FDA Arthritis Advisory Committee (AAC)

FDA Introductory Remarks

NDA 203214 (supplement 17) and NDA 208246 (supplement 3): Tofacitinib and tofacitinib extended release for the treatment of adult patients with active psoriatic arthritis

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Center for Drug Evaluation and Research
August 3, 2017

Psoriatic Arthritis (PsA): Overview

- PsA is a chronic, progressive, inflammatory arthritis associated with psoriasis (PsO)
- Can result in permanent joint damage and disability
- Multiple therapeutic options approved over the last 15 years

Overview

- **Product:**
  - Tofacitinib (Xeljanz®)
- **Mechanism of action:**
  - Janus kinase (JAK) inhibitor
- **Approved indication and dosage:**
  - Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX)
  - 5 mg orally twice daily
- **Proposed indication and dosage:**
  - Treatment of adults with active psoriatic arthritis (PsA)
  - 5 mg orally twice daily

Background—Tofacitinib

- Initially approved on November 6, 2012, for the treatment of moderately to severely active RA (immediate release tablet)
  - Extended release tablet subsequently approved in 2016

- In October 2015, the Agency issued a complete response for tofacitinib for the treatment of moderate to severe plaque psoriasis

Overview of Tofacitinib Safety

- Boxed warnings
  - **Serious infections** leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections
  - **Malignancies**, including lymphoma and other malignancies
- Warnings/Precautions
  - Serious Infections, including tuberculosis and viral reactivation
  - Malignancies, lymphoproliferative disorders and non-melanoma skin cancers
  - Gastrointestinal (GI) perforations
  - Laboratory abnormalities, including lymphocyte abnormalities, neutropenia, anemia, liver enzyme elevations, and lipid elevations
  - Vaccinations

Clinical Development Program for PsA

Study	Population	Primary Endpoints	Treatment Arms
Placebo and active-controlled studies			
A3921091 (**1091**) Phase 3, R, DB, DD, PC, AC, 12-month study	cDMARDs-IR, TNFi-naïve N=422	ACR20 @ Month 3 Change from Baseline in HAQ-DI @ Month 3	• Tofa 5 BID • Tofa 10 BID • PBO until Month 3* • Adalimumab 40 mg SC q2w *PBO randomized to Tofa 5 or 10 BID @ Month 3
A3921125 (**1125**) Phase 3, R, DB, PC, 6-month study	TNFi-IR N=394	ACR20 @ Month 3 Change from Baseline in HAQ-DI @ Month 3	• Tofa 5 BID • Tofa 10 BID • PBO until Month 3* *PBO randomized to Tofa 5 or 10 BID @ Month 3
Open label extension study			
A3921092 **(1092)** OLE, 3 years per subject	Participation in 1091 or 1125 N=685	Safety/tolerability of Tofa 5 and 10 BID	Patients were placed on 5 BID and escalated to 10 BID if thought beneficial by investigator; patients on 10 BID could be decreased to 5 BID for safety

R: randomized; DB: double-blind; DD=double dummy; PC: placebo-controlled; AC=active-controlled; cDMARDs: conventional disease modifying anti-rheumatic drugs; TNFi: tumor necrosis factor inhibitor; ACR: American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire-Disability Index; Tofa: tofacitinib; PBO: placebo; SC: subcutaneously; q2wks: every two weeks; BID: twice daily; OLE: open label extension

Efficacy Considerations

- Efficacy for signs and symptoms (ACR Responses) and physical function (HAQ-DI)
- Totality of data does not provide substantial evidence that tofacitinib has an effect on radiographic progression
  - Evidence of radiographic benefit has not been considered necessary for approval of PsA drugs

Safety Considerations

- In general, the safety profile of tofacitinib in PsA appears consistent with the known safety profile of tofacitinib in RA
- Tofacitinib was associated with adverse events related to immunosuppression, such as serious infections and herpes zoster
  - There were also malignancies, major adverse cardiovascular events (MACE), gastrointestinal (GI) perforation, and laboratory abnormalities in the PsA development program

Issues for Consideration

- Efficacy of tofacitinib for the treatment of PsA
- Safety of tofacitinib in PsA
- Overall risk/benefit considerations and overall approval recommendation for PsA

Purpose of Proceedings Before an Advisory Committee (21 CFR 14.5)

a. An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner

b. The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee

CFR=Code of Federal Regulations


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA Arthritis Advisory Committee (AAC)
Introduction and Clinical Overview

NDA 203214 (supplement 17) and NDA 208246 (supplement 3): Tofacitinib and tofacitinib extended release for the treatment of adult patients with active psoriatic arthritis

Raj Nair, MD
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
August 3, 2017

Overview of FDA Presentations

- **Introduction and Clinical Overview**
  - Raj Nair, MD
- **Statistical Considerations on Efficacy**
  - Rebecca Rothwell, PhD
- **Summary of Safety and Risk/Benefit Considerations**
  - Raj Nair, MD

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  - 5 mg orally twice daily

Key Regulatory Interactions for PsA Program

- The Applicant initially proposed a 6-month placebo-controlled trial of tofacitinib in patients with psoriatic arthritis
- The Agency requested the study be revised so that patients would not be subject to uncontrolled disease activity and requested patients be on background DMARD therapy
- The Applicant made additional protocol modifications, but the Agency remained concerned that all patients would be at high risk of radiographic progression
- The Applicant proposed studies 1091 and 1125. In these studies, all patients received at least one background DMARD and all patients randomized to placebo advanced to tofacitinib at Month 3

Clinical Development Program for PsA

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FDA Arthritis Advisory Committee (AAC)
Statistical Considerations on Efficacy

NDA 203214 (supplement 17) and NDA 208246 (supplement 3): Tofacitinib and tofacitinib extended release for the treatment of adult patients with active psoriatic arthritis

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Office of Translational Sciences, Center for Drug Evaluation and Research
Food and Drug Administration
August 3, 2017

