Fostamatinib Analyst Briefing

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AstraZeneca

Item owner: Christopher Sampson

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Today's Agenda

1. The opportunity in RA
2. What is Fostamatinib
3. Mechanism of action
4. Phase II data and safety
5. Design of Phase III and the OSKIRA programme
6. Questions and Answers

Presenters

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Global Product VP

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Medical Science Director

Jens Lindberg
Global Marketing Director

Why rheumatoid arthritis?

A prevalent disease with significant unmet need

1 in 100 people worldwide are affected by RA[1]

35 – 50 years old is the typical age when RA symptoms appear,[2] with women 3x more likely to be affected than men[3]

9 Million RA patients treated with disease-modifying therapy (traditional and biologic)[4,5]

7 Million RA patients do not achieve remission with a traditional disease modifying anti-rheumatic drug (DMARD) alone[6]

1 Centers for disease control and prevention (CDC). Rheumatoid Arthritis. Available online Accessed September 2012.
2 Temprano K, Smith HR, Diamond HS Medscape Reference - Rheumatoid Arthritis, Epidemiology
3 ArthritisCare.org.uk. Living with rheumatoid arthritis booklet; 2010
4 Decision Resource Pharmacor 2010
5 IMS Health MIDAS sales database
6 Blumberg SN, Fox DA. Rheumatoid arthritis: guidelines for emerging therapies. Am J Manag Care 2001 ; 7 (6): 617 -26

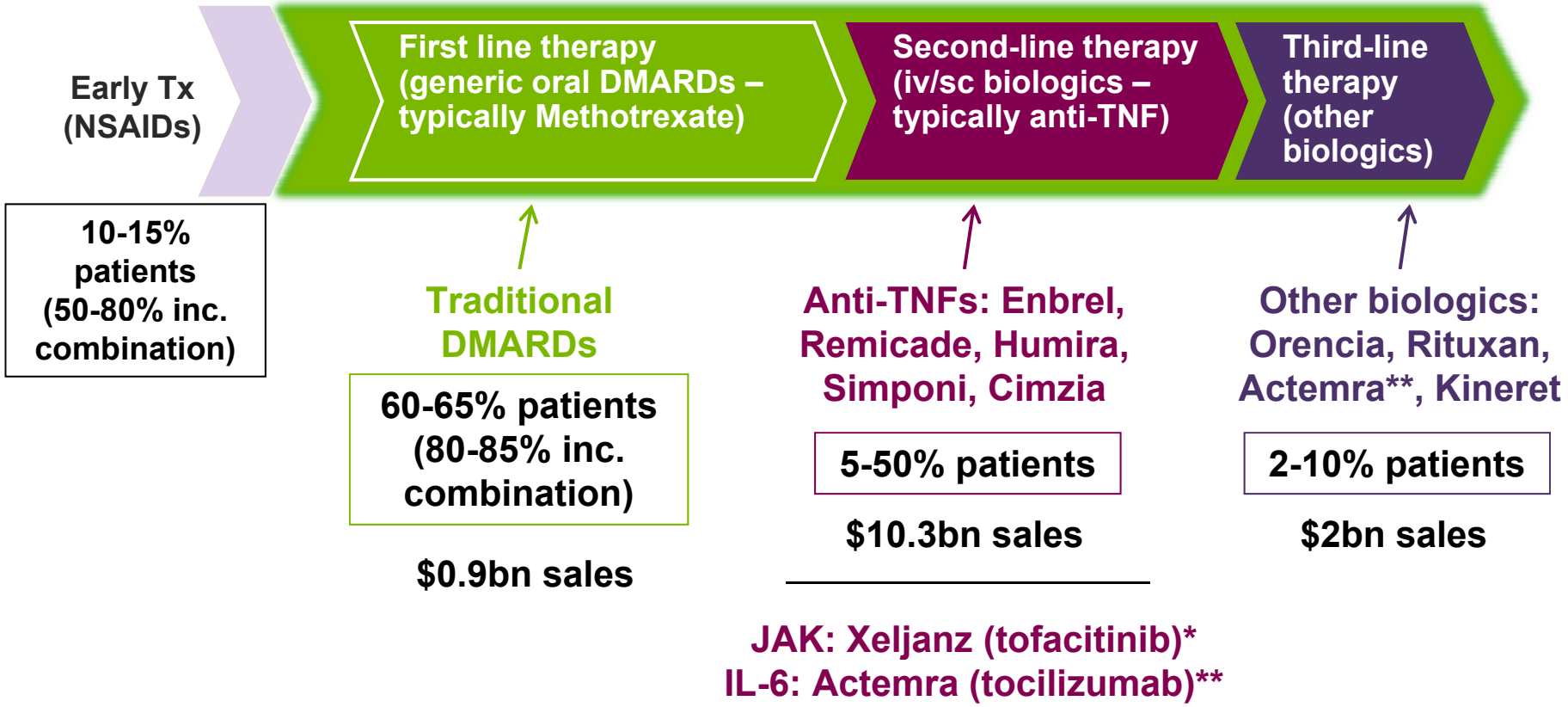
Rheumatoid arthritis is painful and debilitating

Early RA → RA with moderate joint deformity → severe RA

- Chronic, systemic, autoimmune disease
- RA causes painful, swollen, and tender joints
- Over time, inflammation in the joints can lead to joint damage including erosion of cartilage and bone

Patients go through several lines of treatment

~$14bn RA market expected to reach $18bn in 2022



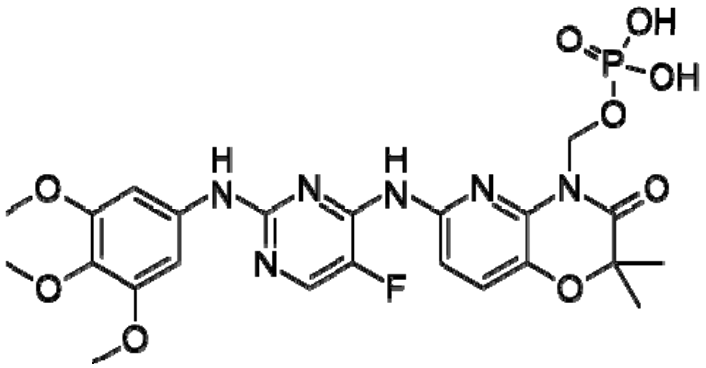
*XELJENZ approved Nov 2012 in RA patients who have had an inadequate response to, or intolerant of, methotrexate

**In Oct 2012, the FDA approved an expanded indication for ACTEMRA in RA patients who have had an inadequate response to one or more DMARDs.

