A Closer Look: Clinical Trials and the PRESIDIO Study

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Myositis Support & Understanding
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SELECTIVE TARGETS. BROAD IMPACT
Uniquely Powerful Approaches to Tackling the Toughest Diseases

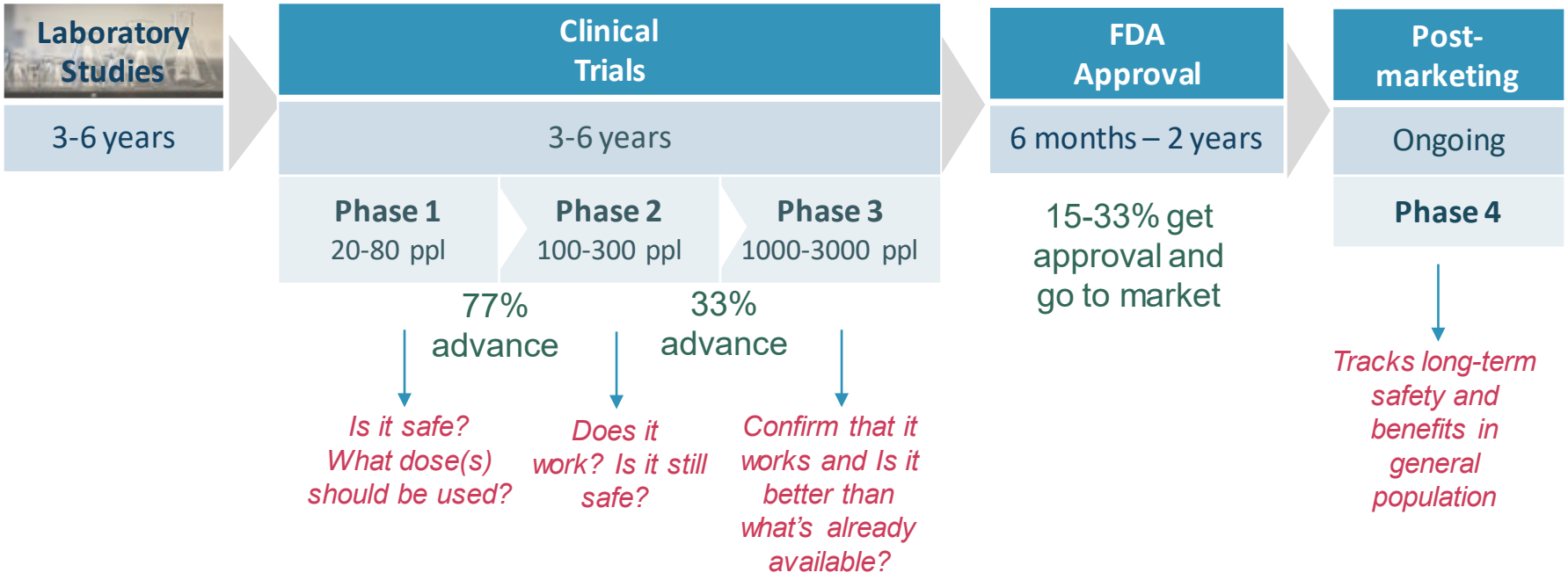
A Closer Look: Clinical Trials

What is a Clinical Trial?

