GO-NICE

NON-INTERVENTIONAL STUDY

INVESTIGATING THE USE OF GOLIMUMAB (SIMPONI®)

IN PATIENTS WITH RHEUMATOID ARTHRITIS,
PSORIATIC ARTHRITIS, AND ANKYLOSING SPONDYLITIS

“Nicht interventionelle klinische Evaluierung der Anwendung
von Golimumab (Simponi®) bei Patienten mit rheumatoider
Arthritis, Psoriasis-Arthritis bzw. ankylosierender Spondylitis”

STUDY CODE: P06554

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VERSION: FINAL 2.0
DATE: August 15, 2016

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1 Synopsis

**Title of the Study:** NON-INTERVENTIONAL STUDY INVESTIGATING THE USE OF GOLIMUMAB (SIMPONI®) IN PATIENTS WITH RHEUMATOID ARTHRITIS, PSORIATIC ARTHRITIS AND ANKYLOSING SPONDYLITIS

*Nicht interventionelle klinische Evaluierung der Anwendung von Golimumab (Simponi®) bei Patienten mit rheumatoider Arthritis, Psoriasis-Arthritis bzw. ankylosierender Spondylitis* – GO-NICE

**Unique Identifier:** Sponsor: P06554 Vendor: OS-090205

**Investigator(s):** Center-specific questionnaires

- N=144 (data available)
- N= 26 (no data available)

Mean age was 49.8 ± 7.79 years, 71.5% male.

Physicians were working in their specialist area for 15.7 ± 7.15 years.

52.8% of centers were located in big cities (>100,000 inhabitants)

38.2% of centers were medical practices, mainly run by a single physician.

72.2% of centers were large centers with more than 800 health insurance vouchers per quarter.

65.3% of physicians reported to see their individual patients 2 times per month.

**Study Center(s):** 158 active centers in Germany, most of them specialized in rheumatology (n=133, 92.4%)

**Publication(s):** The results of the 3rd interim analysis were presented at the 2015 ACR/ARHP Annual Meeting in San Francisco (6 – 11 NOV 2015). The final results were accepted for presentation at the 2016 EULAR Annual European Congress of Rheumatology in London, UK (8 – 11 June 2016).

Further publications are listed in the Reference List (see Section 12).

**Studied Period:** First patient in: 01 April 2010; Last patient out: 11 September 2015

Individual patients were observed for up to 24 months.

**Clinical Phase:** Post-marketing evaluation, Non-interventional study (NIS)

**Objective(s):** To evaluate

- The clinical safety of Simponi® under real-life, clinical practice conditions as assessed by the incidence and type of (serious) adverse events
- The changes in clinical status of patients as assessed by clinical parameters, disease activity scores, and laboratory parameters
- Patients’ everyday life (pharmacoeconomic aspects)
- Patient-reported outcomes (quality of life, user-friendliness and satisfaction with the autoinjector)

**Methodology:** Online and paper based, non-interventional, observational study following the recommendations for the conduct of non-interventional studies in Germany (BfArM/PEI).

**Number of Subjects:**

A total of 1613 patients (100%) were documented in 158 centers in Germany between 01 April 2010 (first patient in) and 11 September 2015 (last patient out). Of these, 524 patients had rheumatoid arthritis (RA), 546 patients had psoriatic arthritis (PsA) and 543 patients had ankylosing spondylitis (AS).

**Analysis sets (final analysis)**

<table>
<thead>
<tr>
<th>Analysis set</th>
<th>Rheumatoid arthritis (RA)</th>
<th>Psoriatic arthritis (PsA)</th>
<th>Ankylosing spondylitis (AS)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAF population</td>
<td>524 (100.0)</td>
<td>546 (100.0)</td>
<td>543 (100.0)</td>
<td>1613 (100.0)</td>
</tr>
<tr>
<td>ALL population</td>
<td>493 (94.1)</td>
<td>511 (93.6)</td>
<td>501 (92.3)</td>
<td>1505 (93.3)</td>
</tr>
<tr>
<td>EVA population</td>
<td>474 (90.5)</td>
<td>501 (91.8)</td>
<td>483 (89.0)</td>
<td>1458 (90.4)</td>
</tr>
<tr>
<td>- Completer</td>
<td>188 (35.9)</td>
<td>231 (42.3)</td>
<td>245 (45.1)</td>
<td>664 (41.2)</td>
</tr>
<tr>
<td>- Non-completer</td>
<td>286 (54.6)</td>
<td>270 (49.5)</td>
<td>238 (43.8)</td>
<td>794 (49.2)</td>
</tr>
<tr>
<td>PTT population</td>
<td>251 (47.9)</td>
<td>219 (40.1)</td>
<td>191 (35.2)</td>
<td>661 (41.0)</td>
</tr>
</tbody>
</table>

EVA= evaluable; SAF=Safety; PTT =Premature treatment termination/discontinuation

The analyses of all data sets were based on non-missing data. There was no imputation of missing values for any efficacy or pharmacoeconomic endpoints.

