Fostamatinib Analyst Briefing

15 November 2012
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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

Chris O’Brien
Medical Science Director

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Global Marketing Director
Why rheumatoid arthritis?
A prevalent disease with significant unmet need

<table>
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<tr>
<th>1 in 100</th>
<th>people worldwide are affected by RA¹</th>
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<tr>
<td>35 – 50</td>
<td>years old is the typical age when RA symptoms appear,² with women 3x more likely to be affected than men³</td>
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<td>9 Million</td>
<td>RA patients treated with disease-modifying therapy (traditional and biologic)⁴,⁵</td>
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<td>7 Million</td>
<td>RA patients do not achieve remission with a traditional disease modifying anti-rheumatic drug (DMARD) alone⁶</td>
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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
Rheumatoid arthritis is painful and debilitating

- 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

First line therapy (generic oral DMARDs – typically Methotrexate)

Early Tx (NSAIDs)

10-15% patients (50-80% inc. combination)

Traditional DMARDs

10-15% patients

60-65% patients (80-85% inc. combination)

$0.9bn sales

Second-line therapy (iv/sc biologics – typically anti-TNF)

Anti-TNFs: Enbrel, Remicade, Humira, Simponi, Cimzia

5-50% patients

$10.3bn sales

Third-line therapy (other biologics)

Other biologics: Ocrenica, Rituxan, Actemra**, Kineret

2-10% patients

$2bn sales

JAK: Xeljanz (tofacitinib)*
IL-6: Actemra (tocilizumab)**

*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.
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
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.

Ph IIa TASKi1 ACR Response Rates at Week 12

** p < 0.01  *** p < 0.001

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

Ph II TASKi2 Study Design

Active RA, despite treatment with MTX

Fostamatinib 100 mg bid po + MTX, n = 152

Fostamatinib 150 mg qd po + MTX, n = 152

Placebo bid po + MTX, n = 76

Placebo qd + MTX, n = 77

Fostamatinib + MTX

ACR20 (Primary endpoint)

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

Open-label extension study (monthly safety and efficacy assessments)

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.

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

**Ph II Taski2 Patient Reported Adverse Events**

**Most Frequent Adverse Events (>5%)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fostamatinib 150 mg qd</th>
<th>Fostamatinib 100 mg bid</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>3.0%</td>
<td>11.8%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>7.1%</td>
<td>7.2%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>4.6%</td>
<td>3.3%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.7%</td>
<td>6.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>5.2%</td>
<td>6.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.6%</td>
<td>6.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.6%</td>
<td>5.9%</td>
<td>4.6%</td>
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**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.

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

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.

OSKIRA Clinical Programme
OSKIRA Ph III Studies Reporting in 1H 2013

MTX Combination, N=922, 12 months
Status: Enrollment completed

DMARD Combination, N=913, 12 months
Status: Enrollment completed

MTX Combination in αTNF failures, N=322, 6 months
Status: Enrollment completed

Phase 2b Monotherapy, 6 month
DMARD naive and IR, n=284
Status: Enrollment completed (sub study recruiting)

Long-term Extension

Clinical Pharmacology Package (~15 studies)

Ambulatory Blood Pressure Monitoring in RA, N=130

Phase 2 MTX-IR, N=175
Status: Recruiting

Planned US/EU Regulatory Submission 2H 2013
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.
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.

Randomisation to one of three dosing regimens (1:1:1)  
N = 922/913

0  
Placebo controlled period

Fostamatinib 100 mg bid + MTX/DMARD

24 weeks  
Active extension period

Fostamatinib 100 mg bid for 4 weeks, followed by 150 mg qd + MTX / DMARD

52 weeks  
Continue

Placebo + MTX / DMARD

Switch: Fostamatinib 100 mg bid + MTX / DMARD

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

Randomisation to one of three dosing regimens (1:1:1)
N = 322

- Fostamatinib 100 mg bid + MTX
- Fostamatinib 100 mg bid for 4 weeks + MTX, followed by 150 mg qd + MTX
- Placebo + MTX

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

**Induction* = Fostamatinib 100 mg bid po + placebo injection q2w**

- **Patients with active RA not receiving DMARDs**
  - **Month 0:** Fostamatinib 100 mg bid po + placebo injection q2w
  - **Month 1:** Fostamatinib 150 mg qd po + placebo injection q2w
  - **Month 2:** Fostamatinib 100 mg qd po + placebo injection q2w
  - **Month 3:** Adalimumab 40 mg q2w sc + placebo bid po
  - **Month 4:** Fostamatinib 100 mg bid po + placebo injection q2w
  - **Month 5:** Fostamatinib 150 mg qd po + placebo injection q2w

**Long-term extension study (OSKIRA-X):** Patients completing 52 weeks of treatment

**Primary endpoint:** DAS28 (week 6 and 24)