New Evidence reports on presentations given at EULAR 2011

Tocilizumab for the Treatment of Rheumatoid Arthritis and Juvenile Idiopathic Arthritis
Report on EULAR 2011 presentations

- Benefit of continuing tocilizumab therapy (8 mg/kg every 4 weeks) in RA patients who have not responded adequately within the first 8 weeks (Keystone E, et al. EULAR 2011: Abstract FRI0350)


- Tocilizumab treatment in patients with RA and inadequate response to DMARDs and/or TNF inhibitors: ACT-SURE final results (Bykerk V, et al. EULAR 2011: Abstract SAT0306)

- Comparison of TCZ as monotherapy or with add-on DMARDs in patients with RA and an inadequate response to previous treatments: ACT-SURE results (Sibilia J, et al. EULAR 2011: Abstract FRI0365)

RA = rheumatoid arthritis; TNF = tumour necrosis factor; DMARDs = disease-modifying anti-rheumatic drugs; TCZ = tocilizumab.
Report on EULAR 2010 presentations (cont’d)

- Long-term safety of tocilizumab in RA clinical trials
  (Genovese M, et al. EULAR 2011: Abstract SAT0270)

- Long-term efficacy of tocilizumab in RA patients who have inadequate response to anti-TNF therapy
  (Emery P, et al. EULAR 2011: Abstract SAT0286)

- Tocilizumab plus methotrexate is not superior to TCZ alone in RA patients with inadequate response to MTX:
  24-week results of the ACT-RAY study
  (Dougados M, et al. EULAR 2011: Abstract OP0020)

- Efficacy and safety of tocilizumab in patients with systemic JIA: TENDER 52-week data
  (De Benedetti, et al. EULAR 2011: Abstract OP0006)

RA = rheumatoid arthritis; TNF = tumour necrosis factor; TCZ = tocilizumab; MTX = methotrexate; JIA = juvenile idiopathic arthritis.
Benefit of continuing tocilizumab therapy (8 mg/kg every 4 weeks) in RA patients who have not responded adequately within the first 8 weeks

Background

- A subset of patients with RA will respond to treatment with biologic agents quickly, while others will not. For those who do not, continuation of treatment may still allow them to achieve clinical response.¹

- The RADIATE study demonstrated that a significantly greater proportion of patients who received TCZ 4 mg/kg or 8 mg/kg plus MTX compared with patients who received placebo plus MTX achieved ACR 20 response.²

- Keystone and colleagues set out to determine whether patients who did not achieve adequate responses within the first eight weeks of therapy could achieve clinical responses at later time points with continued treatment at the same dose of TCZ.¹ The findings of this study were presented at EULAR 2011.

Study design

- This was a post-hoc, exploratory analysis of TNFi-IR patients who were enrolled in the RADIATE study.
- Patients were randomized to receive TCZ 4 mg/kg, tocilizumab 8 mg/kg, or placebo, every four weeks plus weekly MTX, for 24 weeks.
- For patients who did not achieve their endpoints by week 8, they were assessed for the following clinical responses at week 24:
  - 28-joint DAS28 improvement $\geq 1.2$


TNFi-IR = inadequate response to tumour necrosis factor inhibitor; MTX = methotrexate; DAS = disease activity score; TCZ = tocilizumab.
Study design (cont’d)

- LDAS [DAS28 ≤3.2]
- DAS28 <2.6
- Low CDAI (≤10) was assessed for patients who did not achieve ≥50% improvement in SJC from baseline by week 8
Key findings

- By week 8, approximately 50% of patients in the TCZ 8 mg/kg group and the TCZ 4 mg/kg group achieved ≥50% improvement in SJC.

- By week 8 and also at week 24, a higher proportion of patients in the TCZ 8 mg/kg group than in the TCZ 4 mg/kg and control groups achieved LDAS, DAS28 <2.6, CDAI ≤10 and SDAI ≤11.

- Similar responses at week 24 were observed in patients who did not achieve ≥50% improvement in TJC or ≥50% improvement in either TJC or SJC at week 8.


CDAI = clinical disease activity index; DAS = disease activity score; SJC = swollen joint count; TJC = tender joint count; SDAI = simplified disease activity index; LDAS = low disease activity state; TCZ = tocilizumab.
Key findings (cont’d)

- Among the patients who did not achieve LDAS by week 8, a substantial proportion in the TCZ 8 mg/kg group (26.1%), but few in the TCZ 4 mg/kg group went on to achieve LDAS at week 24.


LDAS = low disease activity state; TCZ = tocilizumab.
Figure 1. Week 24 clinical responses in patients who did not achieve optimal responses by week 8

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

<table>
<thead>
<tr>
<th></th>
<th>LDAS (DAS28 ≤ 3.2)</th>
<th>DAS28 &lt; 2.6</th>
<th>CDAI ≤ 10</th>
<th>SDAI ≤ 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX, n</td>
<td>157</td>
<td>158</td>
<td>150</td>
<td>152</td>
</tr>
<tr>
<td>TCZ 4 mg/kg + MTX, n</td>
<td>154</td>
<td>160</td>
<td>157</td>
<td>151</td>
</tr>
<tr>
<td>TCZ 8 mg/kg + MTX, n</td>
<td>138</td>
<td>151</td>
<td>147</td>
<td>148</td>
</tr>
</tbody>
</table>

CDAI = clinical disease activity index; DAS28 = 28-joint disease activity score; LDAS = low disease activity state; MTX = methotrexate; SDAI = simplified disease activity index; TCZ = tocilizumab
Key findings (cont’d)

- Among the patients who did not achieve DAS28 <2.6, CDAI ≤10, or SDAI ≤11 by week 8, 18.5% to 20.7% in the TCZ 8 mg/kg group achieved the endpoint by week 24, compared with 5.0% to 7.2% in the TCZ 4 mg/kg group.


CDAI = clinical disease activity index; DAS = disease activity score; SDAI = simplified disease activity index; TCZ = tocilizumab.
Key conclusions

- In TNFi-IR patients, approximately 50% of patients receiving TCZ 8 mg/kg and TCZ 4 mg/kg achieved at least 50% improvement in SJC by week 8.

- Of patients in the TCZ 8 mg/kg group who did not achieve an optimal response (at least 50% improvement in SJC) by week 8, a substantial proportion of patients in the 8 mg/kg group achieved LDAS at week 24 with continued TCZ treatment.

- However, of patients randomly assigned to TCZ 4 mg/kg or placebo who did not achieve an optimal response by week 8, very few achieved LDAS at later time points with continued randomized treatment.


TNFi-IR = inadequate response to tumour necrosis factor inhibitor; SJC = swollen joint count; DAS = disease activity score; LDAS = low disease activity state; TCZ = tocilizumab.
Key conclusions (cont’d)

- Clinicians may consider escalating the TCZ dose to 8 mg/kg in patients who receive 4 mg/kg and do not respond by week 8 because they are unlikely to respond to continued therapy at the lower dose.


TCZ = tocilizumab.
Long-term efficacy of tocilizumab in patients with RA

Background

- Previous phase III studies have confirmed the efficacy and safety of TCZ in RA patients for up to two years, and the long-term efficacy of this therapy has been shown for a median duration of approximately three years.

