Kinase Inhibitors in RA

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Disclosures

- Dr. Weinblatt has been a consultant to the following companies involved in the JAK and SYK pathways in RA
  - Pfizer
  - Vertex
  - Astellas
  - Lilly
  - Rigel
  - Astra-Zeneca
  - Portolo
- Off label discussion in the lecture—
  - JAK inhibitors in transplant
  - psoriasis, inflammatory bowel disease
Key References


Kinase Inhibitors

- P38 MAP kinase
- MEK
- JAK-3/ JAK 1 & 2
- Syk kinase

P38 INHIBITORS

- A LOT OF ACTIVITY OVER THE PAST 10 YEARS BUT UNTIL RECENTLY VERY LITTLE IN THE PUBLIC DOMAIN
- POSITIVE PRE-CLINICAL EFFECTS INCLUDING ANIMAL MODELS
- EFFICACY RESULTS HAVE BEEN DISAPPOINTING TO DATE
JAK Inhibitors

- Critical for signal transduction for multiple interleukins
- Important for lymphocyte activation, function and proliferation
- There are 4 identified JAKs 1, 2, 3, and Tyk 2
- Studies in transplant, myelofibrosis, RA, psoriasis, IBD
- Positive results in animal models of arthritis
- Positive Phase 2 and 3 studies in RA
- Several JAK inhibitors in development

JAK and Activating Cytokines

<table>
<thead>
<tr>
<th>JAK</th>
<th>CYTOKINE</th>
<th>PHENOTYPE OF KO MOUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK 1</td>
<td>Gp 130 cytokines IL6, type 1,2 IFN, γchain cytokines IL-2,4,7,9,15,21</td>
<td>Perinatally lethal Neurological defects and SCID</td>
</tr>
<tr>
<td>JAK 2</td>
<td>EPO, INF, IL-12, GCSF, IL-6 type 1,2 IFN,</td>
<td>Embryonically lethal: defective erythropoiesis</td>
</tr>
<tr>
<td>JAK 3</td>
<td>γchain cytokines IL-2,4,7,9,15,21</td>
<td>SCID</td>
</tr>
<tr>
<td>TYK 2</td>
<td>Gp 130 cytokines, type 1 IFNs, IL 12/23</td>
<td>Modest viral susceptibility</td>
</tr>
</tbody>
</table>
Selectivity of Tofacitinib

- Reasonably selective for Jaks
- Selectivity amongst Jaks?
  - Limitations of assay
- Cellular selectivity for Jaks: Jak3, Jak1 > Jak2 >> Tyk2
- Relevance to efficacy? Blocks innate and adaptive responses

Description
Tofacitinib (CP-690.550) is a Janus-Kinase inhibitor. Inhibits cytokine signaling through the common \( \gamma \) chain family of cytokine receptors.

Block innate and adaptive immunity
Cellular selectivity for Jaks: Jak3, Jak1 > Jak2 >> Tyk2
Tofacitinib (CP-690.550): Phase 2 Studies

- Transplant in combination with Cell Cept
- RA
  - Monotherapy - Dose ranging studies
  - Combo with MTX - Dose ranging studies
  - Doses of 1-30 mg bid, 20 mg qd

Tofacitinib: Phase 3 Studies

- Monotherapy study
- Combination with DMARDs
- Structural damage study
- TNF failures
- Combination with MTX with anti-TNF anchor
- Tofa vs MTX
Tofacitinib Phase 3 Study: Monotherapy
NEJM 2012; 367: 495

- 24 wk RCT of 2 doses of tofacitinib (5,10 mg) bid vs Placebo
- Monotherapy Phase 3 Study
- At 12 wks placebo- blindly advanced to tofacitinib
- 3 co-primary endpts- ACR 20, change from baseline in HAQ, DAS (esr) remission
- 611 pts, disease duration >8 yrs , most (85%), had received MTX in past, 15% prior anti-tnf
- At wk12-

