Long-Term Safety of Upadacitinib in Clinical Trial and Clinical Practice Settings: Risk of Infection, Malignancy, Cardiovascular Events, and Thromboembolism in Patients With Rheumatoid Arthritis, Psoriatic Arthritis, or Axial Spondyloarthritis

Gerd R. Burmester,[1] Stanley B. Cohen,[2] Eduardo Mysler,[3] Andrew Östör,[4] Louis Bessette,[5] Torsten Witte,[6] Denis Poddubnyy,[7] Axel J. Hueber,[8] Benjamin Wolfe,[9] Ivan Lagunes,[9] Sebastian Meerwein,[10] Lauren D. Smith,[9] Derek Coombs,[9] Kevin L. Winthrop[11]

[1]Charité University Medicine, Berlin, Germany; [2]Metroplex Clinical Research Center, Dallas, TX, USA; [3]Organización Medica de Investigación, Rheumatology, Buenos Aires, Argentina; [4]Monash University, Melbourne & ANU, Canberra, Australia; [5]Université de Laval, Quebec City, QC, CAN; [6]Department of Rheumatology and Clinical Immunology, Hannover Medical School, Hannover, Germany; [7]University of Toronto, Toronto, ON, CAN; [8]Department Internal Medicine 5, Division of Rheumatology, Klinikum Nuremberg, Paracelsus Medical University, Nuremberg, Germany; [9]AbbVie Inc., North Chicago, IL, USA; [10]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany; [11]Oregon Health & Science University, Portland, OR, USA

Presented at the European Alliance of Associations for Rheumatology (EULAR), June 3–6, 2026, London, UK (DV-020145)

OBJECTIVE

- To describe the long-term safety profile of upadacitinib (UPA) among patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or axial spondyloarthritis (axSpA), focusing on safety aspects of interest, including incidence of serious infections, herpes zoster, malignancy, major adverse cardiovascular events (MACE), and venous thromboembolism (VTE), in clinical trial and clinical practice settings

BACKGROUND

- The safety profile of UPA, an oral JAK inhibitor, has largely been characterized within the SELECT randomized controlled clinical trial programs in RA, PsA, and axSpA[1]
- These studies included long-term extensions and, in some cases, active-comparator arms, permitting integrated evaluation of UPA's long-term risks and contextualization against established therapies
- Still, stringent eligibility criteria of clinical trials may limit generalizability, making it uncertain whether observations within these controlled settings extend to clinical practice

METHODS

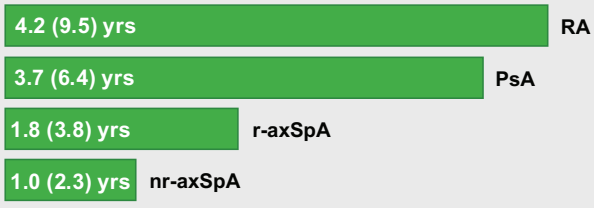
- Results from 11 clinical trials and 5 observational studies were analyzed
- Safety was assessed in 8722 patients receiving UPA 15 mg across rheumatologic indications
- Safety was evaluated across >17,000 patient-years of UPA exposure in clinical trials and >4000 patient-years in observational studies
- Overall, >21,000 patient-years of UPA exposure were analyzed

Comprehensive View of UPA Safety Across >21,000 Patient-Years

11 phase 3 UPA clinical trials within the SELECT program

RA = 6	PsA = 2	r-axSpA = 2[a]	nr-axSpA = 1

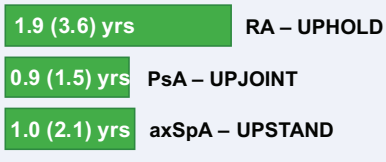
Median (maximum) exposure to UPA 15 mg in clinical trials:



5 observational studies in routine clinical practice settings

RA = 3	PsA = 1	axSpA = 1

Median (maximum) exposure to UPA 15 mg in observational studies:



axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axSpA; PsA, psoriatic arthritis; RA, rheumatoid arthritis; r-axSpA, radiographic axSpA; UPA, upadacitinib.
[a]Also known as ankylosing spondylitis. One trial was phase 2b/3.

JAKa-US-00123-MC v1.0 Approved 8/2026
©AbbVie Inc. 2026

METHODS (CONTINUED)

- All SELECT clinical trials have completed, except for SELECT-COMPARE, which remains ongoing (data cutoff: August 15, 2025)
- Previous exposure to JAK inhibitors were not permitted in any of the SELECT trials
- All studies were phase 3 studies, except for SELECT-AXIS 1, which was a phase 2/3 study

Safety Across >17,000 Patient-Years of UPA Exposure in Clinical Trials

Characteristic	RA SELECT Phase 3 Clinical Trial Program[1-7]						PsA SELECT Phase 3 Clinical Trial Program[1,8,9]		r-axSpA SELECT Phase 2b/3 Clinical Trial Program[1,10,11]		nr-axSpA SELECT Phase 3 Trial[1,12]
	SELECT EARLY	SELECT MONOTHERAPY	SELECT BEYOND	SELECT NEXT	SELECT COMPARE	SELECT CHOICE	SELECT-PsA 1	SELECT-PsA 2	SELECT-AXIS 1 Upadacitinib	SELECT-AXIS 2 Upadacitinib	SELECT-AXIS 2 Upadacitinib
Patient population	MTX naïve[2]	MTX-IR[3]	bDMARD-IR[4]	csDMARD-IR[5]	MTX-IR[6]	bDMARD-IR[7]	Non-bDMARD-IR[8]	bDMARD-IR[9]	bDMARD naïve[10]	bDMARD-IR[11]	NSAID-IR[12]
N	947	648	499	661	1629	613	1705	642	187	420	314
Background therapy	–	–	MTX	csDMARD(s)	csDMARD(s)	csDMARD(s)	±Non-bDMARD	±Non-bDMARD	–	–	–
Duration	5 years	5 years	5 years	5 years	10 years (ongoing)	4.2 years	5 years	3 years	2 years	2 years	2 years
Exposure groups	UPA 15 mg QD N = 3209 PY = 12909.0						UPA 15 mg QD N = 907 PY = 2974.9		UPA 15 mg QD N = 596 PY = 1016.6		UPA 15 mg QD N = 286 PY = 380.9
	MTX N = 314 PY = 860.1				ADA 40 mg EOW N = 579 PY = 2154.8		ADA 40 mg EOW N = 429 PY = 1536.0				

ADA, adalimumab; axSpA, axial spondyloarthritis; bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; EOW, every other week; IR, inadequate responder; nr-axSpA, non-radiographic axSpA; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; r-axSpA, radiographic axSpA; UPA, upadacitinib.

- The included observational studies evaluating UPA 15 mg have all been completed

Safety Across >4000 Patient-Years of UPA Exposure in Observational Studies

Characteristic	RA Observational Studies[13–15]			PsA Observational Study[16]	axSpA Observational Study[17]
	UPHOLD	UPwArds	CLOSE UP	UPJoint	UPSTAND
Patient population	Mixed	Mixed	Mixed	Mixed	Mixed
N	1699	533	412	381	699
Background therapy	± csDMARD	± MTX	± csDMARD	± csDMARD	—
Duration	2 years	1 year	2 years	1 year	1 year
Exposure groups	UPA 15 mg QD PY = 2607.4	UPA 15 mg QD PY = 447.4	UPA 15 mg QD PY = 682.6	UPA 15 mg QD PY = 298.2	UPA 15 mg QD PY = 574.1

axSpA, axial spondyloarthritis; csDMARD, conventional synthetic DMARD; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

RESULTS

Baseline Characteristics of Patients Receiving UPA

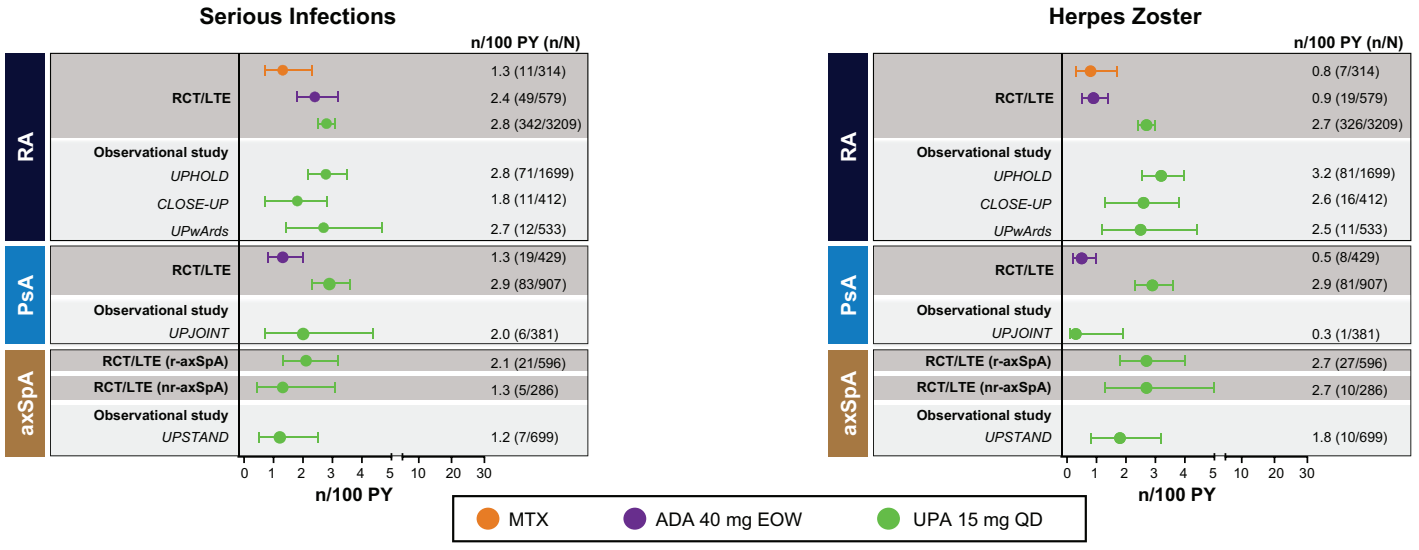
Characteristic	RCT/LTE – UPA 15 mg QD				Observational Studies – UPA 15 mg QD		
	RA N = 3209	PsA N = 907	r-axSpA N = 596	nr-axSpA N = 286	RA - UPHOLD N = 1699	PsA - UPJOINT N = 364[a]	axSpA - UPSTAND N = 699
Age, mean, years (SD)	54.3 (12.0)	51.5 (12.1)	43.3 (12.3)	42.2 (12.2)	56.9 (12.4)	53.9 (11.8)	44.5 (12.4)
Age ≥ 65 years, n (%)	643 (20.0)	129 (14.2)	32 (5.4)	8 (2.8)	478 (28.1)	68 (18.7)	37 (5.3)
Sex (female), n (%)	2581 (80.4)	478 (52.7)	162 (27.2)	167 (58.4)	1358 (79.9)	241 (66.2)	331 (47.4)
Time since diagnosis (years), mean (SD)	8.5 (8.4)	7.2 (7.8)	7.4 (7.9)	4.6 (5.8)	10.1 (9.1)	8.2 (8.5)[b]	7.9 (8.8)
Disease activity score, mean (SD)	DAS28(CRP) 5.8 (1.0)[c]	DAPSA 57.5 (29.7)[d]	ASDAS(CRP) 3.8 (0.8)[e]	ASDAS(CRP) 3.6 (0.6)	DAS28(CRP) 4.6 (1.2)	DAPSA 29.7 (15.9)[f]	ASDAS(CRP) 3.9 (1.0)[g]
≥1 CV risk factor, **n (%)**	2472 (77.0)	758 (83.6)	454 (76.2)	199 (69.6)	1059 (62.3)	NE	374 (53.5)

CV, cardiovascular; LTE, long-term extension; NE, not estimable; RCT, randomized controlled trial; QD, once daily; UPA, upadacitinib.
[a]Baseline characteristics are shown for the effectiveness analysis set from UPJOINT (Werner SG, et al. *Rheumatol Ther.* 2026;13:45–64) and exact values may differ from those in the safety analysis set (N = 381) used here.
[b]Disease duration was calculated based on sample size of 350 patients.
[c]n = 3193.
[d]n = 575.
[e]n = 900.
[f]n = 354.
[g]n = 385.

