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): October 9, 2023

Reneo Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-40315**	**47-2309515**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

18575 Jamboree Road, Suite 275-S	
Irvine, California	**92612**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (858) 283-0280

N/A
(Former name or former address, if changed since last report.)

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

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, par value $0.0001 per share	RPHM	The Nasdaq Stock Market LLC

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 October 9, 2023, Reneo Pharmaceuticals, Inc. (the "Company") hosted a Key Opinion Leader ("KOL") meeting utilizing the slide presentation furnished as Exhibit 99.1 to this Current Report on Form 8-K. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.1.

The information in this Item 7.01 of this Current Report on Form 8-K and Exhibit 99.1 shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that Section, nor shall it be deemed to be incorporated by reference into any filing of the Company 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 October 9, 2023, the Company announced last patient last visit in the pivotal STRIDE study of mavodelpar in primary mitochondrial myopathies. Topline data results from the STRIDE study are expected in December 2023. In addition, the Company has enrolled over 85% of eligible patients in the Company's ongoing STRIDE AHEAD study.

The Company anticipates completing the final steps in the clinical process for the STRIDE study in the coming months. Subsequently, the Company plans to share the results of data analysis with the United States Food and Drug Administration ("FDA") in the first quarter of 2024. The Company expects that the STRIDE and STRIDE AHEAD studies will form the basis of a New Drug Application ("NDA") to the FDA which is planned for submission in the first half of 2024 and thereafter to additional regulatory agencies.

Forward-Looking Statements

Statements contained in this Current Report on Form 8-K regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements include statements regarding, among other things, the timing of topline data from the STRIDE study, the timing of the final steps in the clinical process for the STRIDE study and for sharing the results of data analysis with the FDA, the prospects of the STRIDE AHEAD study, and the potential filing and timing of an NDA to the FDA and thereafter to additional regulatory agencies. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "plans," "will," "believes," "anticipates," "expects," "intends," "goal," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon the Company's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks and uncertainties associated with the Company's business in general, and the other risks described in the Company's filings with the Securities and Exchange Commission. All forward-looking statements contained in this Current Report on Form 8-K speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Reneo Pharmaceuticals, Inc. KOL Event Presentation, dated October 9, 2023
104	Cover Page Interactive Data File (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.

Reneo Pharmaceuticals, Inc.

Date: October 10, 2023

By: /s/ Gregory J. Flesher
Gregory J. Flesher
Chief Executive Officer

Focused on Improving the Lives of Patients with Rare Genetic Mitochondrial Diseases

Forward-Looking Statements

This presentation contains "forward-looking" statements that are based on our management's beliefs and assumptions and on information currently available to management. Forward-looking statements include all statements other than statements of historical fact contained in this presentation, including information concerning our business strategy, objectives and opportunities. Forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors that may cause our actual results, performance or achievements to differ materially and adversely from those anticipated or implied by our forward-looking statements, including, but not limited to, those related to our dependence on third-party clinical research organizations, manufacturers, suppliers and distributors; our ability to obtain necessary additional capital; our ability to obtain necessary regulatory approvals for our products and, if and when approved, market acceptance of our products; the commercialization plans and expectations for commercializing mavodelpar (REN001) in the United States and rest of world, estimates of the number of patients impacted by PMM or LC-FAOD and who are appropriate for treatment with mavodelpar, the potential benefits of mavodelpar, the financial impact or revenues from any commercialization we undertake, the impact of competitive products and therapies; our ability to attract and retain key employees; the costs of our commercialization plans and development programs; the design, implementation, timing and outcomes of our clinical trials; our ability to manage the growth and complexity of our organization; our ability to maintain, protect and enhance our intellectual property; and our ability to continue to stay in compliance with applicable laws and regulations. You should refer to the section entitled "Risk Factors" set forth in our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and other filings we make with the Securities and Exchange Commission (SEC) from time to time for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Neither we nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements. We undertake no obligation to update any forward-looking statements after the date of this presentation except as may be required by law.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Projections, assumptions and estimates of the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. The trademarks included herein are the property of the owners thereof and are used for reference purposes only.

Mavodelpar is an investigational drug product candidate that is under clinical investigation, and which has not yet been approved for marketing by the U.S. Food and Drug Administration, European Medicines Agency, or any other global regulatory agency. No representation is made as to the safety or effectiveness of this product candidate for the use for which it is being studied.

We use our website (https://www.reneopharma.com) and LinkedIn page (https://www.linkedin.com/company/reneo-pharmaceuticals) as channels of distribution of information about our company, product candidates, planned announcements, attendance at upcoming conferences and other matters. Such information may be deemed material information, and we may use these channels to comply with our disclosure obligations under Regulation Fair Disclosure. Therefore, investors should monitor our website and LinkedIn page in addition to following our SEC filings, press releases, public conference calls and webcasts.

Today's Speakers

Welcome & Opening Remarks

Gregory J. Flesher
President & CEO
Reneo Pharmaceuticals, Inc.

Overview of Mitochondrial Disease

Amel Karaa, MD
Director of the Mito Clinic
Massachusetts General Hospital
Harvard Medical School

Mavodelpar Development Program

Alejandro Dorenbaum, MD
Chief Medical Officer
Reneo Pharmaceuticals, Inc.

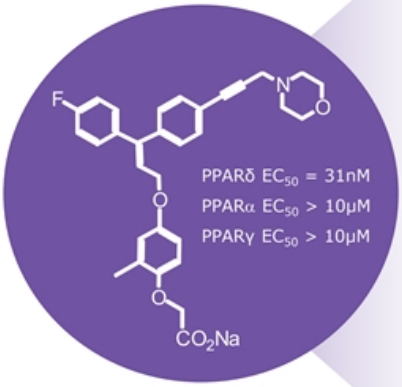
Addressable Patients (US)

Michael Cruse
Chief Operating Officer
Reneo Pharmaceuticals, Inc.

Mavodelpar Overview

Biology

- *Potent and selective agonist of peroxisome proliferator-activated receptor delta (PPARδ)*
- *Regulates generation of cellular energy*
- *Present in multiple tissue types including muscle, brain, kidney, and liver*
- *Activation in response to increased cellular energy needs*



1. Increases transcription of genes central to mitochondrial function

2. May drive production of new mitochondria

3. Increases oxidation of fatty acids and cellular energy production

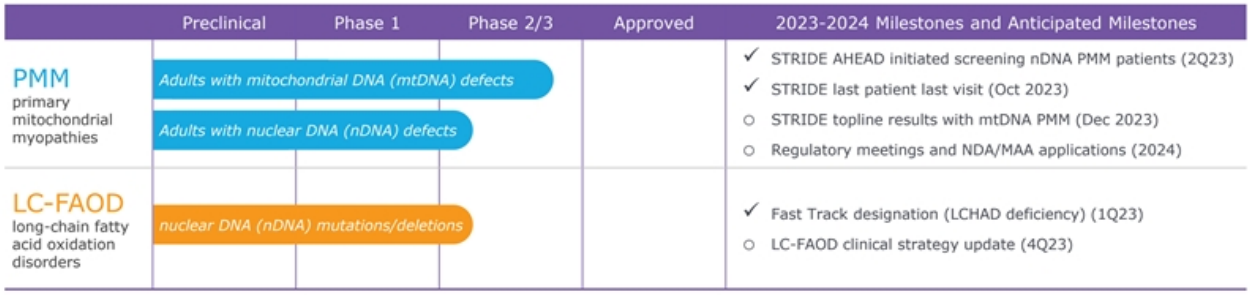
Mavodelpar Clinical Trials

STUDY	DESIGN	SUBJECTS	DOSE	DURATION	KEY OBSERVATIONS
1	Phase 1 SAD	Healthy	25-250 mg	Single-dose	✓ *Well tolerated*
2	Phase 1 MAD	Obese (dyslipidemic)	50-200 mg	14 days	✓ *Well tolerated* ✓ *Dose-dependent decrease in lipids*
3	RDBPC† Phase 1 (leg immobilization)	Healthy	200 mg	28 days	✓ *Well tolerated* ✓ *Increase in expression of PPARδ regulated genes* ✓ *Increase in muscle strength*
4	Open-label Phase 1b	PMM (mtDNA)	100 mg	12 weeks (+36 weeks)	✓ *Well tolerated* ✓ *Increase in expression of PPARδ regulated genes* ✓ *Increase in 12MWT, 30STS, and peak VO_2 / decrease in fatigue and pain*
5	Open-label Phase 1b	McArdle Disease	100 mg	12 weeks	✓ *Well tolerated* ✓ *Increase in oxidation of fatty acids*
6	Open-label Phase 1b	LC-FAOD (nDNA)	100 mg	12 weeks	✓ *Well tolerated* ✓ *Increase in expression of PPARδ regulated genes* ✓ *Increase in 12MWT / decrease in fatigue (certain genotypes)*
7	RDBPC Phase 2b (STRIDE Study)	PMM (mtDNA)	100 mg	24 weeks	○ *Ongoing; topline data expected Dec 2023*
8	Open-label safety (STRIDE AHEAD Study)	PMM (mtDNA + nDNA)	100 mg	2 years	○ *Ongoing; interim data expected 2024*

† randomized double-blind placebo-controlled clinical trial

Reneo Pipeline

Reneo is initially developing mavodelpar for patients with rare genetic mitochondrial diseases that typically present with myopathy and have a high unmet medical need



Primary Mitochondrial Myopathies (PMM)

Characteristics

- PMMs are rare disorders caused by mutations within mitochondrial DNA (mtDNA) or nuclear DNA (nDNA)
- Mutations hamper the ability of mitochondria to generate energy
- Most pronounced in tissues with high energy demand (muscle, brain, and heart)

Symptoms

- Debilitating fatigue
- Myopathy
- Exercise intolerance
- Muscle pain
- Severe lack of endurance
- Reduced life expectancy

Prevalence*

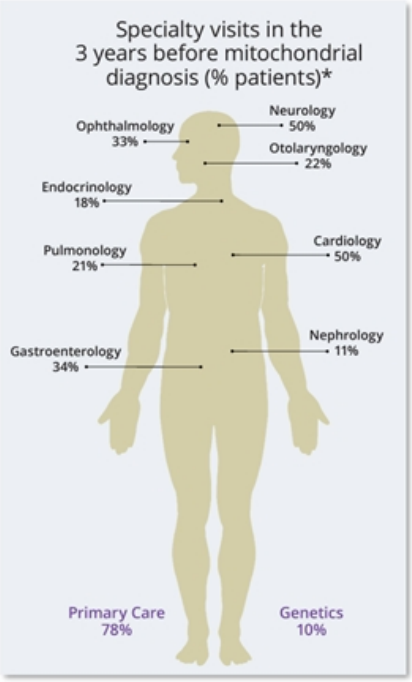
- All adult PMM (23:100,000)
  - Symptomatic mtDNA (9.6:100,000)
  - Symptomatic nDNA (2.9:100,000)

Current Treatments

- No approved therapies
- Over-the-counter vitamins and supplements commonly used

** Adult mtDNA and nDNA PMM Prevalence – Gorman G. et al., Ann Neurol. 77(5): 753–759 (2015)*

Multisystem Manifestation and Burden of PMM



M. Sirimanne et al; UMDF 2023

Greater severity of myopathy

Comorbid Signs/Symptoms and Conditions,[a] % of Patients with Suspected PMM in Segment					
Nervous system	13%	23%	40%	50%	69%
Respiratory	38%	52%	55%	58%	64%
Abdominal/GI	35%	49%	53%	55%	58%
Circulatory	23%	36%	37%	41%	50%
Hypertension	39%	44%	46%	49%	46%
Depression	24%	35%	36%	40%	44%
Esophageal	25%	34%	36%	44%	41%
Kidney disease	21%	21%	22%	24%	26%
Diabetes	21%	24%	25%	23%	26%
Pain	62%	79%	83%	86%	78%*

Overview of Mitochondrial Disease

Amel Karaa, MD
Director of the Mito Clinic
Massachusetts General Hospital
Harvard Medical School

STRIDE Principal Investigator

Mitochondrial Myopathy Primer

AMEL KARAA, MD
DIRECTOR OF THE MITO CLINIC
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

Disclosures & Disclaimers

UMDF: fellow, SMAB Chair-Elect, Planning committee.

