**Supplementary Appendix**

Sirukumab for Rheumatoid Arthritis: the Phase 3 SIRROUND-D Study

Contents

[Table S1. Summary of Biologics Taken for RA Prior to the Study 2](#_Toc482903461)

[Table S2. ACR20 Response Rates at Week 16 Stratified by Baseline Methotrexate Use 3](#_Toc482903462)

[Table S3. Summary of Percent Improvement in ACR Components at Week 16 4](#_Toc482903463)

[Table S4. Summary of Safety Through Week 18 (Before EE) 5](#_Toc482903464)

[Table S5. Incidence Rates for AEs of Interest Through Week 52 6](#_Toc482903465)

[Figure S1.  Study design. 8](#_Toc482903466)

[Figure S2. Probability plot of change from baseline in SHS at Week 52. 9](#_Toc482903467)

[Figure S3. Mean observed laboratory assessments by visit through Week 52: A) neutrophils; B) platelets; C) hemoglobin; D) alanine aminotransferase; and E) aspartate aminotransferase. 10](#_Toc482903468)

# Table S1. Summary of Biologics Taken for RA Prior to the Study

|  |  |
| --- | --- |
| **Biologic use, n (%)** | **Total (N = 1,670)** |
| Took ≥1 biologic | 583 (34.9) |
| Took 2 biologics | 77 (4.6) |
| Took ≥3 biologics | 25 (1.5) |
| Tocilizumab | 128 (7.7) |
| Golimumab | 96 (5.7) |
| Etanercept | 66 (4.0) |
| Adalimumab | 54 (3.2) |
| Infliximab | 52 (3.1) |
| Abatacept | 51 (3.1) |
| Certolizumab | 39 (2.3) |
| Rituximab | 35 (2.1) |
| Anakinra | 3 (0.2) |
| Yisaipu | 1 (0.1) |
| Other biologicsa | 197 (11.8) |

 RA, rheumatoid arthritis.

aMostly composed of investigational biologics.

# Table S2. ACR20 Response Rates at Week 16 Stratified by Baseline Methotrexate Use

|  |  |  |  |
| --- | --- | --- | --- |
| **Patients stratified by baseline MTX** | **Placebo** | **Sirukumab 50mg q4w** | **Sirukumab 100mg q2w** |
| No MTX at baseline, n | 71 | 71 | 71 |
|  ACR20 response, n (%) | 10 (14.1) | 34 (47.9) | 35 (49.3) |
|  Difference (95% CIa) |  | 0.338 (0.196, 0.480) | 0.352 (0.210, 0.494) |
| >0 to <12.5 mg/wk MTX, n | 140 | 139 | 140 |
|  ACR20 response, n (%) | 39 (27.9) | 81 (58.3) | 82 (58.6) |
|  Difference (95% CIa) |  | 0.304 (0.194, 0.415) | 0.307(0.197, 0.417) |
| ≥12.5 mg/wk MTX, n | 345 | 347 | 346 |
|  ACR20 response, n (%) | 98 (28.4) | 190 (54.8) | 181 (52.3) |
|  Difference (95% CIa) |  | 0.263 (0.193, 0.334) | 0.239 (0.168, 0.310) |

ACR, American College of Rheumatology; CI, confidence interval; MTX, methotrexate.

aThe confidence intervals were based on Wald statistic.

# Table S3. Summary of Percent Improvement in ACR Components at Week 16

|  |  |  |  |
| --- | --- | --- | --- |
| **ACR Componenta** | **Placebo (n = 556)** | **Sirukumab 50 mg q4w (n = 557)** | **Sirukumab 100 mg q2w (n = 557)** |
| Swollen joint count (0-66) | 26.0 (58.2) | 55.3 (41.4) | 55.6 (39.9) |
| Tender joint count (0-68) | 22.9 (58.2) | 44.8 (45.1) | 48.0 (43.3) |
| Patient’s assessment of pain (VAS; 0-10)  | 6.5 (76.9) | 23.6 (120.9) | 32.0 (54.0) |
| Patient’s global assessment of disease activity (VAS; 0-10) | 8.4 (74.8) | 26.2 (94.2) | 26.8 (89.6) |
| Physician’s global assessment of disease activity (VAS; 0-10)  | 29.3 (42.1) | 46.3 (34.0) | 48.1 (44.7) |
| HAQ-DI score (0-3) | 5.6 (72.2) | 24.7 (65.8) | 26.5 (55.0) |
| CRP (mg/dL) | −36.7 (309.5) | 92.4 (24.0) | 93.9 (24.2) |

aMean (SD) percent improvement at Week 16.