- At EULAR 2011, Khraishi and colleagues presented data from LTEs for patients treated with TCZ with or without MTX or other DMARDs, to further characterize the efficacy of TCZ.¹

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RA = rheumatoid arthritis; LTEs = long-term extension studies; MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs; EULAR = European League Against Rheumatism; TCZ = tocilizumab.
Study design

- Patients who received at least one dose of TCZ in one of three 24-week phase III studies (OPTION, TOWARD, AMBITION), in two long-term open-label extension studies of the phase III trials (GROWTH95, GROWTH96), or in the two-year phase III study (LITHE) or its extension were included in the analysis.

- DMARD-IR patients (OPTION, TOWARD, and LITHE) received TCZ in combination with MTX or other DMARDs.

MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs; DMARD-IR = DMARD inadequate response; TCZ = tocilizumab.

Study design (cont’d)

- Patients who were never exposed to or had never failed MTX (NE/NF MTX patients; [AMBITION]) received monotherapy during the 24-week phase and could add MTX or other DMARDs to the extension phase if they had suboptimal responses (>50% reduction in SJC or TJC in the 24-week phase).

- The baseline for this analysis was considered to be the first active dose of TCZ.

MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs; SJC = swollen joint count; TJC = tender joint count; TCZ = tocilizumab.

Study design (cont’d)

- Efficacy data were included up to week 216 for the DMARD-IR and NE/NF MTX groups, after which patient numbers for the NE/NF MTX group were <10% of the baseline patient number and therefore were insufficient for evaluation.

- Numbers of patients with assessments decreased over time because some patients had either not yet reached later assessments or had withdrawn from the study.

MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs.

Key findings

- The analysis was conducted in 2,904 DMARD-IR patients and 618 NE/NF MTX patients.
- By the data cut-off date, the median treatment duration was 3.55 years (range: 0.0–5.1 years).
- By week 216, 30.0% of DMARD-IR patients and 26.4% of NE/NF MTX patients had withdrawn from treatment.
- Approximately half withdrew for safety reasons and the other half for non-safety reasons.
- In both the DMARD-IR and NE/NF MTX groups, withdrawals due to insufficient response were approximately 3%.

MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs; DMARD-IR = DMARD inadequate response.
Key findings (cont’d)

- The proportion of patients who achieved ACR70 responses increased over time in both DMARD-IR and NE/NF MTX groups.
- Similar patterns were observed for patients in both groups who achieved ACR50 responses.
- By week 144, 21% of DMARD-IR patients and 26% of NE/NF MTX patients had achieved the major clinical response of ACR70 maintained for 24 consecutive weeks.
- At week 120, patients in both groups had achieved clinically significant improvements in ACR core set components.


MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs; DMARD-IR = DMARD inadequate response; ACR = American College of Rheumatology.
Key findings (cont’d)

- At week 120, 52.6% and 38.5% of DMARD-IR patients and 60.2% and 39.4% of NE/NF MTX patients had ≤1 SJC and ≤1 TJC, respectively.

- Absolute numbers of DMARD-IR and NE/NF MTX patients achieving low disease activity (LDA; 28-joint [DAS28] ≤3.2) and DAS28 <2.6 increased or were maintained through week 120.

- The decrease thereafter was likely caused by the decreasing numbers of patients who reached these time points.
Table 1. Responses to tocilizumab over time in DMARD-IR and NE/NF MTX patients

<table>
<thead>
<tr>
<th>Week</th>
<th>24</th>
<th>72</th>
<th>120</th>
<th>168</th>
<th>192</th>
<th>216</th>
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<td></td>
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<tr>
<td>DMARD-IR [n = 2904], % (n/n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>35 (929/2693)</td>
<td>50 (1162/2320)</td>
<td>56 (1172/2097)</td>
<td>59 (1052/1797)</td>
<td>64 (840/1304)</td>
<td>65 (453/693)</td>
</tr>
<tr>
<td>ACR70</td>
<td>16 (423/2693)</td>
<td>30 (692/2312)</td>
<td>35 (725/2097)</td>
<td>40 (712/1797)</td>
<td>45 (584/1304)</td>
<td>45 (313/693)</td>
</tr>
<tr>
<td>LDA</td>
<td>43 (1138/2660)</td>
<td>62 (1408/2269)</td>
<td>69 (1393/2030)</td>
<td>69 (1187/1725)</td>
<td>73 (922/1265)</td>
<td>73 (482/664)</td>
</tr>
<tr>
<td>DAS28 &lt;2.6</td>
<td>27 (722/2660)</td>
<td>47 (1070/2269)</td>
<td>54 (1088/2030)</td>
<td>55 (951/1725)</td>
<td>60 (754/1265)</td>
<td>57 (377/664)</td>
</tr>
<tr>
<td>Never exposed to or never failed MTX [n = 618], % (n/n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>40 (223/563)</td>
<td>52 (256/488)</td>
<td>58 (265/460)</td>
<td>63 (213/339)</td>
<td>70 (127/181)</td>
<td>63 (30/48)</td>
</tr>
<tr>
<td>ACR70</td>
<td>22 (126/563)</td>
<td>31 (152/488)</td>
<td>38 (174/460)</td>
<td>43 (147/339)</td>
<td>45 (81/181)</td>
<td>50 (24/48)</td>
</tr>
<tr>
<td>LDA</td>
<td>50 (277/556)</td>
<td>67 (314/472)</td>
<td>71 (314/440)</td>
<td>73 (238/325)</td>
<td>68 (114/167)</td>
<td>59 (26/44)</td>
</tr>
<tr>
<td>DAS28 &lt;2.6</td>
<td>37 (204/556)</td>
<td>51 (243/472)</td>
<td>56 (247/440)</td>
<td>59 (191/325)</td>
<td>59 (98/167)</td>
<td>46 (20/44)</td>
</tr>
</tbody>
</table>

Baseline (week 0) was first active TCZ dose. n/n = patients who responded/patients assessed. LDA = DAS28 ≤3.2.
ACR = American College of Rheumatology; DAS28 = 28-joint disease activity score; DMARD-IR = disease-modifying anti-rheumatic drug inadequate responders; LDA = low disease activity; MTX = methotrexate; NE/NF MTX = never exposed to or never failed MTX; TCZ = tocilizumab

Key conclusions

- In an observed case analysis of DMARD-IR or NE/NF MTX patients, efficacy was maintained during long-term TCZ treatment.

- This is an indication of the long-lasting effects of TCZ.

- This analysis showed that TCZ can provide benefit for a median duration of 3.55 years. The low patient withdrawal rate during the long-term follow-up period also supports TCZ as an effective, long-term treatment for RA patients.


MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs; DMARD-IR = DMARD inadequate response; RA = rheumatoid arthritis; TCZ = tocilizumab.
Tocilizumab treatment in patients with RA and inadequate response to DMARDs and/or TNF inhibitors: ACT-SURE final results

Bykerk V, et al. EULAR 2011: Abstract SAT0306
Background

- At EULAR 2011, Bykerk and colleagues presented the final results of the ACT-SURE study, which evaluated the efficacy and safety of TCZ in a setting that resembled a real-life clinical practice.
  - Patients who were inadequate responders to DMARD-IR or TNFi-IR from a large number of tertiary academic centres, non-academic centres, and private practices worldwide were included.
- The objectives of the ACT-SURE study were to confirm the safety and efficacy of TCZ in a setting representing real-life practice, and to evaluate the safety of switching from a TNFi to TCZ without a washout period.¹


DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; TNFi = tumour necrosis factor inhibitor; TNFi-IR = inadequate response to tumour necrosis factor inhibitor; EULAR = European League Against Rheumatism; TCZ = tocilizumab.
Study design

- ACT-SURE was a multinational, multicentre, phase IIIb, open-label, single-arm, 24-week trial of DMARD-IR/TNFi-IR RA patients.
- Patients were treated with TCZ 8 mg/kg every four weeks alone, or with DMARDs.
- Safety endpoints included rates of AEs and SAEs, serious infections, infusion reactions, increase in liver transaminase levels, and rates for discontinuation for safety reasons.

DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; TNFi-IR = inadequate response to tumour necrosis factor inhibitor; AEs = adverse events; SAEs = serious adverse events; TCZ = tocilizumab.
Study design (cont’d)

- Efficacy endpoints included ACR20, ACR50, ACR70, and ACR90 responses; 28-joint DAS, DAS28 <2.6; and select ACR core components (SJC, TJC, and patient assessment of pain VAS).

- After the release of the 2010 ACR/ EULAR recommendations on the reporting of disease activity in clinical trials, the following additional exploratory efficacy endpoints were added:
  - CDAI, LDA (CDAI <10), and remission (CDAI <2.6).
  - SDAI, LDA (SDAI <11), and remission (SDAI <3.3).


ACR = American College of Rheumatology; DAS = disease activity score; SJC = swollen joint count; TJC = tender joint count; VAS = visual analogue scale; EULAR = European League Against Rheumatism; CDAI = clinical disease activity index; LDA = low disease activity; SDAI = simplified disease activity index.
Analyses were stratified by pre-study TNFi use as follows:

- TNFi-naive (DMARD-IR) patients
- Previous TNFi users (more than two months since TNFi use)
- Recent TNFi users (two or less months since TNFi use)

A sub-analysis of TCZ monotherapy was also performed.
Key findings

- The safety and ITT populations were identical and included 1,681 patients who were treated with TCZ monotherapy (n = 239) or TCZ plus DMARD(s) (n = 1,442).

- For this analysis, patients were stratified by TNFi use with 58% being TNFi-naive (DMARD-IR), 18% being previous TNFi users, and 24% being recent TNFi users.

Safety

- Overall, 215 patients (12.8%) discontinued the study.
  - Fewer patients withdrew for safety reasons (4.8%) than for non-safety reasons (8.0%).

TNFi = tumour necrosis factor inhibitor; DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; ITT = intent-to-treat; TCZ = tocilizumab.
Key findings (cont’d)

- Rates of withdrawal for safety reasons were low and similar amongst the study groups.
  - Rates/100 PY for AEs, SAEs, AEs leading to withdrawal, serious infections, and infusion reactions were slightly lower in DMARD-IR patients than in TNFi-IR previous use patients.

Efficacy

- At week 24, 26.4% of patients achieved ACR70 responses.
  - More DMARD-IR patients (31.8%) achieved ACR70 responses than TNFi-IR previous use (17.8%) or TNFi-IR recent use (19.7%) patients.
  - Similar patterns were observed for ACR20, ACR50, and ACR90 responses at 24 weeks.

TNFi-IR = inadequate response to tumour necrosis factor inhibitor; DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; PY = patient years; AEs = adverse events; SAEs = serious adverse events; ACR = American College of Rheumatology.

Key findings (cont’d)

- The onset of efficacy was rapid with 36.5% of patients achieving ACR20 responses at four weeks.
  - More DMARD-IR patients (40.9%) achieved ACR20 responses at week 4 than TNFi-IR previous use (27.5%) or TNFi-IR recent use (32.4%) patients.

ACR = American College of Rheumatology; TNFi-IR = inadequate response to tumour necrosis factor inhibitors; DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response.
### Table 1. Safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>DMARD-IR (n = 976)</th>
<th>TNFi-IR Previous use (n = 296)</th>
<th>TNFi-IR Recent use (n = 407)</th>
<th>All patients (n = 1,681)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pt- yrs</td>
<td>452.1</td>
<td>132.4</td>
<td>183.3</td>
<td>787.3</td>
</tr>
<tr>
<td>AE rate/100 pt- yrs (95% CI)</td>
<td>561.1 (529.6–573.1)</td>
<td>653.5 (610.8–698.6)</td>
<td>652.6 (616.1–690.6)</td>
<td>580.0 (575.9–610.4)</td>
</tr>
<tr>
<td>SAE rate/100 pt- yrs (95% CI)</td>
<td>18.6 (14.8–23.0)</td>
<td>28.0 (19.7–30.5)</td>
<td>18.0 (12.4–25.3)</td>
<td>20.1 (17.0–23.5)</td>
</tr>
<tr>
<td>AEs leading to withdrawal, % (n) (95% CI)</td>
<td>4.5 (44) (3.3–6.0)</td>
<td>7.0 (21) (4.4–10.6)</td>
<td>5.2 (21) (3.2–7.8)</td>
<td>5.1 (86) (4.1–6.3)</td>
</tr>
<tr>
<td>Serious infections, rate/100 pt- yrs (95% CI)</td>
<td>4.2 (2.5–6.6)</td>
<td>6.8 (3.1–12.9)</td>
<td>6.0 (3.0–10.7)</td>
<td>5.1 (3.6–6.9)</td>
</tr>
<tr>
<td>Infusion reactions,* % (n) (95% CI)</td>
<td>6.8 (66) (5.3–8.5)</td>
<td>7.4 (22) (4.7–11.0)</td>
<td>6.1 (25) (4.0–8.9)</td>
<td>6.7 (113) (5.6–9.0)</td>
</tr>
<tr>
<td>ALT shift from normal at baseline to &gt;3x ULN, % (n)</td>
<td>2.4 (23)</td>
<td>3.0 (9)</td>
<td>0.7 (3)</td>
<td>2.1 (35)</td>
</tr>
</tbody>
</table>

*Continued on AEs recurring during Infusion.

**AE** = adverse event; **ALT** = alanine transaminase; **CI** = confidence interval; **DMARD-IR** = disease-modifying anti-rheumatic drug inadequate responder; **pt- yrs** = patient-years; **SAE** = serious adverse event; **TNFi-IR** = tumour necrosis factor inhibitor inadequate responder; **ULN** = upper limit of normal

Figure 1. ACR20, 50, 70, and 90 responses at week 24

ACR = American College of Rheumatology; DMARD-IR = disease-modifying anti-rheumatic drug inadequate responder; TNFi-IR = tumour necrosis factor inhibitor inadequate responder.
Key findings (cont’d)

- All groups experienced rapid and significant improvements from baseline in mean DAS28 as early as week 4 and the improvements continued through week 24.
  - As expected, at each time point, improvement from baseline in mean DAS28 was numerically greater for DMARD-IR patients than for TNFi-IR previous use patients and TNFi-IR recent use patients.

- More DMARD-IR patients than TNFi-IR previous use patients or TNFi-IR recent use patients achieved DAS28 <2.6 at each time point through week 24, and the onset of efficacy was rapid and increased over time.