Source: IMS Health; Q4 2011 MAT MIDAS Quantum, based on AZ selected Markets - 53 Countries

About fostamatinib

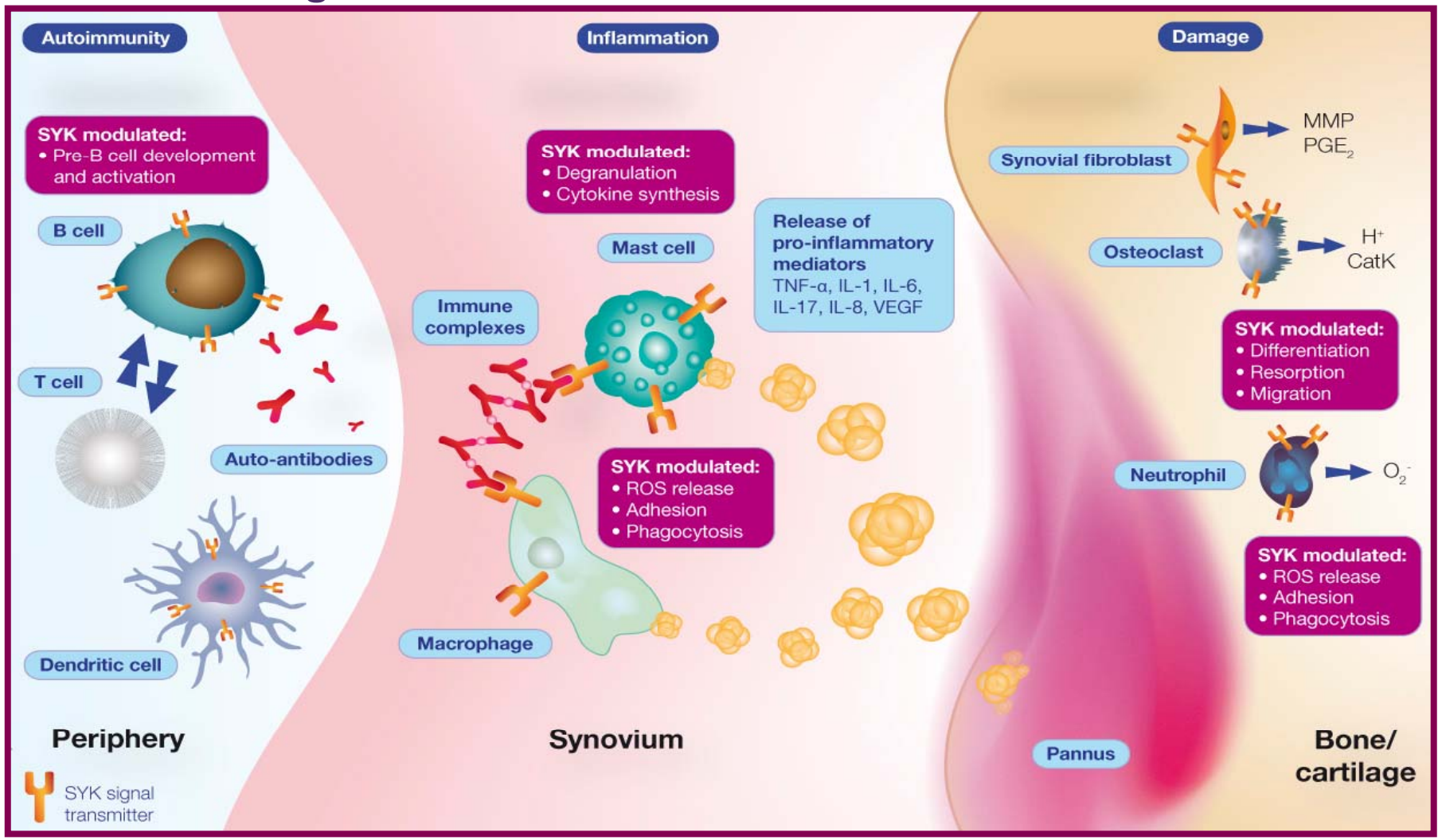
- Fostamatinib was in-licensed from **Rigel Pharmaceuticals, Inc.** in February 2010 for an initial upfront payment of $100m AZ has full development and commercial rights (except respiratory indications).
- Fostamatinib is a novel MOA, oral kinase inhibitor that has selectivity for SYK
- The Phase III programme, OSKIRA, started in Sep 2010 and is designed to investigate fostamatinib as a therapeutic option for patients who have an inadequate response to currently available therapies, such as traditional disease modifying anti-rheumatic drugs (DMARDs) and anti-TNFs
- We expect Phase III studies to report in the first half of 2013 and plan to file in US and EU in 2H 2013.



