Rheumatol Ther
https://doi.org/10.1007/s40744-026-00845-2

ORIGINAL RESEARCH

Achievement and Maintenance of Remission with Upadacitinib in Patients with Moderate-to-Severe Rheumatoid Arthritis in Italy: 1-Year Data from UPHOLD, a Prospective Real-World Observational Study

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Received: December 16, 2025 / Accepted: March 12, 2026

ABSTRACT

***Introduction*:** Upadacitinib (UPA) is approved for moderate-to-severe rheumatoid arthritis (RA) based on SELECT trials, but data on real-world effectiveness are limited. UPHOLD is a

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-026-00845-2.

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Published online: 12 April 2026

multicountry study of patients with RA receiving UPA 15 mg.

Methods: The present interim analysis was based on the Italian cohort performed across 28 centers. Co-primary endpoints were (i) the proportion of patients receiving UPA who achieved DAS28(CRP) remission (< 2.6) at 6 months and (ii) the proportion of patients achieving DAS28(CRP) remission at 6 months who continued to receive UPA and maintained remission (or had no more than a 0.6-point increase in DAS28[CRP]) at 12 months, analyzed by modified non-responder imputation (mNRI) and as observed (AO). Modified full analysis sets (mFAS1 and mFAS2) included patients completing 6 and 12 months, respectively. Safety analysis included reporting of adverse events and treatment-emergent adverse events (TEAEs), as exposure-adjusted event rates (EAERs; events per 100 patient-years [E/100PY]).

Results: Among 270 patients, 74 (27.4%) discontinued by 12 months because of lack of efficacy (13.7%) or adverse events (8.1%). In mFAS1 (N = 168), 50.6% (mNRI) and 62% (AO) achieved DAS28(CRP) remission at 6 months. In mFAS2 (N = 55), 80% (mNRI) and 91.7% (AO) maintained DAS28(CRP) remission at 12 months. CDAI and SDAI remission rates at 12 months were 31.3%. Patients on UPA monotherapy at 12 months showed remission rates of 49.5% (DAS28[CRP]), 27.2% (CDAI), and 27.4% (SDAI). Significant improvements in patient-reported pain and physical function were also observed. A total of 278 TEAEs were reported (80.8 E/100PY), including herpes zoster, liver disorders, and

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serious infections with EAERs of 2.0, 1.5, and 1.2 E/100PY, respectively.

Conclusion: UPA 15 mg was observed to effectively treat moderate-to-severe RA in the real-world setting, with ≥ 80% maintaining DAS28(CRP) remission at 12 months, showing a favorable benefit–risk profile.

Trial Registration: ClinicalTrials.gov identifier, NCT04497597.

PLAIN LANGUAGE SUMMARY

Rheumatoid arthritis is a chronic autoimmune disease that causes joint pain, swelling, and disability. Although several effective treatments exist, many people with rheumatoid arthritis still struggle to achieve remission and fully control their symptoms. Upadacitinib is a once-daily oral treatment that has shown strong results in clinical trials, but less is known about how well it works in everyday medical practice.

This study followed 270 people with moderate-to-severe rheumatoid arthritis who began treatment with upadacitinib across 28 centers in Italy. Rheumatologists monitored their disease activity, pain, physical function, and any side effects over 12 months. After 6 months of treatment, about half of the patients had achieved remission according to a commonly used disease activity measure (DAS28-CRP). After 1 year, more than 80% of those who reached remission were able to maintain it. Other measures of disease control (CDAI and SDAI) also improved, and many patients reported less pain and better ability to perform daily activities. Upadacitinib was seen to be effective both when used alone and when combined with other standard rheumatoid arthritis medications.

Side effects were generally consistent with what has been seen in clinical trials, with low rates of serious infections, liver issues, or blood clots, and no major cardiovascular events recorded.

Overall, this real-world study shows that upadacitinib is an effective and well-tolerated option for helping people with rheumatoid arthritis achieve and sustain meaningful improvements in symptoms and quality of life.

Keywords: Effectiveness; Safety; Rheumatoid arthritis; Upadacitinib; Real-world

Key Summary Points
Why carry out this study?
Rheumatoid arthritis (RA) is a chronic inflammatory disease with a substantial symptom burden and many patients fail to achieve sustained remission with currently available therapies.
Although upadacitinib (UPA) has demonstrated efficacy in clinical trials, real-world evidence, particularly on remission maintenance and patient-reported outcomes, remains limited.
The study aimed to evaluate the real-world effectiveness, safety, and impact on pain and physical function of UPA 15 mg in Italian patients with moderate-to-severe RA.
What was learned from the study?
After 6 months, approximately half of patients achieved DAS28(CRP) remission, and more than 80% maintained remission at 12 months, alongside significant improvements in pain and disability and a manageable safety profile.
UPA was effective and well tolerated across both biologic-naïve and treatment-experienced patients, with benefits observed even in those previously refractory to advanced therapies.
These findings support UPA as a valuable treatment option in routine clinical practice, reinforcing its role in helping patients achieve and sustain treat-to-target goals in moderate-to-severe RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease primarily affecting the joints, leading to pain, disability, and reduced quality of life (QoL) [1]. RA affects approximately 0.5–1% of individuals in Europe and North America, with higher prevalence in women around 50 years of age [2, 3].

Despite treatment advances, only 20–40% of patients on biologic or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) achieve sustained clinical remission, defined as the long-term absence of disease symptoms, leaving many patients suboptimally managed. A significant proportion of these patients also continue to suffer from residual pain and fatigue [4, 5].

International recommendations suggest a treat-to-target approach, aiming for remission or at least low disease activity (LDA) to prevent long-term damage [6, 7]. A number of Janus kinase (JAK) inhibitors are now approved for the treatment of RA [8]. Treatment with these agents in appropriate patients, as suggested by current recommendations, may enable more patients to achieve disease control targets [1, 8–10].

Upadacitinib (UPA), an oral, selective and reversible JAK inhibitor, represents a major advancement in RA treatment [11]. It inhibits key inflammatory pathways, helping to reduce disease activity and improve outcomes. In the phase 3 SELECT RA trials, 15 mg daily dose of UPA demonstrated efficacy in achieving remission or LDA, both as a monotherapy and in combination with other csDMARDs, in patients with inadequate response (IR) to conventional and advanced treatments [9, 10, 12–17]. UPA once-daily oral dose offers patients an alternative to injectable biologics, providing convenience with its strong efficacy and safety profile [11].

