

# American College of Rheumatology

2011 Analyst and Investor Meeting

November 6, 2011



# Chuck Triano

## Senior Vice President, Investor Relations



# Forward-Looking Statements

- Our discussions during this meeting will include forward-looking statements. Actual results could differ materially from those projected in the forward-looking statements
- The factors that could cause actual results to differ are discussed in Pfizer's 2010 Annual Report on Form 10-K and in our reports on Form 10-Q and Form 8-K
- These reports are available on our website at [www.pfizer.com](http://www.pfizer.com) in the "Investors – SEC Filings" section

# **Geno Germano**

**President & General Manager  
Specialty Care and Oncology**



# RA: A Serious Disease and Growing Patient Population

- The RA market is large and growing, \$12.7 billion in 2010, projected to be \$17.3 billion in 2015<sup>1</sup>
- 4.6+ million RA patients in 2010 (US, France, Germany, Italy, Spain, UK and Japan)<sup>2</sup>
  - » Forecasts increase to 5.2 million patients in 2019<sup>2</sup>
- Progressive disease worsens over time and may lead to irreversible joint damage, work disability and functional decline<sup>3,4</sup>
- 20% to 40% of patients fail to achieve ACR 20 with biologic therapies and some lose response over time<sup>5,6,7</sup>

1. Vision Gain Report: Rheumatoid Arthritis: World Drug Market 2011-2021; Sept. 2011

2. Datamonitor, Stakeholder Insight: Rheumatoid Arthritis; Sept. 2010

3. Weaver AL. The impact of new biologicals in the treatment of rheumatoid arthritis. *Rheumatology*. 2004; 43(3):iii17-iii23

4. Emery P. et al. Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis. *Rheumatology*. 2008; 47:392-398

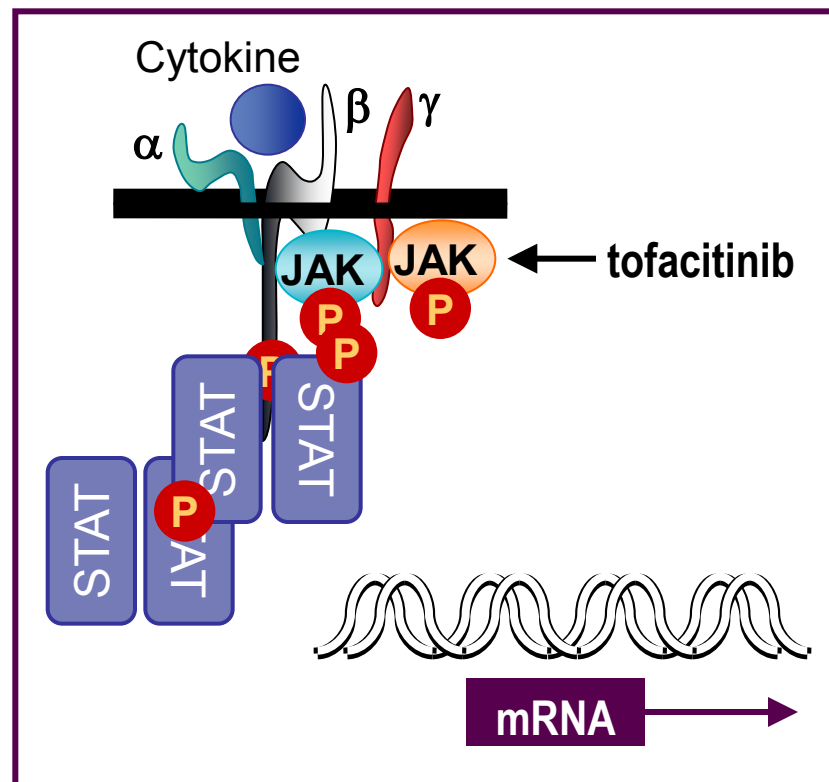
5. Klareskog L et al. *Lancet* 2004;363:675-681

6. Keystone EC et al. *Arthritis Rheum* 2004;50:1400-1411

7. Lipsky P et al. *New Engl J Med* 2000;343:1594-1602

# Tofacitinib: A Novel JAK Inhibitor

- Tofacitinib, a novel, oral JAK inhibitor being investigated as a targeted immunomodulator and disease modifying therapy for RA
  - Discovered by Pfizer scientists at labs in Groton, CT
- Novel mechanism of action
  - JAK 1 and 3 specific, with functional specificity over JAK 2
  - Unlike biologics, which target extracellular molecules such as pro-inflammatory cytokines, tofacitinib targets the intracellular signaling pathways that operate as hubs in the inflammatory cytokine network
- Potentially the first new oral DMARD for RA in more than 10 years



# Tofacitinib in RA: The ORAL Trials

## RA Clinical Trials Program is Extensive

- Close to 5,000 RA patients and 5,700 patient years of exposure
- Approximately 35 countries, 350 sites in the Phase 3 program
  - 23% of patients in North America, 34% in Europe, 28% in Asia, 15% in Latin America
- Active control (adalimumab) included in ORAL Standard Trial
- Randomized clinical trials up to 24 months' duration
- Extensive open-label program, long-term experience up to 3 years and ongoing

## Tofacitinib was Evaluated Across a Variety of Settings and Patient Populations

- As monotherapy and in combination with MTX or other traditional DMARDs
- Inadequate responders to MTX, DMARDs or TNF inhibitors

# The ORAL Trials: Pivotal Studies

## **ORAL Solo (A3921045)**

- 6-month monotherapy study in inadequate responders to a DMARD (traditional or biologic) receiving tofacitinib monotherapy

## **ORAL Sync (A3921046)**

- 12-month study in inadequate responders to a DMARD (traditional or biologic) receiving tofacitinib and background traditional DMARD(s)

## **ORAL Scan (A3921044)**

- 24-month study in inadequate responders to MTX receiving tofacitinib and background MTX

## **ORAL Standard (A3921064)**

- 12-month study in inadequate responders to MTX receiving tofacitinib and background MTX, with active control of adalimumab and background MTX

## **ORAL Step (A3921032)**

- 6-month study in inadequate responders to TNF-inhibiting therapy receiving tofacitinib and background MTX



# Additional Tofacitinib Trials

## Ongoing P3 Study

### ORAL Start (A3921069)

- 24-month study in MTX-naïve patients receiving tofacitinib monotherapy or MTX (not part of the initial registration package)

## Long-term Extension Studies

### ORAL Sequel (A3921024)

- Phase 2/3 open label follow-up study evaluating patients who had participated in a prior randomized Phase 2 or Phase 3 study of tofacitinib (monotherapy or in combination with traditional DMARDs)

### Study A3921041

- Long-term extension (LTE) open-label trial in Japanese subjects

# Tofacitinib: Efficacy

## **In Clinical Trials to Date, Tofacitinib Demonstrated Clinically Meaningful and Statistically Significant Results, with:**