Mitochondrial clinical network founder and governance board member.

North American Mitochondrial Disease Consortium site PI

Immediate past President of the Mitochondrial Medicine Society and MitoAction medical board.

Grants and research support from Stealth BioTherapeutics, Reata pharmaceuticles, Astellas, MitoBridge, Reneo, Cyclerion, Sanofi Genzyme, Shire, Portalix, Idorsia…

Consulting for Sanofi Genzyme, Stealth Biotherapeutics, Alexion, Lumleian, Homology, MitoBridge, Akros, Astellas, Neurovive, Mivovia, Reneo, Zogenix, Cyclerion, UCB, Pretzels Therapeutics, Nanna Therapeutics ….

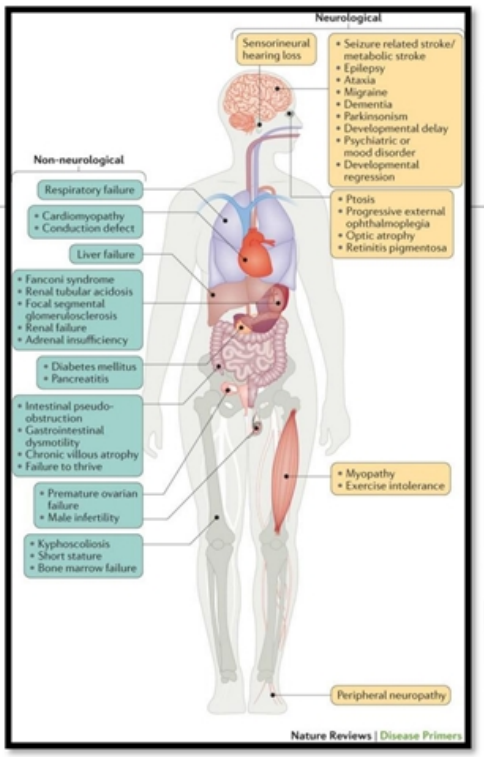
Disclaimer:

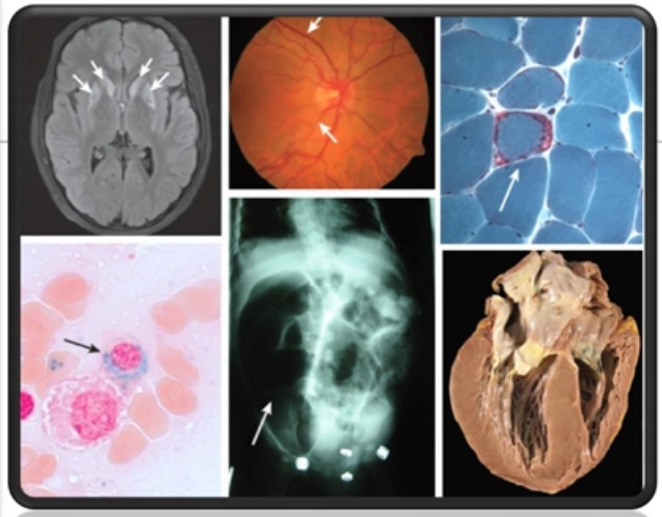
The information presented are my own professional and not that of my employer, organization, committee or other group or individual I work with.

Overview of mitochondrial disease

"Any symptom, any organ, any age, any mode of inheritance"

- Munnich & Rustin (Am.J.Med.Genet. 2001, 106:4-17)





Vafai and Mootha, Nature 2012

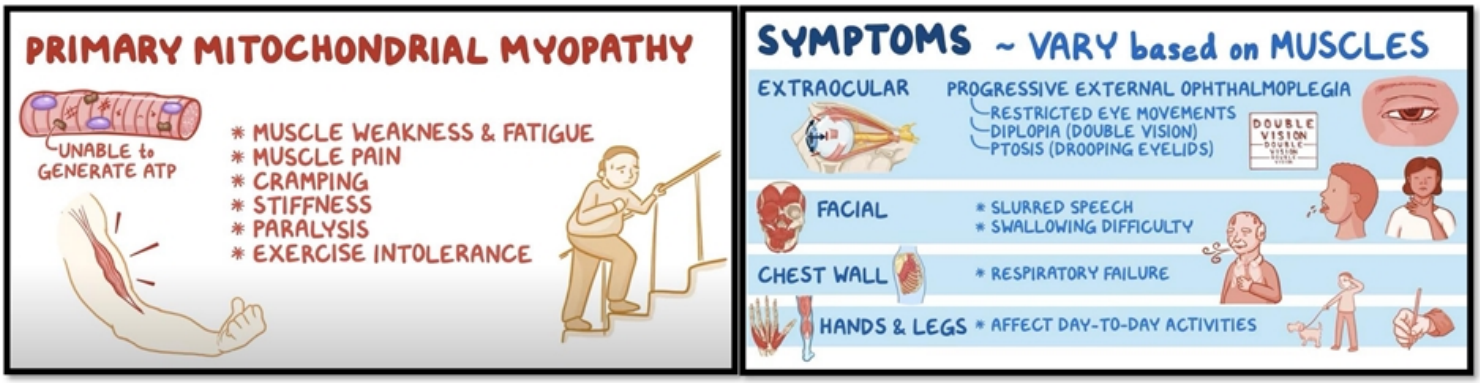
Primary Mitochondrial Myopathy

(Consortium of International Experts in Mitochondrial Disease)

- PMM refers to a subset of primary mitochondrial disease that predominantly but not exclusively affect skeletal muscles.

Neuromuscul Disord. 2017 December ; 27(12): 1126–1137. doi:10.1016/j.nmd.2017.08.006.

Myopathy can be the only clinical feature of a mitochondrial disease

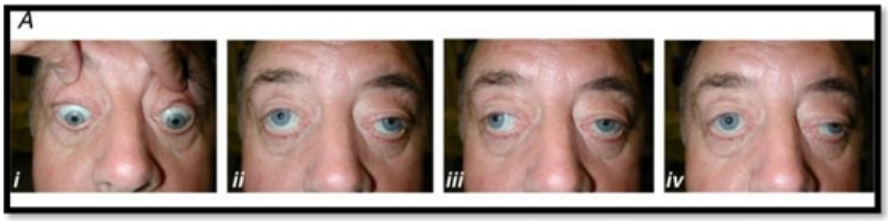


PMM includes a number of clinical syndromes like CPEO, CPEO +, isolated mitochondrial myopathy

Arturito, TK2 myopathy

https://www.fairfaxfamilyfun.com/

Chronic progressive external ophthalmoplegia (CPEO)



Gorman et al. Saudi Journal of Ophthalmology. Volume 25, Issue 4, 2011, 395-404

Myopathy can be associated with additional manifestations

Tissue or Area	Symptom or Sign	Kearns–Sayre Syndrome	Myoclonus Epilepsy with Ragged-Red Fibers	Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes	Neuropathy, Ataxia, Retinitis Pigmentosa	Maternally Inherited Leigh Syndrome
Central nervous system	Seizures	–	+	+	+	+
	Ataxia	+	+	+	+	±
	Myoclonus	–	+	±	–	–
	Psychomotor retardation	–	–	–	–	+
	Psychomotor regression	+	±	+	–	–
	Hemiparesis or hemianopia	–	–	+	–	–
	Cortical blindness	–	–	+	–	–
	Migraine-like headache	–	–	+	–	–
	Dystonia	–	–	+	–	+
Peripheral nervous system	Peripheral neuropathy	±	±	±	+	–
Muscle	Weakness or exercise intolerance	+	+	+	+	+
	Ophthalmoplegia	+	–	–	–	–
	Ptosis	+	–	–	–	–
Eye	Pigmentary retinopathy	+	–	–	+	±
	Optic atrophy	–	–	–	±	±
Blood	Sideroblastic anemia	±	–	–	–	–
Endocrine	Diabetes mellitus	±	–	±	–	–
	Short stature	+	+	+	–	–
	Hypoparathyroidism	±	–	–	–	–
Heart	Conduction block	+	–	±	–	–
	Cardiomyopathy	±	–	±	–	±
Gastrointestine	Exocrine pancreatic dysfunction	±	–	–	–	–
Ear, nose, throat	Sensorineural hearing loss	–	+	+	±	–
Kidney	Fanconi's syndrome	±	–	±	–	–
Laboratory results	Lactic acidosis	+	+	+	–	±
	Ragged-red fibers on muscle biopsy	+	+	+	–	–
Inheritance	Maternal	–	+	+	+	+
	Sporadic	+	–	–	–	–

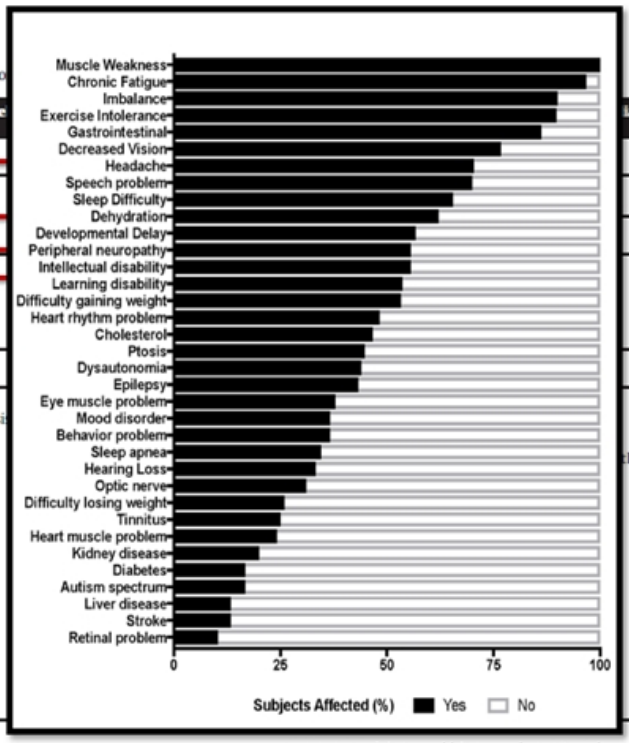
NEJM 2010. 354(10):1096-7

Clinical Manifestations in Percent (number positive/number recorded)			
Manifestation	Overall	Pediatric	Adults
Weakness	41.8 (308/737)	41.6 (138/332)	42.0 (170/405)
Developmental Delay	41.2 (319/775)	72.8 (273/375)	11.5 (46/400)
Exercise Intolerance	40.4 (289/716)	34.8 (110/316)	44.8 (179/400)
Fatigue	35.5 (262/738)	26.2 (85/325)	42.9 (177/413)
Hypotonia	35.4 (260/735)	65.1 (231/355)	7.6 (29/380)
Myopathy	34.1 (255/747)	31.0 (105/339)	36.8 (150/408)
Seizures	31.1 (237/763)	42.5 (151/355)	21.1 (86/408)
Ataxia	28.7 (216/753)	32.5 (112/345)	25.5 (104/408)
Hearing Loss	26.3 (194/739)	16.4 (54/330)	34.2 (140/409)
Ptosis	25.9 (199/769)	18.6 (65/350)	32.0 (134/419)
Dysphagia	22.0 (162/738)	26.7 (90/337)	18.0 (72/401)
Thinness	19.8 (144/726)	23.2 (77/332)	17.0 (67/394)
Migraine Headaches	18.2 (131/720)	9.7 (31/319)	24.9 (100/401)
Hearing Loss	17.3 (124/718)	13.2 (42/319)	20.6 (82/399)
Growth Delay	16.0 (113/708)	27.2 (88/323)	6.5 (25/385)
Depression	15.9 (111/700)	3.8 (12/316)	25.8 (99/384)
Anxiety	15.3 (107/699)	10.5 (33/315)	19.3 (74/384)
Ophthalmoparesis	15.3 (111/727)	6.5 (21/324)	22.3 (90/403)
Mental Retardation	13.6 (97/715)	25.1 (79/315)	4.5 (18/400)
Motor Regression	13.1 (96/733)	23.8 (81/341)	3.8 (15/392)
Total number	878	402	476

