Rheumatology, 2024, **00**, 1–11
https://doi.org/10.1093/rheumatology/keae012
Advance access publication 22 January 2024
Original Article

Clinical science

Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis up to 6.5 years of treatment: results of a long-term study

Roberto Caporali [1,*], Peter C. Taylor [2], Daniel Aletaha[3], Raimon Sanmartí[4], Tsutomu Takeuchi[5], Daojun Mo[6], Ewa Haladyj[6], Natalia Bello[6], Liliana Zaremba-Pechmann[7], Ying Fang[6], Maxime Dougados[8]

[1]Department of Clinical Sciences & Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano and ASST Gaetano Pini CTO, Milano, Italy
[2]Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[3]Department of Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria
[4]Rheumatology Department, Hospital Clínic de Barcelona and IDIBAPS, Barcelona, Spain
[5]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo and Saitama Medical University, Saitama, Japan
[6]Eli Lilly and Company, Indianapolis, IN, USA
[7]HaaPACS GmbH, Schriesheim, Germany
[8]Rheumatology Department, Cochin Hospital, APHP, Paris and INSERM U-1153, CRESS Paris-Sorbonne, Paris, France

*Correspondence to: Roberto Caporali, Department of Clinical Sciences & Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano and ASST Gaetano Pini CTO, Piazza Cardinal Ferrari, 1 - Presidio Ospedaliero Gaetano, Pini, 20122 Milano MI, Italy.
E-mail: roberto.caporali@unimi.it

Abstract

Objectives: To evaluate the long-term efficacy of once-daily baricitinib 4 mg or 2 mg in patients with active rheumatoid arthritis who had inadequate response (IR) to MTX, csDMARDs or bDMARDs.

Methods: Data from three completed phase III studies—RA-BEAM (MTX-IR), RA-BUILD (csDMARD-IR) and RA-BEACON (bDMARD-IR)—and one completed long-term extension study (RA-BEYOND) were analysed up to 6.5 years [340 weeks (RA-BEAM) and 336 weeks (RA-BUILD and RA-BEACON)]. Low disease activity (LDA) [Simplified Disease Activity Index (SDAI) ≤11], clinical remission (SDAI ≤3.3) and physical function [Health Assessment Questionnaire Disability Index (HAQ-DI) ≤0.5] were the main outcomes assessed. Completer and non-responder imputation (NRI) analyses were conducted on each population.

Results: At week 340 or 336, LDA was achieved in 37%/83% of MTX-IR, 35%/83% of csDMARD-IR and 23%/73% of bDMARD-IR patients treated with baricitinib 4 mg, assessed by NRI/completer analyses, respectively. Remission was achieved in 20%/40% of MTX-IR, 13%/32% of csDMARD-IR and 9%/30% of bDMARD-IR patients treated with baricitinib 4 mg, assessed by NRI/completer analyses, respectively. HAQ-DI ≤0.5 was reached in 31%/51% of MTX-IR, 25%/46% of csDMARD-IR and 24%/38% of bDMARD-IR patients treated with baricitinib 4 mg, assessed by NRI/completer analyses, respectively.

Conclusion: Treatment with baricitinib 4 mg or 2 mg demonstrated efficacy up to 6.5 years with maintained LDA/remission results across SDAI, CDAI and DAS28-hsCRP consistent with previously reported data, and was well tolerated.

Trial registration: United States National Library of Medicine clinical trials database www.clinicaltrials.gov; RA-BEYOND; NCT01885078.

Keywords: baricitinib, clinical remission, long-term efficacy, low disease activity, rheumatoid arthritis.

Rheumatology key messages

- Across all groups, discontinuation rates due to adverse events or lack of efficacy were low.
- Similar proportions of patients achieved SDAI, CDAI and DAS28-hsCRP LDA by NRI/completer analyses.
- Similar proportions of patients achieved SDAI, CDAI, DAS28-hsCRP and Boolean remission by NRI/completer analyses.

Received: 24 August 2023. **Accepted:** 21 December 2023

Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory, autoimmune disease characterised by progressive joint damage, loss of physical function and disability [1]. RA is a chronic disease that can greatly impact a patient's quality of life, often associated with comorbidities that can affect mortality [2]; therefore, treatments that are safe and efficacious in the long term are required to reduce disease burden, in line with the treat-to-target approach [3].

Baricitinib, an oral selective Janus kinase 1/2 inhibitor, is approved for the treatment of adults with moderately-to-severely active RA, moderate-to-severe atopic dermatitis, severe alopecia areata and hospitalized patients with coronavirus disease 2019 [4]. Baricitinib has demonstrated efficacy in RA for treatment-naive patients (RA-BEGIN; NCT01711359) [5] and those who have had an inadequate response (IR) to biologic disease-modifying antirheumatic drugs (bDMARDs) (RA-BEACON; NCT01721044) [6], conventional synthetic DMARDs (csDMARDs) (RA-BUILD; NCT01721057) [7] or methotrexate (MTX) (RA-BEAM; NCT01710358) [8].

The long-term safety profile of baricitinib has been demonstrated for 3770 patients with RA following up to 9.3 years of treatment, amounting to 14 744 patient-years of exposure [9]. However, as RA is a chronic disease with some patients receiving therapy for decades, it is important to understand not only the safety profile of a particular treatment but also the discontinuation rates and efficacy over the longest duration possible. Efficacy has been reported for up to 3 years of treatment with baricitinib 4 mg and 2 mg in the long-term extension (LTE) study RA-BEYOND (NCT01885078) [10, 11].

Here, we evaluate treatment discontinuation and achievement and maintenance of low disease activity (LDA), remission and a normative state of physical function in patients treated with baricitinib 4 mg or 2 mg for up to 6.5 years in the completed LTE study RA-BEYOND.

Methods

Patients and study design

RA-BEYOND is a phase III, multicentre, LTE study which evaluated the long-term safety and efficacy of baricitinib in patients with RA, providing data for up to 7 years of additional treatment with baricitinib. Patients were enrolled into RA-BEYOND following completion of final active treatment in specified studies, including RA-BEAM (NCT01710358), RA-BUILD (NCT01721057) and RA-BEACON (NCT01721044).

RA-BEAM is a completed phase III clinical study that evaluated the efficacy and safety of baricitinib over 52 weeks in adults (at least 18 years of age) with moderately-to-severely active RA who had an IR to MTX.

RA-BUILD and RA-BEACON are completed phase III clinical studies that evaluated the efficacy and safety of baricitinib over 24 weeks in adults (at least 18 years of age) with moderately-to-severely active RA. Patients enrolled in RA-BUILD had an IR or intolerance to at least one csDMARD (including MTX) and had not previously been treated with a bDMARD. Patients enrolled in RA-BEACON had an IR to prior treatment with at least one bDMARD and were on stable doses of concomitant conventional DMARD therapy.

Detailed descriptions of the designs of these studies have been published [6–8], and the treatment course in the originating study and LTE is given in Supplementary Fig. S1, available at *Rheumatology* online.

Patients who enrolled in RA-BEAM (MTX-IR) were randomized to once-daily baricitinib 4 mg, adalimumab 40 mg subcutaneous once every 2 weeks, or placebo (Supplementary Fig. S1A, available at *Rheumatology* online). All patients continued treatment with MTX as concomitant therapy throughout the study. Patients enrolled in RA-BUILD and RA-BEACON were randomized 1:1:1 to receive once-daily doses of placebo, baricitinib 2 mg, or baricitinib 4 mg added to any stable background therapies (Supplementary Fig. S1B, available at *Rheumatology* online). Patients randomized to placebo were switched to baricitinib treatment at week 24 per the study protocols for all three studies. Patients randomized to adalimumab in RA-BEAM were switched to open-label baricitinib 4 mg (+MTX) in the LTE study. Patients randomized to baricitinib 2 mg or 4 mg in RA-BUILD or RA-BEACON continued blinded treatment in RA-BEYOND after 24 weeks.

At week 16 of all originating studies, patients considered to be non-responders from any treatment group were given baricitinib 4 mg as rescue therapy; this treatment continued into the LTE study. Rescue therapy with baricitinib 4 mg was available in RA-BEYOND for all patients with a Clinical Disease Activity Index (CDAI) score over 10 at 3 months or later following the LTE study entry.

All studies informing this analysis were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by each centre's institutional review board or ethics committee. Written informed consent was provided by all patients.

