New Evidence reports on presentations given at EULAR 2009

Safety and Efficacy of Tocilizumab as Monotherapy and in Combination with Methotrexate
Tocilizumab inhibits structural joint damage, improves physical function, and increases DAS28 remission rates in rheumatoid arthritis patients who respond inadequately to methotrexate: the LITHE study (Kremer J, et al. EULAR 2009: Abstract OP-0157)

Efficacy of tocilizumab versus methotrexate monotherapy in patients with rheumatoid arthritis with no prior methotrexate or DMARD exposure: the AMBITION study (Jones G, et al. EULAR 2009: Abstract FRI0252)

Efficacy of tocilizumab in rheumatoid arthritis: interim analysis of long-term extension trials of up to 2.5 years (Smolen JS, et al. EULAR 2009: Abstract FRI0133)

Long-term safety and tolerability of tocilizumab in patients with a mean treatment duration of 1.5 years (Van Vollenhoven RF, et al. EULAR 2009: Abstract SAT0111)

DAS28 = 28-joint Disease Activity Score
DMARD = disease-modifying anti-rheumatic drug
Tocilizumab inhibits structural joint damage, improves physical function, and increases DAS28 remission rates in rheumatoid arthritis patients who respond inadequately to methotrexate: the LITHE study

Background

- Tocilizumab has been shown to improve the signs and symptoms of RA in patients who have an inadequate response to MTX.¹

- At EULAR 2009, Kremer and colleagues presented data from the CORE (year 1) database of the LITHE study (Tocilizumab Safety and THE Prevention of Structural Joint Damage).

- The LITHE study was designed to assess the safety and efficacy of tocilizumab in combination with MTX in RA patients with an inadequate response to MTX.²

Study design

- The LITHE study was a double-blind, randomized, placebo-controlled two-year trial that enrolled patients with moderate-to-severe RA who had an inadequate response to MTX.

- Analyses were planned for weeks 24 and 52.

- Patients were randomized to receive tocilizumab (4 mg/kg or 8 mg/kg) or placebo intravenously every 4 weeks plus weekly MTX (10–25 mg orally or parenterally) and could receive blinded rescue therapy from week 16.

- The primary endpoints of the study included:
  - ACR20 response at week 24
  - change from baseline in GmTSS at week 52
  - physical function (AUC of change from baseline in the HAQ-DI) at week 52

- A key secondary endpoint was DAS28 remission at each time point.

ACR = American College of Rheumatology
AUC = area under the curve
DAS28 = 28-joint Disease Activity Score
GmTSS = Genant-modified Total Sharp Score
HAQ-DI = Health Assessment Questionnaire Disability Index
MTX = methotrexate; RA = rheumatoid arthritis

Key findings

- Primary endpoints were met in the intent-to-treat population (n = 1,190).

- At week 52, patients in the tocilizumab (8 mg/kg) group had significantly greater inhibition of radiographic progression (mean GmTSS) versus the placebo group (74%).

- At week 52, significantly more patients in the tocilizumab groups were without radiographic progression from baseline versus the placebo group (p ≤0.0001).

- Improvement in physical function was significant for both tocilizumab groups versus the placebo group (p ≤0.0001).

GmTSS = Genant-modified Total Sharp Score
Key findings (cont’d)

- ACR20 at week 24 was achieved by 56% of patients in the tocilizumab (8 mg/kg) group, 51% in the tocilizumab (4 mg/kg) group and 27% in the placebo group ($p < 0.0001$).

- Significantly more patients in both tocilizumab groups versus the placebo group achieved ACR20/50/70 at week 52 ($p \leq 0.0001$).

- DAS28 remission rates (DAS28 < 2.6) for weeks 24 / 52 were significantly higher in the tocilizumab (8 mg/kg) group (33% / 47%) and tocilizumab (4 mg/kg) group (18% / 30%) versus the placebo group (4% / 8%) ($p \leq 0.0002 / p < 0.0001$).

