Secukinumab Demonstrates Consistent Safety over Long-term Exposure in Patients with Psoriatic Arthritis and Moderate to Severe Plaque Psoriasis: Updated Pooled Safety Analyses

606

PJ Mease[1], IB McInnes[2], K Reich[3], P Nash[4], M Andersson[5], K Abrams[6], L Pricop[6], T Fox[5]

[1]Swedish Medical Center and University of Washington, Seattle, United States; [2]University of Glasgow, Glasgow, United Kingdom; [3]Dermatologikum Hamburg and Georg-August-University Göttingen, Hamburg, Germany; [4]University of Queensland, St Lucia, Australia; [5]Novartis Pharma AG, Basel, Switzerland; [6]Novartis Pharmaceuticals Corp., East Hanover, United States

INTRODUCTION

- Secukinumab, a fully human monoclonal antibody that selectively neutralizes interleukin-17A, has shown significant efficacy in the treatment of psoriatic arthritis (PsA)[1,2] and moderate to severe psoriasis[3], demonstrating rapid onset of action and sustained responses with a consistent safety profile
- Pooled safety data from the PsA and psoriasis clinical trials of secukinumab, of duration over 1 year, have been reported previously[4,5]
- Here, we present updated analyses following additional exposure (up to 5 years), derived from a large study pool (psoriasis program) and/or an extended follow-up period (psoriasis/PsA program) in a cohort of 6561 secukinumab-treated patients

METHODS

Study Design

- The PsA pool consisted of three Phase III studies in active PsA and psoriasis data pool consisted of fifteen Phase III or IV studies in moderate to severe plaque psoriasis (**Figure 1**)
- Secukinumab doses differed in the studies and included intravenous (up to 10 mg/kg) or subcutaneous (s.c.; 75–300 mg) loading, followed by s.c. maintenance dosing (300, 150 or 75 mg)
- Placebo patients were re-randomized to secukinumab between 12–24 weeks in the various studies
- The design of each study has been reported in detail elsewhere[1–3,6–11]

Figure 1. Summary of studies included in the pooled safety analysis from an integrated database of clinical secukinumab trials

Psoriasis[3,6–11]					PsA[1,2]
GESTURE NCT01806597 N = 199 *vs. PBO*	FIXTURE NCT01358578 N = 936 *vs. ETN and PBO*	JUNCTURE NCT01636687 N = 177 *vs. PBO*	CARIMA NCT02559622 N = 150 *vs. PBO*	PRIME NCT02474082 N = 105 *vs. Fumaderm*	FUTURE 1 NCT01392326 N = 587 *vs. PBO*
TRANSFIGURE NCT01807520 N = 190 *vs. PBO*	SCULPTURE NCT01406938 N = 966 *Fixed regimen vs Re-treatment*	CLEAR NCT02074982 N = 335 *vs. UST*	PSORITUS NCT02362789 N = 130 *vs. PBO*	AJP01 NCT02547714 N = 34 -	FUTURE 2 NCT01752634 N = 387 *vs. PBO*
ERASURE NCT01365455 N = 702 *vs. PBO*	FEATURE NCT01555125 N = 174 *vs. PBO*	2PRECISE NCT02008890 N = 214 *vs. PBO*	GAIN NCT02474069 N = 772 *Dose optimization*	SCALP NCT02267135 N = 97 *vs. PBO*	FUTURE 3 NCT01989468 N = 406 *vs. PBO*

N, number of patients in the safety pool
ETN, etanercept; PBO, Placebo; PsA, Psoriatic arthritis; UST, ustekinumab

Patients

- Eligible patients aged ≥18 years with active PsA or moderate to severe plaque psoriasis were enrolled based on pre-specified inclusion criteria, reported in detail elsewhere[1–3,6–11]
- Patients were allowed to enroll even if they had: latent tuberculosis (if prophylactic treatment was administered prior to enrollment), active/ongoing cardiovascular disease (unless severe or uncontrolled), history of inflammatory bowel disease (unless active/ongoing), or history of malignancy (successfully treated)[1–3,6–11]

Statistical Analyses

- Safety analyses included all patients who had received ≥1 dose of study medication
- Data included were collected up to June 25, 2017 (cut-off date), and were pooled at the individual patient level separately for the psoriasis and PsA studies
- Adverse events (AEs), serious AEs (SAEs) and AEs of selected interest are expressed as exposure-adjusted incidence rate (EAIR) per 100 patient-years for the entire treatment period
- Anti-drug antibodies (ADAs) were measured using a Meso-scale Discovery bridging assay

RESULTS

Baseline Characteristics

- Demographics and baseline disease characteristics of the pooled secukinumab group is provided in **Table 1**