- Onset of action as measured by significant ACR 20 response versus placebo seen as early as 2 weeks
- Improvements in signs and symptoms and disease severity
- Halting of radiographic progression
  - 10 mg BID met primary endpoint (mTSS) at six months
- Improvements in patient reported outcomes, such as physical function, pain and fatigue
- Efficacy across patient populations – prior DMARD use, TNF failures – and over time, with sustained improvements over 3 years

# Tofacitinib: Safety

- In clinical trials to date, tofacitinib 5 and 10 mg BID has demonstrated a consistent safety profile
- Most adverse events have been mild or moderate in nature and the most frequently reported class of AEs was infections
- Serious AEs, including serious infections, and adverse events leading to discontinuation were infrequent
- Dose-dependent decreases in mean neutrophil counts and increases in mean LDL, HDL and total cholesterol were observed
- Transaminase increases and small increases in mean serum creatinine were also observed
- All-cause mortality rates in Phase 3 and LTE are consistent with rates reported in the literature for patients with RA treated with DMARDs
- Pfizer is conducting additional studies, including the continuation of LTE studies, to further understand the safety profile of tofacitinib

# Why We're Excited About Tofacitinib's Potential

## Powerful Efficacy in a Pill

- Efficacy demonstrated across a variety of patient populations
- Efficacy demonstrated alone or in combination with MTX
- Improvements in signs and symptoms observed as early as two weeks

## Consistent Safety Profile

## Potential to Help Patient Population in Need of New Therapeutic Options

# Next Steps: Filing

**Based on the Safety and Efficacy Results Observed in the tofacitinib RA Clinical Development Program, Pfizer Believes the Risk/Benefit Profile Supports Regulatory Submission for Both the 5 and 10 mg Doses**

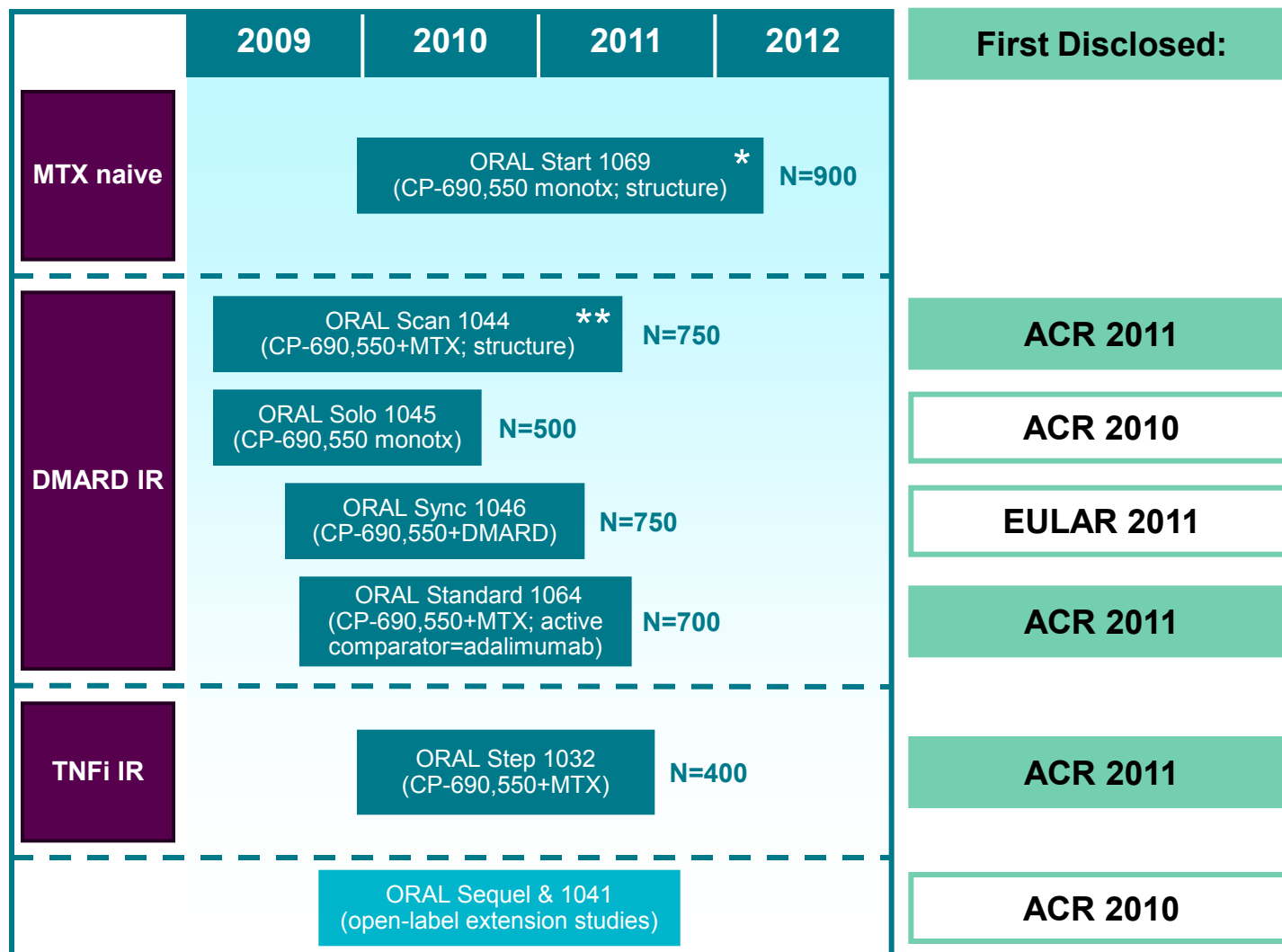
**We Continue to Anticipate Accepted Filings in the U.S. and Europe and a Filing in Japan Before the End of This Year**

