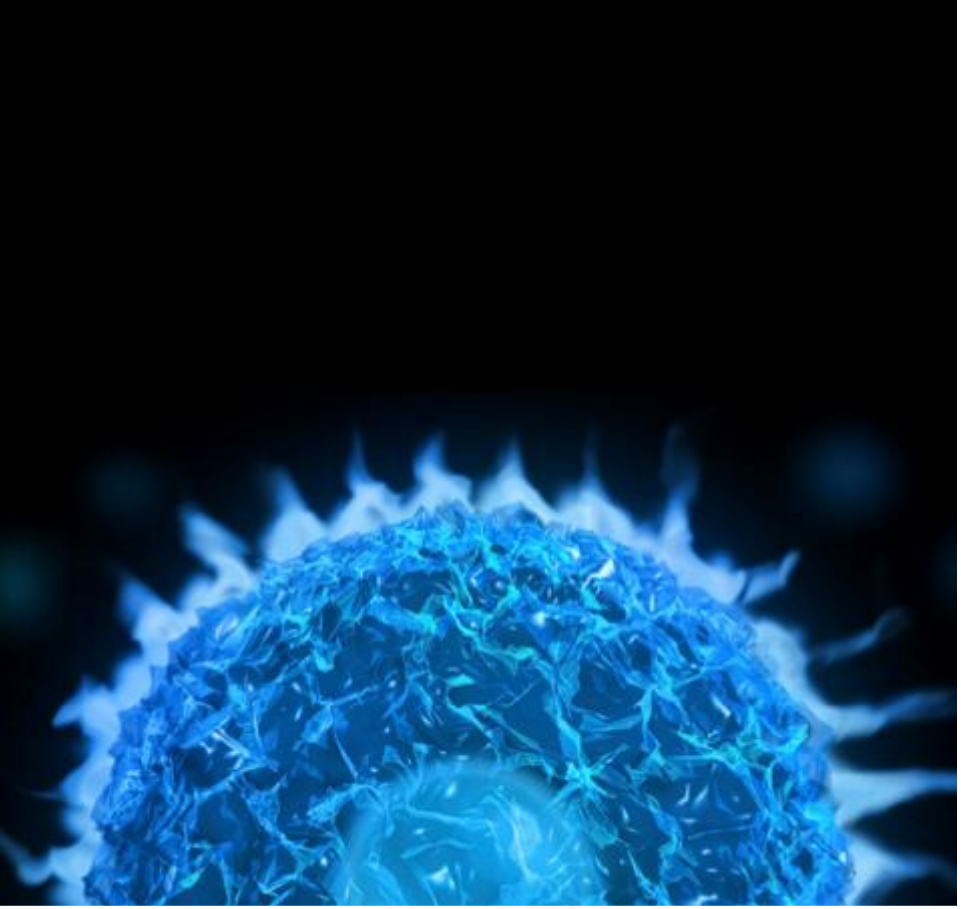

STATISTICAL ANALYSIS IN RA TRIALS
Programming view

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AGENDA

- Rheumatoid Arthritis
- Endpoints
- Data handling rules
- Analysis/Derivation Rules

THERAPEUTIC AREA

- **Rheumatology and Orthopedics**
  - **Rheumatology**
    - **Rheumatoid Arthritis**

RHEUMATOID ARTHRITIS (RA)

- **Long-lasting autoimmune systemic inflammatory disease**
- **Primarily affects joints, 15-25% individuals other organs are affected**
- **Goal of treatment**
  - No cure for RA, treatment improve symptoms and slow the progress of disease
  - Reduce pain
  - Decrease inflammation
  - Improve a person's overall functioning
- **Analysis processing**
  - How much is it improved in pain, inflammation, physical function

ENDPOINTS

- **American College of Rheumatology (ACR)**
  - ACR20, ACR50
  - Proportion of subjects who achieved ACR20/50
- **Disease Activity Score 28 (DAS28)**
  - Change from baseline
  - DAS28 remission
- **Clinical Disease Activity Index (CDAI)**
- **Simplified Disease Activity Index (SDAI)**
- **QOL assessment by SF-36 questionnaire (SF36 score)**
- **Number of Work Days Missed**
- **Etc.**

ENDPOINTS - ACR

- ACR is an organization of and for physicians, health professionals, and scientists that advances rheumatology through programs of education, research, advocacy and practice support that foster excellence in the care of people with arthritis and rheumatic and musculoskeletal diseases.
- **ACR Score**
  - A scale to measure change in RA signs and symptoms
  - Composite measurement
  - Presented as improvement in multiple disease assessment criteria
    - Improvement from baseline in both swollen and tenderness joint count
    - Improvement from baseline in at least 3 of the 5 assessments

ENDPOINTS - ACR EVALUATIONS

❖ Evaluations

- Joint Assessments (TJC68, SJC66)
- Patient's Global assessment of joint pain (PAIN)
- Patient's Global Assessment of Disease Activity (GDPT)
- Physician's Global Assessment of Disease Activity (GDEV)
- Patient's Assessment of Physical Function as Measured by HAQ-DI
- Level of C reactive protein (CRP) / Level of erythrocyte sedimentation rate (ESR)

ENDPOINTS - ACR SCORE DERIVATION

- **Component level**
  - Yes: Percent change from baseline meet criteria (eg. <= -20%)
- **Five Assessments' Cumulative Response Status**

PAIN	GDPT	GDEV	HAQ-DI	CRP/ESR
At least 3 of assessment with response status is 'Yes'				
Cumulative Response Status: Yes				

- **ACR Score Response Status**

Tender Joint Count	Swollen Joint Count	Other 5 assessments	ACR Score
Yes	Yes	Yes	Yes

ENDPOINTS - ACR SCORE ANALYSIS RESULT

	ACZ885 (Canakinumab) : RA Patients	Placebo Comparator: RA Patients
Overall Participants [units: participants]	50	10
Response to Treatment (ACR20) in Adult Patients With Established Rheumatoid Arthritis (RA) [units: Participants]		
ACR20 response rate at 6 weeks	17	2
ACR20 response rate at 12 weeks	27	2

Source: https://clinicaltrials.gov/ct2/show/results/NCT00504595?sect=X970156&term=rheumatoid+arthritis&rank=20#outcome3

ENDPOINTS - ACR SCORE ANALYSIS RESULT

Number of Subjects Who Achieved an ACR 20 Response at Week 24; Full Analysis Set		
	Placebo	Active Drug
Analysis set: Full Analysis Set	xx	xx
ACR 20		
n	xx	xx
Subjects in response	xx (xx.x%)	xx (xx.x%)
% Difference (95% CI)		xx.x (xx.x, xx.x)
p-value		x.xxx
Risk Ratio (95% CI)		x.x (x.x, x.x)

ACR RELATED ENDPOINTS

- **ACR20/ACR50/ACR70/ACR90**
  - ≥ [20/##]% improvement from baseline in both tender joint count (68 joints) [TJC68] and swollen joint count (66 joints) [SJC66]

  AND

  - ≥ [20/##]% improvement from baseline in at least 3 of the 5 assessments

- **Major clinical response (MCR)**
  - the subject achieves an ACR70 response for any 6 continuous months (24 weeks)

ENDPOINTS - DAS28

- Is a system developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of Rheumatoid Arthritis.
- DAS28 higher values mean a higher disease activity.

ENDPOINTS - DAS28

❖ DAS28 Derivation

- derived score combining
  - tender joint count (28 joints) (TJC28)
  - swollen joint count (28 joints) (SJC28)
  - CRP / ESR
  - Patient's Global Assessment of Disease Activity (GDPT)

❖ Calculation

DAS28 (CRP) = 0.56*SQRT(TJC28) + 0.28*SQRT(SJC28) + 0.36*Ln($CRP_{mg/L}$ +1) + 0.014*$GDPT_{mm}$ + 0.96

DAS28 (ESR) = 0.56*SQRT(TJC28) + 0.28*SQRT(SJC28) + 0.70*Ln(ESRmm/hr) + 0.014*$GDPT_{mm}$

ENDPOINTS - DAS28

❖ DAS28 response Categorization

- ➢ DAS28 score >5.1 indicates high disease activity
- ➢ DAS28 score <3.2 indicates low disease activity
- ➢ DAS28 score <2.6 indicates clinical remission.