- In subgroup analyses, tocilizumab efficacy was observed regardless of baseline parameters, such as disease duration, disease status, or baseline rheumatoid factor.
### Table 1. Efficacy of tocilizumab versus placebo at week 52

<table>
<thead>
<tr>
<th>Efficacy at week 52</th>
<th>Tocilizumab (8 mg/kg) + MTX n = 398</th>
<th>Tocilizumab (4 mg/kg) + MTX n = 399</th>
<th>Placebo + MTX n = 393</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GmTSS change from baseline (SD)</td>
<td>0.29 (1.3)*</td>
<td>0.34 (1.5)*</td>
<td>1.13 (3.0)</td>
</tr>
<tr>
<td>No GmTSS progression, % (n/n)</td>
<td>85 (294/348)</td>
<td>81 (273/338)*</td>
<td>67 (195/290)</td>
</tr>
<tr>
<td>Mean AUC of HAQ-DI change from baseline</td>
<td>−144.1*</td>
<td>−128.4*</td>
<td>−58.1</td>
</tr>
<tr>
<td>ACR20, % (n)</td>
<td>56 (222)*</td>
<td>47 (186)*</td>
<td>25 (97)</td>
</tr>
<tr>
<td>ACR50, % (n)</td>
<td>36 (145)*</td>
<td>29 (116)*</td>
<td>10 (39)</td>
</tr>
<tr>
<td>ACR70, % (n)</td>
<td>20 (80)*</td>
<td>16 (65)*</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

* p ≤ 0.0001 versus placebo. (n/n) = patients with response/evaluable patients

ACR = American College of Rheumatology; AUC = area under the curve; GmTSS = Genant-modified Total Sharp Score; HAQ-DI = Health Assessment Questionnaire Disability Index; MTX = methotrexate; SD = standard deviation.
Key conclusions

- Tocilizumab with MTX inhibited the progression of structural joint damage and improved physical function and clinical disease activity significantly more than MTX alone.

- DAS28 remission increased from week 24 to week 52, indicating increasing magnitude of clinical benefit over time.

- Tocilizumab (8 mg/kg) was numerically superior to tocilizumab (4 mg/kg) in all endpoints.


DAS28 = 28-joint Disease Activity Score
MTX = methotrexate
Efficacy of tocilizumab versus methotrexate monotherapy in patients with rheumatoid arthritis with no prior methotrexate or DMARD exposure: the AMBITION study

Background

- Tocilizumab has a manageable safety profile that has been characterized across different RA patients.\textsuperscript{1–3}

- The effects of previous exposure to MTX or other DMARDs on the efficacy of tocilizumab monotherapy have not yet been investigated.

- The AMBITION (\textit{Actemra Versus Methotrexate Double-Blind Investigative Trial In MONotherapy}) study compared the efficacy and safety of tocilizumab monotherapy with that of MTX monotherapy in MTX-naïve patients with active RA.

- At EULAR 2009, Jones and colleagues presented an exploratory analysis of data from the AMBITION study, designed to assess the efficacy of tocilizumab monotherapy versus MTX monotherapy in two subgroups: patients never exposed to MTX and those never exposed to DMARDs.\textsuperscript{4}


DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
MTX = methotrexate; RA = rheumatoid arthritis
The AMBITION study was a prospective, double-blind, double-dummy, multicentre, phase III, randomized controlled trial.

Patients were excluded if they had been treated with MTX in the previous 6 months, discontinued MTX because of AEs or a lack of efficacy at any time in the past, or undergone previous unsuccessful treatment with a TNF-I.

Patients were randomly assigned to receive:
- tocilizumab (n = 288) – 8 mg/kg intravenously every 4 weeks
- MTX (n = 284) – initial dose of 7.5 mg/wk orally, increased to 15 mg/wk at week 4, and 20 mg/wk at week 8 (mean dose 15.5 mg/wk), together with folate ≥5 mg/wk
Study design (cont’d)

- This exploratory post-hoc analysis was conducted in three groups:
  - ITT population – all randomly assigned patients who received ≥1 administration of study treatment (analyzed prospectively)
  - two subgroups of the ITT population:
    - MTX-naïve patients – defined as those who had never been exposed to MTX (post hoc analysis)
    - DMARD-naïve patients – defined as those who had never been exposed to MTX or any traditional DMARD (a subset of the MTX-naïve group, analyzed prospectively)
- All comparisons were between tocilizumab and MTX.
- Cochran-Mantel-Haenszel analysis was used to calculate p values.
- Logistic regression analysis was used to compare EULAR response and DAS remission between treatment groups.