Outline

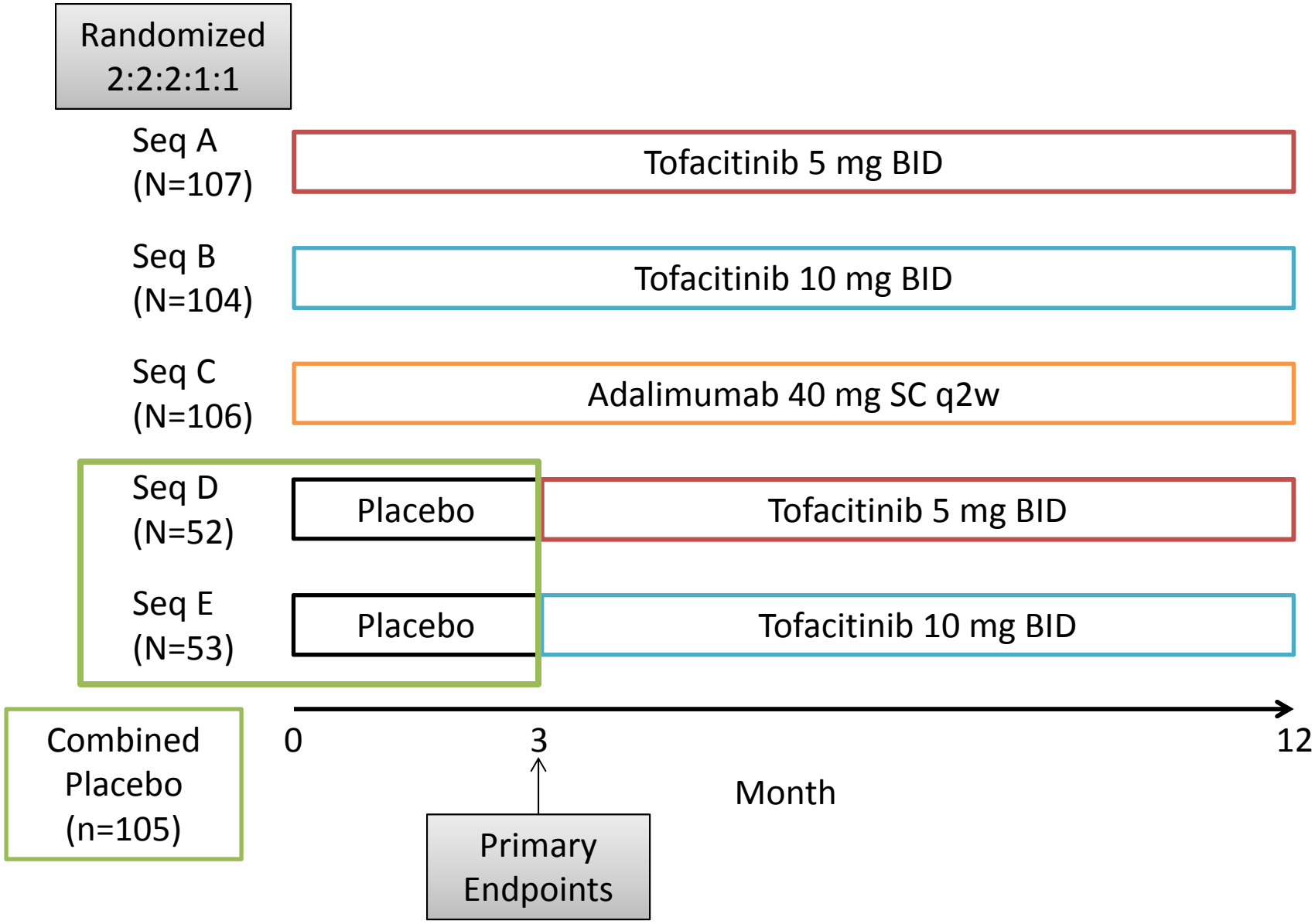
1. Overview of Efficacy Evaluation
2. Key Efficacy Results from Primary and Secondary Endpoints
   - Signs and Symptoms
   - Physical Function
   - Prevention of Radiographic Progression
3. Conclusions

Efficacy Endpoints

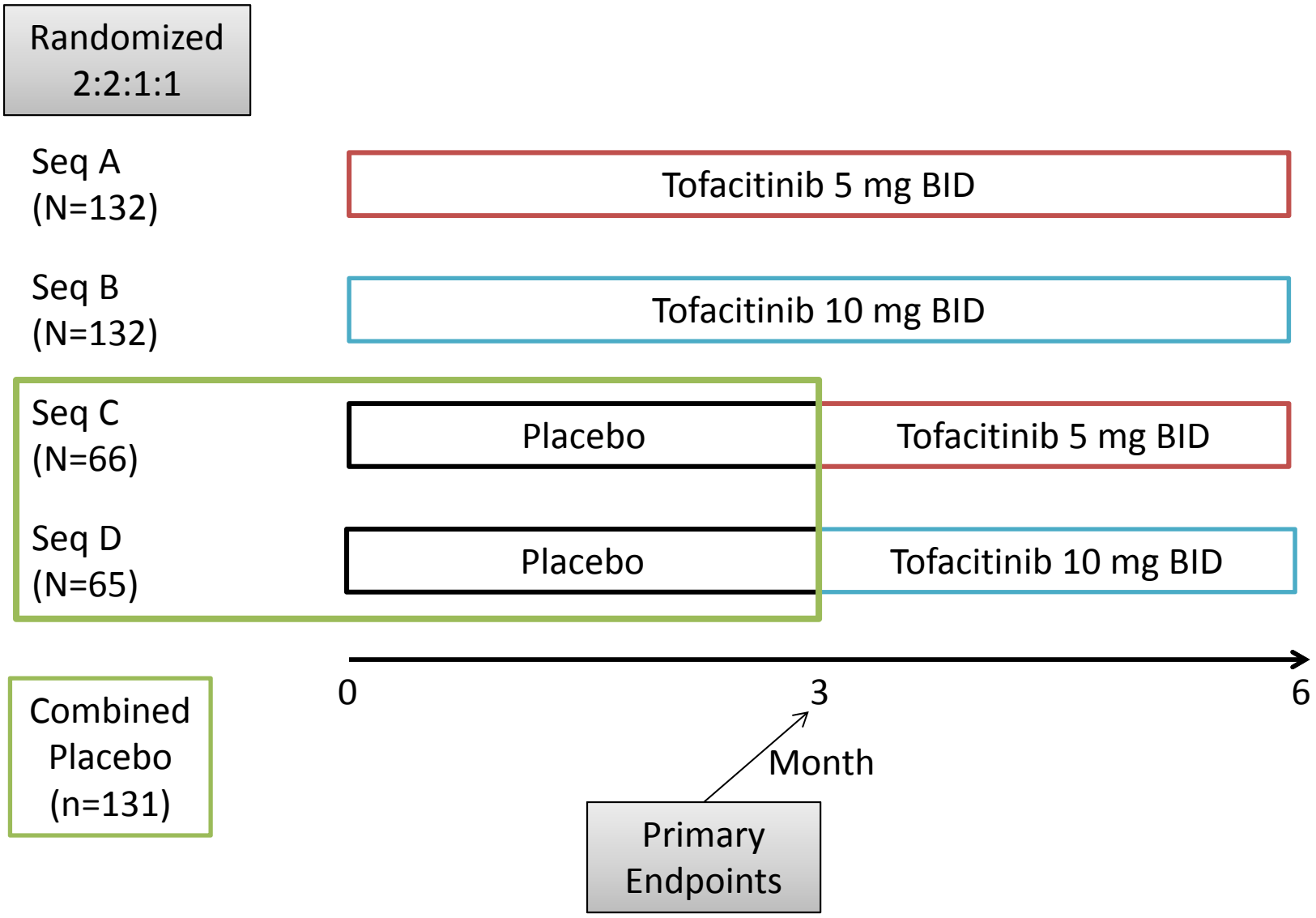
- Based on evaluation of two Phase 3, multi-center, randomized, parallel-group, double-blind, placebo-controlled studies
- Primary Endpoints:
  - Proportion of subjects with >20% improvement as defined by American College of Rheumatology (**ACR20**) at Month 3
  - Change from baseline in Health Assessment Questionnaire-Disability Index (**ΔHAQ-DI**) Score at Month 3
- Secondary endpoints included assessment of enthesitis (LEI), dactylitis (DSS), quality of life (SF-36) and radiographic outcome (mTSS)

SF-36: 36 item short form health survey, mTSS: modified total Sharp score

Reminder of Study 1091 Design



Reminder of Study 1125 Design



EFFICACY RESULTS

ACR20 Response at Month 3

Treatment group	%	Comparison to Placebo		
		Difference (%)	95% CI	p-value
Study 1091				
Placebo (N=105)	33	--	--	--
Tofa 5 mg BID (N=107)	51	17	(4, 30)	0.0102
Tofa 10 mg BID (N=104)	61	27	(14, 40)	<0.0001
Adalimumab (N=106)	52	19	(6, 32)	0.0055
Study 1125				
Placebo (N=131)	24	--	--	--
Tofa 5 mg BID (N=131)	49	26	(14, 37)	<0.0001
Tofa 10 mg BID (N=132)	47	23	(12, 35)	<0.0001

N=number randomized and received ≥ 1 dose, %=percent subjects achieving ACR20 response, CI=confidence interval, Non-Responder Imputation for missing data

Change From Baseline in HAQ-DI Score at Month 3

Treatment group	n	Adjusted Mean Change	Comparison to Placebo		
			Difference	95% CI	P-value
Study 1091					
Placebo (N=105)	102	-0.18	--	--	--
Tofa 5 mg BID (N=107)	103	-0.35	-0.17	(-0.29, -0.05)	0.0058
Tofa 10 mg BID (N=104)	103	-0.40	-0.22	(-0.34, -0.10)	0.0004
Adalimumab (N=106)	101	-0.38	-0.20	(-0.32, -0.08)	0.0009
Study 1125					
Placebo (N=131)	117	-0.14	--	--	--
Tofa 5 mg BID (N=131)	124	-0.39	-0.25	(-0.38, -0.13)	<0.0001
Tofa 10 mg BID (N=132)	120	-0.35	-0.22	(-0.34, -0.09)	0.0007

N=number randomized and received ≥ 1 dose, n= number obs. at Month 3, Adjusted Mean= Mean from mixed effect model of repeated measurements (MMRM) with treatment, visit, treatment-by-visit interaction, geographic location, and baseline value, HAQ-DI Range: 0 to 3

Mean Change from Baseline in ACR Components at Month 3

Component	Tofa 5 mg BID vs. Placebo Difference (CI)	
	Study 1091	Study 1125
Tender/Painful Joint Count (68)	-1.9 (-4.7, 0.9)	-5.4 (-8.1, -2.7)
Swollen Joint Count (66)	-1.8 (-3.4, -0.3)	-4.9 (-6.5, -3.2)
Patient's Assessment of Pain (100 mm VAS)	-11.5 (-17.6, -5.5)	-14.0 (-20.0, -8.0)
Patient's Global Assessment (100 mm VAS)	-8.9 (-17.6, -5.5)	-14.4 (-20.6, -8.3)
Physician's Global Assessment (100 mm VAS)	-5.2 (-10.4, 0.1)	-11.4 (-16.7, -6.1)
C-Reactive Protein (mg/L)	-4.8 (-6.9, -2.7)	-6.9 (-11.9, -1.9)

VAS=visual analog scale, Values in table are adjusted means from MMRM model with treatment, visit, treatment-by-visit interaction, geographic location, and baseline value

Enthesitis and Dactylitis Mean Change From Baseline at Month 3

Endpoint (Score Range)	Study 1091			Study 1125		
	Tofa 5 mg BID (N=74)	Placebo (N=65)	P-Value	Tofa 5 mg BID (N=82)	Placebo (N=91)	P-Value
Leed's Enthesitis Index Score (0 to 6)	-0.82	-0.43	0.1663	-1.34	-0.48	0.0012
Dactylitis Severity Score (0 to 60)	-3.50	-2.02	0.2263	-5.24	-1.92	0.0017

Values in table are adjusted means from MMRM model with treatment, visit, treatment-by-visit interaction, geographic location, and baseline value, N=number in analysis population (LEI analysis population limited to subjects with baseline LEI>0, DSS analysis population limited to subjects with baseline DSS>0), P-Value for Tofa 5 mg BID vs. Placebo

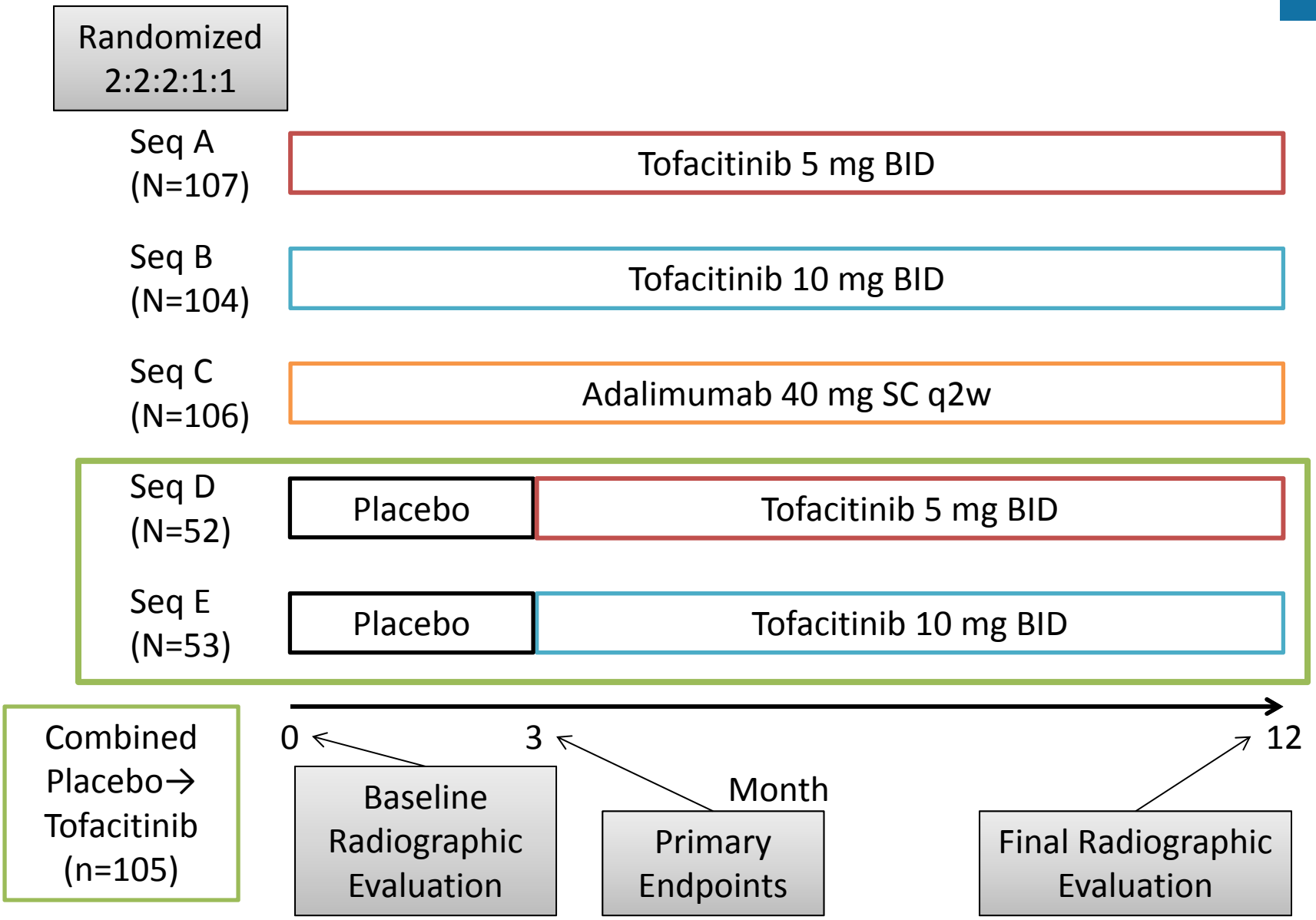
Impact of Missing Data

- At time of primary efficacy evaluation (Month 3), discontinuation was relatively low (<10% in each study)
- To explore sensitivity of results to missing data assumptions, conducted several additional analyses for the co-primary endpoints
  - Multiple imputation-jump-to-reference (ΔHAQ-DI)
  - Tipping point analysis (ACR20 response, ΔHAQ-DI)
- Missing data analyses supported significant treatment effects

RADIOGRAPHIC OUTCOME: VAN DER HEIJDE MODIFIED TOTAL SHARP SCORE[1] (MTSS)

van der Heijde D, et al. Ann Rheum Dis 2005;64(suppl II):ii61-ii64.

Reminder of Study 1091 Design



Change From Baseline in mTSS at Month 12

Treatment Group	n	Adjusted Mean	95% CI
Placebo → Tofa 5 mg BID (N=52)	48	0.001	(-0.18, 0.19)
Placebo → Tofa 10 mg BID (N=53)	45	0.093	(-0.10, 0.29)
Combined Placebo → Tofacitinib (N=105)	93	0.044	(-0.10, 0.19)
Tofa 5 mg BID (N=107)	98	0.014	(-0.12, 0.15)
Tofa 10 mg BID (N=104)	99	-0.010	(-0.14, 0.12)
Adalimumab (N=106)	95	-0.069	(-0.21, 0.07)

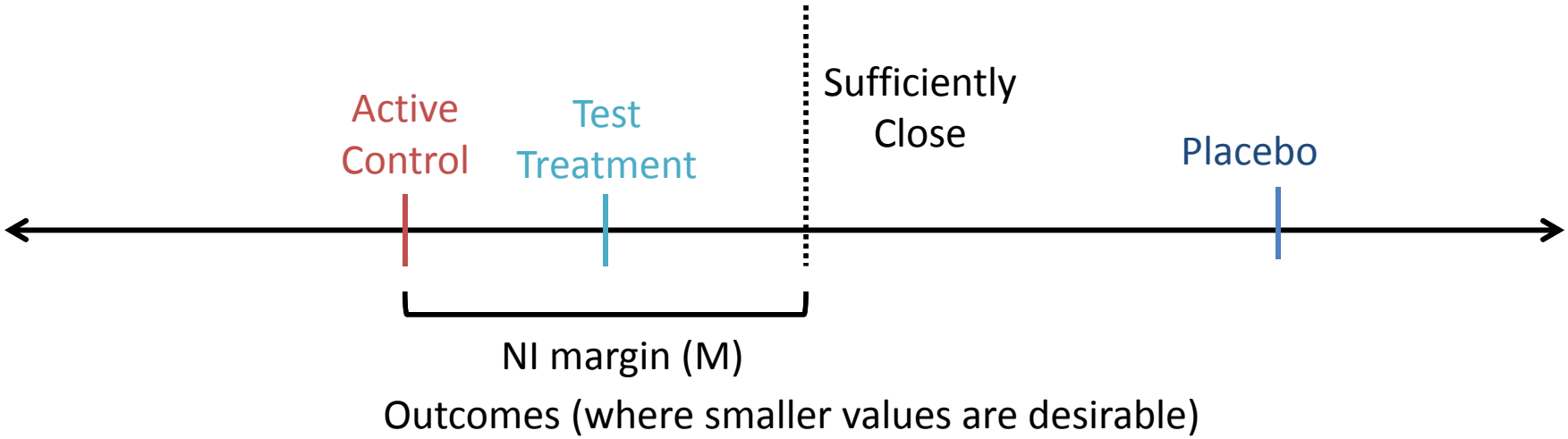
Comparison	Difference	95% CI	P-Value of Difference
Tofacitinib 5 mg vs Combined Placebo→ Tofacitinib	-0.031	(-0.20, 0.14)	0.72
Tofa 5 mg BID vs Adalimumab	0.082	(-0.08, 0.25)	0.33

N=number randomized and received ≥ 1 dose, n= number of individuals observed at Month 3, Adjusted mean= mean from ANCOVA model with treatment, geographic location, and baseline value, *=Based on ANCOVA model with 4 treatment groups: tofa 5 mg, tofa 10 mg, adalimumab, combined placebo, Linear extrapolation for missing data imputation

Evaluating Evidence of Effect on Radiographic Progression

- Superiority vs. Combined Placebo → Tofacitinib Arm
  - Difference: -0.031, P-Value: 0.72
  - Not surprising because of small sample size and 3-month placebo arm
- Non-inferiority (NI) vs. Active Comparator Adalimumab
  - Requires defining a NI margin for testing
  - Margin was not pre-specified by applicant
  - Several possible NI margin options

Non-Inferiority Tests

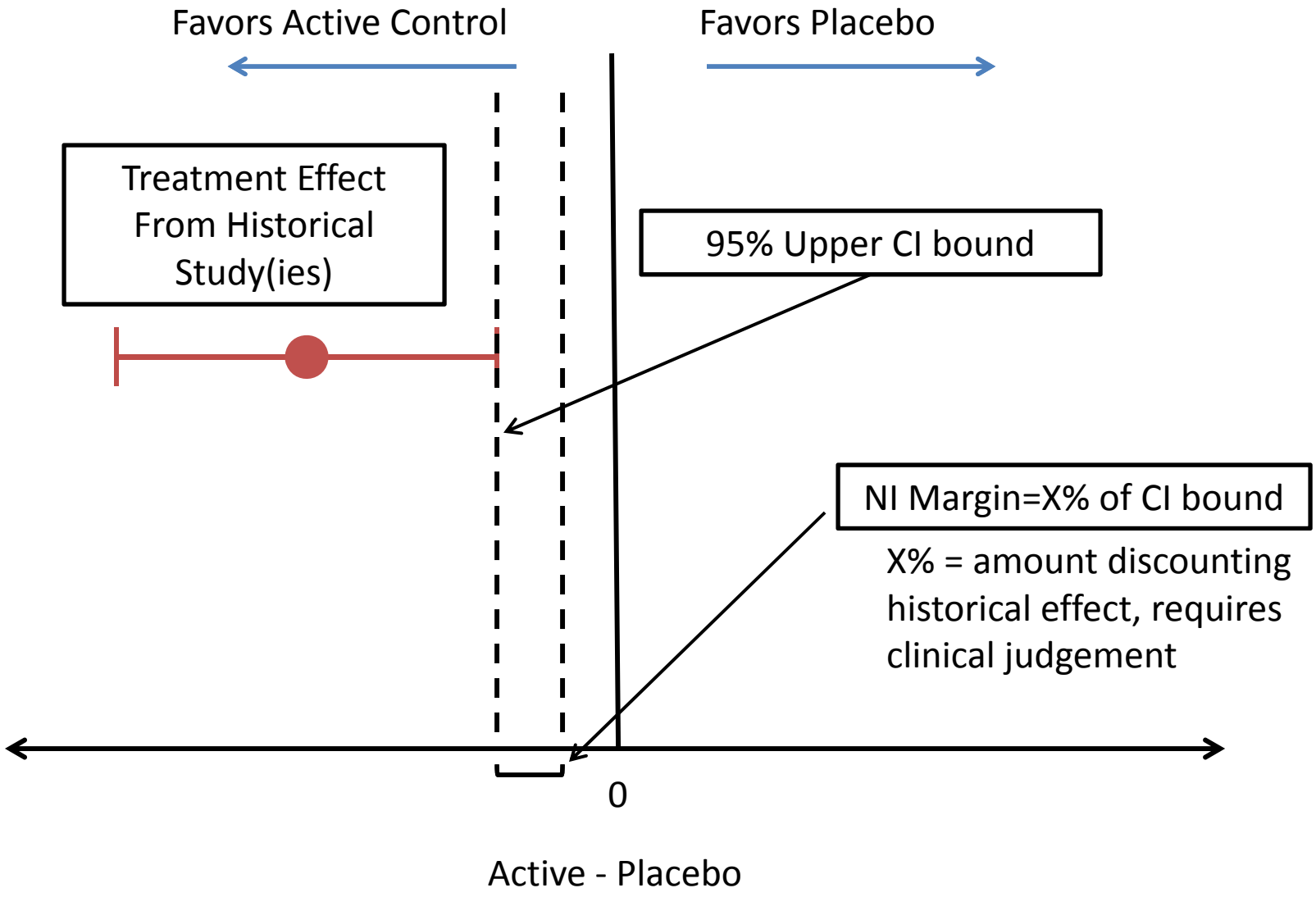


- Goal is to demonstrate that the test drug has an effect by showing **sufficiently close** to the effect of active control[1]
- Sufficiently close is determined by showing **Test Treatment-Active Control** is within a pre-specified NI margin (M)
- Determining NI margin is based on historical placebo-controlled studies of the active control

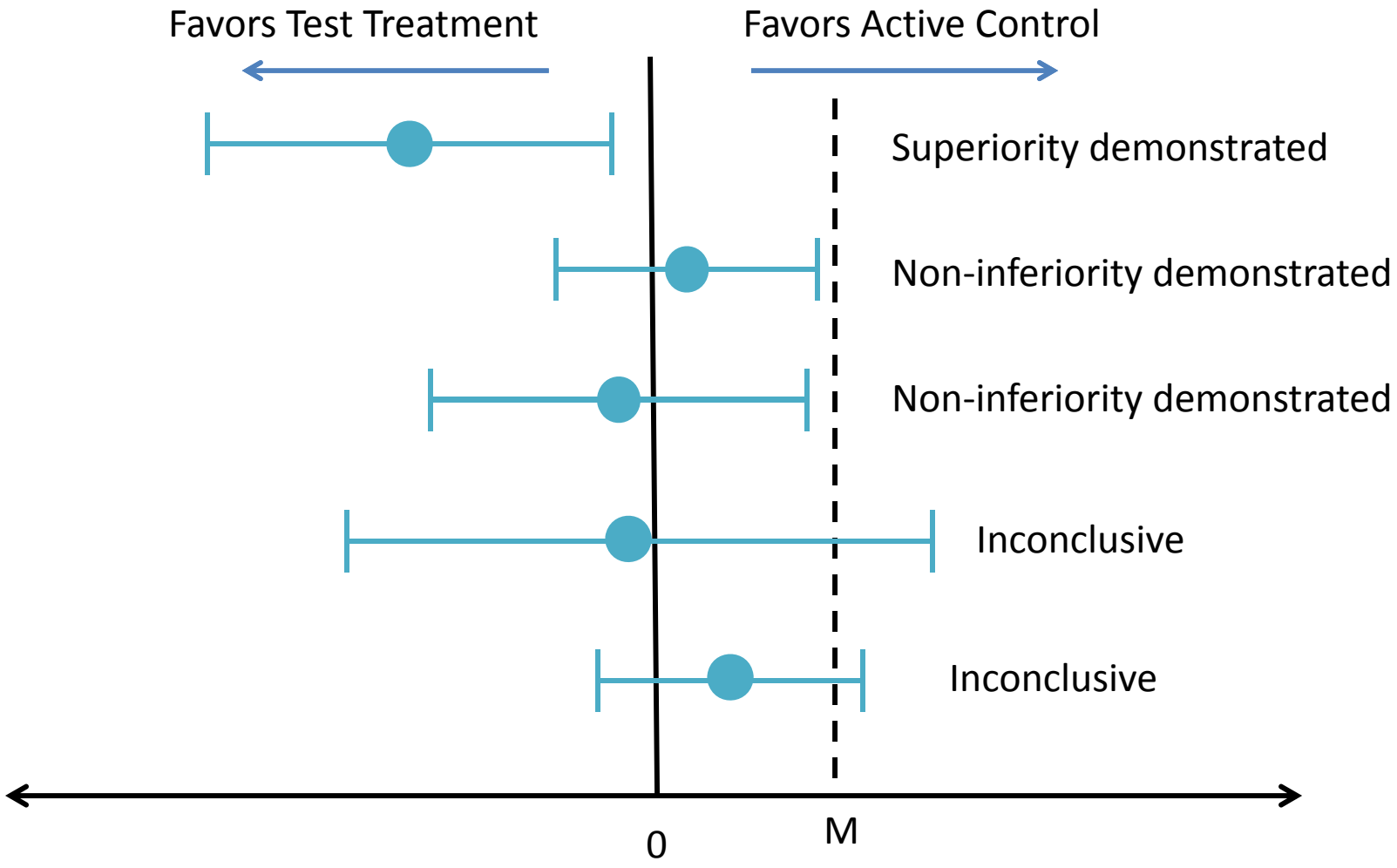
*Figure adapted from Hahn, Understanding noninferiority trials, *Kor Journal of Ped*. 2012

[1]FDA Guidance for Industry *Non-Inferiority Clinical Trials to Establish Effectiveness*

Determining a Non-Inferiority Margin



Test vs. Active Comparisons



Non-Inferiority Margin Options

1. Informed by multiple historical studies of TNF inhibitors on radiographic progression in PsA
   - Relies on assumption that historical estimate of effect across treatments is a reliable estimate of effect of adalimumab (effect is similar across TNF inhibitors)
2. Informed by adalimumab study only
   - Relies on single study (does not capture study to study variation)

Option 1: Previous Studies in mTSS

- Restrict to PsA studies of TNF inhibitors for similarity to active control adalimumab
- Calculate meta-analysis confidence intervals for average effect of active comparator in historical studies
- Use mean change from baseline in mTSS at Month 6
- Though some studies are 12 months, in each study, placebo arm crosses over to the experimental treatment at Month 6
- Expect treatment difference would be larger at later time points, therefore provides a conservative estimate

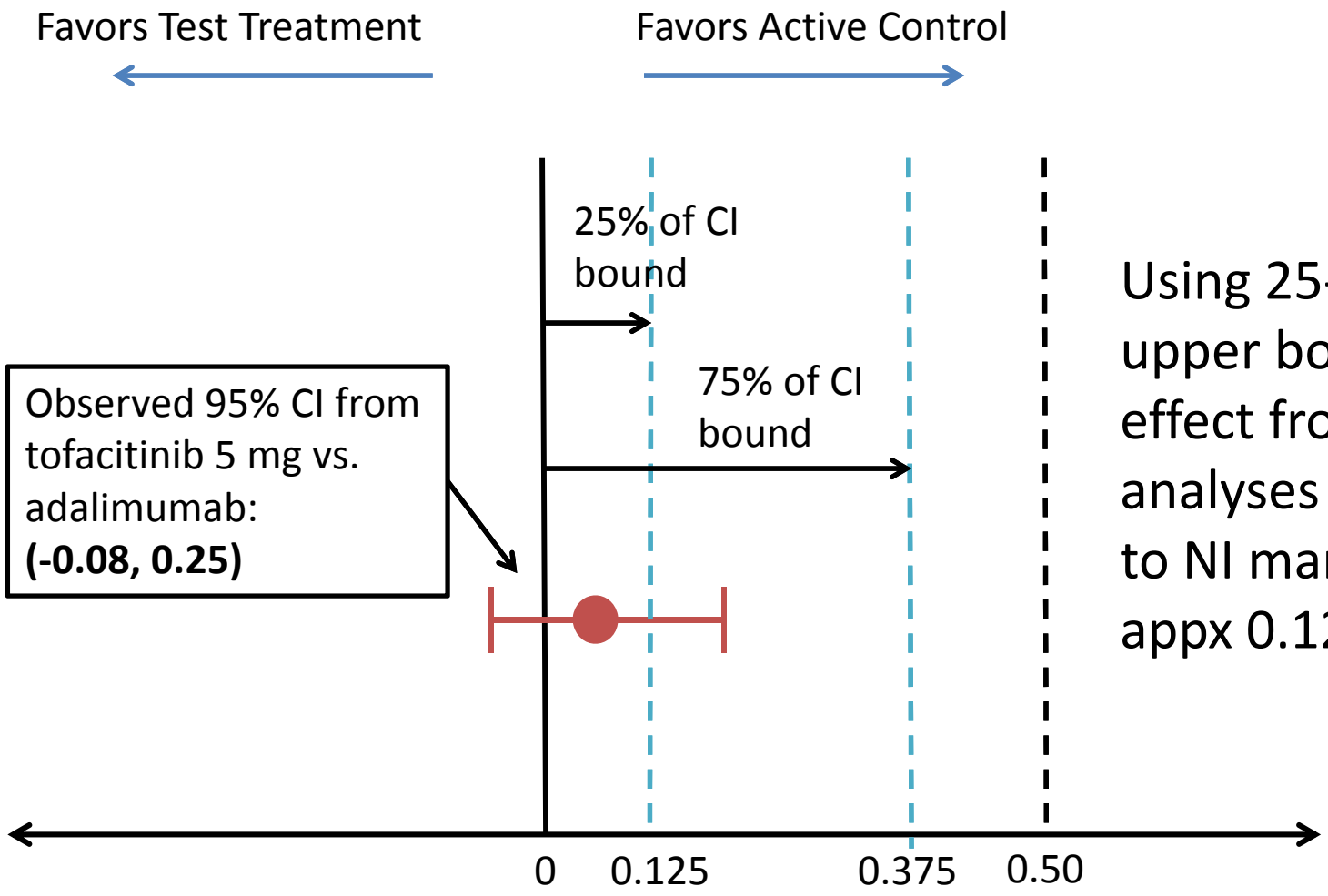
Option 1: Previous Studies in mTSS

Historical Effect of TNF Inhibitors on Mean Change from Baseline in mTSS in Randomized Clinical Trials of Adult Patients with PsA

Study	Treatment	Treatment Arm			Placebo Arm			
		N	ΔmTSS	SD	N	ΔmTSS	SD	Difference
Humira Label[1,2]	Adalimumab	133	-0.1	1.7	141	0.9	3.1	-1.0
Mease[3]	Etanercept	101	-0.05	0.5	104	0.55	0.75	-0.60
van der Heijde[4]	Infliximab	100	-0.70	2.53	100	0.82	2.62	-1.52
Kavanaugh[5]	Golimumab	146	-0.16	1.31	113	0.27	1.26	-0.43
Meta-Analysis (fixed effects): Difference (95% CI)								-0.63 (-0.77,-0.48)
Meta-Analysis (random effects): Difference (95% CI)								-0.75 (-1.09,-0.42)
Heterogeneity p-value								0.027

[1]*HUMIRA Injection Package Insert*. Abbvie Inc, (Results from ADEPT Trial)
[2]Mease, P.J., et al., Arthritis & Rheumatism, 2005.
[3]Mease, P.J., et al., Arthritis & Rheumatism, 2004.
[4]Van der Heijde, D., et al, Arthritis & Rheumatism, 2007.
[5]Kavanaugh, A., et al., Arthritis & Rheumatology, 2012.

Option 1: Test vs. Active Comparison

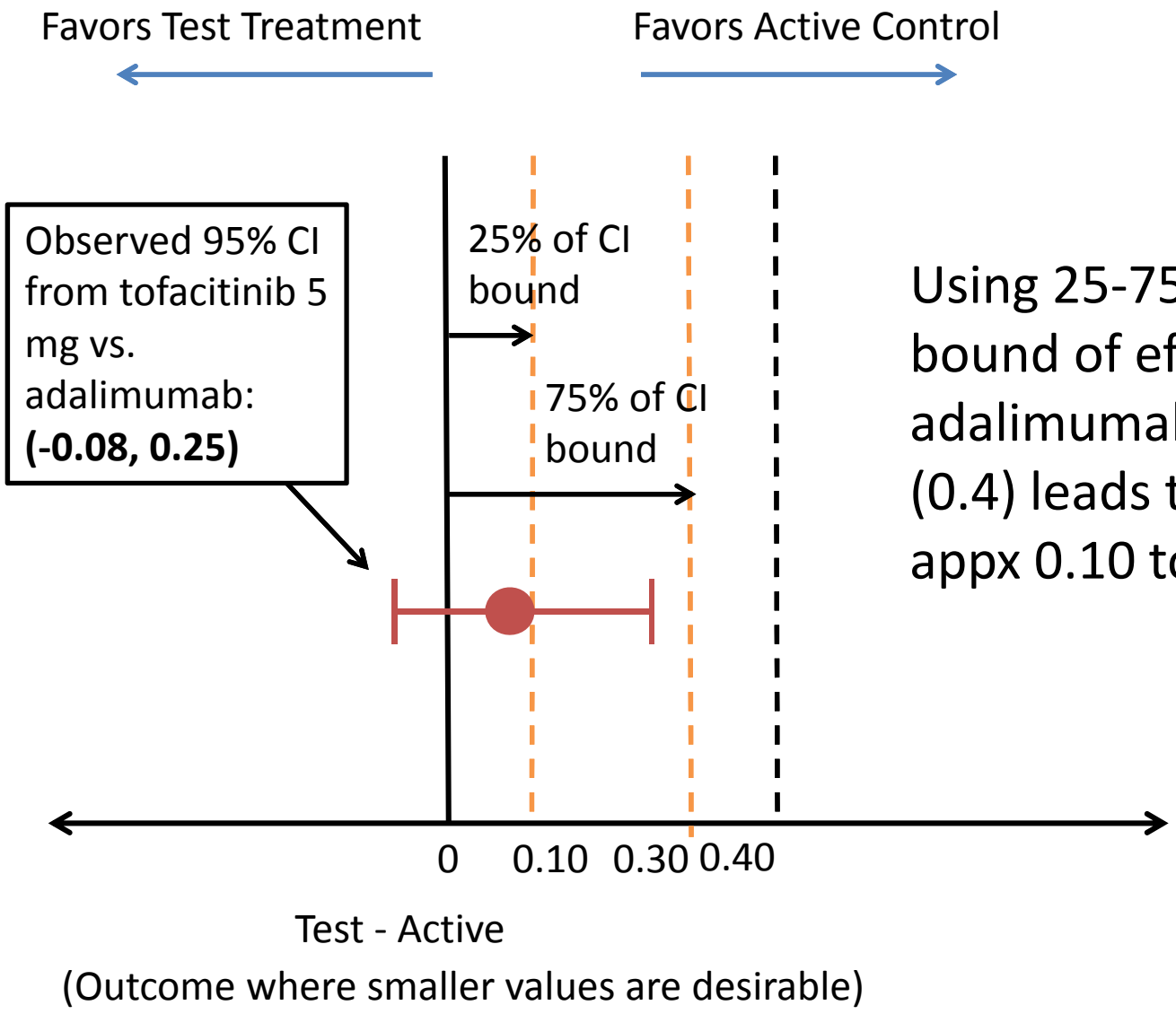


Using 25-75% of the upper bound of effect from meta-analyses (~0.5) leads to NI margins of appx 0.125 to 0.375

Option 2: Adalimumab Study Only

- Effect of adalimumab on prevention of radiographic progression in PsA evaluated in a single study
- Estimated treatment difference: -1.0
- 95% confidence interval: (-1.60, -0.40)

Option 2: Test vs. Active Comparison



Using 25-75% of the upper bound of effect from adalimumab study alone (0.4) leads to NI margins of appx 0.10 to 0.30

Additional Considerations in Selecting an NI Margin

- Single Non-Inferiority Study
- Sensitivity to Detect Differences and Level of Similarity of Current Study to Historical Studies
  - Placebo progression
  - Baseline patient characteristics

Sensitivity to Detect Differences

- Compare current study with 7 published studies of bDMARDs in PsA with Month 6 radiographs (adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab)
- Baseline CRP and mTSS previously identified as prognostic factors for radiographic progression in PsA and RA

		Study 1091 (Current Study)	Historical Studies[1-7] (7 studies)	Adalimumab Study[1] (1 study)
Placebo Progression (mean ΔmTSS)		0.04*	0.18 to 1.0	0.9
Baseline Characteristics	**Mean CRP**	10.8	12.6 to 23.0	14.0
	Mean mTSS	13.7	18.0 to 39.1	20.8

*Evaluated at Week 12

[1]Mease, P.J., et al., Arthritis & Rheumatism, 2005. (Results from ADEPT Trial, reported in Humira label)

[2]Mease, P.J., et al., Arthritis & Rheumatism, 2004.

[3]Van der Heijde, D., et al, Arthritis & Rheumatism, 2007.

[4]Kavanaugh, A., et al., Arthritis & Rheumatology, 2012

[5]Mease, P.J., et al., Ann Rheum Dis, 2014.

[6]Kavanaugh, A., et al., Ann Rheum Dis, 2014

[7]Mease, P.J., et al., New England Journal of Medicine, 2015

Radiographic Outcome Conclusions

- Totality of data does not provide substantial evidence that tofacitinib has an effect on radiographic progression
  - Superiority comparison vs. combined placebo → tofacitinib does not provide significant evidence of treatment effect
  - NI comparison vs. adalimumab is not persuasive and based on a single study
  - Observed results on placebo and patient characteristics in this study vs. observed in historical studies lead to questions about sensitivity of study to detect differences
- Larger active-controlled studies in populations enriched for progression and rigorous discussion about NI margin may provide more persuasive evidence

Overall Efficacy Conclusions

- Evidence of efficacy on signs and symptoms and function endpoints
  - Co-Primary Endpoints: ACR20 Response, HAQ-DI
  - ACR Components
  - Secondary endpoints: LEI, DSS
  - Robust to varying missing data assumptions
- No substantial evidence to support a radiographic claim though lack of progression is a positive sign and evidence of radiographic benefit not considered necessary for approval of PsA drugs

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FDA Arthritis Advisory Committee (AAC)
Summary of Safety and Risk/Benefit Considerations

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Raj Nair, MD
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
August 3, 2017

Overview of Tofacitinib Safety

- Boxed Warnings
  - **Serious infections** leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections
  - **Malignancies**, including lymphoma and other malignancies
- Warnings/Precautions
  - Serious infections, including tuberculosis and viral reactivation
  - Malignancies, lymphoproliferative disorders, and non-melanoma skin cancers
  - Gastrointestinal (GI) perforations
  - Laboratory abnormalities, including lymphocyte abnormalities, neutropenia, anemia, liver enzyme elevations, and lipid elevations
  - Vaccinations

Post-marketing Requirement

- Required at the time of approval for RA
- Controlled clinical trial to evaluate the long term safety of tofacitinib in patients with RA
  - Evaluating safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy
- Trial is ongoing
  - Estimated primary completion date: August 2019[1]
  - Estimated enrollment 4400[1] (approximately 3835 enrolled[2])

[1]https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=1&StepSize=1&Paging=Yes
[2]https://clinicaltrials.gov/ct2/show/NCT02092467?term=tofacitinib&cond=Rheumatoid+Arthritis&draw=2&rank=15

Number of Patients with and Patient-year Exposure in PsA and Other Indications

Duration of exposure	PsA	RA	PsO
At least 1 dose, n (PYs)	783 (775)	6300 (21886)	3662 (8537)
≥6 months, n	665	5406	3027
≥12 months, n	437	4904	2648
≥24 months, n	44	4158	2044

n: number of patients; PY: patient-years; PsO=psoriasis

Focus of Safety Presentation

- Deaths
- Serious Adverse Events (SAEs)
- Adverse events of special interest
  - Malignancy
  - Serious infections
  - Herpes zoster
  - Opportunistic infections
  - MACE

Safety—Study Cohorts

- **Cohort 1 (3-month placebo-controlled period)**
  - 3-month pooled data from 1125 and 1091
  - Comparisons: Tofa 5, Tofa 10, and placebo
- **Cohort 2a (12-month comparisons)**
  - Pooled data from 1125 (6 months) and 1091 (12 months)
  - Comparisons: All Tofa 5, All Tofa 10
- **Cohort 3 (all tofacitinib psoriatic arthritis)**
  - All pooled data from 1125, 1091, and 1092 (All Tofa, all doses)

Deaths in PsA Program

- 3-month placebo-controlled period
  - 0 deaths in any treatment arm

- 12-month period
  - 1 death in All Tofa 5

- All tofacitinib PsA cohort
  - 4 deaths in All Tofa, all doses (IR: 0.25/100 PYs)

Deaths in All Tofacitinib PsA Cohort

Cause of death	Gender/ Race/Age	Randomized Drug	Cumulative days on tofacitinib
Sudden cardiac death	Female/white/73	Placebo→ Tofa 5 mg BID	56
Pancreatic cancer metastatic	Male/white/54	Ada 40 mg q2w	84 (336 days on Ada)
Hypertensive heart disease	Female/white/57	Placebo→ Tofa 5 mg BID	274
Large bilateral pulmonary embolism	Female/white/46	Tofa 5 mg BID	346

SAEs in PsA Program

- 3-month placebo-controlled period
  - 4 patients with SAEs in Tofa 5 (IR: 7.4/100 PYs), 4 patients with SAEs in Tofa 10 (IR: 7.4/100 PYs), and 4 patients with SAEs in placebo (IR: 7.5/100 PYs)

- 12-month period
  - 15 patients with SAEs for All Tofa 5 (IR: 7.6/100 PYs) and 15 patients with SAEs for All Tofa 10 (IR: 7.8/100PYs)

- All tofacitinib PsA cohort
  - 65 patients with SAEs in All Tofa, all doses (IR: 8.5/100 PYs)

Malignancies (excluding NMSC) in PsA Program

- 3-month placebo-controlled period
  - 2 malignancies in Tofa 5, 0 malignancies in placebo and Tofa 10
- 12-month period
  - 3 malignancies for All Tofa 5 (IR: 1.5/100 PYs) and 0 malignancies for All Tofa 10
- All tofacitinib PsA cohort
  - 5 malignancies in All Tofa, all doses (IR: 0.63/100 PYs)

NMSC=non-melanoma skin cancer

Malignancy (excluding NMSC) in All Tofacitinib PsA Cohort

Preferred term	Gender/ Race/Age	Treatment randomized to	Cumulative days on tofacitinib
Bladder transitional cell carcinoma	Male/white/58	Tofa 5 mg BID	48
Renal cell carcinoma	Male/other/44	Ada 40 mg q2w	32 (342 days on Ada)
Pancreatic carcinoma metastatic	Male/white/54	Ada 40 mg q 2w	84 (336 days on Ada)
Squamous cell carcinoma of vulva	Female/white/65	Tofa 5 mg BID	65
Invasive ductal breast carcinoma	Female/white/67	Tofa 5 mg BID	244

Serious Infections in PsA Program

- 3-month placebo-controlled period
  - 2 patients with serious infections in Tofa 10 (IR: 3.7/100PYs), 0 serious infections in placebo and Tofa 5
- 12-month period
  - 4 patients with serious infections for All Tofa 5 (IR: 2/100 PYs) and 3 patients with serious infections for All Tofa 10 (IR: 1.5/100 PYs)
- All tofacitinib PsA cohort
  - 11 patients with serious infections in All Tofa, all doses (IR: 1.4/100 PYs)

Herpes Zoster in PsA Program

- 3-month placebo-controlled period
  - 2 patients with herpes zoster in Tofa 5 (IR: 3.67/100 PYs) and 1 patient with herpes zoster in Tofa 10 (IR: 1.85/100 PYs); 0 herpes zoster events in placebo
- 12-month period
  - 3 patients with herpes zoster for All Tofa 5 (IR: 1.2/100 PYs) and 4 patients with herpes zoster for All Tofa 10 (IR: 2.0/100 PYs)
- All tofacitinib PsA cohort
  - 16 patients with herpes zoster in All Tofa, all doses (IR: 2.1/100 PYs)

Opportunistic Infections in PsA Program

- 3-month placebo-controlled period
  - 1 patient with opportunistic infection in Tofa 5 (IR: 1.8/100 PYs), 0 events in Tofa 10 and placebo
- 12-month period
  - 1 patient with opportunistic infection for All Tofa 5 (IR: 0.5/100 PYs) and 0 events in All Tofa 10
- All tofacitinib PsA cohort
  - 3 patients with opportunistic infections in All Tofa, all doses (IR: 0.4/100 PYs)

MACE in PsA Program

- 3-month placebo-controlled period
  - 0 events in all arms

- 12-month period
  - 1 patient with MACE for All Tofa 5 (IR 0.5/100 PYs) and 1 patient with MACE for All Tofa 10 (IR 0.5/100PYs)

- All tofacitinib PsA cohort
  - 3 patients with MACE in All Tofa, all doses (IR 0.4/100 PYs)

Adverse Events of Special Interest from Study 1091

	Study 1091								
	All Tofa 5 mg bid N=159 PY=127			All Tofa 10 mg bid N=154 PY=124			Ada 40 mg q2w N=106 PY=93		
Safety Event	n	%	IR (95% CI)	n	%	IR (95% CI)	n	%	IR (95% CI)
Malignancies (excl NMSC)	3	1.9	2.4 (0.5, 6.9)	0	0	0 (0, 3)	0	0	0 (0, 4)
Serious infections	2	1.3	1.6 (0.2, 5.7)	1	0.6	0.8 (0, 4.5)	1	0.9	1.1 (0, 6)
Herpes zoster	2	1.3	1.6 (0.2, 5.7)	2	1.3	1.6 (0.2, 5.8)	0	0	0 (0, 4)
Opportunistic infection	1	0.6	0.7 (0, 3.6)	0	0	0	0	0	0
MACE	1	0.6	0.8 (0, 4.4)	0	0	0 (0, 3)	1	0.9	1.1 (0, 6)

CI: confidence interval; NMSC: non-melanoma skin cancer

Overview of Tofacitinib Safety

- Boxed Warnings
  - **Serious infections** leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections
  - **Malignancies**, including lymphoma and other malignancies
- Warnings/Precautions
  - Serious infections, including tuberculosis and viral reactivation
  - Malignancies, lymphoproliferative disorders, and non-melanoma skin cancers
  - Gastrointestinal (GI) perforations
  - Laboratory abnormalities, including lymphocyte abnormalities, neutropenia, anemia, liver enzyme elevations, and lipid elevations
  - Vaccinations

Safety Conclusions

- In general, the safety profile of tofacitinib in PsA appears consistent with known tofacitinib safety profile in RA
- Tofacitinib was associated with adverse events related to immunosuppression, such as serious infections and herpes zoster
  - There were also malignancies, MACE, GI perforation, and laboratory abnormalities in the PsA development program

RISK/BENEFIT CONSIDERATIONS

Tofacitinib for PsA

Benefits

- Superior to placebo for physical function and signs and symptoms

Risks

- Serious infections
- Herpes zoster, opportunistic infections
- Malignancies
- GI perforations
- Laboratory abnormalities

Other considerations

- Totality of data does not provide substantial evidence that tofacitinib has an effect on radiographic progression


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FDA Arthritis Advisory Committee
Charge to the Committee

NDA 203214 (supplement 17) and NDA 208246 (supplement 3): Tofacitinib and tofacitinib extended release for the treatment of adult patients with active psoriatic arthritis

Janet Maynard, MD, MHS
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
August 3, 2017

Efficacy Considerations

- Efficacy for signs and symptoms (ACR Responses) and physical function (HAQ-DI)
- Totality of data does not provide substantial evidence that tofacitinib has an effect on radiographic progression
  - Evidence of radiographic benefit has not been considered necessary for approval of PsA drugs

Safety Considerations

- In general, the safety profile of tofacitinib in PsA appears consistent with the known safety profile of tofacitinib in RA
- Tofacitinib was associated with adverse events related to immunosuppression, such as serious infections and herpes zoster
  - There were also malignancies, major adverse cardiovascular events (MACE), gastrointestinal (GI) perforation, and laboratory abnormalities in the PsA development program

Approval of an Application
21 CFR 314.105 (c)

- “FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling”

Efficacy Standard
21 CFR 314.125 Refusal to Approve an Application

- (b) (5) "… substantial evidence consisting of adequate and well-controlled investigations … that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Safety Standard
21 CFR 314.125 Refusal to Approve an Application

(b) (2) "… do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b) (3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b) (4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Question 1 (Discussion)

- Discuss the efficacy of the proposed dose of tofacitinib for adult patients with active psoriatic arthritis. In your discussion, comment on the following:

  a. The overall efficacy of tofacitinib with respect to signs and symptoms and physical function for adult patients with psoriatic arthritis.

  b. The evaluation of the effect of tofacitinib on radiographic progression in psoriatic arthritis.

Question 2 (Discussion)

- Discuss the safety of tofacitinib for the treatment of adult patients with active psoriatic arthritis.

Question 3 (Vote)

- Overall, do the data provide substantial evidence of the efficacy of tofacitinib for the treatment of adult patients with active psoriatic arthritis?

  a. If not, what further data should be obtained?

Question 4 (Vote)

- Is the safety profile of tofacitinib adequate to support approval of tofacitinib for the treatment of adult patients with active psoriatic arthritis?

  a. If not, what further data should be obtained?

Question 5 (Vote)

- Do you recommend approval of the proposed dose of tofacitinib for the treatment of adult patients with active psoriatic arthritis?


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