NAMDC Registry accessed 01/2017

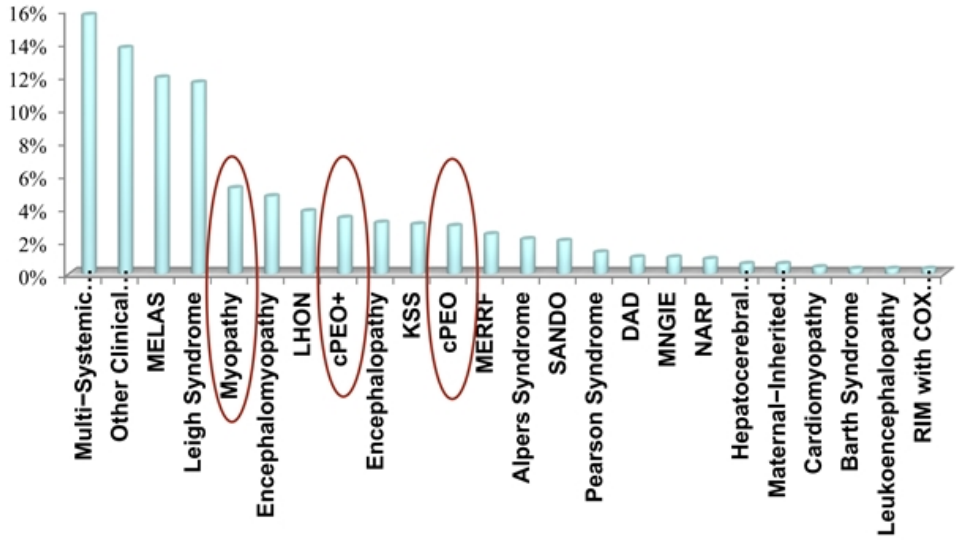
Most frequent patients/parents reported sympto

Constitutional		Musculoske		iac	Other	
Chronic fatigue	61%					
Temperature instability	48%	Myalgia			Anxiety	25%
Exercise intolerance	42.5%					
Difficulty gaining weight	12%	Myoglobinuria		18%	Depression	19%
		Rhabdomyolysis		11%	Thyroid disease	9%
Growth delay	6%			6%	Diabetes	7%
Cachexia	5%			thy 4%	Short stature	7%
Lipoma	3%				Parathyroid disease	7%
					Hypogonadism	2%
					Delayed puberty	3%
					Renal tubulopathy	2%



PLOS ONE | https://doi.org/10.1371/journal.pone.0197513

The most common presentation of PMM in adults is CPEO (+)



Barca et al Neurol Genet 2020;6:e402. doi:10.1212/NXG.0000000000000402

Primary Mitochondrial Myopathy

(Consortium of International Experts in Mitochondrial Disease)

- PMM refers to a subset of primary mitochondrial disease that predominantly but not exclusively affect skeletal muscles.
- Late-onset mild isolated mitochondrial myopathies might be difficult to diagnose (secondary mitochondrial dysfunction)
- Secondary involvement of mitochondria observed in multiple neuromuscular diseases is not considered PMM.

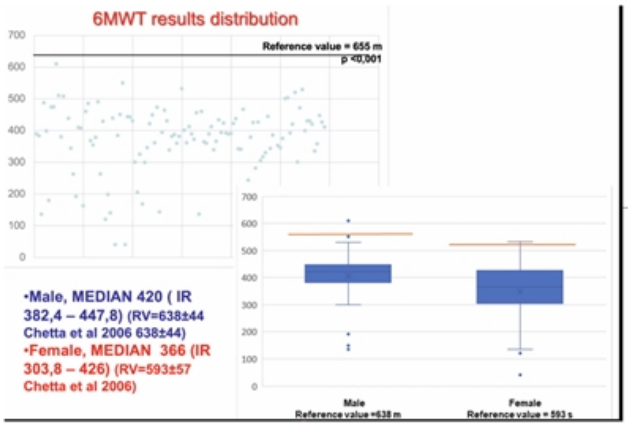
Neuromuscul Disord. 2017 December ; 27(12): 1126–1137. doi:10.1016/j.nmd.2017.08.006.

Primary mitochondrial myopathy

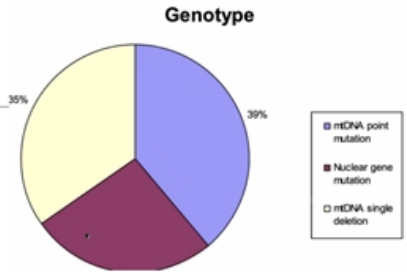
Clinical features and outcome measures in 118 cases from Italy

Vincenzo Montano, MD, Francesco Gruosso, MD, Valerio Carelli, MD, PhD, Giacomo Pietro Comi, MD, Massimiliano Filosto, MD, PhD, Costanza Lamperti, MD, PhD, Tiziana Mongini, MD, Olimpia Musumeci, MD, PhD, Serenella Servidei, MD, PhD, Paola Tonin, MD, PhD, Antonio Toscano, MD, PhD, Angela Modenese, MD, Guido Primiano, MD, PhD, Maria Lucia Valentino, MD, Sara Bortolani, MD, Silvia Marchet, MD, Megi Meneri, MD, PhD, Graziana Tavilla, MD, Gabriele Siciliano, MD, PhD, and Michelangelo Mancuso, MD, PhD

Neurol Genet 2020;6:e519. doi:10.1212/NXG.0000000000000519



- **118 PMM cases**
- **Mean age:** *50,62 ± 12,6 years*
- **Disease onset:** *31,40 ± 14,7 years*
- **Disease duration:** *21,5 ± 12,3 years*



Journal of Neurology (2022) 269:6555–6565
https://doi.org/10.1007/s00415-022-11324-3

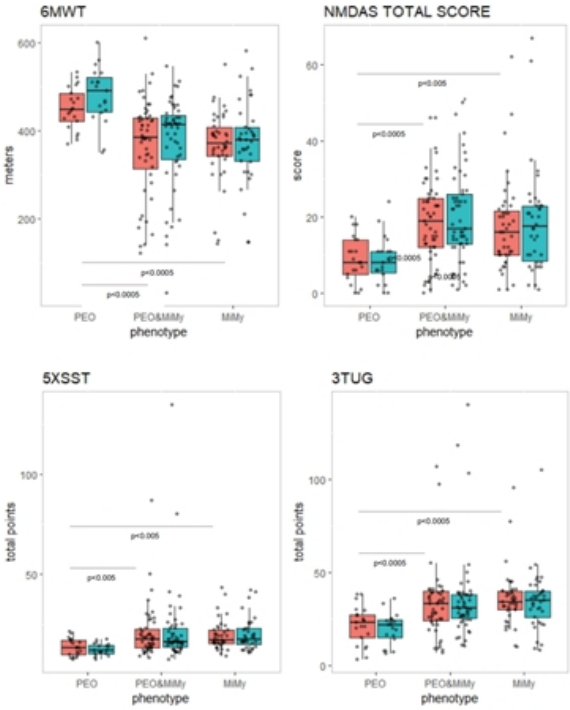
ORIGINAL COMMUNICATION

Primary mitochondrial myopathy: 12-month follow-up results of an Italian cohort

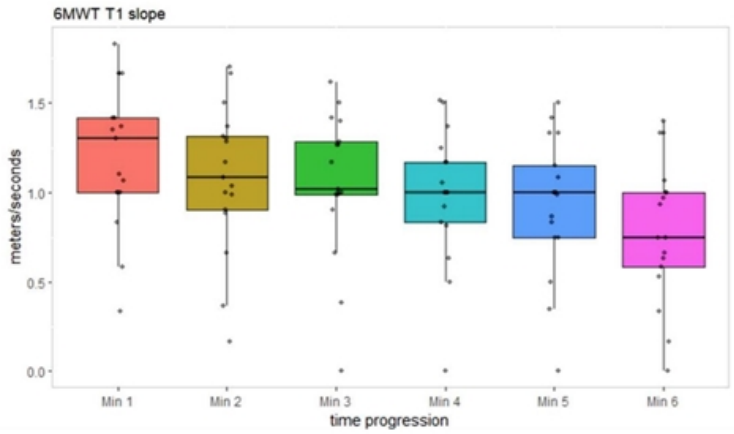
V. Montano[1] · P. Lopriore[1] · F. Gruosso[1] · V. Carelli[2,3] · G. P. Comi[4,5] · M. Filosto[6] · C. Lamperti[7] · T. Mongini[8] · O. Musumeci[9] · S. Servidei[10,11] · P. Tonin[12] · A. Toscano[9] · G. Primiano[10,11] · M. L. Valentino[2,3] · S. Bortolani[8] · S. Marchet[7] · G. Ricci[1] · A. Modenese[13] · S. Cotti Piccinelli[6] · B. Risi[6] · M. Meneri[4,5] · I. G. Arena[9] · G. Siciliano[1] · Michelangelo Mancuso[1]

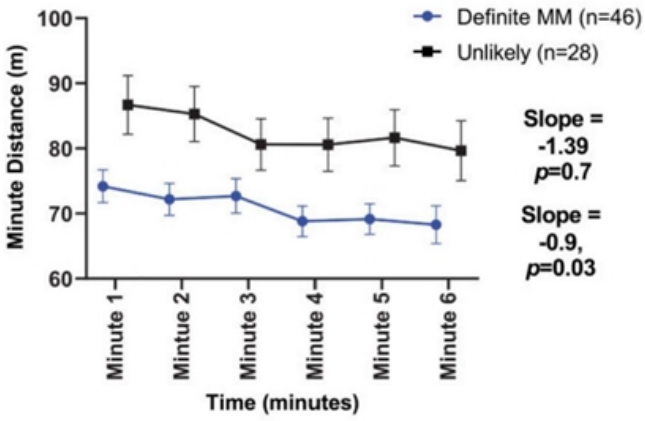
Phenotype distribution	Number of patients	Percentage
Lost at follow-up	1	0.8
PEO	21	17.8
PEO&MiMy	53	44.9
MiMy	43	36.4
Total	118	100.0

PEO progressive external ophthalmoplegia, *MiMy* mitochondrial myopathy



Primary Mitochondrial Myopathy

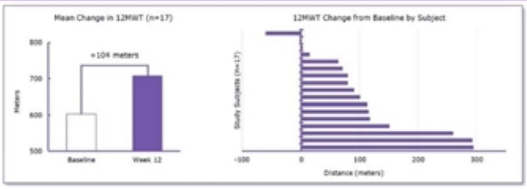




Journal of Neurology (2022) 269:6555–6565 JCSM Clin Rep. Author manuscript; available in PMC 2022 January 21

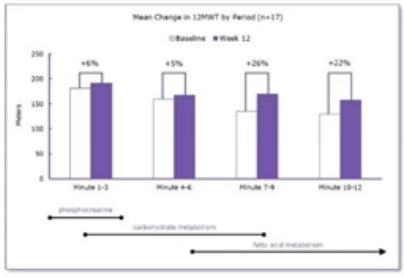
Primary Mitochondrial Myopathy

PMM Phase 1b Clinical Trial Results (12MWT)



