Rilonacept (Arcalyst®) for the Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS)

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Disclosures

- No conflicts of interest
- The views presented here do not necessarily reflect those of the Food and Drug Administration

Objectives

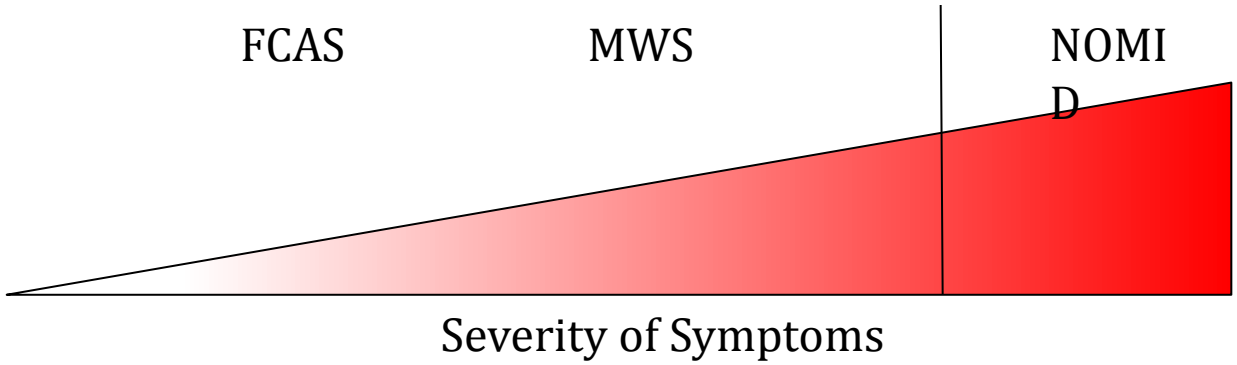
- Identify the challenges related to the design of clinical trials for rare diseases
- Understand the approaches used to address these challenges in the rilonacept development program

Background

- Cryopyrin-Associated Periodic Syndromes (CAPS)
  - "Autoinflammatory" Disorder
  - 200 to 500 patients in the US
  - Autosomal Dominant inherited
  - mutations in *CIAS1* which encodes cryopyrin
  - Cryopyrin regulates caspase-1
  - Caspase 1 regulates the cleavage of pro-IL-1 to active IL-1
  - IL-1 is an proinflammatory cytokine

Background

- 3 Clinical syndromes associated with CAPS
  - Familial Cold Autoinflammatory Syndrome (FCAS)
  - Muckle-Wells Syndrome (MWS)
  - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)



Familial Cold Autoinflammatory Syndrome

- Fever
- Cold-induced urticaria-like lesions
- Conjunctivitis
- Arthralgia/myalgias
- Symptoms provoked by cold stimuli

British J. Dermatol. 2004; 150: 1028-54

Muckle-Wells Syndrome

- Urticaria-like rash
- Conjunctivitis/Iritis
- Limb pain and arthralgias
- Abdominal pain
- Sensineural hearing loss

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CAPS and Potential Treatment

- Natural History Study
  - NIH

- Kineret (IL-1 antagonist)
  - Literature report from a small open-label study demonstrating a clinical benefit of patients with CAPS

Rilonacept (Arcalyst®)

- Fusion protein
- IL-1r and IL-1r accessory protein : Fc IgG1
- Binds both IL-1α and IL-1β
- Approved for use in patients with CAPS in March 2008

Challenges Designing a Trial in CAPS

Challenges with Designing a Trial for CAPS

- Small numbers of patients available for study enrollment
- No validated measures of disease activity or disease progression
- No standard of care for affected patients
- Assessing whether chronic treatment was needed or just treatment during winter months

Three-Stage Design

- Stage 1: All eligible subjects are randomized into a parallel-arm, placebo-controlled phase
- Stage 2: Subjects who responded to study treatment in Stage 1 enter into a randomized withdrawal phase
- Stage 3: randomization of placebo-treated patients who did not respond in Stage 1 but subsequently responded to open-label treatment are entered into a randomized withdrawal phase