TNFi-IR = inadequate response to tumour necrosis factor inhibitors; DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; DAS = disease activity score.
Key findings (cont’d)

- At week 24, 35.3% of patients achieved CDAI LDA and 16.2% of patients achieved CDAI remission.
  - More DMARD-IR patients achieved CDAI LDA and CDAI remission than TNFi-IR previous use patients or TNFi-IR recent use patients.

- Improvements from baseline in TJC, SJC, and pain VAS were observed as early as week 4.
  - Improvements continued through approximately week 12 and were maintained through week 24.
  - Similar degrees of improvements were observed across patient groups.

SJC = swollen joint count; TJC = tender joint count; VAS = visual analogue scale; CDAI = clinical disease activity index; LDA = low disease activity.

Key findings (cont’d)

TCZ monotherapy sub-analysis

- Among the ITT population, 239 patients were treated with TCZ monotherapy.

- At week 24, 66.9%, 43.5%, 23.8%, and 10.0% of patients achieved ACR20, ACR50, ACR70, and ACR90 responses, respectively, and 49.8% of patients achieved DAS28 remission.²

ACR = American College of Rheumatology; DAS = disease activity score; ITT = intent-to-treat; TCZ = tocilizumab.

Figure 2. Mean DAS28 values over time

* p < 0.0001 compared with baseline

DAS28 = 28-joint disease activity score; DMARD-IR = disease-modifying anti-rheumatic drug inadequate responder; TNFi-IR = tumour necrosis factor inhibitor inadequate responder

Key conclusions

- The ACT-SURE study was conducted in a setting closer to clinical practice than is typical of phase III studies and this study confirmed TCZ’s safety profile as show in previous phase III trials.

- TCZ, as monotherapy or in combination with conventional DMARDs, is effective when used as the first-line biologic in DMARD-IR and in TNFi-IR patients.

- As in the phase III studies, TCZ’s efficacy was rapid in onset and responses increased over time.

DMARDs = disease-modifying anti-rheumatic drugs; DMARD-IR = DMARD inadequate response; TNFi-IR = inadequate response to tumour necrosis factor inhibitors; TCZ = tocilizumab.
Key conclusions (cont’d)

- Remission and LDA rates based on CDAI and SDAI demonstrated a negligible impact of acute-phase reactants on the attainment of specific clinical status.

- TCZ safety was similar for patients who were previously or recently treated with TNFis, and this finding supports treatment with TCZ immediately after stopping TNFi use without the need for a washout period.

CDAI = clinical disease activity index; LDA = low disease activity; TNFi = tumour necrosis factor inhibitor; SDAI = simplified disease activity index; TCZ = tocilizumab.

Comparison of TCZ as monotherapy or with add-on DMARDs in patients with RA and an inadequate response to previous treatments: ACT-SURE results

Background

- In the AMBITION trial, TCZ monotherapy showed significantly superior efficacy compared with MTX alone; however, comparative data of TCZ monotherapy vs. TCZ plus add-on DMARDs within the same study are limited.¹

- In the ACT-SURE study, Sibilia and colleagues compared the safety and efficacy of TCZ and TCZ plus DMARDs in RA patients who were DMARD-IR and/or TNFi-IR in a setting that closely resembles real-life clinical practice.¹

- Their findings were presented at EULAR 2011.

Study design

- ACT-SURE was a multinational, multicentre, phase IIIb, open-label, single-arm, six-month study.

- DMARD-IR or TNFi-IR patients received TCZ 8 mg/kg every four weeks, alone or in combination with one or more DMARDs.

- Safety endpoints included rates of AEs, SAEs, and serious infections. Decreases in neutrophil counts and increases in liver transaminase levels as well as AEs leading to study withdrawal were also evaluated.
Study design (cont’d)

- Efficacy endpoints included the assessment of ACR20, ACR50, ACR70, and ACR90 responses, as well as EULAR good and moderate responses, DAS28 remission (DAS28 <2.6), SDAI, CDAI remission rates, and HAQ-DI evaluation.

- Analyses were carried out for the following groups of patients:
  - TCZ monotherapy
  - TCZ plus DMARD(s)
    - TCZ plus one DMARD
    - TCZ plus more than one DMARD

ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; DAS = disease activity score; SDAI = simplified disease activity index; CDAI = clinical disease activity index; HAQ-DI = health assessment questionnaire-disability index; DMARD = disease-modifying anti-rheumatic drug; TCZ = tocilizumab.
Key findings

- Of 1,681 patients in the safety and ITT populations, 239 (14%) received TCZ monotherapy and 1,442 (86%) received DMARDs in addition to TCZ.

- Of the add-on DMARD patients, 37% were TNFi-IR and 22% received more than one DMARD.

- The most commonly used DMARDs were:
  - MTX (79%)
  - Hydroxychloroquine (17%)
  - Sulfasalazine (13%)
  - Leflunomide (13%)
Key findings (cont’d)

- Baseline DAS28 was similar amongst the groups (5.9–6.2).

**Safety**

- The rates of AEs, SAEs, and AEs leading to withdrawal were similar in the TCZ monotherapy group and the TCZ plus DMARD(s) groups.

- Serious infections were the most common SAE and occurred at similar rates in the three study groups.


DMARD = disease-modifying anti-rheumatic drug; DAS = disease activity score; AEs = adverse events; SAEs = serious adverse events; TCZ = tocilizumab.
Key findings (cont’d)

- Grade 3/4 neutropenia occurred more frequently in the TCZ plus more than one DMARD group (5.7%) than in the TCZ plus one DMARD group (2.7%) and the TCZ monotherapy group (1.7%).

- Liver transaminase level elevations above the upper limit of normal occurred less frequently in the TCZ monotherapy group than in the TCZ plus DMARD(s) groups.

DMARDs = disease-modifying anti-rheumatic drugs; TCZ = tocilizumab.
<table>
<thead>
<tr>
<th>Safety outcomes, % (95% CI)</th>
<th>TCZ monotherapy (n = 239)</th>
<th>TCZ + 1 DMARD (n = 1,124)</th>
<th>TCZ + &gt;1 DMARD (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>82.4 (77.0, 87.0)</td>
<td>75.4 (72.8, 77.9)</td>
<td>80.5 (75.7, 84.7)</td>
</tr>
<tr>
<td>SAEs</td>
<td>7.9 (4.9, 12.1)</td>
<td>7.9 (6.4, 9.7)</td>
<td>7.2 (4.6, 10.7)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>5.4 (2.9, 9.1)</td>
<td>4.6 (3.5, 6.0)</td>
<td>6.6 (4.1, 9.9)</td>
</tr>
<tr>
<td>Infections</td>
<td>38.1 (31.9, 44.6)</td>
<td>34.1 (31.3, 36.9)</td>
<td>37.7 (32.4, 43.3)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>2.1 (0.7, 4.8)</td>
<td>2.3 (1.5, 3.4)</td>
<td>1.6 (0.5, 3.6)</td>
</tr>
<tr>
<td>Grade 3/4 neutropenia* at ≥1 time point</td>
<td>1.7</td>
<td>2.7</td>
<td>5.7</td>
</tr>
<tr>
<td>ALT elevations &gt;60 U/L at any time point</td>
<td>12.1</td>
<td>16.6</td>
<td>15.1</td>
</tr>
<tr>
<td>AST elevations &gt;50 U/L at any time point</td>
<td>4.2</td>
<td>7.0</td>
<td>8.2</td>
</tr>
</tbody>
</table>

