rAAV-TNFR:Fc Gene Therapy for Rheumatoid Arthritis Protocol 13E04

Recombinant DNA Advisory Committee

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Philip Mease, MD
Seattle Rheumatology Associates
Director, Swedish Hospital Medical Center Division of Rheumatology Clinical Research
Clinical Professor
University of Washington School of Medicine
Seattle, Washington

Disclosures for P. Mease

- Advisor, clinical investigator
  - Amgen
  - Wyeth
  - Centocor
  - Abbott
  - Biogen
  - Xoma
  - Aventis
  - Pfizer
  - Merck
  - Novartis
  - Smith Kline
  - Targeted Genetics
  - Cypress Bioscience
  - Genelab Technologies

Rationale for Anti-TNFα Therapy

- TNFα: A dominant pro-inflammatory mediator, overproduced in RA
- TNFα blockade ameliorates symptoms and signs of RA
- Repeated treatment with TNF-α antagonists results in
  - Sustained reduction in symptoms and signs of RA in majority of patients
  - Protects joints from structural damage
- Despite the global patient response, individual joints may exhibit persistent synovitis
  - Intra-articular injection of etanercept for active joints reported to be effective

Calculation of ACR 20 and ACR-N

ACR 20

At least 20% improvement in:

- Swollen joint count ***and***
- Tender joint count ***and***
- Three of the five of:
  - MD global assessment
  - Patient global assessment
  - Visual analog scale (VAS) for pain
  - HAQ
  - CRP