EULAR = European League Against Rheumatism
DAS = Disease Activity Score
DMARD = disease-modifying anti-rheumatic drug
ITT = intent-to-treat; MTX = methotrexate
Key findings

- Overall baseline demographics and RA characteristics of MTX-naïve and DMARD-naïve patients were well balanced between treatment groups and were consistent with those of the total ITT population.

- RA duration was shorter in the MTX-naïve and DMARD-naïve patients than in the total ITT population.

- Approximately two-thirds of patients in the total ITT population were truly MTX-naïve (no previous exposure to MTX).

- ACR response rates were not affected by previous exposure to MTX or DMARDs.

- At week 24, ACR responses, with comparable results in the MTX-naïve and DMARD-naïve subgroups ($p <0.05$), were as follows:
  - ACR20 – 69.9% for tocilizumab and 52.5% for MTX
  - ACR50 – 44.1% for tocilizumab and 33.5% for MTX
  - ACR70 – 28.0% for tocilizumab and 15.1% for MTX
Key findings (cont’d)

- Tocilizumab was significantly superior to MTX in EULAR good response rates in the total ITT population, in MTX-naïve patients, and in DMARD-naïve patients.

- At week 24, significantly greater proportions of patients in the total ITT population and in the MTX-naïve and DMARD-naïve subgroups receiving tocilizumab achieved DAS28 remission compared with those receiving MTX.


EULAR = European League Against Rheumatism
DAS28 = 28-joint Disease Activity Score
DMARD = disease-modifying anti-rheumatic drug
ITT = intent-to-treat; MTX = methotrexate
Figure 1. Proportions of methotrexate- and tocilizumab-treated patients with EULAR good and moderate responses at week 24

Figure 2. Proportions of methotrexate- and tocilizumab-treated patients with DAS remission (DAS28 <2.6) at week 24.

*p < 0.05 vs. MTX (MTX-naive and DMARD-naive subgroups)
1 OR (95% CI) = 5.8 (3.3, 10.4) vs. MTX (total ITT population)
CI = confidence interval; DAS28 = Disease Activity Score using 28 joints;
DMARD = disease-modifying anti-rheumatic drug; ITT = intent-to-treat;
MTX = methotrexate; TCZ = tocilizumab


DAS28 = 28-joint Disease Activity Score
Key findings (cont’d)

- Overall AEs and shifts in liver transaminase levels (ALT and AST) were similar for the tocilizumab and MTX groups, regardless of previous MTX or DMARD exposure.

- Serious AEs occurred in approximately 3% to 4% of patients who were treated with tocilizumab and MTX in the overall ITT population and in the MTX-naïve and DMARD-naïve subgroups.

AE = adverse event; ALT = alanine aminotransferase
AST = aspartate aminotransferase
DMARD = disease-modifying anti-rheumatic drug
ITT = intent-to-treat; MTX = methotrexate
### Table 1. Summary of adverse events after 24 weeks of treatment with methotrexate or tocilizumab

<table>
<thead>
<tr>
<th></th>
<th>Total safety population</th>
<th>MTX-naïve subgroup</th>
<th>DMARD-naïve subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX n = 284</td>
<td>TCZ 8 mg/kg n = 288</td>
<td>MTX n = 190</td>
</tr>
<tr>
<td>Patients with ≥1 AE, n (%)</td>
<td>220 (77.5)</td>
<td>230 (79.9)</td>
<td>146 (76.8)</td>
</tr>
<tr>
<td>AEs leading to discontinuation, n (%)</td>
<td>15 (5.3)</td>
<td>11 (3.8)</td>
<td>12 (6.3)</td>
</tr>
<tr>
<td>Patients with ≥1 SAE, n (%)</td>
<td>8 (2.8)</td>
<td>11 (3.8)</td>
<td>7 (3.7)</td>
</tr>
<tr>
<td>No. SAEs</td>
<td>15</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Serious infections per 100 PY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, n (%)*</td>
<td>1.50</td>
<td>2.86</td>
<td>2.24</td>
</tr>
</tbody>
</table>

*The safety population consisted of all patients who were randomly assigned to a treatment group.