However, data from real-world settings on the UPA maintenance of efficacy as well as the impact on patient-reported QoL measures remain limited. Although randomized controlled trials (RCTs) confirm the effectiveness of UPA, real-world populations may vary, and it is important to assess whether these outcomes are replicable in routine clinical practice [18, 19]. In Italy, four small real-life studies have evaluated the effectiveness and safety of UPA up to 6 months and 2 years [20–23]. In the first study, Baldi et al. confirmed the effectiveness of UPA in 71 patients with RA, showing significant clinimetric (DAS28-CRP, SDAI) and ultrasonographic improvements over 6 months with no significant adverse events (AEs) reported [20]. Lo Gullo et al. demonstrated that in 111 patients with RA treated with UPA significant remission and LDA were achieved at 6 and 12 months. In a third study (the UPARAREMUS study), the efficacy of UPA in achieving both clinical and ultrasonographic remission up to 24 weeks in 60 patients with RA was evaluated [22]. In that longitudinal, multicenter study, 63.6% of patients achieved remission, with bio-naïve status being the most significant predictor. In the fourth study 108 patients treated with UPA showed a 2-year persistence of UPA that was greater than 85% [23].

The present study, part of the larger multicountry UPHOLD study [24], aims to evaluate the effectiveness and safety of UPA in the real-world setting in Italy. This 12-month interim analysis based on 270 patients with RA in Italy evaluated remission rates and long-term disease control with UPA in a real-world setting, providing data to compare its effectiveness and safety with clinical trial outcomes.

METHODS

Patients and Study Design

The UPHOLD study (NCT04497597) is an ongoing non-interventional, prospective, multicountry, open-label multicenter, post-marketing observational cohort study evaluating remission achievement and maintenance with daily dose of 15 mg UPA in patients with moderate-to-severe RA over 12 months.

Interim analyses were conducted at 6 and 12 months, with further follow-up extending to 24 months. This 12-month interim analysis includes data collected from October 16, 2020 to August 10, 2023 (data cutoff), focusing exclusively on the Italian cohort, performed across 28 centers.

Eligible patients were adults (≥18 years) with moderate-to-severe RA, in whom the physician independently chose UPA treatment as per label before study enrolment. UPA was used either with csDMARDs or as monotherapy, alongside other antirheumatic treatments at the physician's discretion. Prior targeted synthetic disease-modifying antirheumatic drug (tsDMARD) and/or biological disease-modifying antirheumatic drug (bDMARD) use was permitted, while patients involved in concurrent clinical trials, previously treated with UPA, or unable to receive UPA were excluded.

Ethical Approval

This study adhered to STROBE guidelines [25] and was conducted according to International Council for Harmonisation standards, local regulations, and the Declaration of Helsinki. All participants provided written informed consent, and the protocol was approved by institutional review boards or ethics committees at each study site (Prof. Carlo Selmi; Ethics Committee, Humanitas; Milan Italy on 30/04/2021; protocol number: CE HUMANITAS ex D.M. 8/2/2013 346/21).

Effectiveness

The co-primary efficacy endpoints included (i) the proportion of patients receiving UPA who achieved DAS28(CRP) remission (<2.6) at 6 months [26]; and (ii) the proportion of patients achieving DAS28(CRP) remission at 6 months who continued to receive UPA and maintained remission (or had no more than a 0.6-point increase in DAS28[CRP]) at 12 months [24]. Therefore, patients were required to remain below the established DAS28(CRP) remission threshold of <2.6; the ≤0.6 margin was permitted only within the remission range. Therefore, a patient with a DAS28(CRP) of 1.8 at 6 months could increase to 2.4 and still be considered in remission, whereas any DAS28(CRP) value ≥2.6 at 12 months was not considered as remission maintenance. Secondary and exploratory endpoints included the proportion of patients achieving DAS28(CRP) ≤3.2 (LDA) at 6 months and maintaining this status (or had no more than a 0.6-point increase in their DAS28[CRP]) at 12 months [27].

Other endpoints evaluated disease activity by visit, using DAS28(CRP), CDAI, and SDAI scores, categorizing patients into remission, LDA, moderate disease activity (MDA), or high disease activity (HDA). The study also assessed the proportion of patients who maintained remission/LDA while remaining on their initial treatment strategy, whether UPA monotherapy or combination with csDMARDs.

Patient-Reported Outcomes

The Health Assessment Disability Index (HAQ-DI) and patient assessment of their pain in the previous 7 days using the visual analogue scale for pain (VAS-pain) were used to assess changes in patient-reported disability and pain at baseline and every 3 months up to 12 months. The HAQ-DI questionnaire covers 20 items in eight domains related to measuring difficulty in performing activities of daily living. Each question is rated on a 0–3 scale, where 0 indicates "without difficulty" and 3 indicates "unable to do" [28, 29]. The VAS is a pain rating scale where a single handwritten mark is placed at one point along the length of a 10-cm line representing "no pain" on the left end (0 cm) of the scale and "worst pain" on the right end of the scale (10 cm) [30].

Safety

All treatment-emergent adverse events (TEAEs) (defined as AEs occurring after the first dose of study drug and within 30 days after the last dose) were recorded up to the cutoff date of August 10, 2023. This included serious TEAEs and selected AEs of special interest, such as herpes zoster, serious infections, hepatic disorders, malignancies, major adverse cardiovascular (CV) events (MACE), and thrombotic events. Clinical significance, determined by the investigator, referred to new, unintended, and unfavorable laboratory abnormalities.

Statistical Analysis

Baseline interim analyses were performed on the enrolled analysis set (EAS), comprising all patients who signed informed consent and met study eligibility criteria. Data are presented as number

(frequency) and relative percentage and 95% confidence intervals (CI) for primary (DAS28-CRP remission at 6 and 12 months and secondary efficacy outcomes; DAS28-CRP LDA at 6 and 12 months). Patient-reported outcome (PRO) measures are presented as mean and standard deviation. Safety and baseline effectiveness were analyzed in the full analysis set (FAS), which included all patients receiving at least one UPA dose. The first co-primary endpoint was assessed using the modified FAS (mFAS1), which consisted of patients in the FAS who completed 6 months of treatment and had DAS28(CRP) data available at that time, or who discontinued prematurely before the 6-month mark. The second co-primary endpoint was evaluated using mFAS2, which included patients within mFAS1 who achieved remission at 6 months, completed 12 months of treatment, and had DAS28(CRP) data available at the 12-month visit, or who discontinued between 6 and 12 months.