<table>
<thead>
<tr>
<th></th>
<th>ACR 20</th>
<th>HAQ</th>
<th>Das remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>27%</td>
<td>-0.2</td>
<td>4%</td>
</tr>
<tr>
<td>5 mg bid</td>
<td>60% *</td>
<td>-0.5*</td>
<td>6%</td>
</tr>
<tr>
<td>10 mg bid</td>
<td>66% *</td>
<td>-0.6*</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

* p <0.0001

- AE’s 10-20% increase in LDL, Serious infections 6 pts
- Confirms the results of the Phase 2 monotherapy study

Tofacitinib Phase 3 Study: DMARDs
EULAR 2011

- 52 wk RCT of 2 doses of tofacitinib (5,10 mg) bid vs placebo plus DMARDs- Phase 3 Study
- At 12 wks non responder placebo- blindly advanced to tofacitinib
- Primary endpts- ACR 20, DAS (esr) remission -month 6
- change from baseline in HAQ- mo3
- 792 pts, disease duration >8 yrs, DAS >6.1
- At wk24-

<table>
<thead>
<tr>
<th></th>
<th>ACR 20</th>
<th>Das remission</th>
<th>HAQ ( 3 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>31%</td>
<td>3%</td>
<td>-0.21</td>
</tr>
<tr>
<td>5 mg bid</td>
<td>53% *</td>
<td>11%</td>
<td>-0.46*</td>
</tr>
<tr>
<td>10 mg bid</td>
<td>58% *</td>
<td>15%*</td>
<td>-0.56*</td>
</tr>
</tbody>
</table>

* p <0.0001

- AE’s 4 deaths ( 5 mg- traumatic brain, RA, 10 mg chf, resp failure
- 4 opportunistic infections ( TB china, thailand, Crypto- australia, zoster finland)
- lab abnormalities- neutropenia, increased creatinine and lipids
Tofacitinib Phase 3: Prior Anti-TNF Study
ACR 2011

- 24 wk RCT of 2 doses of tofacitinib (5,10 mg) bid vs Placebo in combo with MTX in pts who had received >1 ant-tnf
- At 12 wks placebo- blindly advanced to tofacitinib
- 3 co-primary endpts- ACR 20, change from baseline in HAQ, DAS (esr) remission
- 399 pts, disease duration >11 yrs, 30%> 2 anti-tnf
- At wk12-
  - ACR 20      HAQ    Das remission
  - Placebo 24%  -0.2  2%
  - 5 mg bid 42% * -0.4* 7%+
  - 10 mg bid 48% * -0.4* 11%+
  - * p <0.0001  +p<0.05
- AE’s consistent with other studies

Tofacitinib Phase 3: Anti-tnf anchor study
NEJM 2012; 367: 508

- 717pt, 52 wk RCT of 2 doses of tofacitinib (5,10 mg) bid vs Placebo vs Adalimumab 40 mg q2wks in combo with MTX
- At 12 wks placebo- blindly advanced to tofacitinib at mo 3 if non responder ( <20% reduction in joint scores) at mo 6 all PBO advanced
- Co-primary endpts- ACR 20, DAS (esr) remission at mo 6, change from baseline in HAQ at mo 3
  - ACR 20      HAQ    Das remission
  - Placebo 28%  -0.2  1%
  - 5 mg bid 52% * -0.6* 7%+
  - 10 mg bid 53% * -0.6* 12%*
  - Adalimumab 47%* -0.5 6%+
  - * p <0.0001  +p<0.05
- AE’s consistent with other studies, serious infections in 3-4% of Tofa pts and 1.5% adalimumab pts
Tofacitinib Phase 3: XRAY study
ACR 2011

- 797 pt 104 wk RCT of 2 doses of tofacitinib (5, 10 mg) bid vs Placebo with MTX. At 12 wks placebo blindly advanced to tofacitinib at mo 3 if non responder (<20% reduction in joint scores) at mo 6 all PBO advanced.
Criteria for entry: elevated ESR or CRP and either three joint erosions or RF+ or anti-CCP+
- Co-primary endpts: ACR 20, DAS (esr) remission at mo 6,
  change from baseline in HAQ at mo 3
- Primary outcomes
  - ACR 20          HAQ            TSS
    - Placebo 25% -0.1 0.47
    - 5 mg bid 52% * -0.4 0.12
    - 10 mg bid 62% * -0.5* 0.06+
  * p <0.0001  +p<0.05
  - AE’s consistent with other studies