*Only one case of grade 4 neutropenia was reported in the study (in the TCZ + >1 DMARD group)
AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; pt-ys = patient-years; SAE = serious adverse event; TCZ = tocilizumab
Figure 1. Percentages of patients who achieved ACR20/50/70/90 responses at week 24

Patients with ACR response at week 24 (%)

<table>
<thead>
<tr>
<th>Response</th>
<th>TCZ monotherapy (n = 239)</th>
<th>TCZ + DMARDs (n = 1,422)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>66.9</td>
<td>66.9</td>
</tr>
<tr>
<td>ACR50</td>
<td>43.5</td>
<td>47.2</td>
</tr>
<tr>
<td>ACR70</td>
<td>23.8</td>
<td>26.8</td>
</tr>
<tr>
<td>ACR90</td>
<td>10.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; DMARD = disease-modifying anti-rheumatic drug; TCZ = tocilizumab

Efficacy

- At week 24, efficacy endpoints including ACR20, ACR50, ACR70, and ACR90 responses were similar in all three study groups ($p > 0.5$ for all comparisons).
- ACR20, ACR50, and ACR70 responses occurred as early as week 4, and ACR90 responses occurred by week 8. The responses improved through week 24 for all groups.
- EULAR good and moderate responses were observed as early as week 4, and the percentages of patients who achieved EULAR responses were maintained through week 24 and were similar in all three groups.


ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.
The onset of efficacy (by DAS28 <2.6) occurred as early as week 4, and percentages of patients who achieved DAS28 <2.6 increased through week 20 for patients in the TCZ monotherapy group and through week 24 for the TCZ plus DMARD(s) group.

- At week 24, there was no statistically significant difference between percentages of patients in the TCZ monotherapy group and the TCZ plus DMARD(s) group ($p = 0.70$).

- At week 24, similar percentages of patients in the TCZ monotherapy group and the TCZ plus DMARD(s) group achieved SDAI remission ($p = 0.31$) and CDAI remission ($p = 0.18$).
Key findings (cont’d)

- Slightly higher percentages of patients in the TCZ plus DMARD(s) groups than in the TCZ monotherapy group achieved a SDAI and CDAI LDA status at week 24.

- Clinically meaningful improvements in HAQ-DI occurred in a substantial proportion of patients in the TCZ monotherapy group and the TCZ plus DMARD(s) group as early as week 4.
  - At week 24, a higher percentage of patients in the TCZ plus DMARD(s) group (73.4%) than in the TCZ monotherapy group (68.4%) achieved a clinically meaningful improvement in HAQ-DI ($p = 0.037$).

DMARD = disease-modifying anti-rheumatic drug; CDAI = clinical disease activity index; SDAI = simplified disease activity index; LDA = low disease activity; HAQ-DI = health assessment questionnaire disease index; TCZ = tocilizumab.
Key findings (cont’d)

- Improvements in the ACR core set of parameters and the degrees of improvements from baseline to week 24 were similar between patient groups.


ACR = American College of Rheumatology.
Figure 2. Percentages of patients who achieved DAS28 <2.6 over time

ACR = American College of Rheumatology; DAS28 = 28-joint disease activity score; DMARD = disease-modifying anti-rheumatic drug; TCZ = tocilizumab

Discussion

- ACT-SURE differed from most phase III programs in that it closely resembled real-life practice.
  - Tertiary academic centres, non-academic centres, and private practices participated in the study.
  - There were no restrictions with respect to DMARD and TNFi types, dosages, and combinations.
  - Patients were also treated with a variety of add-on DMARDs and other concomitant medications.

DMARD = disease-modifying anti-rheumatic drug;
TNFi = tumour necrosis factor inhibitor.
ACT-SURE was an open-label, prospective study.

- Patients were not randomly assigned to receive monotherapy or combination therapy and 72% of patients who received monotherapy were TNFi-IR while 63% of patients who received combination therapy were DMARD-IR.

DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; TNFi-IR; inadequate response to tumour necrosis factor inhibitor.

The safety of TCZ monotherapy in the open-label, prospective ACT-SURE study and the double-blind, randomized ACT-RAY\(^2\) study was generally comparable.

- Rates of AEs and SAEs were slightly lower in the TCZ monotherapy group of ACT-RAY than that of ACT-SURE.
  - AEs: 72.5% in ACT-RAY vs. 82.4% in ACT-SURE.
  - SAEs, 5.8% in ACT-RAY vs. 7.9% in ACT-SURE.

This may have been a result of the less restrictive exclusion criteria in ACT-SURE.
Discussion (cont’d)

- The efficacy of TCZ monotherapy in ACT-SURE and ACT-RAY\(^2\) study were also generally comparable.
  - Percentages of patients who achieved an ACR70 response (25.7% and 23.8%, respectively) were comparable for TCZ monotherapy.
  - However, the percentages of patients who achieved DAS28 <2.6 were slightly higher for TCZ monotherapy in ACT-SURE (49.8%) than in ACT-RAY (34.8%).


ACR = American College of Rheumatology; DAS = disease activity score; TCZ = tocilizumab.
Key conclusions

- In a setting that closely resembles real-life clinical practice, the ACT-SURE study confirms the safety and efficacy of TCZ in DMARD-IR or TNFi-IR patients as observed in phase III studies.
- This is the first study to demonstrate that TCZ is highly effective as monotherapy or when combined with DMARDs.
- The safety profile was similar for patients who received TCZ monotherapy and for patients who were treated with TCZ plus DMARD(s).


DMARD = disease-modifying anti-rheumatic drug; DMARD-IR = DMARD inadequate response; TNFi = tumour necrosis factor inhibitor; TNFi-IR = inadequate response to tumour necrosis factor inhibitor; TCZ = tocilizumab.
Long-term safety of tocilizumab in RA clinical trials

Background

- Genovese and colleagues assessed the long-term safety of TCZ in patients with RA using pooled data of patients who received at least one dose of TCZ from initial exposure through to February 17, 2010 and presented their findings at EULAR 2011.¹

Study design

- Patients who received at least one dose of TCZ in five phase III trials (OPTION, TOWARD, RADIATE, AMBITION, and LITHE) or ongoing long-term extension studies (GROWTH 95, GROWTH96, and LITHE extension phase) from the first dose of TCZ to the cut-off date of February 17, 2010 were included in this analysis.

- The study population included all patients who were randomized to receive TCZ in the core trials, control patients who received rescue therapy in the core trials, and control patients who transitioned into the extension studies.


TCZ = tocilizumab.
Key findings

- 4,009 patients were included in this analysis.
- The mean treatment duration was 3.1 years (median 3.6 years; range: 0.0–5.1 years) and the total follow-up was 12,293 PY.
  - 3,701 patients (92%) had completed 24 weeks of treatment.
  - 2,936 patients (73%) had been treated with TCZ for at least 2.3 years.
  - 1,246 patients (31%) withdrew from treatment for safety-related (16%) or non-safety related (15%) reasons.


PY = patient years; TCZ = tocilizumab.
Key findings  (cont’d)

- AEs occurred at an overall rate of 314.6/100 PY (95% CI: 311.5–317.7).
  - Infections were the most frequently reported AE and occurred at a rate of 103.7/100 PY (95% CI: 101.9–105.5).
- The rate of AEs leading to withdrawal was 5.2/100 PY.