Similar mFAS subsets were used for secondary and exploratory analyses, based on timepoints and specific outcomes. For co-primary and selected secondary endpoints, modified non-responder imputation (mNRI) was employed, with discontinuations treated as non-responders. Effectiveness data were also analyzed as observed (AO) without imputing missing data.

Safety assessed for all FAS patients. All AEs were investigator-reported and categorized using Medical Dictionary for Regulatory Activities (MedDRA, version 26.0) terminology. TEAEs were recorded up to August 10, 2023, and expressed as exposure-adjusted event rates (EAERs; events per 100 patient-years [E/100PY]) and exposure-adjusted incidence rates (EAIRs; *n*/100PY). Laboratory parameters were summarized descriptively, with the number of patients showing clinically significant abnormal laboratory results reported.

RESULTS

Patient Baseline Clinical Characteristics

UPHOLD enrolled 270 patients (FAS) with moderate-to-severe RA across 28 Italian centers, with the majority (80.7%; *N* = 218) being female (Table 1). Patients were aged 58.1 ± 10.9 years and mean disease duration was 10.3 ± 9.1 years.

Table 1 Patient baseline clinical characteristics

Clinical characteristic	FAS (*N* = 270)
Age (years)	58.1 ± 10.9
Sex female, *n* (%)	218 (80.7)
RA disease duration (years)	10.3 ± 9.1
Use of the Smolen treat-to-target algorithm, *n* (%)	189 (70.3)
Presence of any CV risk factor, *n* (%)	171 (63.3)
History of hypertension	62 (23.0)
Diabetes mellitus	12 (4.4)
Tobacco/nicotine use	127 (47)
Elevated LDL-C (≥ 130 mg/dL)	16 (5.9)
Lowered HDL-C (40 mg/dL)	4 (1.5)
BMI (kg/m^2)	24.9 ± 4.7
Erosions on X-ray, *n* (%)	112 (41.5)
DAS28-CRP, mean (SD)	4.5 ± 1.2
VAS-pain (past 7 days), 0–10 NRS	6.7 ± 2.3
HAQ-DI	1.3 ± 0.72
Concomitant RA treatment	224 (83)
Corticosteroids	161 (59.6)
Immunosuppressants[a]	131 (48.5)
UPA monotherapy *n* (%)	148 (54.8)
UPA with csDMARDs, *n* (%)	122 (45.2)
ts/bDMARD-naive	105 (38.9)
Prior discontinued therapies, *n* (%)	250 (92.6)
ts/bDMARD-IR	165 (61.1)
tsDMARD-IR	48 (17.8)
TNF-IR only	46 (17.0)

Data are presented as mean ± standard deviation (SD) unless stated otherwise

BMI body mass index, *csDMARD* conventional synthetic disease-modifying antirheumatic drugs, *CV* cardiovascular, *DAS-28* disease activity based on 28 joints, *DMARD* disease-modifying antirheumatic drug, FAS full analysis set, *HAQ-DI* health assessment questionnaire disability index, *IR* inadequate response, *LDL-C* low-density lipoprotein cholesterol, *NRS* numeric rating score, *PGA* patient global assessment using the visual analogue scale (VAS) , *RA* rheumatoid arthritis, *TNF* anti-tumor necrosis factor alpha treatment, *tsbDMARD* targeted synthetic biological dis-

Table 1 continued

ease-modifying antirheumatic drugs, *tsDMARD* targeted synthetic disease-modifying antirheumatic drugs, *UPA* upadacitinib

[a]Include methotrexate, hydroxychloroquine, leflunomide, azathioprine, filgotinib

Of the 270 participants, 74 (27.4%) prematurely discontinued by 12 months; 37 (13.7%) discontinued with a primary reason of lack of efficacy, and 22 (8.1%) as a result of AEs.

Comorbidities were common, with 63.3% of patients having CV risk factors, such as a history of hypertension (23%) and current tobacco/nicotine use (47%). Diabetes mellitus was observed in 4.4% of patients, while other metabolic indicators such as elevated LDL-C and reduced HDL-C were present in 5.9% and 1.5% of patients, respectively. Patients also presented with significant disease activity, pain, and disability as reflected by baseline DAS28(CRP) (4.5 ± 1.2), VAS-pain score of 6.7 ± 2.3, and HAQ-DI of 1.3 ± 0.72. The majority (83%) of patients were receiving concomitant RA medication including corticosteroids (*N* = 161; 59.6%) or immunosuppressants and/or hydroxychloroquine (*N* = 131; 48.5%). The total equivalent dose of prednisone during the first week of the study was 8.7 ± 11.3 mg/day and mean dose over the entire study was 8.0 ± 8.7 mg/day. Just over half (54.8%) of patients were receiving UPA as monotherapy, while 45% received UPA in combination with csDMARDs. The majority of patients (92.9%) took (csDMARDs, tsDMARDs, bDMARDs, and corticosteroids only) prior RA therapies, with 61.1% having received ts/bDMARD and 38.9% were naïve to ts/bDMARDs.

Effectiveness of UPA at 6 and 12 months (Disease Activity Outcomes)

In the mFAS1 cohort (*N* = 168; data up to 6 months), 50.6% (95% CI 43.0–58.2%) of patients achieved DAS28(CRP) (< 2.6) remission at 6 months (mNRI), increasing to 62% (95% CI 53.9–70.2%) when using the AO method. Of 55 patients in mFAS2, 80% (95% CI 69.4–90.6%; mNRI) and 91.7% (95% CI 83.8–99.5%; AO) maintained remission or had no more than a 0.6-point increase in their DAS28-CRP at 12 months (12-month results; Fig. 1a). The achievement and maintenance of DAS28(CRP) LDA (≤ 3.2) followed a similar trend: in the mFAS1 cohort (*N* = 168) LDA was achieved by 61.3% (95% CI 53.9–68.7%) and 75.2% (95% CI 67.9–82.4%) by mNRI and AO approaches at 6 months and was maintained by 77.6% (95% CI 67.6–87.6%) and 92.9% (95% CI 86.1–99.6%) of patients respectively at 12 months (mFAS2 cohort (*N* = 67) (Fig. 1b).

