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2. Legislative and regulatory developments and economic conditions;
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4. Fluctuations in currency exchange rates and general financial market conditions;
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7. Interruptions in production;
8. Loss of or inability to obtain adequate protection for intellectual property rights;
9. Litigation;
10. Loss of key executives or other employees; and
11. Adverse publicity and news coverage.

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**Agenda**

**Building a new franchise in Autoimmune Diseases/ Inflammation**
- Dr. Urs Schleuniger, VP, Head of Inflammation Strategic Marketing

**AMBITION, RADIATE & REFLEX (2yr) – data presented at EULAR**
- Prof. Paul Emery, arc Professor of Rheumatology, Head of Academic Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds and Clinical Director (Rheumatology), Leeds Teaching Hospitals Trust, Leeds, UK

**Switching to MabThera vs. another anti-TNF – data presented at EULAR**
- Dr. Axel Finckh, Head of Clinical Research, Division of Rheumatology, University of Geneva, Switzerland

**Autoimmune/ Inflammation program overview**
- Dr. Jonathan Leff, VP, Head of Inflammation Clinical Development

**Questions & Answers**

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**Roche: building upon existing franchises**

[Diagram showing the maturity of portfolio with categories such as Oncology, Autoimmune Diseases/Inflammation, Metabolism, Virology, CNS, and Maturity of portfolio.]
RA: Majority of patients still treated with DMARDs…
…but biologics account for majority sales & projected growth

RA treated population (2007)

Sales of RA treatments

Worldwide (excl. Japan)

DMARDs = Disease-modifying Anti-Rheumatic Drugs e.g. methotrexate
Sources: Decision Resources, Evaluate Pharma, IMS, Roche consensus

RA: The search for improved efficacy…
…is main reason behind physicians’ increasing use of biologics

Reasons given by Rheumatologists for predicted increases in use of biologics in next 5 years

Source = Synovate RA Therapy Monitor Top 5 EU, 2007
Building a new Inflammation franchise

Dr. Urs Schleuniger,
VP, Head of Strategic Marketing Inflammation

Roche’s vision in Inflammation
Fighting inflammation – rebuilding patients’ lives

“To become the Leader in Inflammation by shaping future treatment and rebuilding patients’ lives”
### Integrated Inflammation strategy

**Focus on 3 core areas - complementing with line extensions in other autoimmune diseases**

Shaping future treatment in Inflammatory Diseases and rebuilding patients’ lives

Focus R&D on core indications

Maximise current assets

### Roche’s Inflammation portfolio

**Innovative molecules with diversity of mechanisms**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Filed</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>R7377 AP-1 Ra</td>
<td>Ocrelizumab RA</td>
<td>MabThera</td>
<td>Actemra – EU/US RA</td>
<td>MabThera aTNF IR</td>
</tr>
<tr>
<td></td>
<td>R687 Ab-12 Asthma</td>
<td></td>
<td>(MabThera IR) L.N</td>
<td></td>
<td>Actemra – J Ra, sJIA, pPsA</td>
</tr>
<tr>
<td>Respiratory</td>
<td>R7102 Wk22 COPD</td>
<td>Ocrelizumab</td>
<td>MabThera</td>
<td>Actemra – EU/US RA</td>
<td>MabThera aTNF IR</td>
</tr>
<tr>
<td></td>
<td>R1671 Ab-12 Asthma</td>
<td>GEN Ab-12 Asthma</td>
<td>(MabThera IR) L.N</td>
<td></td>
<td>Actemra – J Ra, sJIA, pPsA</td>
</tr>
<tr>
<td>Other AI</td>
<td>R2477 P13</td>
<td>B1</td>
<td>CellCept</td>
<td>CellCept</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFN-α Ab Ab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>R3477 Ab13</td>
<td>Ocrelizumab</td>
<td>MabThera</td>
<td>Actemra</td>
<td>Transition to CNS DBA</td>
</tr>
</tbody>
</table>

Additional Indications: GEN=Genentech managed, CHU=Chugai managed, ISO=Isotekniska opt-in, B7=BoE opt-in
The treatment gap in RA: only 20% of patients are prescribed biologics

- Biologics use limited by cost, convenience, adverse reactions
- Increasing evidence suggests joint destruction occurs early in disease
- Data supports positive effects of aggressive treatment with biologics
- Approx 30–40% patients do not achieve adequate disease control
- Recognised need to identify inadequate response sooner and switch therapy

Sources: Decision Resources, GfK Performance Tracker, Roche consensus, RA Registries
Opportunity space: continued market growth
Biologics account for majority sales & projected growth

Short to mid-term growth driver
- Market penetration by Biologics

Mid to long-term growth drivers
- Novel oral ‘biologic’ DMARDS
- New combination regimens
- Sequential therapy
- Biomarker defined differentiation / segmentation

Sources: Decision Resources, Roche analysis, RA Registries

Still far away from achieving true remission

Goal
- improve signs and symptoms
- halt disease progression

Response current Tx* (% pts)
- ACR 20
- ACR 50
- ACR 70
- Slowing progression of joint damage
- Clinical remission DAS28<2.6

Future Drivers
- Increase % with major response
- Decrease structural damage
- Increase remission rates

New RA therapies are needed to increase treatment options and the percentage of patients achieving adequate disease control