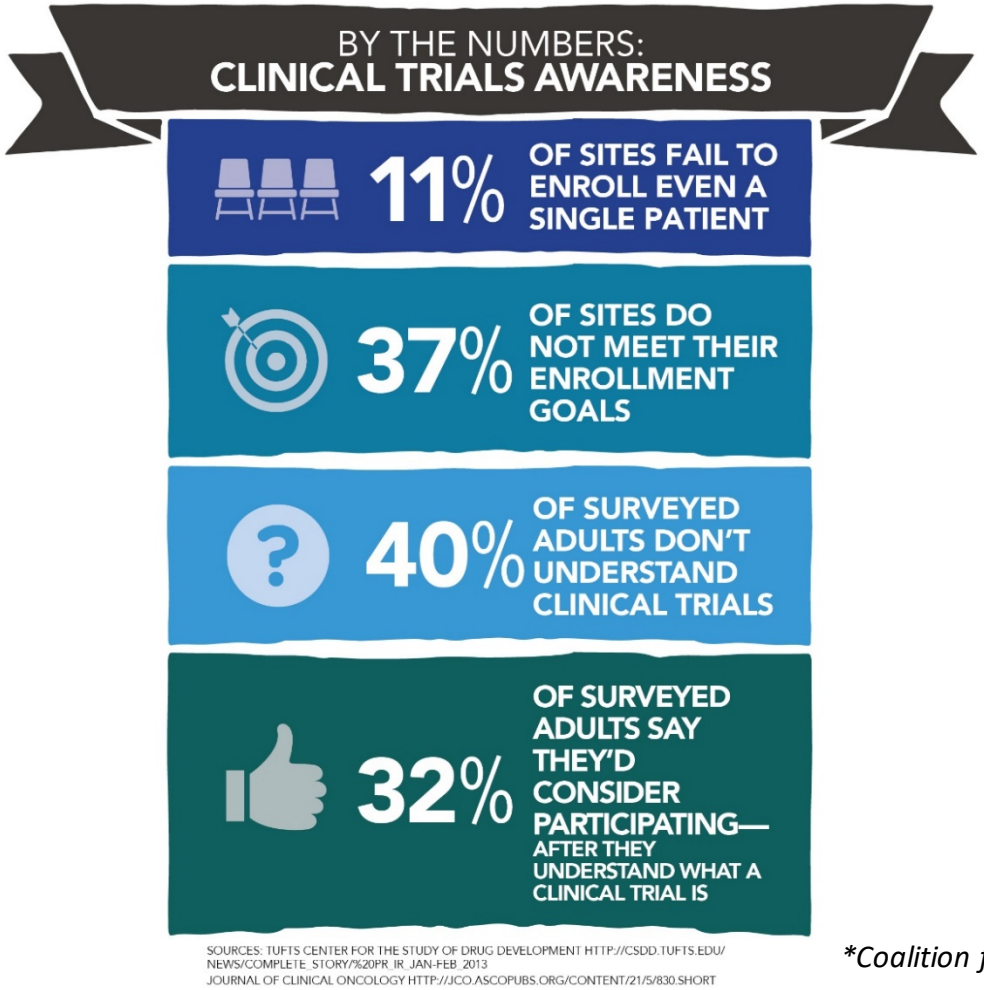
- Clinical trials are research studies that are carefully designed to figure out if a therapy is safe and effective. They are at the heart of all medical advances and look at new ways to prevent, detect, or treat disease
- Before new drugs are tested in people, they undergo rigorous testing in the laboratory (pre-clinical research to determine that it is safe to give to people)
- There are several phases of clinical trials that assess whether the drug is safe and works, so it can eventually be made widely available to people

The Phases of Clinical Trials – Start to Finish is ~10 Years

- The trials at each phase have a different purpose and help scientists answer different questions
- Volunteers are sought to participate, and the exact number of volunteers depends on the disease being studied



We Need To Do A Better Job Increasing Awareness Around Clinical Trials



**Coalition for Clinical Trial Awareness*

What are Some of the Basics of Clinical Trials?

- The Food & Drug Administration, or FDA and the National Institutes of Health (NIH) have great resources for learning about the clinical trial process
- Clinicaltrials.gov lists most clinical trial being conducted, and advocacy groups also typically have information on ongoing trials

- Terms you might hear in reference to a clinical trial:
  - **Protocol** – this is the plan for how the clinical trial is designed and conducted
  - **Institutional Review Board (IRB)** – trials in the U.S. are approved and monitored by an Institutional Review Board (IRB) to ensure participants are protected and risks are reduced and are outweighed by potential benefit
  - **Informed consent** – the process provides you with key information on the research study
  - **Clinical Trial sponsor** – people, institutions, companies, government agencies, or other organizations that are responsible for initiating, managing or financing the clinical trial
  - **Placebo** – inactive product that resembles the test product but without the treatment value
  - **Blinded** – designed to prevent bias in clinical trials
  - **Open-Label** – all participants receive the treatment

Why is Participating in Clinical Trials Important?