RESULTS (CONTINUED)

- Safety outcomes are presented as exposure-adjusted incidence rates of treatment-emergent adverse events (TEAEs), defined as any adverse event occurring on or after the first dose of study drug and ≤30 days after the last dose of study drug for UPA 15 mg and MTX or ≤70 days after the last dose for adalimumab (ADA)
- Assignment of adverse events was based on drug exposure at the time of event
- Across disease indications, incidence rates of serious infection appeared similar between clinical trial and clinical practice settings
- Herpes zoster (HZ) rates were elevated with UPA 15 mg vs active comparators in RA and PsA, with similar rates observed across disease states in clinical trials and observational studies (except 1 observational PsA study, which reported lower HZ rates)

Rates of Serious Infections and Herpes Zoster in Clinical Trial and Practice Settings[a]

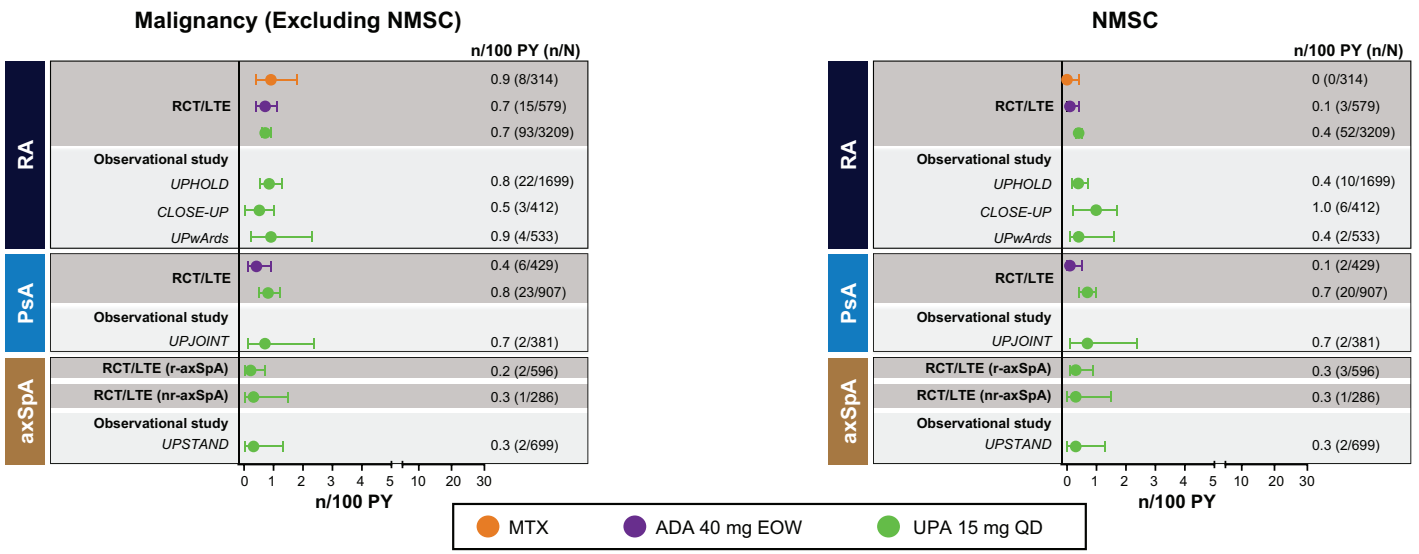


ADA, adalimumab; axSpA, axial spondyloarthritis; EOW, every other week; LTE, long-term extension; nr-axSpA, non-radiographic axSpA; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; RCT, randomized controlled trial; r-axSpA, radiographic axSpA; UPA, upadacitinib.

[a]Safety outcomes are presented as exposure-adjusted incidence rates of treatment-emergent adverse events, defined as any adverse event occurring on or after the first dose of study drug and ≤30 days after the last dose of study drug for UPA 15 mg and MTX or ≤70 days for ADA. Assignment of adverse events was based on drug exposure at the time of event.

- Malignancy rates, excluding nonmelanoma skin cancer (NMSC), were similar across treatment groups in RA and higher for UPA 15 mg than ADA in PsA
- NMSC rates were numerically higher with UPA 15 mg than active comparators in RA and PsA clinical trials
- Incidence rates for malignancy with UPA 15 mg appeared consistent across clinical trials and observational studies

Rates of Malignancy in Clinical Trial and Practice Settings[a]