- Following 12 weeks of 100 mg once-daily dosing with REN001, subjects achieved an average increase of 104 meters in distance walked during the 12MWT compared to baseline
- 15 of 17 subjects (88%) had an increase in distance walked, with 13 of 17 (76%) increasing by 60 meters or greater

PMM Phase 1b Clinical Trial Results (12MWT by Period)



- The largest improvement in distance walked during the 12MWT occurred in the second half of the 12-minute period

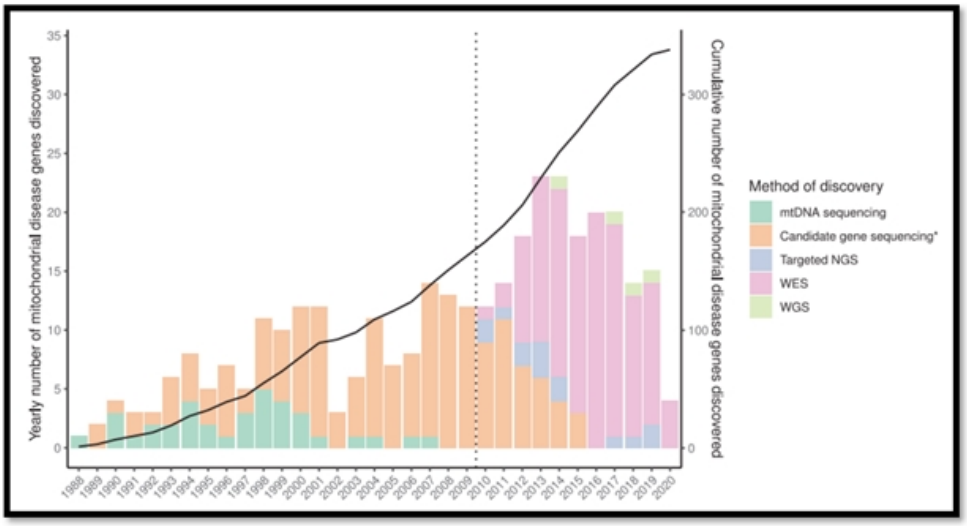
Courtesy of Reneo Pharmaceuticles

Overview of the unmet needs

Mitochondrial diseases remain difficult to diagnose

- Lack of diagnostic consensus
- No gold standard diagnostic method

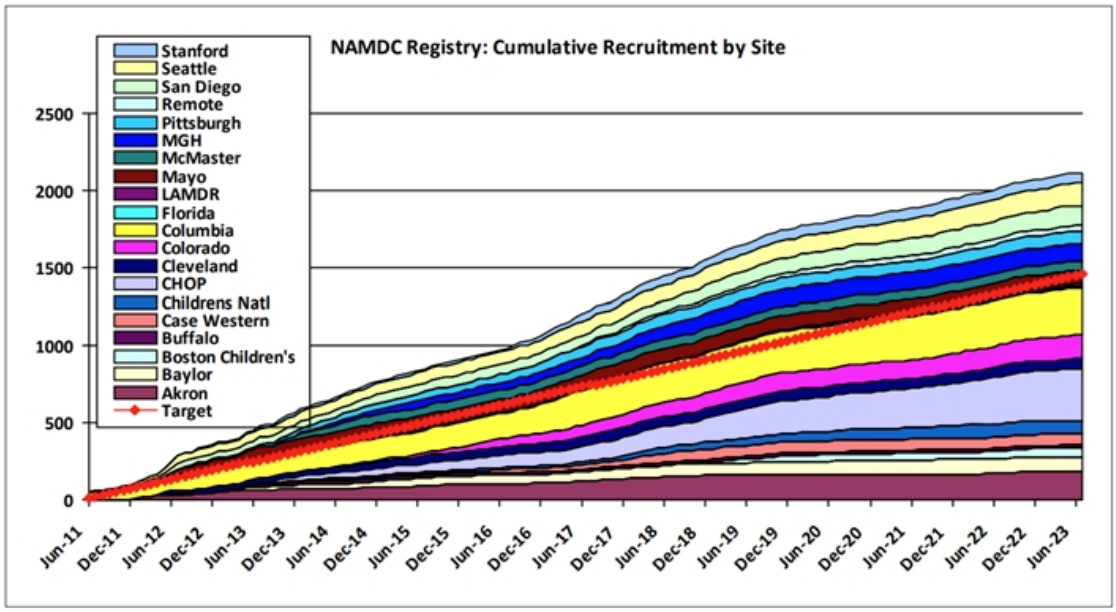
Diagnostic Evaluation



Complicated genotypes

mDNA (37 genes)
nDNA (~400 genes)

~1500 various genes



NAMDC registry

The diagnostic yield of next generation sequencing in suspected mitochondrial disease.

	Genes analysed	Publication	Size of cohort	Biochemical confirmation	Age group	mt-DNA analysis	Diagnostic rate
Panel	<500	Calvo et al. [22]	60	+	P	Included*	22 (13)
		DaRe et al. [23]	148	+/-	P and A	Included*	9% (13)
		Legati et al. [24]	125	+/-	P and A	Included*	15% (19)
	>500	Calvo et al. [25]	42	+	P	Included*	31% (13)
		Vasta et al. [26]	26	+/-	P	Excluded prior	23% (6)
		Lieber et al. [27]	84	+/-	P and A	Included*	7% (6)
		Panel summary	485				14% (70)
WES	20,000	Haack et al. [30]	10	+	P	Included*	70% (7)
		Taylor et al. [31]	53	+	P	Excluded prior	54% (28)
		Ohtake et al. [32]	104	+	P	Excluded prior	43% (45)
		Wortmann et al. [33]	109	–	P	Excluded prior	39% (42)
		Legati et al. [24]	10	+	P and A	Included*	60% (6)
		Kohda et al. [34]	142	+	P	Included*	35% (49)
		Pronicka et al. [35]	113	–	P	Included*	59% (67)
		Puusepp et al. [36]	28	–	P	Included*	57% (16)
		Theunissen et al. [38]	63	–	P and A	Included*	62% (39)
		WES Summary	632				47% (299)

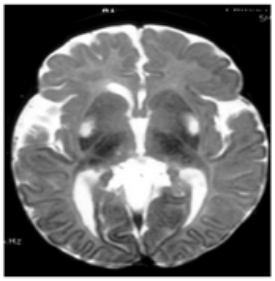
Diagnostic Evaluation

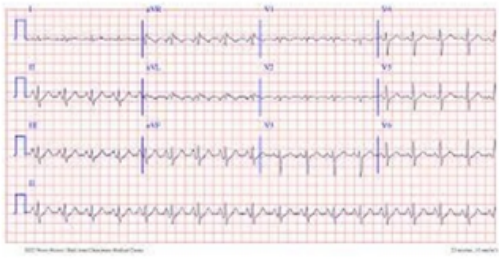
Symptoms
Family history

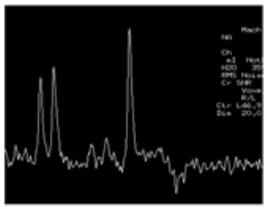
Testing:

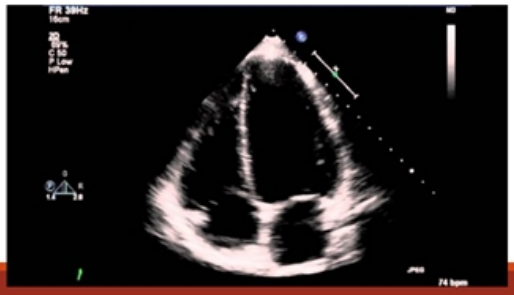
Diagnostic Evaluation

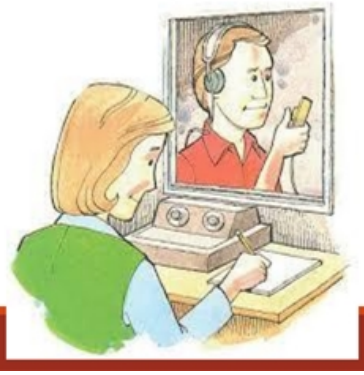
Evaluating organ involvement



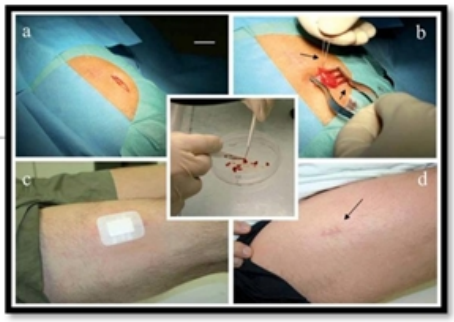






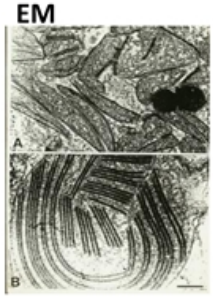


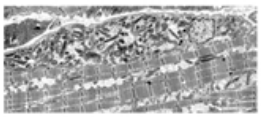
Diagnostic Evaluation



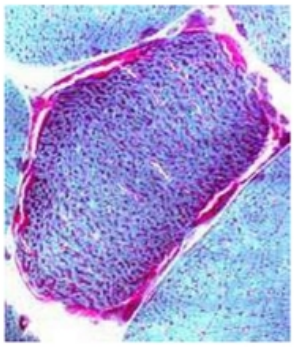
- Tissue pathology (muscle)

EM

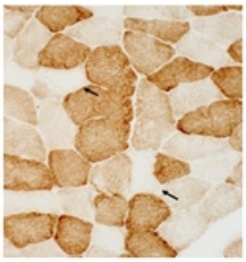




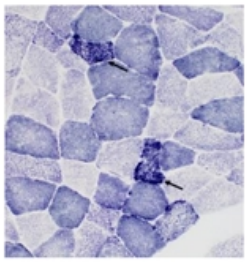
Histochemistry



RRF



COX



SDH

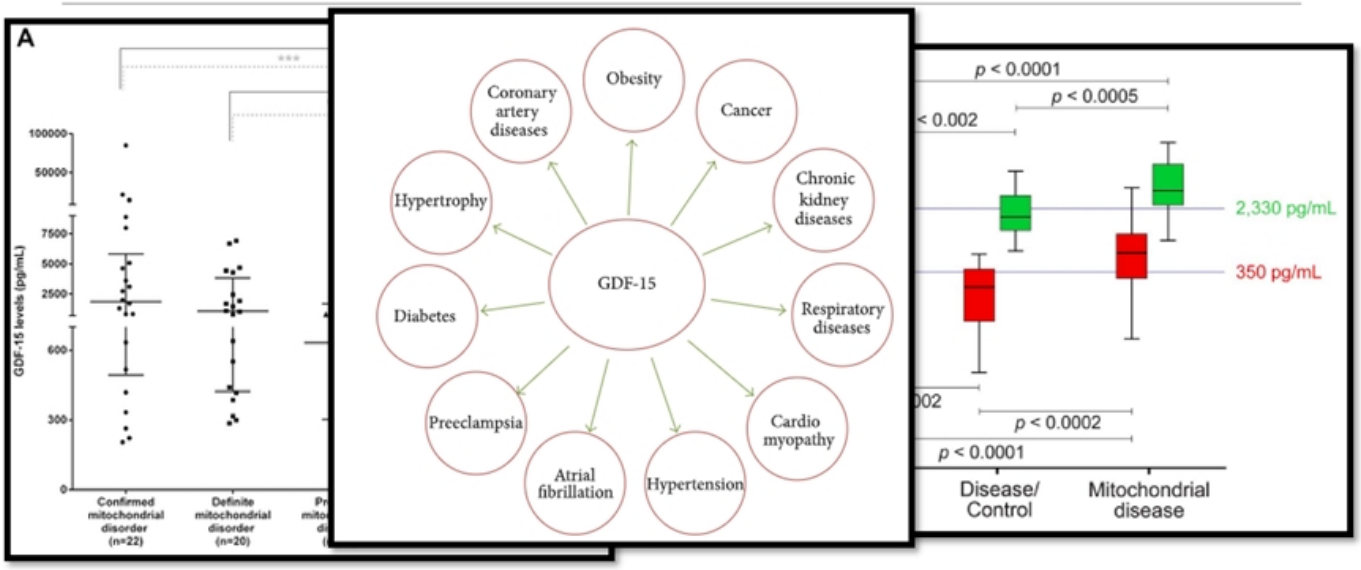
Diagnostic Evaluation

- Tissue pathology (muscle)
- Functional assays (EMG, PFT, Swallow, sniff test…)
- Biochemical tests (lactate, CPK, UOA, …)

Current Limitations of biochemical testing
- ► Imperfect sensitivity and specificity.
- ► Secondary mitochondrial dysfunction leading to abnormal results.
- ► Interlab variability of methods and reference ranges.
- ► Challenges with tissue processing.