PY = patient years; AEs = adverse events.
Key findings (cont’d)

- SAEs occurred at a rate of 14.7/100 PY (95% CI: 14.0–15.4) and continued TCZ treatment was not associated with an increasing rate of any SAE.
  - Infections were the most frequently reported SAE and occurred at a rate of 4.6/100 PY (95% CI: 4.3–5.0).
  - The overall rate of death was 0.4/100 PY (95% CI: 0.3–0.6) and the death rate from infection was 0.1/100 PY (95% CI: 0.1–0.2).
  - The overall rate of serious infections was 4.6/100 PY (95% CI: 4.3–5.0) and continued exposure to TCZ was not associated with an increase in the rate of serious infections.
Figure 1. Mean (95% CI) serious adverse event rates

SAEs per 100 patient-years

<table>
<thead>
<tr>
<th>Months</th>
<th>SAEs, n</th>
<th>Exposure, pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12</td>
<td>546</td>
<td>2,471</td>
</tr>
<tr>
<td>13–24</td>
<td>479</td>
<td>3,026</td>
</tr>
<tr>
<td>25–36</td>
<td>414</td>
<td>2,723</td>
</tr>
<tr>
<td>37–48</td>
<td>220</td>
<td>2,325</td>
</tr>
<tr>
<td>49–60</td>
<td>101</td>
<td>814</td>
</tr>
</tbody>
</table>

SAE = serious adverse event
Key findings (cont’d)

- The overall rate of malignancies, including non-melanoma skin cancer was 1.2/100 PY (95% CI: 1.1–1.5) and this remained stable with continued TCZ therapy.

- Eight patients experienced anaphylactic reactions and withdrew from the study.

- There have been no fatal anaphylactic events in clinical trials. A fatal anaphylactic reaction has been previously reported outside of clinical trials.


PY = patient years; TCZ = tocilizumab.
Key conclusions

- The results of this study suggest that the safety profile of TCZ seen in long-term extension studies does not change with longer treatment exposure.

- Rates of SAEs, serious infections, malignancies, and cardiovascular events were stable during continued exposure to TCZ in long-term extension studies and were similar to those experienced by RA patients treated with different biologic agents.

SAEs = serious adverse events; RA = rheumatoid arthritis; TCZ = tocilizumab.
Long-term efficacy of tocilizumab in RA patients who have inadequate response to anti-TNF therapy

Background

- Patients with RA are usually treated with TNFi only when they have failed treatment with one or two DMARDs including MTX.
- The efficacy and safety of TCZ in RA patients who were inadequate responders to TNFi (TNFi-IR) have been demonstrated in RADIATE, a 24-week, phase III, randomized controlled trial.\(^1\)
- At EULAR 2011, Emery and colleagues presented their findings of an analysis of the maintenance of response to TCZ in TNFi-IR patients who are now enrolled in an ongoing long-term extension study (GROWTH96).\(^1\)

RA = rheumatoid arthritis; TNFi = tumour necrosis factor inhibitor; DMARDs = disease-modifying anti-rheumatic drugs; MTX = methotrexate; TNFi-IR = inadequate response to tumour necrosis factor inhibitor; EULAR = European League Against Rheumatism; TCZ = tocilizumab.
Study design

- Patients who received at least one dose of TCZ in RADIATE or GROWTH96 were included in the analysis.
- Patients transitioned from RADIATE to GROWTH96 at their own discretion and that of the investigator.
- Patients received TCZ at a dose of 8 mg/kg every four weeks and MTX 10-25 mg/week for the first 48 weeks (unless adjustment was needed for safety reasons) but they were allowed to switch from MTX to another DMARD after 48 weeks.
Study design (cont’d)

- The baseline for this analysis was the first active dose of TCZ.
- Outcomes were assessed every four weeks in RADIATE and every 12 weeks in GROWTH96 from initial TCZ exposure until the cut-off date of February 17, 2010.
- Efficacy data are shown up to week 216, after which patient numbers were less than 10% of the baseline patient number and therefore were insufficient for evaluation.
- The numbers of patients with assessments decreased over time because some patients had either not yet reached later assessments or had withdrawn.
Key findings

- The long-term efficacy analysis included 464 of 496 patients from RADIATE.
- The median treatment duration was 3.01 years (range: 0.06–4.53 years).
- By the data cut-off date, 43.3% of patients had withdrawn from the study and 77.4% of patients had completed 48 weeks of treatment.
- The overall withdrawal rate was stable over time and the proportion of patients who withdrew for insufficient therapeutic response was low (12.5%).

Key findings (cont’d)

- The proportion of patients who achieved ACR50 responses increased over time, while the number of patients assessed at each time point decreased over time.
- Absolute numbers of patients who achieved ACR50 responses increased to week 72 and were maintained thereafter.
- A similar pattern was observed for patients who achieved ACR70 responses.
- At week 156, 17.0% of patients had achieved the major clinical response of ACR70 maintenance for 24 consecutive weeks.
Key findings (cont’d)

- At week 120, 24.5% of patients (with valid assessments) had $\leq 1$ TJC and 36.6% had $\leq 1$ SJC.
  - Mean SJC and mean TJC decreased by the first assessment at week 12, and improvement was maintained over time.

- At week 120, 23.6% of patients (with valid assessments) had a HAQ-DI of $\leq 0.5$.

- Absolute numbers of patients achieving LDA (DAS28 $\leq 3.2$) and DAS28 $<2.6$ peaked at week 64 but remained relatively stable through week 156.

SJC = swollen joint count; TJC = tender joint count; HAQ-DI = health assessment questionnaire-disability index; LDA = low disease activity; DAS = disease activity score.
Key findings (cont’d)

- At week 156, 13% and 16% of 276 patients with assessable data were in remission, according to the new ACR/EULAR Boolean-based (TCJ ≤1, SJC ≤1, C-reactive protein ≤1 mg/dL) and index-based (SDAI ≤3.3) criteria, respectively.

SJC = swollen joint count; TJC = tender joint count; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; SDAI = simplified disease activity index.
### Table 1. Long term response to tocilizumab 8 mg/kg in TNFi-IR patients (n = 464)

<table>
<thead>
<tr>
<th>Week</th>
<th>24 n = 405</th>
<th>48 n = 354</th>
<th>72 n = 320</th>
<th>96 n = 293</th>
<th>120 n = 275</th>
<th>144 n = 263</th>
<th>168 n = 237</th>
<th>192 n = 165</th>
<th>216 n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20,% (n)</td>
<td>54.6 (221)</td>
<td>63.6 (225)</td>
<td>68.4 (219)</td>
<td>70.6 (207)</td>
<td>74.5 (205)</td>
<td>77.9 (205)</td>
<td>72.2 (171)</td>
<td>75.2 (124)</td>
<td>74.2 (46)</td>
</tr>
<tr>
<td>ACR50,% (n)</td>
<td>28.1 (114)</td>
<td>37.0 (131)</td>
<td>44.7 (143)</td>
<td>44.7 (131)</td>
<td>50.2 (138)</td>
<td>50.6 (133)</td>
<td>49.4 (117)</td>
<td>49.7 (82)</td>
<td>51.6 (32)</td>
</tr>
<tr>
<td>ACR70,% (n)</td>
<td>10.1 (41)</td>
<td>18.6 (66)</td>
<td>23.4 (75)</td>
<td>23.5 (69)</td>
<td>28.0 (77)</td>
<td>30.0 (79)</td>
<td>27.4 (65)</td>
<td>29.7 (49)</td>
<td>24.2 (15)</td>
</tr>
</tbody>
</table>

*ACR = American College of Rheumatology; TNFi-IR = tumour necrosis factor Inadequate responder*
Key conclusions

- In this analysis of patients with highly refractive disease, efficacy during long-term treatment with TCZ was maintained as measured by ACR50, ACR 70, LDA, and DAS28 <2.6.