* 24 weeks Tx in established disease
Roche’s portfolio: innovative and first-in-class
Designed to further reduce unmet medical need in RA

Two first-in-class biologics with different modes of action:
• MabThera
• Actemra

Extensive development program:
• Lifecycle management (Ocrelizumab)
• Line extensions (new indications, formulations)
• New products (orals)

Well positioned to shape future therapy standards:
• New combinations
• Sequential treatment algorithms
• Biomarker guided therapy

Targeting therapies where they work best
Strategically integrating biomarker research into clinical trials

• Predict responder/non-responder patient populations
• Understand individual resistance to specific drugs
• Possible dose differentiation within a responder patient population
**MabThera**

Comprehensive development program covering all treatment stages

- **Actemra**
  - AMBITION* (6 mnth MTX free/MTX naive, monotherapy)
  - TOWARD* (DMARDs IR)
  - LITHE** (MTX IR, X-ray study)

- **MabThera**
  - IMAGE** (MTX naive, X-ray study)
  - MIRROR** (MTX IR, dose escalation)
  - SCORE** (DMARDs IR)
  - REFLEX (Anti-TNF IR)

- **Current Tx paradigm**

1. **NSAIDs or Cox-2**
2. **DMARDs**
3. **TNF inhibitors (+/- MTX)**
4. **2nd biologic (+/- MTX)**

* Indication not yet approved, awaiting regulatory approval
** Phase III trial in progress

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**MabThera: The first and only B cell therapy in RA**

_Further evidence for therapy of choice in TNF-IR_

- Achieved ~500 m CHF sales in 2007 in RA (in labelled indication)
- Strong additional data:
  - Efficacy maintained or increased over time
  - Inhibition of radiographic progression maintained at 2 years
  - First choice for anti-TNF inadequate-responders

**MabThera: Increased RA experience and use among Rheumatologists**

- More rheumatologists are prescribing MabThera
- More rheumatologists have adopted MabThera as part of standard therapy

*Source: GfK Performance Tracker*  

**Actemra: The first IL-6 receptor inhibitor**

*Unprecedented level of remission in moderate to severe patients with RA*

- Largest clinical programme of any biologic coming to RA
- Consistently high & durable remission rates - across different disease stages
- Rapid treatment response - as early as 2 weeks
- Statistically significant improvements in patients who have failed up to 3 anti-TNF inhibitors
- Only biologic to have demonstrated superiority vs. methotrexate as monotherapy

*Filed in US & EU Nov '07 (RA)*  
*Approved in Japan Apr '08 (RA, sJIA, pJIA)*

1 Emery et al., EULAR 2008, Abstract OP-0251  
2 Jones et al., EULAR 2008, Abstract OP-0131
Roche: An important player in Rheumatology
Firm foundation with future opportunities

Roche poised to become a leader in Rheumatoid Arthritis
Future opportunities to enter new markets in inflammatory disease

Roche: In RA and other inflammatory diseases
Building tomorrow’s business

- Two first-in-class drugs in RA, with different modes of action
- Full pipeline with diversity of mechanisms
- Large investment in development program (second only to oncology)
  - Arthritis, asthma, COPD
- Scientific and commercial collaboration with co-marketing partners Genentech and Chugai, as well as other 3rd parties
- Strategic focus on biomarkers to better target therapies where they work best
Tocilizumab Significantly Improves Disease Outcomes in Patients with Rheumatoid Arthritis whose Anti-TNF Therapy Failed: the RADIATE Study

Paul Emery*, Ed Keystone, Hans-Peter Tony, Alain Cantagrel, Ronald van Vollenhoven, Adriana Sanchez, Emma Alecock, Janet Lee, Joel Kremer

*Leeds Teaching Hospitals Trust, The University of Leeds, UK

Presentation # OP-0251
The RADIATE Study: Research on Actemra Determining efficacy after Anti-TNF failure

Objectives

- To assess the efficacy and safety of tocilizumab (TCZ) in combination with methotrexate vs. placebo with methotrexate in patients with inadequate responses to anti-TNFs

Patients

- Moderate-to-severe RA ≥6 months duration, with inadequate response to ≥1 anti-TNFs (etanercept, adalimumab or infliximab)
- MTX treatment for ≥12 weeks and stable dose (10-25 mg/week) for ≥8 weeks
- Oral corticosteroids (≤10 mg/day prednisone or equivalent) and NSAIDs permitted if dose stable for ≥6 weeks prior to baseline