# Yvonne Greenstreet

Senior Vice President, Head of Medicines Development  
Specialty Care



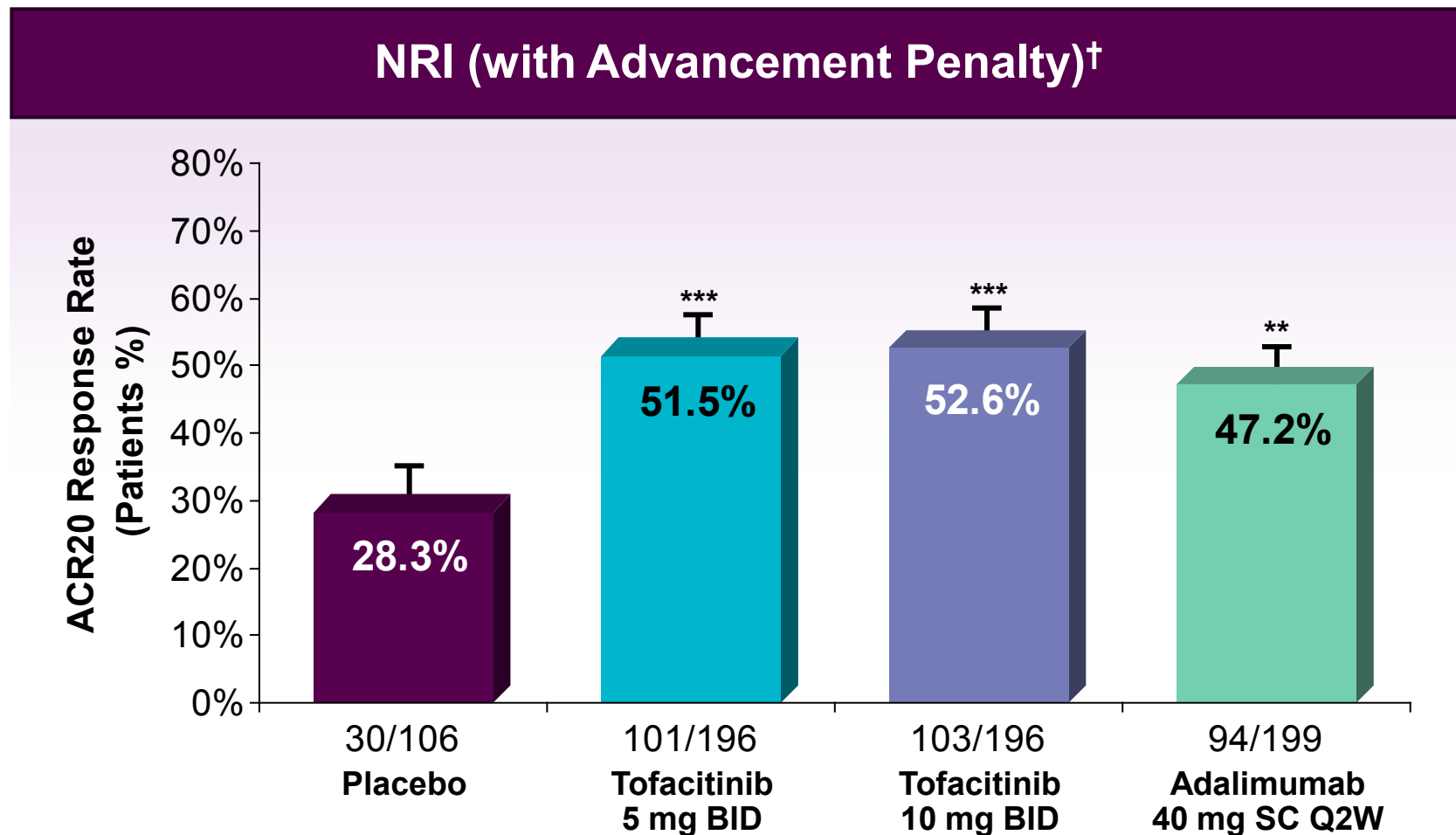
# RA Phase 3 Development Program



\* Interim analysis, study end 2013

\*\* Interim analysis, study end 2012

# ORAL Standard: ACR20 at Month 6

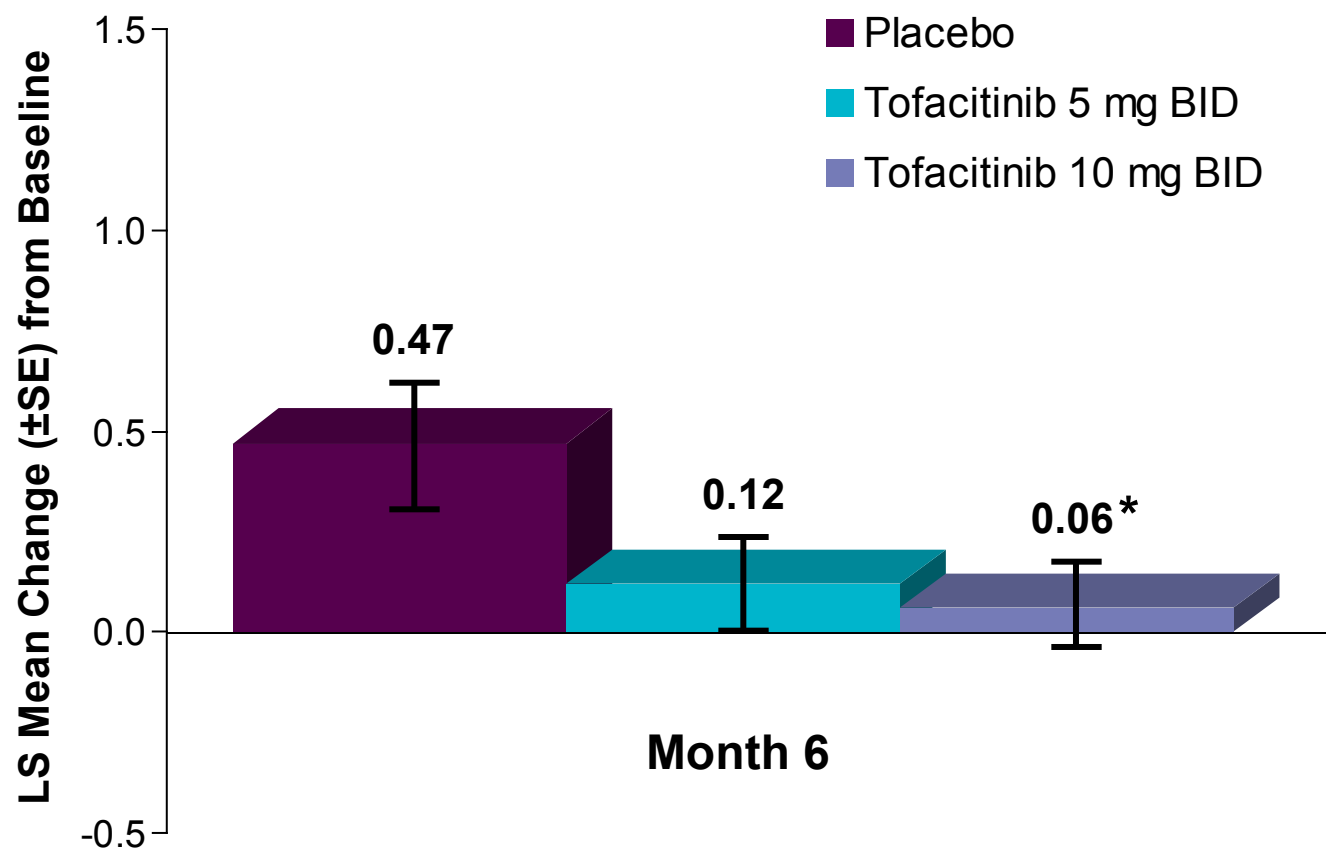


<sup>†</sup> Primary analysis; NRI (with advancement penalty): non-responder patients at Month 3 are considered as treatment failures for the remainder of the trial, even if they subsequently achieved response after Month 3