Three-Stage Design

- Pros:
  - Reduces sample size by 20-30% compared to randomized control trial
  - Provides additional information about efficacy
  - Provides information about need for continued treatment
- Cons:
  - Limited experience
  - Ethical issues of placebo treatment
  - Same limitations as for Randomized Withdrawal Design

Choice of Primary Endpoint

- Which symptoms would be targeted during the trial?
  - "Defining" symptoms of the disease differed in severity between individuals
  - Surrogate endpoint was not feasible
  - Whether to use a single symptom or a composite index

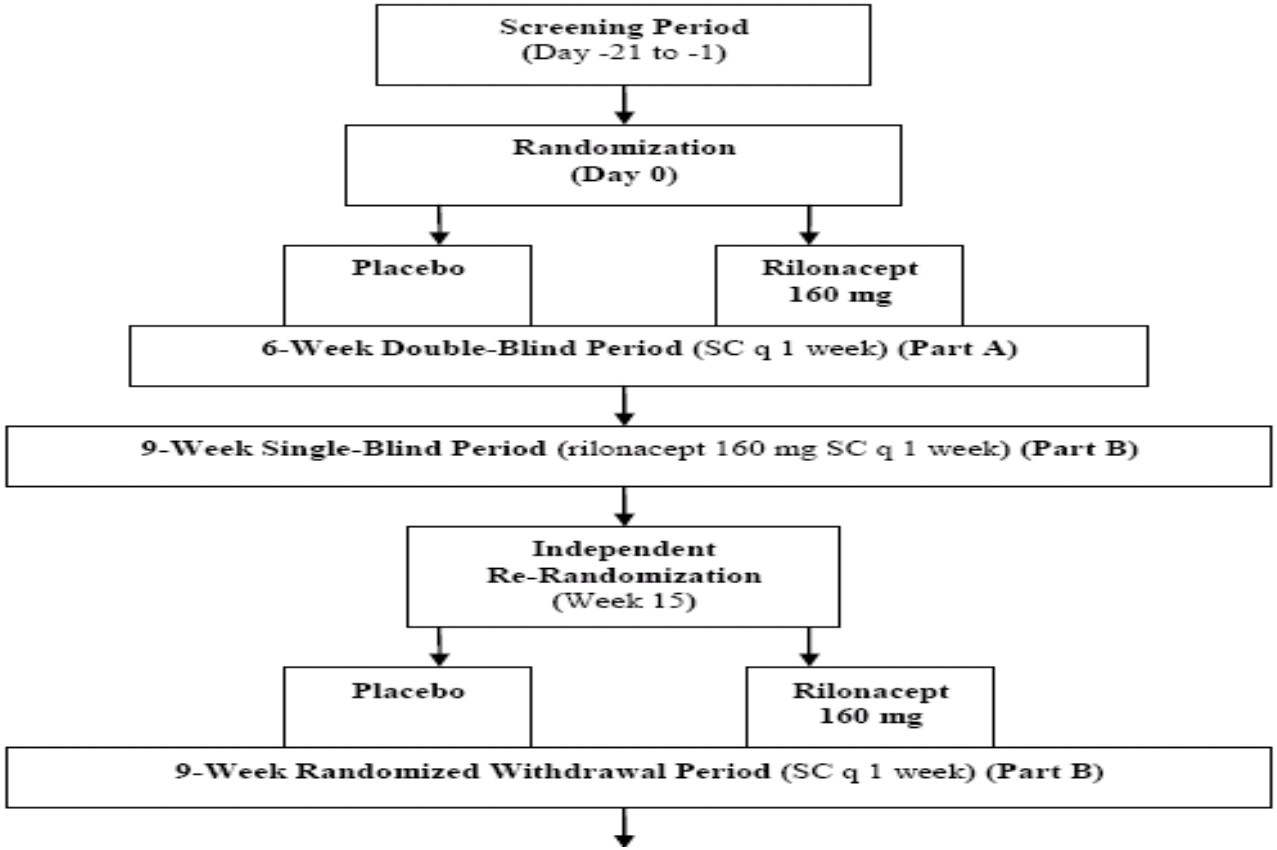
Choosing the Primary Endpoint

- Composite index of Symptoms
  - 5 symptoms using a VAS scale from 0-10 cm via 0.5cm increments
    - Fever, Rash, Joint Pain, Eye Pain/Redness, Fatigue
  - For each day, the 5 scores were summed and divided by 5 (daily mean score)