FDA Presentation: X-Ray
2012
Tofacitinib vs MTX  Phase 3 Study
ACR 2012 #2486

- 24 mo RCT of 2 doses of tofacitinib (5,10 mg) bid vs MTX – dose escalation to 20 mg
- Primary endpts at wk 24- ACR 70, XRay Score
- 952 pts, MTX naive
- At wk 24-
- ACR 20  ACR 70  mTSS
  - Placebo  51%  12  0.84
  - 5 mg bid  71% *  26*  0.18*
  - 10 mg bid  76% +  38*  0.04*
  - * p <0.0001  +p<0.0501
- AE’s consistent with other studies

Baricitinib (INCBO 28050) in RA: Phase 2
ACR 2012- 2487

- 301 pts -24 wk RCT of 4 doses of Bara (1,2,4,8 mg)qd vs placebo plus MTX. International study
- At 12 wk
- Bari  ACR 20  ACR 50  ACR 70
  - 1 mg  57%  31%  12%
  - 2 mg  54% *  17%*  8%
  - 4 mg  75% *  35%*  23%*
  - 8 mg  78%*  40%*  20%*
  - Placebo  41%  10%  2%
  - P<0.05
- Adverse events- Decreases in Hb, increase in LDL.
VK-509 in RA: Phase 2 Study
ACR 2011 LB

- VK-509 based on in vitro data more selective for inhibition of JAK-3, also observed in vivo with a dose dependent inhibition of a JAK-3 dependent biomarker
- 12 wk RCT of 4 doses of monotherapy VK 509 (25, 50, 100, 150 mg) bid vs placebo. No background MTX. Study performed in USA and Europe
- At 12 wk

<table>
<thead>
<tr>
<th>Dose</th>
<th>ACR 20</th>
<th>ACR 50</th>
<th>ACR 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>39%</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>50 mg</td>
<td>61% *</td>
<td>32% *</td>
<td>12%</td>
</tr>
<tr>
<td>100 mg</td>
<td>65% *</td>
<td>38% *</td>
<td>18% *</td>
</tr>
<tr>
<td>150 mg</td>
<td>66% *</td>
<td>49% *</td>
<td>22% *</td>
</tr>
</tbody>
</table>

* p <0.01

Placebo (41)
29% 7% 2%

- Adverse events - infections, nausea, headaches, ALT and increase in LDL.
- No declines in Hb or neutrophils

JAK inhibitors

- Positive Phase 2 Studies
  - Psoriasis
  - Ulcerative Colitis

- Negative Phase 2 study
  - Crohn’s Disease
## Table 7: Exposure to Tofacitinib by Dose and Duration in Phase 2, Phase 3 and LTE Studies in RA

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>5 mg BID (n=1677)</th>
<th>10 mg BID (n=1755)</th>
<th>5 mg/10 mg BID* (n=1178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 months</td>
<td>1366</td>
<td>1321</td>
<td>1135</td>
</tr>
<tr>
<td>≥ 12 months</td>
<td>1107</td>
<td>939</td>
<td>905</td>
</tr>
<tr>
<td>≥ 24 months</td>
<td>580</td>
<td>8</td>
<td>105</td>
</tr>
</tbody>
</table>

Source: Table 12. Integrated Summary of Safety (clinical data cut-off March 29, 2011);
*Subjects in 5 mg/10 mg BID group represent those who received different doses between the index study and the extension study.

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### Exposure to Tofacitinib in Phase 2, Phase 3 and LTE Trials in RA

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 exposure</td>
<td>1369</td>
<td>420</td>
</tr>
<tr>
<td>Phase 3 exposure</td>
<td>3030</td>
<td>2211</td>
</tr>
<tr>
<td>Long-Term Extension studies</td>
<td>3227*</td>
<td>3085</td>
</tr>
<tr>
<td>Total exposure at any dose</td>
<td>4816</td>
<td>5716</td>
</tr>
<tr>
<td>Exposure at any dose, by duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 month</td>
<td>4664</td>
<td>5320</td>
</tr>
<tr>
<td>≥ 3 months</td>
<td>4213</td>
<td>4580</td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>3768</td>
<td>3565</td>
</tr>
<tr>
<td>≥ 12 months</td>
<td>2703</td>
<td>1897</td>
</tr>
<tr>
<td>≥ 18 months</td>
<td>905</td>
<td>1008</td>
</tr>
<tr>
<td>≥ 24 months</td>
<td>696</td>
<td>623</td>
</tr>
</tbody>
</table>
JAK Inhibitors—AE profile

- Infections
  - Opportunistic infections
  - Zoster
- Lipid abnormalities
- Neutropenia
- Anemia
- Increase serum creatinine –
  - clinical significance?
- LFTs
- Malignancy

FDA Presentation: Lymphopenia
5/2012

- Five patients treated with tofacitinib 10 mg BID in the Phase 3 studies (all on background DMARD) experienced marked lymphopenia (two consecutive ALC<500/mm3). Of these, 3 (60%) developed infections (periodontitis, Herpes simplex, anda urinary tract infection).
- In the LTE studies, 10 patients experienced marked lymphopenia. Notably, 80% (8/10) of these patients developed infections, including 4 serious infections (3 cases of herpes zoster, 1 of which later developed disseminated TB, and 1 case each of pyelonephritis,
Tofacitinib plus Atorvastatin  
Eular 2011

- Background: Total cholesterol and LDL increased up to 25% in tofacitinib studies. No drug interactions between Tofa and atorvastatin
- Objective: Evaluate safety and LDL with atorvastatin plus tofa
- Design: 6 wk open run in of Tofa 10 mg bid and then 6 wk DB of tofa plus atorvastatin 10 mg vs tofa plus placebo
- Endpoint: Percent change in LDL from wk 6 (start of DB) to wk 12
- Demographics: 86% white, 43% Asian population, LDL 135 mg/dl
- Results: 35% reduction of LDL in the atorvastatin group to mean of 80. Total cholesterol, Apo B and triglycerides also decreased. No safety signal with the combination
Tofacitinib in RA

- Approved Nov 2012 as Xeljanz
- Indication- Active RA, inadequate response or intolerance to MTX
- Monotherapy or combo
- 5 mg bid dose approved
- Black Box on infections and malignancy
- Monitoring- CBC, lymphocytes, lipids 4-8 wks after dosing and CBC every 3 months, LFTs
- Cost- approx $ 23000

April 25,2013: Press Release

- NEW YORK--(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a negative opinion for XELJANZ® (tofacitinib citrate) for the treatment of adult patients with moderate-to-severe active rheumatoid arthritis (RA). The CHMP is of the opinion that XELJANZ does not demonstrate a favorable risk:benefit profile at this time and recommended against marketing authorization. Pfizer intends to appeal this opinion and immediately seek a re-examination of the opinion by the CHMP.
JAK Inhibitors

- JAK inhibitors work as monotherapy or in combination with MTX in RA
- Works quickly
- Narrow therapeutic dose window
- AEs relate to biological activity
  - Lipid elevations, hematological, infections
- Extensive Phase 3 program in RA
- Studies in psoriasis, psa, ibd

Questions about JAK Inhibitors

- Is there a differential response between monotherapy and combination with MTX?
  - If so what is the mechanism?
- If there a difference in response and toxicity between Tofa 5 and 10mg? What happens if the dose is reduced from 10 to 5 or increased from 5 to 10?
- What about lab toxicities - is this class or drug specific
  - Anemia - who develops this
  - Creatinine - what does this mean?
  - Lipids - is the increase pathogenic-
- What about long term infection and malignancy risk?
- What about pregnancy and conception?
- Where will it be positioned and where will it be used?
- Will more selective JAK inhibitors be as effective and offer a toxicity advantage?
Spleen Tyrosine Kinase (Syk)

- Cytoplasmic tyrosine kinase
- Found in a variety of cells including mast cells, macrophages, neutrophils and B cells. Syk plays a key role in signaling downstream of the B cell receptor
- Important mediator of immunoreceptor signalling in mast cells, macrophages, neutrophils and B cells
- Distal to Syk are a series of MAP kinases
- Syk expression detected in RA synovium as compared to OA
- Syk activation important in TNF induced cytokine and MMP production in RA synoviocytes
- Blocks TNF activation of JNK with reduced expression of JNK regulated genes IL-6 and MMP-3 (RA fibroblast synoviocytes)
- Positive results in standard models of arthritis and SLE in rodents
- Initial positive results in pts with ITP
- Positive studies in RA in combination with MTX

Syk Inhibitor R788 (Fostamatinib Disodium)

R788 is a pro-drug of R406, a moderately selective splenic tyrosine kinase (Syk) inhibitor, also inhibits other kinases including jak and vegf

Pharmacology- rapid oral absorption, terminal half life of 13-21 hrs, steady state achieved in 3-4 days
SYK INHIBITOR IN RA
NEJM 2010; 363:1303-1312

- 24 WK RCT, Active RA on background mtx, phase 2 study. Prior biologic rx was allowed in no more than 30% of population
- 457 PTS, international study
- R 788- 100 mg bid, 150 mg qd vs placebo
- Wk 24 responses-ACR 20
  - Pla 35%
  - R100 mg bid 67%
  - R150 mg qd 57%
- Clinical effect by wk1
- Aes- diarrhea increase in bp, elevated lfts, neutropenia
### ACR20 Responses at Month 6 by Region and Prior Biologic Use

- Consistent responses across all geographic areas

<table>
<thead>
<tr>
<th>Treatment Assigned</th>
<th>United States (n=109)</th>
<th>Latin America (n=223)</th>
<th>Eastern Europe (n=124)</th>
<th>Prior Biologic Therapy (n=67)</th>
<th>No Prior Biologic Therapy (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>22%</td>
<td>37%</td>
<td>42%</td>
<td>14%</td>
<td>38%</td>
</tr>
<tr>
<td>R788 150 mg qd</td>
<td>50% <em>(p=0.012)</em></td>
<td>66% <em>(p&lt;0.001)</em></td>
<td>50% <em>(p=0.425)</em></td>
<td>46% <em>(p=0.021)</em></td>
<td>59% <em>(p&lt;0.001)</em></td>
</tr>
<tr>
<td>R788 100 mg bid</td>
<td>56% <em>(p=0.003)</em></td>
<td>69% <em>(p&lt;0.001)</em></td>
<td>74% <em>(p=0.004)</em></td>
<td>43% <em>(p&lt;0.037)</em></td>
<td>71% <em>(p&lt;0.001)</em></td>
</tr>
<tr>
<td>Difference in R788 100 mg bid Placebo ACR20 % response</td>
<td>34%</td>
<td>32%</td>
<td>32%</td>
<td>29%</td>
<td>33%</td>
</tr>
</tbody>
</table>

### Treatment-Emergent Adverse Events Most Common (>5%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>R788 150 mg qd</th>
<th>R788 100 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract Infections</td>
<td>4.2%</td>
<td>3.3%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>3.0%</td>
<td>2.0%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0%</td>
<td>11.8%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2%</td>
<td>5.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Headache</td>
<td>5.2%</td>
<td>6.6%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>
### Blood Pressure Changes

<table>
<thead>
<tr>
<th>Mean Blood Pressure - mmHg</th>
<th>Placebo</th>
<th>R788 150 mg qd</th>
<th>R788 100 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (systolic/ diastolic)</td>
<td>125/76</td>
<td>125/77</td>
<td>125/77</td>
</tr>
<tr>
<td>Total # patients</td>
<td>153</td>
<td>152</td>
<td>152</td>
</tr>
<tr>
<td>Change from Baseline to Month 1 All patients (systolic/ diastolic)</td>
<td>-2.0/-0.3</td>
<td>+2.5/+2.5</td>
<td>+3.3/+3.1</td>
</tr>
<tr>
<td>Change from Baseline to Month 6 (LOCF) All patients (systolic/ diastolic)</td>
<td>-1.8/-0.4</td>
<td>+0.2/+0.3</td>
<td>+0.6/+1.4</td>
</tr>
<tr>
<td>Total patients initiated or changed anti-hypertensives</td>
<td>11 (7%)</td>
<td>27 (18%)</td>
<td>35 (23%)</td>
</tr>
<tr>
<td># pts with history of HTN or hypertensive at baseline</td>
<td>73 (48%)</td>
<td>84 (55%)</td>
<td>71 (47%)</td>
</tr>
<tr>
<td>Change from Baseline to Month 6 (LOCF) HTN patients (systolic/ diastolic)</td>
<td>-4.1/-0.8</td>
<td>+1.1/+3.1</td>
<td>+4.7/+3.1</td>
</tr>
<tr>
<td>Change from Baseline to Month 6 (LOCF) HTN patients (systolic/ diastolic)</td>
<td>-5.1/-1.0</td>
<td>-3.6/-0.7</td>
<td>-0.1/+0.9</td>
</tr>
</tbody>
</table>

- Hypertension responsive to standard therapies

### Syk inhibitor: Phase 2 study in pts with hx of prior biologics

*Arthritis Rheum 2011; 63: 337-345*

- **Objective**
  - Assess efficacy of R788 100 mg PO bid as compared to placebo over 3 months in patients with active RA who had failed biologic therapies
- **Study Design**
  - 3 month, randomized, placebo control, parallel dose clinical trial
- **Primary Efficacy Measure**
  - ACR20 at Month 3 (withdrawals prior to study conclusion were calculated as non-responders)
- **Secondary**
  - Change in radiologic/structural response at 3 months by MRI (modified RAMRIS)
  - ACR20, ACR50, ACR70, ACRn over the course of the study
  - DAS28-CRP and DAS28-ESR over time
  - 219 patients randomized (2:1 Active: Control)
  - R788 100 mg bid (146 patients)
  - Placebo bid (73 patients)
ACR Response R788 Month 3

Treatment | Placebo | 100 mg bid
---|---|---
**ACR 20 %** | 37% | 38%
**ACR 50 %** | 12% | 22%
**ACR 70 %** | 5% | 9%
**DAS28 <2.6, %** | 10% | 12%

*Arthritis Rheum 63: 337, 2011*
### Fostamatinib—AE profile

- Infections
- Diarrhea
- Neutropenia
- LFTs
- HBP

### Fostamatinib: Studies

- **PHASE III**
  - MTX IR
  - DMARD IR
  - SINGLE ANTI-TNF FAILURE
  - THREE ARM STUDIES
    - PLACEBO
    - INDUCTION DOSING WITH 100 MG BID
      - 100 MG BID
      - 150 MG QD

- **PHASE II**
  - AMBULATORY BP STUDY
  - MONOTHERAPY
AstraZeneca today announced top-line results of OSKIRA-1, a Phase III study to assess the efficacy and safety of fostamatinib, the first oral spleen tyrosine kinase (SYK) inhibitor in development for rheumatoid arthritis (RA). OSKIRA-1 had two primary endpoints: assessing signs and symptoms of RA as measured by ACR20 response rates, and an X-ray endpoint known as mTSS (modified Total Sharp Score).

In the OSKIRA-1 study, fostamatinib achieved a statistically significant improvement in ACR20 response rate at 24 weeks in both the 100 mg twice daily group and the group that received 100 mg twice daily for four weeks followed by 150 mg once daily (49%, p<0.001 and 44%, p=0.006 respectively) compared to placebo (34%).

Fostamatinib did not demonstrate a statistically significant difference in mTSS compared to placebo at 24 weeks for either dose (p=0.252 and p=0.170, respectively).

923 pts enrolled in this 52 wk study.

An inhibitor of the spleen tyrosine kinase pathway has demonstrated efficacy in Phase 2 studies.

The drug worked quickly achieving response as early as one week in combination with MTX.

One phase 2 study in pts who failed prior biologics was not positive - this may have been due to study design and patient selection.

Toxicity included diarrhea and hypertension these AEs were responsive to dose reduction and/or anti-BP meds.

Phase 3 studies are in progress.