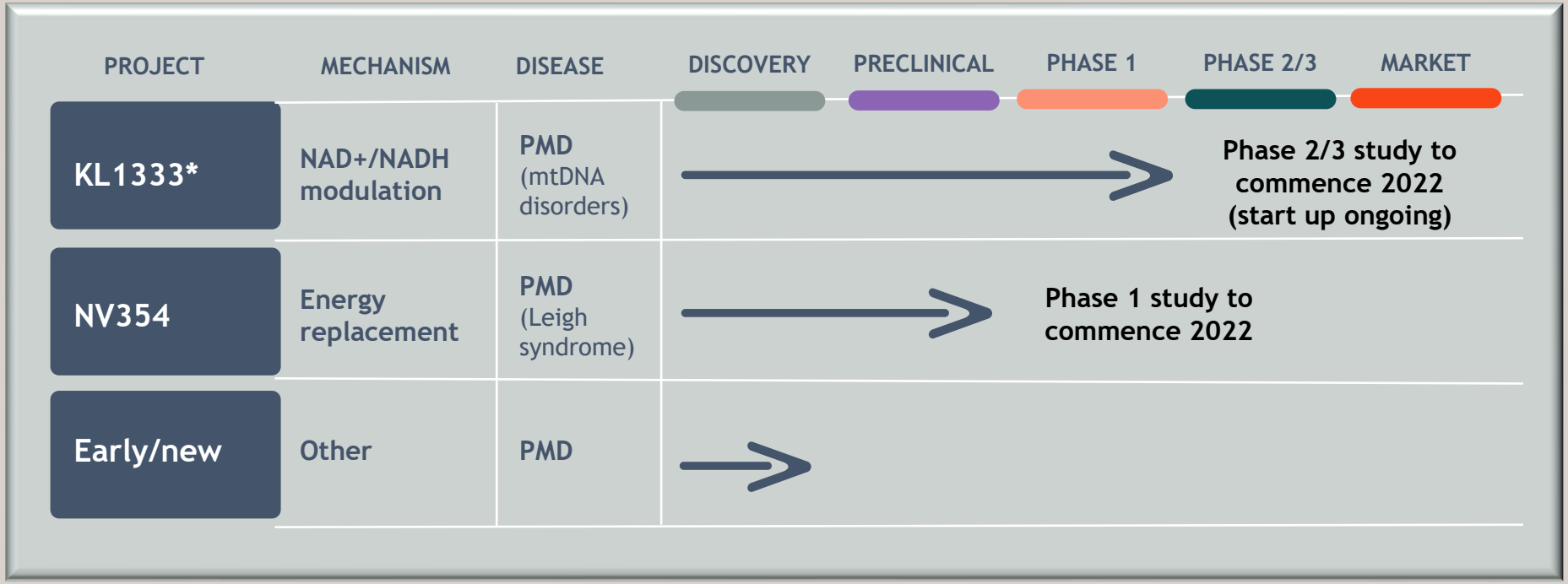
Portfolio of complementary, first-in-class therapies for patients suffering from PMD



*Orphan drug designation in the US and Europe

PMD= Primary Mitochondrial Disease, mtDNA disorders are disorders resulting from a mutation in the mitochondrial DNA.

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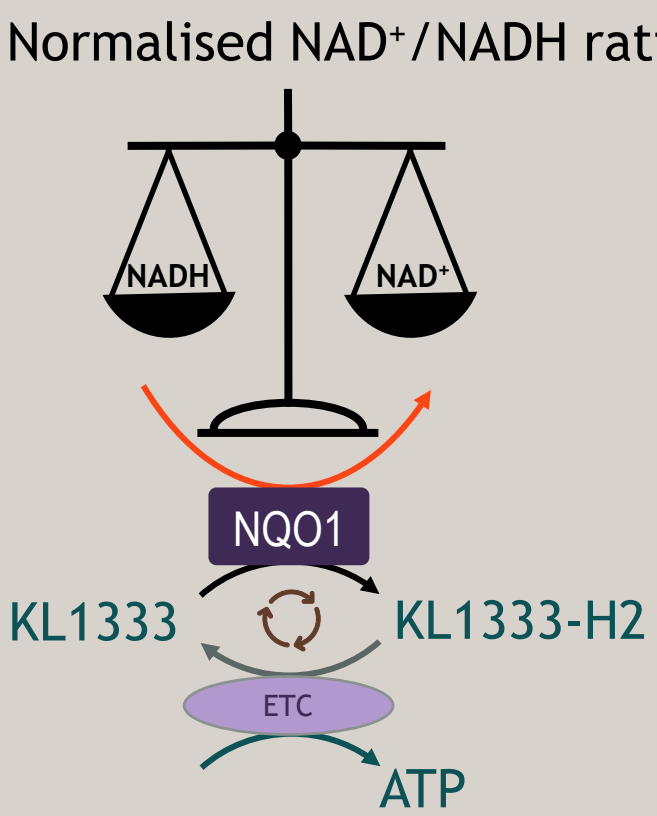
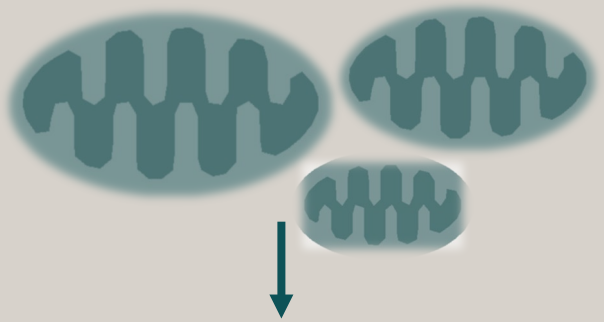
KL1333 corrects underlying pathophysiology of mito disease



Mitochondrial biogenesis



Restored energy metabolism

1. Restored energy regulation and improved ETC function
2. Mito biogenesis stimulated

Overall results: Symptom reduction, disease modification

NAD= Nicotinamide adenine dinucleotide, NQO1= NAD(P)H quinone dehydrogenase oxidoreductases 1, ETC=Electron Transport Chain

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KL1333 increases NAD+ and mitochondrial biogenesis in MELAS patient fibroblasts[1]