\*\*  $p \leq 0.001$ ; \*\*\*  $p \leq 0.0001$  vs. placebo



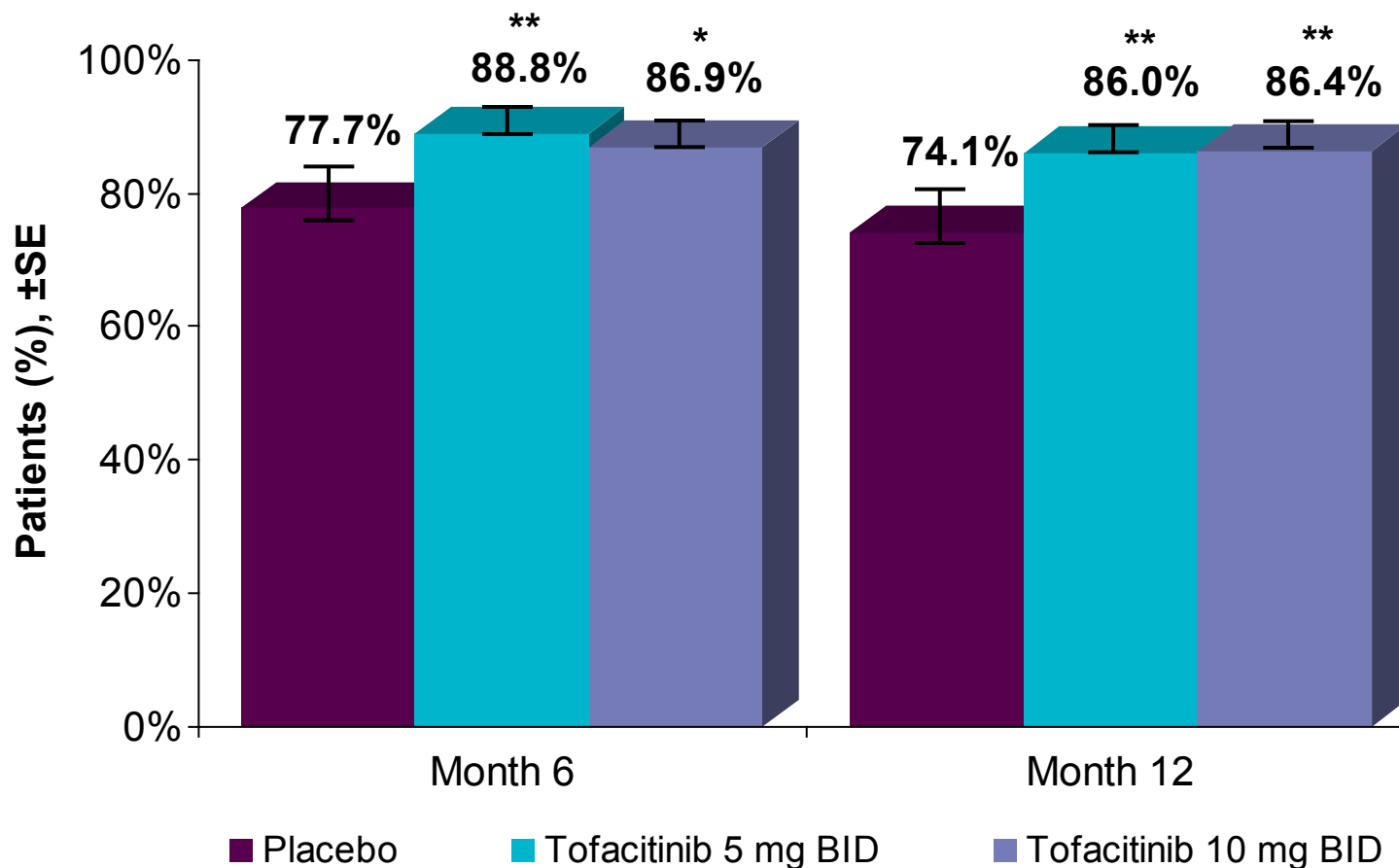
# ORAL Scan: mTSS (Primary Endpoint)