*Pneumonia was the only serious infection reported in more than one patient in the study.*

*AE = adverse event; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; PY = patient-years; SAE = serious adverse event; TCZ = tocilizumab*
Table 2. Shifts in ALT and AST after 24 weeks of treatment with methotrexate or tocilizumab

<table>
<thead>
<tr>
<th></th>
<th>Total safety population</th>
<th>MTX-naïve subgroup</th>
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<tbody>
<tr>
<td></td>
<td>MTX n = 284 TCZ 8 mg/kg</td>
<td>MTX n = 190 TCZ 8 mg/kg</td>
<td>MTX n = 129 TCZ 8 mg/kg</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shift from normal to &gt;1–3x ULN</td>
<td>86 (30.3)</td>
<td>59 (31.0)</td>
<td>39 (30.2)</td>
</tr>
<tr>
<td></td>
<td>10 (3.5)</td>
<td>8 (4.2)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Shift from normal to &gt;3x ULN</td>
<td>5 (1.7)</td>
<td>3 (1.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shift from normal to &gt;1–3x ULN</td>
<td>67 (23.6)</td>
<td>47 (24.7)</td>
<td>31 (24.0)</td>
</tr>
<tr>
<td></td>
<td>4 (1.4)</td>
<td>3 (1.6)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Shift from normal to &gt;3x ULN</td>
<td>59 (20.5)</td>
<td>38 (19.7)</td>
<td>31 (24.0)</td>
</tr>
<tr>
<td></td>
<td>3 (1.0)</td>
<td>1 (0.5)</td>
<td>2 (1.6)</td>
</tr>
</tbody>
</table>

The safety population consisted of all patients who were randomly assigned to a treatment group.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; TCZ = tocilizumab; ULN = upper limit of normal.
Key conclusion

- This analysis of data from the AMBITION study showed that after 24 weeks of treatment RA patients receiving tocilizumab (8 mg/kg) as monotherapy experienced significantly greater ACR20, ACR50, and ACR70 responses, EULAR good responses, and DAS28 remission rates than patients receiving MTX monotherapy, regardless of previous MTX or DMARD exposure.


ACR = American College of Rheumatology
DAS28 = 28-joint Disease Activity Score
DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
MTX = methotrexate; RA = rheumatoid arthritis
Efficacy of tocilizumab in rheumatoid arthritis: interim analysis of long-term extension trials of up to 2.5 years

Background

- The efficacy and safety of tocilizumab in RA patients have been evaluated in four 24-week, phase III, randomized, double-blind, placebo-controlled clinical trials.\(^1\)\(^-\)\(^4\)

- Data from a five-year open-label study of 143 patients with RA treated initially in a Japanese randomized controlled trial suggest that tocilizumab is effective and safe during long-term therapy.\(^5\)

- At EULAR 2009, Smolen and colleagues presented efficacy data for tocilizumab from RA patients participating in two ongoing, open-label, long-term extension studies (GROWTH95 and GROWTH96).\(^6\)


EULAR = European League Against Rheumatism
RA = rheumatoid arthritis
Study design

- Adult RA patients who were 18 years of age or older and had participated in one of four international, 24-week, phase III studies (OPTION, AMBITION, RADIATE, or TOWARD) were eligible for inclusion into one of two long-term extension studies (GROWTH95 or GROWTH96).\(^1\sim^4\)

- Patients completing treatment in the OPTION trial were eligible for inclusion in GROWTH95 from August 2005 until February 2007.

- Patients completing treatment in the AMBITION, RADIATE, or TOWARD trials were eligible for inclusion into GROWTH96 from September 2005 until February 2008.

- Patients continued background DMARD therapy unless adjustments or interruptions were required for safety reasons.

- Patients who had received placebo therapy in the phase III controlled trials transitioned to tocilizumab (8 mg/kg) once every 4 weeks.

DMARD = disease-modifying anti-rheumatic drug
RA = rheumatoid arthritis

Study design (cont’d)

- Analysis of efficacy (study baseline) began with the first dose of tocilizumab (4 mg/kg or 8 mg/kg), whether at baseline of one of the phase III studies, at week 16 when tocilizumab (8 mg/kg) rescue therapy was allowed during OPTION and RADIATE, or when control patients transitioned to a long-term extension study with the first dose of tocilizumab (8 mg/kg).

- Efficacy assessments were conducted every 12 weeks in the ITT population, defined as all patients who received ≥1 dose of tocilizumab in GROWTH95 or GROWTH96.