KL1333 / NQ01

↓

NAD+ / NADH ↑

↓

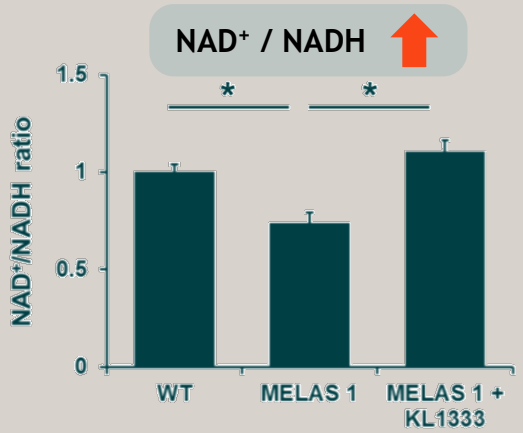
Sirtuins and AMPK ↑

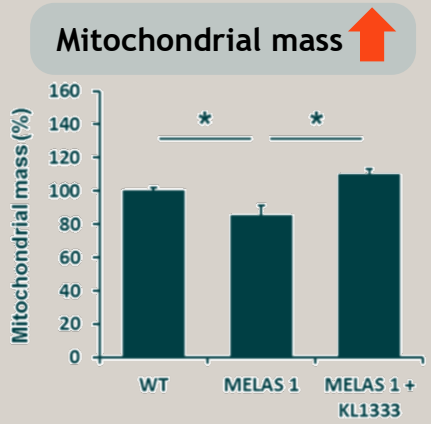
↓

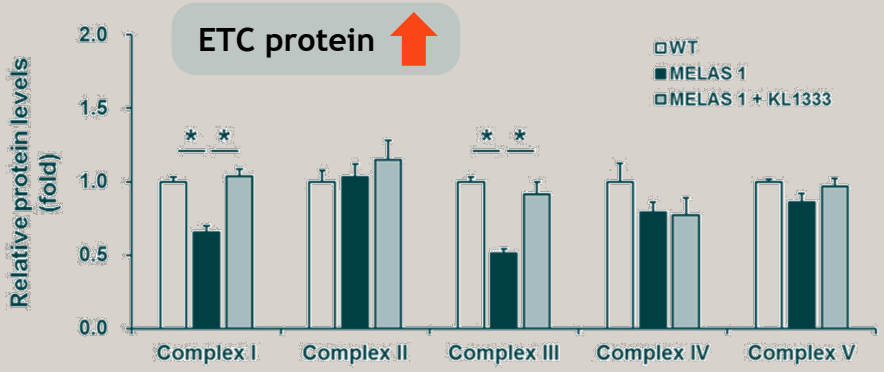
PGC-1α ↑

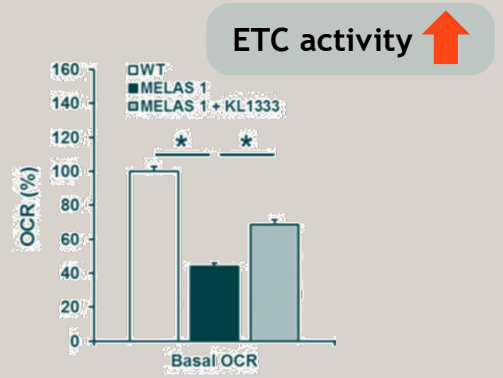
↓

Mitochondrial Function and Biogenesis









(1) Seo et al. 2018. KL1333, a Novel NAD+ Modulator, Improves Energy Metabolism and Mitochondrial Dysfunction in MELAS Fibroblasts (https://www.frontiersin.org/articles/10.3389/fneur.2018.00552/)

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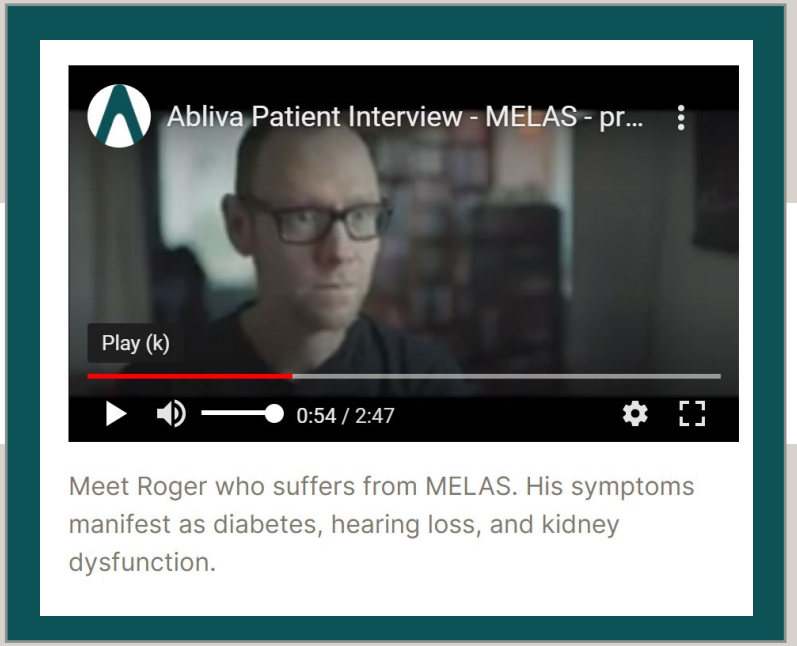
Mechanism confirmed, we then turned to the patients

Meet Rebecca. She's like any other five-year-old, but she can't do all that a healthy child can do.



Meet Roger who suffers from MELAS. His symptoms manifest as diabetes, hearing loss, and kidney dysfunction.

https://abliva.com/primary-mitochondrial-diseases/patients/

Mitocon
Insieme per lo studio e la cura delle malattie mitocondriali Onlus

LILY

imp
international mito-patients

UNITED MITOCHONDRIAL DISEASE FOUNDATION.