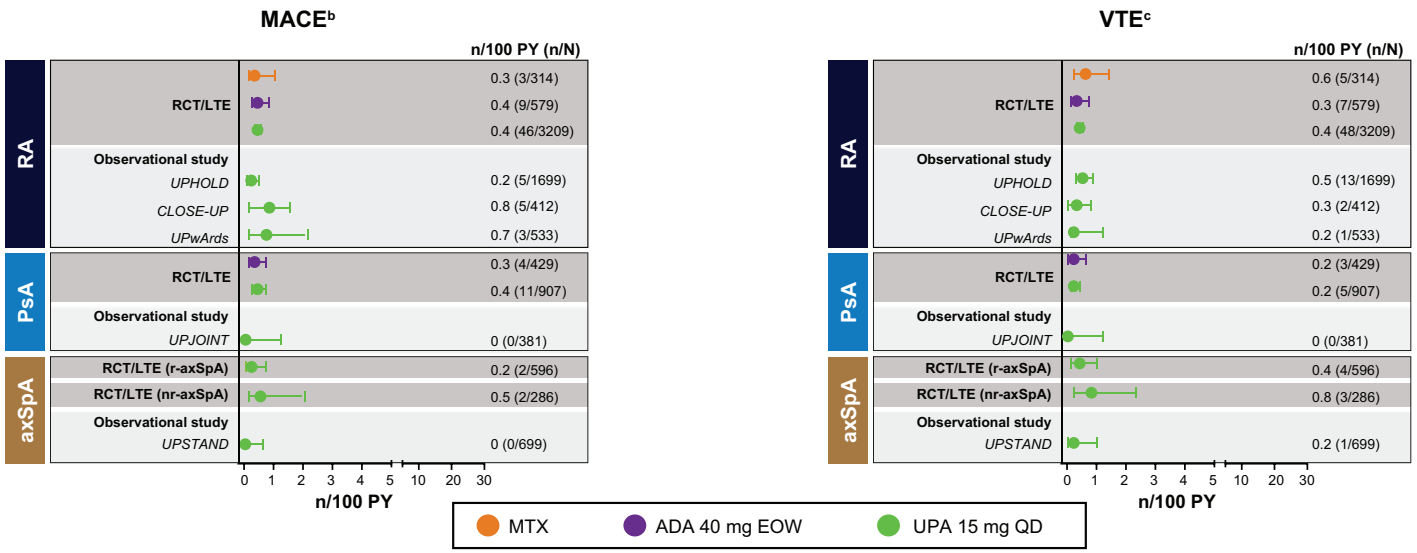
ADA, adalimumab; axSpA, axial spondyloarthritis; EOW, every other week; LTE, long-term extension; NMSC, nonmelanoma skin cancer; nr-axSpA, non-radiographic axSpA; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; RCT, randomized controlled trial; r-axSpA, radiographic axSpA; UPA, upadacitinib.

[a]Safety outcomes are presented as exposure-adjusted incidence rates of treatment-emergent adverse events, defined as any adverse event occurring on or after the first dose of study drug and ≤30 days after the last dose of study drug for UPA 15 mg and MTX or ≤70 days for ADA. Assignment of adverse events was based on drug exposure at the time of event.

RESULTS (CONTINUED)

- MACE and VTE rates for UPA 15 mg remained consistent across trial and real-world settings
- In clinical trials, MACE and VTEs were adjudicated by a blinded, independent committee using prespecified definitions; in observational studies, these events were assessed and assigned by the investigator

Rates of MACE and VTE in Clinical Trial and Practice Settings[a]



ADA, adalimumab; axSpA, axial spondyloarthritis; EOW, every other week; LTE, long-term extension; MACE, major adverse cardiovascular events; nr-axSpA, non-radiographic axSpA; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; RCT, randomized controlled trial; r-axSpA, radiographic axSpA; UPA, upadacitinib; VTE, venous thromboembolism.

[a]Safety outcomes are presented as exposure-adjusted incidence rates of treatment-emergent adverse events, defined as any adverse event occurring on or after the first dose of study drug and ≤30 days after the last dose of study drug for UPA 15 mg and MTX or ≤70 days for ADA. Assignment of adverse events was based on drug exposure at the time of event.

[b]Defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. MACE was independently adjudicated in the SELECT clinical program and investigator assigned in the observational studies.

[c]Includes deep vein thrombosis and pulmonary embolism (fatal and nonfatal). VTE was independently adjudicated in the SELECT clinical program and investigator assigned in the observational studies.