- For the purpose of the analysis, the long-term population was divided into three groups:
  - monotherapy (AMBITION)
  - TNF-I inadequate response (RADIATE)
  - pooled DMARD inadequate response (TOWARD and OPTION)

DMARD = disease-modifying anti-rheumatic drug
ITT = intent-to-treat
TNF-I = tumour necrosis factor inhibitor

Study design (cont’d)

- Analyses included:
  - proportions of patients achieving ACR20, ACR50, or ACR70 responses
  - proportions of patients with sustained ACR70 response for 24 weeks (3 consecutive visits, reflecting an MCR) or 48 consecutive weeks (5 consecutive visits)
  - proportions of patients with the highest possible degree of efficacy in ACR criteria: SJC or TJC = 0 or ≤1, VAS = 0, HAQ-DI = 0
  - proportions of patients with DAS28 remission (DAS28 <2.6), low disease activity score (DAS28 ≤3.2), or good response according to EULAR criteria

- All data available up to and including the cut-off date (March 10, 2008) were included.

ACR = American College of Rheumatology
DAS28 = 28-joint Disease Activity Score
EULAR = European League Against Rheumatism
HAQ-DI = Health Assessment Questionnaire Disability Index
MCR = major clinical response; SJC = swollen joint count
TJC = tender joint count; VAS = Visual Analogue Scale

Key findings

- Of the 3,015 patients randomly assigned in the primary study populations, 2,733 patients (91%) reached week 24.
- A total of 2,583 patients (86%) of 3,015 received tocilizumab up to the interim analysis cut-off (March 10, 2008).
- The percentage of patients participating from each of the four primary studies was comparable.
- Twenty percent (20%) of patients withdrew from the overall population: 3% for insufficient therapeutic response, 10% because of safety, and 7% for other reasons.
- For DMARD-IR patients, data were included up to week 132.
- Fewer than 60 patients were in the monotherapy and TNF-I IR groups at visits after week 108. Data were therefore included up to week 108 in the monotherapy and TNF-I IR groups.

DMARD = disease-modifying anti-rheumatic drug
IR = inadequate response
TNF-I = tumour necrosis factor inhibitor

ACR response rates were maintained in all populations of patients who were treated with tocilizumab.

At week 108, 16.7% of patients in the monotherapy group, 10.9% in the TNF-I IR group, and 16.9% in the DMARD-IR group achieved an MCR (maintenance of ACR70 response for 24 consecutive weeks).

At week 108, 13.6% of patients in the monotherapy group, 5.8% in the TNF-I IR group, and 10.6% in the DMARD-IR group had maintained ACR70 for 48 consecutive weeks.

At week 132, 13.8% of DMARD-IR patients had maintained an ACR70 response for 48 consecutive weeks.
Figure 1. ACR70 response rates over time during long-term treatment with tocilizumab (8 mg/kg)

**Monotherapy**  
Baseline: 566  
12: 545  
24: 538  
36: 504  
48: 486  
60: 415  
72: 360  
84: 252  
96: 166  
108: 84  
120:  
132:  

**Anti-TNF-IR**  
Baseline: 400  
12: 391  
24: 389  
36: 367  
48: 354  
60: 318  
72: 295  
84: 241  
96: 170  
108: 103  
120:  
132:  

**DMARD-IR**  
Baseline: 1,617  
12: 1,578  
24: 1,551  
36: 1,441  
48: 1,421  
60: 1,373  
72: 1,279  
84: 1,156  
96: 948  
108: 653  
120: 403  
132: 228  

**DMARD** = disease-modifying anti-rheumatic drug; **IR** = inadequate response; **TNF** = tumour necrosis factor.

Note: n values shown are the total number of patients who reached the time points and had valid assessments.