The proportion of patients (AO) who met the criteria for remission according to CDAI (≤ 2.8) increased from 0.4% (1/239) at baseline to 23.1% (34/147) at 6 months and 31.3% (41/131) at 12 months (Fig. 2a). A similar increase was observed for SDAI (≤ 3.3) remission from baseline (0%) to 6 months (24.1%; 32/133) and 31.3% (35/112) at 12 months (Fig. 2b). The proportion of patients achieving LDA (CDAI or SDAI) increased from about 5% at baseline to approximately 40% at 12 months. In contrast, the proportion of patients with HDA (by CDAI or SDAI) decreased from about 50% at baseline to < 5% at 12 months (Fig. 2a, b). A similar decrease was also observed in the proportion of patients with MDA (39–50% at baseline decreasing to approximately 30% at 12 months).

Disease Activity Outcomes by Treatment Strategy (by Analysis Visit)

Stratifying the population by treatment strategy revealed that 49.5% (48/97; 95% CI 39.5–59.4%) of patients receiving UPA monotherapy and 22.9% (16/70; 95% CI 13.0–32.7%) of patients receiving UPA in combination with csDMARDs were in DAS28(CRP) remission at 12 months while remaining on monotherapy and on combination therapy respectively. Corresponding values for CDAI in this group at 12 months were 27.2% (28/103) and 10.7% (8/75), respectively, and for SDAI remission were 27.4% (26/95) and 5.9% (4/68), respectively (Supplementary Table 1).

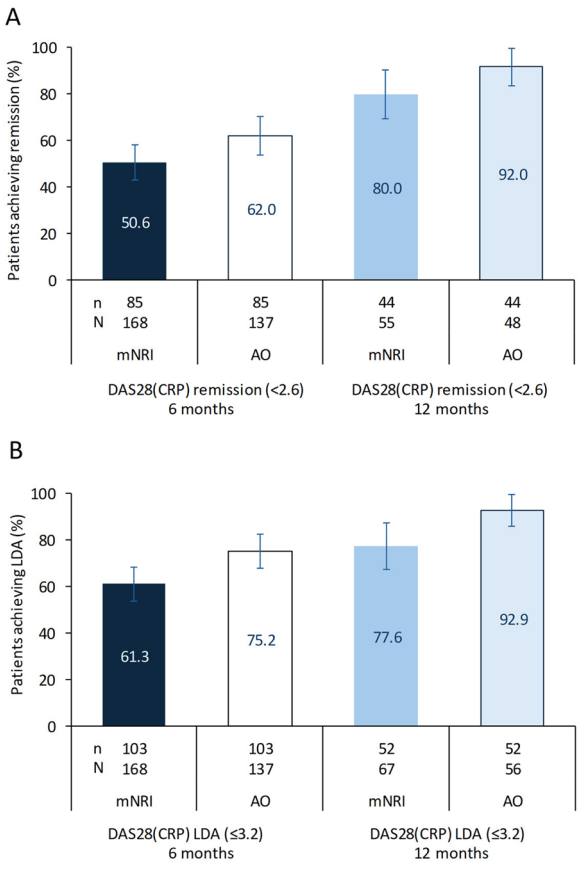

Fig. 1 Achievement and maintenance of DAS28(CRP) remission (< 2.6). **a**, **b** LDA (≤ 3.2) in patients with RA at 6 and 12 months (mNRI and AO). Data are presented percent and 95% confidence intervals. *AO* as observed, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *LDA* low disease activity, *mNRI* modified non-responder imputation, *RA* rheumatoid arthritis. *n* refers to the number of patients who achieved remission or LDA at 6 (mFAS1) or 12 months (mFAS2) whereas *N* refers to the total number of patients who had DAS28 values who were being treated with UPA up to 6 (mFAS1) and 12 months (mFAS2) with non-missing data

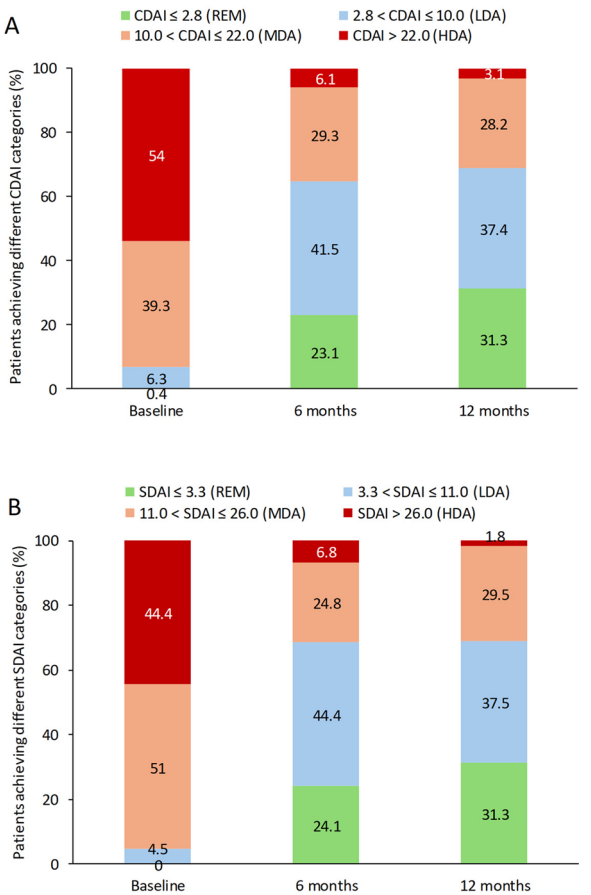

Fig. 2 The proportion of patients with RA achieving target levels of disease activity according to CDAI (**a**) or SDAI (**b**) specific cutoff values/ranges. Data presented as %. *CDAI* clinical disease activity index, *HAD* high disease activity, *LDA* low disease activity, *MDA* moderate disease activity, *REM* remission, *SDAI* simplified disease activity index. The total numbers of patients that CDAI was available for at baseline, 6 months, and 12 months were 239, 147, and 131, respectively. The total numbers of patients that SDAI was available for at baseline, 6 months, and 12 months were 198, 133, and 112, respectively. Analysis based on the FAS population (non-responder imputation)

Disease Activity Outcomes by Prior Treatment Exposure

Subanalysis by prior treatment exposure (ts/bDMARD-naïve, ts/bDMARD-IR, TNFi-IR, and tsDMARD-IR) revealed that 17.2% (5/29) to 67.9% (19/28) of patients reached DAS28(CRP) remission (< 2.6) at 6 months, while 60.0% (3/5) to 80.0% (28/35) sustained remission at 12 months (FAS population; see Supplementary Table 2). A similar trend was observed for the proportion of patients who achieved DAS28(CRP) LDA (≤ 3.2), with 27.6% (8/29) to 75.0% (21/28) of patients achieving LDA at 6 months, and 50.0% (3/6) to 80.0% (20/25) maintaining LDA at 12 months (mNRI). The tsDMARD-experienced subgroup achieved the lowest rates of DAS28(CRP) remission and LDA.

Furthermore, in the treatment exposure subgroups between 10.0% (2/20) and 40.0% (20/50) of patients achieved CDAI (≤2.8) remission and a similar range (0.0%; 0/16 to 37.2%; 16/43) achieved or SDAI (≤3.3) remission at 12 months with the tsDMARD-IR subgroup experiencing the lowest rates of remission (Supplementary Table 2).

Effect of UPA on Patient-Reported Outcomes

Across the entire cohort, improvements in PROs, such as pain and physical function, were observed at both 6 and 12 months. This included significant reductions in VAS for pain (mean decrease from baseline of 3.1 ± 2.8 at 12 months) and improvements in HAQ-DI scores (mean decrease from baseline of 0.5 ± 0.77 at 12 months) (Fig. 3a, b).

Evaluating levels of PGA and HAQ-DI scores by treatment strategy did not reveal marked differences in patients receiving UPA as monotherapy compared to those receiving UPA as combination treatment (Supplementary Table 3). At 12 months, VAS (pain) decreased by 3.7 ± 3.2 in patients receiving UPA monotherapy compared to a decrease of 3.1 ± 2.8 in patients receiving UPA as combination therapy. Similarly, for HAQ-DI, a decrease of 0.6 ± 0.8 was observed at 12 months (compared to baseline) with a similar reduction in those patients receiving UPA combination treatment (0.4 ± 0.7). Apart from the tsDMARD-IR subgroup that generally were observed to experience a lower level of improvement at 12 months compared to the other treatment exposure subgroups, levels of VAS and HAQ-DI scores all improved in the other subgroups of patients by different treatment exposure (Supplementary Table 4).

Safety

The safety profile of UPA was consistent with that observed in clinical trials, with an exposure-adjusted event rate (EAER) of 80.78 (95% CI 71.6–90.9) events per 100 patient-years (PY) (Table 2). Discontinuations due to treatment-emergent adverse events (TEAEs) occurred in 9.9% (95% CI 6.8–13.8) of the cohort. The most frequently reported AEs were herpes zoster at a rate of 2.0 (95% CI 0.8–4.2)/100 PY. Other AEs included hepatic disorders (rate of 1.5; 95% CI 0.47–3.4/100 PY), serious infections (rate of 1.2; 95% CI 0.32–2.98/100 PY).

The number of patients with investigator-determined abnormal laboratory test results was low (three events reporting an increase in blood creatine phosphokinase and one event of a decrease in hemoglobin levels). Importantly, no major adverse CV events (MACE) were reported. The rates of malignancies were 1.2/100 PY (one adenocarcinoma of colon, one colorectal cancer, one renal cancer, and one unspecified event) and thrombotic events were 0.87/100 PY (one pulmonary embolism, one deep vein thrombosis, and one unspecified event) respectively.

DISCUSSION

UPA is gaining significant interest for treating patients with RA in real-life clinical practice, particularly those patients considered difficult to treat [31, 32]. While its efficacy and safety have been demonstrated in RCTs [9, 10, 12–17], real-world data play an essential role in our understanding of its performance in broader, more heterogeneous patient populations.

This 12-month interim analysis of the Italian UPHOLD study confirms the real-world effectiveness and safety of UPA in managing RA. Patients had longstanding disease duration (mean of 10 years) and moderate-to-severe disease activity, with 46% having previously used bDMARDs. In this real-life observational study, UPA was shown to be effective, with 50.6% (mNRI) and 62.0% (AO) achieving DAS28(CRP) remission at 6 months, and 80.0% (mNRI) and 91.7% (AO) maintaining it at 12 months. In addition to objective outcome measures such as DAS28(CRP), CDAI and SDAI, we also collected PROs. In keeping with efficacy results, both pain (VAS) and disability (HAQ-DI) were observed to improve from baseline to 12 months, independent of patients receiving UPA as monotherapy or as combination treatment. These results were also seen for PRO outcome measures. These

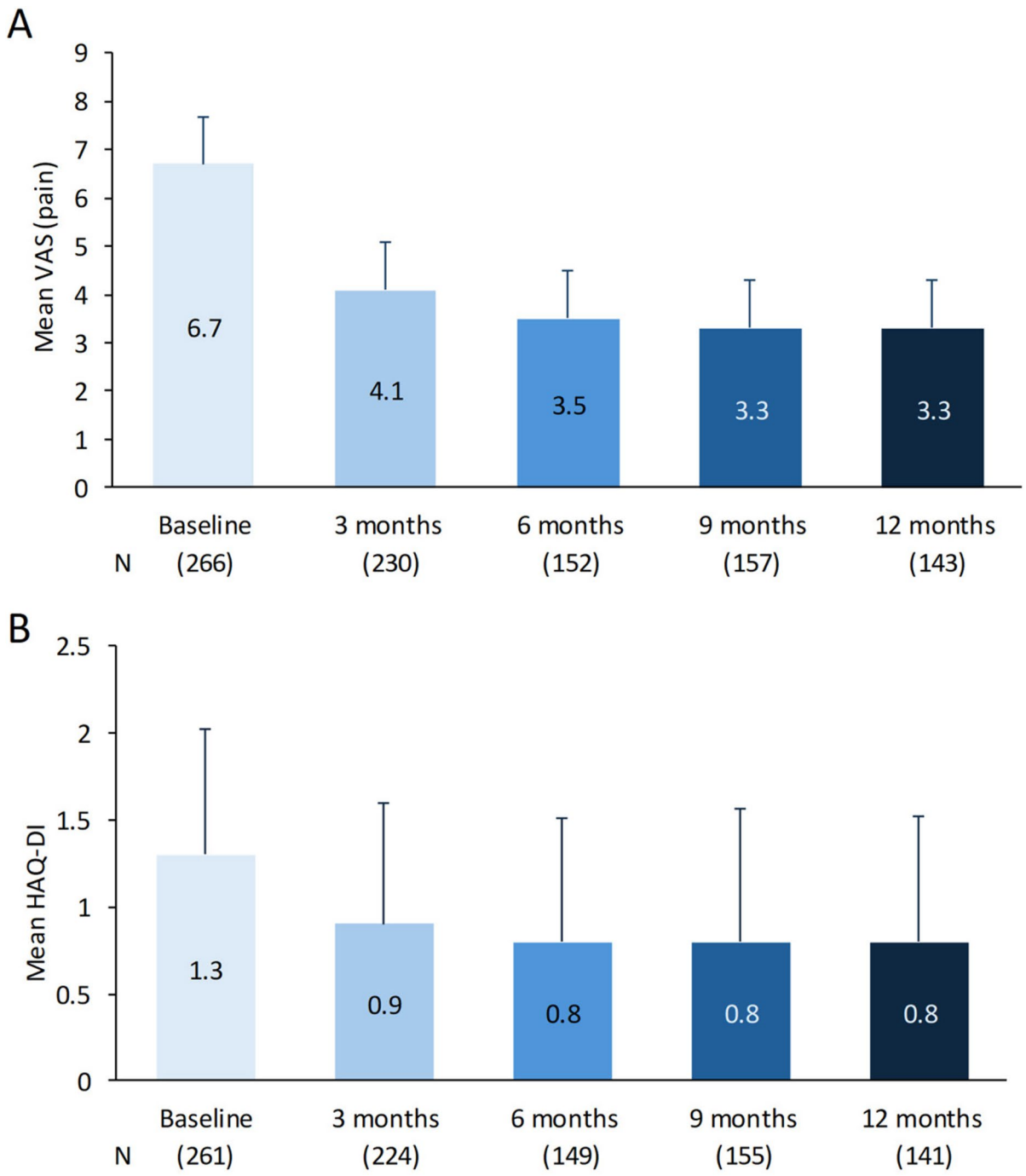

Fig. 3 Mean change in VAS-pain (**a**) and HAQ-DI (**b**) patient-reported outcomes in patients with RA from baseline to 2 months. Data are presented as mean ± SD. Analysis based on the FAS population. The number of patients (*N*) at each visit is shown

findings highlight UPA's effectiveness across varied prior treatments and its potential benefit for patients who are refractory to previous therapies [33–35].

Table 2 Summary of treatment emergent events recorded in the FAS population

Event type	Events (*N*)	EAER (95% CI) per 100 PY
All TEAEs	278	80.8 (71.6–90.9)
Serious TEAEs	17	4.9 (2.9–7.9)
Serious TEAEs related to UPA	7	2.0 (0.8–4.2)
TEAEs related to UPA withdrawal	34	9.9 (6.8–13.8)
Herpes zoster	7	2.0 (0.8–4.2)
Hepatic disorders	5	1.5 (0.47–3.4)
Malignancy	4	1.2 (0.32–2.98)
Malignancy excluding NMSC	4	1.2 (0.32–2.98)
Serious infections	4	1.2 (0.32–2.98)
Thrombotic events	3	0.87 (0.18–2.6)
Opportunistic infection[a]	1	0.29 (0.01–1.6)
TEAEs resulting in death	0	0.0 (0.0–1.1)
MACE	0	0.0 (0.0–1.1)
NMSC	0	0.0 (0.0–1.1)

Data are presented as number of events and EAER per 100 PY. 95% confidence intervals are calculated based on the exact method for the Poisson mean (Garwood, 1936)

EAER exposure-adjusted event rate, *FAS* full analysis set, *MACE* major adverse cardiovascular events, *NMSC* non-melanoma skin cancer, *PY* patient years, *TEAE* treatment-emergent adverse event

[a]Excluding tuberculosis and herpes zoster

Our findings corroborate those from the global UPHOLD study [24] that included 1701 patients (FAS population), although a higher proportion of patients in our cohort achieved the primary outcome (80% (mNRI) and 91.7% (AO) vs. 79.1% (mNRI) and 84.9% (AO) at 12 months for DAS28-CRP remission) and improvement over CDAI (31.3% vs. 28%) and SDAI (31.3% vs. 28.3%) remission at 12 months. This difference (albeit marginal) may be explained by the difference in some features of the patients, namely race (70% white in the global study vs. 100% in the local study, BMI of 26.9 ± 5.5 vs. 24.9 ± 4.7, and higher proportion with previous exposure to bDMARDs (64.3% vs. 46% in the present study) while all other clinical characteristics remained similar.

Although RCTs have demonstrated promising outcomes [9, 10, 12–17], real-world evidence on the use of JAK inhibitors in RA is limited. In Italy, several real-life studies have examined the efficacy and safety different JAK inhibitors in patients with RA. Lo Gullo et al. observed DAS28(CRP) remission rates of 18% at 6 months and 31.5% at 12 months in a cohort largely pretreated with biologics [21]. In the UPHOLD Italian cohort, we observed DAS28 remission rates between 50% and 60% at 6 months and 80–90% at 12 months. LDA was also higher (60–75%) at 6 months increasing to 80–90% at 12 months. While we cannot explain these notable differences, they may be attributed to the high proportion of patients having previously failed biologic treatment and low proportion naïve to biologics and more advanced disease at baseline (DAS28-CRP of 5.0 vs. 4.5 in our study).

Another Italian real-life study demonstrated significant improvements in both clinimetric

and ultrasound scores at 6 months with no AEs being reported [20], while Benucci et al. found UPA effective alongside other JAK inhibitors (tofacitinib, baricitinib, filgotinib), with consistent DAS28 improvements over 12 months and no major differences in AE rates [36]. All four medications showed significant improvement in DAS28 scores starting at the 3-month mark, which was sustained through 12 months ($p=0.0001$), with no notable differences between treatments. AEs included one thrombotic event and a major CV event in patients treated with baricitinib, cases of herpes zoster in those on filgotinib and tofacitinib, while non-melanoma skin cancer accounted for 1% of AEs after UPA treatment.

Another real-world safety study in Italy evaluated the safety of different JAK inhibitors in patients with RA and in the subgroup of patients treated with UPA (follow up of 7 months) an AE rate of 8% was reported, similar to that observed in our cohort (8.1%) [37].

Farina et al. reported results of a study on 365 Italian patients who underwent a total of 463 therapy courses. The average treatment duration was 24 ± 17 months [23]. At 24 months, the overall drug retention rate (DRR) was 86%, with no significant differences observed among the various JAK inhibitors. The only baseline predictor of treatment discontinuation was prior use of a bDMARD (hazard ratio 1.65, 95% CI 1.08–2.53; $p=0.021$). Significant reductions in DAS28-CRP and CDAI were observed 1 year after treatment initiation [23].

The UPARAREMUS study assessed 66 patients with RA and reported that 63.6% achieved clinical and ultrasonographic remission by 24 weeks, aligning closely with our findings [22]. Safety outcomes were also consistent, with few non-serious AEs and an 8% dropout rate.

Although patients previously exposed to tsDMARDs showed slightly lower response rates, more than 50% still reached remission or LDA at 12 months. Overall, many patients can achieve and maintain remission with UPA despite varied prior biologic use. Caporali et al. compared switching from a TNF inhibitor to UPA vs. switching to another TNF inhibitor or a different mechanism [31]. Among 503 patients, UPA treatment led to higher remission (67.7% vs. 40.3%), no pain (55.7% vs. 25.4%), and improved adherence (60.0% vs. 34.2%) compared to those cycling TNF inhibitors or switching to another mechanism of action. These results suggest UPA is particularly effective for patients failing or intolerant to anti-TNF therapy, consistent with Australian data [38].

In our cohort, 54.8% of patients received UPA as monotherapy. JAK inhibitors are recognized to be effective when administered as monotherapy [39]. The European Alliance of Associations for Rheumatology (EULAR) recommends that in patients who cannot use csDMARDs as comedication, interleukin (IL)-6 pathway inhibitors and tsDMARDs may afford some advantage compared with other bDMARDs [6]. The UPHOLD global study showed greater remission rates in patients receiving UPA as monotherapy, albeit to a lesser extent (41.2% vs. 37.5% for mono- and combination therapy respectively) [24]. Although remission rates In the local study were generally the same with monotherapy and combination therapy (although slightly favoring monotherapy) up to 6 months, larger differences (favoring monotherapy) were evident at 12 months (DAS28-CRP remission of 49.5% for monotherapy vs. 22.9% for combination treatment). The larger sample size in the UPHOLD global study and differences in aforementioned clinical features, disease characteristics, and clinical management of these patients may account for these variations [24].

However, the higher remission rates observed with UPA monotherapy at 12 months should be interpreted cautiously. In the global UPHOLD cohort [24], remission and low disease activity rates at 12 months were similar between monotherapy and combination therapy. This suggests that the present findings may be influenced by patient selection, baseline characteristics, or treatment tolerability rather than a true benefit from monotherapy. In addition, treatment allocation was not randomized and patient numbers were limited, restricting adjustment for confounding factors. As such, these results are only descriptive in nature and do not support definitive conclusions regarding the comparative effectiveness of UPA as monotherapy vs. combination therapy.

These findings are in line with results from the SELECT phase 3 clinical trial program, in which UPA achieved the primary endpoints for efficacy in different RA populations (e.g., MTX-naïve, csDMARD- and bDMARD-refractory), and achieved high remission/LDA rates regardless of the applied criteria (e.g., DAS28[CRP], CDAI, SDAI, or Boolean criteria) or therapy strategy (in combination with MTX or other csDMARDs, or as monotherapy) [11, 40]. However, in general, these results are consistent with previous findings on the real-world effectiveness of UPA [32, 38, 41, 42] and were also confirmed recently by Baldi et al. [43]. In this multicenter prospective observational study, UPA was used as monotherapy in 128 (59.5%) subjects, and 178 (82.8%) patients had previously been treated with other biologic agents. UPA demonstrated rapid and sustained effectiveness over 24 months in the treatment of RA in a real-world setting, with a manageable safety profile and an excellent retention rate of 80% (95% CI 75.0–86.0%) at 24 months [43]. The findings from this study could help tailor therapeutic strategies and improve patient monitoring, particularly for patients with multi-refractory RA and when monotherapy is preferred.

In our Italian UPHOLD cohort, a total of 74 (27.4%) patients prematurely discontinued the study; 37 (13.7%) discontinued with a primary reason of lack of efficacy, and 22 (8.1%) with a primary reason of AEs. Similar results were observed for the UPHOLD global study [24] in which 23.3% prematurely discontinued; 9.9% discontinued because of lack of efficacy, 6.6% as a result of AEs. The overall safety profile was consistent with previous reports; malignancies and thrombotic events were also observed and should be interpreted with caution with rates of 1.2/100 PY and 0.87/100 PY, respectively. The small number of patients contributing to remission-maintenance analyses limits the ability to draw firm conclusions with regard to the incidence of infrequent but clinically relevant AEs. Larger studies with longer follow-up are therefore required.

The rate of TEAEs leading to discontinuation (most frequent being herpes zoster, 2.0/100 PY; hepatic disorders, 1.5/100 PY; and serious infection, 1.2/100 PY) in this study aligns with recent real-world data on UPA [32, 44]. Although higher than phase 3 trial data (9.9% vs. 4.9%), the real-world setting and overlap with the recent COVID-19 pandemic likely contributed. The COVID-19 pandemic may have contributed to higher TEAEs as patients and rheumatologists may have been more cautious about continuing therapy in the setting of infections or concerns about immunosuppression. In addition, disruptions to routine care, such as reduced in-person visits and laboratory monitoring, as well as COVID-19 or suspected infections, may have influenced treatment discontinuation [45].

Discontinuation rates for other JAK inhibitors, such as tofacitinib, are generally less than 10% [46], except for one study showing a 25% rate [47]. Patients with RA face increased CV and venous thromboembolism risks, yet recent real-world safety data suggest JAK inhibitors, including UPA, carry acceptable risks without major differences between JAK inhibitors or bDMARDs [48, 49]. Since JAK inhibitors have proven to effectively suppress inflammatory conditions, including rheumatological conditions, a thorough risk evaluation should consider personal risk factors alongside the benefits of lowered RA disease activity [50].