Table 1. Demographics and Baseline Disease Characteristics

Characteristic	Psoriasis program Any secukinumab (N = 5181)	PsA program Any secukinumab (N = 1380)
Age (years), mean (SD)	45.7 (13.3)	48.8 (12.0)
Female, n (%)	1743 (33.6)	742 (53.8)
Weight (kg), mean (SD)	86.7 (22.1)	84.8 (19.8)
Caucasian, n (%)	4236 (81.8)	1212 (87.8)
Relevant medical history or current medical condition, n (%)		
Hypertension	1089 (21.0)	551 (39.9)
Hyperlipidemia	667 (12.9)	318 (23.0)
Diabetes mellitus	341 (6.6)	171 (12.4)
Crohn's disease	5 (0.1)	2 (0.1)
Ulcerative colitis	10 (0.2)	2 (0.1)
Current smoker	1585 (30.6)	262 (19.0)

N, number of patients in the analysis; SD, standard deviation

Adverse Events and Serious Adverse Events

- The incidences of AEs and SAEs with longer-term secukinumab treatment are shown in **Table 2**
- There was no discernible pattern with regards to SAEs across the treatment groups
- 20 deaths (9 [0.2%] in the psoriasis and 11 [0.8%] in the PsA programs) were reported in secukinumab-treated patients

Table 2. Summary of Clinical Safety: Entire Treatment Period

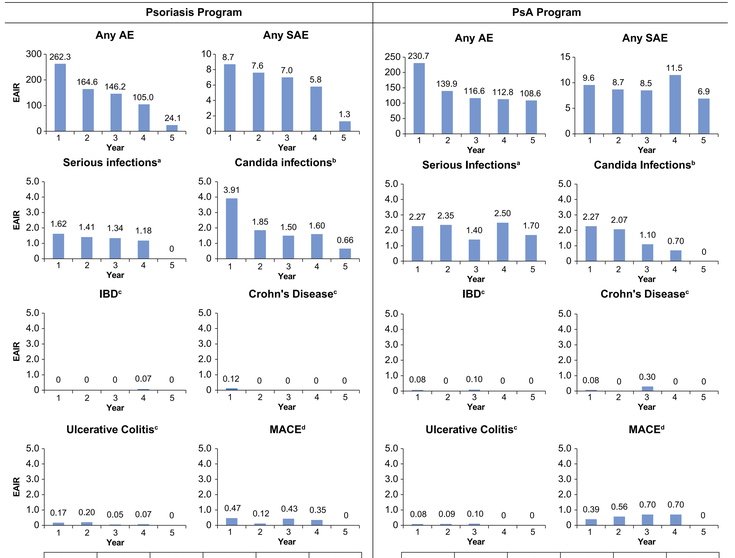
Variable	Psoriasis program Any secukinumab (N = 5181)	PsA program Any secukinumab (N = 1380)
Total exposure, patient-years	10416.9	3866.9
Exposure (days), mean (SD)	734.4 (562.9)	1023.5 (472.3)
Min–max exposure (days)	1–1825	8–1827
Death, n (%)	9 (0.2)	11 (0.8)
EAIR per 100 patient-years (95% CI)		
Any AE	204.4 (198.4, 210.5)	147.0 (138.9,155.5)
Any serious AE	6.9 (6.3, 7.4)	7.9 (7.0, 8.9)
Most common AEs[a]		
Viral upper respiratory tract infections	21.0 (19.9, 22.0)	12.1 (10.9, 13.4)
Headache	6.2 (5.8, 6.8)	3.8 (3.2, 4.5)
Upper respiratory tract infections	5.4 (4.9, 5.9)	9.1 (8.1, 10.2)
AEs of Selected Interest with Secukinumab		
Serious Infections and infestations[b]	1.4 (1.2, 1.6)	1.9 (1.5, 2.4)
Candida Infections[c]	2.2 (1.9, 2.5)	1.5 (1.1, 2.0)
Inflammatory bowel disease[d]	0.01 (0, 0.1)	0.1 (0, 0.2)
Crohn's disease[d]	0.1 (0, 0.1)	0.1 (0, 0.2)
Ulcerative colitis[d]	0.1 (0.1, 0.2)	0.1 (0, 0.2)
MACE[e]	0.3 (0.2, 0.5)	0.4 (0.3, 0.7)

[a]Adverse events in the secukinumab group that occurred with an EAIR ≥5.0 during the entire treatment period in either of the pooled groups; [b]Rates are for system organ class which includes multiple associated preferred terms (PT); [c]Rates are for *Candida* infections high level term which includes multiple associated PTs; [d]Rates are for PT (IBD PT data are reported for unspecified IBD); [e]Rates are for Novartis MedDRA Query term which includes multiple associated PTs
N, number of patients in the analysis
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate per 100 patient-years; SD, standard deviation; MACE, major adverse cardiac event

Rate of Adverse Events year-on-year

- Data on a year-on-year basis showed no increase in the EAIR of AEs with secukinumab treatment over time in the PsA and psoriasis programs (**Figure 2**)

Figure 2. EAIR of Adverse Events year-on-year with secukinumab



Year	1	2	3	4	5
N	5181	3268	2246	1627	1210

Year	1	2	3	4	5
N	1380	1183	948	587	290

[a]Rates are for system organ class which includes multiple associated preferred terms (PT); [b]Rates are for candida infections high level term which includes multiple associated PTs; [c]Rates are for PT (IBD PT data are reported for unspecified IBD); [d]Rates are for Novartis MedDRA Query term which includes multiple associated PTs
N, number of patients in the analysis
AE, adverse event; EAIR, exposure adjusted incidence rate per 100 patient-years; IBD, inflammatory bowel disease; MACE, major adverse cardiac event

Adverse Events of Selected Interest

- The EAIRs of AEs of special interest were similar across the PsA and psoriasis programs (**Table 2**), and comparable with those reported previously[8,9]

Infections and Infestations

- Serious infections were infrequent, with no clinically meaningful difference in EAIR across indications
- Candidiasis occurred with a low frequency overall
- Confirmed reactivation of tuberculosis was not reported in any of the studies

Crohn's Disease and Ulcerative Colitis

- The incidence and prevalence of Crohn's disease and ulcerative colitis with secukinumab was low in the PsA and psoriasis programs, and within the expected range of incidence rates in these populations[12–14]

Immunogenicity/Anti-Drug Antibodies (ADAs)

- Treatment emergent anti-drug antibodies were reported with secukinumab in <1% of patients across studies, and generally not associated with adverse events

Suicidality

- Across secukinumab programs patients with psychiatric disorders were allowed to enter clinical trials based on investigators discretion
- Overall, the incidence of suicidality related AEs in the longer-term was low in the PsA and psoriasis programs with most cases occurring during the open label extension period
  - 3 cases (EAIR of 0.08 per 100 patient years) of suicide/self-injury were reported in the PsA program (all the three were cases of suicidal ideation)
  - 9 cases (EAIR of 0.09 per 100 patient years) of suicide/self-injury were reported in the psoriasis program: Four cases of attempted suicide and 1 completed suicide, 3 cases of suicidal ideation and 1 case of suicidal depression
  - The incidence of suicidality related AEs in the longer-term was comparable with rates reported previously[15], which was numerically lower than that for placebo in the short-term

CONCLUSIONS

- Secukinumab demonstrated a favorable safety profile during long term treatment (up to 14283.8 patient-years of exposure) in a large cohort of 6561 patients with PsA or moderate-to-severe plaque psoriasis
- This longer-term (out to 5 years) safety assessment showed that the safety profile of secukinumab was consistent with previous reports[1–11] and comparable across PsA and psoriasis patients supporting its long-term use in these chronic conditions
- Secukinumab safety related AE and SAE remained stable or decreased over time out to 5 years

REFERENCES

1. Mease PJ, et al. *N Engl J* Med. 2015;373:1329–39.
2. McInnes IB, et al. *Lancet* 2015;386:1137–46.
3. Langley RG, et al. *N Engl J* Med. 2014;371:326–38.
4. Van de Kerkhof PCM, et al. *J Am Acad Dermatol*. 2016;75:83–98.
5. Mease PJ, et al. *Arthritis Rheumatol*. 2016;68(suppl 10).
6. Blauvelt A, et al. *Br J Dermatol*. 2015;172:484–93.
7. Paul C, et al. *J Eur Acad Dermatol Venereol*. 2015;29:1082–90.
8. Mrowietz U, et al. *J Am Acad Dermatol*. 2015;73:27–36.
9. Thaçi D, et al. *J Am Acad Dermatol*. 2015;73:400–9.
10. http://clinicaltrials.gov/ct2/show/NCT02008890 (accessed: 25th September 2017).
11. Armstrong AW, et al. *J Clin Aesthet Dermatol*. 2016;9:S12-16.
12. Li WQ, et al. *Ann Rheum Dis*. 2013;72:1200–5.
13. Egeberg A, et al. *Br J Dermatol*. 2016 Mar 9. [Epub ahead of print]
14. Scosyrev E and Primatesta P. Poster presentation: 5th Congress of the Psoriasis International Network, 7–9 July 2016, Paris, France.
15. Mease PJ, et al. *Arthritis Rheumatol*. 2015; 67 (suppl 10).

ACKNOWLEDGEMENTS

The authors thank Vivek Sanker MK (Novartis, India) for medical writing support.

The study was sponsored by Novartis Pharma AG, Basel, Switzerland.

Poster presented at: American College of Rheumatology Annual Meeting (ACR), November 3–8, 2017, San Diego, United States.

Scan to download this poster