ACR = American College of Rheumatology
Key findings (cont’d)

- At week 96, proportions of patients in the monotherapy, TNF-I IR, and DMARD-IR groups, respectively, who:
  - achieved an SJC of 0 were 38.1%, 22.5%, and 34.9%
  - achieved an SJC and a TJC of 0 were 16.8%, 8.9%, and 19.0%
  - had HAQ-DI scores of 0 were 24.6%, 8.9%, and 17.1%
  - had patient global VAS scores of 0 mm were 13.2%, 3.0%, and 4.5%
  - had physician global VAS scores of 0 mm were 10.8%, 2.4%, and 8.4%

DMARD = disease-modifying anti-rheumatic drug
HAQ-DI = Health Assessment Questionnaire Disability Index
IR = inadequate response; SJC = swollen joint count
TNF-I = tumour necrosis factor inhibitor
TJC = tender joint count; VAS = Visual Analogue Scale

Key findings (cont’d)

- Proportions of patients with low disease activity (DAS28 ≤3.2) were maintained over time for patients in all three groups.
- Proportions of patients who achieved EULAR good response were maintained over time in all three groups.
- Proportions of patients achieving DAS28 remission (DAS28 ≤2.6) were maintained in all three groups.
Figure 2. Proportions of patients who achieved low disease activity (DAS28 ≤ 3.2) during long-term treatment with tocilizumab (8 mg/kg)
Figure 3. Proportions of patients who achieved EULAR good response during long-term treatment with tocilizumab (8 mg/kg)

DMARD = disease-modifying anti-rheumatic drug; IR = inadequate response; TNF = tumour necrosis factor-α

Note: n values shown are the total number of patients who reached the time points and had valid assessments
Figure 4. Proportions of patients who achieved DAS28 clinical remission (DAS28 <2.6) during long-term treatment with tocilizumab (8 mg/kg)

**Figure Caption:**

- **Monotherapy n =** 564, 552, 531, 494, 466, 402, 344, 239, 160, 81
- **Anti-TNF-IR n =** 399, 384, 377, 353, 334, 292, 270, 232, 159, 93
- **DMARD-IR n =** 1,609, 1,566, 1,526, 1,401, 1,382, 1,311, 1,236, 1,119, 898, 620, 386, 211

**Legend:**

- DMARD = disease-modifying anti-rheumatic drug; IR = inadequate response; TNF = tumour necrosis factor-α.
- Note: n values shown are the total number of patients who reached the time points and had valid assessments.

**Abbreviation:**

DAS28 = 28-joint Disease Activity Score
Key conclusions

- Efficacy with longer term tocilizumab therapy was maintained over time in ACR response rates, DAS28 scores, and EULAR good response rates in patients receiving tocilizumab monotherapy, patients in the TNF-I IR group, and patients in the DMARD-IR group.

- These findings are supported by clinically significant improvements in ACR core components at week 96 in all three groups.

- Tocilizumab effectiveness was also reflected in the low number of patients (3%) who withdrew from the long-term studies because of insufficient therapeutic response.

ACR = American College of Rheumatology
DAS28 = 28-joint Disease Activity Score
DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
IR = inadequate response
TNF-I = tumour necrosis factor inhibitor

Long-term safety and tolerability of tocilizumab in patients with a mean treatment duration of 1.5 years

Background

- At EULAR 2009, Van Vollenhoven and colleagues presented an interim analysis of pooled data from the two ongoing, open-label, long-term extension studies (GROWTH95 and GROWTH96) and one controlled study (LITHE).

- The analysis assessed the long-term safety and tolerability of tocilizumab in patients with rheumatoid arthritis.¹

Study design

- Long-term extension studies GROWTH95 and GROWTH96 included:¹⁻⁵
  - adult RA patients who were 18 years of age or older and had participated in one of four international, 24-week, phase III studies (OPTION, AMBITION, RADIATE, and TOWARD)
  - patients participating in a small clinical pharmacology study (n = 23)

- Patients from GROWTH95 and GROWTH96 and patients from an ongoing controlled study (LITHE)⁶ were included as the all-exposure population for this analysis.

- Safety data from the all-exposure population were pooled and analyzed from the time of initial tocilizumab exposure to the clinical cut-off date (March 10, 2008) for the long-term extension studies (GROWTH95 and GROWTH96) and up to 52 weeks for the LITHE study.


RA = rheumatoid arthritis
Study design (cont’d)

- General safety measures including AEs, SAEs, AEs leading to withdrawals, and deaths were recorded throughout the studies.
  - AEs were defined as any untoward medical occurrence in a patient who had been administered study treatment that did not necessarily have a causal relationship with the treatment.
  - SAEs were defined as any event that fulfilled the seriousness criteria, including events leading to hospitalization, persistent or significant disability, or death.