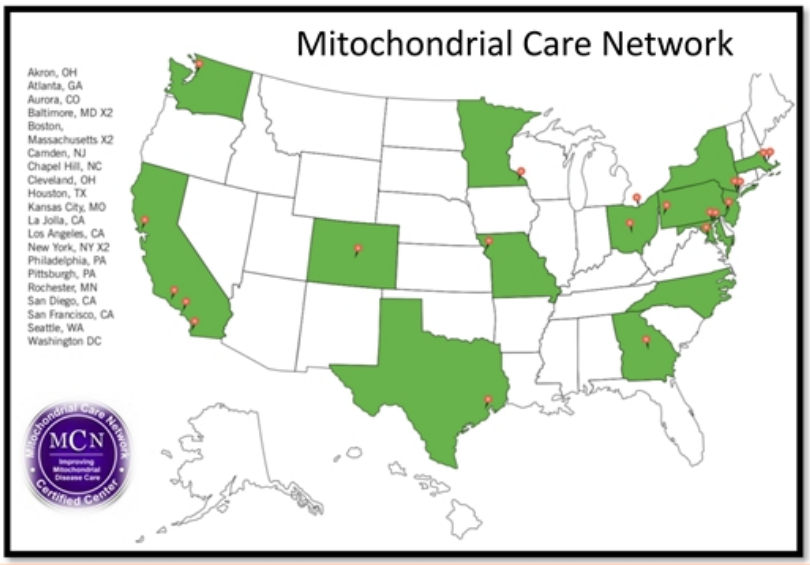
Parikh S, Karaa A, et al. J Med Genet. 2019 Mar;56(3):123-130.

Diagnostic Evaluation



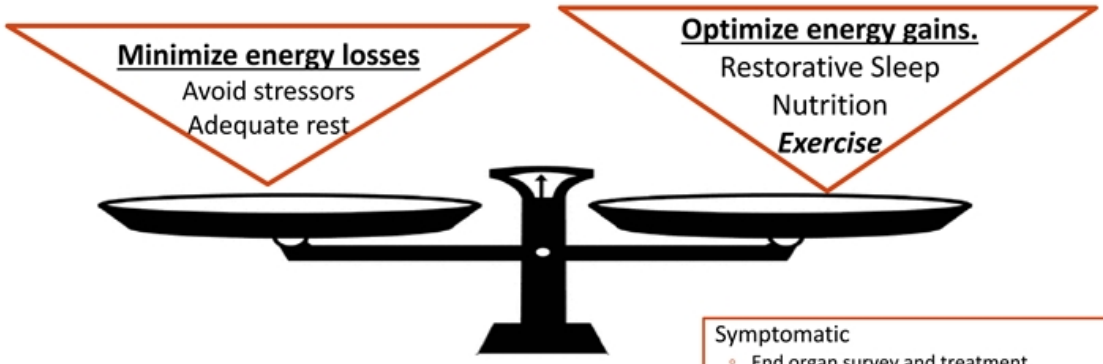
Montero, et al (2016). PLOS ONE. 11. e0148709. 10.1371/journal.pone.0148709.
Neurology® 2016;86:2010–2015
Journal of Diabetes Research Volume 2015, Article ID 490842

Other diagnostic barriers



- Disease complexity
- Lack of awareness
- Lack of education
- Insurance

Treatment and Management



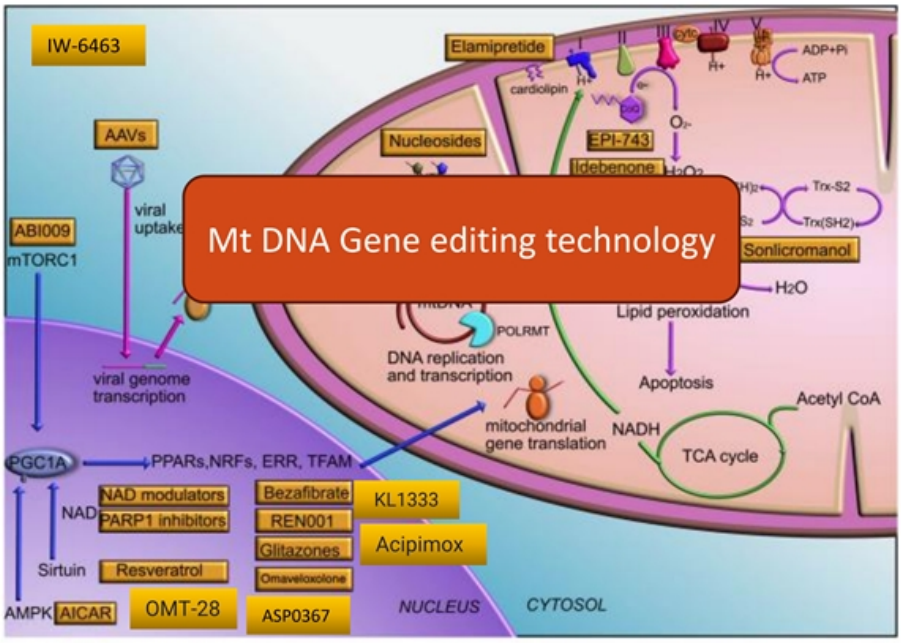
- Avoid environmental toxins: (ETOH, smoking, drugs..)

Symptomatic
- End organ survey and treatment

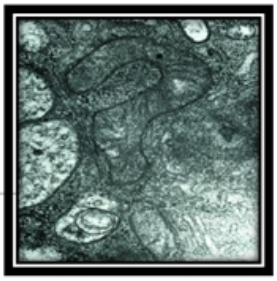
Supportive
- Overall disease burden
- Supplements (CoQ10)

Non curative

What is new in research and development?



J Inherit Metab Dis. 2020;1–20.



Thank you, and any questions?

For any questions:

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Harvard Medical School

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Mavodelpar Development Program

Alejandro Dorenbaum, MD
Chief Medical Officer
Reneo Pharmaceuticals, Inc.

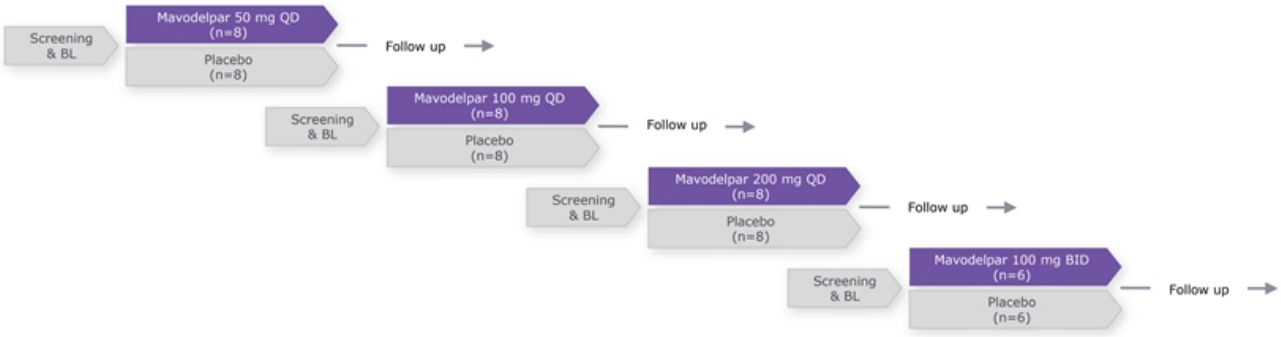
Mavodelpar Clinical Trials

STUDY	DESIGN	SUBJECTS	DOSE	DURATION	KEY OBSERVATIONS
1	Phase 1 SAD	Healthy	25-250 mg	Single-dose	✓ *Well tolerated*
2	Phase 1 MAD	Obese (dyslipidemic)	50-200 mg	14 days	✓ *Well tolerated* ✓ *Dose-dependent decrease in lipids*
3	RDBPC† Phase 1 (leg immobilization)	Healthy	200 mg	28 days	✓ *Well tolerated* ✓ *Increase in expression of PPARδ regulated genes* ✓ *Increase in muscle strength*
4	Open-label Phase 1b	PMM (mtDNA)	100 mg	12 weeks (+36 weeks)	✓ *Well tolerated* ✓ *Increase in expression of PPARδ regulated genes* ✓ *Increase in 12MWT, 30STS, and peak VO_2 / decrease in fatigue and pain*
5	Open-label Phase 1b	McArdle Disease	100 mg	12 weeks	✓ *Well tolerated* ✓ *Increase in oxidation of fatty acids*
6	Open-label Phase 1b	LC-FAOD (nDNA)	100 mg	12 weeks	✓ *Well tolerated* ✓ *Increase in expression of PPARδ regulated genes* ✓ *Increase in 12MWT / decrease in fatigue (certain genotypes)*
7	RDBPC Phase 2b (STRIDE Study)	PMM (mtDNA)	100 mg	24 weeks	○ *Ongoing; topline data Dec 2023*
8	Open-label safety (STRIDE AHEAD Study)	PMM (mtDNA + nDNA)	100 mg	2 years	○ *Ongoing; interim data 2024*

† randomized double-blind placebo-controlled clinical trial

Phase 1 Pharmacodynamic Study: Overview

Randomized, double-blind, placebo-controlled, multiple-dose clinical trial in obese individuals with dyslipidemia



Primary Objective

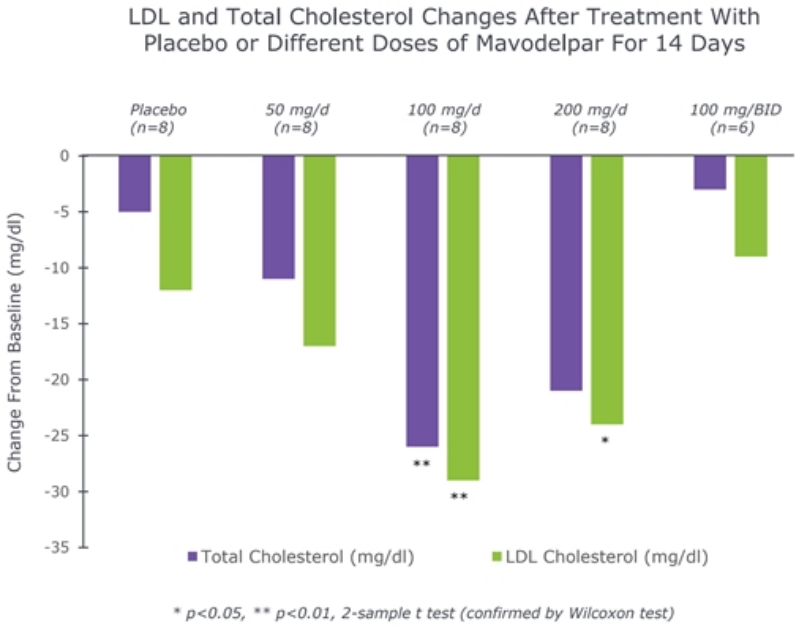
- Evaluate safety and tolerability of mavodelpar at doses of 50 mg to 200 mg daily for 14 days in obese individuals with moderate dyslipidemia

Secondary Objectives

- Establish the multiple dose pharmacokinetics profile of mavodelpar
- Evaluate the pharmacodynamics effect of mavodelpar on changes from baseline to day 14 in measures of lipid metabolism

Study HPP593-102. Data on file.