\*  $p \leq 0.05$  vs. placebo

# ORAL Scan: Proportion of Non-Progressors

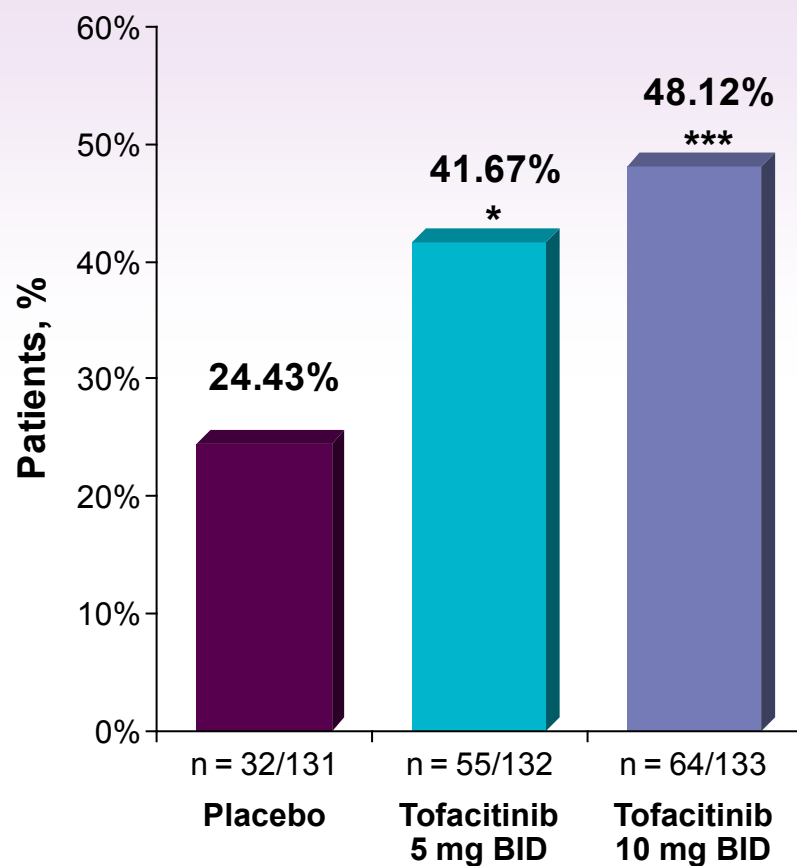
mTSS  $\Delta \leq 0.5$



\* p<0.05; \*\*p<0.01 vs. placebo

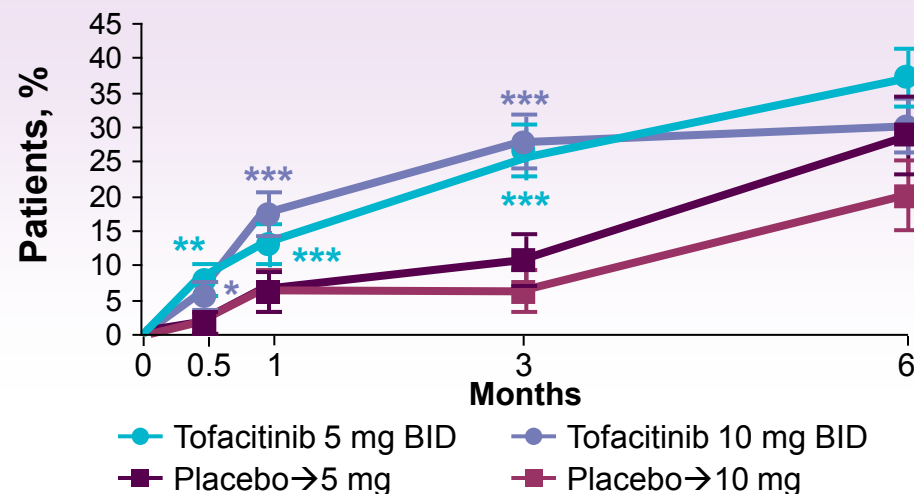
# ORAL Step: ACR Response Rates

## ACR20 (Month 3)

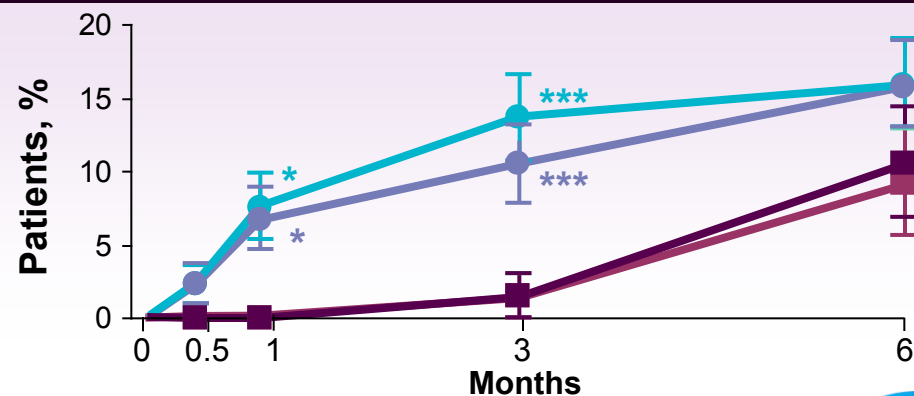


ACR20: \* $p \leq 0.05$ ; \*\*\* $p < 0.0001$  vs. PBO at Month 3 (unadjusted)

## ACR50



## ACR70



ACR50/70: No preservation of type I error was applied for secondary endpoints; no multiple-comparisons correction was applied to p-values; and statistical significance was defined as \* $p \leq 0.05$ ; \*\* $p \leq 0.01$ ; \*\*\* $p < 0.0001$  vs. baseline

# Introduction to Safety

- Pfizer has now evaluated tofacitinib in close to 5,000 patients with approximately 5,700 patient-years of exposure in a large, global program with broad geographic spread

<b>Exposure in Phase 3</b>	<ul style="list-style-type: none"><li>➤ Tofacitinib: 2,211 patient-years of exposure</li><li>➤ Placebo: 202 patient-years of exposure</li><li>➤ Adalimumab: 179 patient-years of exposure</li></ul>
<b>AEs</b>	<ul style="list-style-type: none"><li>➤ Majority of AEs were mild or moderate and resolved and the most frequently reported were infections and infestations. Serious AEs and discontinuations were infrequent</li></ul>
<b>Serious AEs Uncommon</b>	<ul style="list-style-type: none"><li>➤ Incidence varied<ul style="list-style-type: none"><li>– Within different time intervals in individual studies (M0-3, M3-6, M6-12)</li><li>– Between studies</li></ul></li><li>➤ Overall Phase 3 and LTE safety experience is more informative</li></ul>

# Mortality

Phase 3						LTE		
	Tofacitinib 5 mg BID N=1216	Tofacitinib 10 mg BID N=1214	All tofacitinib Doses N=3030	Placebo N=681	ADA N=204	Tofacitinib 5 mg BID N=1321	Tofacitinib 10 mg BID N=1906	All tofacitinib Doses N=3227
<b>All-cause Mortality (Including Those Occurring ≥30 Days After the Last Dose)</b>								
Unique Patients with Events, n (%)	7 (0.6)	4 (0.3)	12 (0.4)	1 (0.2)	1 (0.5)	17 (1.3)	3 (0.2)	20 (0.6)
Exposure, Pt-yrs	904	910	2098	203	179	2236	882	3118
IR, Events/100 Pt-yrs (95% CI)	0.78 (0.37, 1.63)	0.44 (0.17, 1.17)	0.57 (0.33, 1.01)	0.49 (0.07, 3.51)	0.56 (0.08, 3.97)	0.76 (0.47, 1.22)	0.34 (0.11, 1.06)	0.64 (0.41, 0.99)
<b>All-cause Mortality (Up to 30 Days After the Last Dose)</b>								
Unique Patients with Events, n (%)	5 (0.4)	4 (0.3)	10 (0.3)	1 (0.1)	1 (0.5)	8 (0.6)	2 (0.1)	10 (0.3)
Exposure, Pt-yrs	904	910	2098	203	179	2236	882	3118
IR, Events/100 Pt-yrs (95% CI)	0.55 (0.23, 1.33)	0.44 (0.17, 1.17)	0.48 (0.26, 0.89)	0.49 (0.07, 3.51)	0.56 (0.08, 3.97)	0.36 (0.18, 0.72)	0.23 (0.06, 0.91)	0.32 (0.17, 0.60)

- All-cause mortality incidence rate in Phase 3 is similar to placebo (no PBO in LTE)
- There were no patterns observed regarding causes of death; the causes of deaths were distributed across a broad spectrum and are consistent with what has been reported for RA, including RA patients treated with other DMARDs
  - 2 deaths in the tofacitinib arms (1 in Phase 3 and 1 in LTE) and 1 in adalimumab (Phase 3) attributed to cardiac events by the Cardiovascular Safety Endpoint Adjudication Committee
- Rates in Phase 3 and LTE are consistent with rates reported in the literature for patients with RA treated with DMARDs (IR 0.51-0.60 and 2.4-4.4)<sup>1-4</sup>

1 Actemra (tocilizumab) injection, Drug Approval Package, Biologics Licensing Application Number: 125276, Medical Reviews; US FDA website

[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/125276s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000MedR.pdf), accessed 02 Sep 2011.

2 Gottlieb AB, Gordon K, Giannini EH, et al. *J Drugs Dermatol* 2011; 10(3): 289-300.

3 Gonzalez, A., Maradit Kremers H, Crowson CS, et al. *Arthritis Rheum* 2007;56(11):3583-7.

4 Björnådal L, Baecklund E, Yin L, et al. *J Rheumatol* 2002;29(5):906-12.

# Serious Infections

Phase 3						LTE		
	Tofacitinib 5 mg BID N=1216	Tofacitinib 10 mg BID N=1214	All tofacitinib Doses N=3030	Placebo N=681	ADA N=204	Tofacitinib 5 mg BID N=1321	Tofacitinib 10 mg BID N=1906	All tofacitinib Doses N=3227
<b>All Serious Infections</b>								
Unique Patients with Events, n (%)	29 (2.4)	27 (2.2)	61 (2.0)	3 (0.4)	3 (1.5)	50 (3.8)	43 (2.3)	93 (2.9)
Exposure, Pt-yrs	901	909	2094	202	179	2222	879	3101
IR, Events/100 Pt-yrs (95% CI)	3.22 (2.24, 4.63)	2.97 (2.04, 4.33)	2.91 (2.27, 3.74)	1.48 (0.48, 4.59)	1.68 (0.54, 5.21)	2.25 (1.71, 2.97)	4.89 (3.63, 6.60)	3.00 (2.45, 3.68)

- No apparent increase in rate of infections or serious infections with longer treatment duration
- Higher incidence rate of infections with 10 mg BID versus 5 mg BID in LTE but no difference between doses in Phase 3
  - Duration of exposure for 10 mg BID largely limited to ~18 months, whereas duration of exposure for 5 mg BID extended out to 36 months
- Rates consistent with rates reported in literature for RA patients treated with non-biologic and biologic DMARDs (IRs 1.4-4.1 and 2.6-18.1, respectively)<sup>1-3</sup>

<sup>1</sup> Kievit W et al. *Rheumatology* (Oxford) 2011; 50: 196-203

<sup>2</sup> Curtis JR et al. *Arthritis Rheum* 2007; 56: 1125-1133

<sup>3</sup> Dixon WG et al. *Arthritis Rheum* 2006; 54: 2368-2376

# Herpes Zoster

Phase 3						LTE		
	Tofacitinib 5 mg BID N=1216	Tofacitinib 10 mg BID N=1214	All tofacitinib Doses N=3030	Placebo N=681	ADA N=204	Tofacitinib 5 mg BID N=1321	Tofacitinib 10 mg BID N=1906	All tofacitinib Doses N=3227
<b>All Herpes Zoster</b>								
Unique Patients with Events, n (%)	39 (3.2)	38 (3.1)	90 (3.0)	3 (0.4)	5 (2.5)	91 (6.9)	43 (2.3)	134 (4.2)
Exposure, Pt-yrs	886	895	2060	202	178	2140	869	3009
IR, Events/100 Pt-yrs (95% CI)	4.39 (3.21, 6.01)	4.23 (3.08, 5.82)	4.36 (3.54, 5.35)	1.49 (0.48, 4.61)	2.81 (1.17, 6.76)	4.25 (3.44, 5.22)	4.95 (3.67, 6.67)	4.45 (3.76, 5.28)
<b>Serious Herpes Zoster</b>								
Unique Patients with Events, n (%)	4 (0.3)	1 (0.1)	5 (0.2)	0	0	7 (0.5)	1 (0.1)	8 (0.3)
Exposure, Pt-yrs	904	910	2098	0	0	2235	882	3117
IR, Events/100 Pt-yrs (95% CI)	0.44 (0.17, 1.18)	0.11 (0.02, 0.78)	0.24 (0.10, 0.57)	0	0	0.31 (0.15, 0.66)	0.11 (0.02, 0.81)	0.26 (0.13, 0.51)

- In development program as a whole, including PBO and ADA cohorts, there were higher incidence rates of all herpes zoster (serious and non-serious) than what has been reported historically in the literature for RA patients treated with biologic and non-biologic DMARDs (IRs 0.56 – 1.32 events per 100 patient yrs)<sup>1-3</sup>
  - Recent work describes an overall trend of increased rates of herpes zoster over time<sup>4</sup>
- Rates similar in both dose groups and did not increase with longer treatment duration
  - Five cases of serious herpes zoster reported in Phase 3, eight in LTE. Serious cases were rare with one case of disseminated herpes zoster (2 dermatomes) across development program

<sup>1</sup> McDonald JR et al. *Clin Infect Dis* 2009; 48: 1364-1371

<sup>2</sup> Strangfeld A et al. *JAMA* 2009; 301: 737-744

<sup>3</sup> Wolfe F et al. *Rheumatology* (Oxford) 2006; 45: 1370-1375

<sup>4</sup> Veetil BMA et al. *Abstract* 1187, ACR 2011

# Laboratory Changes - Summary

## **Changes in Laboratory Parameters Observed for Tofacitinib 5 and 10 mg BID are Consistent Across Studies**

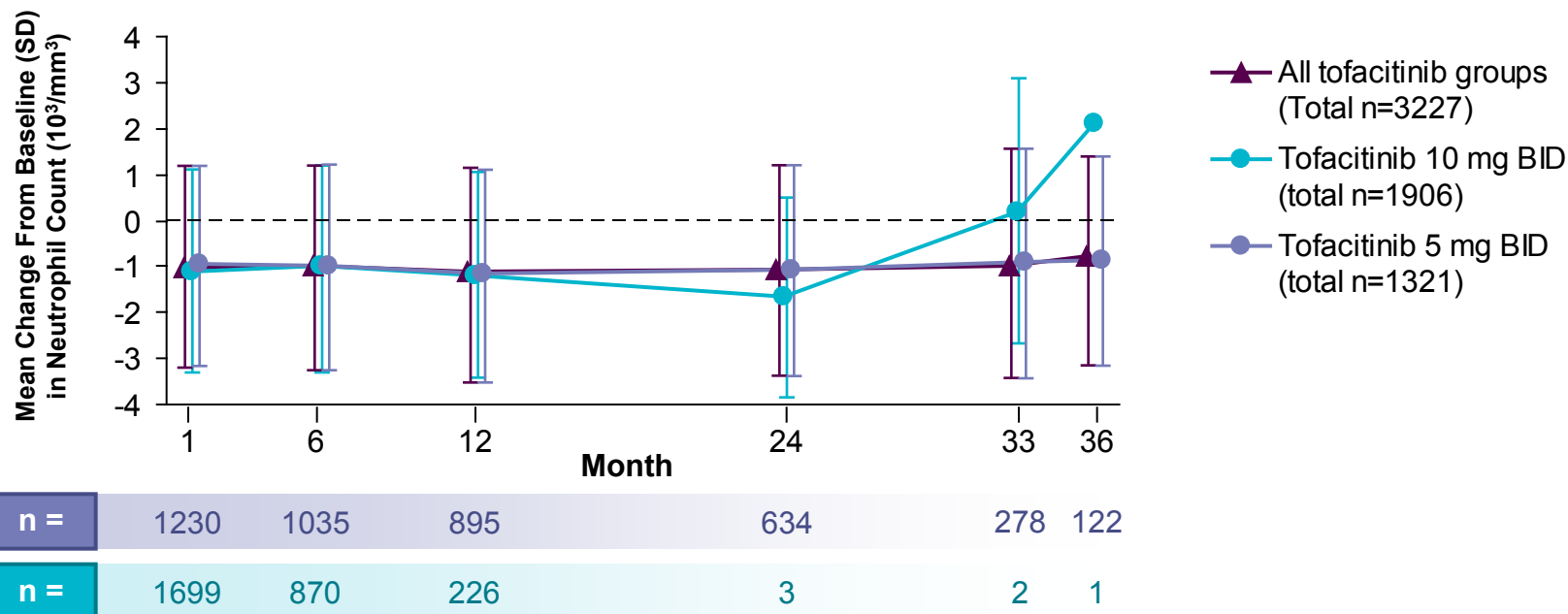
- Dose-dependent decreases in mean neutrophil counts
- Dose-dependent increases in mean LDL, HDL and total cholesterol
- Small increases in mean serum creatinine
- Increases >3XULN in transaminases uncommonly observed

**Mean Overall Values for Laboratory Safety Parameters Generally Stabilized Over Time with Longer Treatment Duration in All Tofacitinib Groups**



# Neutrophils

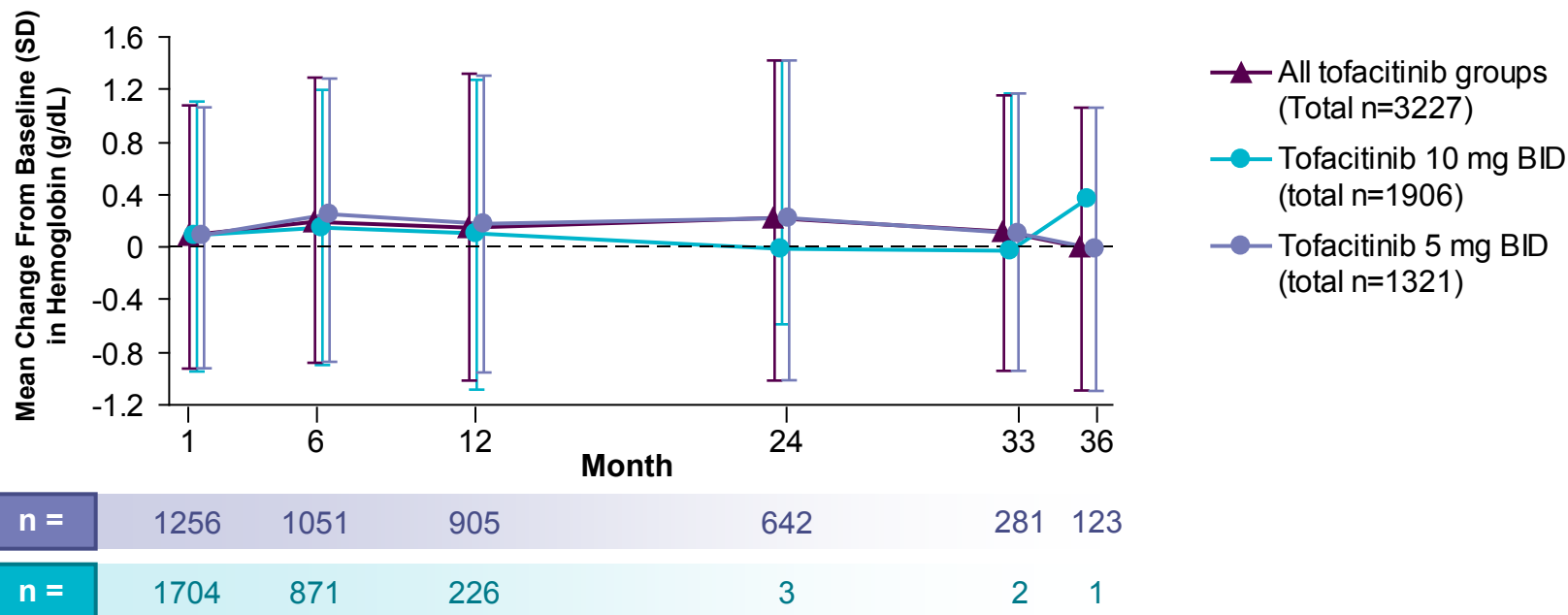
## Neutrophil Count



- Decrease in neutrophils is predictable and reversible: appears early, is dose related, is sustained but non-progressive, and is not associated with an increased risk of infection
  - Similar magnitude of decrease in adalimumab group in ORAL Standard
- No patient experienced a confirmed potential life-threatening neutropenia ( $<500/\text{mm}^3$ ) across development program

# Hemoglobin

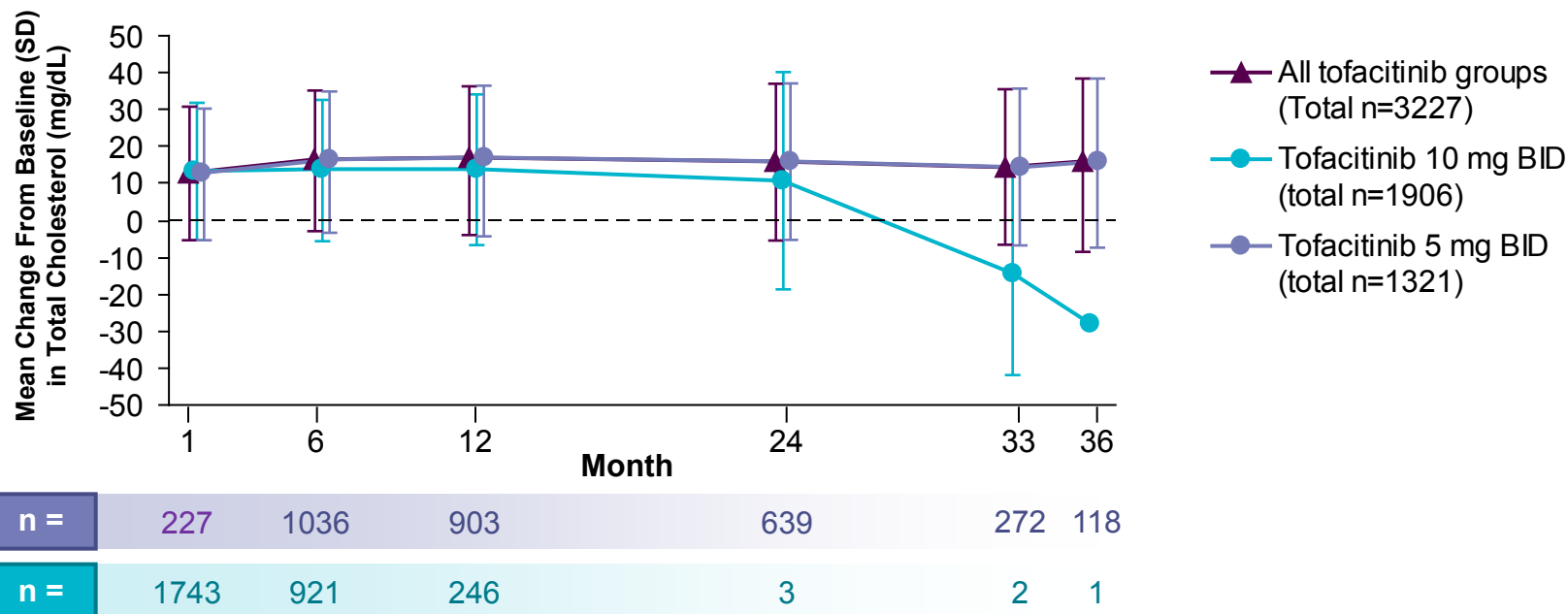
## Hemoglobin



- Mean Hb levels increased from baseline with 5 mg BID with minimal changes from baseline with PBO and 10 mg BID
- Hb levels largely remained within the normal reference range throughout the duration of treatment
- Most cases of anemia were mild to moderate in severity, and occurred with similar frequency in placebo and tofacitinib-treated patients

# Cholesterol

## Total Cholesterol

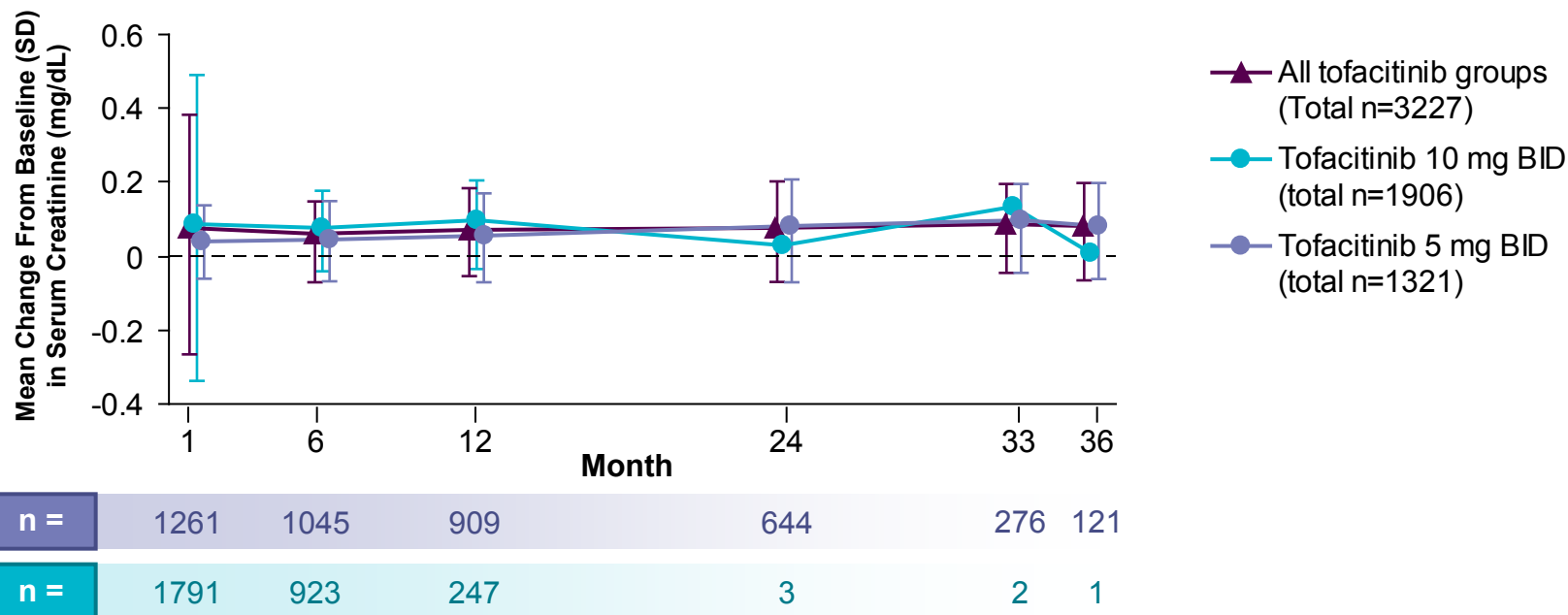


- Dose-dependent increases in serum LDL-c, HDL-c, and total cholesterol observed within 1 to 3 months, and remained stable thereafter. Little change in total cholesterol/HDL-c and LDL-c/HDL-c ratios. Atorvastatin effective in reducing tofacitinib-associated increases in LDL-c<sup>1</sup>
- RA is associated with an increased risk of CV events. Relationship between this increased risk and traditional factors, such as lipid levels, is less clear in patients with RA than in the general population
- To date, Pfizer has not observed any increased risk in ischemic CV events. CV events have been rare and rates are consistent with those reported for patients with RA, including RA treated with various other DMARDs

1. McInnes et al. *Ann Rheum Dis* 2011;70(3):169.

# Serum Creatinine

## Serum Creatinine



- Small increases in mean SCr but largely remain within normal reference range and increases plateau over 3 months remaining stable thereafter
- After a limited (6 wk) treatment period, reversibility of SCr increase was demonstrated
- AEs of renal failure occurred infrequently, and were generally associated with a concurrent illness including infections
- Healthy volunteers showed no change in renal function (mGFR), renal plasma flow or creatinine clearance

# Aminotransferases

- Tofacitinib caused modest, not clinically meaningful, mean elevations in ALT or AST levels
- Potentially important increases ( $>3\times\text{ULN}$ ) in liver enzymes were uncommonly observed. These increases occurred more frequently in patients on background DMARD therapy compared with monotherapy patients
- The risk of drug-induced liver injury appears to be low

# Overall Conclusions

- Tofacitinib is a novel, oral JAK inhibitor that is being investigated as a targeted immunomodulator and disease-modifying therapy for RA
- Extensive development program across patient populations, treatment regimens and endpoints has demonstrated what Pfizer believes is a favorable benefit/risk profile for both the 5 and 10 mg BID regimen
- Consistent safety profile

# Questions