LHON EYE SOCIETY

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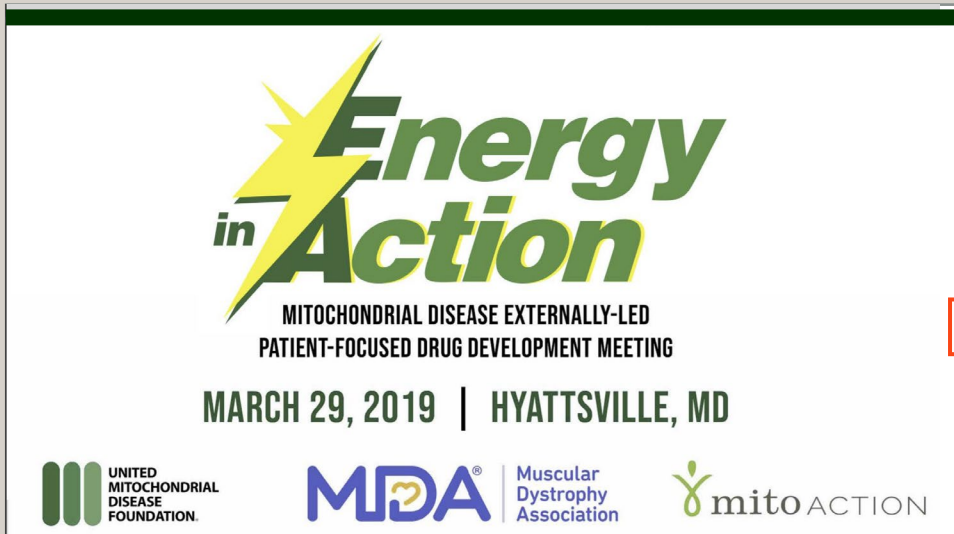
UMDF: FDA meeting clearly highlighted the problem…



Q: What mitochondrial disease symptoms most impact the patient's daily quality of life?

Top answers (n=260):

- Muscle weakness (78%)
- Chronic fatigue (77%)
- Gastrointestinal problems, pain (52%)

Q: Which ability or symptom would you rank as the most important for a possible drug treatment today (select up to 3)?

Top answers (n=260):

- Reduction in chronic fatigue (68%)
- Reduction in muscle weakness (57%)
- Reduced pain (35%)

1. UMDF. Energy in Action – Voice of the Patient Report. https://www.umdf.org/wp-content/uploads/2020/11/UMDF-EL-PFDD-Meeting-VOP-Report_v2019-12-03-JRG.pdf*; 2. UMDF. Energy in Action – Voice of the Patient Report Transcript.* UMDF-EL-PFDD-Meeting-Transcript_final.pdf. 3. UMDF. Energy in Action – Voice of the Patient Post-Meeting Online Survey Results. EL-PFDD-VOP-Report_Online-Survey-Data_Appendix-1.pdf (umdf.org)

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… a problem that was reinforced by the patients. FATIGUE.

"Chronic fatigue contributes to not being able to maintain employment from both physical and mental exhaustion"
-PMD Patient

"I started missing work because I was too exhausted to even get up to use the rest room."
-PMD Patient

"Just do not have enough energy for normal activities."
-PMD Patient

Study of 132 patients in a specialist outpatient clinic in the UK found:

- "Fatigue was common … with **64%** of patients reporting **excessive symptomatic fatigue**"
- Correlated with disease burden (NMDAS), but independent of genotype

Table 2
The rank frequency of fatigue severity as assessed by FIS (Fatigue Impact Scale).

FIS Rank	FIS descriptive	FIS scoring	Results (n=)
0	No fatigue	0–10	16
1	Mild	10–37	31
2	Moderate	38–79	43
3	Severe	80–119	38
4	Very severe	129–160	4

Study of 48 patients in 10 national centers in the US found:

- " …fatigue is very common amongst patients with PMD, with 71–100% of patients reporting fatigue
- …the severity of fatigue correlates with the severity of mitochondrial disease…"

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Should we consider evaluating Patient-Reported Fatigue?

Pros

- Common, debilitating, high impact on daily life
- Represents the highest unmet medical need for a majority of patients
- Independent of genotype
- Correlates with overall disease burden in PMD
- Is likely to be responsive to therapy
- Involves concepts which established assessment tools seem to capture in preliminary models
- Used in other ongoing PMD/PMM drug development programs[1,2,3]
- Extensive psychometric validation of both NeuroQoL and PROMIS Fatigue item banks

Cons

- Assessment tool (fatigue survey) is not indication specific
- Subjective - risk of high placebo response
- May be affected by coping mechanisms

1. Elamipretide: 2-item fatigue score (PMMSA), composite with 6MWT, NeuroQoL fatigue as secondary Kaara et al, J Cachexia Sarcopenia Muscle 2020
2. ASP0367 – Modified FIS and NeuroQoL Fatigue short form CT.gov id: NCT04641962.
3. REN001 – Modified FIS [3] CT.gov id: NCT04535609

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Or follow the others?

6 MWT?

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So we went to the regulators

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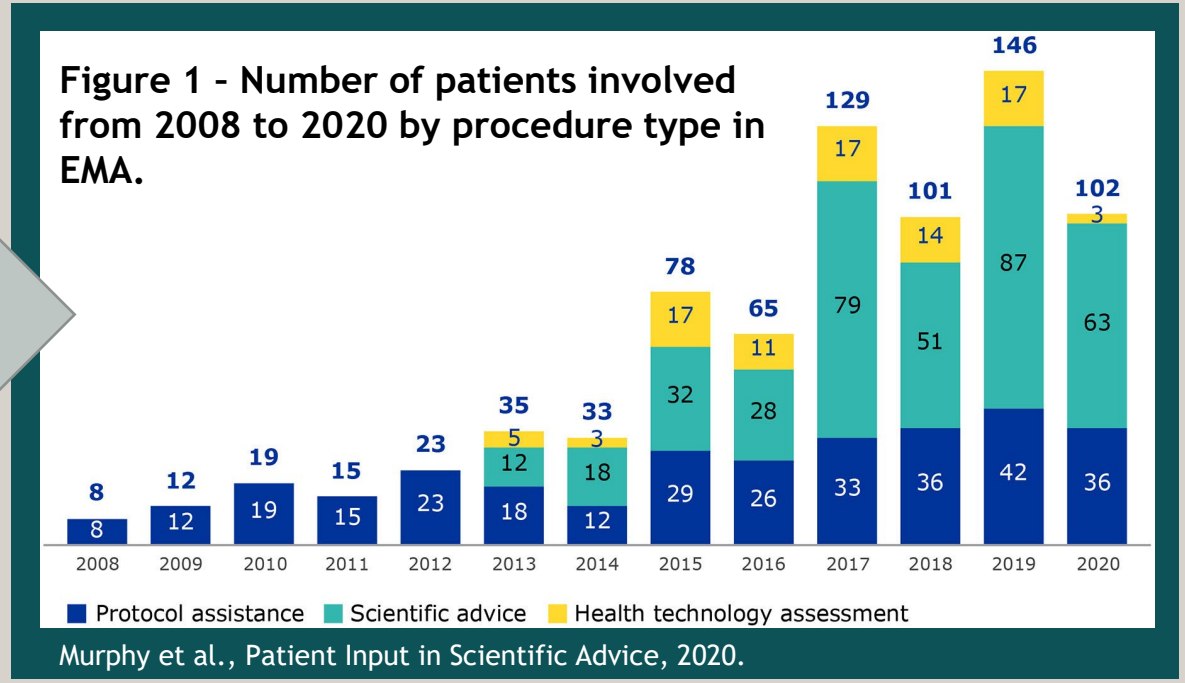
Regulators have recognized the importance of patient input into clinical design