Phase 1 Pharmacodynamic Study: Reduction in Lipids



** p<0.05, ** p<0.01, 2-sample t test (confirmed by Wilcoxon test)*

Study HPP593-102. Data on file.

- No serious adverse events (SAEs) reported
- Treatment-emergent adverse events (TEAEs) were similar between subjects treated with mavodelpar or placebo
- All mavodelpar doses showed reductions in total cholesterol and LDL compared to placebo
  - *Subjects treated with all mavodelpar at doses of 100 mg/day or higher had statistically significant (p<0.01) reductions in total cholesterol and LDL compared to placebo subjects*
  - *Increasing the dose above 100 mg/day did not result in better pharmacodynamic effects*

Mavodelpar Clinical Trials

STUDY	DESIGN	SUBJECTS	DOSE	DURATION	KEY OBSERVATIONS
1	Phase 1 SAD	Healthy	25-250 mg	Single-dose	✓ *Well tolerated*
2	Phase 1 MAD	Obese (dyslipidemic)	50-200 mg	14 days	✓ *Well tolerated* ✓ *Dose-dependent decrease in lipids*
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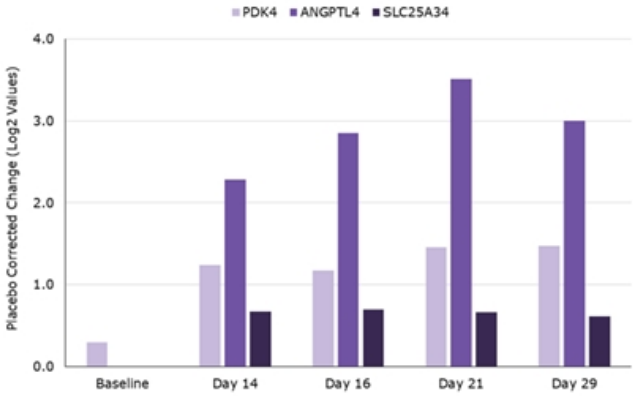
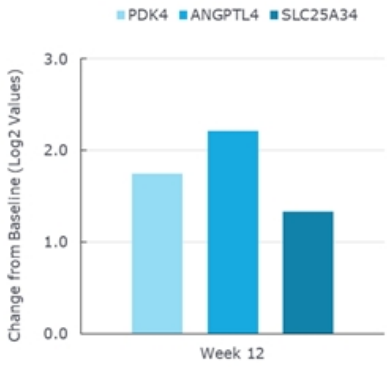
† randomized double-blind placebo-controlled clinical trial

Mavodelpar Effect on Expression of PPARδ-Regulated Genes

Health subjects treated with mavodelpar for 4-weeks showed increased expression of PPARδ-regulated genes



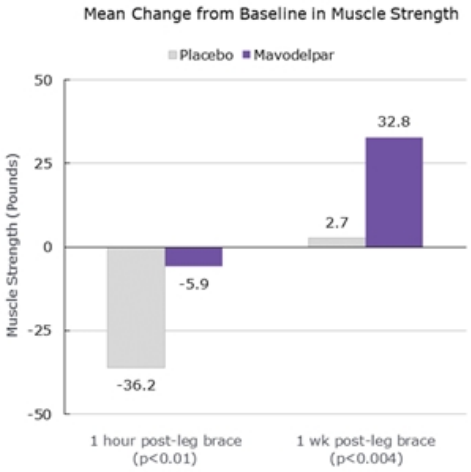
PMM patients treated with mavodelpar for 12-weeks showed increased expression of PPARδ-regulated genes



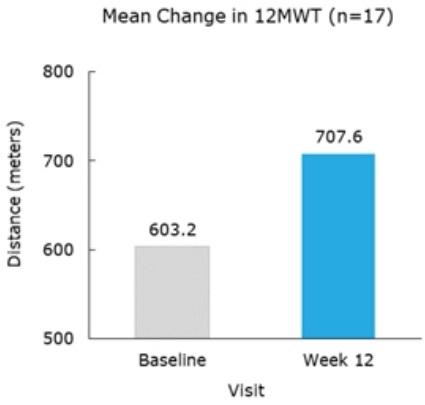
Study HPP593-102. Data on file.

Mavodelpar Effect on Muscle

Health subjects treated with mavodelpar for 4-weeks showed increased muscle strength



PMM patients treated with mavodelpar for 12-weeks showed increased exercise endurance (12MWT)



Study HPP593-102. Data on file.

Mavodelpar Clinical Trials

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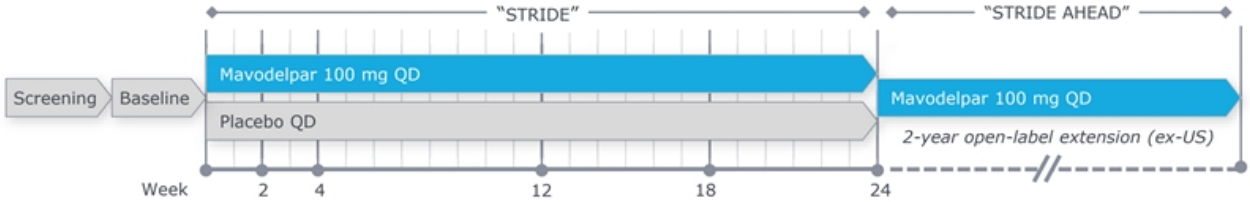
† randomized double-blind placebo-controlled clinical trial

Pivotal PMM Phase 2b Trial and Open-Label Extension Study

RDBPC clinical trial in adult PMM patients with mtDNA defects and myopathy, plus 2-year open-label extension study



STRIDE Primary Objective

- Change from baseline to week 24 in distance walked during 12MWT

STRIDE Secondary/Exploratory Objectives

- Changes from baseline in PROMIS® Short Form Fatigue 13a, Modified Fatigue Impact Scale (MFIS), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), 30 Second Sit-To-Stand (30STS) Test, Brief Pain Inventory (BPI), 36-Item Health Survey (SF-36), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), and Pedometer Step Counts

STRIDE and STRIDE AHEAD Status

- STRIDE: Last patient last visit complete; topline results anticipated Dec 2023
- STRIDE AHEAD: 150 patients enrolled (over 85% of eligible subjects); screening for nDNA PMM patients ongoing

12-Minute Walk Test (12MWT): History

Cooper 1968

- 115 US Air Force male officers and airmen were evaluated on a 12-minute field performance test and on a treadmill maximal-oxygen-consumption test
- The correlation of the 12-minute test with the laboratory determined oxygen-consumption data was 0.897

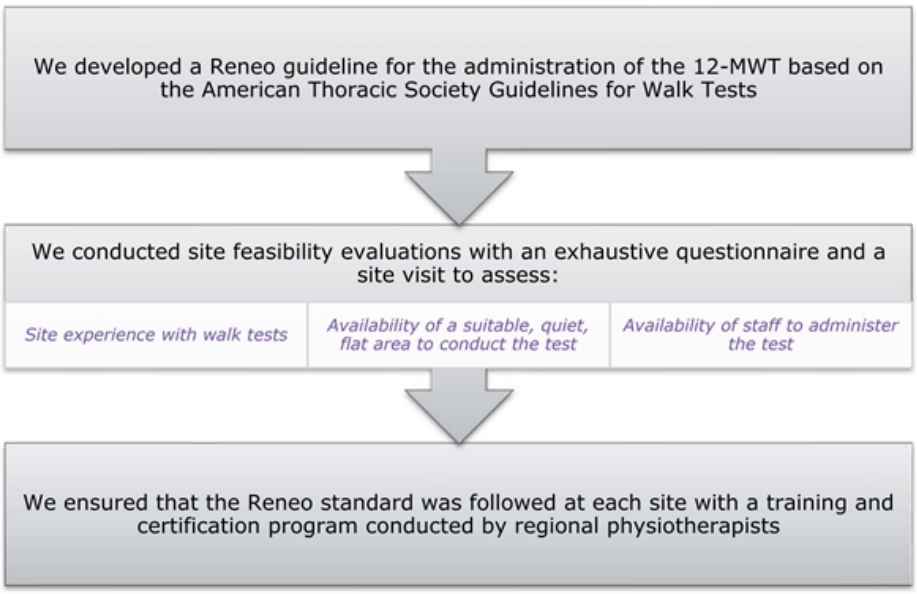
McGavin 1976

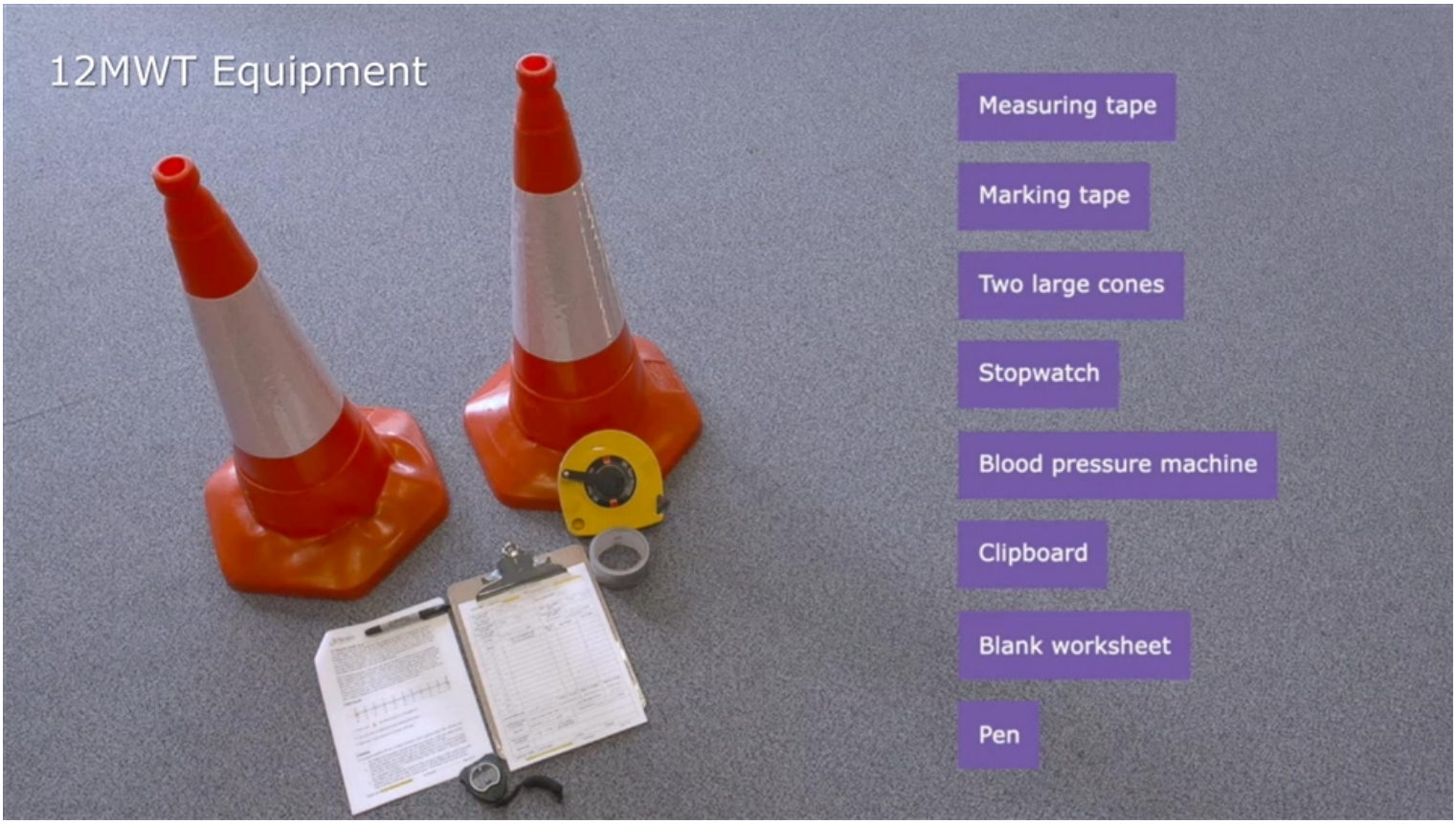
- The distance covered in 12 minutes' walking was used to test exercise tolerance in chronic bronchitis
- Significant relation between distance covered and forced vital capacity, and maximum oxygen consumption and ventilation on a bicycle ergometer