- AEs of special interest were infections, neutropenia, GI perforations, malignancies, infusion-related events, cardiovascular events, dyslipidemia, and hepatic enzyme abnormalities.

- Fasting lipid profile levels including those for total cholesterol, LDL, HDL, and triglycerides were measured at baseline, weeks 6, 14, and 24, and every 4 weeks until the clinical cut-off date.


AE = adverse event; GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAE = serious adverse event
Study design (cont’d)

- Neutrophil counts, liver transaminase levels (ALT and AST), and bilirubin levels were measured at baseline, every 2 weeks to week 16 (except week 10), and every 4 weeks until the clinical cut-off date.

- Laboratory measurements were made before tocilizumab infusions, and investigators were unaware of test results at the time of infusion.

- Tocilizumab was permanently discontinued in any patient with a single ALT or AST measurement ≥5 times the ULN or two measurements ≥3 times ULN, an indirect bilirubin level ≥2 times ULN or a total bilirubin >2.5 mg/dL, or a total neutrophil count <0.5x10⁹/L.

- Tocilizumab infusion was withheld in any patient with an ALT or AST level ≥3 times ULN until the level reached <3 times ULN.

- If the ALT or AST elevation was ≥2 times ULN but <3 times ULN, the patient could receive the tocilizumab infusion (a blood sample was taken just before the infusion to verify that ALT and AST remained <3 times ULN).


ALT = alanine aminotransferase
AST = aspartate aminotransferase
ULN = upper limit of normal
Key findings

- The safety population included 3,857 patients who received at least one dose of tocilizumab.
- All data from the time of the first dose were included in the analysis.
- Median duration of tocilizumab therapy was 1.5 years.
- A total of 2,009 patients (52.1%) had been treated with tocilizumab for at least 1.5 years.
- At the time of analysis, 3,524 patients (91.4%) had completed 24 weeks of treatment.
- Average exposure was 1.5 ± 0.7 years, with a total cumulative exposure and duration of observation of 5,590 and 5,700 p-yrs, respectively.


p-yrs = patient-years
Key findings

- Rate of withdrawals attributed to AEs was 6.5/100 p-yrs.
- Withdrawal rate due to AEs was highest during the first 6 months of treatment (11.2/100 p-yrs), decreased from months 7 to 12 (6.0/100 p-yrs) and from months 13 to 18 (3.7/100 p-yrs), and remained relatively constant thereafter.
- Other reasons for withdrawal were refusal of treatment (4.3%; n = 167) and insufficient therapeutic response (3.1%; n = 121).
- Thirty (30) deaths were reported, and the mortality rate was 0.53/100 p-yrs.


AE = adverse event
p-yrs = patient-years
Key findings (cont’d)

- The overall AE rate was 370/100 p-yrs.
- The rate of AEs was highest during the first 6 months of treatment and decreased thereafter.
- The most common AEs leading to withdrawal were:
  - investigations (1.7/100 p-yrs) – primarily because of elevations in liver enzyme levels
  - infections (0.9/100 p-yrs)
  - neoplasms (0.8/100 p-yrs)
- The SAE rate was 15.1/100 p-yrs of exposure.
- The most frequently reported SAEs were infections (4.2/100 p-yrs).

AE = adverse event
p-yrs = patient-years
SAE = serious adverse event

<table>
<thead>
<tr>
<th></th>
<th>Event rates per 100 patient-years (95% CI)</th>
<th>Event rates per 100 patient-years by 6-month periods (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event rates per 100 patient-years (95% CI)</td>
<td>0–6</td>
</tr>
<tr>
<td>Adverse events</td>
<td>370 (365, 375)</td>
<td>476 (465, 486)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>15.1 (14.1, 16.1)</td>
<td>15.9 (14.0, 17.8)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Key findings (cont’d)

- The overall SIE rate was 4.37/100 p-yrs (95% CI, 3.84–4.95).
- Continued exposure to tocilizumab was not associated with an increasing risk for serious infection.
- A total of 249 serious infections were reported – the most common were pneumonia (n = 66) and cellulitis (n = 31).
- Ten (10) deaths were caused by infection, and the rate of deaths attributed to infections was 0.18/100 p-yrs.
- Nine (9) opportunistic infections were reported (0.2/100 p-yrs): Mycobacterium avium complex infection, tuberculosis (one extrapulmonary and one intrapulmonary), mycobacterial UTI (acid-alcohol-resistant bacillus; BAAR positive), Pneumocystis jiroveci pneumonia, Candida osteomyelitis, GI candidiasis, fungal esophagitis, and fungal sinusitis.
- Grade 3/4 neutropenia was reversible with tocilizumab interruption and was not associated with serious infection.

CI = confidence interval; GI = gastrointestinal p-yrs = patient-years; SIE = serious infection event UTI = urinary tract infection
### Table 2. Rates of serious infections and cardiovascular events in the all-exposure population

<table>
<thead>
<tr>
<th>Event rates per 100 patient-years (95% CI)</th>
<th>Event rates per 100 patient-years by 6-month periods (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td></td>
</tr>
<tr>
<td>4.4 (3.8, 5.0)</td>
<td>4.7 (3.7, 5.8)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>0.26 (0.15, 0.43)</td>
<td>0.35 (0.13, 0.76)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>0.18 (0.08, 0.32)</td>
<td>0.35 (0.13, 0.76)</td>
</tr>
</tbody>
</table>

CI = confidence interval

### Table 3. Patients reporting neutropenia in the all-exposure population

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tocilizumab-treated patients (n = 3,857)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1/2, n (%)</td>
<td>1,230 (31.9)</td>
</tr>
<tr>
<td>Grades 3/4, n (%)</td>
<td>156 (4.0)</td>
</tr>
</tbody>
</table>
Key findings (cont’d)

- The overall infusion reaction rate was 2.8/100 p-yrs, and the overall rate of reactions that occurred within 24 hours of the infusion was 5.7/100 p-yrs.
- Mean and median fasting total cholesterol, LDL, HDL, and triglyceride levels were increased at 6 weeks and remained relatively stable during subsequent assessments.
- A total of 224 patients (5.8%) were treated with a lipid-lowering agent during treatment with tocilizumab, and follow-up lipoprotein evaluation showed that they generally responded to treatment.
- Overall rate of malignant and non-malignant neoplasms was 1.67/100 p-yrs; 81 neoplasms were confirmed malignancies, 9 were benign, and 5 were unspecified.
- Incidence of single ALT or AST elevations >3 times ULN was highest during the first 24 weeks of treatment and decreased with continuing treatment.
- In total, 67 patients (1.7%) discontinued treatment because of elevations in transaminase levels.

ALT = alanine aminotransferase; AST = aspartate aminotransferase
HDL = high-density lipoprotein; LDL = low-density lipoprotein
p-yrs = patient-years; ULN = upper limit of normal

Table 4. Rates of malignancy by tumour type in the all-exposure population

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Tocilizumab-treated patients (n = 3,857)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. malignancies</td>
</tr>
<tr>
<td>Overall</td>
<td>95</td>
</tr>
<tr>
<td>Non-melanoma skin cancers</td>
<td>24</td>
</tr>
<tr>
<td>Solid tumours</td>
<td>42</td>
</tr>
<tr>
<td>Hematological/lymphatic cancers</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
</tr>
</tbody>
</table>

Figure 1. Percentage of patients with single elevations in ALT and AST levels to >1–3 times ULN and >3 times ULN during 6-month periods of follow-up in the all-exposure population

ALT = alanine aminotransferase
AST = aspartate aminotransferase
ULN = upper limit of normal

Key conclusions

- No new safety signals emerged in patients after prolonged exposure to tocilizumab.
- Incidences and types of AEs reported after long-term exposure to tocilizumab were similar to those reported in controlled six-month studies.\(^1\)\(^–\)\(^5\)
- Rates of serious infections, malignancies, and other SAEs did not increase with continued treatment with tocilizumab.
- The incidence of elevations in ALT and AST levels did not increase after prolonged administration with tocilizumab.


AE = adverse event
ALT = alanine aminotransferase
AST = aspartate aminotransferase
SAE = serious adverse event
Key conclusions (cont’d)

- Elevations in lipid levels were observed with tocilizumab treatment and decreased when statins were prescribed.

- Rates of myocardial infarction and stroke were comparable to those reported for RA patients receiving biologic agents (<0.5/100 p-yrs) and remained stable over time.

- Overall tocilizumab has a well-defined and manageable safety profile that supports a favourable risk/benefit ratio for patients with rheumatoid arthritis.