A: Patients who met the criteria of the ALL population and had at least one additional visit after the baseline assessment were included in the evaluable (EVA) population, regardless of any deviations from the observational plan.
B: The Non-completer set (N=794) includes 661 patients who prematurely terminated treatment with Simponi® (PTT population: 251 patients with RA, 219 patients with PsA, 191 patients with AS) and 133 patients who were lost to follow-up (Lost to FUP: 35 patients with RA, 51 patients with PsA, 47 patients with AS).

Diagnosis and Criteria for Inclusion:

Patients were eligible for documentation within this non-interventional study if the following criteria were met:
- Simponi®-naive
- adult patients (≥18 years of age)
- diagnosis of RA, PsA or AS
- indication for and SmPC-conform treatment with Simponi® autoinjector
- absence of any contraindication as listed in the SmPC
- patient consent in pseudonymized use of personal health data and inspection of patient records

Test Product, Dose, Mode of Administration, Batch No(s):

Simponi® (0.5 mL solution containing 50 mg of Golimumab) in a prefilled autoinjector called SmartJect® or in a prefilled syringe (if the autoinjector was not available due to supply issues) was injected subcutaneously once per month, always on the same day of the month. Patients with RA should have administered methotrexate (MTX) concomitantly.

Duration of Treatment:

Documentation was to be recorded at baseline prior to initiation of Simponi® therapy and in the following in approximately 3 months intervals. The documentation ended after a 24-month observational period. Early discontinuation of treatment before end of the observational period was to be documented at the time of the event.

Reference Therapy, Dose, Mode of Administration, Batch No(s):

Not applicable for this study.

Criteria for Evaluation:

Endpoints for the evaluation of clinical safety of Simponi® were:
- incidence of adverse events
- incidence of serious adverse events

Endpoints for the evaluation of changes in clinical status were:
- clinical global impression (CGI)
- clinical effectiveness of Simponi® (CGI)
- functional capacity (FFbH)
- fatigue and its impact upon daily activities and function (FACIT-F)
- disease activity by illness-specific scales (DAS28, PsARC, BASDAI)
- selected laboratory parameters (CRP, ESR, RF, anti-CCP)

Endpoints for the evaluation of patients' everyday life were:
- occupational status
- reason for retirement, if applicable
- limitations in daily routine activities
- additional medical therapy (i.e. physiotherapy, massages, psychotherapy)
- hospital stays (number of days)
- number of days absent from work due to illness and number of days with limited productivity (absenteeism and presenteeism)

Endpoints for the evaluation of real-world patient-reported outcomes were:
- change in quality of life (EQ-5D-3L)
- user-friendliness and satisfaction with the autoinjector

Statistical Methods:

The analysis was performed in an exploratory manner using descriptive statistical methods. For continuous variables the number of patients with non-missing data, mean, standard
deviation, minimum, 25% quartile, median, 75% quartile and maximum were calculated. For ordinal and categorical variables frequencies were calculated based on all observations with non-missing data for this variable. Uncompleted data sets were included in the analysis. Missing Simponi® treatment start date was replaced by date of visit 1. There was no imputation of missing values for any efficacy or pharmacoeconomic endpoint.

The safety population (SAF) consisted of all patients with at least one application of Simponi®. All adverse events (AEs) occurring during this observational study were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1. The incidence of AEs and adverse drug reactions (ADRs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) were calculated (number, frequency) for the total SAF population and by indication (RA, PsA, AS).

All effectiveness analyses were conducted for the evaluable (EVA) population stratified by indication (RA, PsA, AS). The analysis by visit was done for the total EVA population and the subgroups “completer” (patients who completed the study as planned, i.e. date of Visit 9 was 24 months after baseline) and “non-completer” (patients with premature termination).

Clinical results (i.e. CGI, FFbH, FACIT-F, EQ-5D-3L, DAS28, PsARC, BASDAI) were analyzed by visit. Changes from baseline were analyzed by repeated measurement analysis for time trends.

The time to premature discontinuation was analyzed by Kaplan-Meier methods stratified by indication (RA, PsA, AS). Kaplan-Meier estimates for the failure rates were calculated for 3, 6, 12, 18, 21 and 24 months.

**SUMMARY-CONCLUSIONS:**

The final analysis included the data of 1613 patients documented in 158 centers in Germany from 01 April 2010 to 11 September 2015. All 1613 documented patients received at least one application of Simponi® and were included in the safety analysis (SAF population).

Data of 108 patients (6.7% of 1613) were excluded from the analysis in the All Patients (ALL) population because of retrospective data documentation/wrong inclusion1 (102 patients) or withdrawal of consent (6 patients) (ALL: N=1505).

Data of 155 patients (9.6% of 1613) were excluded from the evaluable (EVA) analysis because of retrospective data documentation/wrong inclusion1 (102 patients), less than two visits (47 patients), or withdrawal of consent (6 patients) (EVA: N=1458).

**SAFETY**

Of 1613 patients included in the SAF population, 524 patients had rheumatoid arthritis (RA), 546 patients had psoriatic arthritis (PsA), and 543 patients had ankylosing spondylitis (AS).