CRP, c-reactive protein; HAQ-DI, Health Assessment Questionnaire – Disability Index; SD, standard deviation; VAS, visual analog scale

# Table S4. Summary of Safety Through Week 18 (Before EE)

|  |  |  |
| --- | --- | --- |
|  |  | **Sirukumaba** |
| **Variable**  | **Placebo****(n = 556)** | **50 mg q4w****(n = 557)** | **100 mg q2w****(n = 557)** | **Combined****(n = 1,114)** |
| Patients with ≥1 TEAE, n (%) P value vs placebo | 280 (50.4) | 337 (60.6)<0.001 | 354 (63.4)<0.001 | 691 (62.0)<0.001 |
| Patients with ≥1 TESAE, n (%) P value vs placebo | 17 (3.1) | 16 (2.9)NS | 26 (4.7)NS | 42 (3.8)NS |
| Discontinuations due to an AE, n (%) P value vs placebo | 12 (2.2) | 18 (3.2)NS | 27 (4.8)0.015 | 45 (4.0)0.046 |
| Serious infections, n (%) P value vs placebob | 5 (0.9) | 4 (0.7)NS | 5 (0.9)NS | 9 (0.8)NS |
| Injection-site reactions, n (%) P value vs placebo | 9 (1.6) | 44 (7.9)<0.001 | 76 (13.6)<0.001 | 120 (10.8)<0.001 |
| EE, early escape; q4w, every 4 weeks; q2w, every 2 weeks; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; NS, not significant; AE, adverse event. |

aP values are nominal and from chi-square tests, unless otherwise noted.

bP values are nominal and from Fisher exact tests.

# Table S5. Incidence Rates for AEs of Interest Through Week 52

|  |  |  |
| --- | --- | --- |
|  |  | **Sirukumaba** |
| **Variable** | **Placebo****(n = 556)** | **50 mg q4w****(n = 663)** | **100 mg q2w****(n = 662)** | **Combined****(n = 1,325)** |
| Patients with ≥1 serious infection, n  | 10 | 27 | 22 | 49 |
| Total PY of exposure, y  | 391.21 | 584.30 | 579.64 | 1,163.94 |
| Rate of serious infections per 100 PY (95% CI) | 2.56 (1.23, 4.70) | 4.62(3.05, 6.72) | 3.8(2.38, 5.75) | 4.21(3.11, 5.57) |
| Patients with a malignancy, nb | 2 | 2 | 5 | 7 |
| Total PY of exposure, y  | 393.75 | 591.84 | 584.66 | 1,176.50 |
| Rate of malignancies per 100 PY (95% CI)c | 0.51(0.06, 1.83) | 0.34(0.04, 1.22) | 0.86(0.28, 2.00) | 0.59(0.24, 1.23) |
| Patients with a MACE, n  | 2 | 8 | 3 | 11 |
| Total PY of exposure, y  | 393.70 | 590.68 | 584.86 | 1,175.55 |
| Rate of MACE per 100 PY (95% CI)c | 0.51(0.06, 1.84) | 1.35(0.58, 2.67) | 0.51(0.11, 1.50) | 0.94(0.47, 1.67) |
| Patients who died, nd | 1 | 7 | 3 | 10 |
| Total PY of exposure, y  | 393.95 | 592.13 | 585.72 | 1,177.85 |
| Mortality per 100 PY (95% CI) | 0.25(0.01, 1.41) | 1.18(0.48, 2.44) | 0.51(0.11, 1.50) | 0.85(0.41, 1.56) |

AE, adverse event; q4w, every 4 weeks; q2w, every 2 weeks; PY, patient-year; CI, confidence interval; MACE, major adverse cardiovascular event.

aIncludes patients from the placebo group re-randomized to treatment with sirukumab; thus, patients may be represented in >1 treatment group.

bIncludes nonmelanoma skin cancers.

cThe incidence rate is patient based and only counts 1 occurrence of an AE if a patient has >1 occurrence of that AE. The 95% CIs were exact Poisson CIs.

dPrior to Week 18, there were 3 deaths: 1 in the placebo group (acute respiratory distress syndrome); 1 in the sirukumab 50-mg group (sudden cardiac death); and 1 in the sirukumab 100-mg group (myocardial infarction). From Week 18 to prior to Week 52, there were 8 additional deaths: 3 in the group originally randomized to placebo that switched to sirukumab 50 mg (cerebrovascular accident, road traffic accident, and myocardial infarction); 3 in the sirukumab 50-mg (natural causes, septic shock, and peritonitis); and 2 in the sirukumab 100-mg group (bacterial sepsis, metastatic lung cancer).

# Figure S1.  Study design.



Wk, Week; R, randomization; PE, primary endpoint; EE, early escape; DCIA, initiation/adjustment of DMARDs/corticosteroids; LE, late escape; CO, crossover; q2w, every 2 weeks; q4w, every 4 weeks.

aPatients who have <20% improvement from baseline in swollen and tender joint counts.

Figure S2. Probability plot of change from baseline in SHS at Week 52.**a******

SHS, Sharp/van der Heijde score; SDC, smallest detectable change; q4w, every 4 weeks; q2w, every 2 weeks; EE, early escape.

aBased on imputed values by EE rules and then missing data rules.

# Figure S3. Mean observed laboratory assessments by visit through Week 52: A) neutrophils; B) platelets; C) hemoglobin; D) alanine aminotransferase; and E) aspartate aminotransferase.

A)



B)



C)



D)



E)



SD, standard deviation; Obs, observed; NEUTSG, neutrophils; Q4W, every 4 weeks; Q2W, every 2 weeks; SC, subcutaneous; PLAT, platelet; HGB, hemoglobin; ALT (SGPT), alanine aminotransferase; AST (SGOT), aspartate aminotransferase.