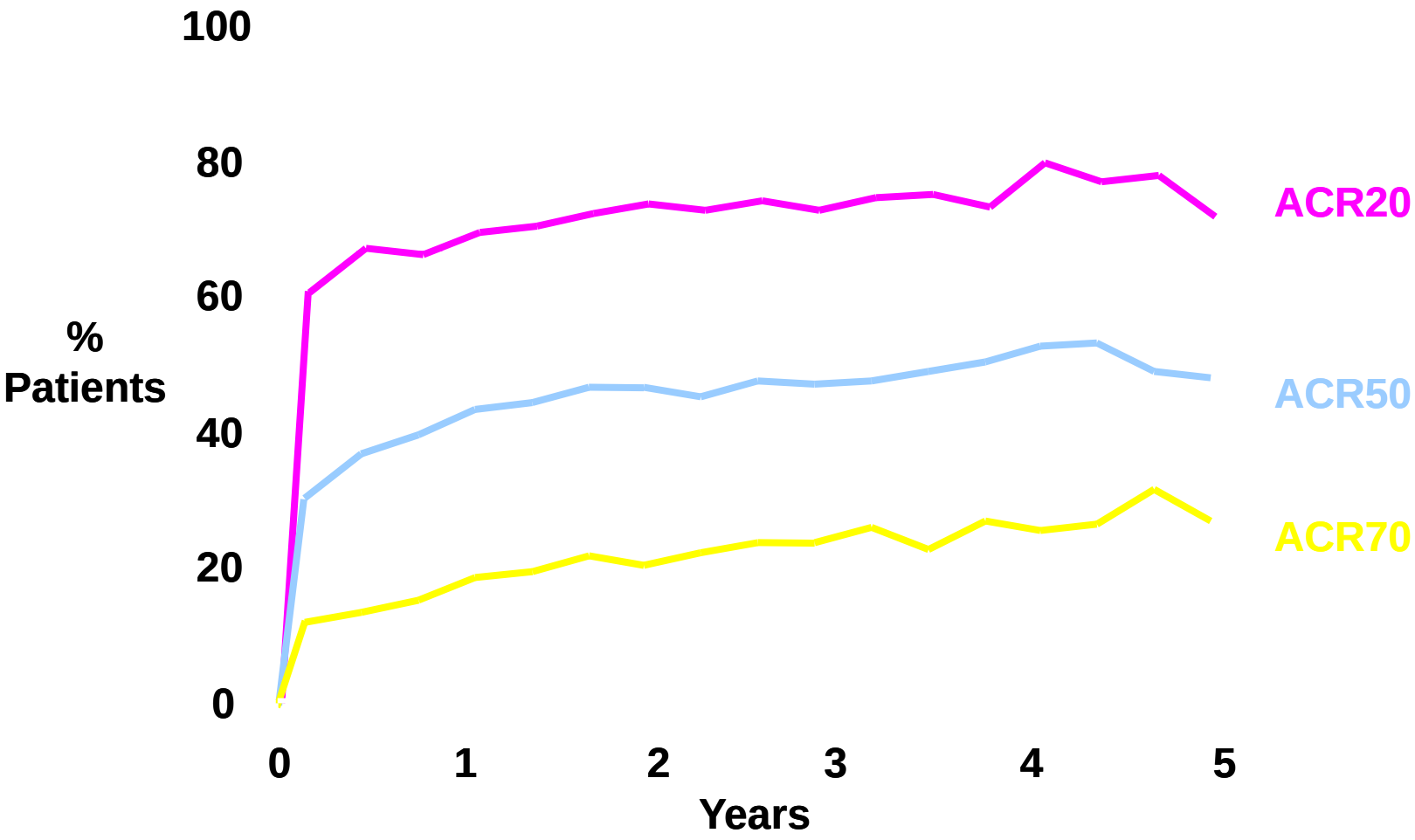
ACR-N

Actual (lowest) % improvement in:

- Swollen joint count ***or***
- Tender joint count ***or***
- 3rd highest of:
  - MD global assessment
  - Patient global assessment
  - VAS for pain
  - HAQ
  - CRP

Etanercept Monotherapy, Open-Label Extension

ACR Responses Are Sustained



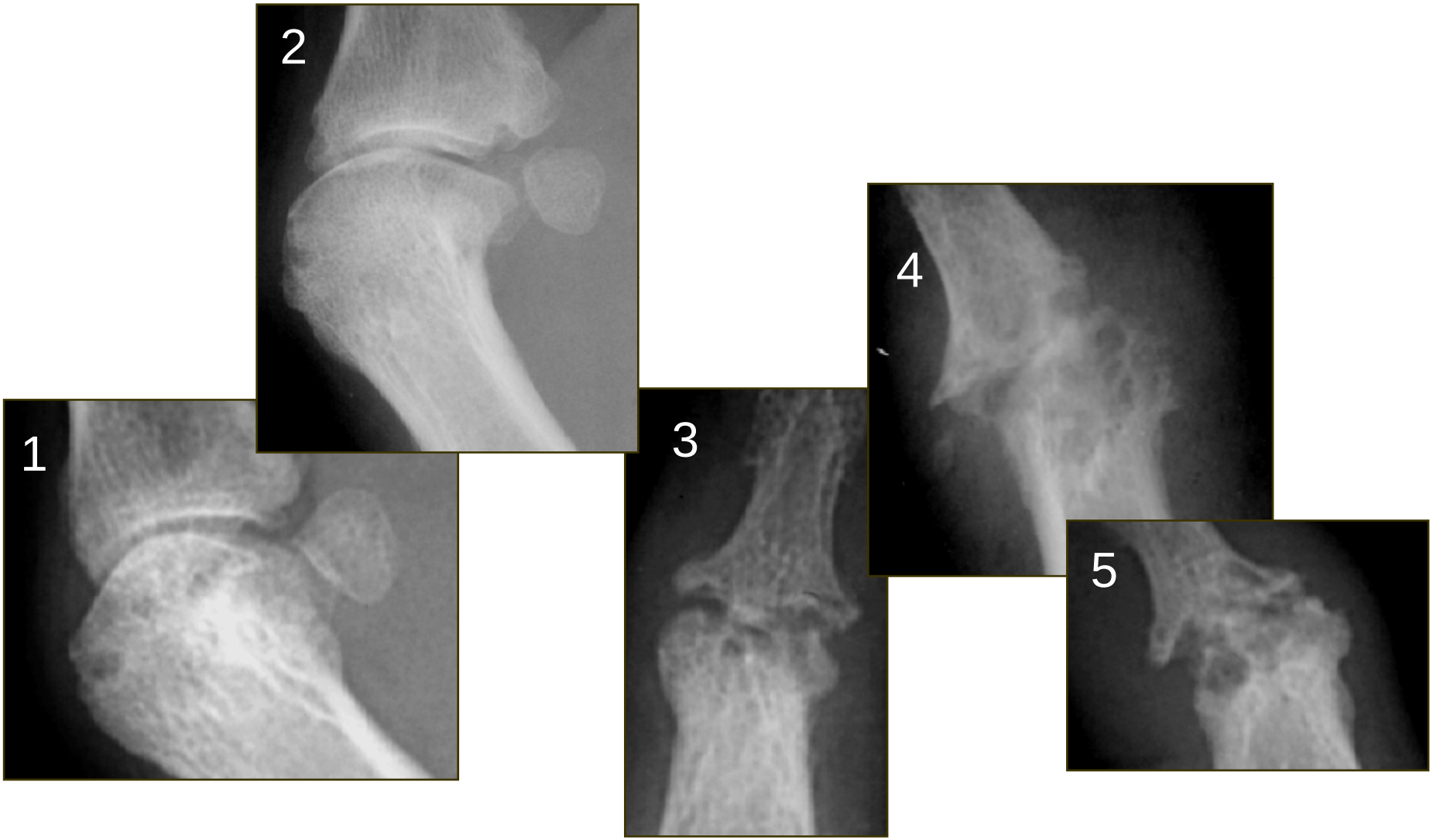
Analysis by completer observation

Moreland LW, et al. *Arthritis Rheum*. 2002;46(suppl). Abstract 1427.