**Adverse events (AEs)**

In total, at least 1 AE was reported for 910 (56.4%) out of 1613 patients treated with Simponi® (SAF). The occurrence of AEs was higher in patients with RA (61.1% of 524 patients) compared to patients with PsA (56.6% of 546 patients) and patients with AS (51.7% of 543 patients).

AEs considered possibly/probably related to Simponi® (ADRs) by the physician were reported for 412 patients (25.5%) of total 1613 with a similar distribution between patients with RA (26.7%), PsA (26.6%) and AS (23.4%). Most frequently reported AEs (affecting ≥2% of 1613 patients) were drug ineffectiveness (19.6%), influenza like-illness (3.7%), nasopharyngitis (3.0%), fatigue (2.8%), and bronchitis (2.0%).

Most frequently reported ADRs (affecting ≥1.0% of 1613 patients) were influenza like-illness (2.2%), nasopharyngitis (1.9%), fatigue (1.4%), rash (1.3% incl. erythematous and pruric rash), headache (1.3%), bronchitis (1.1%), cough (1.0%), and respiratory tract infection (RTI) (1.0% incl. RTI viral).

AEs were most commonly mild (334 patients, 20.7% of 1613) or moderate (366 patients, 22.7%) in intensity (severity assessment not done or missing for 529 patients, 32.8%). Severe AEs were

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1*Retrospective data: Therapy with Simponi® started before Visit 1.*

Wrong inclusion: First Simponi® application was not given by autoinjector (as prescribed and documented by the physician) but by pre-filled syringe (it appeared that the prefilled syringe was given out by the pharmacy).
reported for 79 patients (4.9% of 1613), more commonly in patients with RA and PsA compared to patients with AS (5.3%, 5.1%, and 4.2% of 524, 546 and 543 patients, respectively). AEs of severe intensity reported for more than 3 patients (>0.2% of total 1613) were influenza like illness (0.5%), bronchitis (0.4%), fatigue (0.3%), nasopharyngitis, drug (is) ineffective, febrile infection, psoriasis, and rash (0.2% each).

Serious AEs (SAEs) were reported for 204 patients (12.6% of 1613), with a higher occurrence in patients with RA (14.3% of 524 patients) and PsA (12.8% of 546 patients) compared to patients with AS (10.9% of 543 patients). SAEs reported for more than 5 patients (≥0.3% of total 1613) were hospitalization (11 patients, 0.7%), pneumonia (7 patients, 0.4%), myocardial infarction (5 subjects, 0.3%), and knee arthroplasty (5 subjects, 0.3%). The following SAEs were reported for 4 patients each (0.2% of 1613): pyrexia, subcutaneous abscess, intervertebral disc protrusion, osteoarthritis, cerebrovascular accident, dizziness, syncope, dyspnoea, and synovectomy. 4 patients died in the course of the study, but the causes of their death were considered, by the reporting physicians, unlikely related to Simponi® (1 patient with RA) or not assessable (2 patients with PSA and 1 with AS) (1 patient committed suicide and for 2 patients no information about the cause of death could be obtained).

Overall, 530 (32.9%) out of 1613 patients included in the SAF population discontinued Simponi® therapy due to the occurrence of one AE or more, most commonly due to drug ineffectiveness (310 patients, 19.2%). AEs reported for 167 patients (10.4% of 1613) had no impact on Simponi® administration and treatment was continued unchanged. 109 patients (6.8% of 1613) interrupted Simponi® therapy, and 3 patients (0.2%) had a dose reduction of Simponi® due to AE.

Of total 2125 AEs reported for 910 patients in the SAF population, 1110 AEs (52.2% of 2125 AEs) resolved, 301 AEs (14.2%) improved, 149 AEs (7.0%) were unchanged, and 7 AEs (0.3%) worsened during the observation period (outcome was unknown/missing for 558 AEs, 26.3% of 2125 AEs). The 7 AEs which worsened during the observation period were drug effect decreased, drug ineffective, ankylosing spondylitis, metastases to bone, prostate cancer, nasal dryness and psoriasis (each AE reported for 1 patient, 0.1% of 1613 patients each).

Other AEs of special interest

Tuberculosis (TBC) infection or a positive TBC test was reported as AE for 4 (0.2%) out of 1613 patients. The infection was considered possibly related for 2 patients (pulmonary tuberculosis, mycobacterial infection) and unlikely related for the other 2 patients (tuberculosis, mycobacterium tuberculosis complex test positive). Pulmonary tuberculosis was classified as a serious AE (serious ADR).