Countless examples including:

- FDA Patient-Focused Drug Development guidance documents
- FDA Voice of the Patient
- EMA public hearings
- Patient Representative Programs
- EMA management board
- EMA Patients and Consumer Working Party (PCWP)
- FDA Patient Engagement Collaborative
- Patient review of public docs (package leaflets, safety communications, medicines summaries)
- Input in scientific advice meetings



Murphy et al., Patient Input in Scientific Advice, 2020.

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

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And have supported the use of patient reported outcome (PRO) measures

Table 3. Characteristics of labeling based on PROs (FDA, 2016-2020).

Disease category*	NMEs with PRO labeling (N = 60), n (%)
Placement of PRO endpoints leading to labeling	
Primary	31 (51.7)
Nonprimary	20 (33.3)
Primary and nonprimary	9 (15.0)
Type of PRO measure[†]	
New measures	12 (20.0)
Established	28 (46.7)
Other[‡]	20 (33.3)
Type of concept assessed	
Symptoms	59 (98.3)
Function[§]	19 (31.7)
HRQOL[‖]	3 (5.0)
Other	3 (5.0)

FDA indicates US Food and Drug Administration; HRQOL, health-related quality of life; NME, new molecular entity; PRO, patient-reported outcome.
*Based on International Classification of Diseases, Tenth Revision codes.
[†]Types of PRO measures are presented hierarchically. New measures are emphasized over all other assessment types; an established measure is emphasized over frequency. If multiple PRO measures were included in the label, only the category for the predominant measure was recorded.
[‡]The category "other" includes concepts such as satisfaction, preference, and frequency counts.
[§]The category "function" includes concepts such as physical functioning, activity limitation, and emotional function.
[‖]The category "HRQOL" includes high-level concepts such as quality of life, HRQOL, and perceived wellbeing.

Gnanasakthy et al., 2021

- **What is a PRO?** "Any report of the status of a patient's health condition that comes directly from the patient"[1]
- **What do they assess?** Symptoms, functional outcomes, quality of life aspects, treatment satisfaction
- **Are they being used?**
  - In 2004 – 2007 they were used in 14% of clinical trials[2]
  - By 2016 – 2020, use had increased to 26.3% of NDAs and 66.7% were based on primary endpoints related to the PROs[3]

(1) US FDA Guidance for industry: patient-reported outcome measures; (2) Mercieca-Bebber et al., 2018; (3) Gnanasakthy et al., 2021.

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PROM as primary endpoints are supported by several precedents across a spectrum of diseases

PROs as Key Evidence

- Tocilizumab (Jakafi®) (PROMIS)
- Solriamfetol (RINVOQ®) (FACIT)
- Sarilumab (Kevzara®) (HAQ-DI)
- Tafamadis (Vyndaque®l) (Norfolk QOL-DN)
- Tadalafil (Cialis®) (IPSS)

Fatigue PRO as Primary Endpoint

- Tocilizumab (Actemra®)
- Solriamfetol (Sunosi®)

Approval Based on PRO

- Mitoxantrone (Novantrone®)

Mitoxantrone (J. Clin Oncol. 1996; J Clin Oncol. 1999); Novantrone FDA label https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019297s033s034lbl.pdf); FDA Jakafi label https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202192Orig1s019Rpllbl.pdf. FDA RINVOQ label https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf; Actemra PI https://www.gene.com/download/pdf/actemra_prescribing.pdf

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Payers also confirmed a PROM as a primary endpoint was “compelling”, acceptable and appropriate

PRO AS A PRIMARY ENDPOINT

- All the KOLs and Payers stated that the use of a PRO as a primary endpoint is considered acceptable and appropriate
- Payers stated that the choice of the primary endpoint would likely not pose reimbursement challenges for KL1333

FATIGUE PRO BASED ON PROMIS SHORT-FORM

- Payers had a positive view of the custom PROMIS fatigue short form; using a robust, validated tool gave them more confidence
- Some Payers commented that they were familiar with PROMIS measures as they have been used in other therapy areas
- Reaching the MCID threshold, would be considered satisfactory for KOLs and Payers, however a gap was identified regarding the translation of the T score into tangible clinical benefit
- Payers require some education on the patient burden of fatigue in PMD patients to maximise the value of KL1333

I would say the primary endpoint is compelling

- IT Payer

So the fact that it’s measured using a PROMIS fatigue short form gives it a lot of credibility. PROMIS is a rigorous, validated instrument.

- UK Payer

Fatigue PRO, in a placebo-controlled trial…yes, go ahead. For the transparency committee this is fully acceptable. But for non-HTA Payers, it may be more challenging; probably see it as subjective

- FR Payer

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Phase 1a/1b study design

What? A Randomised, Double-blind, Parallel-group, Placebo-controlled, Phase Ia/Ib, Multiple-site Study

Why? Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of KL1333 after a

How? Single Oral Dose and Multiple Ascending Oral Doses

Who? Healthy Subjects and Patients with Primary Mitochondrial Disease

Study contained 4 parts, with 56 healthy volunteers and 8 PMD patients:

- Part A: SAD with Food effect, 1 cohort 25 mg QD, healthy volunteers
- Part B: MAD, 5 cohorts 25, 50, 75, 150 and 250 mg QD, healthy volunteers
- Part C: 10 days dosing, 50 mg QD, 1 cohort, PMD patients
- Part D: Split dosing (75 mg BID or 50 mg TID), 2 cohorts, healthy volunteers

Healthy volunteer cohorts began in March 2019 and were run at the Covance CRU in Leeds, UK.

Patient cohort was started in October 2020 and was run at University College London (Robert Pitceathly, Chief Investigator) and Newcastle (Grainne Gorman), UK.