Butland 1982

- Demonstrated that in the 12MWT after a slight initial burst of speed, patients walk at constant speed, suggesting that shorter tests could be as good
- 2MWT, 6MWT and 12MWT were highly correlated: 6 vs. 12-minute, r=0.955
- The linear regression equation is: 12-minute distance=2.04 (six-minute distance)

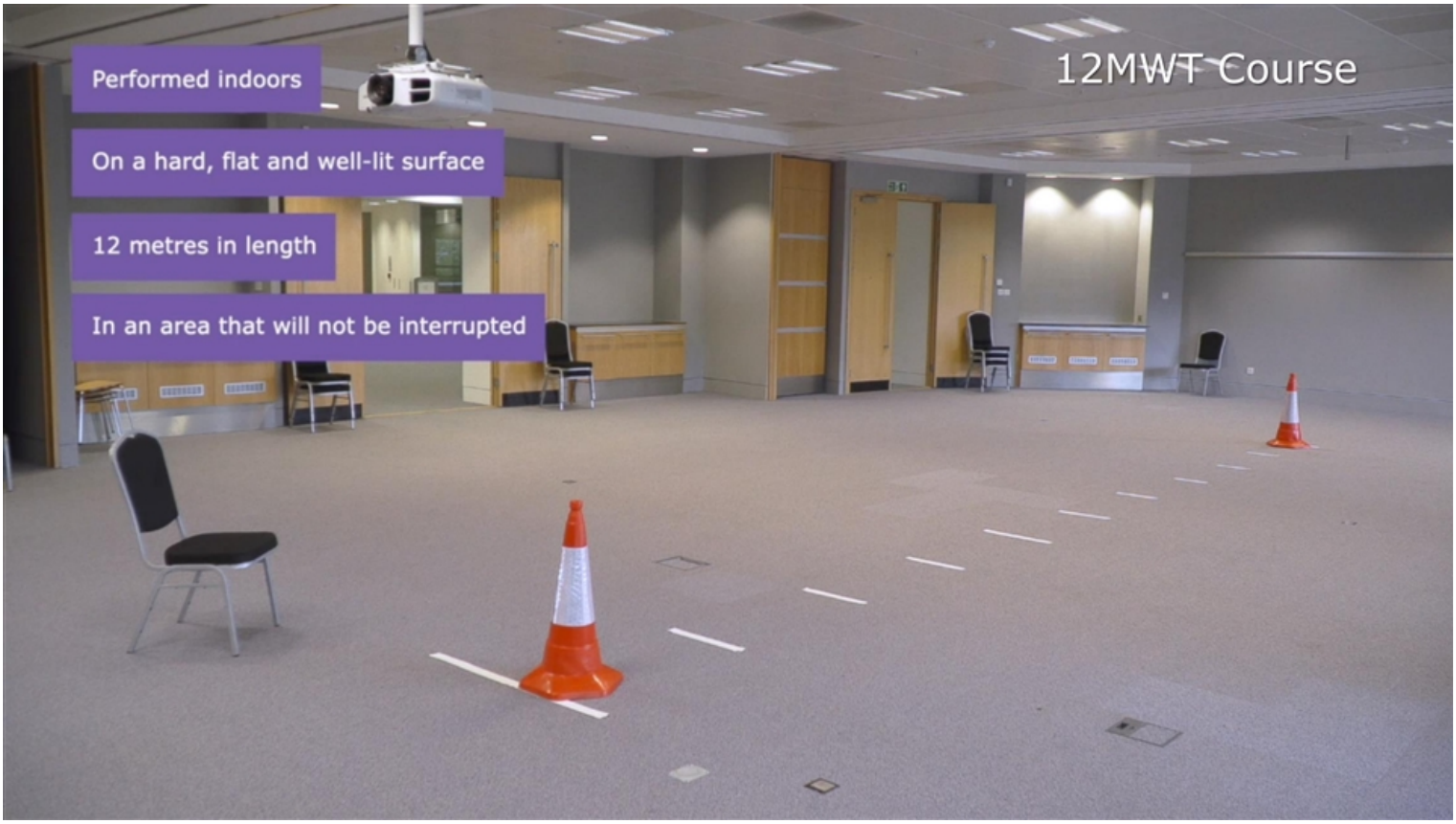
12-Minute Walk Test (12MWT): STRIDE Development

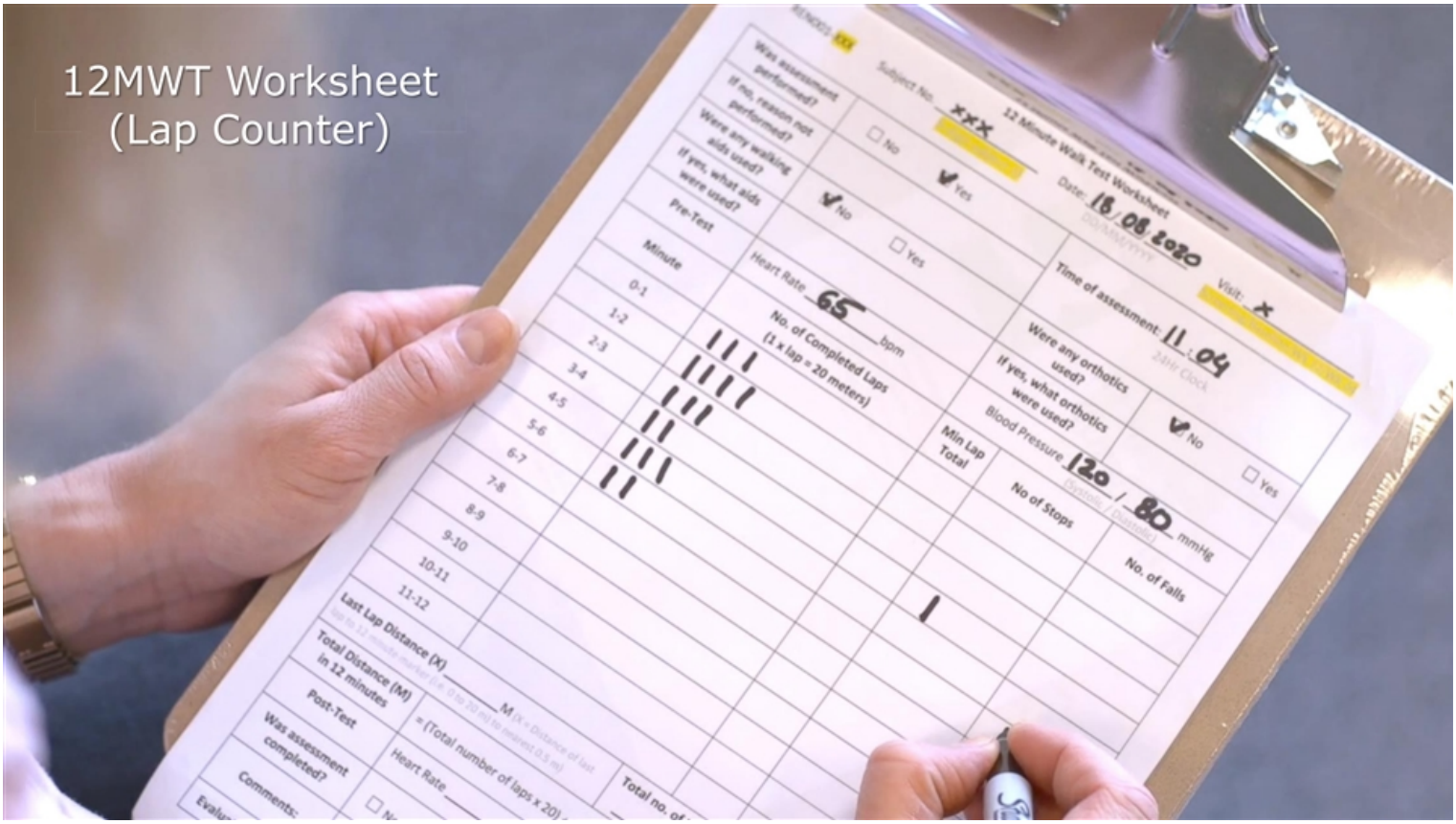



12MWT Equipment
Measuring tape
Marking tape
Two large cones
Stopwatch
Blood pressure machine
Clipboard
Blank worksheet
Pen

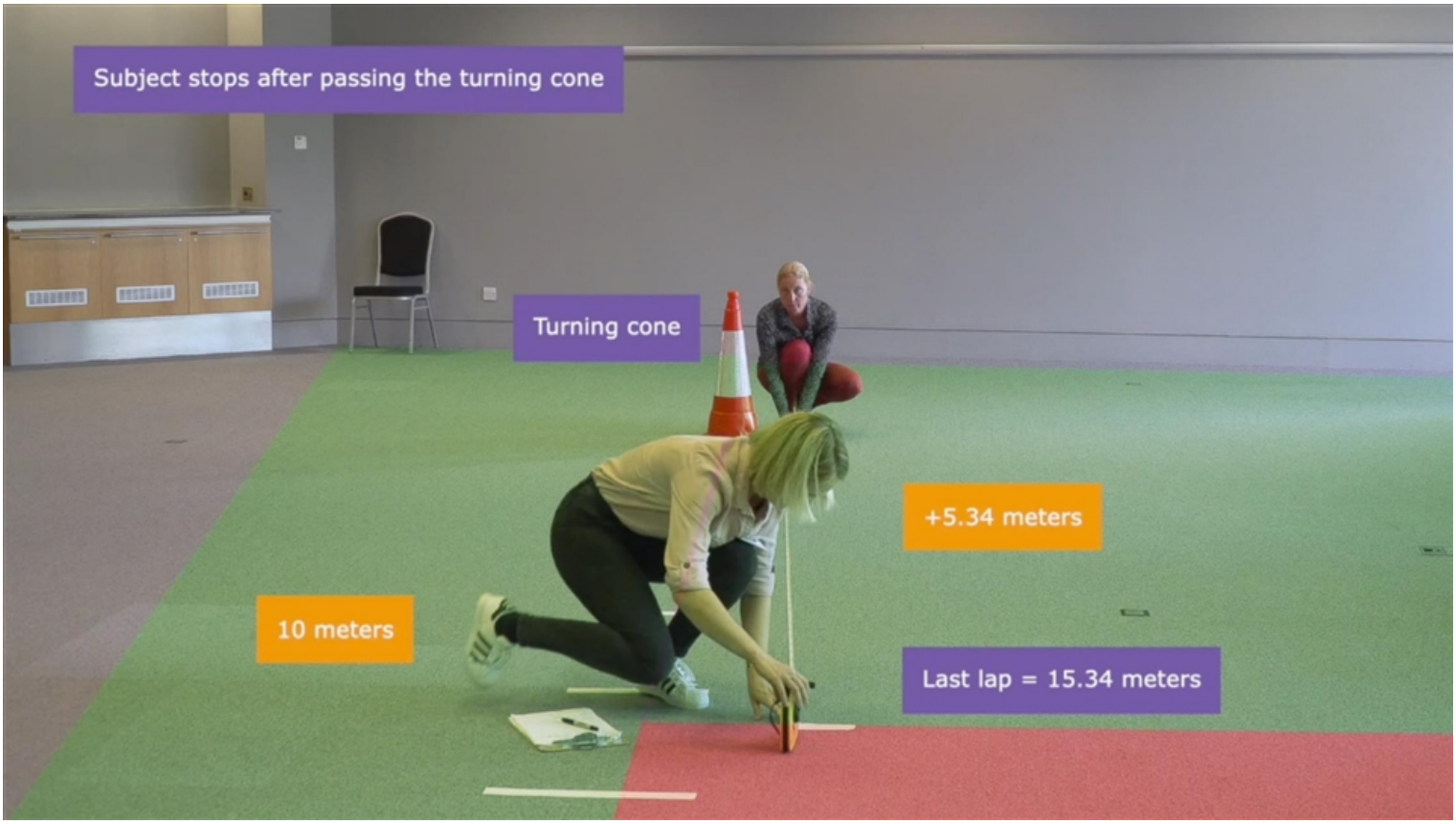
12-Minute Walk Test (12MWT): STRIDE Training & Certification