❖ DAS28 response Criteria

DAS28 (CRP) Response Criteria			
DAS28 (CRP) at the visit	Improvement from Baseline		
	> 1.2	> 0.6 – 1.2	≤ 0.6
≤ 3.2	Good response	Moderate response	No response
> 3.2 – 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

ENDPOINTS - DAS28 MEASURED VALUE EXAMPLE

	ACZ885 (Canakinumab) : RA Patients	Placebo Comparator: RA Patients
Overall Participants [units: participants]	50	10
Efficacy of ACZ885 (Canakinumab) by Assessing the Response to Treatment Using the Disease Activity Score (DAS28) [units: Scores on a scale] Mean (Standard Deviation)		
6 Weeks	5.088 (1.1148)	5.397 (1.0591)
12 Weeks	4.853 (1.1879)	5.400 (0.9321)

Source: https://clinicaltrials.gov/ct2/show/results/NCT00504595?sect=X970156&term=rheumatoid+arthritis&rank=20#outcome3

ENDPOINTS - DAS28 MEASURED VALUE EXAMPLE

Change From Baseline in Disease Activity Score (DAS) 28

	Rheumatoid Arthritis
Number of Participants Analyzed [units: participants]	4400
Change From Baseline in Disease Activity Score (DAS) 28 [units: units on a scale] Mean (Standard Deviation)	
Month 3 (n=3918)	-1.6 (1.3)
Month 6 (n=3347)	-1.8 (1.4)
Month 12 (n=2872)	-2.0 (1.4)
Month 18 (n=2397)	-2.1 (1.4)
Month 24 (n=2099)	-2.2 (1.4)
Month 30 (n=1810)	-2.3 (1.5)
Month 36 (n=1564)	-2.3 (1.5)
Month 48 (n=1261)	-2.3 (1.5)
Month 60 (n=934)	-2.4 (1.5)

Source:https://clinicaltrials.gov/ct2/show/results/NCT01078090?term=rheumatoid+arthritis&rank=15&sect=X01256#all

ENDPOINTS - DAS28 MEASURED VALUE EXAMPLE

Percentage of Participants in DAS28 Remission

	Rheumatoid Arthritis
Number of Participants Analyzed [units: participants]	4400
Percentage of Participants in DAS28 Remission [units: percentage of participants]	
Month 3 (n=3918)	12.8
Month 6 (n=3347)	16.9
Month 12 (n=2872)	19.4
Month 18 (n=2397)	23.0
Month 24 (n=2099)	23.3
Month 30 (n=1810)	24.3
Month 36 (n=1564)	24.0
Month 48 (n=1261)	24.7
Month 60 (n=934)	25.6

Source:https://clinicaltrials.gov/ct2/show/results/NCT01078090?term=rheumatoid+arthritis&rank=15&sect=X01256#all

DATA HANDLING RULES

- **Treatment Failure, criteria**
  - Discontinue study agent infusions due to <any reason>
  - Initiated protocol prohibited medications/therapies for RA
  - Increase the dose of some medication for RA above the baseline dose
  - Meet early escape criteria
  - Etc.
- **Data handling for the endpoints on or after the TF time point**
  - Dichotomous endpoints: not responder (regardless of observed data)
  - Continuous endpoints: not affected

DATA HANDLING RULES

- **Missing data imputation**
  - Continuous endpoints
    - Component: LOCF
    - Composite: LOCF for missing component, then derive composite endpoint
  - Dichotomous responder-type endpoints
    - Missing values will be imputed as non-responder
    - Composite:
      - All component are missing, then non-responder for composite
      - Not all component are missing, LOCF for missing component, then derive composite endpoint

ANALYSIS/DERIVATION RULES

- **Reference Date**
  - First study agent administration Date -> Corresponding visit date for the first study agent administration -> Randomization date
- **Baseline**
  - the closest non-missing value prior to or at the reference date
  - Set to missing if no value meet above criteria
- **Change from Baseline**
  - Assume baseline and post baseline are not missing, otherwise, CHG is missing
- **Percent Change from Baseline**
  - Assume baseline not equal to 0 and neither of baseline and post baseline is missing, otherwise PCHG is missing

THANK YOU