CONCLUSIONS

- Rates of examined TEAEs were generally similar between UPA 15 mg and active comparators in RA (ADA and MTX) and PsA (ADA), except for HZ, NMSC, and serious infections in PsA
- Rates observed in real-world settings were similar to those reported in the SELECT UPA clinical trials, providing important complementary insights across diverse patient populations, though the absence of controlled conditions should be considered when interpreting these results
- Overall findings are consistent with the previously reported safety profile of UPA 15 mg[1] and provide a comprehensive view of the safety profile of UPA in rheumatology across both controlled and real-world settings

REFERENCES

1. Burmester GR, et al. *Adv Ther*. 2025;42:5215–37.
2. van Vollenhoven R, et al. *Arthritis Rheumatol*. 2020;72:1607–20.
3. Smolen JS, et al. *Lancet*. 2019;393:2303–11.
4. Genovese MC, et al. *Lancet*. 2018;391:2513–24.
5. Burmester GR, et al. *Lancet*. 2018;391:2503–12.
6. Fleischmann R, et al. *Arthritis Rheumatol*. 2019;71:1788–800.
7. Rubbert-Roth A, et al. *N Engl J Med*. 2020;383:1511–21.
8. McInnes IB, et al. *Lancet*. 2021;384:1227–39.
9. Mease PJ, et al. *Ann Rheum Dis*. 2021;80:312–20.
10. van der Heijde D, et al. *Lancet*. 2019;394:2108–17.
11. van der Heijde D, et al. *Ann Rheum Dis*. 2022;81:1515–23.
12. Deodhar A, et al. *Lancet*. 2022;400:369–79.
13. Östör A, et al. *Arthritis Res Ther*. 2025;27:84.
14. Witte T, et al. *Clin Exp Rheumatol*. 2024;42:726–35.
15. Bessette L, et al. *Rheumatol Ther*. 2024;11:563–82.
16. Werner SG, et al. *Rheumatol Ther*. 2026;13:45–64.
17. Poddubnyy D, et al. *Ann Rheum Dis*. 2025;84(Suppl 1):1023–25 [Abstract].

ACKNOWLEDGMENTS

AbbVie Inc. funded these studies and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. The authors thank Tianming Gao, Konrad Goetz, Dalinda Liazoghli, Alexander Nichol, Jamie Urbanik, and Saskia Wedel for providing observational study data. Editorial support was provided by S. Michael Austin of AbbVie; medical writing was provided by Matthew Eckwahl, PhD, of AbbVie.

AbbVie and the authors thank the patients, study sites, and investigators who participated in these studies:

Clinical trials: NCT02706873, NCT02675426, NCT02629159, NCT02706951, NCT02706847, NCT03086343, NCT03104400, NCT03104374, NCT03178487, and NCT04169373

Observational studies: NCT04497597, NCT04574492, NCT04267536, NCT04758117, and NCT04846244

DISCLOSURES

Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: G.R. Burmester: Speaking or consulting fees from AbbVie, Lilly, Galapagos, Janssen, MSD, Pfizer, Roche, and UCB. S. Cohen: Consulting fees and research grants from AbbVie, Amgen, BI, Gilead, Pfizer, Roche, and Sandoz. E. Mysler: Consultant of, and received grants/research support from AbbVie, Alpine Immunology, AZ, AnaptysBio, Biogen, BMS, GSK, Hi Bio, Janssen, Lilly, Merck, Novartis, Pfizer, and Roche. A. Östör: Consultant and/or on advisory boards and/or undertaken clinical trials for AbbVie, GSK, Janssen, Lilly, Novartis, and Pfizer. L. Bessette: Consultancy, research grants, and speaker fees from AbbVie, BMS, Janssen, Lilly, Novartis, Pfizer, Sanofi, and UCB. T. Witte: Grant/research support from: AbbVie, Amgen, BMS, Celgene, Chugai, Gilead, Janssen, Lilly, MSD, Mylan, Novartis, Pfizer, Roche, and UCB. D. Poddubnyy: Speaker honoraria, consulting fees, and/or research grants from AbbVie, Biocad, BMS, Lilly, Gilead, GSK, MSD, MoonLake, Novartis, Pfizer, Samsung Bioepis, and UCB. A.J. Hueber: Consultant or speaker for AbbVie, BMS, Galapagos, GSK, Janssen, Lilly, Novartis, and UCB; funding for investigator-initiated studies: Novartis and Galapagos. B. Wolfe, I. Lagunes, S. Meerwein, L.D. Smith, and D. Coombs: Employees of AbbVie and may hold stock or stock options. K.L. Winthrop: Consulting fees and research grants from AbbVie, BMS, Galapagos, Gilead, Lilly, Pfizer, Roche, and UCB.