Cures and Treatments begin with clinical trials – we need them to develop new therapies

- Clinical trials are essential for developing treatments by generating evidence that treatments are safe and effective and can help improve the standards for treatment
- Participation is **ALWAYS VOLUNTARY**
- Numerous safety precautions are taken before clinical trials start and while they are in process
  - *There are always risks with experimental treatments, so always check with your doctor and ask the right questions before considering a clinical trial*
- Participating in clinical trials can help the person participating but also positively impact the lives of hundreds, thousands, and perhaps even millions of lives
- Participants receive additional care from the research team
- Participants access experimental and potential new treatments – sponsors typically cover treatment and travel-related costs and typically provide a stipend as well for time
- Every clinical trial we do in a particular disease helps bring us one step closer to finding treatments and cures

Why is Diversity Important in Clinical Trials?

- Some medicines impact people differently, but ethnically and racially diverse audiences are underrepresented in clinical trials

- Inclusion of participants from diverse backgrounds furthers research and helps find better ways to fight diseases that disproportionately impact these populations
- It's important for individuals of varied races, ethnicities, ages, and gender to participate in clinical trials

A Closer Look: Myositis and the PRESIDIO Study

Idiopathic Inflammatory Myopathies (IIMs) are Rare Heterogenous Disorders Characterized by Muscle Weakness and Muscle Inflammation[1]

IIMs are classified into four main subtypes[2]: PM, DM, IBM, and NM

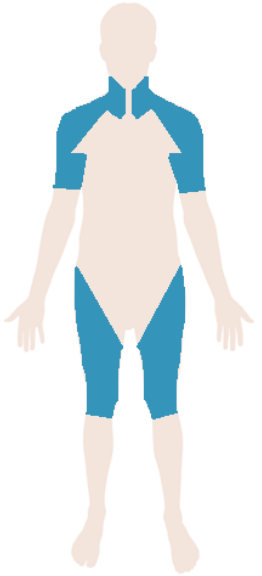
Muscular manifestations include[2]:

- Proximal and symmetric muscle weakness
  - Difficulty with tasks such as rising from a chair, climbing stairs, and lifting objects
- Neck and pharyngeal muscle weakness
  - Difficulty holding up the head or swallowing
- Distal muscle weakness (advanced cases)
  - Difficulty with tasks such as buttoning or holding objects

Extramuscular manifestations include[2]:

- Rash (DM)
- Fever, arthralgia, and Raynaud's syndrome
- Cardiac and pulmonary complications

Muscles typically involved in IIMs[3]



Abbreviations: DM, dermatomyositis; IBM, inclusion body myositis; NM, necrotizing myopathy; PM, polymyositis.

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[1]Lundberg IE, et al. *Ann Rheum Dis*. 2017;76(12):1955-1964. [2]Dalakas MC. *N Engl J Med*. 2015;372(18):1734-1747. [3]Muscular Dystrophy Association. https://www.mda.org/disease/polymyositis

PM is Characterized by Subacute Proximal Symmetric Weakness in the Absence of Other Causes

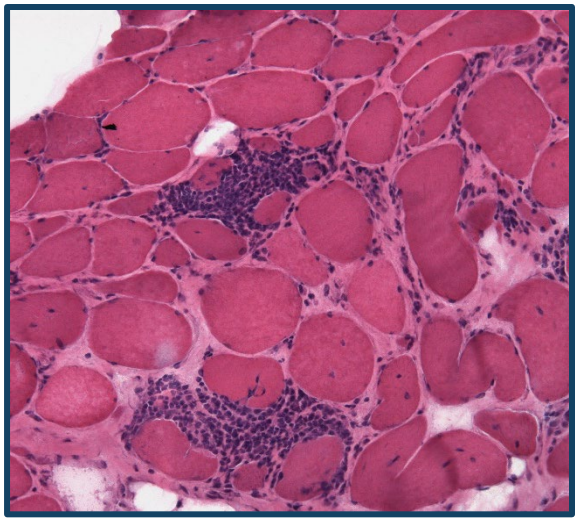
PM is a diagnosis of exclusion

- Diagnosis is made after drug-induced myopathies, inflammatory and muscular dystrophies, IBM, NM, fasciitis, and fibromyalgia are ruled out

The following conditions and symptoms should be absent with a PM diagnosis:

- Rash
- Family history of neuromuscular disease
- Exposure to myotoxic drugs such as statins or penicillins
- Facial and extraocular muscle involvement
- Endocrinopathies such as hyper- or hypothyroidism

PM muscle fiber H&E staining



Abbreviations: H&E, hematoxylin and eosin; IBM, inclusion body myositis; NM, necrotizing myopathy; PM, polymyositis

Dalakas MC. *N Engl J Med*. 2015;372(18):1734-1747.