- Detailed exercise manual (v1.0) provided to each site
- Standardized tools, equipment, and script for performing the 12MWT
- Required training video developed with an expert physiotherapist
- All sites underwent training and certification during a site visit by a regional physiotherapist
  - *Visits were conducted face to face (preferred) or remotely*
  - *Site performed a 12MWT that was reviewed by the regional physiotherapist*
  - *The regional physiotherapist approved the physical area as suitable for conducting the test and the ability of staff to perform the test*
  - *Refresher 12MWT training was conducted by regional physiotherapists*
  - *Training records were collected and retained*
  - *Regional physiotherapists review all subjects screening 12MWT worksheets for errors or issues*


12MWT Course
Performed indoors
On a hard, flat and well-lit surface
12 metres in length
In an area that will not be interrupted


12MWT Worksheet
(Lap Counter)
12 Minute Walk Test Worksheet
Subject No. XXX
Date: 18/08/2020
Visit: X
Time of assessment: 11:04
Was assessment performed?
If no, reason not performed?
Were any walking aids used?
If yes, what aids were used?
Were any orthotics used?
If yes, what orthotics were used?
Pre-Test
Minute
Heart Rate 65 bpm
No. of Completed Laps (1 x lap = 20 meters)
Min Lap Total
Blood Pressure 120 / 80 mmHg
No of Stops
No. of Falls
Last Lap Distance (X) M
Total Distance (M) in 12 minutes
Post-Test
= (Total number of laps x 20)
Was assessment completed?
Heart Rate
Comments:


Completed 12MWT
(Marked Final Step)


Subject stops after passing the turning cone
Turning cone
+5.34 meters
10 meters
Last lap = 15.34 meters

STRIDE Study Key Secondary Endpoint

Fatigue – Short Form 13a (FACIT-Fatigue)

- Ranges from mild subjective feelings of tiredness to severe overwhelming, debilitating, and sustained sense of exhaustion
- Universal rather than disease-specific instrument
- Score is calculated by adding all the individual question scores to give a total score
  - *Range between 13 and 65 with a higher score indicating a greater level of fatigue*
- Total raw scores can be converted into T-scores
  - *The T-score is a standardized score with a mean of 50 and a standard deviation (SD) of 10*
  - *A person with a T-score of 60 is one SD above the mean*

During the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	1	2	3	4	5
I feel weak all over	1	2	3	4	5
I feel listless ("washed out")	1	2	3	4	5
I feel tired	1	2	3	4	5
I have trouble starting things because I am tired	1	2	3	4	5
I have trouble finishing things because I am tired	1	2	3	4	5
I have energy	5	4	3	2	1
I am able to do my usual activities	5	4	3	2	1
I need to sleep during the day	1	2	3	4	5
I am too tired to eat	1	2	3	4	5
I need help doing my usual activities	1	2	3	4	5
I am frustrated by being too tired to do the things I want to do	1	2	3	4	5
I have to limit my social activity because I am tired	1	2	3	4	5

Addressable Patients (US)

Michael Cruse
Chief Operating Officer
Reneo Pharmaceuticals, Inc.

Addressable Patients (US)

- Prevalence of all pathogenic mtDNA and nDNA mutations estimated at 23:100,000[1]
  - *~32,000 adults with symptomatic mtDNA of (9.6:100,000)*
  - *~9,600 adults with symptomatic nDNA of (2.9:100,000)*

- To prepare for US commercialization, Reneo purchased claims data to validate prevalence and identify the addressable patient population

- Key findings from the claims data:
  - *~3,900 healthcare professionals see ~70% of known patients*
  - *Projected prevalence of ~56,000 adults with symptomatic mtDNA*

[1] *Adult mtDNA and nDNA PMM Prevalence – Gorman G. et al., Ann Neurol. 77(5): 753–759 (2015)*

Patient Identification Through US Payor Data

Identification of Mitochondrial Disorders

There is not a specific ICD-10 code for PMM, but there are codes for the syndromes that are included within PMM

- *Mitochondrial metabolism disorder, unspecified*
- *MELAS syndrome*
- *MERRF syndrome*
- *Other mitochondrial metabolism disorders*
- *Leigh's encephalopathy*
- *Mitochondrial myopathy, not elsewhere classified*
- *Progressive external ophthalmoplegia*
- *Kearns-Sayre syndrome*

Filter for Myopathy

Only patients with certain diagnosis codes for PMM specific symptoms are retained

- *Muscle weakness*
- *Ataxia,*
- *Myopathy*
- *Rhabdomyolysis*
- *Myalgia*
- *Fatigue*
- *Procedure code for muscle biopsy*

Removal of Secondary Mitochondrial Disorders

Patients with secondary mitochondrial disease are excluded

- *Spinal Muscular Atrophy (SMA)*
- *Friedreich's Ataxia (FRDA)*
- *Wilson's Disease*
- *Charcot-Marie-Tooth (CMT)*
- *Hereditary Spastic Paraplegia 7 (SPG7)*
- *Duchenne Muscular Dystrophy (DMD)*
- *Inclusion Body Myositis (IBM)*
- *Limb-Girdle Muscular Dystrophy (LGMD)*
- *Ullrich Myopathy*
- *Bethlem Myopathy*
- *Kennedy Disease*

Removal of nDNA Patients

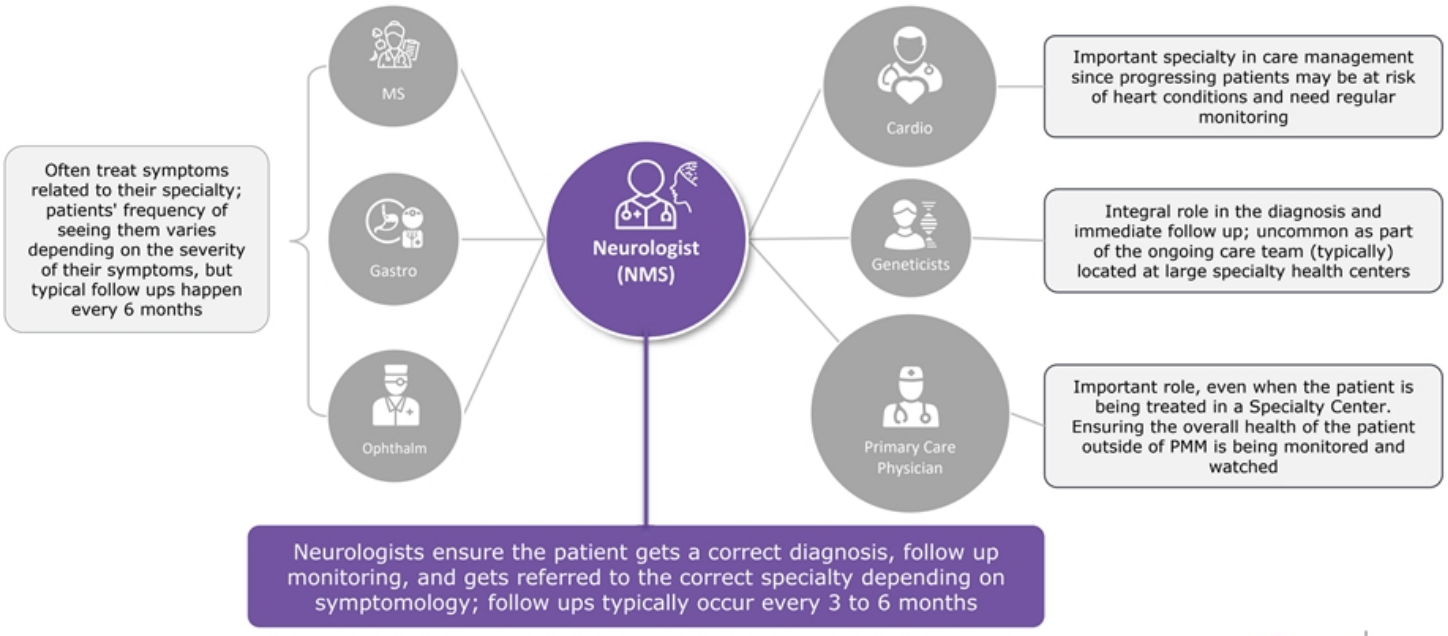
General assumption of 80/20 (mtDNA/nDNA) for adults with PMM

Segmentation of mtDNA Patients (n=56,000)

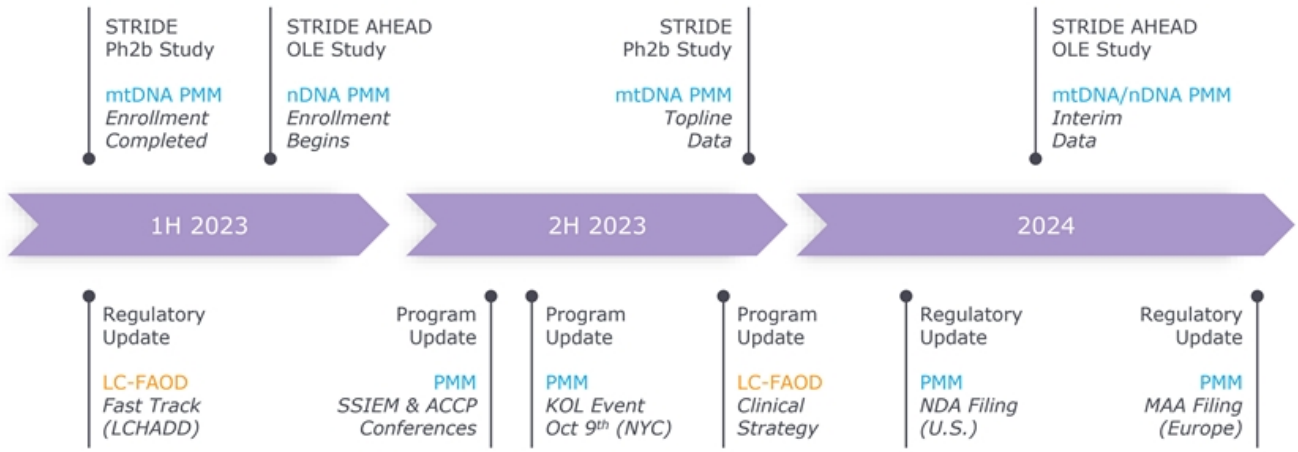
Segment by recent symptom frequency and healthcare utilization

- *34% no recent myopathy, low healthcare utilization*
- *30% myopathy, moderate healthcare utilization*
- *36% moderate myopathy and healthcare utilization, presence of co-morbidities and/or ER/hospital visits*

Management of US PMM Patients



Mavodelpar Roadmap



Thank You!