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
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 0.5 cm 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

Screening Period (Day -21 to -1)

Randomization (Day 0)

- Placebo
- Rilonacept 160 mg

6-Week Double-Blind Period (SC q 1 week) (Part A)

9-Week Single-Blind Period (rilonacept 160 mg SC q 1 week) (Part B)

Independent Re-Randomization (Week 15)

- Placebo
- Rilonacept 160 mg

9-Week Randomized Withdrawal Period (SC q 1 week) (Part B)
Study Results

- Stage 1 (Part A)
Study Results

- Stage 2 (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 TV 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