RADIATE: Study design

Double-blind, randomised, placebo-controlled trial
### RADIATE: Demographics and baseline disease characteristics (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Placebo + MTX (n = 158)</th>
<th>TCZ 4 mg/kg + MTX (n = 161)</th>
<th>TCZ 8 mg/kg + MTX (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr mean (±SD)</td>
<td>53.4 (±13.3)</td>
<td>50.9 (±12.5)</td>
<td>53.0 (±12.7)</td>
</tr>
<tr>
<td>Disease duration, yr mean (±SD)</td>
<td>11.4 (±9.2)</td>
<td>11.0 (±8.5)</td>
<td>12.6 (±9.3)</td>
</tr>
<tr>
<td>SJC mean (±SD)</td>
<td>18.9 (±11.1)</td>
<td>19.5 (±10.4)</td>
<td>18.9 (±10.9)</td>
</tr>
<tr>
<td>TJC mean (±SD)</td>
<td>30.4 (±16.8)</td>
<td>31.3 (±15.1)</td>
<td>31.7 (±15.4)</td>
</tr>
<tr>
<td>CRP, mg/dL mean (±SD)</td>
<td>3.71 (±14.12)</td>
<td>3.11 (±3.61)</td>
<td>2.80 (±3.37)</td>
</tr>
<tr>
<td>ESR, mm/h mean (±SD)</td>
<td>54.8 (±32.7)</td>
<td>51.3 (±28.3)</td>
<td>49.1 (±27.9)</td>
</tr>
<tr>
<td>RF positive, %</td>
<td>75</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>HAQ mean (±SD)</td>
<td>1.7 (±0.6)</td>
<td>1.7 (±0.6)</td>
<td>1.7 (±0.6)</td>
</tr>
<tr>
<td>DAS28 mean (±SD)</td>
<td>6.80 (±1.06)</td>
<td>6.78 (±0.97)</td>
<td>6.79 (±0.93)</td>
</tr>
</tbody>
</table>

### RADIATE: Therapies at baseline (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Placebo + MTX (n = 158)</th>
<th>TCZ 4 mg/kg + MTX (n = 161)</th>
<th>TCZ 8 mg/kg + MTX (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroid use, %</td>
<td>58</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>mean MTX dose, mg/wk (±SD)</td>
<td>16.5 (±4.8)</td>
<td>16.2 (±5.0)</td>
<td>15.7 (±4.4)</td>
</tr>
<tr>
<td>mean # previous DMARDs (±SD)</td>
<td>2.1 (±1.6)</td>
<td>2.0 (±1.6)</td>
<td>1.9 (±1.7)</td>
</tr>
<tr>
<td># previous anti-TNFs (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>≥3</td>
<td>14</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Previous anti-TNF therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>31</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Infliximab</td>
<td>29</td>
<td>26</td>
<td>31</td>
</tr>
</tbody>
</table>
**RADIATE**: High clinical response in difficult-to-treat patients across all ACR scores

*  p<0.0001 vs. placebo + MTX  **  p=0.0002 vs. placebo + MTX

$$\begin{array}{c|c|c|c}
\text{Patients (%)} \\
\hline
\text{ACR20} & \text{ACR50} & \text{ACR70} \\
\hline
10.1 & 3.8 & 1.3 \\
30.4 & 16.8 & 5.0 \\
5.0 & 28.8 & 12.4 \\
\end{array}$$

**RADIATE**: 30% of patients went into remission following 24 weeks tocilizumab treatment

*  p=0.0533  **  p<0.0001

$$\begin{array}{c|c|c}
\text{Patients (%)} \\
\hline
\text{remission} & \text{low disease activity} \\
\hline
1.6 & 51.2 \\
7.6 & 30.1 \\
4.9 & 15.2 \\
\end{array}$$
RADIATE: Response seen as early as 2 weeks
Close to 50% reduction at 24 weeks with TCZ

DAS28 over time (ITT)

- MTX
- TCZ 4mg/kg + MTX
- TCZ 8mg/kg + MTX

* p<0.0001 vs. placebo + MTX

RADIATE: Normalisation of CRP
Effect seen as early as 2 weeks

Mean CRP Levels (mg/dL)

- MTX
- TCZ 4mg/kg + MTX
- TCZ 8mg/kg + MTX

Upper limit normal=0.29
RADIATE: Patients experiencing elevations in total cholesterol levels

Patients (%)

<table>
<thead>
<tr>
<th>No change</th>
<th>≥240 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>TCZ 4 mg/kg</td>
</tr>
<tr>
<td>63.8</td>
<td>46.6</td>
</tr>
<tr>
<td>6.3</td>
<td>22.1</td>
</tr>
</tbody>
</table>

RADIATE: Patients experiencing elevations in LDL cholesterol levels

Patients (%)

<table>
<thead>
<tr>
<th>No change</th>
<th>≥160 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>TCZ 4 mg/kg</td>
</tr>
<tr>
<td>65.0</td>
<td>46.6</td>
</tr>
<tr>
<td>3.8</td>
<td>15.3</td>
</tr>
</tbody>
</table>
**RADIATE: Patients experiencing elevations in HDL cholesterol levels**

![Bar chart showing patients experiencing elevations in HDL cholesterol levels.](chart)

**RADIATE: Safety summary**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo + MTX (n=160)</th>
<th>TCZ 4 mg/kg + MTX (n=163)</th>
<th>TCZ 8 mg/kg + MTX (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>129 (80.6)</td>
<td>142 (87.1)</td>
<td>147 (84.0)</td>
</tr>
<tr>
<td>Severe adverse event</td>
<td>31 (19.4)</td>
<td>22 (13.5)</td>
<td>24 (13.7)</td>
</tr>
<tr>
<td>Related adverse event</td>
<td>86 (53.8)</td>
<td>107 (65.6)</td>
<td>111 (63.4)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>18 (11.3)</td>
<td>12 (7.4)</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Adverse event leading to</td>
<td>8 (5.0)</td>
<td>10 (6.1)</td>
<td>10 (5.7)</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event leading to dose</td>
<td>13 (8.1)</td>
<td>24 (14.7)</td>
<td>12 (6.9)</td>
</tr>
<tr>
<td>modification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
RADIATE: Conclusions