Laboratory values

Overall laboratory tests (CRP, ESR, hemoglobin, WBC, platelets, sodium, potassium, GOT, GPT, alkaline phosphatase, gamma-GT, total bilirubin, creatinine, ANA) revealed no time-related increase in abnormal individual findings. Abnormal laboratory results that were considered clinically significant by the physician were recorded in single patients at different time points of assessment, but the incidence was usually low (≤3.0% of 1458 patients, EVA), except for a higher incidence of RA patients with significantly elevated levels of CRP at Visits 2 and Visit 3 (3.8% and 4.1% of 395 respectively 295 patients) and significantly increased ESR at Visit 2 and Visit 4 (3.8% and 3.1% of 395 respectively 256 patients). Changes in laboratory values that were reported as ADR included increase in hepatic enzymes (5 patients, 0.3% of 1613, SAF), increase in CRP (4 patients, 0.2%), increase in gamma-GT (3 patients, 0.2%), increase in transaminases (3 patients, 0.2%), and for 1 (0.1%) patient each increase in GPT, positive antinuclear antibodies, abnormal alkaline phosphatase, increase in cholesterol, decrease in hemoglobin, increase in inflammatory marker, platelet count increased, increased ESR, and sputum abnormal.

Physical examination / body measurements

Overall, physical examination of rhythm of the heart, thorax, abdomen and lymph nodes revealed no time-related increase in abnormal individual findings.

Changes in body weight were reported as AE for 10 patients (2 patients with decrease in weight, 8 patients with increase in weight). Weight decrease in 1 patient and weight increase in 6 patients was considered possibly drug-related. Changes in weight led to premature discontinuation of Simponi® therapy in 4 patients (2 had an increase in weight and 2 patients had a decrease in weight).
Vital signs

Mean values for systolic/diastolic blood pressure (BP), heart and breathing rate revealed no time-related increases or decreases from Visit 2 to Visit 9. An increase in BP was reported as ADR (probably related) for 1 patient and resulted in premature discontinuation of Simponi® therapy.

The physician considered the increase in blood pressure reported for 1 patient with RA and hypertensive crisis reported for 2 patients (1 with PsA and 1 with AS) probably or possibly related to Simponi® therapy. Blood pressure increase/hypertension led to discontinuation of Simponi® therapy in 6 patients (blood pressure increased: 1 patient with RA; essential hypertension: 1 patient with RA, hypertension: 2 patients, 1 with RA and 1 with PsA; hypertensive crisis: 2 patients, 1 with PsA and 1 with AS).

Concomitant diseases

No increase in concomitant diseases and disorders were observed (i.e., cardiovascular, pulmonal, cerebrovascular, and liver diseases, diabetes mellitus, metabolic syndrome, depressive disorders or other diseases/mental illness).

EFFECTIVENESS

The analysis of effectiveness parameters was done in the EVA population (N=1458) which included 474 patients with RA, 501 patients with PsA, and 483 patients with AS.

The majority patients in the EVA population were German (1385 patients, 95.0% of 1458 patients; data missing for 8 patients), 53.4% were female and 46.6% were male. There was higher proportion of females than males in the subgroups of patients with RA (72.8% vs. 27.2%) and PsA (54.1% vs. 45.9%) compared with the subgroup of patients with AS (33.5% vs. 66.5%) which included more males. Patients with RA had a higher mean age (54.9 years) than patients with PsA (50.3 years) and patients with AS (43.6 years). The mean body mass index (BMI) at Visit 1 was comparable between patients with RA, PsA and AS (26.5, 28.1 and 26.7 kg/m², respectively).

821 patients (56.3% of 1458) provided data for Month 12 (Visit 5) and 664 patients (45.5%) provided data for Month 24 (Visit 9/regular visit documentation).

Change in concomitant medication

There was no relevant change from Visit 1 (Baseline) to Visit 9 (Month 24) in the use of disease-specific medication except for a marked decrease in the percentage of patients (>10.0%) using systemic glucocorticoids in the RA subgroup (from 75.9% of 474 to 56.4% of 188) and the PsA subgroup (from 41.1% of 501 to 20.8% of 231), and the percentage of patients using NSAR/Analgesics in the RA subgroup (from 43.9% of 474 to 33.5% of 188) and the AS subgroup (from 60.5% of 483 to 45.3% of 245). The percentage of patients with RA, PsA and AS using other medications increased by 7.5%, 11.6% respectively 3.6% from Visit 1 to Visit 9.

Inflammatory markers

Mean CRP levels and mean ESR of patients with RA, PsA and AS showed a marked decrease from baseline values within the first 3-6 months of treatment and remained on this level (with small fluctuations) up to the end of the 24-month observation period. The treatment effect was most prominent in patients with AS. CRP and ESR exhibited a high inter-subject variability at all time points of assessment (Visits 1-9).

The number of patients with CRP levels above upper limit of normal range (ULN) decreased from baseline 46.9% to 27.1% (-19.8%) at Visit 9 in patients with RA, from 31.1% to 13.8% (-17.3%) in patients with PsA and from 45.8% to 15.1% (-30.7%) in patients with AS.

The number of patients with ESR above ULN decreased from baseline 40.9% to 23.8% (-17.1%) at Visit 9 in patients with RA, from 29.5% to 12.9% (-16.6%) in patients with PsA and from 36.5% to 15.1% (-21.4%) in patients with AS.

