Introduction: RA Endpoints for Drug Development

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Overview

- Summary of historical trial design features and claims for RA and differences relative to the 1999 RA Guidance
- Considerations regarding efficacy information in labeling

Drug Development Trials in RA

- Populations
  - TNF inhibitor inadequate responders
  - DMARD inadequate responders
  - MTX naïve/early RA
- Claims/Endpoints
  - Foundational: Signs/Symptoms
    - Proportion of ACR Responders (12 week minimum duration)

Drug Development Trials in RA

- Other Claims/Endpoints
  - Major Clinical Response
    - ACR 70 for continuous 6-month period
  - Improving Physical Function (previous “prevention of disability” claim)
    - Mean change in HAQ-DI from baseline to week 12 or longer
  - Slowing/Inhibition of the Progression of Structural Damage
    - Historically, demonstrated as mean change from baseline in Total Sharp Score (or similar) in as short a time possible to demonstrate a difference; minimum of 24 weeks

Differences from 1999 Guidance

Claim	Trial Duration*	Endpoints	Differences from 1999 RA Guidance
Reduction in signs and symptoms	≥ 3 months (≥6 mos if new class)	ACR response criteria or other well-accepted composite endpoints or signs/symptoms measures	≥ 3 months
Major clinical response	≥ 7 months	ACR70 for 6 consecutive months	Placebo-controlled period must be limited to 12 to 16 wks; active-control needed to accommodate duration of controlled period
Complete clinical response Remission	≥ 12 months ≥ 12 months	Remission by ACR criteria and no x-ray progression for 6 consecutive months Remission by ACR criteria and no x-ray progression for 6 consecutive months while off all anti-rheumatic therapy	These claims have not been historically pursued. Alternative definition of remission is needed representing milestone of very high level of response that could be practical to pursue in clinical trials
Improvement in physical function ("Prevention of disability*")	2 to 5 years	HAQ or AIMS with SF-36 not worsening	Claim of improvement in physical function can be demonstrated in duration of ≥ 3 months; short-term benefit may not represent "prevention of disability."
Slowing or inhibition of progression of structural damage	≥ 1 year	Modifed Sharp score or other validated radiographic index	Placebo-controlled period must be limited to 12 to 16 wks; short duration makes demonstration of relative reduction in radiographic scores impractical.

ACR: American College of Rheumatology; AIMS: Arthritis Impact Measure Scales
HAQ: Health Assessment Questionnaire
* as per 1999 RA Guidance

Efficacy Claims in Current Labels

Efficacy Claims in Currently Approved Labels of Recent (>1998) Disease Modifying Anti-Rheumatic Drugs (DMARDs)										
	Arava	Remicade	Enbrel	Kineret	Humira	Orencia	Rituxan	Cimzia	Simponi	Actemra
ACR 20/50/70 Responses	x	x	x	x	x	x	x	x	x	x
Time course of response	x	x	x		x	x	x	x	x	x
Open-label maintenance	x	x	x		x	x				
Major Clinical Response		x	x		x	x		x		x
ACR components	x	x	x	x	x	x	x	x	x	x
Radiographic response	x	x	x	x	x	x	x	x		x
Proportion of nonprogressors		x	x		x	x	x			x
Open-label maintenance			x		x					
Physical function										
HAQ-DI	x	x	x	x	x	x	x	x	x	x
SF-36	x	x	x	x	x	x				
Open-label maintenance	x	x	x		x	x	x			
DAS28 <2.6										
Proportion of responders						x				x
Residual active joints						x				x
Morning stiffness	x		x			x				

- Up to 13 efficacy items for a single indication
- PROs include: patient global assessment, patient pain, patient-reported disability (HAQ-DI), morning stiffness, SF-36

What Efficacy Claims Should be Included in the Label?

- "[The clinical studies section of the label] is not intended to describe all available effectiveness data"
- "The clinical studies section should present those endpoints that establish the effectiveness of the drug or show the limitations of effectiveness"

Physicians' Labeling Rule Clinical Studies Section Guidance, January 2006

Efficacy Outcomes that Drive Treatment Decisions in RA

- "The goal for each RA patient should be low disease activity or remission."

  -2012 ACR Treatment Guidelines

- The commonly used disease activity indices include tender joint count, swollen joint and patient global assessment
  - Some also include physician global assessment, patient pain on VAS, functional assessment, and/or acute phase reactants

Where Does Fatigue Fit In?

- Important to patients
- Multidimensional and multifactorial
- Improvement in fatigue is consistently noted as an ancillary benefit when measured in clinical trials of DMARDs but has not been specifically described in currently approved labels

Labeling Considerations

- Labels should maintain a balance between efficacy and safety
- Efficacy outcomes which establish the effectiveness of a product or the limitations of effectiveness of a product are likely to be included
- Other ancillary claims could be considered if not already captured in the foundational efficacy outcomes