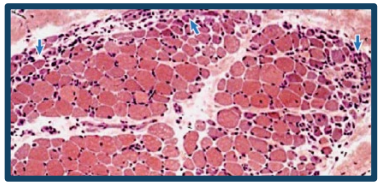
DM is Characterized by Subacute Proximal Symmetric Weakness in the Presence of Distinct Skin Manifestations

Distinct skin manifestations include:

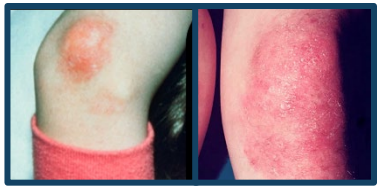
- Periorbital heliotrope (red/purple) rash
- Erythematous (red) rash on the ankles, back, chest, elbows, knees, knuckles, neck, and shoulders
- "Mechanic's hands" (ie, cracked fingertips, dilated nail capillaries, thickened cuticles)

DM that overlaps with other conditions, such as antisynthetase syndrome and Sjogren's syndrome, presents with a more transient or faint skin rash

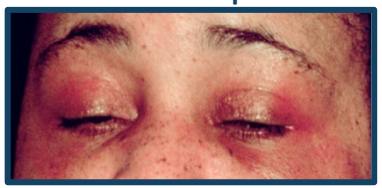
DM muscle fiber H&E staining



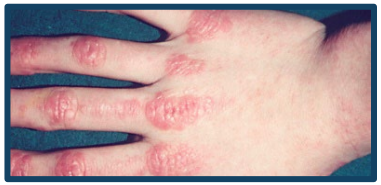
Elbow and knee rash



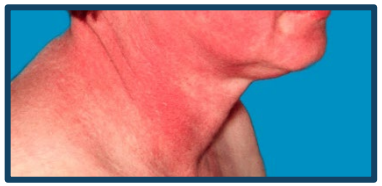
Facial heliotrope rash



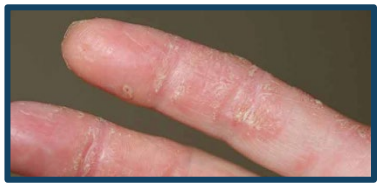
Gottron's rash



Back or neck rash



Mechanic's hands



Abbreviations: DM, dermatomyositis; H&E, hematoxylin and eosin

Dalakas MC. *N Engl J Med*. 2015;372(18):1734-1747.

IIMs Impose a Substantial Disease Burden

PM/DM are associated with reduced QoL

Lower energy and worsened isolation have been observed for individuals with PM/DM in comparison to people with other rheumatologic conditions[5]

IIMs can impair patients' ability to work

Average annual lost economic productivity is $3,600[1]

Average annual health care costs for people with PM/DM are >$23,000[1]

- Estimates are higher among older people and those with recent diagnosis[2]

Hospitalizations of patients with PM/DM are associated with higher rates of morbidity, mortality, and resource utilization[3,4]

Abbreviations: DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; PM, polymyositis; QoL, quality of life.

[1]Rice JB,et al. *Arthritis Rheumatol*. 2016; 68 (suppl 10). [2]Bernatsky S, et al. *J Rheumatol*. 2011;38(5):885-8. [3]Ungprasert P, et al. *Joint Bone Spine*. 2020;87(4):327-330. [4]Kwa MC, et al. *Arthritis Care Res*. 2017;69(9):1391-1399. [5]Leclair V, et al. *PLoS One*. 2016;11(8):e0160753.

Treatment Goals in IIM

- Increase QoL
- Reduce morbidity
- Limit inflammation
- Restore muscle strength
- Preserve muscle and organ function
- Use a multidisciplinary treatment approach

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Abbreviations: IIM, idiopathic inflammatory myositis; QoL, quality of life.