Clinical global impression (CGI) of patient’s health status

The CGI of patient’s health status was assessed by the physician on a 10 mm VAS ranging from “0” (free of complaints) to “10” (strong discomfort). Within the first 3 months of Simponi® therapy (Visit 1-Visit 2), mean VAS values decreased (i.e., improved) from 5.7 to 3.4 mm in patients with RA (-2.3 mm), from 5.5 to 3.2 mm in patients with PsA (-2.3 mm), and from 5.7 to 2.9 mm in patients with AS (-2.8 mm), and further decrease to mean values of 2.2, 2.1 and 2.1 mm in the 3 patient groups at Visit 9 (Month 24). The CGI ratings exhibited a high inter-subject variability at all time.
Disease-specific outcome measures

- DAS28

In patients with RA, the mean DAS28 score decreased (i.e., improved) from baseline 5.0 \pm 1.30 to 2.9 \pm 1.32 points at Visit 9 (Month 24) which corresponds to an improvement from baseline of 38.5\% (\pm 28.77\%). Least squares (LS) means for difference to baseline (range: -1.24 to -2.05 points) were statistically significant at all time points of assessment from Month 3 to Month 24 (p<0.0001; repeated measurement analysis). Improvement in RA is shown by an increase in the rates of remission (DAS28 <2.6 points) from baseline 4.9\% of 471 patients to 44.6\% of 184 patients (+39.7\%) at Visit 9 (Month 24), and an increase in the number of patients with low disease activity (DAS28 2.6-3.2 points) from baseline 3.4\% to 19.0\% of patients (+15.6\%) at Visit 9. Concurrently, the number of patients with high disease activity (DAS28 >5.1 points) decreased from baseline 45.0\% to 6.5\% (-38.5\%) and patients with moderate disease activity (DAS28 3.1-5.1 points) decreased from baseline 46.7\% to 29.9\% (-16.8\%).

- PsARC

In patients with PsA, the number of patients with improvement in PsARC increased from 54.1\% of 394 patients at Visit 2 to 67.9\% of 221 patients (+13.8\%) at Visit 9 (Month 24).

- BASDAI

In patients with AS, the mean BASDAI score (range: 0-10) decreased (i.e., improved) from baseline 5.1 \pm 1.97 to 2.4 \pm 2.01 points at Visit 9 (Month 24) which corresponds to an improvement from baseline of 33.6\% (\pm 169.67\%). LS means for difference to baseline (range: -2.09 to -2.69 points) were statistically significant at all time points of assessment from Month 3 to Month 24 (p<0.0001; repeated measurement analysis).

Patient reported outcome measures

- FACIT-F

The mean FACIT-F score (range: 0=lowest to 52=highest possible quality of life), increased (i.e., improved) from baseline 32.4 \pm 11.50 to 38.3 \pm 10.42 points in patients with RA, from 30.0 \pm 11.90 to 35.9 \pm 11.37 points in patients with PsA, and from 29.9 \pm 10.84 to 37.9 \pm 10.78 points in patients with AS at Visit 9 (Month 24). The mean changes in patients with RA, PsA and AS correspond to improvements from baseline of 30.9\% (\pm 88.73\%), 30.7\% (\pm 75.98\%), respectively 28.9\% (\pm 65.22\%), respectively 28.9\% (\pm 65.22\%). Overall (RA, PsA, AS), LS mean differences to baseline in FACIT-F ranged from +2.85 to +8.01 score points at Visits 2-9. LS mean changes were statistically significant at all time points of assessment from Month 3 to Month 24 (p<0.0001 to 0.0003; repeated measurement analysis).

- EQ-5D-3L

The mean EQ-5D-3L health profile sum score (range: 1=no problems to 15=severe problems) decreased (i.e., improved) from baseline 8.3 \pm 1.83 to 7.2 \pm 1.84 points in patients with RA, from 8.5 \pm 1.89 to 7.2 \pm 1.90 points in patients with PsA, and from 8.4 \pm 1.73 to 6.9 \pm 1.75 points in patients with AS at Visit 9 (Month 24). The mean changes in patients with RA, PsA and AS correspond to improvements from baseline of 11.8\% (\pm 22.83\%), 10.6\% (\pm 20.04\%), respectively 15.3\% (\pm 19.65\%). Overall (RA, PsA, AS), LS mean differences to baseline in EQ-5D-3L health profile sum score ranged from -0.69 to -1.51 score points at Visits 3-9. LS mean changes were statistically significant at all time points of assessment from Month 6 to Month 24 (p <0.0001; repeated measurement analysis).

The frequency of patients reporting problems on any of the 5 dimensions of the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) decreased in all patients. Marked improvements were achieved on the dimensions “mobility” and “usual activities” in patients with PsA and AS.

Patient’s health state was assessed on a 100 mm VAS with 0 being the worst and 100 being the best imaginable health status (EQ VAS). The mean EQ VAS values increased (i.e., improved) from baseline 51.0 \pm 21.18 to 63.4 \pm 23.26 mm in patients with RA, from 48.4 \pm 21.15 to 64.3 \pm 22.77 mm in patients with PsA, and from 46.8 \pm 20.13 to 66.5 \pm 22.10 mm in patients with AS at Visit 9 (Month 24). The mean changes in patients with RA, PsA and AS correspond to improvements from
baseline of 59.0% (± 116.50%), 60.5% (± 144.55%) and 84.9% (± 140.73%).