Example Calculation of ACR-N Compared to an ACR Score

Parameters	Patient #1 % Improvement	Patient #2 % Improvement
Swollen joint count	28%	42% ←
Tender joint count	25% ←	45%
MD global assessment	40%	52%
Patient global assessment	35%	51%
VAS for pain	26%	49%
HAQ	22%	22%
CRP	47%	47%
ACR 20	Yes ←	Yes ←
ACR 50	No	No
ACR 70	No	No
ACR-N	25% ←	42% ←

Erosions



Local Anti-TNFα Gene Therapy

- Selective treatment of persistent “sentinel” joints in polyarticular disease as well as mono- or oligo-articular arthritis
- Maximal effective therapy to affected joint
- Reduced systemic exposure to improve safety
- Sustained effect with significantly less frequent administration
- Maximize potential for inhibiting disease progression

tgAAC94: rAAV human TNFR:FC

- Single stranded DNA encoding huTNFR:Fc
- huTNFR:Fc cDNA sequence identical to the cDNA used for etanercept production
- Packaged in AAV2 capsid
- Extensively purified

Summary: Preclinical Studies to Support Phase I Protocol 13E04

rAAV-TNFR:Fc Therapy:

- Efficacious at doses of 1 x 10^{12} DRP/mL joint volume in arthritic rats
- Safe at doses of up to ~1 x 10^{13} DRP /mL joint volume in rats
- Limited and transient biodistribution to extra-articular tissues
- Local expression of TNFR:Fc confirmed in the joint
- Low level of TNFR:Fc protein in serum
  - <0.025 μg/mL in < 4% (4/102) treated animals
  - Cmax of etanercept in patient serum is 3μg/mL

Systemic Effects of Localized Therapy

- Low levels of circulating TNFR:Fc protein
  - Local injection of etanercept (8mg per joint) did not result in systemic effect
- Dissemination of vector
  - Low levels of vector DNA in contralateral joint (average of ~0.002 copies /cell)
  - Transgene (luciferase) expression not detected in contralateral joint
- Trafficking of genetically or functionally modified immune cells
  - Effect of deactivation of the pro-inflammatory cytokine cascade at site of inflammation
  - Modulation of antigen presenting cells or Dendritic cells

TGC Protocol 13E04

A Phase 1 Dose Escalation Study of
Intra-Articular Administration of tgAAC94, a
Recombinant Adeno-Associated Vector containing
the TNFR:Fc Fusion Gene,
in Rheumatoid Arthritis

Objectives

- Primary endpoint
  - Safety of intra-articular injection of tgAAC94
- Secondary endpoints
  - Change in tenderness and swelling in injected joint
  - Change in tenderness and swelling in non-injected joints
  - Change in disease activity (ACR20, DAS)
  - Distribution of TNFR:Fc protein in joint fluid and serum
  - Development of neutralizing antibodies to AAV2
  - Distribution of tgAAC94 in systemic circulation (PBMCs)

Study Regimen

- Single intra-articular injection of tgAAC94 or placebo
- Dosing based on joint volume
  - Knee, 5 mL
  - Ankle, 2 mL
  - Wrist, 1 mL
  - MCP, 0.5 mL

Study Design

- Multi-center study
- Double blind, placebo controlled, dose escalation
- Four cohorts of 8 subjects each
- Oversight by Safety Review Board

Dose DRP/mL joint volume	Active	Placebo
$1x10^{10}$	6	2
$1x10^{11}$	6	2
$1x10^{12}$	6	2
“highest safe dose”	6	2

