**Design of a randomized, double-blind, placebo-controlled Phase 2 clinical trial of the Toll-like receptor antagonist IMO-8400 in patients with dermatomyositis**

Joanna Horobin, Julia Bravard, Olga Polonskaya, Mark Hurst, Kirstin Lees, Victoria Worth, David Fiorentino

**BACKGROUND**

Dermatomyositis (DM) is a rare idiopathic inflammatory myopathy characterized by an auto-inflammatory immune response in muscle and skin. Multiple lines of evidence suggest Toll-like receptors (TLRs), a key component of the innate immune system, play a critical role in DM pathogenesis. Retrospective studies evaluating muscle biopsy samples have shown that TLRs were overexpressed in skeletal muscle and infiltrating cells in DM subjects compared to controls. Type I and II interferons and other cytokines were also overexpressed, and expression of certain cytokines correlated with TLR expression. IMO-8400 is an investigational oligonucleotide-based antagonist of endosomal TLRs 7, 8, and 9 that has demonstrated activity in preclinical models of autoimmune disease and in patients with psoriasis. Here, we describe the design of a recently initiated Phase 2 clinical trial of IMO-8400 in DM patients.

**DESIGN**

**PIONEER: a Phase 2 clinical trial of IMO-8400 in dermatomyositis**

**Study design**

- 24-week randomized, double-blind, placebo-controlled
- Primary endpoint: Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score

- **Major inclusion criteria**
  - Aged ≥18 years
  - Definite or probable DM based on Bohan and Peter criteria
  - Patients without hematologic test and Gottron’s sign are eligible with presence of DM antibodies
  - Active skin disease defined by a CDASI activity score ≥1.5

- **Major exclusion criteria**
  - Reacted background therapies:
    - Stable dose of prednisolone (or equivalent) ≥20 mg/day or ≥60 mg/week for ≤6 weeks
    - Stable regimen that does not exceed approved dosages for ≥12 weeks of no more than one of the following immunosuppressive medications: intravenous immunoglobulin (IVIG), mycophenolate mofetil, cyclophosphamide, cyclosporine, infliximab, tacrolimus, or rituximab
    - Stable regimes of topical treatments for skin involvement for ≥12 weeks
  - Cancer screening:
    - If DM diagnosis is ≥2 years prior to screening, one of the following must be confirmed or in a patient’s medical history:
      - Age and gender-appropriate screening and a PET/CT or PET/CT
      - On cancer workup is not confirmed in the medical history of a patient when it is required, a PET/CT should be performed during screening

- **Data in the literature demonstrate the role of TLR overexpression and downstream innate immune activation in DM**
  - TLRs, including TLR7 and TLR8, were significantly upregulated in biopsies of DM muscle
  - Evidence for TLR activation included overexpression of pro-inflammatory cytokines and activation of CD8+ T-cells
  - Changes in type I interferon gene and chemokine scores and expression of other proinflammatory cytokines correlated with changes in dermatomyositis disease activity

- **IMO-8400 blocks TLR signaling and immune system activation**

- **IMO-8400 is a synthetic oligonucleotide-based antagonist of TLRs 7, 8, and 9**
  - Activity observed in preclinical disease models
  - Evidence of TLR antagonism established in human clinical trials in psoriasis

- **IMO-8400 generally well tolerated in ~100 subjects to date at dose levels up to 2.4 mg/kg per week**
  - Phase 1 trial in healthy subjects
  - Phase 2 trial in patients with psoriasis
  - Phase 1/2 trial in patients with Widmer’s maculopapular/eosinosis

- **IMO-8400 activity observed in preclinical disease models**

- **Evidence of cancer (except for treated, non-invasive carcinoma of the skin or cured cervical dysplasia)**

- **Planned statistical analysis**
  - Repeated measures mixed model assessing change from baseline on CDASI activity score

- **Additional exploratory clinical endpoints**

- **Assessment of CDASI natural history dataset supported selection of a 7-point target treatment difference**

- **Programs to support trial participation**

- **In-Home Nursing Care**
  - For visits not requiring efficacy assessments, research nurse administers study drug, takes vitals and assesses adverse events at patient’s home or workplace
  - Provides source documents to site
  - Visits with site staff and offers visit to discuss any concerns with the patient
  - Site staff work with home nurse to determine how and when the patient will be contacted

- **Travel Support Program**
  - Dedicated travel vendor provides concierge and reimbursement services
  - Airfare, hotel, meals and incidentals for approved long-distance travel
  - Mileage, meals and incidentals for local travel

- **Text message appointment reminders**

**PIONEER: US clinical sites**

**United States**

- Brigham & Women’s Hospital (Boston, MA)
- Northeastern University (Boston, MA)
- Washington University (Washington, MO)
- Johns Hopkins University (Baltimore, MD)
- Medical University of South Carolina (Charleston, SC)
- Northwell Health (Great Neck, NY)
- Ohio State University (Columbus, OH)
- Florida Neurological Associates (Miami, FL)

**United Kingdom**

- University of Liverpool (Liverpool)
- University College London Hospital (London)

**Hungary**

- University of Debrecen (Debrecen)

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  - Todd Lerner
  - Galina Marder
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**Sample size assumptions**

- Stanford University CDASI natural history dataset with longitudinal data from routine clinical management of 115 subjects with DM

- Distribution is shown for patients with a baseline score ≤5 and a follow-up visit at 24 weeks (N=16)

- Reference line indicates a 7-point CDASI activity score decrease for 52% of patients

- 65% and 47% of patients had at least a 5- and 10-point change in CDASI activity score from baseline, respectively (not shown on figure)

- Publication of data planned

**Sample size calculations based on simulation**

- Power = 80%
- Standard deviation of 8.5 points
- 1-sided significance level = 0.05

**Analysis of CDASI activity score change from baseline**

- Mean = -8.38, SD = 10.49

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**PIONEER: UK and EU sites**

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