Study Limitations

Several limitations need to be considered. First, our analysis was descriptive and comparisons between subgroups was not performed because of the small sample size and unequal distribution of patients in some subgroups. In particular, subgroup analyses, including monotherapy versus combination therapy, were strictly descriptive and not intended to support any comparison among subgroups. Second, the follow-up period of 12 months may not fully capture the long-term safety and efficacy of UPA. Third, remission maintenance at 12 months was evaluated in a selected subgroup of early responders who remained on treatment, limiting the generalizability to the broader treated population. Fourth, maintenance of remission at 12 months was defined as continued DAS28(CRP) remission, i.e., a DAS28(CRP) value remaining <2.6 at 12 months, with the additional requirement that

the increase from the 6-month value did not exceed +0.6 points. The ≤0.6 threshold accounts for expected variability in DAS28(CRP) over time and was used to assess stability of disease control rather than point-in-time remission, as in the global UPHOLD study [24]. Finally, reliance on PROs introduces potential subjectivity. Although PROs such as pain VAS and HAQ-DI are critical for assessing QoL, they can be influenced by psychological and social factors unrelated to RA disease activity. Combining PROs with imaging or biomarker data in future analyses would offer a more comprehensive evaluation.

CONCLUSIONS

This 12-month interim analysis of the UPHOLD Italian study demonstrates that UPA 15 mg can be considered as an effective therapeutic option in achieving and maintaining stringent disease control targets in patients with moderate-to-severe RA in real-world clinical practice. Approximately half of patients achieved remission with more than 50% of patients achieving LDA at 6 months, and more than 80% maintaining treatment response through 12 months. Significant improvements in disease activity, PROs, and QoL were observed, establishing UPA as a leading option for bDMARD-naïve patients with RA. While infection and CV risk have been noted with JAK inhibitors, they highlight the value of careful patient selection. Ongoing longer-term studies will help provide further evidence on the overall benefit–risk profile of UPA.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Medical Writing/Editorial Assistance. The authors wish to thank Colin Gerard Egan, PhD (CE Medical Writing SrLs, Pisa, Italy) for providing assistance in the preparation of this manuscript (funded by AbbVie SrL).

Author Contribution. All authors (Caterina Baldi, Eleonora Celletti, Serena Bugatti, Marcello Govoni, Massimiliano Cazzato, Andrea Picchianti Diamanti, Marco Fornaro, Giuliana Guggino, Luca Navarini, Maria Antonietta D'Agostino, Luca Quartuccio, Francesco Ciccia, Lorenzo Dagna, Paolo Stobbione, Massimo Triggiani, Ombretta Viapiana, Annarita Giardina, Gianluca Moroncini, Roberto Caporali, Chiara Bazzani, Enrico Tirri, Claudia Lomater, Sara Di Fino, Francesca Morello and Carlo Selmi) contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, investigation, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Caterina Baldi confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (e.g., not under consideration by another journal), the integrity of the data presented, and statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

Funding. AbbVie SrL sponsored the study and provided funding for editorial assistance and the Rapid Service Fee. AbbVie SrL contributed to the design; participated in data collection, analysis, and interpretation of the data, in writing, reviewing and approval of the publication. No honoraria or payments were made for this publication.

Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Sara Di Fino and Francesca Morello are AbbVie employees and may own AbbVie stocks/options. Caterina Baldi declares having collaborated with AbbVie and Lilly. Serena Bugatti received speaking fees from AbbVie, Alfasigma, Fresenius Kabi, Lilly, Novartis, UCB. Marcello Govoni received speaking fees from AbbVie, Eli Lilly, Alfasigma, GSK, Pfizer, AstraZeneca and research grant from Eli Lilly and AbbVie. Massimiliano Cazzato

declares having collaborated with the following companies: AbbVie, Lilly and UCB. Andrea Picchianti Diamanti received speaking fees from AbbVie, Johnson & Johnson, AstraZeneca, GSK, Novartis, UCB and research grants from AbbVie and Pfizer. Marco Fornaro received speaking fees from AbbVie, GSK, Lilly and Boehringer Ingelheim. Giuliana Guggino received speaking fees from AbbVie, Alfasigma, Lilly, Novartis, UCB, GSK. Luca Navarini received speaking fees from AbbVie, Janssen, Novartis, Celgene, BMS, Galapagos, Italfarmaco, Eli Lilly, Roche, UCB. Maria Antonietta D'Agostino received speaking fees from AbbVie, Alfasigma, Amgen, AstraZeneca, BMS, Eli Lilly, GSK, J&J, MSD, Novartis, Pfizer, UCB; consultancies with Eli Lilly, J&J, MSD, Novartis, UCB. Grants: Pfizer, Novartis, AbbVie, AstraZeneca, UCB, Alfasigma. Luca Quartuccio received speaking fees from AbbVie, Johnson & Johnson, AstraZeneca, GSK, CSL Vifor, and research grant from Roche, AbbVie, Pfizer. Francesco Ciccia received speaking fees from AbbVie, Alfasigma, Amgen, AstraZeneca, BMS, Eli Lilly, GSK, J&J, Novartis, Otsuka, Pfizer, UCB; consultancies with Eli Lilly, J&J, Novartis, UCB. Grants: Pfizer, Novartis. Lorenzo Dagna: received consultation honoraria from AbbVie, Alfasigma, Amgen, AstraZeneca, Biogen, Eli Lilly, Galapagos, GSK, Johnson & Johnson, Kiniksa Pharmaceuticals, Merck Sharp & Dohme, Novartis, Sanofi, SOBI, UCB and Vifor. Ombretta Viapiana received speaker and consultant fees from Eli Lilly, AbbVie, Angelini, Grunenthal, Amgen, UCB, Fresenius Kabi. Gianluca Moroncini received research grants from AbbVie. Roberto Felice Caporali received speaker honoraria from AbbVie, Lilly, Alfasigma, Pfizer, Novartis, UCB, J&J. Chiara Bazzani received speaking fees from AbbVie, Novartis, UCB. Claudia Lomater: declares no conflicts of interest. Carlo Selmi: Consulting/speakers fee (AbbVie, Amgen, Alfasigma, Biogen, Eli-Lilly, Recordati Rare Diseases, Johnson & Johnson, Novartis, Octapharma, Pfizer, Recordati Rare Disease, SOBI, UCB); Research support (AbbVie, Amgen, Johnson and Johnson, Novartis, Pfizer) Paolo Stobbione, Eleonora Celletti, Massimo Triggiani, Annarita Giardina, Enrico Tirri declare that they have no conflicts of interest.

Ethical Approval. This study adhered to STROBE guidelines [25] and was conducted according to International Council for Harmonisation standards, local regulations, and the Declaration of Helsinki. All participants provided written informed consent, and the protocol was approved by institutional review boards or ethics committees at each study site (Prof. Carlo Selmi; Ethics Committee, Humanitas; Milan Italy on 30/04/2021; protocol number: CE HUMANITAS ex D.M. 8/2/2013 346/21).

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