• Tocilizumab + MTX provides rapid and significant improvement in signs and symptoms of RA in TNF inadequate-responders
  – ACR20/50/70 responses consistent with OPTION and TOWARD
• Tocilizumab + MTX produced remission in 30% of patients (DAS28 score)
• Readily manageable safety profile

Tocilizumab monotherapy is superior to methotrexate monotherapy in reducing disease activity in patients with rheumatoid arthritis: the AMBITION study

Graeme Jones,* Anthony Sebba, Jieruo Gu, Mitchell B. Lowenstein, Armando Calvo, Juan J. Gomez-Reino, Daniel A. Siri, Matija Tomšič, Rebecca Blackburn, Thasia Woodworth, and Mark C. Genovese

*Menzies Research Institute, University of Tasmania, Hobart, Australia
The **AMBITION** Study: *Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy*

**Objectives**

- To assess the efficacy and safety of tocilizumab (TCZ) monotherapy vs. methotrexate (MTX) monotherapy

**Patients**

- Moderate-to-severe RA ≥3 months duration
- MTX-naïve or have not received methotrexate ≥6 months preceding randomization
- Have not previously failed methotrexate or biologic treatment
- Oral corticosteroids (≤10 mg/day prednisone or equivalent) and NSAIDs permitted if dose stable for ≥6 weeks prior to randomization

**AMBITION: Study design**

*Randomised, double-blind, double dummy, parallel group, multi-center study*

- **Randomisation**
  - MTX 7.5-20 mg/week* (n = 284)
  - TCZ 8 mg/kg (n = 288)

- **Primary endpoint**
  - Proportion of patients achieving ACR20

- **Week IV infusion**
  - 0 4 8 12 16 20 24
  - Placebo then TCZ 8 mg/kg from wk 8 (n = 101)

- **Rescue therapy offered in sub-study only**

* Starting at 7.5 mg/week and titrated to 20 mg weekly within 8 weeks
## AMBITION: Demographics and baseline disease characteristics (ITT population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TCZ 8mg/kg</th>
<th>MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=286</td>
<td>n=284</td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>50.7±13.1</td>
<td>50.0±12.9</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>236 (83)</td>
<td>224 (79)</td>
</tr>
<tr>
<td>RF positive (%)</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Mean disease duration, yrs</td>
<td>6.4±7.9</td>
<td>6.2±7.8</td>
</tr>
<tr>
<td>Disease &lt;2 years, n (%)</td>
<td>117 (41)</td>
<td>125 (44)</td>
</tr>
<tr>
<td>Previous DMARDs, n</td>
<td>1.2±1.3</td>
<td>1.1±1.4</td>
</tr>
<tr>
<td>DMARD naïve, n (%)</td>
<td>115 (40.2)</td>
<td>129 (45.4)</td>
</tr>
<tr>
<td>MTX naïve, n (%)</td>
<td>191 (67)</td>
<td>190 (67)</td>
</tr>
<tr>
<td>Oral steroid use, n (%)</td>
<td>137 (48)</td>
<td>133 (47)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TCZ 8mg/kg</th>
<th>MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=286</td>
<td>n=284</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.8±1.0</td>
<td>6.8±0.9</td>
</tr>
<tr>
<td>TJC</td>
<td>31.8±14.8</td>
<td>31.1±14.1</td>
</tr>
<tr>
<td>SJC</td>
<td>19.1±11.0</td>
<td>19.2±10.6</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>3.0±3.3</td>
<td>3.1±3.4</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
<td>49.9±27.9</td>
<td>49.4±26.1</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.6±0.7</td>
<td>1.5±0.6</td>
</tr>
</tbody>
</table>

* Mean ± SD
AMBITION: Treatment with tocilizumab is superior to treatment with methotrexate

* $p<0.0001$ vs. MTX  ** $p=0.0023$ vs. MTX  *** $p=0.0002$ vs. MTX

AMBITION: Clinical disease remission and EULAR response at week 24
AMBITION: Rapid and sequential improvement in ACR response rates

AMBITION: Rapid reduction in CRP levels

* Adjusted mean difference (95% CI) = -0.89 (-1.50, -0.28)
**AMBITION: Significant improvement in hemoglobin levels over time**

Adjusted mean difference (95% CI) = 1.12 (0.85, 1.39)

**AMBITION: Hepatic aminotransferase elevation is more common with methotrexate**

*Highest elevations at any time point*
**AMBITION: Patients experiencing elevations in cholesterol levels along with reduced inflammation**

![Graph showing cholesterol levels](image)

*Improvement in the HDL cholesterol levels

**AMBITION: Conclusions**

- Tocilizumab demonstrates superior efficacy to methotrexate for
  - ACR20, ACR50, ACR70
  - EULAR good/moderate response
  - DAS28 remission
- Rapid onset of action (within 2 weeks)
- Normalisation of mean CRP by week 12 and substantial improvement in haemoglobin levels, consistent with other tocilizumab studies
- Safety profile consistent with the mechanism of action and immunomodulatory properties of IL-6 inhibition
Continued inhibition of structural damage in rheumatoid arthritis patients treated with rituximab at 2 years: REFLEX study

S Cohen, E Keystone, MC Genovese, P Emery, C Peterfy, PP Tak, M Cravets, T Shaw, D Hagerty

Poster # THU0167

REFLEX: Study design

Primary endpoint
ACR20 at week 24

Treatment period

Long-term follow-up

Rituximab or placebo infusion

Potential for subsequent courses of rituximab in patients with ≥20% reduction in SJC and TJC from week 24

Cohen et al, Arthritis Rheum 2006;54:2793–2806
REFLEX: Inhibition of radiographic progression after 1 year in patients with an inadequate response to anti-TNFs

**Primary analysis:** Radiographs within time window, linear extrapolation from Week 24 for missing values

*At week 56*


REFLEX: Inhibition of radiographic progression with Rituximab over 2 years

Total Sharp Score

- **Δ 59%**
- **Δ 63%**
- **Δ 54%**

Cohen, et al., EULAR 2008 poster THU0167

Primary analysis: radiographs outside time window included, linear extrapolation from Week 24 or 56 for missing values

REFLEX: Patients with no radiological changes after 2 years*

- 87% of rituximab-treated patients who did not progress the first year had no progression the second year

* No change in Total Genant-modified Sharp Score

Cohen, et al., EULAR 2008 poster THU0167
REFLEX: Conclusions

- Previously shown that earlier treatment with rituximab inhibited structural damage progression at week 56 in rituximab-treated patients cf. baseline placebo\textsuperscript{1}
- New results demonstrate that rituximab treatment continues to inhibit joint damage with longer treatment in patients with an inadequate response to TNF inhibitors\textsuperscript{2}
- Rituximab is the only biologic agent with unique radiographic data in patients with an inadequate response to TNF inhibitors

2. Cohen, et al. EULAR 2008 poster THU0167

Breaking the cycle: The benefits of an alternative biological treatment strategy

Dr. Axel Finckh, Head of Clinical Research, Division of Rheumatology, University of Geneva, Switzerland
Inadequate response to anti-TNF therapy

*What are the options?*

- Around 30% of patients experience an inadequate response to anti-TNF therapy or lose efficacy during therapy
- What are the therapeutic options?
  - switch to another anti-TNF agent?
  - initiate treatment with a biological agent with a different mechanism of action?


Switching to an alternative anti-TNF agent

- Anti-TNF cycling may work because anti-TNFs differ in their
  - mechanisms of action
  - Pharmacokinetic properties
  - mode of administration

Furst et al, Ann Rheum Dis 2005; 64(Suppl. 3):427

DAS28 improvement at 4 months in patients who either continued etanercept or switched to infliximab
Decreased effectiveness to a 2nd anti-TNF


- The lack of effectiveness to a soluble receptor and one of the anti-TNF antibody predicts the lack of effectiveness to a 3rd anti-TNF antibody (0% of responders in 13 patients)
- With the exception of treatment interruptions for adverse events (7/9 patients (78%) were responders)

Salau-Gervais E. et al. (French (Lille) RA cohort) Rheumatology 2006; 45:1121–1124: Lack of efficacy of a third tumour necrosis factor alpha antagonist after failure of a soluble receptor and a monoclonal antibody
Initiate treatment with a biological agent with a different mechanism of action:

Lasting change in DAS28 over 24 weeks with rituximab

- In RA patients with an inadequate response to anti-TNFs, the REFLEX trial has demonstrated that rituximab is more effective than placebo

![Graph showing mean change in DAS28 over 24 weeks](image)

Cohen et al, Arthritis Rheum 2006; 54: 2793–2806

Which Subgroup of Rheumatoid Arthritis Patients Benefit Most From Switching to Rituximab Versus Alternative Anti-TNF Agents After Previous Failure to Anti-TNF Agents?


Objectives:

- What is influence of prior history of resistance to anti-TNFs on the effectiveness of these agents?
  - Sub-analysis according to reason for prior anti-TNF interruption
  - Sub-analysis based on number and type of prior anti-TNF agents used

- What is the impact of concomitant DMARDs?
  - Sub-analysis with and without concomitant DMARDs
Study methodology

Design:
• Longitudinal observational, population-based, cohort-study

Study population:
• Swiss Clinical Quality Management in rheumatoid arthritis (SCQM-RA) cohort
• Private rheumatology practices (~50%), hospitals (~50%)

Inclusion criteria:
• Diagnosis of RA by a rheumatologist
• Inadequate response to anti-TNFs whilst on infliximab, etanercept, adalimumab
• Initiation of either a 2nd or 3rd alternative anti-TNF or rituximab
• Longitudinal follow-up (DAS baseline + 1 other DAS ≤12 months)

Exclusion criteria:
• Rituximab for lymphoma


Method analysis

Primary outcome:
• Evolution in disease activity (DAS28)

Adjustments for potential confounders:
• Baseline DAS28, rheumatoid factor, age, gender, disease duration, concomitant steroids, concomitant DMARDs, nb anti-TNF failures, educational level

Multivariate Regression models for longitudinal data (Mixed models, random intercept & slope)

Effect modification (multiplicative interaction)
  – by type of previous anti-TNF interruption (failure or other (AEs++))
  – by number of previous anti-TNF failures (1 versus 2 or more)
  – by type of anti-TNF switch (anti-TNF-AB to anti-TNF-RA vs anti-TNF-AB & other anti-TNF-AB)
  – by presence of co-therapy with conventional DMARDs (Methotrexate…)
Mean change from baseline in DAS28
Effect modification according to reasons for prior anti-TNF interruption

Effect modification: $p = 0.001$
Finckh et al, EULAR 2008, Abstract OP-0249

Mean change from baseline in DAS28
Effect modification according to number of prior anti-TNF agents

Effect modification: $p = 0.48$
Finckh et al, EULAR 2008, Abstract OP-0249
Mean change from baseline in DAS28
Effect modification according to type of anti-TNF switch

Effect modification: p = 0.21

Finckh et al, EULAR 2008, Abstract OP-0249

Mean change from baseline in DAS28
Effect modification according to concomitant DMARD use

Effect modification: p = 0.28

Finckh et al, EULAR 2008, Abstract OP-0249
Conclusions

- Improvement in DAS28 was significantly better in patients treated with rituximab than in those receiving an alternative anti-TNF agent.