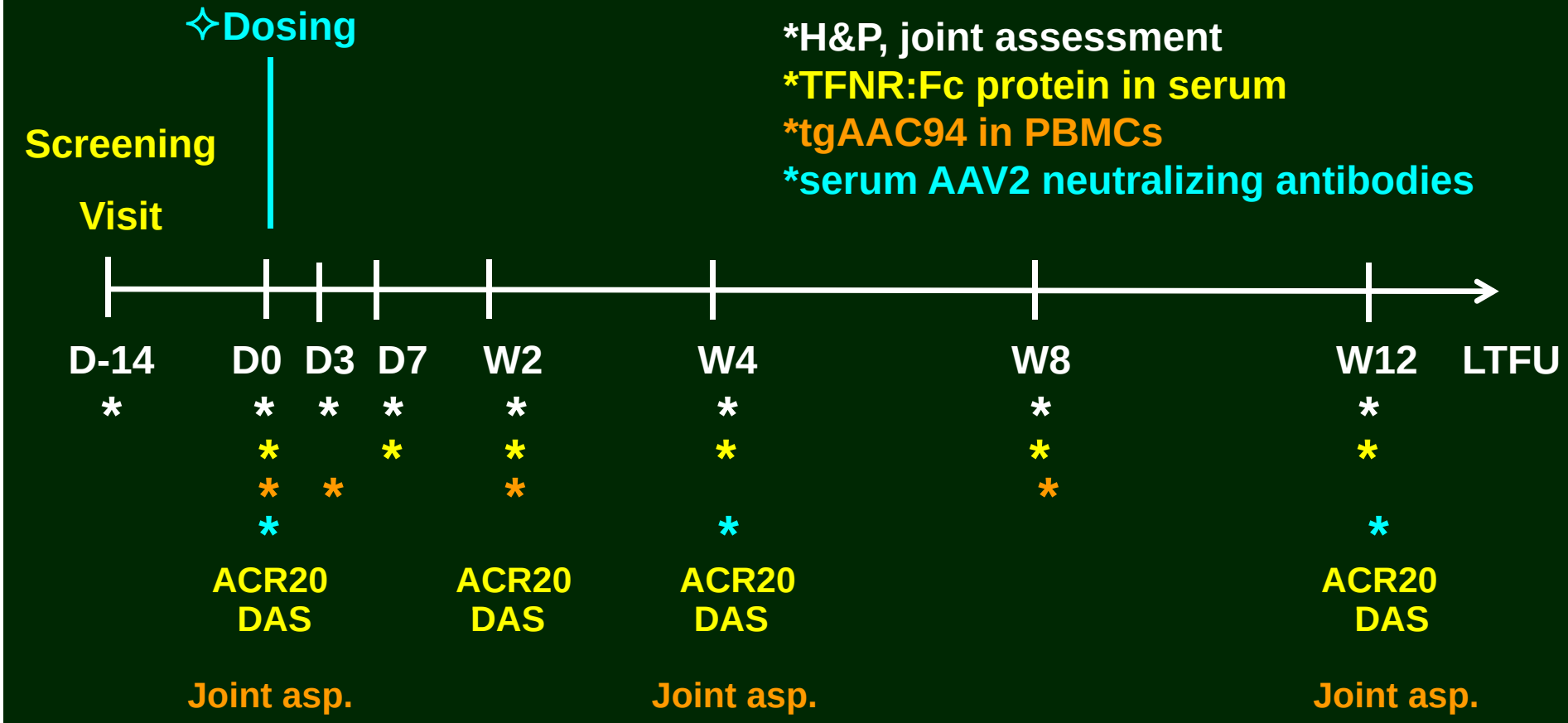
Inclusion Criteria

- Adults with rheumatoid arthritis
- ACR functional status I, II or III
- Persistent swelling in one or more joints despite stable medical regimen, including DMARD x 3 months, with no changes in dose x 4 weeks
- No past or current use of TNFα antagonists, or planned use in next 3 months

Exclusion Criteria

- Corticosteroids at dose > 10 mg prednisone/day
- Known HIV infection, known Hep C infection, known positive Hep B surface Ag
- Positive PPD, unless already treated
- Serious medical disease
- Abnormal lab values:
  Hb <8.5 gm/dL, WBC <3500 per mm3,
  plts <100 K/μL, Cr >2 mg/dL, BR >2 mg/dl, AST or ALT >2 x ULN, prolonged PT or PTT

Schedule of Events



STUDY DAYS (D)/WEEKS (W)

Safety Review Board

- Independent oversight of clinical trial
- Consists of clinicians and scientists who collectively have experience in treating RA and in the conduct of clinical trials
- Will follow SRB Charter
  - Full safety data will be reviewed by SRB between cohorts to review cumulative, unblinded SAEs, AEs, & lab data
  - Study enrollment pauses during SRB review
  - Chairman to review SAEs as they occur, and call full meeting if indicated
  - May recommend study discontinuation for safety concerns at any time

Summary

- Despite advances in ability of systemic therapies to achieve general control of RA, many patients display persistent synovitis in one or more joints
- Current systemic therapies carry risk, sometimes significant
- Available local therapies yield transient utility
- TNFR:Fc transgene should not impact future use of other DMARDs
- Local long-term expression is not a significant risk factor
  - Transgene does not lead to selective growth of cells
  - Integration of vector DNA is a rare event