Therapies for PM/DM

- Nonpharmacologic treatment includes exercise and physical therapy[1]

Class	Condition	Medication	Mechanism	Common Adverse Events
Corticosteroids	New onset disease	Prednisone (Deltasone)[2]	Inhibits inflammation via activation of glucocorticoid receptors	• Fluid retention • Cushingoid state • Hyperglycemia • Hypertension • Osteoporosis
	Late or severe disease onset	Methylprednisolone (Medrol)[3]		
Biologics	Steroid refractory	Rituximab (Rituxan)[4]	Mediates B cell lysis via targeting of CD20 antigen	• Cardiotoxicity • Renal toxicity • Serious infections
Immune globulins	Steroid refractory	IVIg[5]	Exact mechanism is unknown; may reduce production of autoantibodies, works through complement fixation, or cause cytokines suppression or blockage	• Headache • Nausea and vomiting
Antimalarials	Cutaneous manifestations	Hydroxychloroquine (Plaquenil)[6]	Unknown mechanism for anti-inflammatory and immunomodulatory effects	• Retinopathy • Cardiomyopathy

Abbreviations: CD, cluster of differentiation; DM, dermatomyositis; IL, interleukin; IMPDH, inosine monophosphate dehydrogenase; IVIg, intravenous immunoglobulin; PM, polymyositis

[1]Barsotti S, et al. *Curr Treatm Opt Rheumatol*. 2018;4(4):299-315. [2]Prednisone. Package insert. Jubilant Cadista Pharmaceuticals, Inc.; 2018.
[3]Methylprednisolone. Package insert. Jubilant Cadista Pharmaceuticals, Inc.; 2018.
[4]Rituxan. Package insert. Genentech, Inc.; 2020. [5]Patwardhan A. *Cureus*. 2020;12(2):e7049. [6]Plaquenil. Package insert. Concordia Pharmaceuticals, Inc.; 2020.

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Therapies for PM/DM (cont'd)

Class	Condition	Medication	Mechanism	Common Adverse Events
Immunosuppressants	Steroid-sparing	Methotrexate (Trexall)[1]	Inhibits dihydrofolic acid reductase	• Abdominal distress • Leukopenia • Nausea • Ulcerative stomatitis
		Azathioprine (Azasan)[2]	Unknown mechanism for anti-inflammatory and immunomodulatory effects	• Leukopenia • Malignancy • Serious infections • Thrombocytopenia
		Cyclosporine (Sandimmune)[3]	Inhibits production and release of IL-2 and TCGF	• Gum hyperplasia • Hirsutism • Hypertension • Renal dysfunction • Tremor
		Mycophenolate mofetil (CellCept)[4]	Inhibits IMPDH	• Leukopenia • Serious infections
		Cyclophosphamide (Cytoxan)[5]	Unknown mechanism for anti-inflammatory and immunomodulatory effects	• Cardiotoxicity • Liver disease • Neutropenia • Pulmonary toxicity • Renal toxicity • Serious infections
		Tacrolimus (Prograf)[6]	Inhibits calcineurin	• Hyperglycemia • Hypertension • Infection • Renal toxicity

Abbreviations: DM, dermatomyositis; IL, interleukin; IMPDH, inosine monophosphate dehydrogenase; PM, polymyositis; TCGF, T cell growth factor.

[1]Trexall. Package insert. Teva Women's Health, Inc.; 2016. [2]Azasan. Package insert. Salix Pharmaceuticals, Inc.; 2019. [3]Sandimmune. Package insert. Novartis Pharmaceuticals; 2020. [4]CellCept. Package insert. Genentech, Inc.; 2019. [5]Cyclophosphamide. Package insert. ANI Pharmaceuticals, Inc.; 2019. [6]Prograf. Package insert. Astellas Pharma US, Inc.; 2019.

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There are Many Unmet Treatment Needs in IIM

IIMs are heterogenous diseases

- Better diagnostic algorithms are needed to avoid misdiagnosis or delayed treatment because of uncertain diagnosis[1]
- Better understanding of IIM pathophysiology can help guide treatment and future research[1]

IIMs are associated with increased risk of morbidity and mortality, with 10-year survival rates of 55% and 53% for PM and DM, respectively[2]

- Standardized mortality ratio for combined PM/DM shows about 3-fold higher mortality compared to the general population[2]
- Malignancy and diseases of the circulatory, respiratory, and musculoskeletal systems are among the largest contributors to mortality[3]

Most SOC treatments manage symptoms of IIMs but do not address underlying causes

- Muscle weakness, atrophy, and increased risk of infection are common AEs associated with SOC treatments
- 80% of patients do not achieve remission with current therapies

Abbreviations: AE, adverse event; DM, dermatomyositis; FDA, US Food and Drug Administration; IIM, idiopathic inflammatory myopathy; PM, polymyositis; SOC, standard of care

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[1]Yang SH, et al. *J Transl Autoimmun*. 2019;2:100018. [2]Airio A, et al. *Clin Rheumatol*. 2006;25(2):234-9. [3]Dobloug GC, et al. *Ann Rheum Dis*. 2018;77(1):40-47.

Investigational Drugs for PM/DM

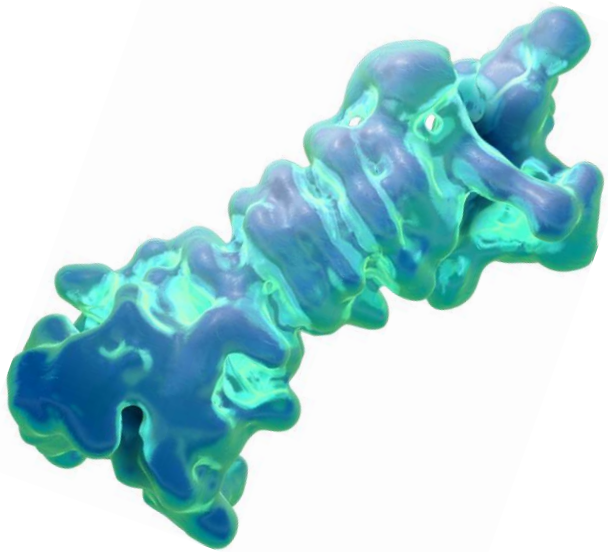
Indication	Medication	Manufacturer	Mechanism	Phase[a]
DM	**Apremilast (Otezla)**	Amgen	PDE4 inhibitor	Phase 2
	IgPro20 (Hizentra)	CSL Behring	Neutralizing IgG antibodies	Phase 3 (RECLAIM)
	Lenabasum	Corbus Pharmaceuticals	CB2 agonist	Phase 3 (DETERMINE)
	PF-06823859	Pfizer	IFNB1 inhibitor	Phase 2
PM and DM	**Abatacept (Orencia)**	Bristol-Myers Squibb	Costimulation modulator	Phase 3
	Belimumab (Benlysta)	GlaxoSmithKline	BLyS inhibitor	Phase 3
	KZR-616	Kezar Life Sciences	Selective immunoproteasome inhibitor	Phase 2 (PRESIDIO)
	Pirfenidone (Esbriet)	Genentech	MAP kinase inhibitor	Phase 3
	Tocilizumab (Actemra)	Roche	IL-6 inhibitor	Phase 2
	Ustekinumab (Stelara)	Janssen	IL-12 and IL-23 inhibitor	Phase 3

[a]Updated February 2021.

Abbreviations: BLyS, B lymphocyte stimulator; CB2, cannabinoid receptor 2; DM, dermatomyositis; IFNB1, interferon beta 1; Ig, immunoglobulin; IL, interleukin; MAP, mitogen activated protein; PDE, phosphodiesterase; PM, polymyositis; TNF-α, tumor necrosis factor-alpha; TLR, toll-like receptor.

Targeting the Immunoproteasome Represents a Unique and Powerful Approach to Treating Autoimmunity and Inflammation

Immunoproteasomes are special cell structures found in cells of the immune system, like T-cells and B-cells; they help with an immune response to protect the body from foreign substances



- In autoimmune disease, the number and activity of immunoproteasomes are increased, and the immune system begins attacking the body's own healthy tissues or organs
- Research in animals has shown that by inhibiting the immunoproteasome, we can decrease the activity of the immune cells attacking the body– which means we can block the inflammation in multiple ways, including reducing the harmful activity of autoreactive T-cells and B-cells
- Doing so has the potential to bring the immune system back to a more harmonious state

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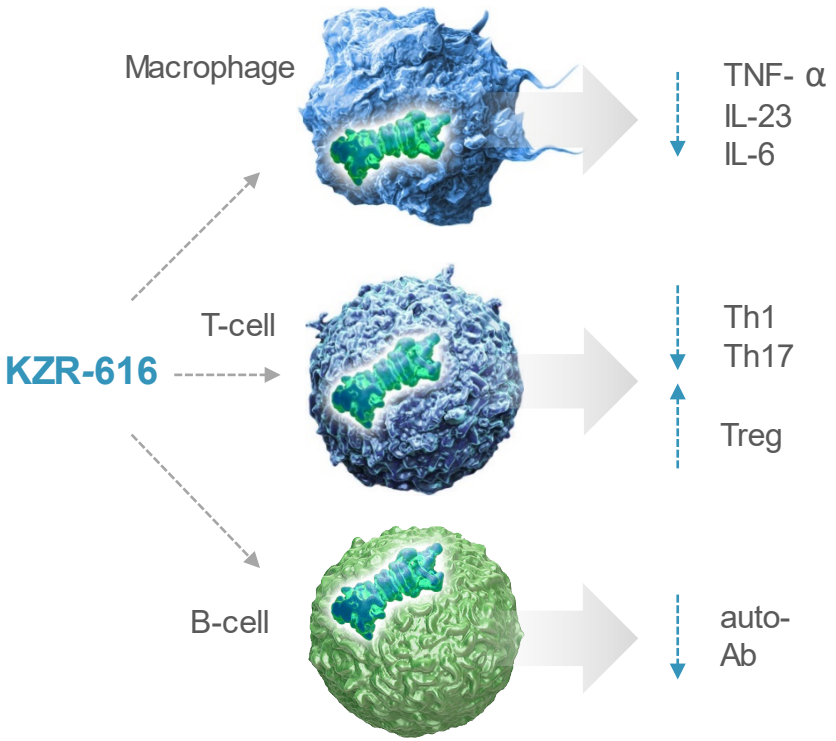
KZR-616 is the First Selective Immunoproteasome Inhibitor to be Tested in Clinical Trials

KZR-616 helps limit some unhealthy immune responses by regulating cells in the immune system



Like an orchestra conductor, KZR-616 works to turn down the volume of the overactive immune system and bring it to a harmonious level

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KZR-616 is an investigational product and has not been approved for commercial use in the United States or any other country for any indication

Immunoproteasome Inhibition Improved Muscle Function in a Mouse Model of Polymyositis (PM) and Dermatomyositis (DM)

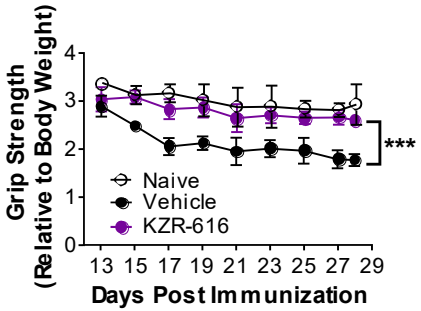
CIM MODEL

- Mice are immunized against their own muscle protein
- They develop myositis with many features that are similar to PM and DM

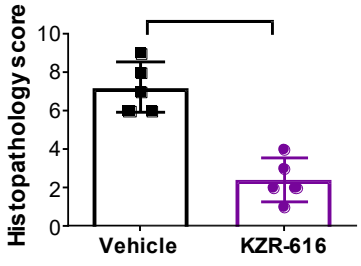
13 days

- We treated mice with KZR-616
- **KZR-616 improved muscle function and reduced muscle damage**

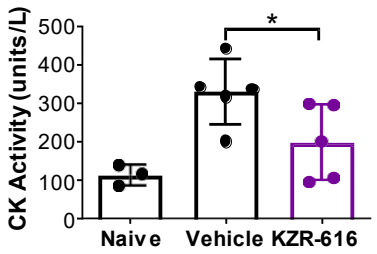
Muscle Strength



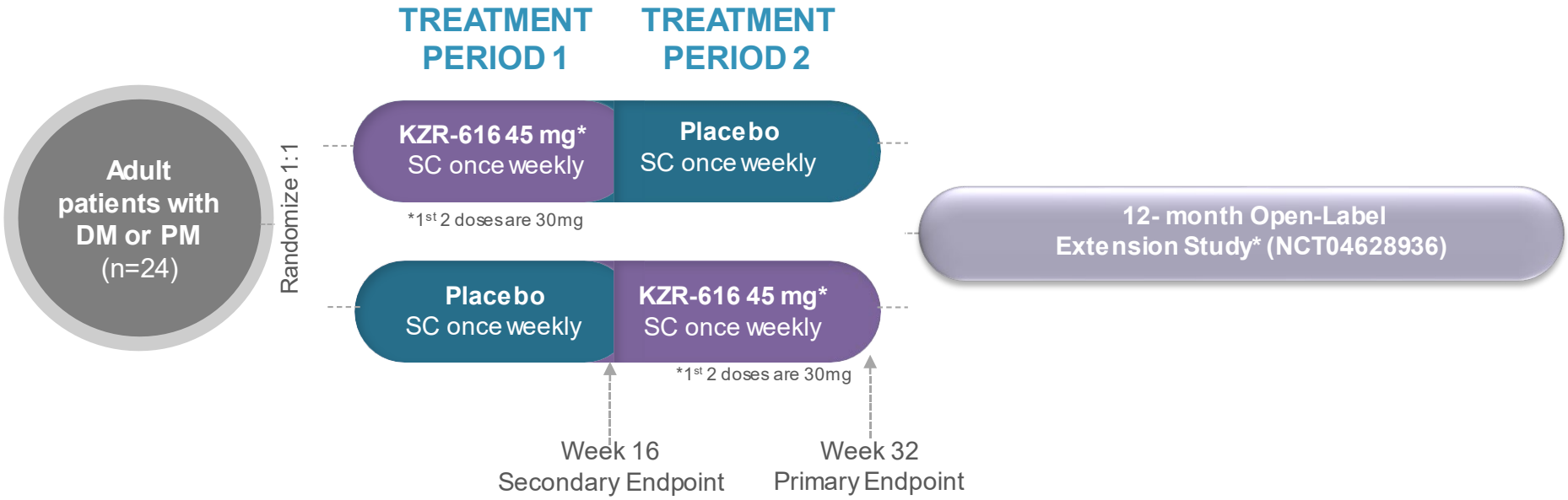
Muscle Histology



Muscle Enzymes



PRESIDIO Phase 2 Placebo-Controlled Cross-over Study for the Treatment of Dermatomyositis and Polymyositis



ENDPOINTS

1º: Efficacy - Total Improvement Score (TIS)

2º: Safety and tolerability; Patient Reported Outcomes (PROs), PK

Exploratory: Biomarkers, PK/PD relationship

Study NCT04033926

Abbreviations: SC, subcutaneous; PK, pharmacokinetic; PD, pharmacodynamics

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Who Might Qualify for PRESIDIO?

- Patients with active PM or DM (including immune-mediated necrotizing myopathy)
  - Antisynthetase syndrome and secondary Sjögrens
  - Stable interstitial lung disease (ILD)
  - Use of assistive devices (walker, cane, rollator, etc…)
- Active disease and some muscle weakness are both required
  - Active disease by recent MRI/EMG/muscle biopsy
  - Active disease by active DM rash
  - Elevated CPK/CK
  - Muscle weakness determined by standardized muscle testing
- No absolute requirement to be taking medications for myositis, but you can take the following during the study:
  - Up to 20 mg per day of prednisone
  - Steroid, one immunosuppressant (azathioprine, methotrexate, mycophenolate mofetil, tacrolimus) and one antimalarial (for DM) such as hydroxychloroquine

Abbreviations: MRI, magnetic resonance imaging; EMG, electromyography; CPK, creatine phosphokinase; CK, creatine kinase

What's Unique About PRESIDIO?

- Everyone gets KZR-616! Most studies have some or most trial participants receiving the active drug, but for PRESIDIO, everyone gets the chance to receive it
- Study sites can utilize home health services to administer weekly injections for a majority of study visits
  - Helpful for those who work or are physically limited
  - Nurse will come to your preferred location
- Services are available where applicable per local regulations to assist in study participant travel and expense management
- Doctor visits, assessments, testing, and KZR-616 are free to the study participant
- Frequent contact with study site
- Opportunity to continue treatment for an additional year with the Open-Label Extension (OLE) Study

KZR-616 Shows Promise for PM and DM

- Clinical trials are essential to development of new drug treatments by generating evidence and serve to advance health care services by raising standards of treatment
- Encouraging data from laboratory research in animal models of autoimmunity including polymyositis and dermatomyositis
- Our long-term goal is to establish KZR-616 as standard of care for the treatment of severe autoimmune disorders, including DM and PM
- KZR-616 is the only selective immunoproteasome inhibitor in clinical trials right now for PM/DM

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THANK YOU

Visit: https://presidio-study.com

Email: clinicaltrials@kezarbio.com