Fostamatinib's chemical structure

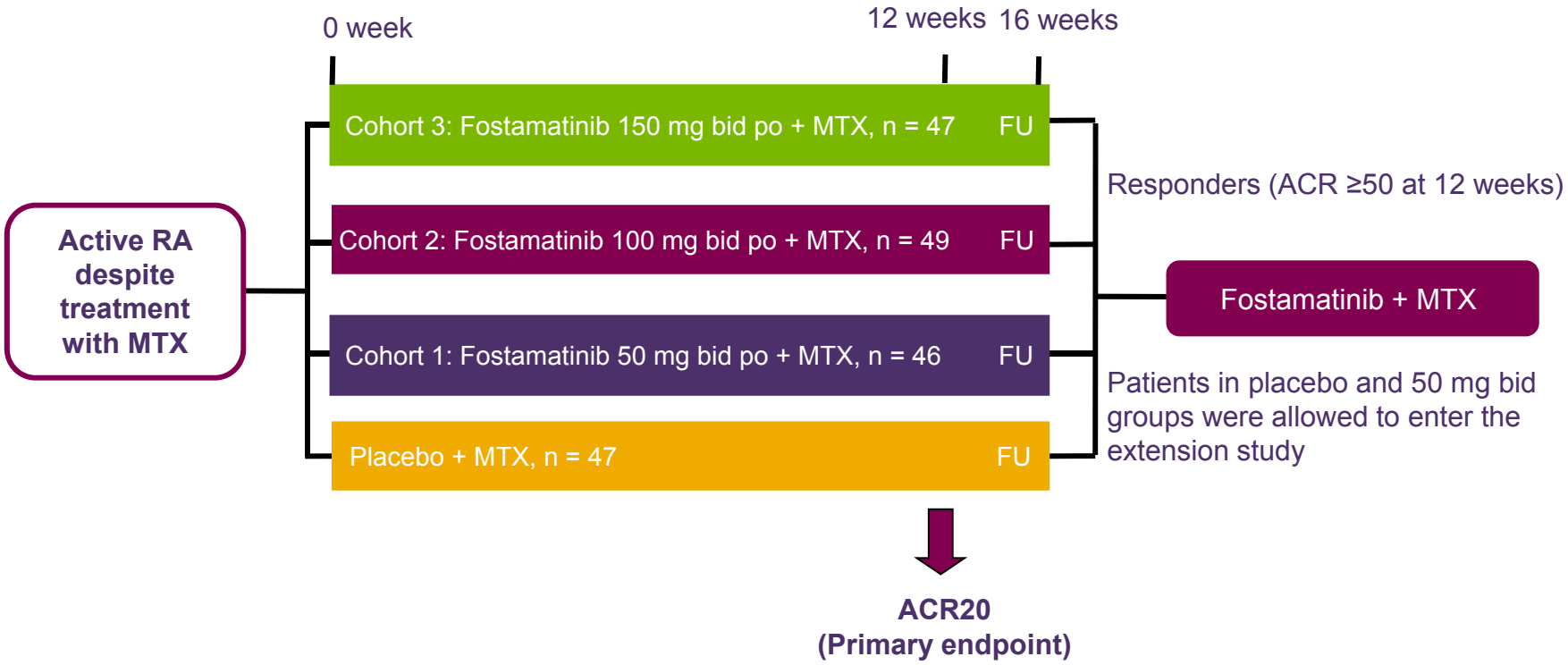
Mechanism of action

- Fostamatinib is an oral kinase inhibitor that has selectivity for SYK
- SYK has a broad role in RA autoimmunity, inflammation, and tissue damage



Fostamatinib Phase II data

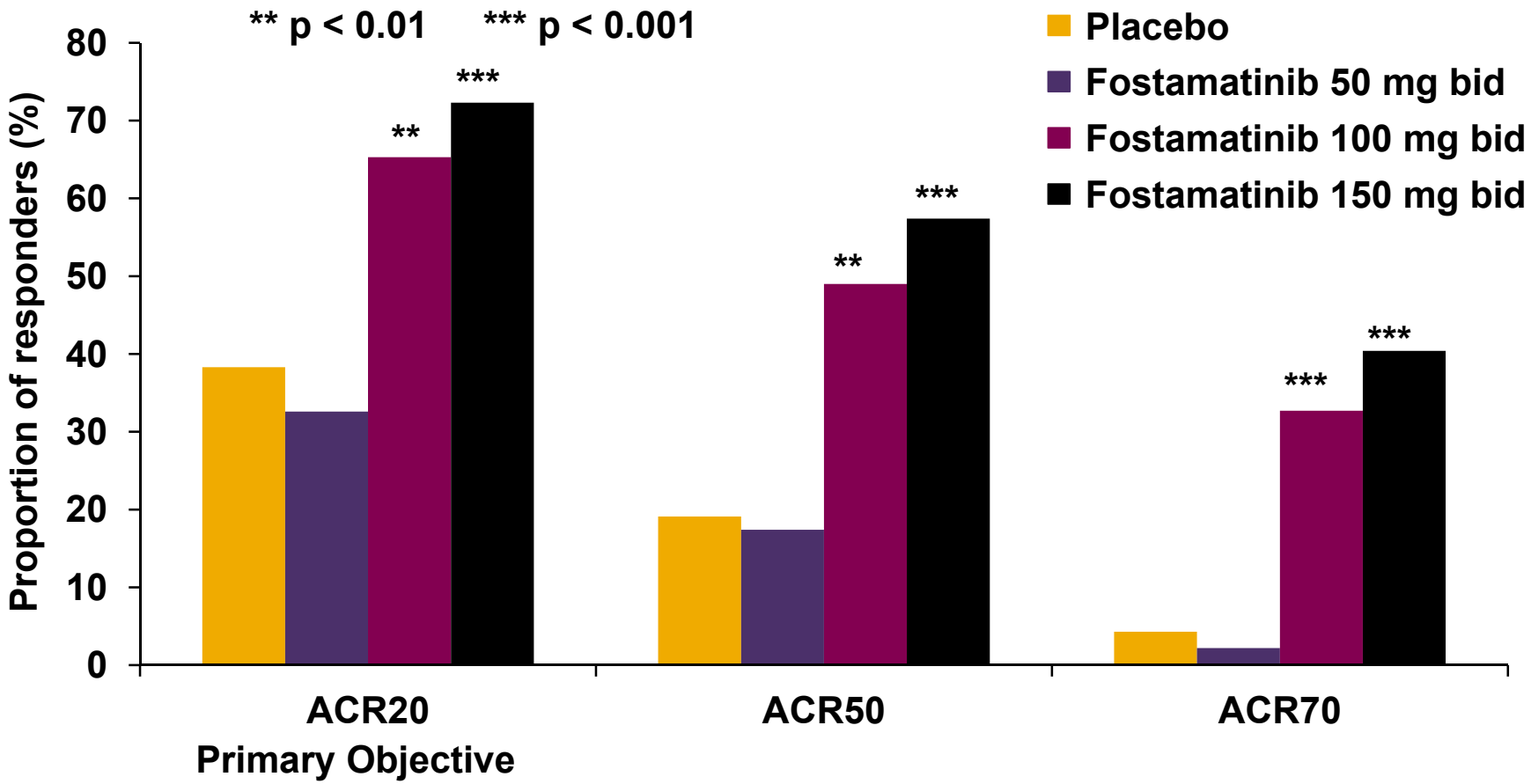
Ph IIa TASKi1 Study Design



Primary Objective: To compare efficacy of three different doses of fostamatinib as determined by American College of Rheumatology (ACR) 20 responder rates at 12 weeks

Weinblatt ME, et al. *Arthritis Rheum.* 2008;58:3309–3318. Link to publication

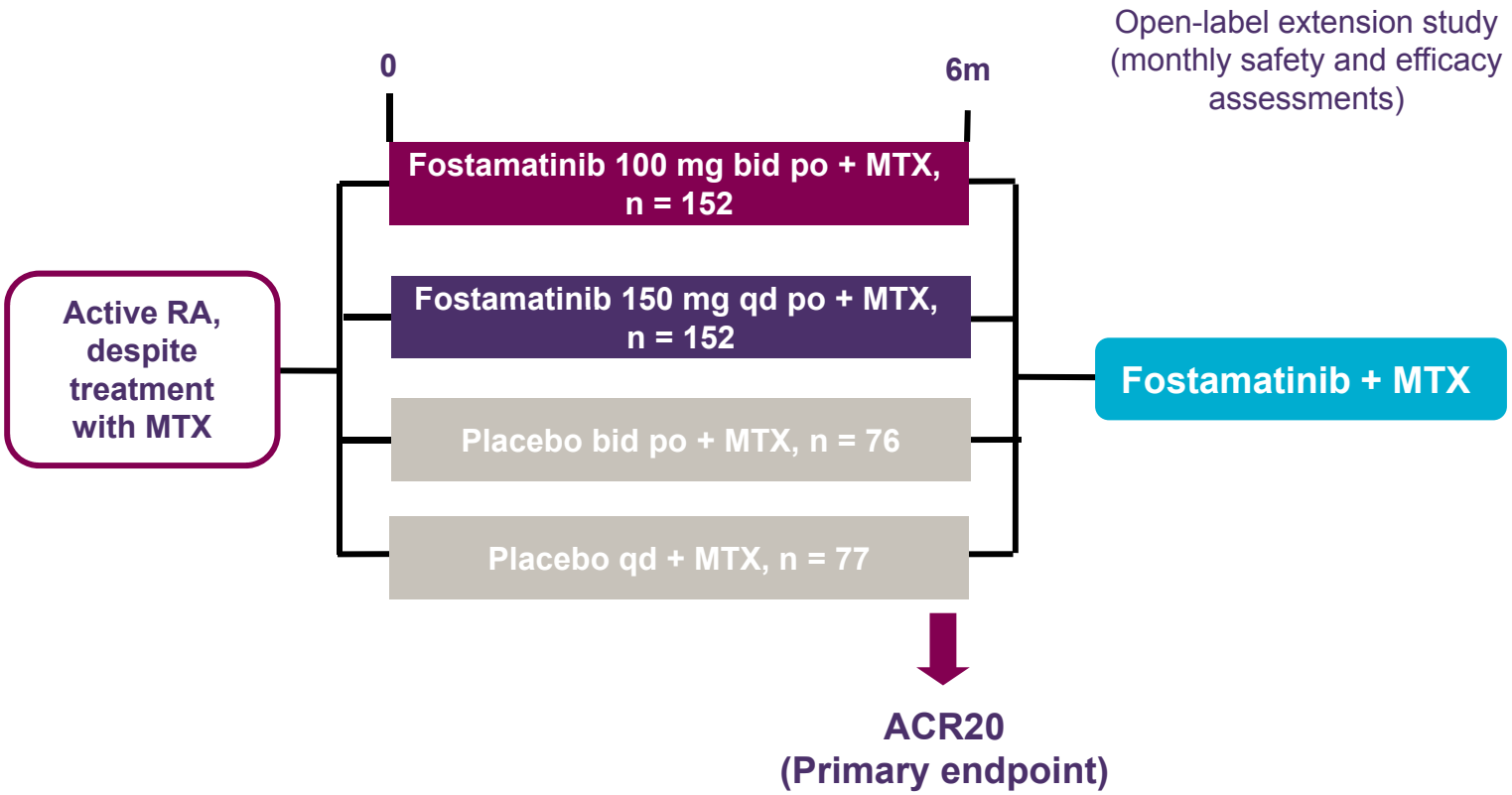
Ph IIa TASKi1 ACR Response Rates at Week 12



As pre-specified, all dropout patients were considered ACR non-responders at all time points after withdrawal

Weinblatt ME, et al. *Arthritis Rheum*. 2008;58:3309–3318.

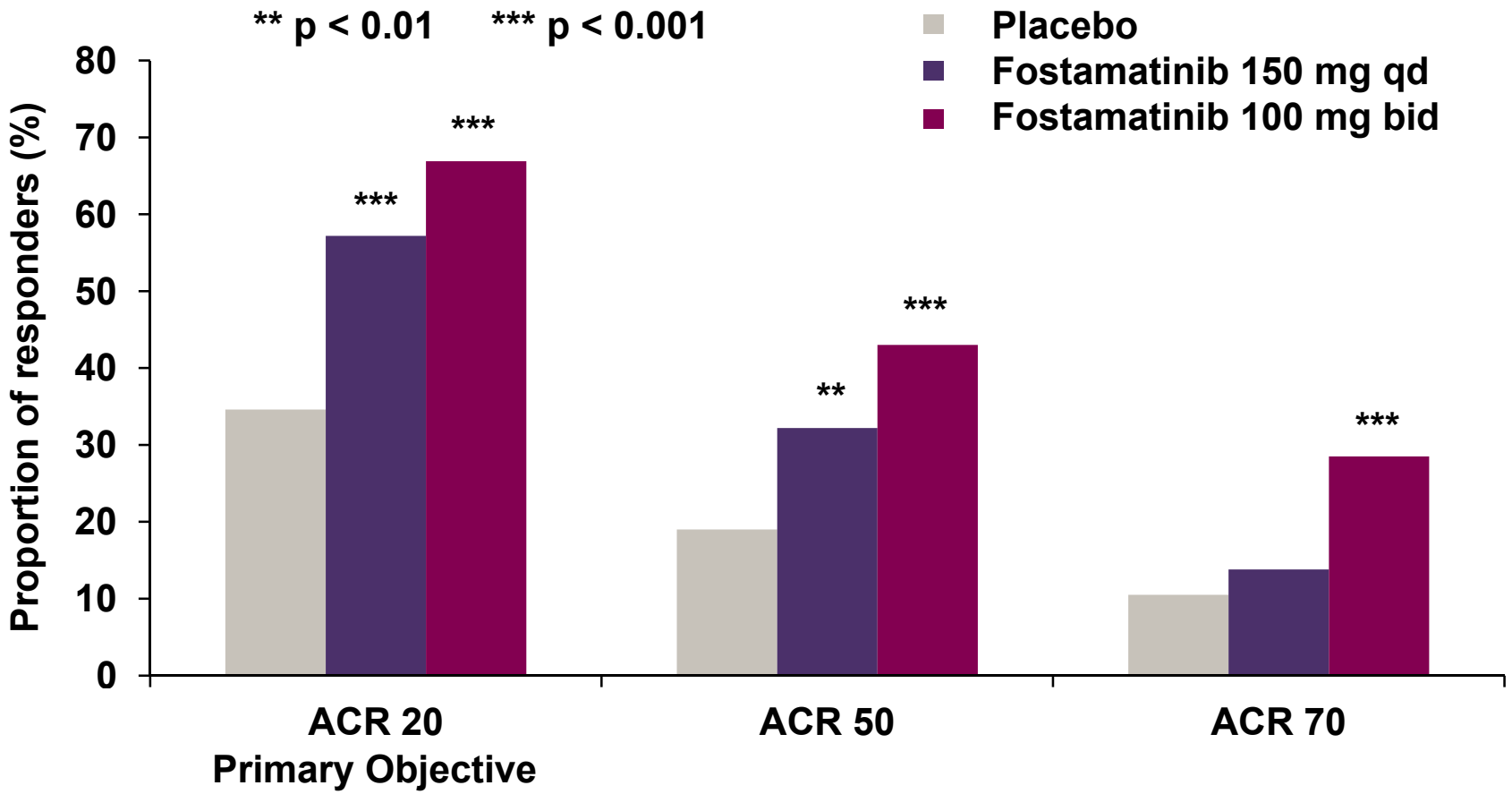
Ph II TASKi2 Study Design



Primary Objective: To confirm efficacy of fostamatinib 100 mg bid po as determined by ACR20 responder rates at 6 months

Weinblatt ME, et al. *N Engl J Med*. 2010;363:1303–1312. Link to publication

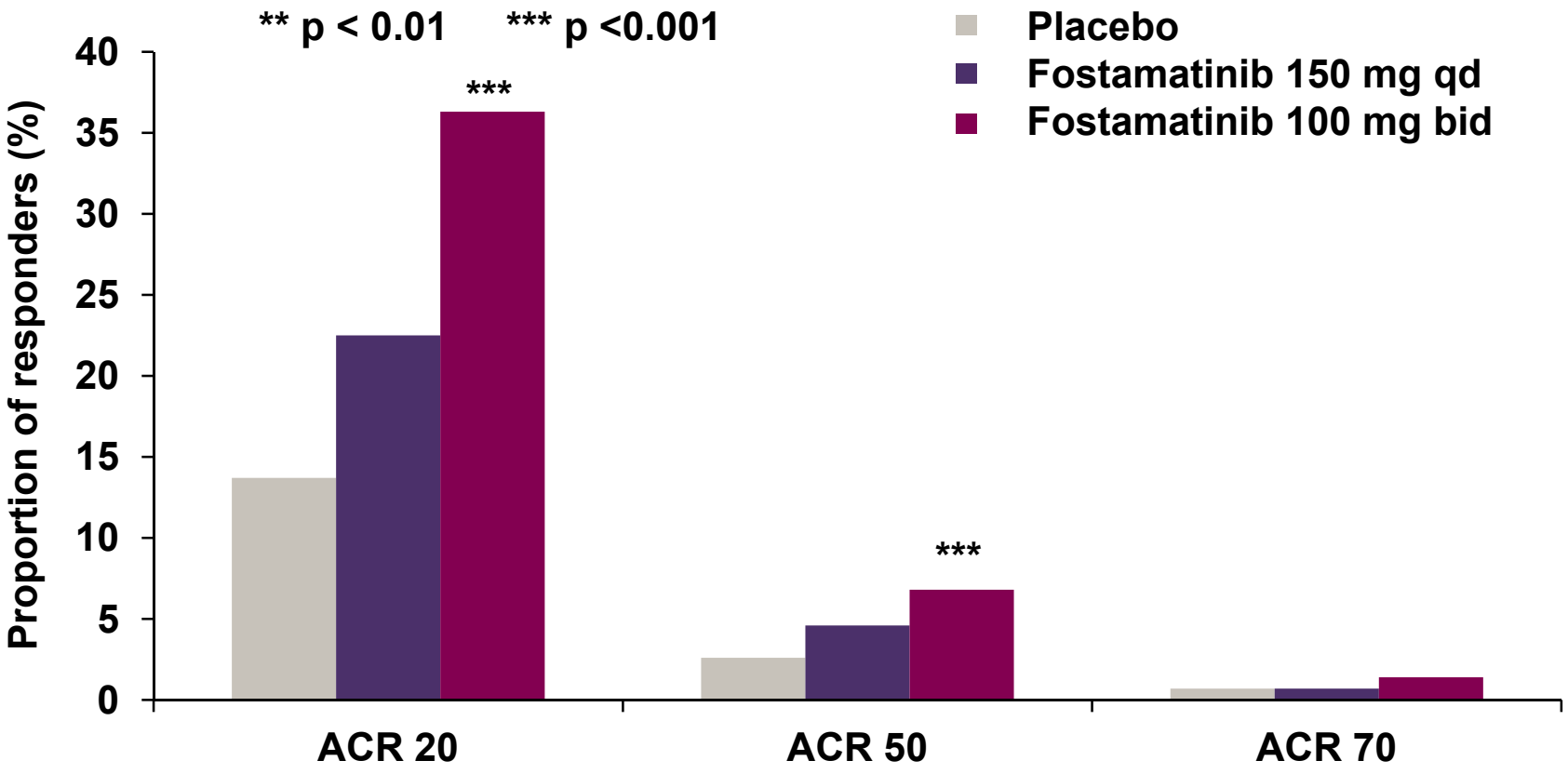
Ph II TASKi2 ACR Response Rates at Month 6



As pre-specified, all dropout patients were considered ACR non-responders at all time points after withdrawal

Weinblatt ME, et al. *N Engl J Med.* 2010;363:1303–1312.

Ph II TASKi2 ACR Response Rates at Week 1



As pre-specified, all dropout patients were considered ACR non-responders at all time points after withdrawal

Weinblatt ME, et al. *N Engl J Med*. 2010;363:1303–1312.

Ph II Taski2 Patient Reported Adverse Events

Most Frequent Adverse Events (>5%)

	Placebo	Fostamatinib 150 mg qd	Fostamatinib 100 mg bid
Diarrhea	3.0%	11.8%	19.1%
Upper Respiratory Infection	7.1%	7.2%	14.5%
Urinary Tract Infections	4.6%	3.3%	5.9%
Neutropenia	0.7%	6.6%	5.9%
Headache	5.2%	6.6%	5.9%
Abdominal pain	2.6%	6.6%	5.9%
Nausea	4.6%	5.9%	4.6%

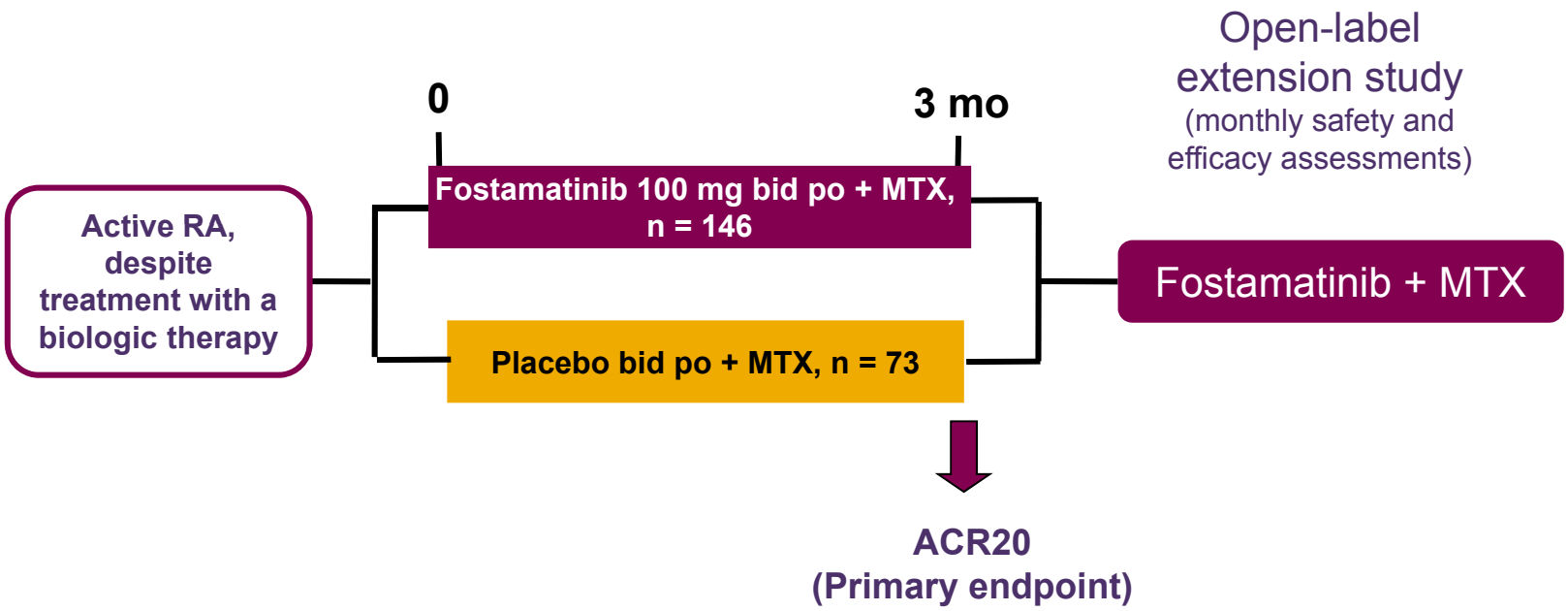
Additional safety findings:

•Increased blood pressure (≥ 140 SBP or ≥ 90 DBP mmHg) was more common among patients taking fostamatinib than placebo. Elevated blood pressure generally occurred within the first few weeks of therapy and was responsive to conventional anti-hypertensive medications and/or dose reduction/interruption.

•Serum alanine aminotransferase (ALT) elevations were more common in patients taking fostamatinib than placebo. The majority of these patients completed the study with a reduced fostamatinib dose and did not have a recurrence of an elevated ALT.

Weinblatt ME, Kavanaugh A, Genovese MC, *et al.* An Oral Spleen Tyrosine Kinase (Syk) Inhibitor for Rheumatoid Arthritis.*The New England Journal of Medicine,* 2010;363:1303-1312.

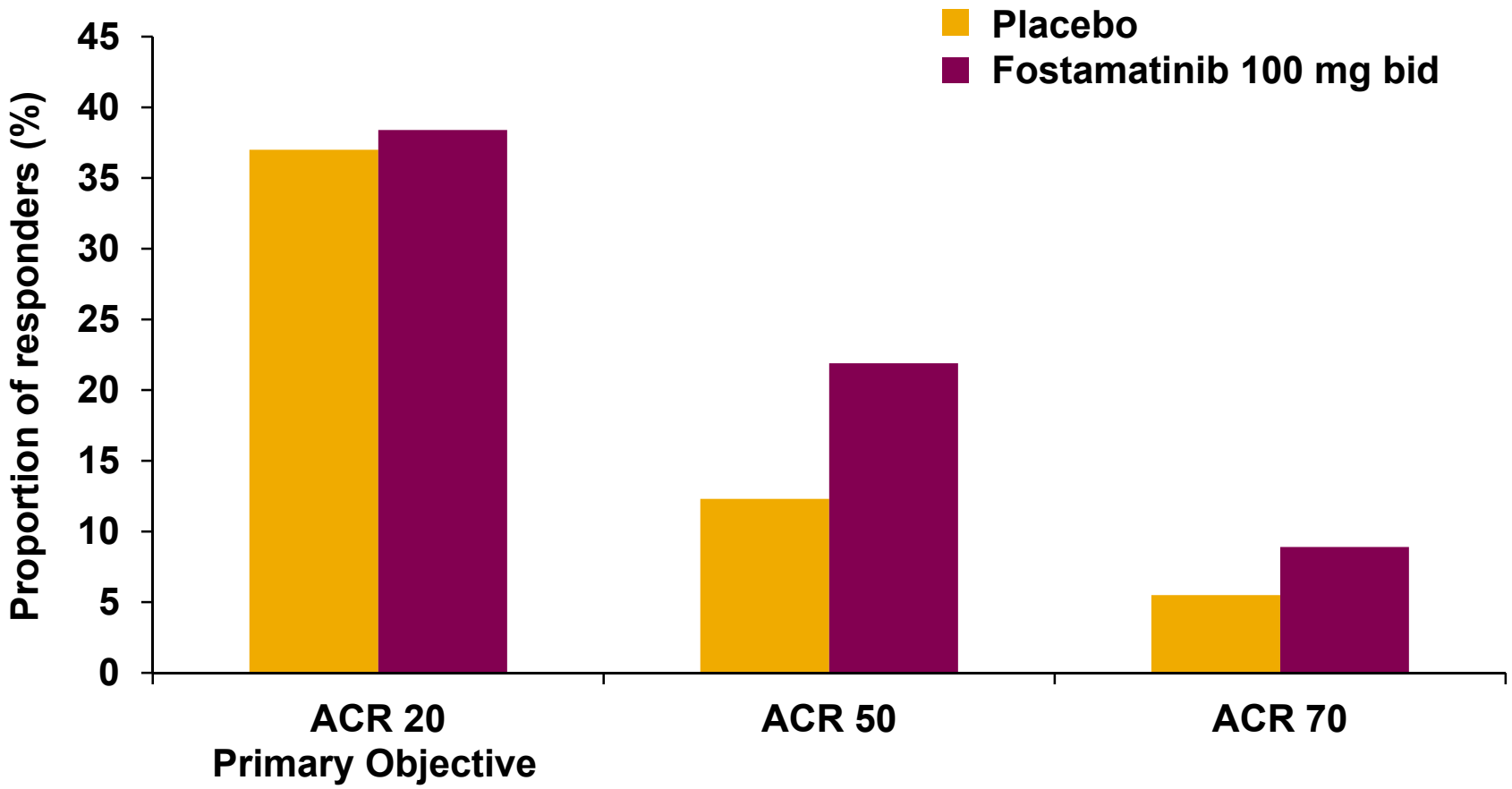
Ph II TASKi3 Study Design



Primary Objective: To assess efficacy of fostamatinib 100 mg bid po as determined by ACR20 responder rates at 3 months

Genovese MC, et al. *Arthritis Rheum.* 2011;63:337–345. Link to publication

Ph II TASKi3 ACR Response Rates at Month 3

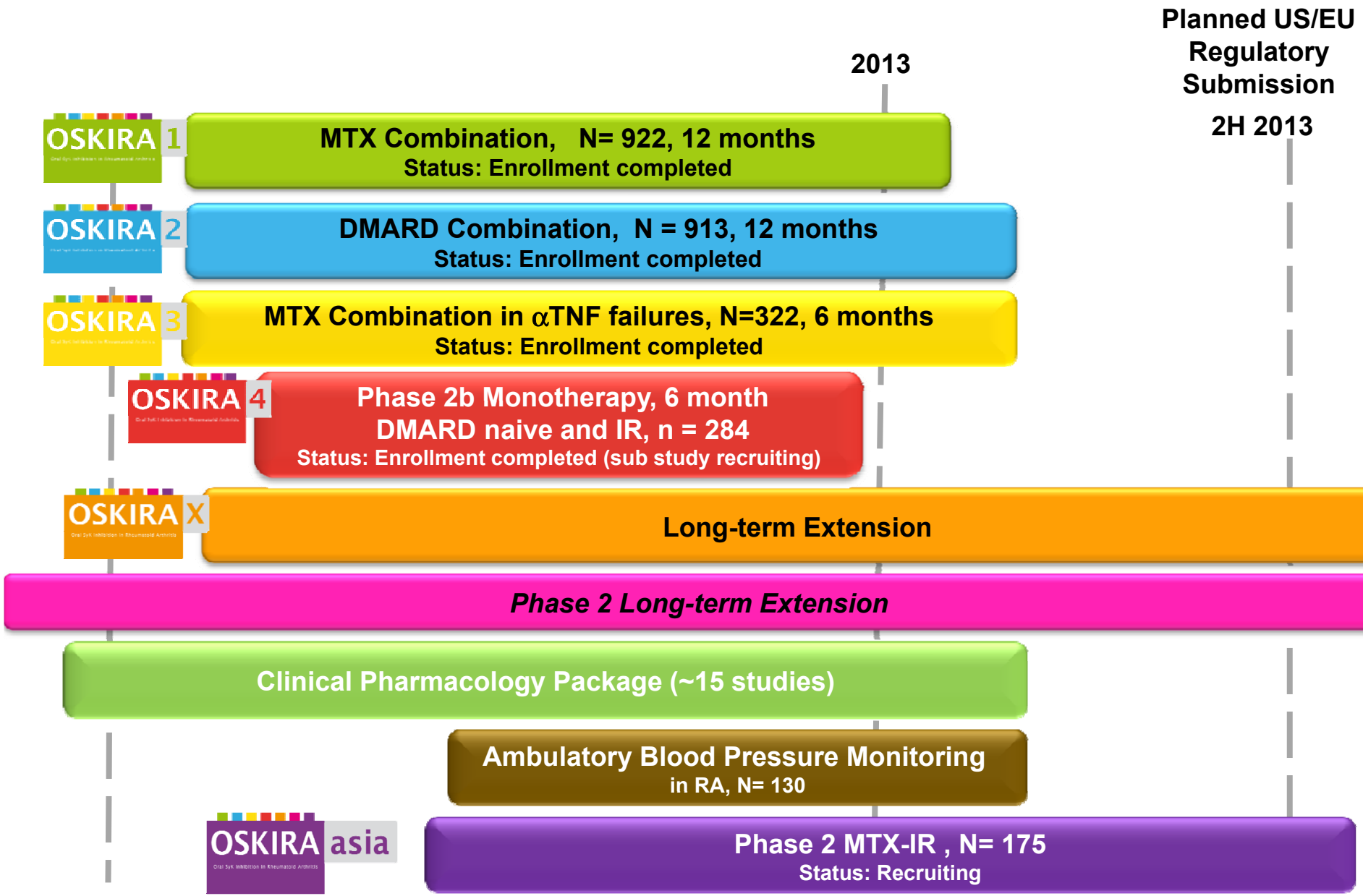


As pre-specified, all dropout patients were considered ACR non-responders at all time points after withdrawal

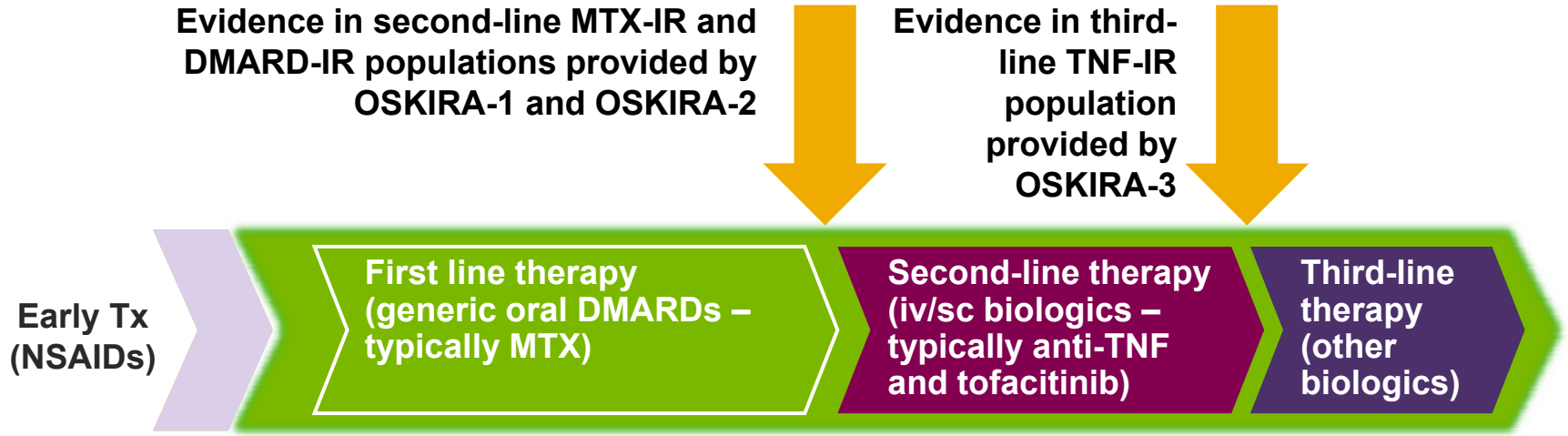
Genovese MC, et al. *Arthritis Rheum*. 2011;63:337–345.

OSKIRA Clinical Programme

OSKIRA Ph III Studies Reporting in 1H 2013



Fostamatinib evidence base in RA



Fostamatinib is being evaluated for both efficacy and safety in patients who are incomplete responders to DMARDs and a single anti-TNF in Phase III.

Q&A

BACKUP SLIDES

Fostamatinib and rheumatoid arthritis

Key facts

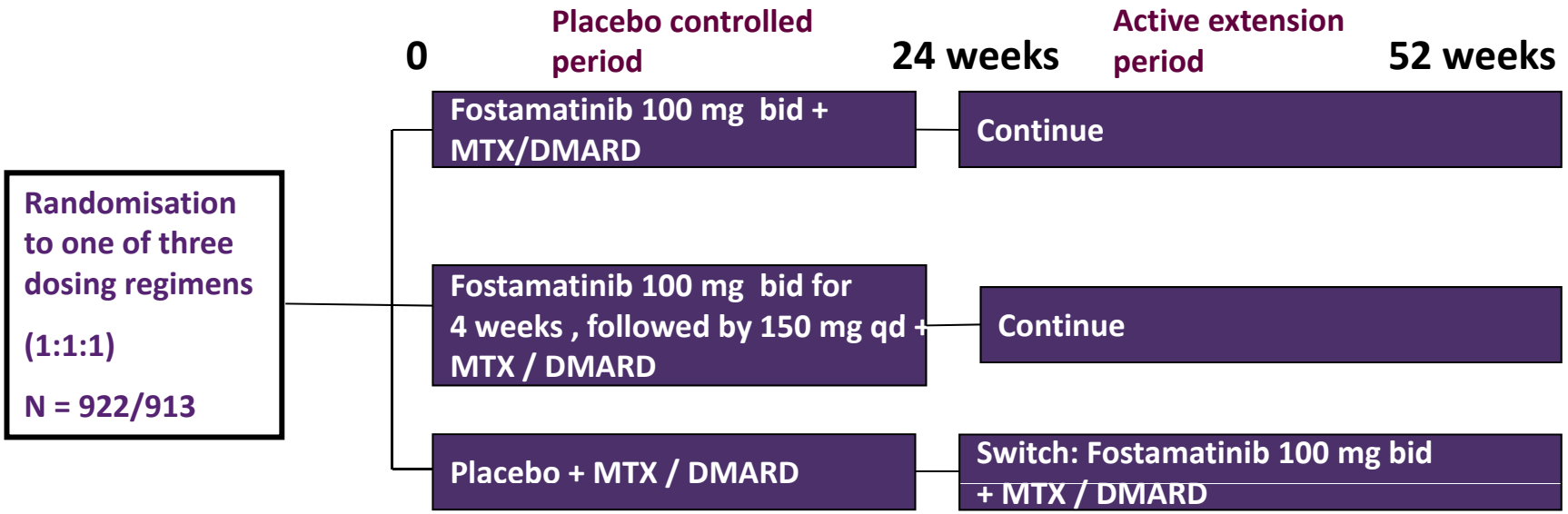
1 Fostamatinib is an oral kinase inhibitor that has selectivity for spleen tyrosine kinase (SYK) in development for rheumatoid arthritis. It is being studied as an **alternative to injectable therapies for rheumatoid arthritis**.

2 Rheumatoid arthritis is a painful, disabling, chronic inflammatory disease, which **causes damage to the joints** and other organs, affecting approximately 1 in 100 people.

3 Not all rheumatoid arthritis patients will respond to the same treatment because the disease pathology may differ from one individual to another. Therefore **new treatment options are needed**.

Phase III design: OSKIRA 1 (MTX-IR) and 2 (DMARD-IR)

Male and female patients aged 18 years or over, with active RA despite current treatment.



Rescue

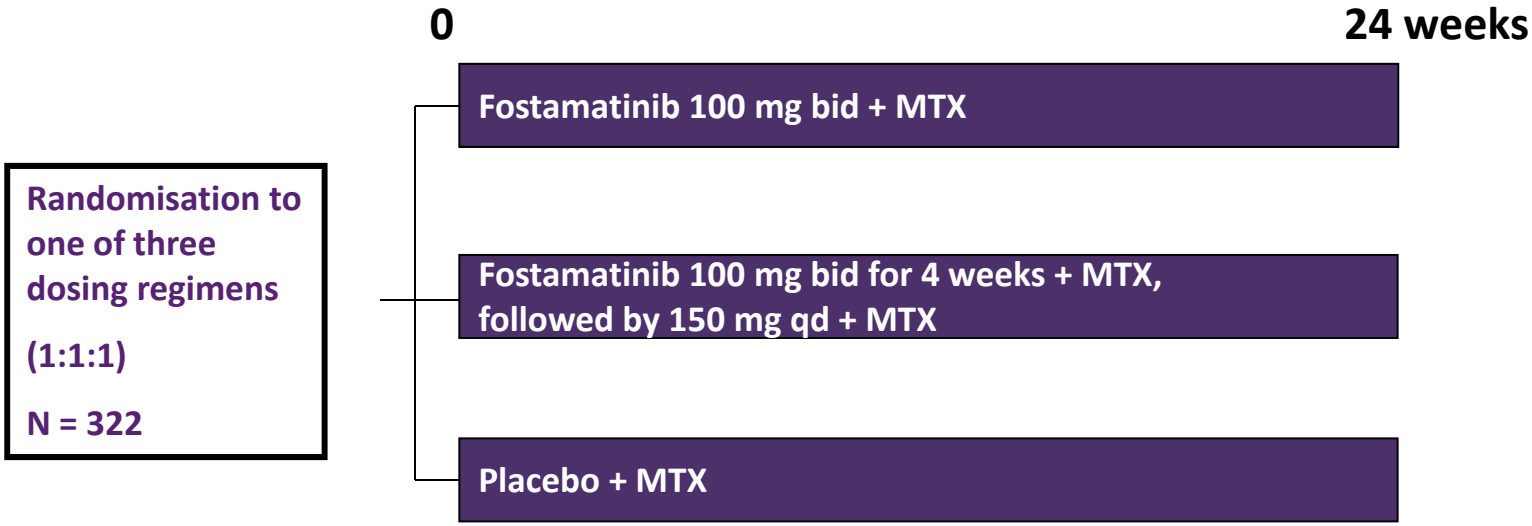
Non-responders rescued at week 12 to Long-Term Extension study

A reduced dosing regimen of 100 mg qd is available if patient meets dose reduction criteria

Patients receiving placebo will be switched to active treatment at 24 weeks

Phase III design: OSKIRA 3

Patients with an inadequate response to a single TNFα antagonist



Placebo arm until study end

Rescue: Non-responders rescued at 12 weeks onwards to Long -Term Extension Study

A reduced dosing regimen of 100 mg qd is available if patient meets dose reduction criteria

Design of Phase II OSKIRA-4 study