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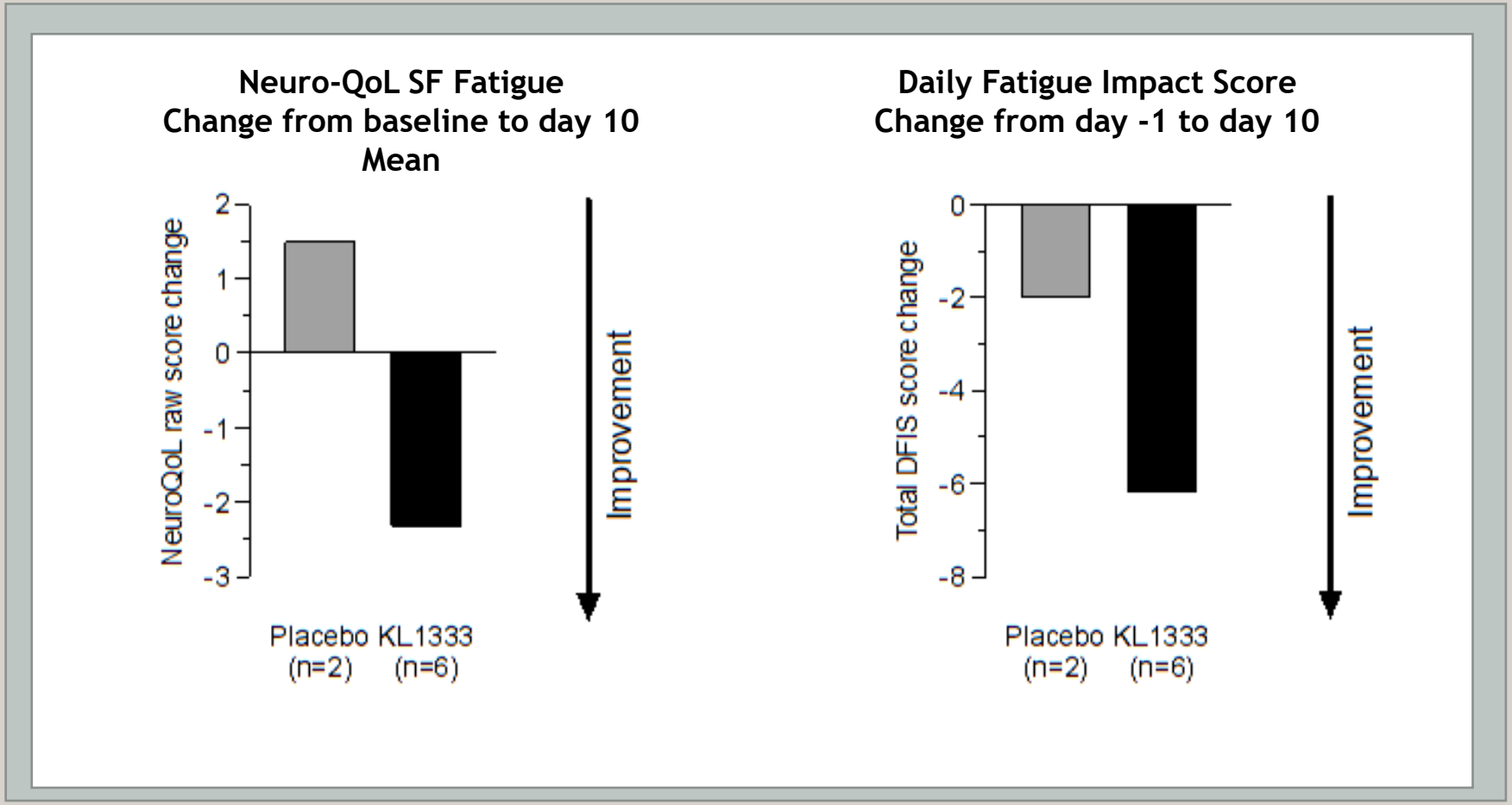
Patients given KL1333 showed a marked improvement in fatigue with only 10 days of dosing.



Minimally important differences for fatigue scales ranges from 2.5-5 in T-score (Yost et al 2011); DFI-S ranges from 3-4 as extrapolated from Nordin et al. 2016.

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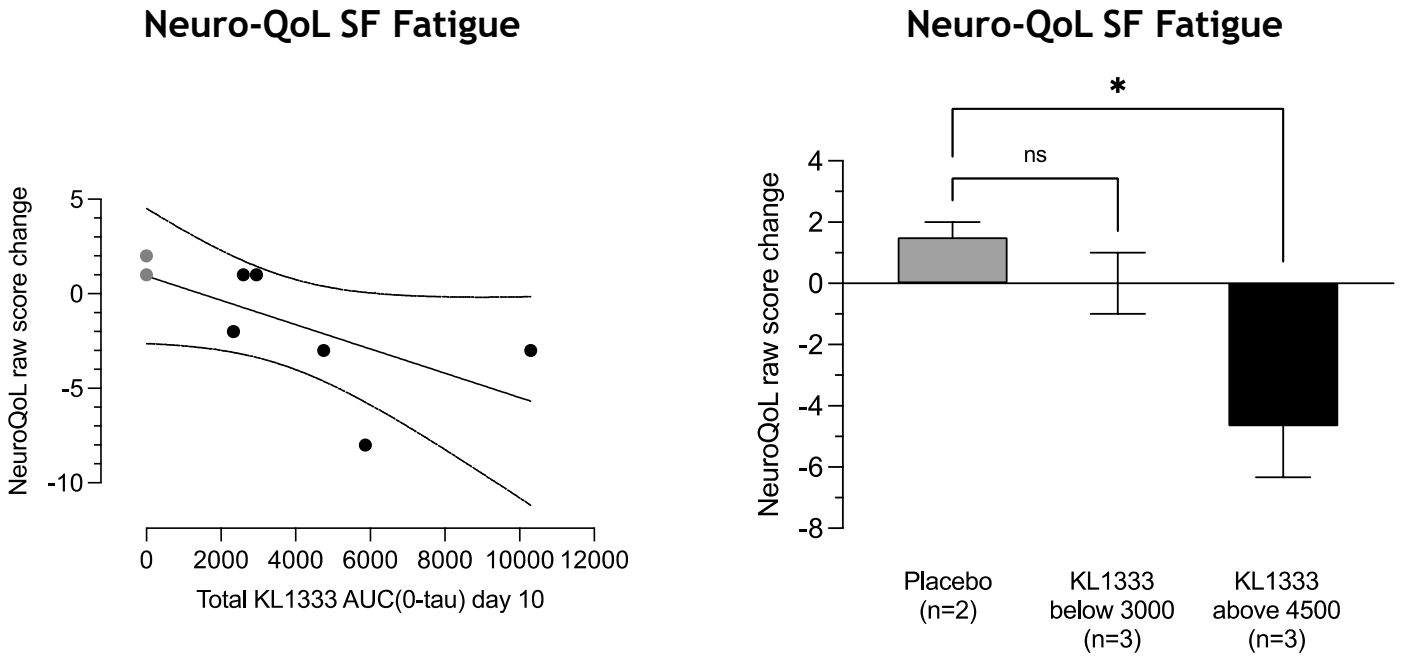
Exposure and effect were correlated across these clinical outcome measures

Reduction of fatigue in relation to exposure of KL1333



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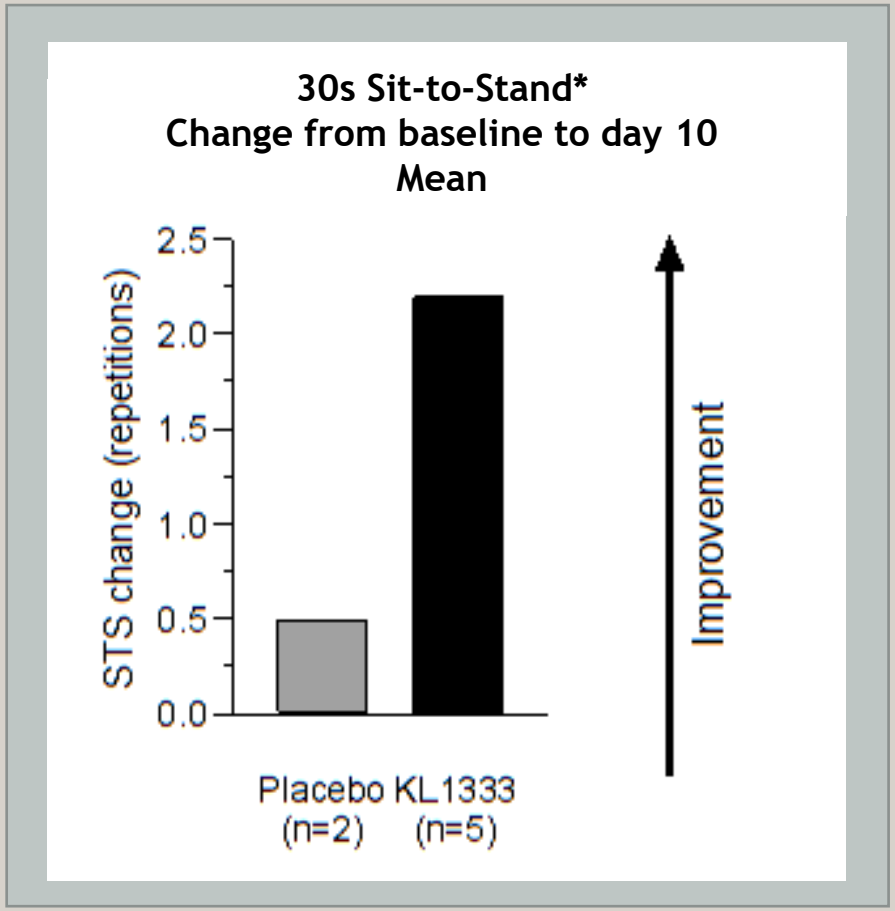
The 30 sec Sit-to-Stand endpoint also showed signs of efficacy in PMD patients.



Notes on Sit-to-Stand:

- Score = number of repetitions (higher score = better muscle strength/endurance)
- ≥2 repetitions has been defined as the minimum clinically important difference in osteoarthritis and COPD**

* One subject in the KL1333 group did not perform test (excluded from analysis)
**Wright et al 2011 (Osteoarthritis), Zanini et al. 2019 (COPD)

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We initiated work to establish, and validate, a PMD-specific fatigue form

Neuro-QoL Short Form Fatigue

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
I felt exhausted……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt that I had no energy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt fatigued……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was too tired to do my household chores.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was too tired to leave the house……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was frustrated by being too tired to do the things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I had to limit my social activity because I was tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Key:

- Use reliable and validated questions as source
- Eliminate any ambiguity
- Find questions that are specific to PMD
- Ensure adequate response range and variability in the response
- Ability to detect change

SPROUT Health Solutions

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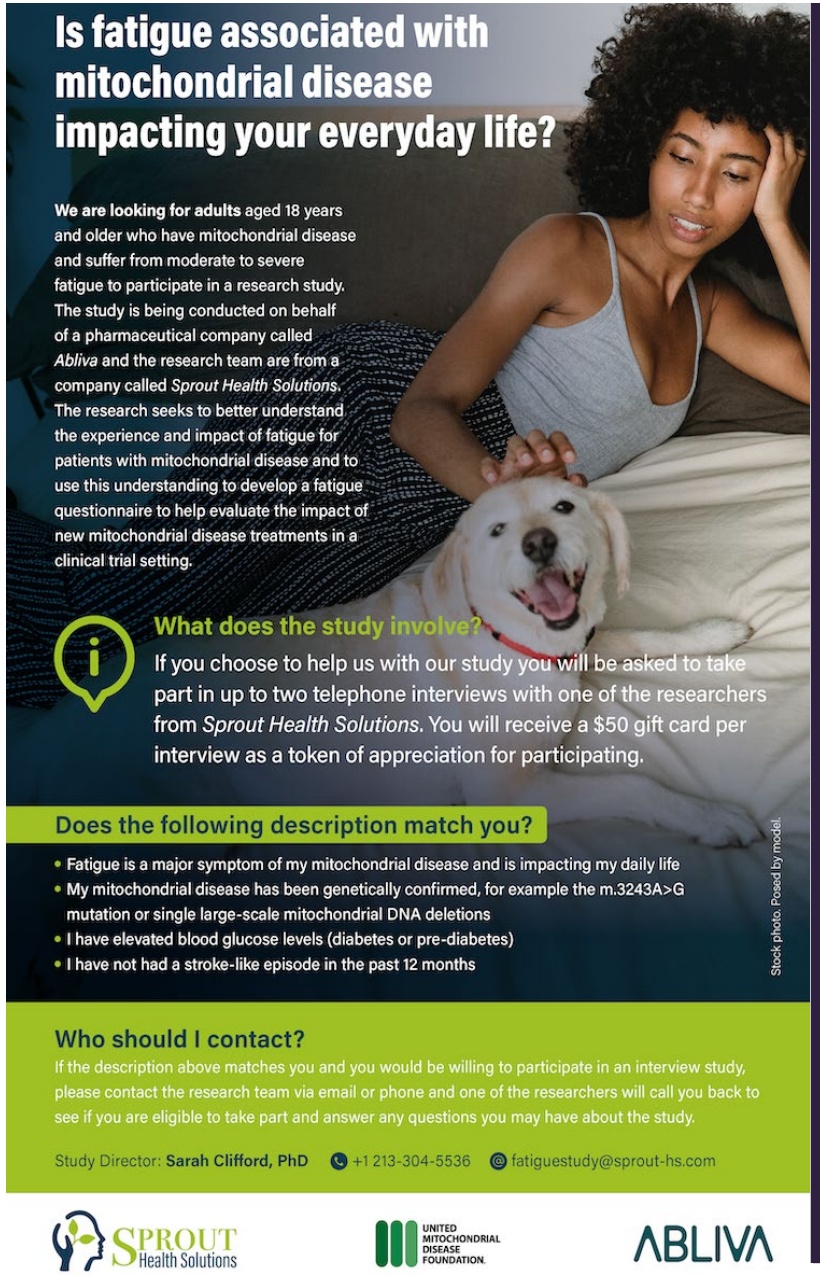
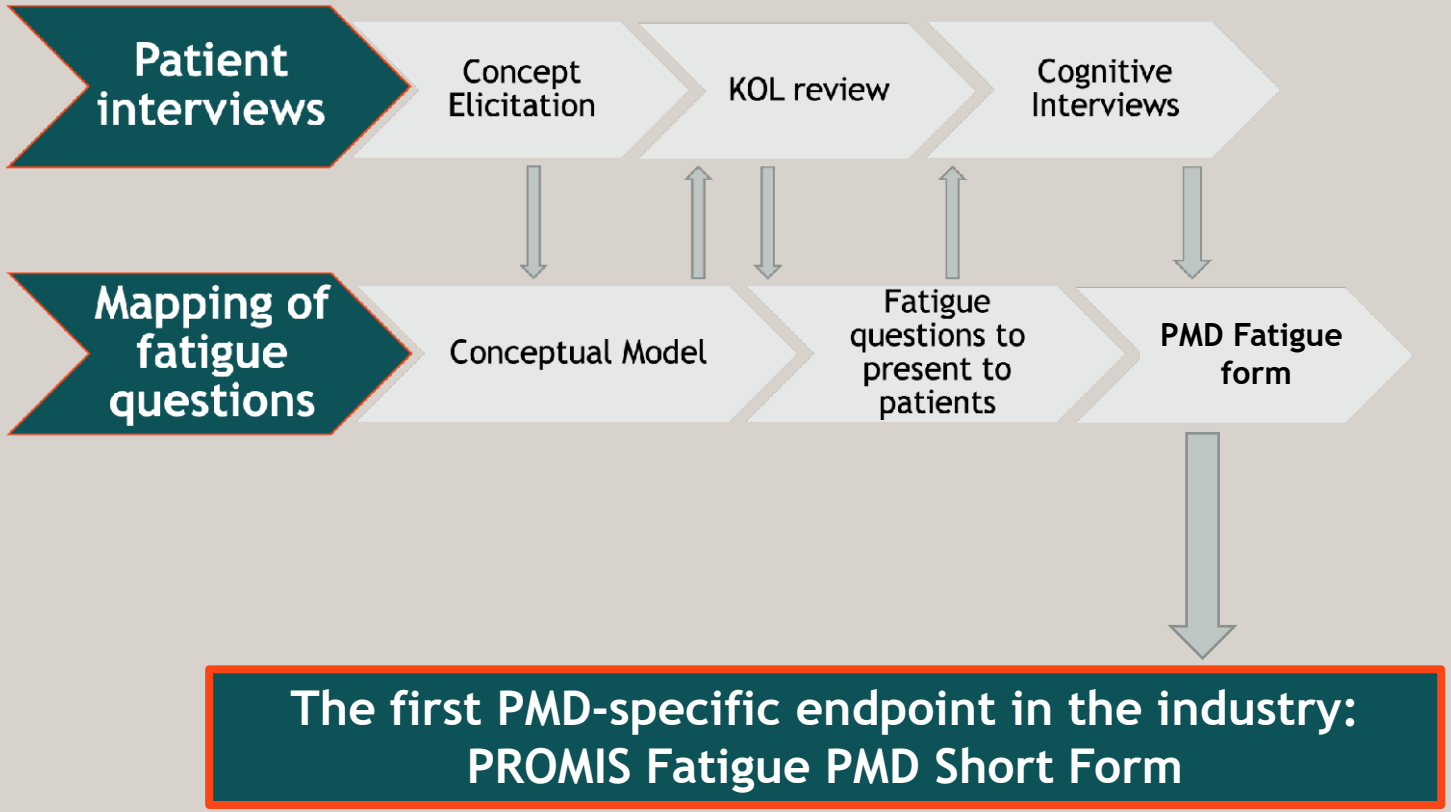


PMD patients tested validated questions



The first PMD-specific endpoint in the industry: PROMIS Fatigue PMD Short Form

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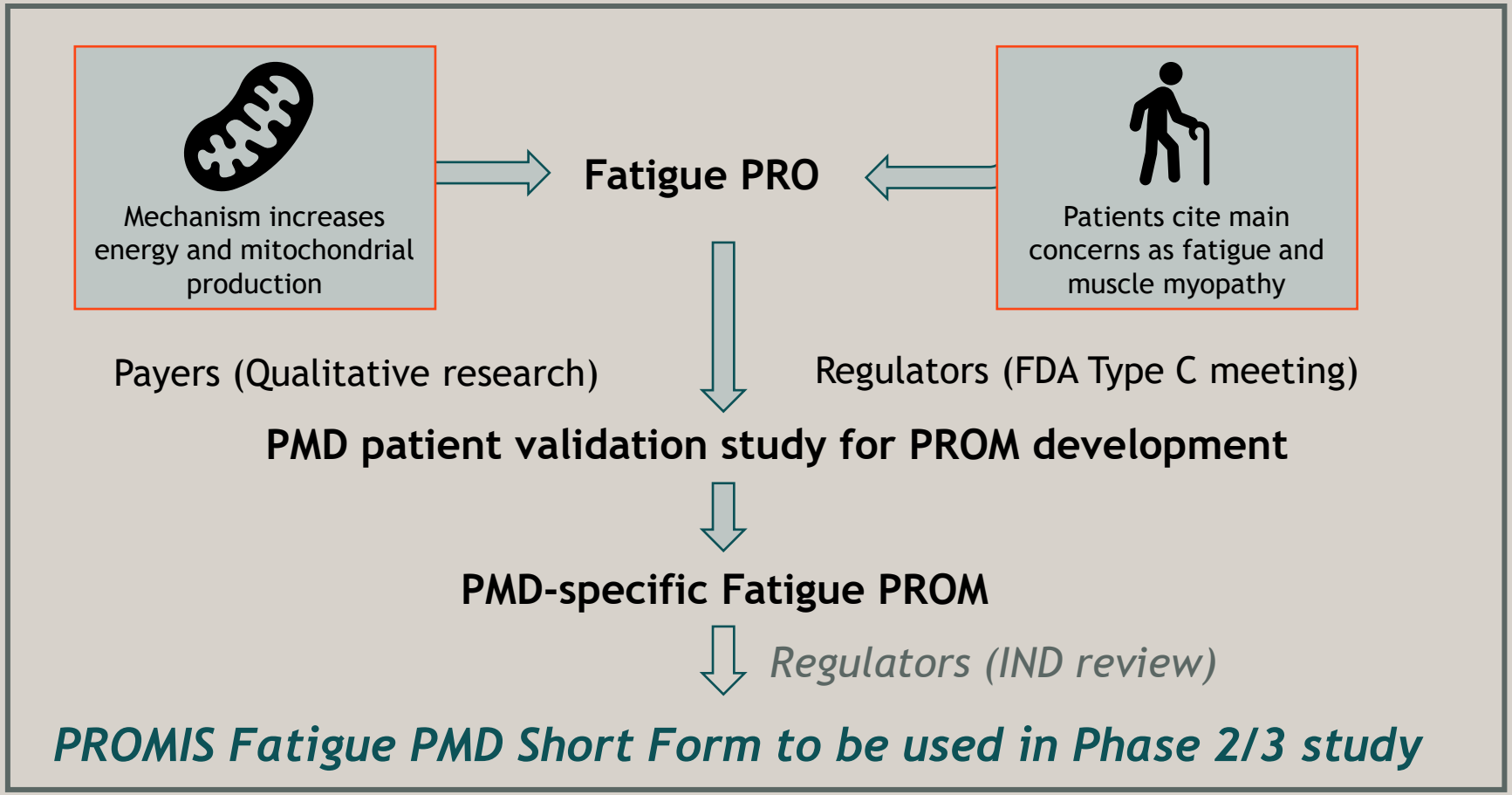
Fatigue: Identified by MOA and patients; confirmed by regulators and payers



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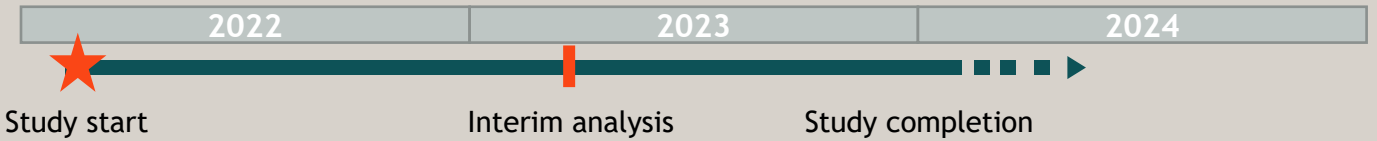
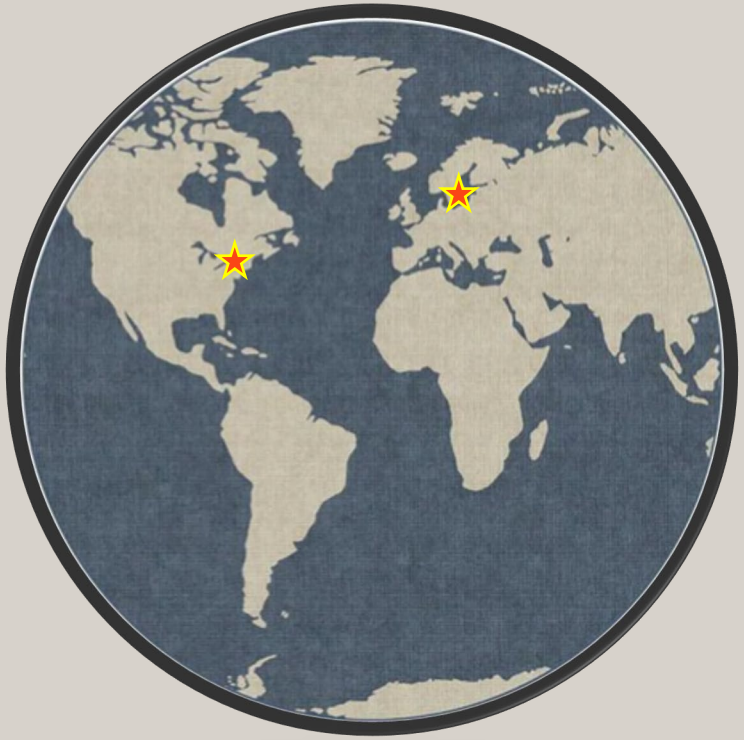
Global, registrational Phase 2/3 study is currently in study start up



- **Design:** Randomized, double-blind, parallel-group, placebo-controlled (2 placebo:3 active)
- **Patients:** Adult 'Mito-disease' patients with:
  - Multisystemic mitochondrial DNA-related disease
  - Chronic fatigue
  - Mitochondrial myopathy/exercise intolerance
- **Treatment:** Two pills daily for 12 months
- **Size:** 120-180 patients (determined at interim analysis)
- **Endpoints:**
  - Alternate Primary: PMD Fatigue, 30 Second Sit-to-Stand
  - Secondary: Clinician assessments; patient-specific activity assessments

*Including MIDD-MELAS-m.3243A>G associated spectrum disease, single large scale mtDNA deletion associated KSS-CPEO spectrum disorders, MERRF, and other multisystemic mitochondrial DNA-related disease.; ** Newcastle Mitochondrial Disease Adult Scale (NMDAS) (Schaefer et al., 2006)

In Summary: Abliva



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