Study Design

- Modified Three-Stage Design

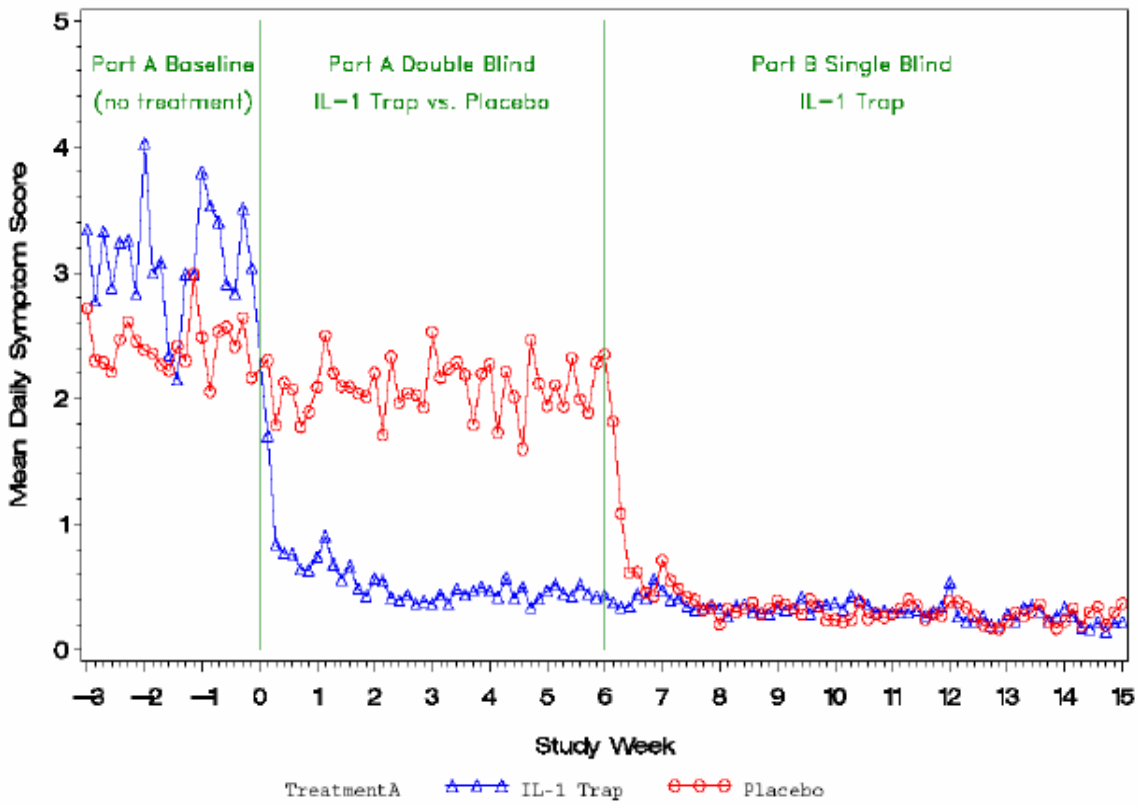
Figure 1 Study Design Schematic



Study Results

- Stage 1 (Part A)