- Overall, this analysis demonstrates that TCZ can provide benefit for up to 4.2 years with a low patient withdrawal rate during the long-term follow-up period.

- The data show that TCZ is an appropriate long-term therapeutic option for RA patients who are TNFi-IR.

ACR = American College of Rheumatology; DAS = disease activity score; LDA = low disease activity; RA = rheumatoid arthritis; TNFi-IR = inadequate response to tumour necrosis factor inhibitor; TCZ = tocilizumab.
Tocilizumab plus methotrexate is not superior to TCZ alone in RA patients with inadequate response to MTX: 24-week results of the ACT-RAY study

Background

- The efficacy and safety of TCZ combined with MTX and TCZ monotherapy have been established in RA.
- However, data comparing TCZ alone vs. MTX in combination with TCZ are currently lacking.\(^1\)
- At EULAR 2011, Dougados and colleagues presented results of the ACT-RAY study after evaluating the efficacy and safety of adding TCZ to MTX compared with switching from MTX to TCZ monotherapy in MTX-IR, biologic naive, adult patients with moderate-to-severe active RA (28-joint DAS>4.4).

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MTX = methotrexate; RA = rheumatoid arthritis; EULAR = European League Against Rheumatism; MTX-IR = methotrexate inadequate responders; DAS = disease activity score; TCZ = tocilizumab.
Study design

- This was a double-blind, two-year phase IIIb study.
- Patients receiving MTX therapy were randomized to receive TCZ 8 mg/kg in addition to MTX, or were switched to placebo controlled TCZ 8 mg/kg monotherapy.
- Patients were evaluated at the time of randomization (baseline) and at 24, 52, and 104 weeks.

MTX = methotrexate; TCZ = tocilizumab.
The objective of the study was to assess the efficacy and safety of adding TCZ to MTX therapy or switching to TCZ monotherapy in MTX-IR patients with moderate-to-severe, active RA.

- The primary endpoint was the percentage of patients to reach DAS28 remission by week 24.
- Since this was a superiority trial, the add-on approach will be declared beneficial with a 30% remission rate and the switch approach will be declared beneficial with a 42.5% remission rate.
Key findings

- 556 patients were randomized and 92% (n = 512) completed the initial 24-week period.
- The baseline demographic characteristics were similar for both groups.
- There was no significant difference in the DAS28 remission rates at week 24 for the TCZ combination group (40.4%) and for the TCZ monotherapy group (34.8%; p = 0.19).
- There were no significant differences in the ACR scores and core set components between the two treatment groups.
Figure 1. Primary endpoint (DAS28 remission rate at week 24)

Not significant
($\Delta = 5.65, p = 0.19, 95\% \text{ CI} [-2.41, 13.71]$)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>TCZ + MTX</th>
<th>TCZ + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 112/277</td>
<td>40.4</td>
<td>34.8</td>
</tr>
</tbody>
</table>

CI = confidence interval; TCZ = tocilizumab; MTX = methotrexate

### Table 1. Week 24 efficacy results (ITT population)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TCZ 8 mg/kg + MTX (n = 277)</th>
<th>TCZ 8 mg/kg + Placebo (n = 276)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 remission rate (DAS28 &lt;2.6)</td>
<td>40.4 (112)</td>
<td>34.8 (96)</td>
<td>0.189</td>
</tr>
<tr>
<td>LDAS (DAS28 ≥3.2)</td>
<td>61.7 (171)</td>
<td>51.5 (142)</td>
<td>0.028</td>
</tr>
<tr>
<td>EULAR good or moderate response</td>
<td>89.5 (248)</td>
<td>85.8 (237)</td>
<td>0.190</td>
</tr>
<tr>
<td>SJC (mean change from baseline [SD])</td>
<td>−11.3 (8.07)</td>
<td>−11.7 (9.46)</td>
<td>0.834</td>
</tr>
<tr>
<td>TJC (mean change from baseline [SD])</td>
<td>−17.2 (13.57)</td>
<td>−17.0 (13.63)</td>
<td>0.945</td>
</tr>
<tr>
<td>ACR 20</td>
<td>71.8 (199)</td>
<td>70.7 (195)</td>
<td>0.862</td>
</tr>
<tr>
<td>ACR 50</td>
<td>45.1 (125)</td>
<td>40.9 (113)</td>
<td>0.436</td>
</tr>
<tr>
<td>ACR 70</td>
<td>24.9 (69)</td>
<td>25.7 (71)</td>
<td>0.679</td>
</tr>
<tr>
<td>ACR 90</td>
<td>5.8 (16)</td>
<td>5.1 (14)</td>
<td>0.837</td>
</tr>
</tbody>
</table>

Data are presented as % (n) unless otherwise specified.

ACR = American College of Rheumatology; DAS28 = 28-Joint disease activity score; EULAR = European League Against Rheumatism; ITT = Intent to treat; LDA = low disease activity; SJC = swollen Joint count; TCZ = tocilizumab; TJC = tender joint count
Key findings (cont’d)

- Onset of action was rapid with 18.1% and 15.2% of patients achieving DAS28 remission at week 8 in the TCZ combination and TCZ monotherapy groups, respectively.

- The rates of AEs, SAEs, and serious infections per 100 PY were 491, 21, and 6 for TCZ combination therapy, and 467, 18, and 6 for TCZ monotherapy groups, respectively.
  - The most frequent AEs and SAEs were infections.
  - AE-related discontinuations occurred in 3.9% of patients in the TCZ combination therapy group and in 2.9% of patients in the TCZ monotherapy group.


DAS = disease activity score; AEs = adverse events; SAEs = serious adverse events; PY = patient years; TCZ = tocilizumab.
Key findings (cont’d)

- AE-related dose modifications occurred in 27.4% of patients in the TCZ combination therapy group and in 18.5% of the TCZ monotherapy group.

- ALT elevations >60 U/L were slightly higher in the TCZ combination group compared with the TCZ monotherapy group (16% and 6%, respectively).

AEs = adverse events; ALT = alanine transaminase; TCZ = tocilizumab.
<table>
<thead>
<tr>
<th></th>
<th>TCZ + MTX (n = 277)</th>
<th>TCZ + Placebo (n = 276)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total exposure to TCZ, patient-years</strong></td>
<td>118.31</td>
<td>116.40</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients with at least 1 AE, % (n)</td>
<td>70.0% (194)</td>
<td>72.5% (200)</td>
</tr>
<tr>
<td>Total no. of AEs</td>
<td>581</td>
<td>544</td>
</tr>
<tr>
<td>Rate of AEs (per 100 pt-yrs)</td>
<td>491</td>
<td>467</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients with at least 1 SAE, % (n)</td>
<td>6.1% (17)</td>
<td>5.8% (16)</td>
</tr>
<tr>
<td>Total no. of SAEs</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Rate of SAEs (per 100 pt-yrs)</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td><strong>Serious infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients with at least 1 SIE, % (n)</td>
<td>2.2% (6)</td>
<td>2.2% (6)</td>
</tr>
<tr>
<td>Total no. of SIEs</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Rate of SIEs (per 100 pt-yrs)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total no. of deaths</strong></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*AE = adverse event; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; pt-yrs = patient-years; SAE = serious adverse events; SIE = serious Infections; TCZ = tocilizumab*
Key conclusions

- ACT-RAY did not demonstrate superiority of TCZ combination therapy over TCZ monotherapy.

- No overt differences in the safety profiles of the two study groups were observed, and safety results were consistent with previous findings in that the combination of TCZ and MTX was associated with transaminase increases.

- The results of this study suggest that unlike with traditional biologics, background MTX may not be necessary with TCZ in order to achieve clinically meaningful responses.


MTX = methotrexate; TCZ = tocilizumab.
Efficacy and safety of tocilizumab in patients with systemic JIA: TENDER 52-week data

De Benedetti, et al. EULAR 2011: Abstract OP0006
Background

- Treatment options for sJIA are limited as patients respond poorly to traditional DMARDs and TNFis. Excessive interleukin-6 (IL-6) production has been implicated in several manifestations of sJIA.

- Tocilizumab, an IL-6 receptor inhibitor, has been shown to improve arthritis and systemic symptoms associated with sJIA.

- At EULAR 2011, De Benedetti and colleagues presented the results of the single-group, open-label extension of the TENDER study where they determined the efficacy and safety of TCZ in patients with active sJIA who were treated for ≥52 weeks.¹

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sJIA = systemic juvenile idiopathic arthritis; DMARDs = disease-modifying anti-rheumatic drugs; TNFi = tumour necrosis factor inhibitor; EULAR = European League Against Rheumatism; TCZ = tocilizumab.
Study design

- The study population included 112 patients aged 2–17 years who had active sJIA for six or more months and inadequate response to systemic CS and NSAIDs.

- Patients were randomized in a two to one ratio to TCZ or placebo every two weeks for 12 weeks in the first part of the study.

- In the second part of the study, all patients received open-label TCZ 8 or 12 mg/kg every two weeks for 92 weeks.
  - Patients who escaped to open-label TCZ also entered part two.

CS = corticosteroids; NSAIDs = non-steroidal anti-inflammatory drugs; sJIA = systemic juvenile idiopathic arthritis; TCZ = tocilizumab.
Study design (cont’d)

- Oral CS tapering was permitted at weeks 6 and 8 in part one, and in the open-label extension in patients who achieved JIA ACR70 response, had ESR <20 mm/h, and had no fever.

- Efficacy data are presented for patients who reached week 52 of TCZ treatment by May 10, 2010 (n = 88).

- Safety data through May 10, 2010 are presented for all patients (n = 112).

- Week 52 baseline was the first TCZ dose and part one placebo patients were re-baselined when they escaped or entered part two of the study.
Key findings

Efficacy

- The proportion of TCZ patients who achieved JIA ACR30 in the absence of fever, or JIA ACR70 or JIA ACR90 progressively improved to week 52.

JIA = juvenile idiopathic arthritis; ACR = American College of Rheumatology; TCZ = tocilizumab.
### Table 1. JIA ACR responses at 12 and 52 weeks

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 37)</td>
<td>TCZ (n = 75)</td>
</tr>
<tr>
<td>JIA ACR responses, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR30 + absence of fever</td>
<td>9 (24)</td>
<td>64 (85)</td>
</tr>
<tr>
<td>ACR70</td>
<td>3 (8)</td>
<td>53 (71)</td>
</tr>
<tr>
<td>ACR90</td>
<td>2 (5)</td>
<td>28 (37)</td>
</tr>
</tbody>
</table>

*ACR = American College of Rheumatology; JIA = Juvenile Idiopathic arthritis; TCZ = tocilizumab*
Figure 1. TENDER JIA ACR responses and the absence of fever over 52 weeks

ACR = American College of Rheumatology; JIA = Juvenile Idiopathic Arthritis
Key findings (cont’d)

- The mean (± standard deviation) number of joints with active arthritis or with limitation of movement decreased from 19.8 ± 15.7 and 19.8 ± 15.6, respectively, at baseline to 3.0 ± 7.0 and 7.5 ± 11.7, respectively, at week 52, with 48.5% of patients having no joints with active arthritis or limitation of movement.

- At baseline, 55% of patients (n = 62) had fever.
  - The proportion of patients with fever decreased to 9% (n = 8) at week 52.
Figure 2. TENDER: Mean active joints and joints with limited motion over 52 weeks

![Graph showing the mean active joints and joints with limited motion over 52 weeks with a decreasing trend. The graph indicates that 48.5% have 0 active joints.](image)

Key findings *(cont’d)*

- The mean (± standard deviation) CHAQ-DI score improved from $1.7 \pm 0.9$ at baseline to $0.7 \pm 0.8$ at week 52.

- The mean physician global assessment VAS (0–100 mm) and patient/parent global assessment VAS (0–100 mm) improved from $64.9 \pm 22.3$ and $58.7 \pm 24.4$, respectively, at baseline to $9.7 \pm 12.8$ and $12.6 \pm 18.5$, respectively, at week 52.

- There was a marked reduction in mean CS dose from $0.30 \pm 0.20$ mg/kg/d at baseline to $0.06 \pm 0.08$ at week 52, with 52.5% having discontinued CS.

CS = corticosteroids; CHAQ-DI = childhood health assessment questionnaire disability index; VAS = visual analogue scale.
Figure 3. TENDER: Mean oral corticosteroid dose over 52 weeks

- Mean dose decreased to 0.06 mg/kg/day
- 52.5% are off corticosteroids at week 52

Prednisolone Equivalent mean ± SE (mg/kg/day)

Time (weeks)

n = 112 111 111 110 105 107 105 99

SE = standard error
Key findings (cont’d)

Safety

- Thirty-three SAEs were observed in 25 patients.
  - Twelve SAEs were considered related (remote, possible, or probable) to TCZ.
  - The SAE rate was 0.23/PY in part one and 0.25/PY in part two.
- Fifteen serious infections occurred.
  - Six were considered related to TCZ.
  - All resolved and none led to discontinuation of therapy.


SAEs = serious adverse events; PY = patient years; TCZ = tocilizumab.
Twelve patients withdrew from the study.
  • Four patients withdrew because of AEs and four withdrew due to insufficient response.

One patient died of a suspected tension pneumothorax unrelated to treatment.
Key conclusions

- The first year of results from this first global phase III study demonstrate that TCZ is highly effective for the treatment of sJIA.
  - Efficacy increased over time.
  - More than 50% of patients were able to discontinue oral CS by week 52.
  - 49% of patients had no joints with active arthritis by week 52.
- In this population of sJIA patients, TCZ was generally well tolerated.


sJIA = systemic juvenile idiopathic arthritis; CS = corticosteroids; TCZ = tocilizumab.