- **FFbH**

Patients’ functional limitations in activities of daily living based on the 18-item self-assessment Hannover functional ability questionnaire (FFbH: 0%=minimal function, 100%=optimal function). The mean FFbH score increased (i.e., improved) from baseline 68.7 ± 22.01 to 76.1 ± 22.14 points in patients with RA, from 69.0 ± 22.04 to 76.8 ± 22.62 points in patients with PsA, and from 69.0 ± 19.04 to 78.5 ± 19.76 points in patients with AS. The mean changes in patients with RA, PsA and AS correspond to improvements from baseline of 18.1% (± 39.92%), 16.4% (± 67.18%), respectively 18.2% (± 41.12%).

- **Effect of pre-treatment and concomitant basic therapeutics on DAS28, PsARC, BASDAI, FACIT-F, and FFbH**

Effects of a pre-treatment with another biologic and of additional basic therapeutics have been observed (EVA subgroup analyses). They are more or less prominent depending on the parameter under evaluation.

**Clinical assessment of Simponi® therapy**

The clinical assessment of Simponi® therapy was performed by the treating physician in consideration of his/her grading of evidence of therapeutic effect and severity of side effects. According to the physicians’ clinical assessments, treatment with Simponi® was successful for 55.0 to 56.6% of patients with RA, PsA, and AS at Visit 2 (Month 3) and for 63.0 to 76.1% of patients from Visit 3 (Month 6) to Visit 9 (Month 24). Simponi® therapy was not successful in 0.5 to 10.1% of patients with RA, PsA and AS over the total 24-month observation period.

**SOCIOECONOMICS**

The analysis of socioeconomic data was done in the EVA population (N=1458).

**Sick leave**

In the total EVA population (N=1458), the mean duration of sick leave in the past 30 days decreased from baseline 4.0 (± 8.57) to 0.9 (± 3.71) days at Visit 9, and the mean duration of sick leave in the past 6 months decreased from baseline 13.7 (± 32.42) to 3.3 (± 15.79) days at Visit 9 (Month 24). The improvement was most prominent in patients with RA who had a decrease in the mean duration of sick leave in the past 6 months from baseline 16.2 (± 39.53) to 4.1 (± 20.45) days at Visit 9 (Month 24), compared to the corresponding mean decreases in sick leave from 14.7 (± 31.30) to 3.9 (± 17.80) days in patients with AS, and from 10.6 (± 27.08) to 2.0 (± 6.30) days in patients with PsA). Inter-subject variability was high at all time points of assessment.

**Impaired capability**

In the total EVA population (N=1458), the mean duration of impaired capability in the past 30 days decreased from baseline 14.9 (± 11.86) to 4.5 (± 7.99) days at Visit 9, and the mean duration of impaired capability in the past 6 months decreased from baseline 65.8 (± 66.13) to 19.8 (± 41.82) days at Visit 9 (Month 24). The improvement was most prominent in patients with AS who had a decrease in the mean duration of impaired capability in the past 6 months from baseline 66.3 (± 68.55) to 17.3 (± 40.36) days at Visit 9 (Month 24) compared to the corresponding mean decreases in impaired capability from 66.6 (± 65.07) to 19.8 (± 40.21) days in patients with PsA, and from 64.5 (± 64.82) to 23.1 (± 45.54) days in patients with RA. Inter-subject variability was high at all time points of assessment.

**Work productivity**

Work productivity was assessed by the patient using a numeric rating scale (range: 1=no limitation to 10=very strong limitation). In the total EVA population (N=1458), patients’ mean ratings of work productivity in the past 30 days decreased (i.e., improved) from baseline 5.5 (± 2.47) to 2.4 (± 2.42) points at Visit 9, and patients’ mean ratings of work productivity in the past 6 months decreased (i.e., improved) from baseline 5.5 (± 2.33) to 2.5 (± 2.36) points at Visit 9 (Month 24). The decrease (i.e. improvement) in mean scores for limitations in work productivity from Visit 1 (Baseline) to Visit 9 (Month 24) was comparable in patients with RA, PsA and AS (in the past 30 days: -2.9, -2.9, respectively -3.3 points; in the past 6 months: -2.8, -2.7, respectively -3.1 points). Inter-subject variability was high at all time points of assessment.
variability was high at all time points of assessment.

Quality of work

The impact of disease on quality of work was assessed by the patient on a numeric rating scale (range: 0=no impact, 10=very strong impact). In the total EVA population (N=1458), patients’ mean ratings for impact of disease on quality of work during the past 30 days decreased (i.e., improved) from baseline 4.8 (± 2.94) to 2.1 (± 2.39) points at Visit 9, and patients’ mean ratings for impact of disease on quality of work during the past 6 months decreased (i.e., improved) from baseline 4.8 (± 2.84) to 2.2 (± 2.46) points at Visit 9 (Month 24). The decrease (i.e., improvement) in mean scores for impact of disease on quality of work from Visit 1 (Baseline) to Visit 9 (Month 24) was comparable in patients with RA, PsA and AS (in the past 30 days: -2.4, -2.6, respectively -3.0 points; in the past 6 months: -2.4, -2.6, respectively -2.8 points). Inter-subject variability was high at all time points of assessment.