Outcomes

Efficacy was assessed using the proportion of patients who achieved LDA or remission at each time point. Efficacy evaluations were conducted every 3 months (28-day months) from entry to RA-BEYOND (at month 13 of treatment for patients from RA-BEAM and month 6 of treatment for patients from RA-BUILD and RA-BEACON) up to ∼5 years (61 months for patients from RA_BEAM, 54 months for patients from RA-BUILD and RA-BEACON), and every 6 months after year 5. LDA was defined as Simplified Disease Activity Index (SDAI) $\leq$11, DAS28-hsCRP $\leq$3.2 or CDAI $\leq$10. Remission was defined as SDAI $\leq$3.3, DAS28-hsCRP $<$2.6, CDAI $\leq$2.8 or Boolean (2011 ACR-EULAR definition [12]). Physical function was assessed using the proportion of patients who met or exceeded the population normative value of 0.5 based on Health Assessment Questionnaire Disability Index (HAQ-DI). In addition, rates of rescue, discontinuation and reasons were summarized.

Statistical analyses

The analyses of efficacy and physical function were conducted on the modified intention-to-treat population that included all patients who were randomized and received $\geq$1 dose of study drug after randomization in the originating studies.

Two sets of analyses were conducted: modified non-responder imputation (NRI) analysis and completer (as observed) analysis, in line with EULAR recommendations for reporting extension studies [13]. Patients considered non-responders were those who received rescue medication (from the date of rescue onwards),

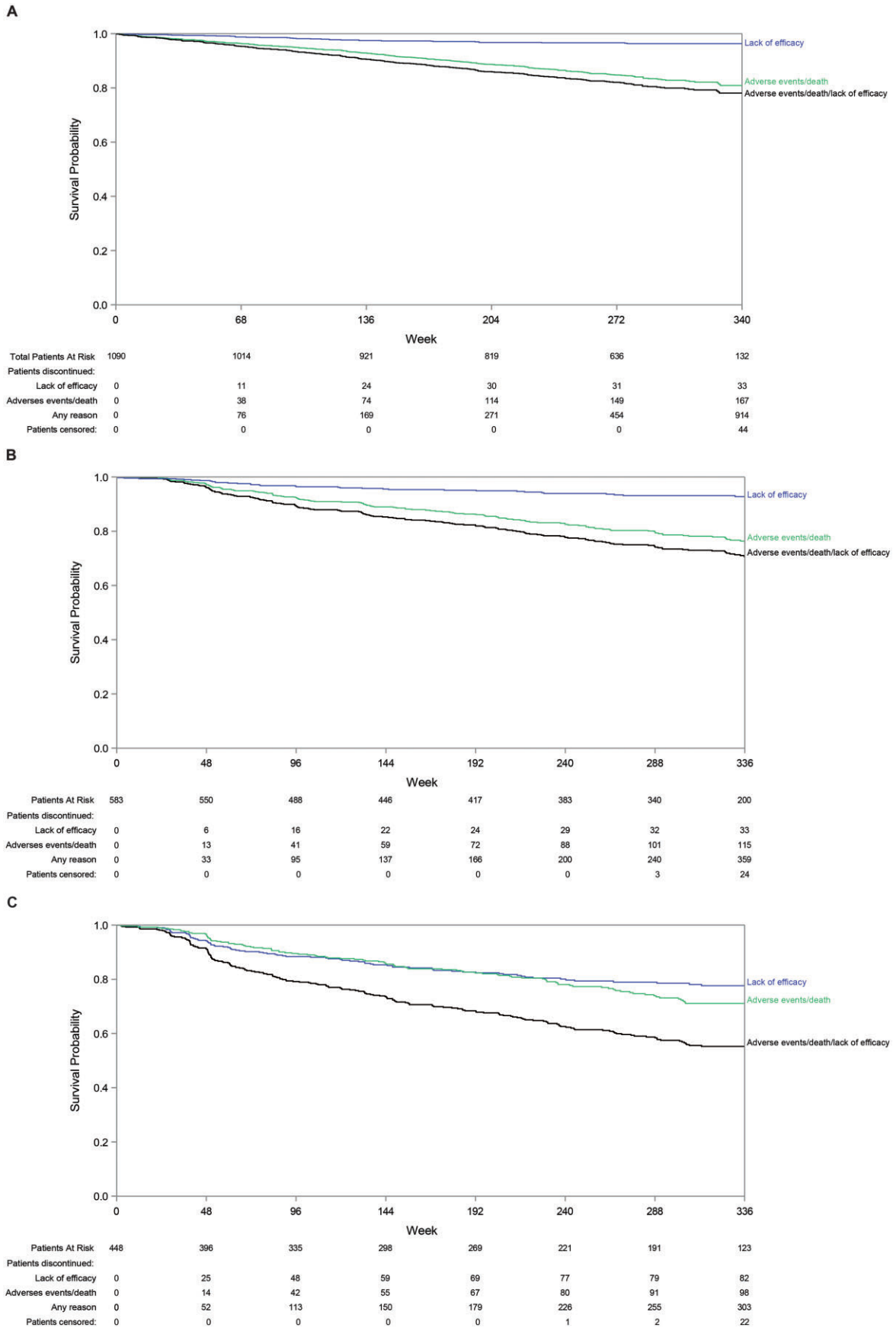
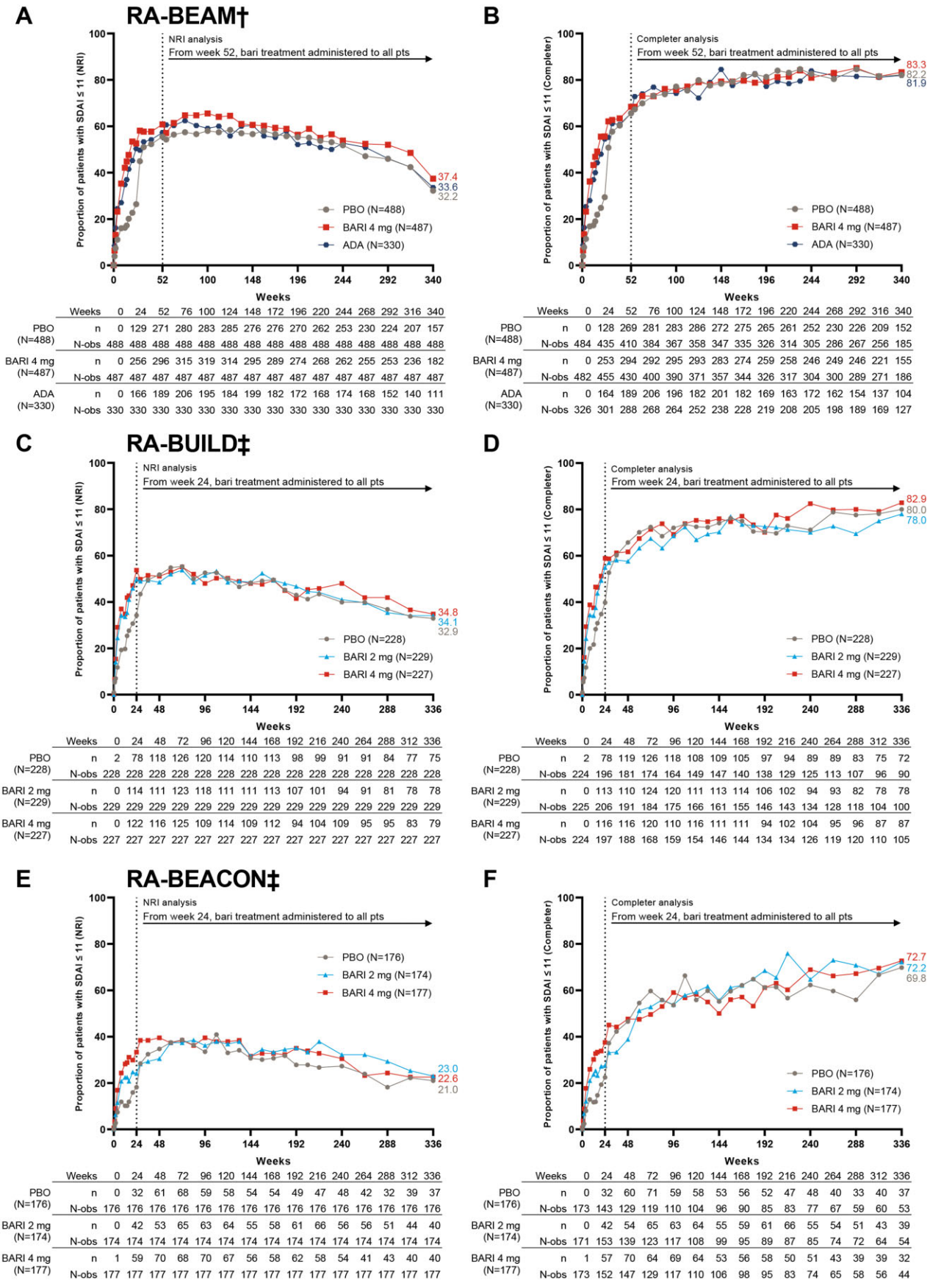


Figure 1. RA-BEYOND discontinuation rates. The discontinuation rates due to reasons of lack of efficacy, adverse event, or death up to 6.5 years for patients who entered the long-term extension study from (**A**) RA-BEAM, (**B**) RA-BUILD, and (**C**) RA-BEACON. Although the full duration of RA-BEYOND was approximately 7 years (388 weeks for RA-BEAM, 360 weeks for RA-BUILD and RA-BEACON), efficacy data are reported up to 6.5 years (340 weeks for RA-BEAM, 336 weeks for RA-BUILD and RA BEACON) due to low patient numbers after these time points. This figure shows discontinuations for the reasons specified for this period of interest only. RA: rheumatoid arthritis



A	Weeks	0	24	52	76	100	124	148	172	196	220	244	268	292	316	340
PBO (N=488)	n	0	129	271	280	283	285	276	276	270	262	253	230	224	207	157
	N-obs	488	488	488	488	488	488	488	488	488	488	488	488	488	488	488
BARI 4 mg (N=487)	n	0	256	296	315	319	314	295	289	274	268	262	255	253	236	182
	N-obs	487	487	487	487	487	487	487	487	487	487	487	487	487	487	487
ADA (N=330)	n	0	166	189	206	195	184	199	182	172	168	174	168	152	140	111
	N-obs	330	330	330	330	330	330	330	330	330	330	330	330	330	330	330

B	Weeks	0	24	52	76	100	124	148	172	196	220	244	268	292	316	340
PBO (N=488)	n	0	128	269	281	283	286	272	275	265	261	252	230	226	209	152
	N-obs	484	435	410	384	367	358	347	335	326	314	305	286	267	256	185
BARI 4 mg (N=487)	n	0	253	294	292	295	293	283	274	259	258	246	249	246	221	155
	N-obs	482	455	430	400	390	371	357	344	326	317	304	300	289	271	186
ADA (N=330)	n	0	164	189	206	196	182	201	182	169	163	172	162	154	137	104
	N-obs	326	301	288	268	264	252	238	228	219	208	205	198	189	169	127

C	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=228)	n	2	78	118	126	120	114	110	113	98	99	91	91	84	77	75
	N-obs	228	228	228	228	228	228	228	228	228	228	228	228	228	228	228
BARI 2 mg (N=229)	n	0	114	111	123	118	111	111	113	107	101	94	91	81	78	78
	N-obs	229	229	229	229	229	229	229	229	229	229	229	229	229	229	229
BARI 4 mg (N=227)	n	0	122	116	125	109	114	109	112	94	104	109	95	95	83	79
	N-obs	227	227	227	227	227	227	227	227	227	227	227	227	227	227	227

D	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=228)	n	2	78	119	126	118	108	109	105	97	94	89	89	83	75	72
	N-obs	224	196	181	174	164	149	147	140	138	129	125	113	107	96	90
BARI 2 mg (N=229)	n	0	113	110	124	120	111	113	114	106	102	94	93	82	78	78
	N-obs	225	206	191	184	175	166	161	155	146	143	134	128	118	104	100
BARI 4 mg (N=227)	n	0	116	116	120	110	116	111	111	94	102	104	95	96	87	87
	N-obs	224	197	188	168	159	154	146	144	134	134	126	119	120	110	105

E	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=176)	n	0	32	61	68	59	58	54	54	49	47	48	42	32	39	37
	N-obs	176	176	176	176	176	176	176	176	176	176	176	176	176	176	176
BARI 2 mg (N=174)	n	0	42	53	65	63	64	55	58	61	66	56	56	51	44	40
	N-obs	174	174	174	174	174	174	174	174	174	174	174	174	174	174	174
BARI 4 mg (N=177)	n	1	59	70	68	70	67	56	58	62	58	54	41	43	40	40
	N-obs	177	177	177	177	177	177	177	177	177	177	177	177	177	177	177

F	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=176)	n	0	32	60	71	59	58	53	56	52	47	48	40	33	40	37
	N-obs	173	143	129	119	110	104	96	90	85	83	77	67	59	60	53
BARI 2 mg (N=174)	n	0	42	54	65	63	64	55	59	61	66	55	54	51	43	39
	N-obs	171	153	139	123	117	108	99	95	89	87	85	74	72	64	54
BARI 4 mg (N=177)	n	1	57	70	64	69	64	53	56	58	50	51	43	39	39	32
	N-obs	173	152	147	129	117	110	106	98	95	83	74	65	58	56	44

Figure 2. Patients who achieved SDAI ≤11 in RA-BEAM, RA-BUILD and RA-BEACON. (**A**) and (**B**): NRI and completer analyses in RA-BEAM and RA-BEYOND. (**C**) and (**D**): NRI and completer analyses in RA-BUILD and RA-BEYOND. (**E**) and (**F**): NRI and completer analyses in RA-BEACON and RA-BEYOND. Rescue treatment was offered at week 16. †At week 24, all patients who received PBO (+MTX) in RA-BEAM were switched to BARI 4 mg

(continued)

those with missing data for a variable at a visit (for that specific visit only) and those who permanently discontinued the study treatment due to adverse event (AE), death or lack of efficacy. For patients who discontinued for other reasons, last observation carried forward was used for missing data after the date of discontinuation. Completer analysis was based on patients who had data available at each time point.

Patients who were rescued or switched to baricitinib 4 mg during any of the three studies were analysed based on the treatment groups to which they were originally randomized; data collected after rescue or switch were analysed as observed.

Results

Patient disposition

Although the full duration of RA-BEYOND was ~7 years (388 weeks for RA-BEAM, 360 weeks for RA-BUILD and RA-BEACON), results here were reported up to 6.5 years (340 weeks for RA-BEAM, 336 weeks for RA-BUILD and RA-BEACON) due to low patient numbers after these time points.

In RA-BEAM, 1305 patients were randomized to placebo (+MTX; $n = 488$), baricitinib 4 mg (+MTX; $n = 487$) and adalimumab (+MTX; $n = 330$; Supplementary Fig. S2, available at *Rheumatology* online). A total of 85% of patients treated with baricitinib 4 mg (+MTX) completed treatment at week 52 and entered RA-BEYOND, along with 82% in the placebo (+MTX) group, who switched to baricitinib 4 mg treatment at week 24, and 85% in the adalimumab (+MTX) group. Through week 340 of treatment, the overall discontinuation rate in patients originating from week 0 of RA-BEAM ($n = 1305$) was 72% ($n = 939$; Supplementary Table S1, available at *Rheumatology* online). The proportion of patients who entered RA-BEYOND from RA-BEAM ($n = 1090$) discontinuing for reasons of lack of efficacy, AE or death up to week 340 is shown in Fig. 1A. By the completion of the study at week 388, 94% ($n = 1027$) of patients had discontinued, and the main reason for discontinuation was sponsor decision ($n = 648$; Supplementary Fig. S2, available at *Rheumatology* online). Across all groups, 15% ($n = 169$) of patients who discontinued from RA-BEYOND were due to AE or death, and 3% ($n = 33$) were due to lack of efficacy.

In RA-BUILD, 684 patients were randomized to placebo ($n = 228$), baricitinib 2 mg ($n = 229$) and baricitinib 4 mg ($n = 227$) (Supplementary Fig. S3, available at *Rheumatology* online). A total of 85% of patients treated with baricitinib 4 mg completed treatment at week 24 and entered RA-BEYOND, along with 86% treated with baricitinib 2 mg and 83% in the placebo group, who switched to baricitinib 4 mg treatment at week 24. Through week 336 of treatment, the overall discontinuation rate in patients originating from week 0 of RA-BUILD ($n = 684$) was 61% ($n = 416$; Supplementary Table S2, available at *Rheumatology* online). The proportion of patients who entered RA-BEYOND from RA-BUILD ($n = 583$) discontinuing for reasons of lack of efficacy, AE or death up to week 340 is shown in Fig. 1A. By the completion of the study at week 360, 70% ($n = 283$) of patients who received baricitinib 4 mg and 73% ($n = 131$) who received baricitinib 2 mg had discontinued (Supplementary Fig. S3, available at *Rheumatology* online). The main reason for discontinuation prior to study completion was sponsor decision (baricitinib 4 mg, $n = 90$; baricitinib 2 mg, $n = 49$). For patients who received baricitinib 4 mg and 2 mg, 20% ($n = 82$) and 19% ($n = 35$) of patients who discontinued from RA-BEYOND, respectively, were due to AE or death, and 6% ($n = 23$) and 6% ($n = 10$), respectively, were due to lack of efficacy (Fig. 1B).

In RA-BEACON, 527 patients were randomized to placebo ($n = 176$), baricitinib 2 mg ($n = 174$) and baricitinib 4 mg ($n = 177$) (Supplementary Fig. S4, available at *Rheumatology* online). A total of 88% of patients treated with baricitinib 4 mg completed treatment at week 24 and entered RA-BEYOND, along with 87% treated with baricitinib 2 mg and 79% in the placebo group, who switched to baricitinib 4 mg treatment at week 24. Through week 336 of treatment, the overall discontinuation rate in patients originating from week 0 of RA-BEACON ($n = 527$) was 67% ($n = 352$; Supplementary Table S3, available at *Rheumatology* online). The proportion of patients who entered RA-BEYOND from RA-BEACON ($n = 448$) discontinuing for reasons of lack of efficacy, AE or death up to week 336 is shown in Fig. 1C. By the completion of the study at week 360, 76% ($n = 250$) of patients who received baricitinib 4 mg and 77% ($n = 90$) who received baricitinib 2 mg had discontinued (Supplementary Fig. S4, available at *Rheumatology* online). For patients who received baricitinib 4 mg and 2 mg, 25% ($n = 82$) and 16% ($n = 19$) of patients who discontinued from RA-BEYOND, respectively, were due to AE or death, and 18% ($n = 58$) and 21% ($n = 24$), respectively, were due to lack of efficacy (Fig. 1C). Sponsor decision accounted for 11% ($n = 38$) and 17% ($n = 20$) of patients who discontinued for baricitinib 4 mg and baricitinib 2 mg, respectively.

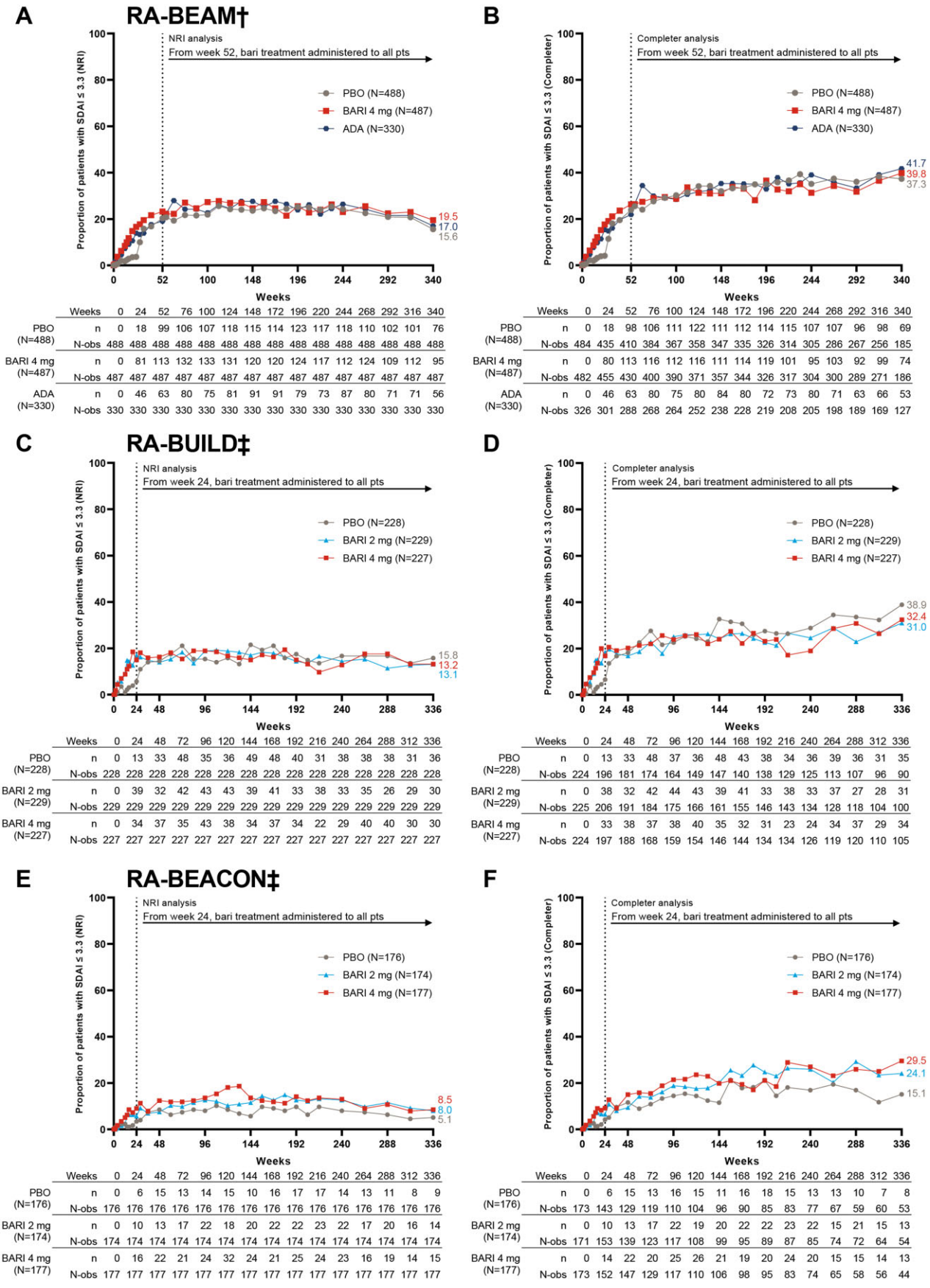
Efficacy

SDAI LDA

Greater proportions of MTX-IR patients from both baricitinib 4 mg (+MTX) and adalimumab (+MTX) treatment groups of RA-BEAM achieved SDAI LDA during the originating study than patients treated with placebo (+MTX) (Fig. 2A and B). At week 340, 37% ($n = 182$), 34% ($n = 111$), and 32% ($n = 157$) of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX), and placebo (+MTX), respectively, achieved SDAI LDA based on the NRI method (Fig. 2A). The responses were maintained from entry to LTE at week 52 through week 244. Using completer analysis, 83% ($n = 155$), 82% ($n = 104$) and 82% ($n = 152$) of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX) and placebo (+MTX), respectively, achieved SDAI LDA (Fig. 2B).

Figure 2. Continued

(+MTX). Upon entering RA-BEYOND at week 52, patients who received ADA (+MTX) in RA-BEAM were switched to BARI 4 mg (+MTX). ‡Upon entering RA-BEYOND at week 24, patients who received PBO in RA-BUILD and RA-BEACON were switched to BARI 4 mg. ADA: adalimumab; BARI: baricitinib; MTX: methotrexate; N: number of patients in the analysis population; n: number of responders; N-obs: number of patients used in the analyses (intention-to-treat population for NRI analysis, observed population for Completer analysis); NRI: non-responder imputation; PBO: placebo; pts: patients; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index



A	Weeks	0	24	52	76	100	124	148	172	196	220	244	268	292	316	340
PBO (N=488)	n	0	18	99	106	107	118	115	114	123	117	118	110	102	101	76
	N-obs	488	488	488	488	488	488	488	488	488	488	488	488	488	488	488
BARI 4 mg (N=487)	n	0	81	113	132	133	131	120	120	124	117	112	124	109	112	95
	N-obs	487	487	487	487	487	487	487	487	487	487	487	487	487	487	487
ADA (N=330)	n	0	46	63	80	75	81	91	91	79	73	87	80	71	71	56
	N-obs	330	330	330	330	330	330	330	330	330	330	330	330	330	330	330

B	Weeks	0	24	52	76	100	124	148	172	196	220	244	268	292	316	340
PBO (N=488)	n	0	18	98	106	111	122	111	112	114	115	107	107	96	98	69
	N-obs	484	435	410	384	367	358	347	335	326	314	305	286	267	256	185
BARI 4 mg (N=487)	n	0	80	113	116	112	116	111	114	119	101	95	103	92	99	74
	N-obs	482	455	430	400	390	371	357	344	326	317	304	300	289	271	186
ADA (N=330)	n	0	46	63	80	75	80	84	80	72	73	80	71	63	66	53
	N-obs	326	301	288	268	264	252	238	228	219	208	205	198	189	169	127

C	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=228)	n	0	13	33	48	35	36	49	48	40	31	38	38	38	31	36
	N-obs	228	228	228	228	228	228	228	228	228	228	228	228	228	228	228
BARI 2 mg (N=229)	n	0	39	32	42	43	43	39	41	33	38	33	35	26	29	30
	N-obs	229	229	229	229	229	229	229	229	229	229	229	229	229	229	229
BARI 4 mg (N=227)	n	0	34	37	35	43	38	34	37	34	22	29	40	40	30	30
	N-obs	227	227	227	227	227	227	227	227	227	227	227	227	227	227	227

D	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=228)	n	0	13	33	48	37	36	48	43	38	34	36	39	36	31	35
	N-obs	224	196	181	174	164	149	147	140	138	129	125	113	107	96	90
BARI 2 mg (N=229)	n	0	38	32	42	44	43	39	41	33	38	33	37	27	28	31
	N-obs	225	206	191	184	175	166	161	155	146	143	134	128	118	104	100
BARI 4 mg (N=227)	n	0	33	38	37	38	40	35	32	31	23	24	34	37	29	34
	N-obs	224	197	188	168	159	154	146	144	134	134	126	119	120	110	105

E	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=176)	n	0	6	15	13	14	15	10	16	17	17	14	13	11	8	9
	N-obs	176	176	176	176	176	176	176	176	176	176	176	176	176	176	176
BARI 2 mg (N=174)	n	0	10	13	17	22	18	20	22	22	23	22	17	20	16	14
	N-obs	174	174	174	174	174	174	174	174	174	174	174	174	174	174	174
BARI 4 mg (N=177)	n	0	16	22	21	24	32	24	21	25	24	23	16	19	14	15
	N-obs	177	177	177	177	177	177	177	177	177	177	177	177	177	177	177

F	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=176)	n	0	6	15	13	16	15	11	16	18	15	13	13	10	7	8
	N-obs	173	143	129	119	110	104	96	90	85	83	77	67	59	60	53
BARI 2 mg (N=174)	n	0	10	13	17	22	19	20	22	22	23	22	15	21	15	13
	N-obs	171	153	139	123	117	108	99	95	89	87	85	74	72	64	54
BARI 4 mg (N=177)	n	0	14	22	20	25	26	21	19	20	24	20	15	15	14	13
	N-obs	173	152	147	129	117	110	106	98	95	83	74	65	58	56	44

Figure 3. Patients who achieved SDAI ≤3.3 in RA-BEAM, RA-BUILD and RA-BEACON. (**A**) and (**B**): NRI and completer analyses in RA-BEAM and RA-BEYOND. (**C**) and (**D**): NRI and completer analyses in RA-BUILD and RA-BEYOND. (**E**) and (**F**): NRI and completer analyses in RA-BEACON and RA-BEYOND. Rescue treatment was offered at week 16. †At week 24, all patients who received PBO (+MTX) in RA-BEAM were switched to BARI 4 mg

(continued)

Greater proportions of csDMARD-IR patients from both baricitinib 4 mg and baricitinib 2 mg treatment groups of RA-BUILD achieved SDAI LDA during the originating study than patients treated with placebo (Fig. 2C and D). At week 336, 35% ($n = 79$), 34% ($n = 78$) and 33% ($n = 75$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved SDAI LDA based on the NRI method (Fig. 2C). The responses were maintained from entry to LTE at week 24 through week 240. Using completer analysis, 83% ($n = 87$), 78% ($n = 78$) and 80% ($n = 72$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved SDAI LDA (Fig. 2D).

Greater proportions of bDMARD-IR patients from both baricitinib 4 mg and baricitinib 2 mg treatment groups of RA-BEACON achieved SDAI LDA during the originating study than patients treated with placebo (Fig. 2E and F). At week 336, 23% ($n = 40$), 23% ($n = 40$) and 21% ($n = 37$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved SDAI LDA based on the NRI method (Fig. 2E). The responses were maintained from entry to LTE at week 24 through week 240. Using completer analysis, 73% ($n = 32$), 72% ($n = 39$) and 70% ($n = 37$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved SDAI LDA (Fig. 2F).

SDAI remission

Greater proportions of MTX-IR patients from both baricitinib 4 mg (+MTX) and adalimumab (+MTX) treatment groups of RA-BEAM achieved SDAI remission during the originating study than patients treated with placebo (+MTX) (Fig. 3A and B). At week 340, 20% ($n = 95$), 17% ($n = 56$) and 16% ($n = 76$) of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX) and placebo (+MTX), respectively, were in SDAI remission based on the NRI method (Fig. 3A). The responses were maintained from entry to LTE at week 52 through to week 316. Using completer analysis, 40% ($n = 74$), 42% ($n = 53$) and 37% ($n = 69$) of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX) and placebo (+MTX), respectively, achieved SDAI remission (Fig. 3B).

Greater proportions of csDMARD-IR patients from both baricitinib 4 mg and baricitinib 2 mg treatment groups of RA-BUILD achieved SDAI remission during the originating study than patients treated with placebo (Fig. 3C and D). At week 336, 13% ($n = 30$), 13% ($n = 30$) and 16% ($n = 36$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, were in SDAI remission based on the NRI method (Fig. 3C). The responses were maintained from entry to LTE at week 24 through week 336. Using completer analysis, 32% ($n = 34$), 31% ($n = 31$) and 39% ($n = 35$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved SDAI remission (Fig. 3D).

Greater proportions of bDMARD-IR patients from both baricitinib 4 mg and baricitinib 2 mg treatment groups of RA-BEACON achieved SDAI remission during the originating study than patients treated with placebo (Fig. 3E and F). At week 336, 9% ($n = 15$), 8% ($n = 14$) and 5% ($n = 9$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, were in SDAI remission based on the NRI method (Fig. 3E). The responses were maintained from entry to LTE at week 24 through week 336. Using completer analysis, 30% ($n = 13$), 24% ($n = 13$) and 15% ($n = 8$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved SDAI remission (Fig. 3F).

Physical function (HAQ-DI)

Greater proportions of MTX-IR patients from both baricitinib 4 mg (+MTX) and adalimumab (+MTX) treatment groups of RA-BEAM achieved HAQ-DI ≤ 0.5 during the originating study than patients treated with placebo (+MTX) (Fig. 4A and B). At week 340, 31% ($n = 153$), 32% ($n = 105$) and 29% ($n = 139$) of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX) and placebo (+MTX), respectively, achieved HAQ-DI ≤ 0.5 based on the NRI method (Fig. 4A). The responses were maintained from entry to LTE at week 52 through to week 244. Using completer analysis, 51% ($n = 95$), 56% ($n = 74$) and 52% ($n = 96$) of patients initially treated with baricitinib 4 mg (+MTX), adalimumab (+MTX) and placebo (+MTX), respectively, achieved HAQ-DI ≤ 0.5 (Fig. 4B).

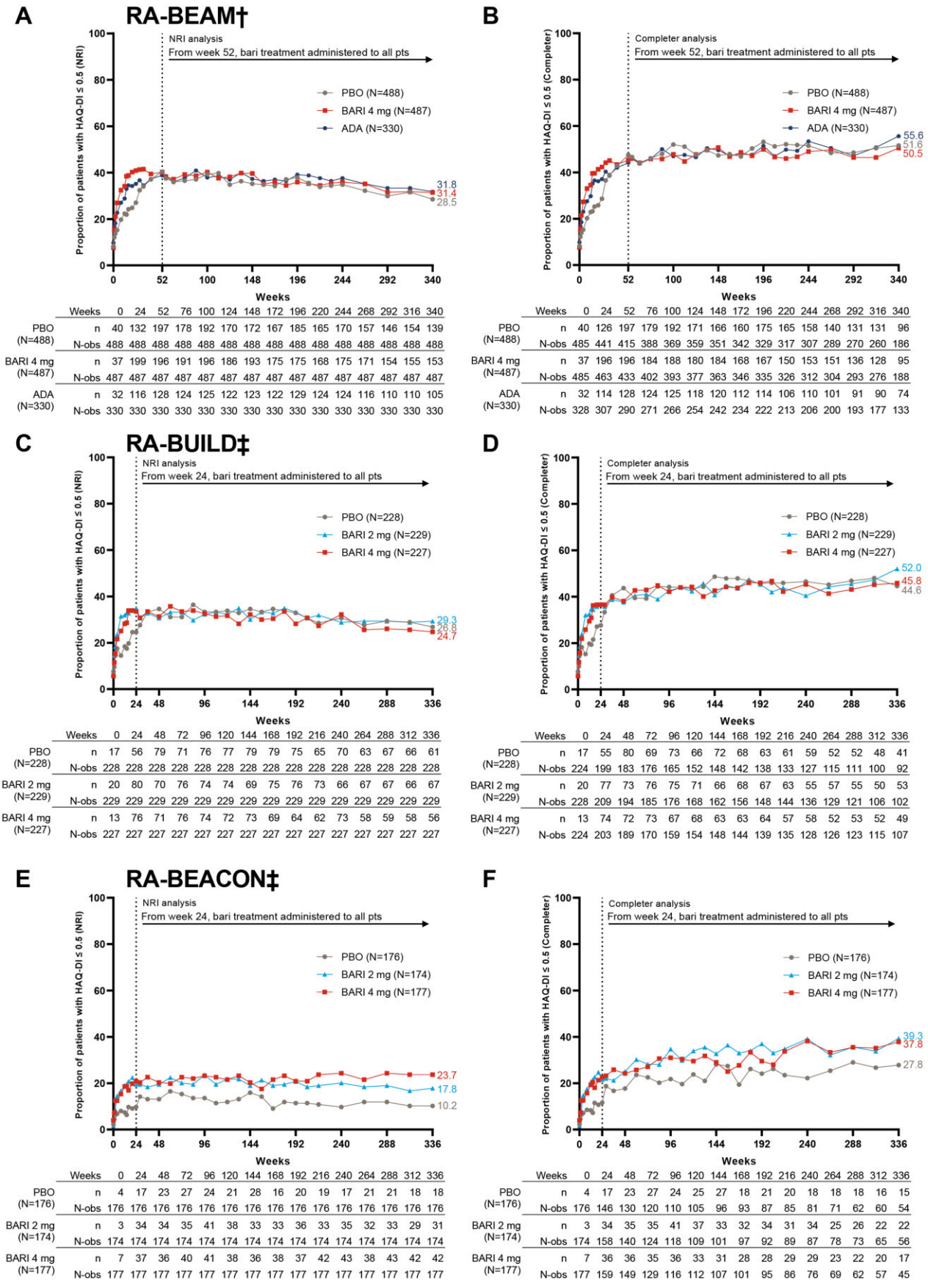
Greater proportions of csDMARD-IR patients from both baricitinib 4 mg and baricitinib 2 mg treatment groups of RA-BUILD achieved HAQ-DI ≤ 0.5 during the originating study than patients treated with placebo (Fig. 4C and D). At week 336, 25% ($n = 56$), 29% ($n = 67$) and 27% ($n = 61$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved HAQ-DI ≤ 0.5 based on the NRI method (Fig. 4C). The responses were maintained from entry to LTE at week 24 through week 336. Using completer analysis, 46% ($n = 49$), 52% ($n = 53$) and 45% ($n = 41$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved HAQ-DI ≤ 0.5 (Fig. 4D).

Greater proportions of bDMARD-IR patients from both baricitinib 4 mg and baricitinib 2 mg treatment groups of RA-BEACON achieved HAQ-DI ≤ 0.5 during the originating study than patients treated with placebo (Fig. 4E and F). At week 336, 24% ($n = 42$), 18% ($n = 31$) and 10% ($n = 18$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved HAQ-DI ≤ 0.5 based on the NRI method (Fig. 4E). The responses were maintained from entry to LTE at week 24 through week 336. Using completer analysis, 38% ($n = 17$), 39% ($n = 22$) and 28% ($n = 15$) of patients initially treated with baricitinib 4 mg, baricitinib 2 mg and placebo, respectively, achieved HAQ-DI ≤ 0.5 (Fig. 4F).

Other outcomes

Similar trends to those observed for SDAI LDA and remission were observed for the proportion of patients achieving CDAI

Figure 3. Continued
(+MTX). Upon entering RA-BEYOND at week 52, patients who received ADA (+MTX) in RA-BEAM were switched to BARI 4 mg (+MTX). ‡Upon entering RA-BEYOND at week 24, patients who received PBO in RA-BUILD and RA-BEACON were switched to BARI 4 mg. ADA: adalimumab; BARI: baricitinib; MTX: methotrexate; N: number of patients in the analysis population; n: number of responders; N-obs: number of patients used in the analyses (intention-to-treat population for NRI analysis, observed population for Completer analysis); NRI: non-responder imputation; PBO: placebo; pts: patients; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index



A	Weeks	0	24	52	76	100	124	148	172	196	220	244	268	292	316	340
PBO (N=488)	n	40	132	197	178	192	170	172	167	185	165	170	157	146	154	139
	N-obs	488	488	488	488	488	488	488	488	488	488	488	488	488	488	488
BARI 4 mg (N=487)	n	37	199	196	191	196	186	193	175	175	168	175	171	154	155	153
	N-obs	487	487	487	487	487	487	487	487	487	487	487	487	487	487	487
ADA (N=330)	n	32	116	128	124	125	122	123	122	129	124	124	116	110	110	105
	N-obs	330	330	330	330	330	330	330	330	330	330	330	330	330	330	330

B	Weeks	0	24	52	76	100	124	148	172	196	220	244	268	292	316	340
PBO (N=488)	n	40	126	197	179	192	171	166	160	175	165	158	140	131	131	96
	N-obs	485	441	415	388	369	359	351	342	329	317	307	289	270	260	186
BARI 4 mg (N=487)	n	37	196	196	184	188	180	184	168	167	150	153	151	136	128	95
	N-obs	485	463	433	402	393	377	363	346	335	326	312	304	293	276	188
ADA (N=330)	n	32	114	128	124	125	118	120	112	114	106	110	101	91	90	74
	N-obs	328	307	290	271	266	254	242	234	222	213	206	200	193	177	133

C	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=228)	n	17	56	79	71	76	77	79	79	75	65	70	63	67	66	61
	N-obs	228	228	228	228	228	228	228	228	228	228	228	228	228	228	228
BARI 2 mg (N=229)	n	20	80	70	76	74	74	69	75	76	73	66	67	67	66	67
	N-obs	229	229	229	229	229	229	229	229	229	229	229	229	229	229	229
BARI 4 mg (N=227)	n	13	76	71	76	74	72	73	69	64	62	73	58	59	58	56
	N-obs	227	227	227	227	227	227	227	227	227	227	227	227	227	227	227

D	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=228)	n	17	55	80	69	73	66	72	68	63	61	59	52	52	48	41
	N-obs	224	199	183	176	165	152	148	142	138	133	127	115	111	100	92
BARI 2 mg (N=229)	n	20	77	73	76	75	71	66	68	67	63	55	57	55	50	53
	N-obs	228	209	194	185	176	168	162	156	148	144	136	129	121	106	102
BARI 4 mg (N=227)	n	13	74	72	73	67	68	63	63	64	57	58	52	53	52	49
	N-obs	224	203	189	170	159	154	148	144	139	135	128	126	123	115	107

E	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=176)	n	4	17	23	27	24	21	28	16	20	19	17	21	21	18	18
	N-obs	176	176	176	176	176	176	176	176	176	176	176	176	176	176	176
BARI 2 mg (N=174)	n	3	34	34	35	41	38	33	33	36	33	35	32	33	29	31
	N-obs	174	174	174	174	174	174	174	174	174	174	174	174	174	174	174
BARI 4 mg (N=177)	n	7	37	36	40	41	38	36	38	37	42	43	38	43	42	42
	N-obs	177	177	177	177	177	177	177	177	177	177	177	177	177	177	177

F	Weeks	0	24	48	72	96	120	144	168	192	216	240	264	288	312	336
PBO (N=176)	n	4	17	23	27	24	25	27	18	21	20	18	18	18	16	15
	N-obs	176	146	130	120	110	105	96	93	87	85	81	71	62	60	54
BARI 2 mg (N=174)	n	3	34	35	35	41	37	33	32	34	31	34	25	26	22	22
	N-obs	174	158	140	124	118	109	101	97	92	89	87	78	73	65	56
BARI 4 mg (N=177)	n	7	36	36	35	36	33	31	28	28	29	29	23	22	20	17
	N-obs	177	159	149	129	116	112	107	101	95	86	76	69	62	57	45

Figure 4. Patients who achieved HAQ-DI ≤0.5 in RA-BEAM, RA-BUILD and RA-BEACON. (**A**) and (**B**): NRI and completer analyses in RA-BEAM and RA-BEYOND. (**C**) and (**D**): NRI and completer analyses in RA-BUILD and RA-BEYOND. (**E**) and (**F**): NRI and completer analyses in RA-BEACON and RA-BEYOND. Rescue treatment was offered at week 16. †At week 24, all patients who received PBO (+MTX) in RA-BEAM were switched to BARI 4 mg

(continued)

LDA, CDAI remission, DAS28-hsCRP LDA, DAS28-hsCRP remission and Boolean remission (Supplementary Figs S5–S9, available at *Rheumatology* online).

Discussion

The final results from the RA-BEYOND LTE study demonstrated the achievement of clinically relevant therapeutic goals following treatment with baricitinib 4 mg or 2 mg, including measures of LDA, remission and normative physical function, which were sustained up to 6.5 years. These results show a relatively stable level of response compared with those previously published for RA-BEYOND, with treatment duration of 148 weeks (RA-BEAM) and 120 weeks (RA-BUILD and RA-BEACON) [10, 11]. In all three originating studies, proportions of patients who achieved measures of LDA and remission tended to decrease throughout RA-BEYOND when analysed using NRI, due to fewer patients with longer follow-up. However, in the completer analyses, these response rates remained consistent throughout the LTE and were consistently higher than those in the NRI analyses. This was expected as patients who discontinued from the study were defined as non-responders in the more conservative method of NRI analysis but excluded from the completer analysis. However, the patients remaining in the study over many years may be due to survivor bias and thus artificially inflate the proportion of responders seen in the completer analyses.

Only 6% of patients originating from RA-BEAM completed RA-BEYOND. However, the largest proportion of patients who discontinued from this study was due to sponsor decision, with fewer than one-fifth of patients discontinuing due to AE, death or lack of efficacy. The majority of the sponsor-decision discontinuations were due to the fulfilment of the study objectives as specified in the protocol (i.e. long-term safety evaluation with treatment period lasting up to 84 months from enrolment and efficacy evaluation of baricitinib) before all enrolled patients had completed the final visit.

As patient numbers decrease over time during LTE studies, the discontinuation rates in RA-BEYOND should be considered alongside any data available from routine care settings. In a European sample of patients with RA in a real-world study, RA-BE-REAL, patients who received baricitinib experienced less discontinuations (38%) over 24 months of treatment in comparison to those treated with tumour necrosis factor inhibitors (59%) or other DMARDs (58–69%) [14]. Discontinuation rates for studies RA-BEAM, RA-BUILD and RA-BEACON were 19%, 23% and 33%, respectively, over 24 months (96 weeks) of treatment beginning from randomization in the originating studies. It is notable that discontinuation rates over a 24-month period in RA-BEYOND were lower than those observed from RA-BE-REAL. The higher discontinuation rate in the whole duration of RA-BEYOND was due to a longer study duration (6.5 years *vs* 24 months) and the sponsor's decision to terminate the study early because the study objectives were fulfilled.

RA is a chronic, progressive disease that can cause structural damage to joints, loss of physical function and disability if adequate disease control is not achieved. Patients with RA also experience extra articular manifestations resulting from chronic systemic inflammation including malignancy [15], infection [16], venous thromboembolism [17, 18], cardiovascular disease [19] and overall early mortality [20], many of which are associated with disease activity. Thus, early, adequate and sustained treatment of RA is vital to control inflammation, thereby preventing joint damage and associated detrimental effect on physical function as well as reducing the risk of associated comorbid conditions.

Clinical practice utilizes a treat-to-target approach, where the goal is to achieve sustained remission or LDA in every patient and the treatment modality is adjusted until the target is reached. The efficacy outcomes measured in RA-BEYOND reflect the EULAR treatment guidelines, which define remission in RA using the ACR-EULAR 2011 remission definition (Boolean or index-based; the design of this study and analyses predated the recent publication of revised Boolean criteria), and LDA can be defined by any validated composite measure that includes joint counts, including SDAI, CDAI and DAS28-hsCRP [3]. In RA-BEYOND, treatment with baricitinib resulted in similar proportions of patients achieving LDA whether measured by SDAI, CDAI or DAS28-hsCRP. For remission, SDAI and CDAI are more stringent measures than DAS28-hsCRP, and the proportions of patients achieving remission by SDAI and CDAI are similar to those achieving Boolean remission using the ACR-EULAR definition. Other LTE studies report similar proportions of remission by completer analysis for outcomes including SDAI and CDAI remission for tofacitinib (up to 8 years) [21] and CDAI and DAS28-hsCRP LDA and remission for upadacitinib (up to 3 years) [22].

An updated assessment of the safety of baricitinib in patients with RA over a median of 4.6 years and up to 9.3 years of treatment was recently reported using pooled data from 3770 patients for a total of 14 744 patient-years of exposure [9]. Incidence rates per 100 patient-years at risk for AEs of special interest such as serious infections, herpes zoster, major adverse cardiovascular events (MACE), deep vein thrombosis, pulmonary embolism and malignancy were similar to those previously reported [23, 24]. Rates of safety events of special interest, including deaths, malignancies, MACE and deep vein thrombosis/pulmonary embolism, remained stable through exposures up to 9.3 years and were generally similar between the 2 mg and 4 mg groups [6].

The study had potential limitations, which should be noted. As in all LTE, only patients completing one of the originating studies were eligible for entry to RA-BEYOND. However, the majority of the patients (82–88%) from the originating studies participated in the LTE. The analyses detailed in this paper were descriptive summaries. Although the originating studies were placebo-controlled, and all patients received background csDMARDs, no comparators were included in the LTE study design, and all patients received baricitinib for the duration of

Figure 4. Continued
(+MTX). Upon entering RA-BEYOND at week 52, patients who received ADA (+MTX) in RA-BEAM were switched to BARI 4 mg (+MTX). ‡Upon entering RA-BEYOND at week 24, patients who received PBO in RA-BUILD and RA-BEACON were switched to BARI 4 mg. ADA: adalimumab; BARI: baricitinib; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; N: number of patients in the analysis population; n: number of responders; N-obs: number of patients used in the analyses (intention-to-treat population for NRI analysis, observed population for Completer analysis); NRI: non-responder imputation; PBO: placebo; pts: patients; RA: rheumatoid arthritis

RA-BEYOND. A large proportion of patients were discontinued before the final study visit when the sponsor ended the LTE due to the fulfilment of the objectives.

In conclusion, these results demonstrated the long-term efficacy of baricitinib 4 mg and 2 mg in patients with RA for up to 6.5 years of treatment. Low rates of discontinuation due to AEs, death and lack of efficacy indicated that baricitinib 4 mg treatment was both efficacious and well tolerated over the long term.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Funding

This work was supported by Eli Lilly and Company, under license from Incyte Corporation.

Disclosure statement: R.C. has received consulting fees and/or honoraria from AbbVie, Celltrion, Eli Lilly and Company, Galapagos, Novartis, Pfizer and UCB. P.C.T. has received grant/research support from Galapagos (made to institution); consulting fees and/or honoraria from AbbVie, Biogen, Eli Lilly and Company, Fresenius Galapagos, Gilead Sciences, GlaxoSmithKline, Janssen, Nordic Pharma, Pfizer Inc and UCB; and participated on a Data Safety Monitoring Board or Advisory Board for Kymab and Immunovant. D.A. has received grant/research support from AbbVie, Amgen, Eli Lilly and Company, Novartis, Roche, SoBi and Sanofi; and consulting fees and/or honoraria from Abbvie, Amgen, Eli Lilly and Company, Janssen, Merck, Novartis, Pfizer, Roche and Sandoz. R.S. has received consulting fees and/or honoraria from AbbVie, BMS, Eli Lilly and Company, Gebro, MSD, Pfizer, Roche and Sanofi; and participated on a Data Safety Monitoring Board or Advisory Board for AbbVie, Eli Lilly and Company, MSD, Pfizer and Sanofi. T.T. has received grant/research support from AbbVie Japan GK, Asahikasei Pharma Corp., Chugai Pharmaceutical Co Ltd, DNA Chip Research Inc., Eisai Co. Ltd, Eli Lilly Japan KK, Mitsubishi-Tanabe Pharma Corp., UCB Japan Co. Ltd; and consulting fees and/or honoraria from AbbVie Japan GK, Astellas Pharma Inc., Ayumi Pharmaceutical Co., Bristol Myers Squibb Co. Ltd, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co. Ltd, Eisai Co. Ltd, Eli Lilly Japan KK, Gilead Sciences Inc., Janssen Pharmaceutical KK, Mitsubishi-Tanabe Pharma Co., Novartis Pharma Co., Pfizer Japan Inc., Sanofi KK, and UCB Japan Co. Ltd. D.M., E.H., N.B. and Y.F. are employees and shareholders of Eli Lilly and Company. L.Z.-P. is a consultant from HaaPACS. M.D. has received grant/research support from AbbVie, Eli Lilly and Company, Merck, Novartis, Pfizer and UCB Pharma; and consulting fees and/or honoraria from AbbVie, Eli Lilly, Merck, Novartis, Pfizer and UCB Pharma.

Acknowledgements

The authors thank the participants, caregivers and investigators. This study was sponsored by Eli Lilly and Company under license from Incyte. Catherine Lynch, PhD, of Eli Lilly and Company provided writing and editorial assistance. The data from this study were presented in part at the EULAR 2022 Congress, 1–4 June, Copenhagen.

References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388:2023–38.
2. Dougados M. Comorbidities in rheumatoid arthritis. Curr Opin Rheumatol 2016;28:282–8.
3. Smolen JS, Landewé RBM, Bergstra SA *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2022;82:107–18.
4. Olumiant [package insert]. Indianapolis, IN: Eli Lilly and Company, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf (24 October 2023, date last accessed).
5. Fleischmann R, Schiff M, van der Heijde D *et al.* Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol 2017;69:506–17.
6. Genovese MC, Kremer J, Zamani O *et al.* Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016;374:1243–52.
7. Dougados M, van der Heijde D, Chen YC *et al.* Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis 2017;76:88–95.
8. Taylor PC, Keystone EC, van der Heijde D *et al.* Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017;376:652–62.
9. Taylor PC, Takeuchi T, Burmester GR *et al.* Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. Ann Rheum Dis 2022;81:335–43.
10. Smolen JS, Xie L, Jia B *et al.* Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study. Rheumatology (Oxford) 2021;60:2256–66.
11. Wells AF, Jia B, Xie L *et al.* Efficacy of long-term treatment with once-daily baricitinib 2 mg in patients with active rheumatoid arthritis: post hoc analysis of two 24-week, phase III, randomized, controlled studies and one long-term extension study. Rheumatol Ther 2021;8:987–1001.
12. David TF, Josef SS, George W *et al.* American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials. Ann Rheum Dis 2011;70:404–13.
13. Buch MH, Silva-Fernandez L, Carmona L *et al.*; European League Against Rheumatism (EULAR). Development of EULAR

recommendations for the reporting of clinical trial extension studies in rheumatology. Ann Rheum Dis 2015;74:963–9.
14. Alten R, Burmester GR, Matucci-Cerinic M *et al.* Comparative effectiveness, time to discontinuation, and patient-reported outcomes with baricitinib in rheumatoid arthritis: 2-year data from the multinational, prospective observational RA-BE-REAL study in European patients. Rheumatol Ther 2023;10:1575–95.
15. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2015;17:212.
16. Mehta B, Pedro S, Ozen G *et al.* Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open 2019;5:e000935.
17. Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. Arthritis Res Ther 2014;16:435.
18. Ogdie A, Kay McGill N, Shin DB *et al.* Risk of venous thromboembolism in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a general population-based cohort study. Eur Heart J 2018;39:3608–14.
19. DeMizio DJ, Geraldino-Pardilla LB. Autoimmunity and inflammation link to cardiovascular disease risk in rheumatoid arthritis. Rheumatol Ther 2020;7:19–33.
20. van den Hoek J, Boshuizen HC, Roorda LD *et al.* Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. Rheumatol Int 2017;37:487–93.
21. Wollenhaupt J, Lee EB, Curtis JR *et al.* Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther 2019;21:89.
22. Fleischmann R, Mysler E, Bessette L *et al.* Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study. RMD Open 2022;8:e002012.
23. Genovese MC, Smolen JS, Takeuchi T *et al.* Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis. Lancet Rheumatol 2020;2:e347–e57.
24. Smolen JS, Genovese MC, Takeuchi T *et al.* Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019;46:7–18.

Consistent safety profile with over 8 years of real-world evidence, across licensed indications[1–3]

Cosentyx® secukinumab

1,000,000 patients treated globally, and counting*[4]

100+ clinical trials*[5]

8+ years of real-world evidence[1–3]

8 indications[1–3]

Click here to visit our HCP portal and learn more

Real-world evidence shows a consistent safety profile over 6 years[6,7]

No trend toward increased AE rates over time (pooled PsA, AS, PsO):†[6]

AEs of select interest (EAIR per 100 PY)	1 year	2 years	3 years	4 years	5 years	6 years	Cumulative rate
Serious infections Cases	2.0 n=149	1.7 n=475	0.7 n=649	1.3 n=1,841	1.3 n=2,285	1.1 n=2,226	1.3 n=8,719
Malignant or unspecified tumours Cases	0.2 n=15	0.2 n=50	0.2 n=225	0.3 n=422	0.3 n=520	0.3 n=573	0.3 n=1,896
MACE Cases	0.2 n=15	0.1 n=39	0.2 n=151	0.2 n=238	0.2 n=264	0.1 n=287	0.2 n=1,031
Total IBD Cases	0.2 n=12	0.2 n=46	0.2 n=185	0.3 n=340	0.2 n=312	0.1 n=261	0.2 n=1,291
Exposure (PY)	7450	28,549	93,744	137,325	182,024	212,636	680,470

No trend towards increased rates of malignancy, MACE or IBD over time[6]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2] Refer to the prescribing information for a summary of adverse events.

Adapted from Novartis Data on File. 2021.[6]

Refer to the Cosentyx Summary of Product Characteristics for full details, dosing and administration, including special populations.

Cosentyx® (secukinumab) licensed indications in rheumatology: Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active **psoriatic arthritis** in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active **ankylosing spondylitis** in adults who have responded inadequately to conventional therapy; active **non-radiographic axial spondyloarthritis** with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active **enthesitis-related arthritis** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active **juvenile psoriatic arthritis** in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[1,2]

Prescribing information, adverse event reporting and full indication can be found on the next page.

*Patients prescribed Cosentyx for any indication since launch.

†Successive time periods of PSUR shown with cumulative rate: 26 Dec 2014 to 25 Dec 2015; 26 Dec 2015 to 25 Dec 2016; 26 Dec 2016 to 25 Dec 2017; 26 Dec 2017 to 25 Dec 2018: 26 Dec 2018 to 25 Dec 2019; 26 Dec 2019 to 25 Dec 2020.[6]

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; EIAR, exposure-adjusted incidence rate; HCP, healthcare professional; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; PsA, psoriatic arthritis; PsO, plaque psoriasis; PY, patient year.

References: 1. Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** European Medicines Agency. European public assessment report. Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed February 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** Novartis. Novartis Cosentyx® positive 16-week PREVENT results advance potential new indication for patients with axial spondyloarthritis. Available at: https://www.novartis.com/news/media-releases/novartis-cosentyx-positive-16-week-prevent-results-advance-potential-new-indication-patients-axial-spondyloarthritis [Accessed February 2024]; **6.** Novartis data on file. Cosentyx Periodic Safety Update Report (PSUR); 26 December 2019 – 25 December 2020. 22 February 2021; **7.** Deodhar A, et al. Arthritis Res Ther 2019;21(1):111.

NOVARTIS

UK | February 2024 | 407722

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 284832 | May 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions*: Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals*: The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 290802 | June 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com