- Relative benefit of rituximab varied according to reason for previous anti-TNF interruption:
  - significantly better if switch due to lack of anti-TNF efficacy
  - similar if switch due to other reasons (AEs...)

- Results were not influenced by concomitant DMARD use or by type of prior anti-TNF agent.

- Rituximab should be considered as a therapeutic alternative after a first anti-TNF therapy if anti-TNF failed to produce low disease activity states.

Roche’s Inflammation program overview

Jonathan Leff, M.D.
VP, Head Inflammation Clinical Development
Building the Rheumatology portfolio

Extending into new areas

Achieving satisfactory patient treatment requires multiple treatment options

- Early and intensive treatment with NSAIDs, methotrexate, and/or traditional DMARDs with corticosteroids, helps to reduce pain and inflammation

<table>
<thead>
<tr>
<th>Anti-TNF-α therapy</th>
<th>B cell therapy</th>
<th>Selective modulation of co-stimulatory activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First therapy to dramatically improve signs and symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Including radiographic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increasingly used alternative in anti-TNF-IRs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Another mechanistic option for some patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is a need for new therapies
**Extensive Actemra clinical development program**

Over 3,700 patients treated

<table>
<thead>
<tr>
<th>Phase II</th>
<th>Phase III</th>
<th>Ongoing Open Label Extension Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose-finding</td>
<td>• Anti-TNF Inadequate Responder (RADIATE)</td>
<td>• WA18695</td>
</tr>
<tr>
<td>– Monotherapy</td>
<td>• MTX Inadequate Responder (OPTION)</td>
<td>• WA18696</td>
</tr>
<tr>
<td>– Combination with MTX (LRO301)</td>
<td>• MTX Inadequate Responder – X-ray (LITHE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DMARD Inadequate Responder (TOWARD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Limited or no MTX exposure (AMBITION)</td>
<td></td>
</tr>
</tbody>
</table>

Approved in Japan (RA, sJIA, pJIA) – Filed in US & EU Nov 2007 (RA)

**Actemra Ph III trials: Unsurpassed efficacy**

Around 30% of patients achieved DAS28 remission at week 24 – regardless of prior therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Placebo + DMARDs</th>
<th>TCZ</th>
<th>TCZ + DMARDs</th>
<th>TCZ + MTX</th>
<th>MTX</th>
<th>TCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTION1</td>
<td>0.8%</td>
<td>3.4%</td>
<td>27.5%*</td>
<td>30.2%*</td>
<td>30.1%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOWARD2</td>
<td>0%</td>
<td>1.6%</td>
<td>12.1%</td>
<td>15.9%*</td>
<td>32.6%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RADIATE3</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>30.2%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMBITION4</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>30.2%*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p ≤ 0.0001; TCZ dose 8 mg/kg

2. Genovese et al., ACR 2007. Abstract L150
3. Emery et al., EULAR 2008. Presentation OP-0251
**Actemra Ph III trials: Rapidly and significantly increased percentage of patients in remission - across all trials**

![Graph showing percentage of patients in remission across different trials over weeks.](image)

**Actemra Ph III trials: Delivers effects beyond the joint**

*Normalises CRP - across all patient groups*

![Graph showing CRP levels across different trials over weeks.](image)

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**AMBITION:** Jones et al., EULAR 2008, Presentation OP-0131
Pooled OPTION & TOWARD: Smolen JS, et al. EULAR 2007, Presentation OP0117; Genovese et al., ACR 2007, Abstract L15; data on file

**RADIATE:** Emery et al., EULAR 2008, Presentation OP-0251;
Actemra Ph III trials: Pooled data OPTION & TOWARD

**Liver function summary**

- There was an increase in mean hepatic transaminases, generally within the normal range, in the Actemra treatment group.
- Of the patients who experienced an increase in ALT to >ULN, the majority were shifts <3xULN.
- After discontinuation of study treatment, in all but 2 cases liver enzyme values were reduced or had normalised by the patient’s last observation.
- No patients met the criteria for Hy’s Rule (ALT ≥3x ULN + bilirubin levels ≥2x ULN)

Six month pooled data from OPTION and TOWARD trials, Smolen et al., EULAR 2008, Poster FR0163
Laboratory changes – Lipid parameters

Response to treatment with statins

Actemra Ph III trials: Summary of efficacy

Consistent results across all trials

- Actemra provided consistent and effective disease control
  - significant improvement seen in all ACR responses
  - improvement in ACR responses maintained

- Around 30% of all patients on Actemra consistently reached DAS28 remission

- Actemra consistently demonstrated rapid onset of action
  - normalised CRP levels
  - normalises Haemoglobin in patients anaemic at baseline

- Improvement in patients’ quality of life shown by HAQ-DI, SF-36 and FACIT-fatigue (data not shown)
Actemra ph III trials: Summary of safety profile

• The adverse events reported are consistent with the known MOA of Actemra
• Manageable with existing guidelines and practice
• Overall benefit-risk profile is positive

Actemra: Next steps in development
Continued investment and lifecycle management

• Open-label long-term extension studies for safety and efficacy
  – Adds to 5 yr Chugai long-term data

• Generate further data
  • Cardiovascular/Inflammation
  • Registries
  • Robust phase IV programme

• Systemic Juvenile Idiopathic Arthritis (sJIA)
  – Phase III ongoing

• Subcutaneous dose form
  – Formulation and pre-clinical work ongoing
New molecules: AP-1 Inhibition is a novel oral DMARD
First-in-class mode of action with potential in RA

- AP-1 binds to DNA and regulates key genes implicated in inflammation and joint destruction
- R7277 is a small molecule AP-1 inhibitor which shows significant efficacy in preclinical models
- Co-development with Toyama
  - Toyama developing in Japan (Ph 2 in 2008)
  - Roche to evaluate higher doses in MAD in 2008

Building the Rheumatology portfolio
Extending into new areas
Respiratory and other related allergic diseases

Emerging opportunities in large markets with high unmet medical need

• Roche is at the forefront of respiratory research with key expertise in place

• 4 molecules in the clinic:
  – Two for asthma (aIL-13, aOx-40L)
  – Two for COPD (RARγ, VPAC2)

• All mechanisms are novel, several potentially first-in-class

• Diversity: 3 large molecules, one small (oral)

OX40L mAb: First-in-class opportunity for Asthma

Collaboration with Genentech

• A fully human IgG1

• Capability of depleting OX40L-expressing cells

• Potent functional inhibition in *in vitro* assays

• Potential for disease modification
**RARγ in Emphysema (R667)**

*Restoring lung repair process/ improving lung function*

- A selective retinoid agonist (RAR-γ)
- Targets underlying disease pathology
- Regenerates lung tissue in animal models
- Data expected 2008-2010
- Big bet – huge return

**Roche in RA and other inflammatory diseases**

*Building tomorrow’s business*

- Two first-in-class drugs in RA, with different modes of action
  - MabThera: new data supporting inhibition of joint damage
  - Actemra: unsurpassed remission rates, across different patient populations
- Large investment in development program
  - RA: combo/ sequential treatment, biomarkers
  - Lupus: MabThera & Ocrelizumab in phase III
- Pipeline of novel molecules
  - Arthritis, asthma, COPD

Roche poised to become a leader in Rheumatoid Arthritis
Future opportunities to enter new areas of unmet need
RA: Roche’s ongoing phase III program – MabThera (RTX)

Moving earlier in treatment regime

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Size</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>REFLEX</td>
<td>Anti-TNFα IR</td>
<td>MTX + RTX 2 x 1g</td>
<td>521</td>
<td>ACR 20 (24 wks) Radiographic Progression</td>
<td>marketed US, EU</td>
</tr>
<tr>
<td>SERENE</td>
<td>DMARD-IR</td>
<td>MTX + RTX 2 x 0.5g MTX + RTX 2 x 1g</td>
<td>509</td>
<td>ACR 20 (24 wks)</td>
<td>Completed Filing planned H1 '09</td>
</tr>
<tr>
<td>MIRROR</td>
<td>DMARD-IR Dose escalation</td>
<td>MTX + RTX 2 x 0.5g retx 2 x 0.5g MTX + RTX 2 x 0.5g retx 2 x 1g MTX + RTX 2 x 1g retx 2 x 1g</td>
<td>375</td>
<td>ACR 20 0-8 wks Effect of further courses and dose escalation</td>
<td>Completed Filing planned H1 '09</td>
</tr>
<tr>
<td>SCORE</td>
<td>DMARD-IR</td>
<td>MTX + RTX 2 x 0.5g MTX + RTX 2 x 1g</td>
<td>180</td>
<td>MRI changes at 6 months</td>
<td>Data expected 2010</td>
</tr>
<tr>
<td>IMAGE</td>
<td>MTX naïve (X-ray study)</td>
<td>MTX + RTX 2x0.5g MTX + RTX 2x1g</td>
<td>852</td>
<td>ACR 20 Inhibition of structural joint damage Improvement in physical function</td>
<td>Initiated Q1 '06 Filing planned H1 '09</td>
</tr>
</tbody>
</table>
RA: Roche’s ongoing phase III program – Actemra (TCZ)

Filed EU & US; LITHE to add long-term data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Size</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTION</td>
<td>MTX IR</td>
<td>TCZ 4mg/kg + MTX TCZ 8mg/kg + MTX MTX</td>
<td>623</td>
<td>ACR 20 (24 wks)</td>
<td>Filed Q4 ’07</td>
</tr>
<tr>
<td>TOWARD</td>
<td>DMARD IR</td>
<td>TCZ 8mg/kg + DMARDs DMARDs</td>
<td>1,200</td>
<td>ACR 20 (24 wks)</td>
<td>Filed Q4 ’07</td>
</tr>
<tr>
<td>RADIATE</td>
<td>anti-TNFα IR</td>
<td>TCZ 4mg/kg + MTX TCZ 8mg/kg + MTX MTX</td>
<td>499</td>
<td>ACR 20 r(24 wks)</td>
<td>Filed Q4 ’07</td>
</tr>
<tr>
<td>AMBITION</td>
<td>MTX naive</td>
<td>TCZ 8mg/kg (esc. dose) MTX</td>
<td>673</td>
<td>ACR 20 (24 wks)</td>
<td>Filed Q4 ’07</td>
</tr>
<tr>
<td>LITHE</td>
<td>MTX IR</td>
<td>TCZ 4mg/kg + MTX TCZ 8mg/kg + MTX MTX</td>
<td>1,196</td>
<td>ACR 20 (24 wks) Sharp Score (52, 104 wks) Physical function (104 wks) met 1° endpoint</td>
<td>Filed Q4 ’07</td>
</tr>
<tr>
<td>WA18695</td>
<td>pts from OPTION</td>
<td>TCZ 8mg/kg + standard anti-rheumatic therapy</td>
<td>537</td>
<td>Open-label long-term extension studies for safety and efficacy</td>
<td>ongoing</td>
</tr>
<tr>
<td>WA18696</td>
<td>pts from AMBITION, RADIATE, TOWARD</td>
<td>TCZ 8mg/kg + standard anti-rheumatic therapy</td>
<td>1,902</td>
<td>Open-label long-term extension studies for safety and efficacy</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

RA: Roche’s ongoing phase III program – Ocrelizumab

Extending the franchise – 2nd generation anti-CD20

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Size</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td>MTX-IR</td>
<td>MTX MTX + Ocrelizumab</td>
<td>1,000</td>
<td>ACR 20 (48 wks) Inhibition of structural joint damage</td>
<td>Initiated Q4 ’06 Data expected 2010</td>
</tr>
<tr>
<td>SCRIPT</td>
<td>Anti-TNFα IR</td>
<td>DMARD DMARD + Ocrelizumab</td>
<td>800</td>
<td>ACR 20 (24 and 48 wks) Inhibition of structural joint damage</td>
<td>Initiated Q2 ’07</td>
</tr>
<tr>
<td>FEATURE</td>
<td>MTX-IR Anti-TNFα IR</td>
<td>MTX MTX + Ocrelizumab</td>
<td>300</td>
<td>ACR 20 (24 and 48 wks)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>FILM</td>
<td>MTX naive</td>
<td>MTX MTX + Ocrelizumab</td>
<td>600</td>
<td>Inhibition of structural joint damage at 52 and 104 Wks</td>
<td>Initiated Q2 ’07 Data expected 2011</td>
</tr>
</tbody>
</table>

Global Phase III program in RA by Roche and Genentech

- Fully humanised
- Potential clinical benefits - less immunogenicity, better tolerability, shorter infusion time, single infusion
**Lupus: MabThera phase III**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Size</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUNAR</td>
<td>Lupus Nephritis</td>
<td>MabThera (2 x 1g) + CellCept</td>
<td>140</td>
<td>Renal response at 52 wks</td>
<td>Enrolment completed Q1 '08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data expected 2009</td>
<td></td>
</tr>
</tbody>
</table>

**Lupus: ocrelizumab phase III**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Size</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BELONG</td>
<td>Lupus Nephritis</td>
<td>SOC + Ocrelizumab (2x 400mg, 2x1000mg)</td>
<td>369</td>
<td>Renal response at 52 wks</td>
<td>Initiated Q4 '07</td>
</tr>
</tbody>
</table>

**RADIATE: Serious adverse events**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo + MTX (n=160)</th>
<th>TCZ 4 mg/kg + MTX (n=163)</th>
<th>TCZ 8 mg/kg + MTX (n=176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with ≥1 SAE</td>
<td>18 (11.3)</td>
<td>12 (7.4)</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Total number of SAEs</td>
<td>23</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5 (3.1)</td>
<td>3 (1.8)</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>5 (3.1)</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (1.3)</td>
<td>2 (1.2)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2 (1.3)</td>
<td>-</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Blood and lymphatic</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>-</td>
</tr>
<tr>
<td>General and administration site</td>
<td>2 (1.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>2 (1.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nervous system</td>
<td>-</td>
<td>2 (1.2)</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td>1 (0.6)</td>
<td>-</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>1 (0.6)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### AMBITION: Safety summary

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>TCZ 8 mg/kg n=288</th>
<th>MTX n=284</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>230 (79.9)</td>
<td>220 (77.5)</td>
<td>0.4842</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>11 (3.8)</td>
<td>8 (2.8)</td>
<td>0.5035</td>
</tr>
<tr>
<td>Related serious adverse event</td>
<td>4 (1.4)</td>
<td>4 (1.4)</td>
<td>0.9841</td>
</tr>
<tr>
<td>Serious infections</td>
<td>4 (1.4)</td>
<td>2 (0.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>11 (3.8)</td>
<td>15 (5.3)</td>
<td>0.4012</td>
</tr>
<tr>
<td>Adverse event leading to dose modification</td>
<td>56 (19.4)</td>
<td>63 (22.2)</td>
<td>0.4198</td>
</tr>
<tr>
<td>Death</td>
<td>3 (1.0)</td>
<td>1 (0.4)</td>
<td>0.3224</td>
</tr>
</tbody>
</table>