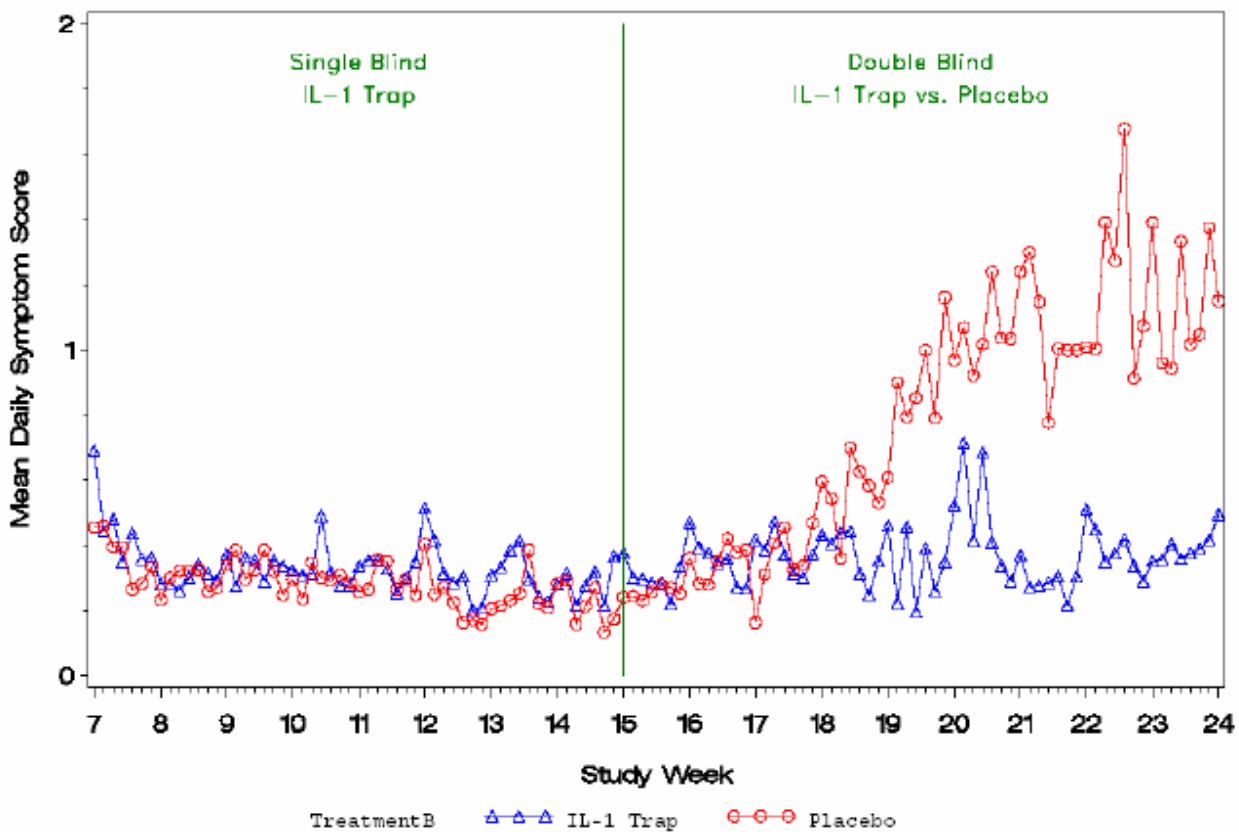
Mean Daily Key Symptom Score by Treatment Group from Week -3 to Week 15 in Study Part A and Part B Single-blind Phase



Study Results

- Stage 2 (Part B)

Mean Daily Key Symptom Score by Treatment Group from Week 6 Single-Blind Phase to Week 24 Randomized Withdrawal Phase in Part B



Summary

- Rare diseases present challenges regarding optimal study design
- Important to devise clinically meaningful endpoints to characterize the benefits of new therapies
- Variety of alternative study designs available that can provide adequate data to demonstrate the efficacy of a new therapy while minimizing prolonged exposure to an ineffective therapy

"YOUR DISEASE IS SO RARE, THERE HASN'T EVEN BEEN A T.V. DRUG AD FOR IT YET."

CME Question

What type of study design was used in the rilonacept development program for CAPS?

A) Add-on Design

B) Crossover Design

C) Three-Stage Design

D) Dose-Response Design