Normal course of life

The impact of disease on the normal course of life was assessed by the patient on a numeric rating scale (range: 0=no impact, 10=very strong impact). In the total EVA population (N=1458), patients’ mean ratings for impact of disease on the normal course of life during the past 30 days decreased (i.e., improved) from baseline 5.2 (± 2.49) to 2.3 (± 2.33) points at Visit 9, and patients’ mean ratings for impact of disease on the normal course of life during the past 6 months decreased (i.e., improved) from baseline 5.3 (± 2.36) to 2.4 (± 2.31) points at Visit 9 (Month 24). The decrease in mean scores for impact of disease on the normal course of life from Visit 1 (Baseline) to Visit 9 (Month 24) was comparable in patients with RA, PsA and AS (in the past 30 days: -2.8, -3.0, respectively -3.0 points; in the past 6 months: -2.8, -2.8, respectively -3.0 points). Inter-subject variability was high at all time points of assessment.

HEALTH ECONOMICS

Consultations

The percentage of patients in the EVA population with specialist consultations declined from Visit 1 (Baseline) to Visit 9 (Month 24) primarily regarding consultations with general practitioners in patients with PsA and AS (-19.7% and -17.8% compared to -6.8% in patients with RA) and radiologists (-28.8%, -25.6% and -29.6% in patients with RA, PsA and AS). A marked decline was also observed in the percentage of patients with PsA having dermatologist consultations (-15.0%).

Physical therapy, and psychotherapy and alternative treatments

The percentage of patients in the EVA population receiving physiotherapy, massages, occupational therapy and packs declined from Visit 1 (Baseline) to Visit 9 (Month 24), primarily the application of physiotherapy (16.9%, 10.9% and 9.1% decrease in patients with AS, PsA and RA). All other types of physical therapies, as well as psychotherapy, patient instruction, nutritional consultation, medically required cosmetic treatment, and acupuncture were reported for a few patients only throughout the observation period.

Hospitalizations

Overall, the frequency of hospitalizations in the EVA population decreased from 10.6% at Visit 1/Baseline (151 out of 1423 patients with data) to 1.6% at Visit 9 (10 out of 641 patients with data). Within the 3 subgroup of patients (RA, PsA, AS), the mean duration increased from baseline by a maximum of 2 days or decreased from baseline by a maximum of 9 days.

Rehabilitation measures

In the total EVA population, the frequency of rehabilitation measures due to the disease under investigation (RA, PsA or AS; retrospective evaluation for the past 6 months) decreased from 4.8% at Visit 1/Baseline (68 out of 1414 patients with data) to 1.6% at Visit 9 (10 out of 643 patients with data). Rehabilitation measures due to other reasons decreased from baseline 1.5% (22 out of 1421 patients with data) to 1.4% (9 out of 642 patients with data).

PREMATURE DISCONTINUATION

Overall, 661 (41.0%) out of 1613 in the SAF population prematurely discontinued treatment with Simponi®, most commonly within the first 6 months of treatment (295 out of 661 patients, 44.6%). The rate of early treatment discontinuation was higher in patients with RA (47.9% of 542 patients) compared to patients with PsA (40.1% of 546 patients), and patients with AS (35.2% of 543 patients) primarily以外の療法の適用（物理療法、マッサージ、作業療法およびパック）が減少し、主に物理療法の適用（16.9%, 10.9% および 9.1% の減少、薬局、PsA、AS）が主な減少を示しました。物理療法、患者の説明、栄養的アドバイス、医療必要の皮膚治療、および著者が症例にのみ報告された治療（皮膚科の診療）は減少しました。

入院

全体としては、入院の頻度は、初回基準値時（151/1423患者中）10.6%（151/1423患者中）から最終回（24ヶ月）時（10/641患者中）1.6%（10/641患者中）に減少しました。薬局、PsA、ASの3グループにおいても、全体の平均日数は、基準値時（2日以内の増加または基準値時より最大9日減少）でした。

リハビリテーションの実施

全体のリハビリテーションの実施頻度は、薬局、PsA、ASの6ヶ月以内の観察期間において4.8%（68/1414患者中）から最終回（9ヶ月）時1.6%（10/643患者中）に減少しました。その他の原因によるリハビリテーションの実施頻度は、基準値時1.5%（22/1421患者中）から最終回（9ヶ月）時1.4%（9/642患者中）に減少しました。

前蓄的中止

全体としては、661（41.0%）/1613の患者の前蓄的中止が観察されました。その中止の主な理由は、治療開始6ヶ月以内の时期に薬局（47.9%の542患者）、PsA（40.1%の546患者）、およびAS（35.2%の543患者）でした。
In the 661 patients of the PTT population, the most common reasons for premature discontinuation of Simponi® therapy were lack of effectiveness (44.2% of patients), conversion to other medication (43.3% of patients [primarily switch to a new biologic, 42.2%]), and the occurrence of AEs/ADRs (21.5% of patients).

