FDA Arthritis Advisory Committee Meeting May 9, 2012: Introductory Remarks

NDA 203214: Tofacitinib for Rheumatoid Arthritis (RA)

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Center for Drug Evaluation and Research

Tofacitinib

- New Molecular Entity (NME)
- New drug class for RA
- Small molecule inhibitor of Janus Kinase (JAK) family kinases for oral administration
- Pharmacokinetic (PK) profile
  - T_{max}: ~0.5 to 1 hour
  - $T_{1/2}$: ~3 hours

Proposed Usage

- Indications and Usage:
  - "Treatment of adult patients with moderately to severely active RA who have had inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs)."
- Dosage and Administration:
  - "The recommended starting dose is 5 mg two times a day. Some patients may benefit from an increase to 10 mg two times a day based on clinical response."

Pivotal Dose Ranging Studies

Pivotal Dose-Ranging Studies				
Protocol	**Design**	**N**	**Treatment Arms**	**Endpoints**
1025				
MTX-IR ***Background MTX***	**R, DB, PC** **6 month**	**509**	**Placebo** **CP BID: 1, 3, 5, 10, 15 mg** **CP QD: 20 mg**	**ACR20 at Week 12**
1035				
DMARD-IR ***Monotherapy***	**R, DB, AC** **6 month**	**386**	**Placebo** **CP BID: 1, 3, 5, 10, 15 mg** **Adalimumab**	**ACR20 at Week 12**

- Primarily investigated dose range with BID dosing interval
- 5 and 10 mg BID doses were selected for Phase 3

Key: MTX-IR= Methotrexate Incomplete Response; R=randomized; DB=double-blind; PC=placebo-controlled; BID=twice daily; QD=once daily; ACR20= American College of Rheumatology 20% Improvement Criteria;

Pivotal Efficacy Studies in RA

Protocol	Design	N	Treatment Arms	Primary EP	Timepoint
Patients with TNF-Incomplete Responders (IR)					
A3921032	R, DB, PC 6 months *Background MTX*	399	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with DMARD (MTX)-IR					
A3921044	R, DB, PC 2 years* *Background MTX*	797	CP 5 mg BID CP 10 mg BID PBO	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921046	R, DB, PC 1 year *Background DMARD*	792	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064	R, DB, AC 1 year *Background MTX*	717	CP 5 mg BID CP 10 mg BID PBO Adalimumab	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921045	R, DB, PC 6 months *Monotherapy*	610	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3

Key: HAQ-DI = Health Assessment Questionnaire Disability Index; DAS28 = Disease Activity Score; mTSS = Modified Total Sharp Score; PBO = placebo; CP = tofacitinib

Efficacy Considerations

- Efficacy for signs and symptoms (ACR Responses, DAS28) and physical function (HAQ-DI) endpoints
- Uncertainty regarding radiographic outcome results
  - Low amount of progression in the placebo control group limiting the treatment effect size that could be demonstrated
  - Small treatment effect size is susceptible to outliers, analytical approach, missing data, and imputation method
  - Data are not consistent with respect to dose
  - Corroborating data are not available to help resolve residual uncertainty

Safety Considerations

- Malignancy
  - Increased risk over time
  - Increased risk of lymphoma
- Serious infection
  - Increased risk, including opportunistic infections
- Laboratory Abnormalities
  - Decreased hematologic parameters
    - Lymphopenia associated with infections
  - Lipid increases
  - Serum creatinine elevation

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

Risk-Benefit Considerations

- Treatment effect on radiographic outcomes
  - How well does tofacitinib actually work in reducing structural damage, and does dose matter?
- Malignancy and infection findings
  - Increased risk, does dose matter?
- What is the optimal dose and dosing interval?
  - Dose-ranging studies suggest lower doses may be efficacious, and PK profile of the product suggests a more frequent dosing interval may allow for even lower nominal doses

Arthritis Advisory Committee Meeting
NDA 203,214
Tofacitinib (CP-690,550) Tablets for Rheumatoid Arthritis

Overview of the Clinical Program and Efficacy Considerations

Nikolay P. Nikolov, M.D.
Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
May 9, 2012

Outline

- Overview of the Clinical Program and Efficacy Considerations

  Nikolay P. Nikolov, M.D.
  Clinical Reviewer, DPARP, CDER, FDA

- Statistical Summary of Radiographic Endpoint Results

  Yongman Kim, Ph.D.
  Statistical Reviewer, DB II, CDER, FDA

- Safety Considerations and Risk-Benefit

  Nikolay P. Nikolov, M.D.
  Clinical Reviewer, DPARP, CDER, FDA

The Proposed Product

- Tofacitinib (CP-690,550) tablets
- Inhibitor of Janus kinase (JAK) family of kinases
- New molecular entity
- Proposed indication:

  "Treatment of adult patients with moderately to severely active RA who have had inadequate response to one or more DMARDs."
- Proposed dosing:

  "Starting dose is 5 mg two times a day. Some patients may benefit from an increase to 10 mg two times a day based on clinical response."

Clinical Pharmacology

- Immediate release formulation
- $T_{1/2}$ is about 3 hours
- T_{max} is about 0.5-1 hour post-dose
- Steady-state by 24-48 hours with multiple dosing
- Extensively metabolized, primarily by CYP3A4
- Excretion: ~80% by the kidneys
- Linear PK in the dose range of 1 to 100 mg
- Pharmacodynamic (PD) profile does not match PK

Dose-Ranging Studies

Pivotal Dose-Ranging Studies				
Protocol	**Design**	**N**	**Treatment Arms**	**Endpoints**
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DMARD-IR ***Monotherapy***	**R, DB, AC** **6 month**	**386**	**Placebo** **CP BID: 1, 3, 5, 10, 15 mg** **Adalimumab**	**ACR20 at Week 12**

Dose-Ranging Studies

Study 1025

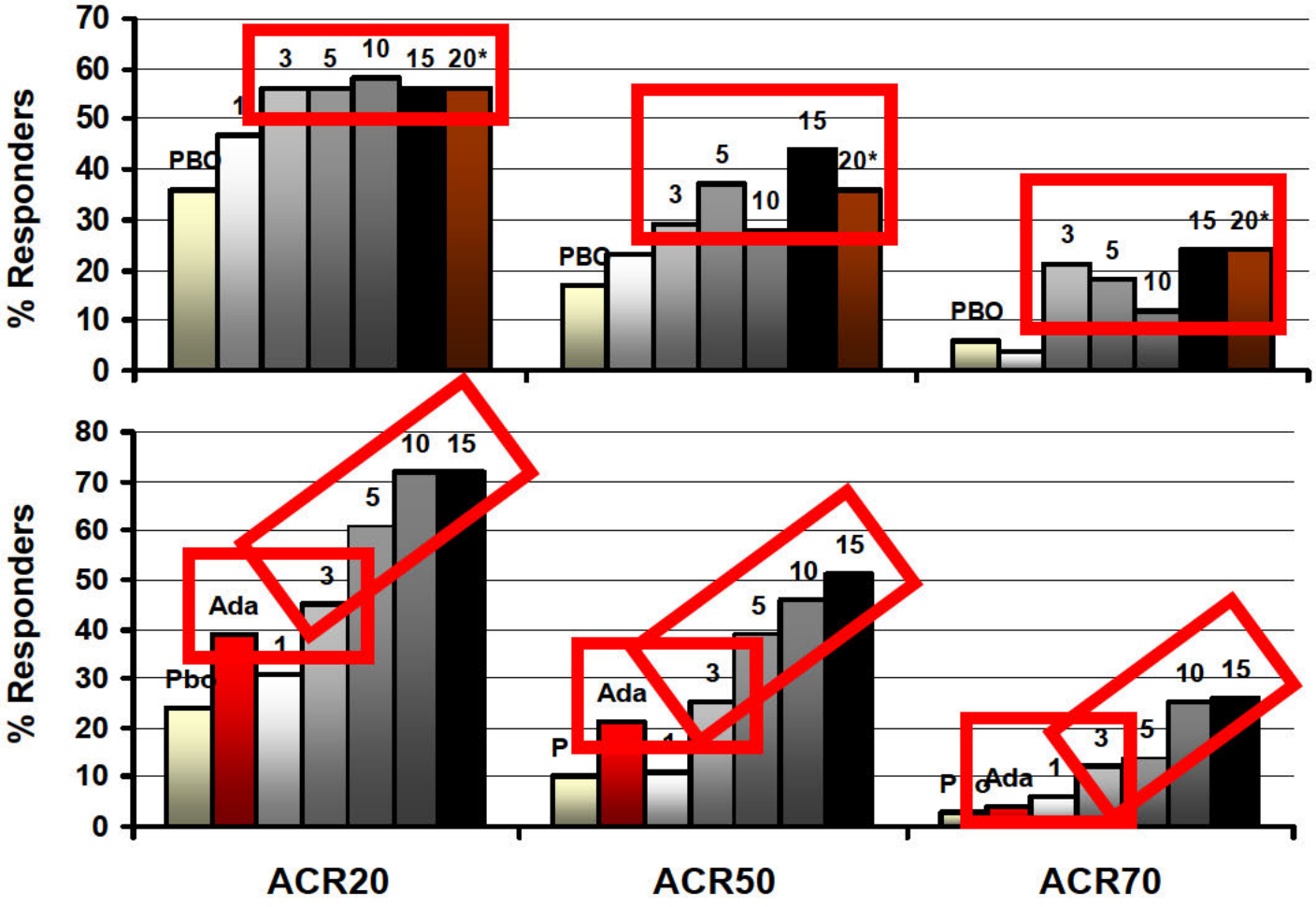
MTX background

***-QD dosing**

Study 1035

Monotherapy

Ada (adalimumab)



Phase 3 Efficacy Trials

Protocol	Design	N	Treatment Arms	Primary EP	Timepoint
Patients with TNF-Incomplete Response (IR)					
1032	R, DB, PC 6 months *Background MTX*	399	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with DMARD (MTX)-IR					
1044	R, DB, PC 2 years* *Background MTX*	797	CP 5 mg BID CP 10 mg BID PBO	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
1046	R, DB, PC 1 year *Background DMARD*	792	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
1064	R, DB, AC 1 year *Background MTX*	717	CP 5 mg BID CP 10 mg BID PBO Adalimumab	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
1045	R, DB, PC 6 months *Monotherapy*	610	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3

EP = endpoint

Evaluation of Efficacy

- Two doses of tofacitinib (5 mg and 10 mg BID) were tested for superiority over placebo-control
- All 5 Phase 3 studies assessed:
  - ACR20 response rates at Month 3 or 6
  - DAS28-4(ESR)<2.6 rates at Month 3 or 6
  - HAQ-DI, change from baseline at Month 3
- Study 1044 assessed:
  - mTSS, change from baseline at Month 6
- Step-down, gate-keeping strategy was used to control for multiplicity

ESR= Erythrocyte Sedimentation Rate

ACR Response Rates

ACR Responders in Phase 3 RCT (FAS Population, NRI)								
	PBO	DMARD		Mono		ADA	p-value*	
		CP5	CP10	CP5	CP10		CP5	CP10
1032	TNF-Incomplete Response (IR), Background MTX						Month 3	
ACR20	24	42	48	-	-	-	0.0025	<0.0001
ACR50	8	26	28	-	-	-	<0.0001	<0.0001
ACR70	2	14	11	-	-	-	0.0001	0.0017
1044	DMARD (MTX)-IR, Background MTX						Month 6	
ACR20	25	51	62	-	-	-	<0.0001	<0.0001
ACR50	8	32	44	-	-	-	<0.0001	<0.0001
ACR70	1	15	22	-	-	-	<0.0001	<0.0001
1046	DMARD (MTX)-IR, Background DMARDs						Month 6	
ACR20	31	53	58	-	-	-	<0.0001	<0.0001
ACR50	13	34	37	-	-	-	<0.0001	<0.0001
ACR70	3	13	16	-	-	-	<0.0001	<0.0001
1064	DMARD (MTX)-IR, Background MTX						Month 6	
ACR20	28	52	53	-	-	47	<0.0001	<0.0001
ACR50	12	37	35	-	-	28	<0.0001	<0.0001
ACR70	2	20	22	-	-	9	<0.0001	<0.0001
1045	DMARD (MTX)-IR, Monotherapy						Month 3	
ACR20	27	-	-	60	66	-	<0.0001	<0.0001
ACR50	13	-	-	31	37	-	<0.0001	<0.0001
ACR70	6	-	-	15	20	-	0.0026	<0.0001

Key: FAS = Full Analysis Set; NRI = Non-Responder Imputation

DAS28 <2.6

Proportion of Patients, (%) Achieving DAS28-4(ESR) <2.6 Responders in Phase 3 RCT (FAS Population, NRI)								
Study	PBO	DMARD		Mono		ADA	p-value*	
		CP5	CP10	CP5	CP10		CP5	CP10
1032	TNF-Incomplete Response (IR), Background MTX						Month 3	
	2	7	9	-	-	-	0.0497	0.0105
1044	DMARD (MTX)-IR, Background MTX						Month 6	
	2	7	18	-	-	-	0.0035	<0.0001
1046	DMARD (MTX)-IR, Background DMARDs						Month 6	
	3	9	13	-	-	-	0.0038	<0.0001
1064	DMARD (MTX)-IR, Background MTX						Month 6	
	1	6	13	-	-	7	0.0151	<0.0001
1045	DMARD (MTX)-IR, Monotherapy						Month 3	
	4	-	-	6	9	-	0.6179	0.1042

HAQ-DI Response

Mean Change from Baseline in HAQ-DI in Phase 3 RCT (FAS Population)								
Study	PBO	DMARD		Mono		ADA	p-value*	
		CP5	CP10	CP5	CP10		CP5	CP10
1032	TNF-Incomplete Response (IR), Background MTX						Month 3	
	-0.23	-0.47	-0.49	-	-	-	0.0002	<0.0001
1044	DMARD (MTX)-IR, Background MTX						Month 6	
	-0.15	-0.4	-0.57	-	-	-	<0.0001	<0.0001
1046	DMARD (MTX)-IR, Background DMARDs						Month 6	
	-0.21	-0.47	-0.57	-	-	-	<0.0001	<0.0001
1064	DMARD (MTX)-IR, Background MTX						Month 6	
	-0.25	-0.56	-0.64	-	-	-0.51	<0.0001	<0.0001
1045	DMARD (MTX)-IR, Monotherapy						Month 3	
	-0.19	-	-	-0.5	-0.57	-	<0.0001	<0.0001

Signs and Symptoms and Physical Function

- Phase 3 studies provided consistent evidence of a treatment benefit with tofacitinib 5 mg and 10 mg BID for
  - Signs and symptoms of RA, based on:
    - ACR20, 50, and 70 response rates and
    - Proportion of patients achieving DAS28-4(ESR)<2.6
  - Physical function, based on change from baseline in HAQ-DI scores

Radiographic Endpoint

- Uncertainty regarding radiographic outcome results
  - Low amount of progression in the placebo control group limiting the treatment effect size that could be demonstrated
  - Small treatment effect size is susceptible to outliers, analytical approach, missing data, and imputation method
  - Data are not consistent with respect to dose
  - Corroborating data are not available to help resolve residual uncertainty

Outline

- Overview of the Clinical Program and Efficacy Considerations

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Statistical Summary of Radiographic Endpoint Results

Yongman Kim, Ph.D.
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Center for Drug Evaluation and Research, FDA
May 9, 2012

Outline

Focus: Radiographic Endpoint from Study 1044

- Overview of Results
- Statistical Analysis Plan
- Radiographic Endpoint Results
- Issues
  - Extreme observations
  - Excluded Data
- Summary

Overview of Results – Study 1044

- There is evidence that CP 10 mg and CP 5 mg may have some activity on radiographic progression. However, there is uncertainty associated with the results for the following reasons:
  - Less progression in the placebo control group limiting the treatment effect size that could be demonstrated
  - Less than 40% of patients had some change in mTSS from baseline and only 16% of patients had some improvement in radiographic scores
  - Data are not consistent with respect to dose
  - The magnitude of effect in CP 10 mg group is sensitive to outliers
  - It is unclear how excluded data may affect the overall conclusion
  - The evidence for an effect in radiographic progression is from a single study

Statistical Analysis Plan

- Primary endpoint: mTSS change from baseline to Month 6
  - mTSS (0 – 448) = Erosion score (0 – 280) + Joint Space Narrowing score (0 – 168)
- Primary Statistical Model:
  - ANCOVA with adjustment for region and baseline score
  - Comparing group means of CP doses to placebo
- Secondary Analysis Statistical Model:
  - Rank-based ANCOVA with adjustment for region and *ranked* baseline score
  - Comparing group mean ranks of CP doses to placebo
- Missing data handling: Linear Extrapolation with valid Baseline & Month 3 (or discontinuation visit) data

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Primary Analysis: ANCOVA

Treatment	N	LS Mean Change from Baseline	Difference vs. PBO		
			LS Mean	95% CI	P-value
CP 5 mg	278	0.12	-0.34	(-0.73, 0.04)	0.079
CP 10 mg	290	0.06	-0.40	(-0.79, -0.02)	0.038
PBO	140	0.47			

Excerpted from the clinical study report A3921044: Table 14.2.15.1.6
LS mean, 95% CI, and p-value are obtained from analysis of covariance with region and baseline score as covariates

LS Mean = Least Squares Mean

Summary: Results from Primary Analysis

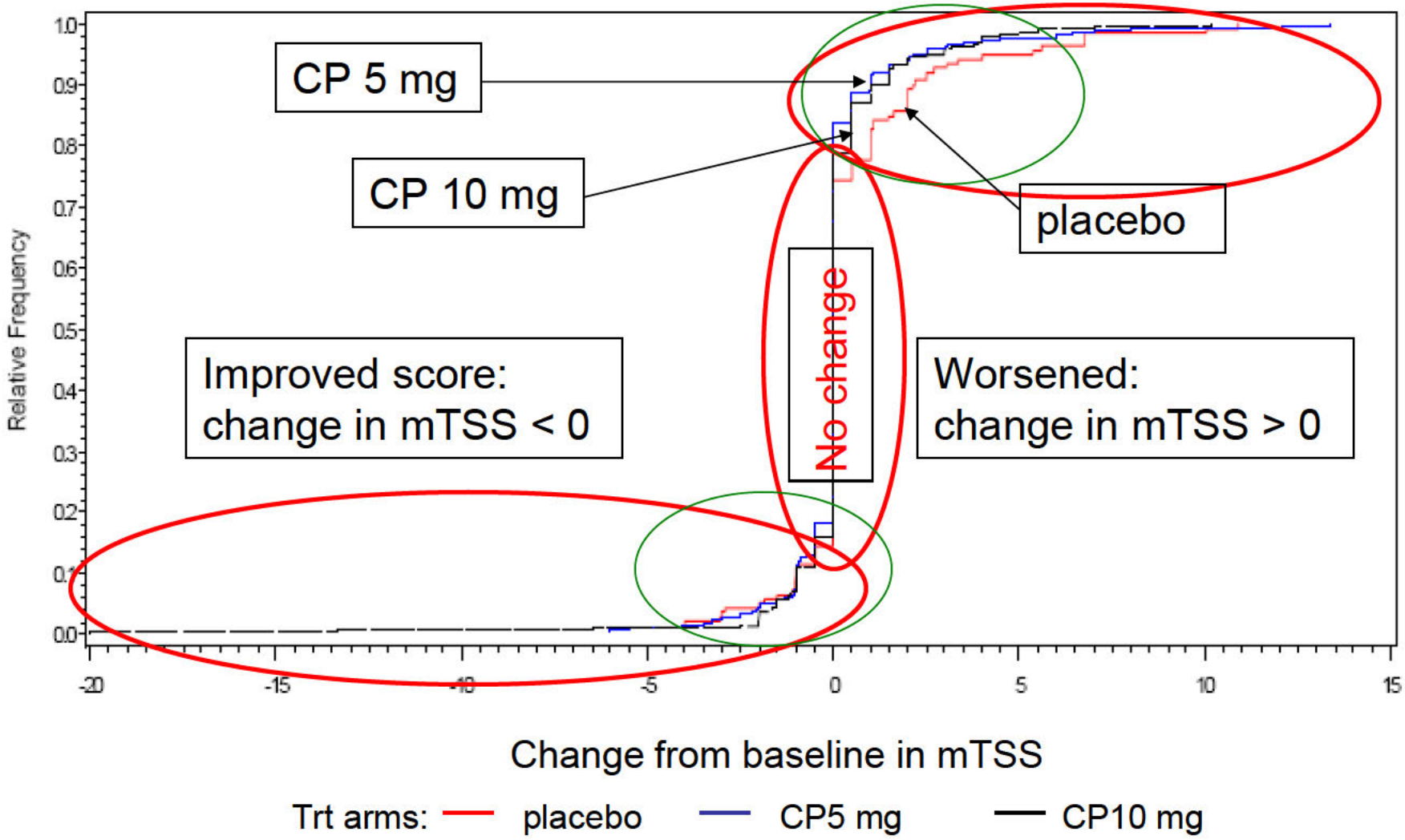
- While the effect is statistically significant for the 10 mg group compared to placebo, the estimated effect is smaller compared to what was assumed when powering for this study (0.4 versus 0.8 units, respectively)
- The placebo group also had less progression compared to what was assumed (0.5 versus 1.4 units, respectively)
- Because the treatment effect is small, additional analyses were conducted to examine the proportion of patients who actually benefit

Responder Analysis #1: Rates of 'No Progression'

Treatment	N	n	Rate	Difference vs. PBO	P-value
Change in mTSS ≤ 0.5* (Applicant's)					
CP 5 mg	278	246	88%	11%	0.003
CP 10 mg	290	252	87%	9%	0.017
PBO	140	108	77%		
Change in mTSS ≤ 0 (Reviewer's)					
CP 5 mg	278	233	84%	10%	0.020
CP 10 mg	290	229	79%	5%	0.277
PBO	140	104	74%		

*Excerpted from the clinical study report A3921044: Table 14.2.15.4.1

Cumulative Distribution Function



Responder Analysis # 2: Proportion of 'Improved,' 'No Change," or 'Worsened'

(From the Cumulative Distribution Function)

	PBO (N=140)	CP 5 mg (N=278)	CP 10 mg (N=290)
Improved score (change in mTSS < 0)	20 (14%)	51 (18%)	46 (16%)
No Change	84 (60%)	182 (66%)	183 (63%)
Worsened score (change in mTSS > 0)	36 (26%)	45 (16%)	61 (21%)

Summary: Results from Responder Analyses

- There is no clear dose response relationship between tofacitinib and radiographic outcome based on the responder analyses
- While the magnitude of effect is numerically larger in the CP 10 mg group, a numerically higher proportion of patients in the CP 5 mg group appears to benefit compared to the CP 10 mg group
- At month 6, less than 40% of patients had some change in mTSS from baseline and about 63% of patients had zero change from baseline
- Based on the CDF, some extreme observations were identified

CDF = Cumulative Distribution Function

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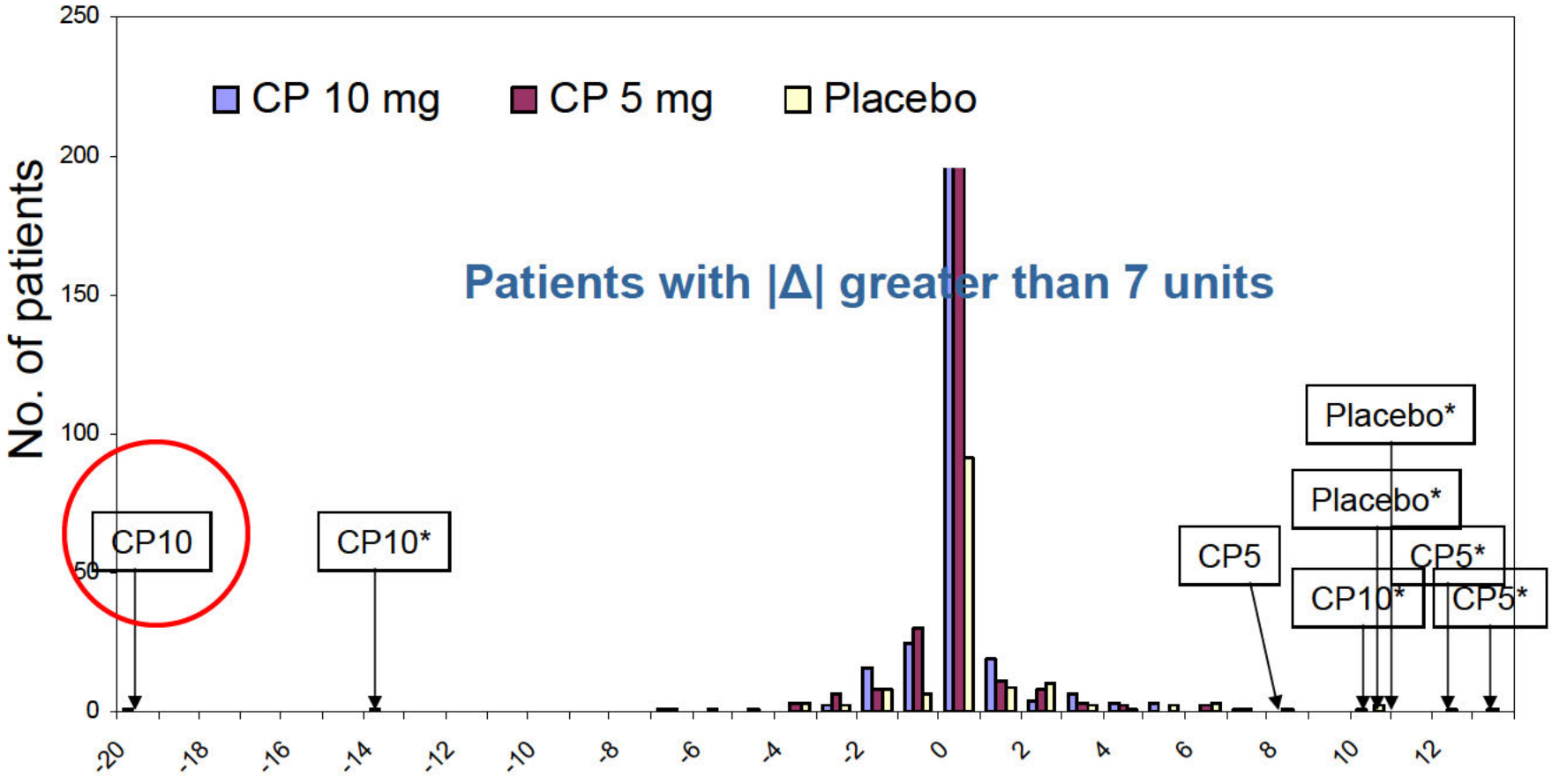
Frequency Distribution



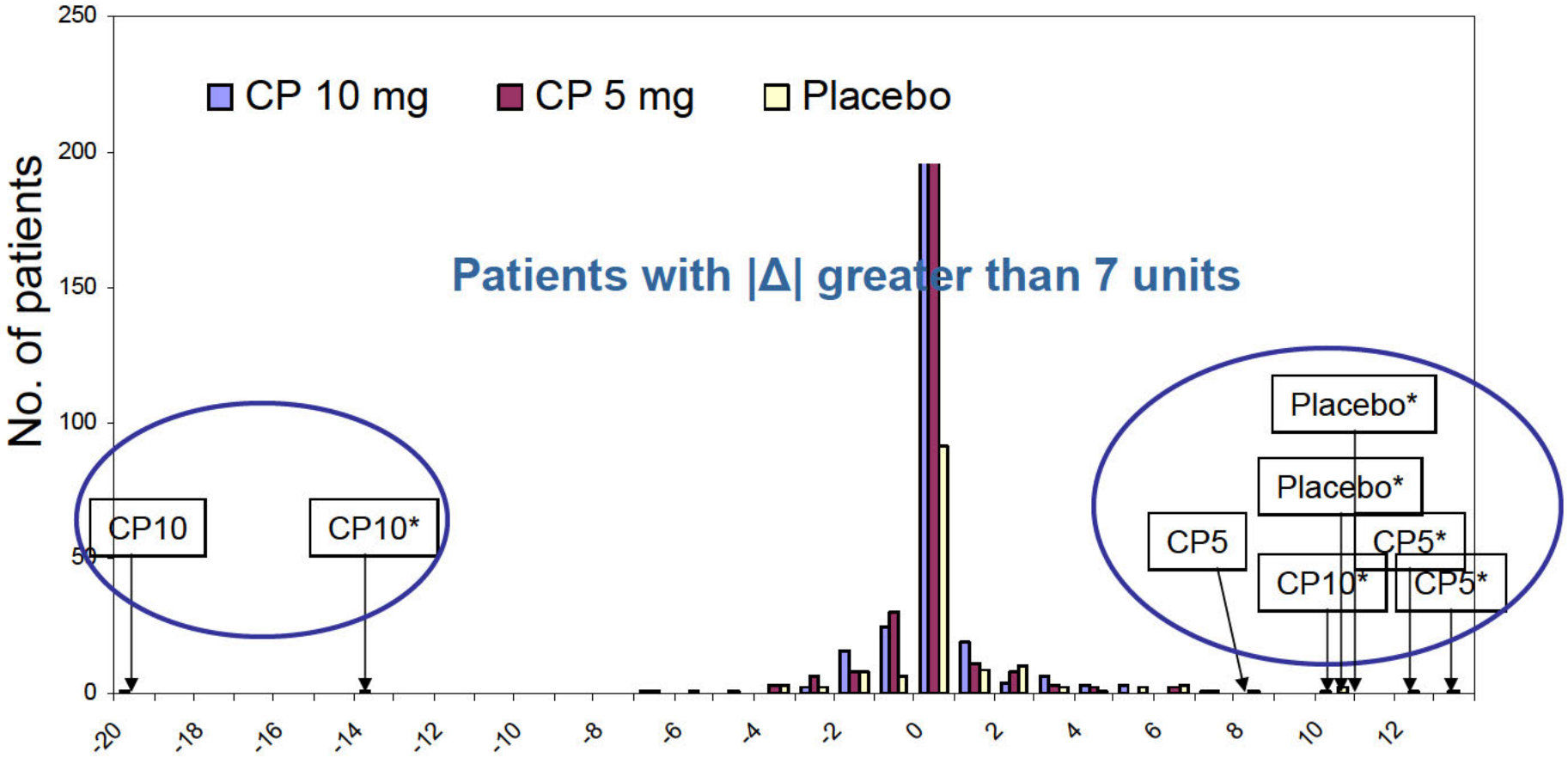
*Extrapolated data

Sensitivity Analysis # 1: Excluding Patients with $|\Delta| \geq 20$ units

Treatment	N	LS Mean	Difference vs. PBO		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set					
CP 5 mg	278	0.12	-0.34	(-0.73, 0.04)	0.079
CP 10 mg	290	0.06	-0.40	(-0.79, -0.02)	0.038
PBO	140	0.47			
Excluding Patient 10421014* from CP10 mg group					
CP 5 mg	278	0.11	-0.34	(-0.69, 0.01)	0.056
CP 10 mg	289	0.12	-0.33	(-0.68, 0.02)	0.061
PBO	140	0.45			

*Patient 10421014's baseline score is 42.5. At Month 6, patient's score is 22.5

Frequency Distribution



*Extrapolated data

Sensitivity Analysis # 2: Excluding patients with |Δ| > 7 units

Treatment	N	LS Mean	Difference vs. PBO		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set					
CP 5 mg	278	0.12	-0.34	(-0.73, 0.04)	0.079
CP 10 mg	290	0.06	-0.40	(-0.79, -0.02)	0.038
PBO	140	0.47			
Excluding patients with |Δ| greater than 7 units					
CP 5 mg	275	-0.003	-0.32	(-0.59, -0.05)	0.021
CP 10 mg	287	0.14	-0.17	(-0.44, 0.09)	0.203
PBO	138	0.32			

Pre-specified Secondary Analysis: Rank ANCOVA

Treatment	N	LS Mean Rank on Change from Baseline	Difference vs. PBO		
			LS Mean Rank	95% CI	P-value
CP 5 mg	278	334	-41	(-77, -6)	0.024
CP 10 mg	290	352	-23	(-59, 12)	0.198
PBO	140	376			

Excerpted from the clinical study report A3921044: Table 14.2.15.1.7

Summary: Results from Sensitivity Analyses

- Magnitude of effect in the CP 10 mg group is sensitive to outliers
  - The average change from baseline in the CP 10 mg group is 0.06. However, one patient in the 10 mg had a change of -20 units, and 3 patients had an absolute change of greater than 7 units
- Lack of consistent findings when data were transformed to ranks

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Radiographic Data Disposition

	PBO	CP 5 mg	CP 10 mg
Randomized	160	321	319
Treated (ITT*)	160 (100%)	321 (100%)	316 (100%)
ITT with Baseline Data	144 (90%)	282 (88%)	296 (94%)
Applicant's FAS*	140 (88%)	278 (87%)	290 (92%)
Linearly Extrapolated (Escape + Dropout)	83 (59%)	88 (32%)	65 (22%)

*ITT: randomized and treated
FAS: applicant-defined full analysis set

Excluded Data

- Site 1048 (n=15): 6 were included and 9 were excluded from the analysis
- Site 1155 (n=9): 1 was included and 8 were not reported
- Site 1174 (n=8): 8 were excluded from the analysis

It is unclear how excluded or unreported data may affect the overall conclusion

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Summary

- There is evidence that CP 10 mg and CP 5 mg may have some activity on radiographic progression. However, there is uncertainty associated with the results for the following reasons:
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  - Data are not consistent with respect to dose
  - The evidence for an effect in radiographic progression is from a single study
  - Less than 40% of patients had some change in mTSS from baseline and only 16% of patients had some improvement in radiographic scores
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- Safety Considerations and Risk-Benefit

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Outline

- Main Safety Results:
  - Deaths
  - Malignancy
  - Serious Infections
  - Laboratory Abnormalities
- Dose-Selection
- Risk-Benefit Considerations

Extent of Exposure

Exposure in Phase 2, Phase 3 and LTE Trials in RA		
	No. of patients	Patient-years
Tofacitinib exposure	4816	5716
Adalimumab exposure	275	190
Placebo-control exposure	954	256

Tofacitinib Exposure in Phase 2, Phase 3 and LTE Trials in RA		
	5 mg BID	10 mg BID
≥ 6 months	1366	1321
≥ 12 months	1107	939
≥ 24 months	580	8

LTE = Long Term Extension

Presentation of Safety Data

Summary of Exposure in Phase 3 Development								
	RCT Pooled Safety				Long-Term Extension (LTE)			
	PBO	ADA	CP5	CP10	CP5	CP10	All CP	All CP Update
Enrolled, N	681	204	1216	1214	1321	1906	3227	3515
Exposure, PY	203	179	904	910	2236	882	3118	4410

- Phase 3 RCT 12-month safety data:
  - Pooled by treatment group (PBO, ADA, CP5, CP10)
  - Adjusted for exposure, as rate per 100 patient-years
- LTE:
  - Pooled by treatment group (CP5, CP10)
  - Adjusted for exposure, as rate per 100 patient-years

RCT = Randomized Controlled Trials

Deaths

- PBO: 1 death from pyelonephritis and sepsis
- ADA: 3 deaths (malignancy, cardiovascular, bone marrow failure)
- Tofacitinib: 45 deaths
  - 15 (33%) infections (12 pneumonias)
  - 12 (27%) malignancies
  - 11 CV (4 cardiac arrest, 2 cerebral vascular accidents, 2 arrhythmia, 1 pulmonary embolism, 1 congestive heart failure, 1 pulmonary hypertension)
  - 7 other (2 suicides, 2 traumatic, 1 chronic obstructive pulmonary disease, 1 aspiration, 1 unknown)

Malignancy

Phase 2, 3, and LTE studies (excluding NMSC):

- PBO: no cases
- ADA: 2 cases (lung and renal cell carcinoma)
- Tofacitinib: 66 solid and hematologic malignancies
  - Most common: Lung, Breast, Gastric and Prostate
  - Dose dependent increased incidence in RCT
  - Dose and exposure dependent increased incidence in LTE studies

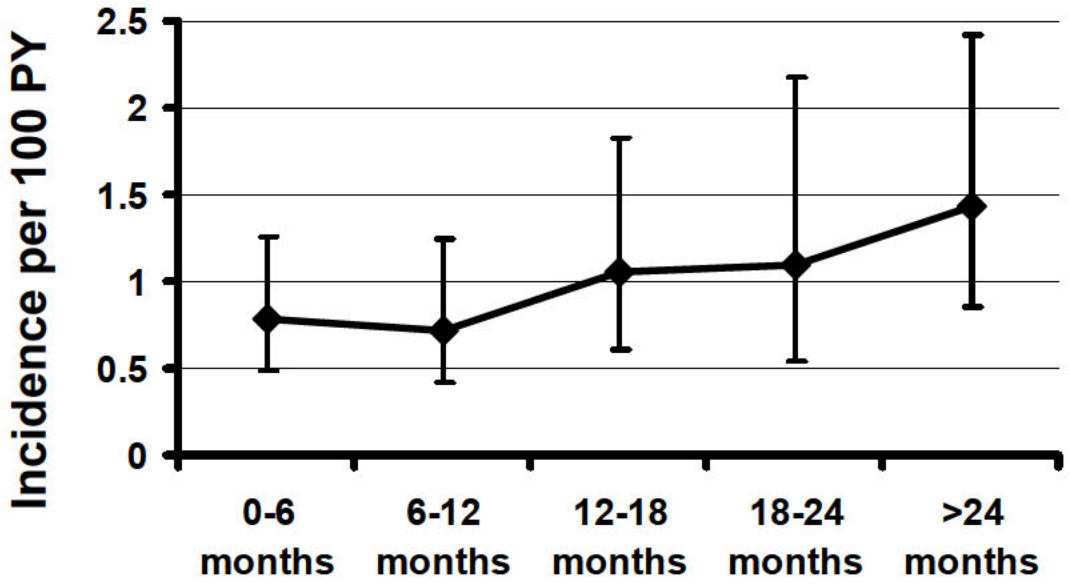
Summary of Malignancy (Excluding NMSC) in Phase 3 Development

	RCT Pooled Safety				Long-Term Extension (LTE)			
	PBO	ADA	CP5	CP10	CP5	CP10	All CP	All CP Update
Patients with ≥1 event, n (%)	-	1 (0.5)	5 (0.4)	8 (0.7)	23 (1.7)	12 (0.6)	35 (1.1)	50 (1.4)
Rate per 100 PY	**0**	**0.6**	**0.6**	**0.9**	**1.0**	**1.4**	**1.1**	**1.1**

NMSC = Non-Melanoma Skin Cancer

Malignancy Rates Over Time

Non-Cumulative Incidence Rates of Malignancy (Excluding NMSC) in RA Program					
	0-6 months	6-12 months	12-18 months	18-24 months	>24 months
Enrolled, n	4791	4012	3126	2054	941
Patients with > 1 event, n (%)	17 (0.4)	13 (0.3)	13 (0.4)	8 (0.4)	14 (1.5)
Incidence per 100 PY	**0.79**	**0.72**	**1.06**	**1.09**	**1.43**



PY = per year

Lymphoma

- 7 cases of lymphoproliferative disorder (LPD) in RA:
  - No cases in placebo and adalimumab control groups
  - 2 cases of atypical location: CNS, Breast
  - Occurred with both 5 mg and 10 mg BID doses
  - Occurred both on background DMARD and monotherapy
  - Median duration of exposure was about 9 months

Cumulative LPD Rates in RA Program			
	29-Mar-11	29-Sep-11	12-Jan-12
Enrolled, n	4789	5563	5677
Patients with LPD, n (%)	3 (<0.1)	5 (<0.1)	6 (0.11)
Rate per 100 PY	**0.05**	**0.06**	**0.07**
SIR	**1.74**	**2.35**	**n.r.**

SIR = standardized incidence ratios

Lymphoma

- 5 cases (2.3% rate) in renal allograft program:
  - All on tofacitinib 15 mg BID x 3-6 months, then 10 mg BID
  - Median duration of exposure was about 10 months
  - Location: 80% CNS
  - All cases Epstein-Barr virus (EBV) positive
- Cynomolgus monkey 39-week study:
  - 3 of 8 monkeys in the high dose group (10 mg/kg/day) developed treatment-related lymphomas:
    - 2 B-cell lymphomas positive for Epstein-Barr virus
    - 1 T-cells lymphoma in the peri-thymic fat

Summary of Malignancy

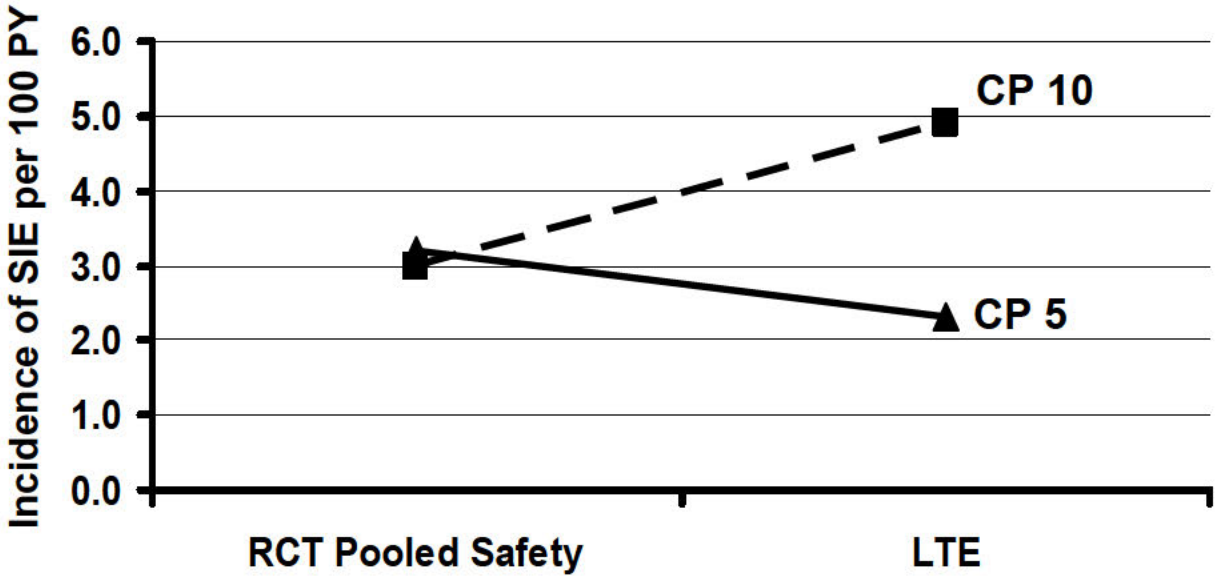
- Malignancy rates in tofacitinib-treated patients increased:
  - In a dose-related manner
  - With increasing exposure in LTE studies
- Lymphomas were reported:
  - In RA development with increasing incidence over time
  - In renal allograft development (80% CNS location)
  - In non-clinical program (cynomolgus monkeys)

Infections

- Most common infections:
  - Upper respiratory infection
  - Urinary tract infection
  - Influenza
  - Herpes zoster
- Herpes zoster:
  - More common in tofacitinib than in controls
  - Incidence about 4.3 per 100 patient-years
  - Few serious Herpes zoster infections

Serious Infections

Summary of Serious Infectious Events in Phase 3 Development								
	RCT Pooled Safety				Long-Term Extension (LTE)			
	PBO	ADA	CP5	CP10	CP5	CP10	All CP	All CP Update
Patients with ≥1 SIE, n (%)	3 (0.4)	3 (1.5)	29 (2.4)	27 (2.2)	50 (3.8)	43 (2.3)	93 (2.9)	131 (3.7)
Rate per 100 PY	**1.5**	**1.7**	**3.2**	**3.0**	**2.3**	**4.9**	**3.0**	**3.0**



SIE = Serious Infectious Event

Opportunistic Infections

Total of 32 opportunistic infections (OI) in RA development program

- Tuberculosis (n=12)
- Esophageal candidiasis (n=7)
- Cytomegalovirus (CMV) (n=4, sialoadenitis, viremia, hepatitis)
- *Pneumocystis carinii* pneumonia (PCP) (n=3)
- Non-tuberculous mycobacterial (n=2)
- Cryptococcus (n=2, meningitis, pneumonia)
- Disseminated herpes zoster (n=1)
- BK virus encephalitis (n=1) on 5 mg BID dose

Summary of Opportunistic Infections (OI) Excluding TB in Phase 3 Development

	RCT Pooled Safety				Long-Term Extension (LTE)			
	PBO	**ADA**	**CP5**	**CP10**	**CP5**	**CP10**	**All CP**	**All CP Update**
Patients with ≥1 OI, n (%)	-	-	3 (0.2)	10 (0.8)	8 (0.6)	5 (0.3)	13 (0.4)	19 (0.5)
Rate per 100 PY	**0**	**0**	**0.3**	**1.1**	**0.4**	**0.6**	**0.4**	**0.4**

Tuberculosis

- 12 cases of tuberculosis (TB), all in tofacitinib-treated patients
- Half of the cases on background methotrexate
- Majority from countries with high prevalence of TB
- Median exposure prior to diagnosis ~260 days
- Relation to dose:
  - 9 cases in 10 mg group
  - 3 cases in 5 mg group, all disseminated TB

Summary of Infections

- Infections in tofacitinib-treated patients were the most common cause of:
  - Deaths
  - Serious Adverse Events (SAEs)
  - Adverse Events (AEs) leading to discontinuation
- Rates for SIE increased in 10 mg group in LTE
- Opportunistic infections, dose-dependent
- Herpes zoster was common (~4.3/100 PY)

Hematologic Abnormalities

- Neutrophils:
  - Dose dependent decreases in mean absolute neutrophil count (ANC)
  - No cases of ANC <500/mm^3 (life-threatening neutropenia)
  - No clear association with infections
- Lymphocytes:
  - Initial lymphocytosis followed by lymphopenia
  - 15 cases with <500/mm^3 (life-threatening lymphopenia)
  - Association with infections:
    - 11/15 developed infection; 4 were serious infection

Serum Creatinine Elevations

- Small elevations in mean values (<0.1 mg/dL)
- Dose and exposure dependent, but plateauing by 12 months

- SAE of acute renal failure were uncommon and were not clearly attributable to tofacitinib treatment
- Study 1033: Tofacitinib 15 mg BID did not affect renal function after 14 days in healthy volunteers

Liver Tests Abnormalities

- Reported in about 20% of patients
- More common in patients on background DMARDs
- Small elevations in:
  - ALT, AST (Mean ~10 IU/L)
  - Total Bilirubin (Mean ~0.05 mg/dL)
- Did not increase in incidence or severity over time
- Hepatic SAE were not increased
- One patient experienced elevated transminases >3 x ULN and bilirubin >2 x ULN who may have had new onset autoimmune hepatitis
  - Drug-induced liver injury could not be ruled out

ULN = Upper Limit of Normal

Lipids and CV Disorders

- LDL, HDL, triglycerides and total cholesterol increased:
  - In a dose dependent manner (5 vs 10 mg BID)
  - Increased 10 to 20% for individual parameters, occurred by one month, and then plateaued
  - LDL/HDL ratio remained stable

- Pre-specified assessment of Major Adverse Cardiovascular Events (MACE), including
  - Cardiovascular death
  - Non-fatal myocardial infarction and cerebro-vascular accidents
- Few events were observed; incidence was similar among treatment groups and stable over time

Tofacitinib: Safety Summary

- Malignancies:
  - Dose and duration of exposure dependent increase in overall malignancy
  - Lymphoproliferative disorder
- Infections:
  - Dose dependent increase in serious infections and
  - Opportunistic infections, including tuberculosis
- Laboratory abnormalities (dose dependent):
  - Clinically relevant levels of lymphopenia

Dose-Selection Revisited

- A lower nominal daily dose might provide:
  - Similar efficacy
  - Lower short and long term toxicity
- An increased dosing frequency, matching tofacitinib's PK profile, might enable even lower nominal daily doses
  - $T_{1/2}$ about 3 hours
  - T_{max} about 0.5-1 hour post-dose
  - Patient compliance would be a consideration

Dose-Selection Revisited

Study 1025

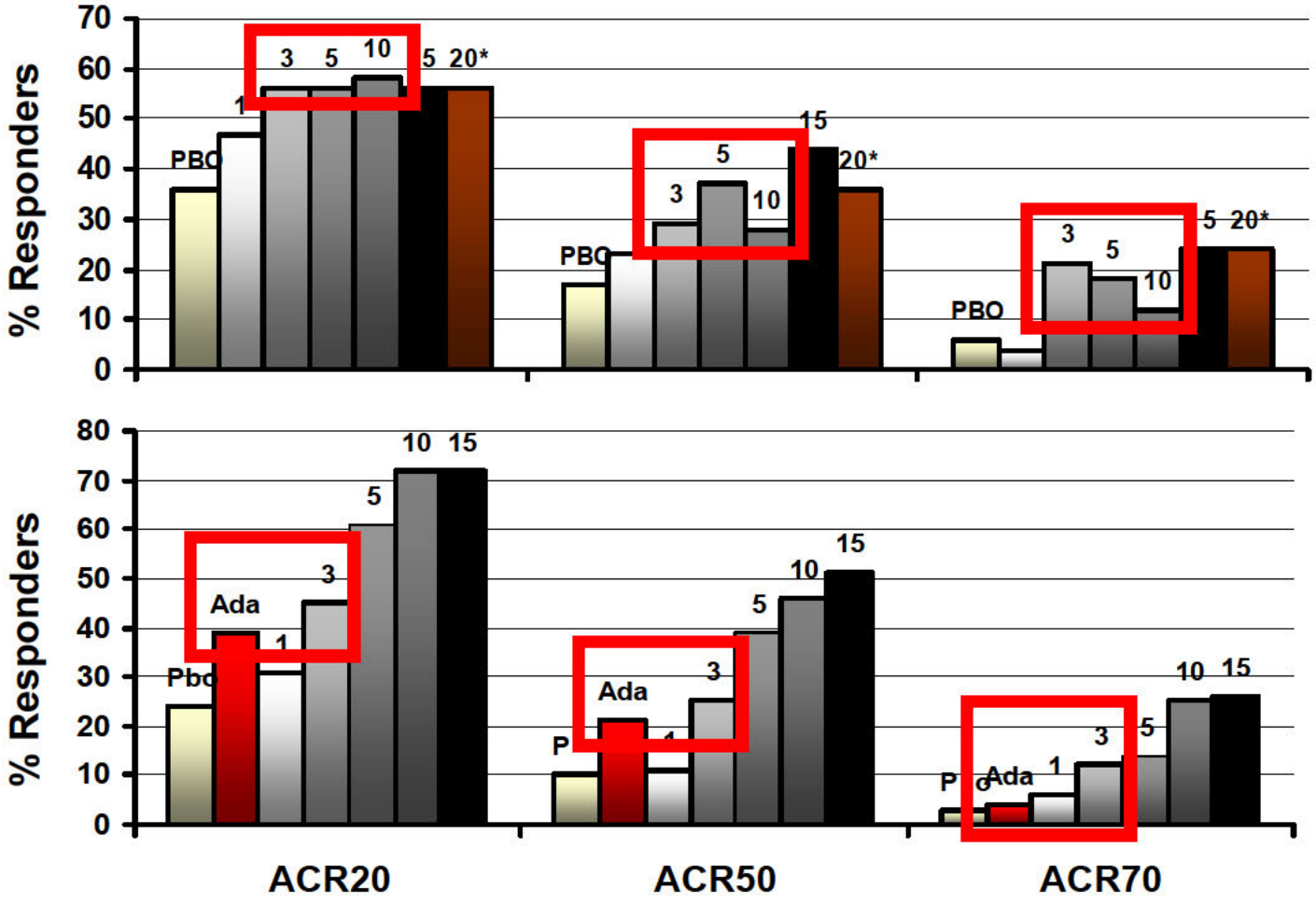
MTX background

***-QD dosing**

Study 1035

Monotherapy

Ada (adalimumab)

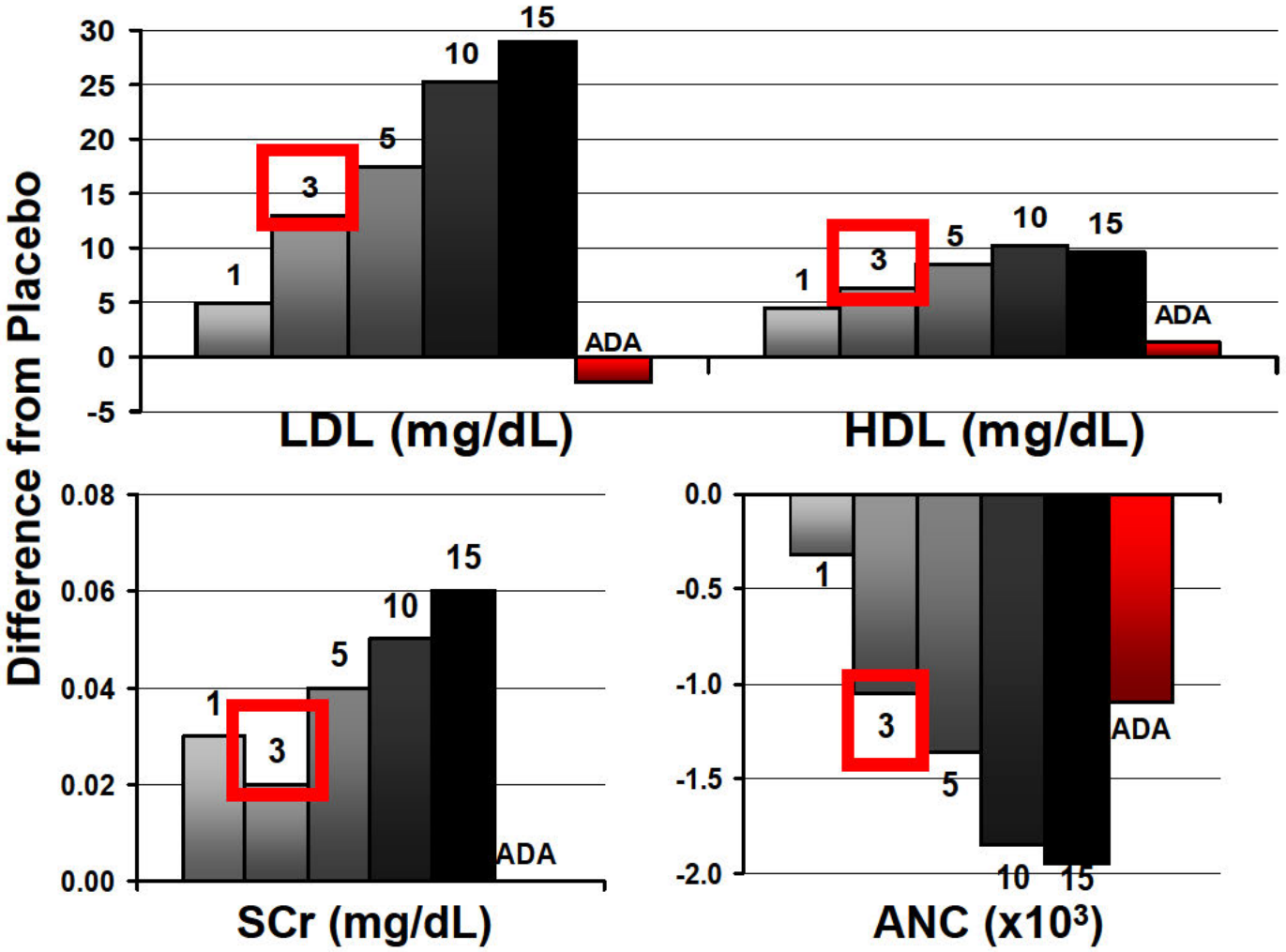


Dose-Selection Revisited

Study 1035

Monotherapy

ADA (adalimumab)



Risk-Benefit Considerations: Efficacy

- **Established for short-term outcomes of**:
- Signs and symptoms of RA:
  - ACR20, 50, and 70 response
  - Proportion of patients achieving DAS28-4(ESR)<2.6
- Physical function:
  - Change from baseline in HAQ-DI scores

- **Uncertain for structural progression due to**:
  - Low amount of progression, even in the placebo control group, limiting treatment effect size
  - Magnitude of effect in 10 mg group is driven by outliers
  - Data not consistent with respect to dose
  - Differences depending on the analysis used
  - Effect of excluded data unknown
  - No corroboration from another study

Risk-Benefit Considerations: Safety

- Malignancies, including lymphoproliferative disorder
- Serious infections, including opportunistic
- Laboratory abnormalities

- **Most safety events were dose dependent**

Concluding Remarks

- Treatment effect on radiographic outcomes
  - How well does tofacitinib actually work in reducing structural damage, and does dose matter?
- Malignancy and serious infection findings
  - Increased risk, does dose matter?
- What is the optimal dose and dosing interval?
  - Dose-ranging studies suggest lower doses may also be efficacious
  - PK profile of the product suggests more frequent dosing interval may allow for even lower nominal daily doses

Thank you!

FDA Arthritis Advisory Committee Meeting May 9, 2012: Charge to the Committee

NDA 203214: Tofacitinib for Rheumatoid Arthritis (RA)

Sarah Yim, M.D.

Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products

Center for Drug Evaluation and Research

Risk-Benefit Considerations

- Treatment effect on radiographic outcomes
  - How well does tofacitinib actually work in reducing structural damage, and does dose matter?
- Malignancy and infection findings
  - Increased risk, does dose matter?
- What is the optimal dose and dosing interval?
  - Dose-ranging studies suggest lower doses may be efficacious, and PK profile of the product suggests more frequent dosing interval may allow for even lower nominal doses

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."

Discussion Item #1: Efficacy of Tofacitinib

- Discuss the radiographic outcomes data for the 5 mg and 10 mg doses of tofacitinib and the impact of these data on the overall assessment of efficacy of tofacitinib for the treatment of rheumatoid arthritis.

Discussion Item #2: Safety of Tofacitinib

- Discuss the safety data for tofacitinib
  - Malignancy overall, and lymphoma in particular
  - Serious infections and opportunistic infections
  - Abnormal hematologic parameters
  - Lipid parameter changes
  - Cardiovascular safety profile
- Include a discussion of the overall safety profile of the 5 mg dose and the 10 mg dose, and whether the data are more favorable for one dose versus the other.

Discussion Item #3: Dose Selection

- Discuss whether the dose and dosing frequency selected are adequately supported by the existing dose exploration data and the pharmacokinetic profile of tofacitinib.

Item #4: Efficacy Voting Question

- Do the data provide substantial evidence of the efficacy of tofacitinib for radiographic outcomes?

Item #5: Efficacy Voting Question

- Overall, do the data provide substantial evidence of the efficacy of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS)?

Item #6: Safety Voting Question

- Is the safety profile of tofacitinib adequate to support approval of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis patients who have had inadequate response to one or more DMARDs?

Item #7: Approvability Voting Question

- Do the efficacy and safety data provide substantial evidence to support approval of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more DMARDs?