In the EVA population, the estimated probability of early treatment discontinuation (Kaplan-Meier estimates) of patients with RA (N=474), PsA (N=501) and AS (N=483) was 8.9%, 7.8% respectively 7.5% at the end of Month 3 (Days 90), increased to 23.2%, 18.7% respectively 16.5% at the end of Month 6, to 40.5%, 32.6% respectively 30.4% at the end of Month 12, and thereafter further continuously increased to 55.1%, 45.4% respectively 40.8% at the end of Month 24.

Subgroup analyses (EVA) done for patients with RA indicate a higher probability of premature discontinuation of Simponi® therapy in patients who do not receive concomitant treatment with methotrexate (RA/sine MTX) and for patients using leflunomide mono concomitantly with Simponi® (RA/LEF mono). The estimated median time to premature treatment discontinuation was 164 days shorter (364.0 days) in RA/sine MTX patients and 59 days shorter (469.0 days) in RA/LEF mono patients compared to all RA patients (528.0 days).

Patients' assessments of the handling and use of Simponi® autoinjector

Overall, the patients had no problems handling the auto-injector and package. The safety mechanism of the auto-injector made sense for most patients.

The reasons that were given in cases where satisfaction with the device was not confirmed were almost always related to the fact, that a patient did not administer the medication him/herself. Most of those patients received the injection at the doctor’s office.

**CONCLUSIONS:**

- The nature and frequency of AEs/ADRs reported in the 24-month observation period of this NIS were consistent with the safety profile of Simponi® corresponding to the current SmPC.
- Discontinuation of Simponi® seems to be a function of adverse events and response to therapy.
- According to the physicians’ clinical assessment, treatment with Simponi® was successful in 55.0 to 56.6% of patients at Month 3 and in 63.0 to 76.1% of patients from Month 6 to Month 24.
- Data gathered so far indicate effectiveness of Simponi® in RA, PsA, and AS by clinical parameters and patient-reported outcomes resulting in improved quality of life.
- The achieved reduction in inflammatory markers in combination with the marked improvement on the EQ-5D-3L dimensions “mobility” and “usual activities” and the decrease in mean duration of impaired capability indicates that patients with AS seem to benefit most from treatment with Simponi® followed by patients with PsA and RA.
- There was no relevant change in the concomitant use of disease-specific medication except for a marked decline in the use of systemic glucocorticoids (RA and PsA patients) and the use of NSAR/Analgesics (RA and AS patients). The use of other medications for pre-existing concomitant diseases and the treatment of AEs increased during the observation period of this NIS.
- Effects of a pre-treatment with another biologic and of additional basic therapeutics have been observed. They are more or less prominent depending on the parameter under evaluation.
- Evidence for positive impacts on socio- and health economic parameters could be observed. Gathered data hints towards a reduction of sick leave during the treatment period with the greatest effect observed in patients with RA. Visits at physicians, ambulatory treatments, and hospitalizations seemed to be reduced during the treatment period while rehabilitation measures remained unchanged.
- Satisfaction with function and handling of the auto-injector was high over all indication groups.
12 Reference List

(1) FACHINFORMATION Simponi® 50 mg Injektionslösung in einer Fertigspritze
   http://www.msd.de/arzneimittel/arzneimittelinformationen/

(2) FACHINFORMATION Simponi® 50 mg/100 mg Injektionslösung in vorgefülltem Injektor
   http://www.msd.de/arzneimittel/arzneimittelinformationen/


(4) Krüger K, Burmester GR, Wassenberg S, Bohl-Buehler M, Thomas MH. A Non-Interventional Clinical Study Evaluating the Use of Golimumab in Patients with Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS) in a real-life setting in Germany [abstract accepted for presentation at the 2016 EULAR Annual European Congress of Rheumatology in London, UK]. doi: 10.1136/annrheumdis-2016-eular.1763

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(14) Funktionsfragebogen Hannover FFbH)
http://dgrh.de/fileadmin/media/Praxis__Klinik/Kriterien/PDFs/RA/FFbH.pdf

(15) Kohlmann, T, Raspe, HH. Der Funktionsfragebogen Hannover zur alltagsnahen Diagnostik der Funktionsbeeinträchtigung durch Rückenschmerzen (FFbH-R). In: Rehabilitation 35 (1996), I-VIII.


(17) EQ-5D. http://www.euroqol.org/home.html

(18) Leitlinien und Empfehlungen zur Sicherung von Guter Epidemiologischer Praxis (GEP), Deutsche Gesellschaft für Epidemiologie (DGEpi), Juli 2008

Websites were accessed in March and April 2016 and relevant contents downloaded. The files are available in the full study documentation.

Further publications:

1\textsuperscript{st} Interim Analysis:

2\textsuperscript{nd} Interim Analysis:

3\textsuperscript{rd} Interim Analysis: