

## Basic science

# Treatment response in rheumatoid arthritis is predicted by the microbiome: a large observational study in UK DMARD-naïve patients

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## Abstract

**Objectives:** Disease-modifying antirheumatic drugs (DMARDs) are a first-line treatment in rheumatoid arthritis (RA). Treatment response to DMARDs is patient-specific, dose efficacy is difficult to predict and long-term results are variable. The gut microbiota are known to play a pivotal role in prodromal and early-disease RA, manifested by *Prevotella* spp. enrichment. The clinical response to therapy may be mediated by microbiota, and large-scale studies assessing the microbiome are few. This study assessed whether microbiome signals were associated with, and predictive of, patient response to DMARD treatment. Accurate early identification of those who will respond poorly to DMARD therapy would allow selection of alternative treatment (e.g. biologic therapy) and potentially improve patient outcome.

**Methods:** A multicentre, longitudinal, observational study of stool- and saliva microbiome was performed in DMARD-naïve, newly diagnosed RA patients during introduction of DMARD treatment. Clinical data and samples were collected at baseline ( $n = 144$ ) in DMARD-naïve patients and at six weeks ( $n = 117$ ) and 12 weeks ( $n = 95$ ) into DMARD therapy. Samples collected ( $n = 365$  stool,  $n = 365$  saliva) underwent shotgun sequencing. Disease activity measures were collected at each timepoint and minimal clinically important improvement determined.

**Results:** In total, 26 stool microbes were found to decrease in those manifesting a minimal clinically important improvement. *Prevotella* spp. and *Streptococcus* spp. were the predominant taxa to decline following six weeks and 12 weeks of DMARDs, respectively. Furthermore, baseline microbiota of DMARD-naïve patients were indicative of future response.

**Conclusion:** DMARDs appear to restore a perturbed microbiome to a eubiotic state. Moreover, microbiome status can be used to predict likelihood of patient response to DMARD.

**Keywords:** gut microbiome, rheumatoid arthritis, disease-modifying antirheumatic drugs, shotgun metagenomic sequencing, minimal clinically important improvement.

### Rheumatology key messages

- RA microbiota differentiates response to DMARDs.
- *Prevotella* spp. reduced in responders following six weeks treatment.
- *Streptococcus* spp. reduced in responders following 12 weeks.
- DMARDs appear to restore a perturbed microbiome to a more eubiotic state.

## Introduction

Rheumatoid arthritis (RA) is an autoimmune, multi-system inflammatory disorder usually treated with disease-modifying antirheumatic drugs (DMARDs) and biologic therapy. Known to be substantially heritable [1], aetiology is a complex interaction of genetic and environmental triggers, not wholly defined. The autoimmune pathogenesis of RA takes place over many years prior to symptom onset [2]. The importance of the microbiota in the development and maintenance immune system function is well recognised [3]. Aberrant immune responsiveness may result from an abnormal microbiome and there is intense research activity to determine whether gut and oral microbes play a role in RA pathogenesis [4].

We previously used an RA polygenic risk score (PRS) in non-affected individuals to show host genetic makeup associates with enrichment for *Prevotella* spp. in the stool of TwinsUK participants who had higher PRS for RA [5]. PRS minimizes confounding by RA and treatment in association studies. Other groups have shown RA patients manifest high levels of *Prevotella copri* (*P. copri*) in stool early in symptom onset [6, 7]. Furthermore, serum anti-*P. copri* antibodies and *P. copri*-derived proteins were detectable in joint synovial fluid of RA patients [8].

DMARDs are currently the first choice of treatment for patients diagnosed with RA in the UK [9]. In some patients, disease activity is reduced, joint damage viewed radiographically is slowed, and remission may be achieved [10]. Methotrexate is the most prescribed DMARD; it inhibits multiple inflammatory pathways that are active in RA [9]. Orally administered methotrexate is metabolised by the gut microbiome and individuals' variability of microbiome abundance and diversity likely contributes to differences in medication efficacy [9]. Treatment strategies in RA currently involve introducing DMARDs at a low dose with escalation over months. Methotrexate monotherapy results in less than half of patients responding well to their prescription [11]. In patients non-responsive to first-line therapy, the iterative process of drug assaying means time is lost taking DMARD medication to which some patients never respond well, irrespective of dose. As early and aggressive therapy (i.e. treat-to-target) improves long-term outcomes, advances in patient stratification towards therapies from which they will benefit are welcome.

Predicting patient response to DMARD therapy via the microbiome would be invaluable for prognosis. Three metagenome studies have reported microbiota predicted DMARD response [12–14], although further validation is required before clinical application. In the present study, we sought to determine whether the microbiome (oral and gut) before treatment in RA predicted response to DMARDs. In this longitudinal, observational, multicentre study we recruited newly diagnosed RA patients and obtained oral and gut samples at DMARD-naïve baseline and at follow-up six weeks and 12 weeks later. We examined metagenomes to determine whether microbiome composition and functionality of DMARD-naïve patients early during RA were predictive of responses to treatment. Furthermore, we compared the microbiota composition of newly diagnosed RA patients with long-term DMARD-treated RA participants from the Norfolk Arthritis Register (NOAR).

## Materials and methods

### Study design and participants

The Influence of Methotrexate on the Rheumatoid Arthritis Microbiome (IMRABIOME) study is a longitudinal, observational study of microbiota observed in DMARD-naïve newly diagnosed RA patients who had inflammatory arthritis symptoms for <12 months and fulfilled the 2010 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for RA [15]. Recruitment was undertaken between April 2017 and July 2019 from 12 outpatient rheumatology clinics in England, UK. All participants were DMARD-naïve at recruitment but due to commence DMARD treatment, prescribed by their consultant rheumatologist in accordance with UK standard treatment and National Institute for Health and Care Excellence (NICE) guidelines. Inclusion criteria comprised: age of 18 or over, with new-onset RA and having received rheumatologist advice to commence DMARD therapy. All interventions and medications were recorded in the study database including corticosteroid treatment (prednisolone <20 mg per day) and non-steroidal anti-inflammatory drugs (NSAIDs). Concurrent non-rheumatic disorders and their treatment were recorded. Exclusion criteria included previous exposure to DMARD or biologic therapy; corticosteroid treatment equivalent to prednisolone  $\geq 20$  mg/day, significant comorbidities (e.g. severe congestive heart failure; renal, hepatic or malignant disease); pregnancy; and enrolment in a clinical trial.

DMARD-naïve participants were assessed at baseline and at six and 12 weeks after commencing DMARD therapy. Intestinal (stool) and saliva samples clinical markers and relevant clinical, demographic and lifestyle information were collected. Participants completed a variety of health, well-being and activities of daily functioning questionnaires. Written informed consent was obtained from all participants and the Declaration of Helsinki (1996) was followed. Study approval was granted by the Health Research Authority (HRA) Research Ethics Committee (REC) IRAS, project 212604. Sample collection is detailed in the [Supplementary Methods](#), available at *Rheumatology* online.

### Microbiome profiling and collection

Shotgun metagenomic analysis was performed on stool and saliva samples collected from study participants, as described in the [Supplementary Methods](#), available at *Rheumatology* online. In short, samples were sent to TwinsUK laboratories within 24 h of collection (stool) and 2 h of collection (saliva), where they were stored at  $-80^{\circ}\text{C}$  until processing. Genomic DNA was extracted and processed at Clinical Microbiomics (Copenhagen, Denmark) for shotgun metagenomics using  $2 \times 150$  bp paired-end chemistry on an Illumina NovaSeq 6000 platform. Quality control of sequencing data was performed by YAMP [16]. Taxonomic profiling was carried out using kracken2/bracken [17], and HUMAnN3 [18] was used for functional profiling (UniRef90 reference database).

### Microbiome profiling: NOAR cohort

Patients with chronic RA were obtained from the Norfolk Arthritis Register (NOAR) (Participant Characteristics [Supplementary Table 1](#), available at *Rheumatology* online). NOAR samples (212 stool and saliva samples) were collected from participants on the registry with RA who had been

taking DMARD therapy >12 months [19], with all participants completing the clinical questionnaire. Samples were sent to Clinical Microbiomics (Denmark) and processed through default settings in YAMP, as outlined above.

## Statistical analysis

### Alpha- and beta-diversity

Chao1 richness, Shannon- and Simpson diversity index were calculated in the Phyloseq R package (v1.40.0) [20]. Alpha-diversity metrics were compared at each time point using linear mixed modelling, adjusting for clinical and demographic covariates such as age, sex, body mass index (BMI), smoking status, ethnicity and hospital centre, within the Vegan R package (v2.6–4) [21].

Before beta-diversity, data were filtered using PERFect (v1.10.0) [22], a novel permutation filter approach based on statistical hypothesis testing in taxa reduction. PERFect removes potential sequencing contaminant and taxa with minimal impact on the overall covariation within microbiome datasets.

Data were normalized with an arcsine square root transformation and clusters were visualized using Bray–Curtis dissimilarity and principal coordinates analysis (PCoA) using Vegan. Permutational Multivariate Analysis of Variation (PERMANOVA) was used to statistically compare cluster centroids and repeat measures were considered using *strata* parameter, where applicable.

### Differential abundance

Comparison of different taxonomic abundances between time points and clinical data was carried out using the limma:voom pipeline (v3.52.4) [23, 24] after normalizing abundances using GMPR (v0.1.3) [25]. Statistical significance threshold was set at 10% false discovery rate (FDR). Clinical Disease Activity Index (CDAI) score was used to classify patients into two groups according to minimal clinically important improvement (MCII), as defined in Gupta and colleagues [13], to determine predictive DMARD treatment response in baseline microbiota. This allowed the comparison of those with a meaningful clinical response to DMARD therapy with participants that did not (Supplementary Methods, available at *Rheumatology* online).

### Predictive model for MCII

A sparse partial least squares discriminant analysis [(s)PLS-DA] model was developed to predict MCII in microbiome data, using the MixOmics package (v6.20.0) [26]. Baseline abundance and MCII status established after six weeks of DMARD treatment were used to train and test the model. Samples were randomly split into two equal subsets, between those that did and did not achieve MCII ( $n = 53$ , with  $n = 32$  MCII+ and  $n = 21$  MCII-), and confusion matrices and area under the curve (AUC) plots were used to evaluate model performance. An additional microbiome dataset obtained from Gupta and colleagues [13] was used as a validation RA cohort for the (s)PLS-DA model.

## Results

### Sample description

The IMRABIOME cohort comprised 144 RA participants assessed at baseline ( $n = 144$ ), at six weeks ( $n = 117$ ) and at 12 weeks ( $n = 95$ ) follow-up. A total of 72.9% of participants

were female and 63.8% northern Europeans. Stool and saliva samples were collected at all timepoints for metagenomics alongside clinical markers, demographic and lifestyle information. All data were available at all three timepoints for 92 participants, 27 had data available at two time points (i.e. baseline and six weeks, or 12 weeks); and 26 with data available only at a single time point (i.e. only baseline).

Demographics and clinical characteristics are presented in Table 1.

### Alpha-diversity

Patient demographics impact on alpha-diversity was examined using Chao1 richness, Shannon- and Simpson's diversity index, in stool and saliva. No significant difference was seen in alpha-diversity metrics at any timepoint for either sample type ( $P > 0.05$ ). Smoking status was significant negatively associated with Shannon and Simpson indices across all three timepoints in saliva (Supplementary Table 2, available at *Rheumatology* online), with current and previous smokers having a reduced diversity compared with non-smokers. Smoking status did not significantly associate with alpha-diversity in the stool microbiome.

Disease activity measured by Disease Activity Score (DAS)28 and CDAI was negatively associated with all three alpha-diversity metrics in stool (Table 2). Sulfasalazine reduced richness in the gut at six weeks ( $P = 0.015$ ), no further DMARD influence was seen in gut or saliva alpha-diversity. Other demographics, such as sex, associated with Shannon diversity at baseline and six weeks, with males showing a reduced diversity compared with females ( $P < 0.05$ ).

### Beta-diversity

Microbial data were analysed with arcsine transformed PERFect-filtered data using PCoA to identify outliers before statistical comparisons. After removing outliers, we recalculated Bray–Curtis dissimilarity and used PERMANOVA models to establish demographic and clinical factors contributing to gut and saliva microbiome variance. Using univariate and multivariate models we assessed impacts of age, sex, BMI, smoking, hospital centre, ethnicity, disease severity as measured by DAS28 score, and DMARD use, at six and 12 weeks.

In multivariate models, the saliva microbiome was significantly different in participant smoking status at all timepoints ( $P < 0.001$ , Supplementary Table 3, available at *Rheumatology* online). Age was the only other variable to significantly differ in the saliva microbiome, which occurred at baseline ( $P = 0.016$ ). In the gut, age and ethnicity significantly differed at all timepoints, while BMI and DAS28 also differed at individual sampling points (Table 3). DMARD monotherapy did not significantly impact microbial communities in stool or saliva models; however, at six weeks' follow-up, for participants on combination therapy, the methotrexate component had a significant effect on gut microbiome beta-diversity.

### Differential abundance

Differential abundance (DA) was carried out using the limma:voom approach with abundance normalized with the GMPR, characterized by improved power and control of false positives compared with other normalization techniques. First, we checked for microbiome abundance changes across time points using linear contrast for pairwise comparisons

**Table 1.** Clinical and demographic characteristics of RA patients

| Trait                       |  | Baseline, <i>n</i> = 144 | 6 weeks, <i>n</i> = 117 | 12 weeks, <i>n</i> = 95 |              |
|-----------------------------|--|--------------------------|-------------------------|-------------------------|--------------|
| Sex <sup>a</sup>            | Female, <i>n</i> (%)   | 105 (72.4)               |                         |                         |              |
|                             | Male, <i>n</i> (%)   | 38 (26.2)                |                         |                         |              |
|                             | Unknown, <i>n</i> (%)  | 2 (1.4)                  |                         |                         |              |
| Age, mean ± SD              |  | 53.8 ± 13.9              |                         |                         |              |
| Smoking status <sup>a</sup> | Never, <i>n</i> (%)  | 66 (45.5)                |                         |                         |              |
|                             | Ever, <i>n</i> (%)   | 52 (35.9)                |                         |                         |              |
|                             | Current, <i>n</i> (%)  | 24 (16.6)                |                         |                         |              |
|                             | Unknown, <i>n</i> (%)  | 3 (2.1)                  |                         |                         |              |
| Diet                        | Diet including meat and fish, <i>n</i> (%)                   | 65 (49.3)                |                         |                         |              |
|                             | Diet excluding meat and fish, <i>n</i> (%)                   | 67 (50.7)                |                         |                         |              |
| Body mass index, mean ± SD  |  | 28.5 ± 6.1               |                         |                         |              |
| Ethnicity                   | Northern European, <i>n</i> (%)                              | 92 (63.8)                |                         |                         |              |
|                             | South Asian, <i>n</i> (%)                                    | 17 (11.8)                |                         |                         |              |
|                             | East Asian, <i>n</i> (%)                                     | 5 (3.4)                  |                         |                         |              |
|                             | Black African, <i>n</i> (%)                                  | 9 (6.2)                  |                         |                         |              |
|                             | Black Caribbean, <i>n</i> (%)                                | 7 (4.8)                  |                         |                         |              |
|                             | Mixed – Other, <i>n</i> (%)                                  | 4 (2.7)                  |                         |                         |              |
|                             | Unknown, <i>n</i> (%)  | 10 (6.9)                 |                         |                         |              |
| Hospital Centre             | North, <i>n</i> (%)  | 13 (9.0)                 |                         |                         |              |
|                             | South, <i>n</i> (%)  | 91 (63.1)                |                         |                         |              |
|                             | East, <i>n</i> (%)   | 19 (13.1)                |                         |                         |              |
|                             | West, <i>n</i> (%)   | 21 (14.5)                |                         |                         |              |
| Anti-CCP                    | Positive, <i>n</i> (%)                                       | 88 (65.7)                |                         |                         |              |
|                             | Negative, <i>n</i> (%)                                       | 46 (34.3)                |                         |                         |              |
| Tender joint score          | Median (min, max)  | 7 (0; 28)                | 3 (0; 27)               | 2 (0; 28)               |              |
| Swollen joint score         | Median (min, max)  | 5 (0; 28)                | 1 (0; 22)               | 1 (0; 23)               |              |
| C-reactive protein          | Median (min, max)  | 7.1 (1; 209)             | 4 (1; 78)               | 4 (1; 122)              |              |
| DAS28 score                 | Median (min, max)  | 4.9 (1.4; 8.2)           | 3.5 (0.0; 7.3)          | 3.8 (0.7; 7.7)          |              |
|                             | High, <i>n</i> (%)   | 65 (45.1)                | 22 (18.8)               | 19 (20.0)               |              |
|                             | Moderate, <i>n</i> (%)                                       | 54 (37.5)                | 42 (35.9)               | 21 (22.1)               |              |
|                             | Low, <i>n</i> (%)  | 22 (15.3)                | 50 (42.7)               | 51 (53.7)               |              |
|                             | Unknown, <i>n</i> (%)  | 3 (2.1)                  | 3 (2.6)                 | 4 (4.2)                 |              |
|                             | Disease activity decreased <i>vs</i> baseline <sup>b</sup>   |                          |                         | 54/112 (48.2)           | 44/88 (50.0) |
|                             | Median (min, max)  | 25 (0; 73)               | 13 (0; 65)              | 8.5 (0; 61)             |              |
| CDAI score                  | High, <i>n</i> (%)   | 80 (55.6)                | 30 (25.6)               | 21 (22.1)               |              |
|                             | Moderate, <i>n</i> (%)                                       | 33 (22.9)                | 34 (29.1)               | 17 (17.9)               |              |
|                             | Low, <i>n</i> (%)  | 23 (16.0)                | 32 (27.4)               | 26 (27.4)               |              |
|                             | Remission/no active disease, <i>n</i> (%)                    | 4 (2.8)                  | 17 (14.5)               | 26 (27.4)               |              |
|                             | Unknown, <i>n</i> (%)  | 4 (2.8)                  | 4 (3.4)                 | 5 (5.3)                 |              |
|                             | Disease activity decreased <i>vs</i> baseline <sup>c</sup>   |                          |                         | 64/106 (60.4)           | 49/82 (59.8) |
| DMARD Treatment             |  |                          |                         |                         |              |
|                             | Monotherapy  |                          |                         |                         |              |
|                             | Combination  |                          |                         |                         |              |
| Monotherapy                 | Methotrexate – monotherapy, <i>n</i>                         | 75                       | 54                      | 32                      |              |
|                             | Sulfasalazine – monotherapy, <i>n</i>                        | 4                        | 3                       | 3                       |              |
|                             | Hydroxychloroquine – monotherapy, <i>n</i>                   | 4                        | 4                       | 3                       |              |
|                             | Methotrexate and Sulfasalazine, <i>n</i>                     | 7                        | 12                      | 6                       |              |
| Combination                 | Methotrexate and Hydroxychloroquine, <i>n</i>                | 51                       | 37                      | 37                      |              |
|                             | Sulfasalazine and Hydroxychloroquine, <i>n</i>               | 2                        | 2                       | 3                       |              |
|                             | Methotrexate, Sulfasalazine and Hydroxychloroquine, <i>n</i> | 1                        | 2                       | 2                       |              |
| Total use (any)             | Methotrexate, <i>n</i> (%)                                   | 134/144 (93.1)           | 105/113 (92.9)          | 77/86 (89.5)            |              |
|                             | Sulfasalazine, <i>n</i> (%)                                  | 16/144 (11.1)            | 19/109 (17.4)           | 14/85 (16.5)            |              |
|                             | Hydroxychloroquine, <i>n</i> (%)                             | 58/144 (40.3)            | 45/110 (40.9)           | 45/87 (51.7)            |              |

<sup>a</sup> One patient did not have microbiome data at baseline, and at follow-up only; accordingly, proportions for sex and smoking at baseline are estimated for 145 individuals.

<sup>b</sup> Patients' disease activity category decreased from high to moderate or low, from moderate to low.

<sup>c</sup> CDAI score decreased for at least 1 unit for those who had low activity, at least 6 units for those who had moderate activity, and at least 12 units for those who had high activity.

RA: rheumatoid arthritis; BMI: body mass index; DAS: Disease Activity Score.

(Supplementary Tables 4 and 5, available at *Rheumatology* online). Differences in the saliva microbiome were inconsistent, as such we focused on the gut microbiome (saliva data in Supplementary Tables 6 and 7, available at *Rheumatology* online). In the gut, when comparing timepoints, we found more differential abundant taxa between baseline and 12 weeks, than baseline and six weeks (Supplementary Table

8, available at *Rheumatology* online). No significant findings were discovered while comparing follow-up time points. Next, we compared our study cohort of early-RA patients to NOAR, a long-term treatment cohort. DMARD-naive baseline, several weeks of DMARD treatment (i.e. combination of six-week and 12-week samples) and long-term (>1 year) use of DMARD (NOAR sample) were compared (FDR < 0.10)

**Table 2.** Disease activity and microbiome alpha-diversity

| Alpha diversity measure | Disease activity and severity scores | Baseline                                | 6 weeks                                 | 12 weeks                                |
|-------------------------|--------------------------------------|---|---|---|
| Chao1 richness          | DAS28                                | $\beta = -161.64 \pm 42.55; P = 0.0002$ | $\beta = -142.15 \pm 38.97; P = 0.0004$ | $\beta = -197.98 \pm 55.06; P = 0.0005$ |
|                         | CDAI                                 | $\beta = -16.03 \pm 4.12; P = 0.0001$   | $\beta = -15.38 \pm 4.48; P = 0.0008$   | $\beta = -19.92 \pm 6.10; P = 0.001$    |
| Shannon index           | DAS28                                | $\beta = -0.59 \pm 0.19; P = 0.003$     | $\beta = -0.46 \pm 0.21; P = 0.027$     | $\beta = -0.49 \pm 0.29; P = 0.094$     |
|                         | CDAI                                 | $\beta = -5.51 \pm 2.07; P = 0.009$     | $\beta = -3.46 \pm 1.83; P = 0.062$     | $\beta = -5.14 \pm 2.69; P = 0.059$     |
| Simpson index           | DAS28                                | $\beta = -2.20 \pm 1.11; P = 0.050$     | $\beta = -3.19 \pm 1.11; P = 0.005$     | $\beta = -2.01 \pm 1.59; P = 0.211$     |
|                         | CDAI                                 | $\beta = -19.10 \pm 12.03; P = 0.114$   | $\beta = -29.56 \pm 9.76; P = 0.003$    | $\beta = -24.75 \pm 14.11; P = 0.095$   |

Alpha diversity was calculated from stool metagenomes. Estimates  $\pm$  standard error and *P*-values for multiple regression of RA activity scores on Chao1, Shannon and Simpson indices; adjusted for age, sex, BMI and smoking status.  
 BMI: body mass index; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; RA: rheumatoid arthritis.

**Table 3.** Disease activity, patient characteristics and gut microbiome variance

| Trait                     | Model      | Baseline       |                 | Six weeks      |                 | 12 weeks       |                 |
|---------------------------|------------|----------------|-----------------|----------------|-----------------|----------------|-----------------|
|                           |            | R <sup>2</sup> | <i>P</i> -value | R <sup>2</sup> | <i>P</i> -value | R <sup>2</sup> | <i>P</i> -value |
| Age                       | Univariate | 1.4            | 0.0186          | 1.8            | 0.0052          | 2.5            | 0.0031          |
|                           | Adjusted   | 1.3            | 0.0288          | 2.0            | 0.0091          | 3.6            | 0.0002          |
| Sex                       | Univariate | 1.3            | 0.0300          | 1.6            | 0.0205          | 1.6            | 0.0617          |
|                           | Adjusted   | 1.0            | 0.1091          | 1.8            | 0.0222          | 1.5            | 0.1591          |
| BMI                       | Univariate | 1.6            | 0.0079          | 0.9            | 0.2834          | 1.0            | 0.5027          |
|                           | Adjusted   | 1.4            | 0.0193          | 1.1            | 0.2833          | 0.9            | 0.6611          |
| Smoking                   | Univariate | 1.0            | 0.8588          | 1.4            | 0.8074          | 1.7            | 0.7808          |
|                           | Adjusted   | 1.2            | 0.7127          | 1.6            | 0.7723          | 2.4            | 0.4017          |
| Diet                      | Univariate | 0.3            | 0.9529          | —              | —               | —              | —               |
|                           | Adjusted   | 0.4            | 0.9738          | —              | —               | —              | —               |
| Site (hospital)           | Univariate | 2.2            | 0.3239          | 3.1            | 0.1496          | 4.1            | 0.0810          |
|                           | Adjusted   | 2.3            | 0.3476          | 3.1            | 0.3599          | 4.9            | 0.0505          |
| Ethnicity                 | Univariate | 7.1            | 0.0003          | 7.6            | 0.0011          | 8.8            | 0.0033          |
|                           | Adjusted   | 6.8            | 0.0002          | 7.3            | 0.0083          | 8.4            | 0.0262          |
| DAS28 score               | Univariate | 1.4            | 0.0173          | 1.6            | 0.0257          | 3.4            | 0.0004          |
|                           | Adjusted   | 0.9            | 0.1824          | 0.8            | 0.5704          | 2.3            | 0.0154          |
| Tender joint score        | Univariate | 0.9            | 0.1605          | —              | —               | —              | —               |
|                           | Adjusted   | 1.1            | 0.0649          | —              | —               | —              | —               |
| Swollen joint score       | Univariate | 0.5            | 0.6861          | —              | —               | —              | —               |
|                           | Adjusted   | 1.1            | 0.0728          | —              | —               | —              | —               |
| C-reactive protein        | Univariate | 0.5            | 0.5949          | —              | —               | —              | —               |
|                           | Adjusted   | 0.6            | 0.5206          | —              | —               | —              | —               |
| Methotrexate–mono         | Univariate | —              | —               | 3.4            | 0.0139          | 3.2            | 0.2030          |
|                           | Adjusted   | —              | —               | 2.2            | 0.2237          | 2.4            | 0.4633          |
| Sulfasalazine–mono        | Univariate | —              | —               | 1.0            | 0.2898          | 1.2            | 0.4938          |
|                           | Adjusted   | —              | —               | —              | —               | —              | —               |
| Hydroxychloroquine–mono   | Univariate | —              | —               | 1.2            | 0.8384          | 2.1            | 0.5215          |
|                           | Adjusted   | —              | —               | —              | —               | —              | —               |
| Use of methotrexate       | Univariate | —              | —               | 1.6            | 0.0287          | 3.4            | 0.3447          |
|                           | Adjusted   | —              | —               | 1.8            | 0.0353          | 1.4            | 0.2626          |
| Use of sulfasalazine      | Univariate | —              | —               | 1.6            | 0.0283          | 2.1            | 0.0211          |
|                           | Adjusted   | —              | —               | 1.1            | 0.2645          | 1.5            | 0.1735          |
| Use of hydroxychloroquine | Univariate | —              | —               | 1.5            | 0.0452          | 1.1            | 0.3945          |
|                           | Adjusted   | —              | —               | 0.8            | 0.6492          | 1.2            | 0.3827          |

Bray–Curtis dissimilarity was calculated using stool microbiome at species level; because of high correlation between DAS28 and CDAI scores, we chose to analyse DAS28 score only.

BMI: body mass index; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score 28; mono: monotherapy.

(Supplementary Tables 9–11, available at *Rheumatology* online). In total, 32 taxa differed in abundance between long-term DMARD use and several weeks of DMARD use. In contrast, 86 taxa significantly decreased in long-term DMARD treated participants compared with DMARD-naïve baseline, with *Porphyromonas gingivalis* and 15 *Prevotella* spp. among the reduced taxa.

Minimal clinically important improvement (MCII) was used to assess microbiome change based on patient response

to DMARD treatment. At baseline, there were no detectable microbiome differences between those that achieved MCII and those who did not. After six weeks of DMARD treatment, 18 taxa differed between MCII groups, of which 13 decreased and five increased in abundance, in those that achieved MCII vs those that did not. Of the 13 decreased taxa, seven (54%) were *Prevotella* spp. At 12 weeks treatment, a further 13 taxa significantly decreased when comparing participants that fulfilled MCII compared with those that

did not, of which 10 were *Streptococcus* spp. (Table 5). Overall, these findings led us to conclude that the gut microbiome normalises in RA patients with longer treatment, but only in patients who respond to DMARD treatment.

### Anti-CCP

Anti-cyclic citrullinated peptide (anti-CCP) values at baseline were positive for 88 participants and negative for 46 participants (defined as <20 u/ml antibody negative, ≥20 u/ml positive), Table 1. We explored the relationship between anti-CCP antibodies and smoking in saliva microbiota using linear regression models. The inclusion of anti-CCP did not significantly alter Shannon diversity ( $P=0.11$ ) or Chao1 richness ( $P=0.67$ ) measures. Furthermore, univariate ( $P=0.22$ ) and multivariate ( $P=0.20$ ) PERMANOVA statistics suggested anti-CCP did not significantly impact the saliva microbiota diversity. The inclusion of anti-CCP in the gut microbiota linear regression did not improve model outcomes, with no significant association between anti-CCP and the gut microbiota (Shannon  $P=0.15$ , Chao1  $P=0.07$ ). *Prevotella* species were, however, elevated in individuals positive for anti-CCP antibodies (Supplementary Table 12, available at *Rheumatology* online).

### Predictive model for MCII

We applied sPLSDA analysis to develop a model to predict MCII status upon short-term treatment (see ‘Materials and methods’). We used baseline species abundances and MCII status as established at six weeks. Furthermore, using Kegg Orthology and Metacyc database microbial gene and biochemical pathways, predictive potential was also explored. To generate train and test samples, we randomly split the dataset with available information into two equal subsets,  $n=53$  each, with  $n=32$  who achieved MCII and  $n=21$  who did not. In the gut, the final model for microbes provided AUC=0.66 ( $P=0.0539$ ); while for Gupta and colleagues [13], AUC=0.60 ( $P=0.3706$ ) (Fig. 1). Saliva samples manifested an AUC=0.61 ( $P=0.14$ ) for microbes and AUC=0.69 ( $P=0.033$ ) for Metacyc pathways, while KO genes for stool and saliva had AUCs <0.55 (Supplementary Tables 13–15, available at *Rheumatology* online).

### Discussion

The microbiome has an established and prominent role in RA disease and early-onset development [27, 28]. Our research focused on early-disease RA patients who were DMARD-naive and examined microbiome changes during initiation of DMARD therapy in a large-scale observation study of oral and gut microbiome in 144 individuals. DMARD therapy is recommended early in disease to improve patient outcomes, but currently a trial-and-error approach is used, with drug dose escalation if response is poor. The ability to determine who will respond to DMARDs would enable a personalised approach to treatment selection, rather than the ubiquitous administration of methotrexate in new-onset RA in the UK. Our interest was in being able to predict how patients will respond to DMARD therapy. There were two main findings from our study. First, microbial abundance among patients that attained MCII (MCII+) and those that did not (MCII-), were different at 6 and 12 weeks of DMARD treatment. In total, 26 different stool microbes decreased in MCII+ compared with MCII-. *Prevotella* spp. and *Streptococcus* spp. were the

predominant taxa to decline after six weeks and 12 weeks, respectively. Interestingly, diet preference had limited impact on the stool microbiota and abundance differences seen in this study, with no changes to microbiota seen (Tables 4 and 5). Second, we found the DMARD-naive microbiome was indicative of clinical response. Metacyc pathways best predicted MCII+ from DMARD-naive samples, particularly saliva, providing a promising target for metabolomics. Furthermore, we found 86 microbes decreased significantly in long-term DMARD-exposed participants from the NOAR cohort, when compared with DMARD-naive patients; *Prevotella* spp. accounted for ~20% of species in decline.

*Prevotella* are commonly associated with RA pathogenesis. In humans, these commensal microbes colonise the skin, vagina, oral cavity, respiratory tract and intestine, and have important roles in metabolism and health [29]. Here we add further evidence in support of gut *Prevotella* spp. involvement in RA prognosis, by contrasting MCII+ and MCII-. After six weeks of DMARD treatment, 18 microbes significantly differed in patients’ gut microbiome showing clinical response to therapy, of those 13 decreased including seven *Prevotella* spp. (see Table 4). Furthermore, 15 *Prevotella* spp. were identified to decline within long-term DMARD-treated NOAR participants, when compared with early-onset DMARD-naive patients. In total, 15 different *Prevotella* spp. were negatively associated with clinical improvement to therapy, including *P. denalis*, *P. denticola*, *P. histicola*, *P. intermedia*, *P. melaninogenica*, *P. nigrescens*, *P. oris* and *P. ruminicola*. These species have been linked to respiratory disease, multiple sclerosis, brain abscess, blood and cardiac infection, musculoskeletal infection, and most commonly periodontal disease [29]. Previously, we reported *Prevotella* spp. play a role in RA development, and microbial abundance increased in those with the genotype predisposing risk for RA even in the absence of disease [5]. Interestingly, we did not detect significant associations between *P. copri*, DMARD treatment and patient clinical response. It is well established that *P. copri* is involved in early RA, with increased abundance thought to stimulate expression of anti-citrullinated proteins and serum antibodies [6, 8]. Genetic factors predispose to RA, with additive influence of acquired environmental risk [30]. Host genetic factors mediate the microbiome and are thought to lead to a pro-inflammatory, hyper-active immune type [5, 30]. The presence of anti-CCP antibodies at baseline may be considered to represent the shared epitope risk, in line with our previous study demonstrating increased *Prevotella* spp. in those positive for the shared epitope [5]. Regression models for stool including anti-CCP antibody status as covariate showed no influence on alpha-diversity in our sample. We identified seven *Prevotella* spp. to be significantly elevated in those having anti-CCP antibodies compared with those without, and several other species including *P. copri* showed a similar trend (Supplementary Table 12, available at *Rheumatology* online) [31].

Of metagenomics studies investigating RA and the microbiome; two reported taxa differences between participants who respond well to DMARD therapies compared with those who do not [12, 13]. In line with our findings, no differential abundance in *P. copri* was reported by either group. Whilst a common theme across RA literature, we speculate that abundance of *P. copri* is more prominent when comparing healthy and disease participants, which may explain the lack of association in this study. *P. copri* comprises four genetically

distinct clades with genetic and functional differences that are influenced by diet and lifestyle [32–34]. For example, in plant-rich ‘non-westernised’ diets, *P. copri* can catabolise plant carbohydrates and fibres; alternatively, in higher protein diets *P. copri* is known to break down branch chain amino acids (BCAAs) from meats [29, 32, 34]. Interestingly, in a recent study gut isolates of *P. copri* strains were shown to differ in RA participants, with more severe arthritis induced in mice from RA patient strains than from healthy controls [34]. These findings warrant further investigation and may extend more broadly to *Prevotella* spp. Of note, periodontal disease appears to commonly be associated with the *Prevotella* spp. we identified (e.g. *P. denalis*, *P. denticola*, *P. histicola*, *P.*

*intermedia*, *P. melaninogenica*, *P. nigrescens*, *P. oris*, *P. ruminicola*) with poor treatment outcome [29].

Periodontal disease is more frequent in RA [35]. Despite environmental niches and segregation, it is common for microbes to translocate from the oral cavity to the gut. Common examples in RA are *Porphyromonas gingivalis* and *P. copri*; however, *Streptococcus* spp. are also associated with oral to gut translocation [36]. In the oral cavity, streptococci are known to form early-plaque biofilms that can support microbes associated with gingival disease, such as *P. gingivalis* [37]. Intriguingly, *P. gingivalis* was identified in higher abundance in baseline samples when compared with long-term DMARD participants in NOAR. Furthermore *Streptococcus* spp. significantly decreased in the gut of early RA patients having MCII+ after 12 weeks of DMARD treatment, in this study.

Our findings support the hypothesis of DMARD restoration of a eubiotic gut microbiome when patient and treatment

**Table 4.** Patient response (MCII+/MCII-) and differentially abundant taxa during the first six weeks of DMARD treatment

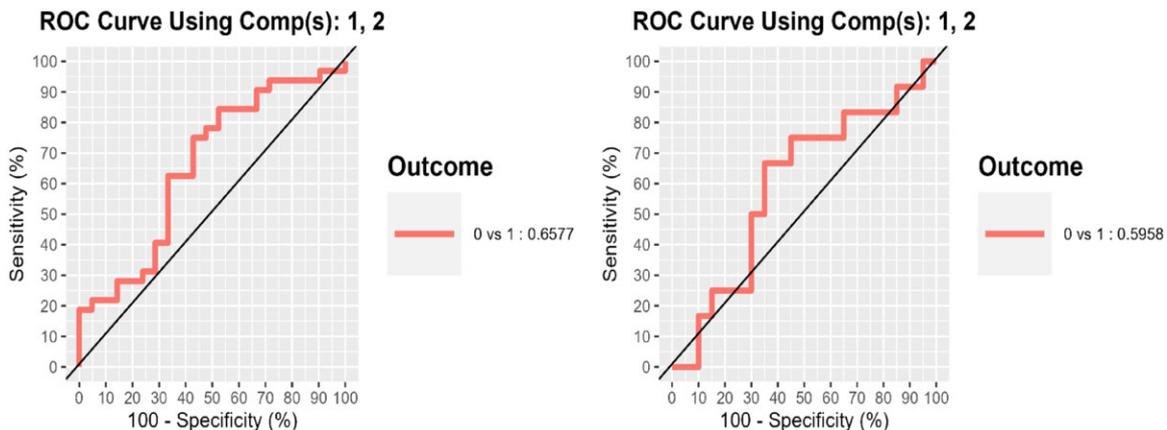
| Taxa  | MCII+ vs MCII- @ Six weeks |         |              |
|---|----------------------------|---------|--------------|
|   | logFC                      | P-value | adj. P-value |
| <i>Phocaeicola salanitronis</i>               | -1.73                      | 0.000   | 0.002        |
| <i>Bacteroides coprosuis</i>                  | -1.68                      | 0.000   | 0.002        |
| <i>Phocaeicola coprophilus</i>                | -1.87                      | 0.000   | 0.008        |
| Candidatus <i>Arthromitus</i> sp. SFB rat Yit | 0.84                       | 0.000   | 0.039        |
| <i>Prevotella jejuni</i>                      | -1.31                      | 0.000   | 0.039        |
| <i>Prevotella intermedia</i>                  | -1.35                      | 0.000   | 0.047        |
| <i>Prevotella nigrescens</i>                  | -1.38                      | 0.000   | 0.047        |
| <i>Propionibacterium australiense</i>         | 0.74                       | 0.001   | 0.078        |
| <i>Prevotella fusca</i>                       | -1.28                      | 0.001   | 0.078        |
| <i>Prevotella oris</i>                        | -1.31                      | 0.001   | 0.078        |
| <i>Streptococcus sobrinus</i>                 | -1.39                      | 0.001   | 0.078        |
| <i>Paraprevotella xylaniphila</i>             | -1.98                      | 0.001   | 0.078        |
| <i>Prevotella</i> sp. WR041                   | -1.31                      | 0.001   | 0.078        |
| <i>Rhodopseudomonas palustris</i>             | 0.65                       | 0.001   | 0.078        |
| <i>Paludibacterium</i> sp. B53371             | 0.75                       | 0.001   | 0.078        |
| <i>Nitrogeniibacter mangrovi</i>              | 0.76                       | 0.001   | 0.078        |
| <i>Prevotella enoeca</i>                      | -1.19                      | 0.002   | 0.094        |
| <i>Parabacteroides distasonis</i>             | -1.49                      | 0.002   | 0.094        |

Differentially abundant taxa between RA patients who achieved minimum clinically important improvement (MCII+) and who did not (MCII-) during the first six weeks of DMARD treatment. Linear contrasts have been constructed and tested for significance using voom: limma approach combined with GMPR normalisation. Adjustment for multiple testing was done using Benjamini–Hochberg false discovery rate within each taxonomic level. Reported are findings with FDR <10% in at least one contrast. No significant results were obtained for comparisons between MCII+ and MCII- at baseline.

**Table 5.** Patient response (MCII+/MCII-) and differentially abundant taxa following 12 weeks of DMARD treatment

| Taxa                                    | MCII+ vs MCII- @ 12 weeks |         |              |
|---|---------------------------|---------|--------------|
|   | logFC                     | P-value | adj. P-value |
| <i>Gemella haemolysans</i>              | -1.7                      | 0.000   | 0.094        |
| <i>Staphylococcus epidermidis</i>       | -1.45                     | 0.000   | 0.094        |
| <i>Veillonella parvula</i>              | -1.92                     | 0.000   | 0.094        |
| <i>Streptococcus mitis</i>              | -1.76                     | 0.000   | 0.094        |
| <i>Streptococcus</i> sp. oral taxon 061 | -1.75                     | 0.001   | 0.094        |
| <i>Streptococcus gordonii</i>           | -1.61                     | 0.001   | 0.094        |
| <i>Streptococcus oralis</i>             | -1.59                     | 0.001   | 0.094        |
| <i>Streptococcus</i> sp. A12            | -1.85                     | 0.001   | 0.094        |
| <i>Streptococcus lactarius</i>          | -1.78                     | 0.001   | 0.094        |
| <i>Streptococcus gallolyticus</i>       | -1.52                     | 0.001   | 0.094        |
| <i>Streptococcus pneumoniae</i>         | -1.21                     | 0.001   | 0.094        |
| <i>Streptococcus parasanguinis</i>      | -1.89                     | 0.001   | 0.094        |
| <i>Streptococcus</i> sp. LPB0220        | -2.02                     | 0.001   | 0.094        |

Differentially abundant taxa between RA patients who achieved minimum clinically important improvement (MCII+) and who did not (MCII-) following 12 weeks of DMARD treatment. Linear contrasts have been constructed and tested for significance using voom: limma approach combined with GMPR normalisation. Adjustment for multiple testing was done using Benjamini–Hochberg false discovery rate within each taxonomic level. Reported are findings with FDR <10% in at least one contrast. No significant results were obtained for comparisons between MCII+ and MCII- at baseline.



**Figure 1.** Area under the ROC curve for predictive model of MCII after short-term treatment. Left panel is for the test sample resulted from the split of our dataset into random train and test samples. Right panel is for external data [13]

align [38, 39]. We had anticipated finding baseline microbiome samples predictive of response to treatment. While baseline differential abundance analysis did not discriminate responders (MCII+) from non-responders (MCII-), longitudinal analysis showed changing microbiota and positive response to DMARDs. At 6 weeks there was a reduction of multiple species of *Prevotella* in responsive participants. At 12 weeks, multiple species of Streptococci were reduced in responders. Methotrexate was associated with beta-diversity difference following six weeks of treatment, even when adjusting for disease activity and other confounders (age, sex, BMI, smoking status, ethnicity, hospital centre, diet and other DMARDs).

Predictive tools for RA treatment outcome utilising oral and gut microbiome are advancing [12–14]. In a small Hispanic cohort ( $n=26$ ) a model using DMARD-naive gut metagenomes from patients receiving monotherapy methotrexate was able to predict non-responsiveness [12]. Gupta and colleagues [13] retrospectively used gut metagenomes from patients ( $n=32$ ) taking DMARDs to predict MCII response with 90% accuracy using a neural network. Similarly, Zhang and colleagues [14] accurately predicted DAS28-ESR response in using long-term DMARD-treated patients and controls, with dental metagenome samples. Our models used gut and oral metagenomes to predict DMARD-naive MCII response. Although our models were not as strong as those cited above, we were able to better identify MCII+ as highlighted by our sensitivity scores (Supplementary Tables 13–15, available at *Rheumatology* online). Northern Europeans accounted for >60% of our sample and patients often received combination therapy to treat RA. The real strength of our work lies in our validation using two external data cohorts, a novel and key contrast to similar studies that may have overfit models with small sample sizes and a lack of external validation. Another strength is that the population cohort of DMARD-naive participants permits the exploration of the influence of therapy.

The range of DAS28 values at baseline was large, although the lower quantile cut-off at baseline was 3.6, therefore comprising those with clinically meaningful disease activity. When low DAS scores were removed from the analysis, the negative linear relationship with alpha diversity was maintained. This association decreased with received treatment; for example, DAS28 negatively associated with alpha-diversity at baseline, although an improvement in DAS28 is seen in patients at six (48.2%) and 12 weeks (50%) (Table 1) following DMARD treatment. Interestingly, when broken down the tender joint score was the principal DAS28 measure that negatively associated with alpha-diversity.

Long-term DMARD comparison came from NOAR: study participants registered to assist arthritis research. Disease activity was from medical records and was participant generated, not clinician scored, so we used available data to calculate DAS28-CRP. Differential abundance analysis in NOAR using the criteria cut-point of DAS28-CRP <2.6 showed one taxa altered, *Actinomyces sp. Oral taxon 414*, between high- vs low disease activity (Supplementary Table 11, available at *Rheumatology* online). Furthermore, the predictive model used in the drug-naive cohort resulted in similar AUC for gut microbiota at 0.65 AUC (Supplementary Table 13, available at *Rheumatology* online).

We acknowledge that there are limitations to this study. Changes in saliva metagenomes were sparse, with smoking

status and the predictive model with metacyc pathways being the only clear signals achieved. Similar predictive results were seen in Zhang and colleagues when examining saliva; however, dental microbiota were able to predict response [14]. The longitudinal data collection was for 12 weeks post recruitment, though longer follow-up of 6–12 months would have been preferable.

A strength of our work is the ethnic mix recruited to the study reflecting an inner-city UK sample: we found beta-diversity to be reduced in northern Europeans compared with south Asians at baseline, likely driven by the small sub-group numbers, but there was no impact of ethnicity on predictive models. Interestingly, *Prevotella* spp. are known to dominate the gut microbiome in ‘non-westernised’ populations [29]. The interplay between ethnicity, the microbiome and RA warrants investigation and may give further insight into patient-specific treatment.

In summary, we identified a partial restoration of the microbiome to a more eubiotic state in RA patients at 6 weeks and 12 weeks DMARD treatment in participants that responded well to DMARD therapy. This was further supported by long-term (>1 year) treated DMARD RA participants with similar community shifts. Finally, microbiomes provide a promising diagnostic tool for guiding therapeutic decisions in future.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

The data underlying this article are available in Sequence Read Archive (SRA) at <https://dataview.ncbi.nlm.nih.gov/object/PRJNA957107?reviewer=e4pj6rso2m8osj2c6hilgqn9ei>, and can be accessed with accession number PRJNA957107.

## Author contributions

Nathan P. Danckert (Data analysis, Methodology, Writing, Writing—Review & Editing), Maxim B. Freidin (Study design, Data analysis, Methodology, Writing, Writing—Review & Editing, Funding acquisition), Isabelle Granville Smith (Data curation, Writing, Writing—Review & Editing), Philippa M. Wells (Data analysis, Methodology, Writing), Maryam Kazemi Naeini (Methodology, Writing—Review & Editing), Alessia Visconti (Data analysis, Methodology), Roger Compte (Methodology, Writing—Review & Editing), Alexander MacGregor (Writing—Review & Editing, Funding acquisition), Frances M. K. Williams (Study design, Data curation, Data analysis, Methodology, Writing, Writing—Review & Editing, Funding acquisition). All authors read and approved the final manuscript.

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with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

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## References

- MacGregor AJ, Snieder H, Rigby AS *et al.* Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000;43:30–7.
- Daikh DI. Rheumatoid arthritis: evolving recognition of a common disease. *Best Pract Res Clin Rheumatol* 2022;36:101740.
- Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell* 2012;148:1258–70.
- Gilbert JA, Blaser MJ, Caporaso JG *et al.* Current understanding of the human microbiome. *Nat Med* 2018;24:392–400.
- Wells PM, Adebayo AS, Bowyer RCE *et al.* Associations between gut microbiota and genetic risk for rheumatoid arthritis in the absence of disease: a cross-sectional study. *Lancet Rheumatol* 2020;2:e418–27.
- Scher JU, Sczesnak A, Longman RS *et al.* Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *Elife* 2013;2:e01202.
- Alghamdi MA, Redwan EM. Interplay of microbiota and citrullination in the immunopathogenesis of rheumatoid arthritis. *Probiotics Antimicrob Proteins* 2022;14:99–113.
- Pianta A, Arvikar S, Strle K *et al.* Evidence of the immune relevance of *Prevotella copri*, a gut microbe, in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2017;69:964–75.
- Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. *Nat Rev Rheumatol* 2020;16:145–54.
- Scher JU, Nayak RR, Ubeda C, Turnbaugh PJ, Abramson SB. Pharmacomicrobiomics in inflammatory arthritis: gut microbiome as modulator of therapeutic response. *Nat Rev Rheumatol* 2020;16:282–92.
- Emery P, Breedveld FC, Hall S *et al.* Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372:375–82.
- Artacho A, Isaac S, Nayak R *et al.* The pretreatment gut microbiome is associated with lack of response to methotrexate in new-onset rheumatoid arthritis. *Arthritis Rheumatol* 2021;73:931–42.
- Gupta VK, Cunningham KY, Hur B *et al.* Gut microbial determinants of clinically important improvement in patients with rheumatoid arthritis. *Genome Med* 2021;13:149.
- Zhang X, Zhang D, Jia H *et al.* The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med* 2015;21:895–905.
- Aletaha D, Neogi T, Silman AJ *et al.* 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
- Visconti A, Martin TC, Falchi M. YAMP: a containerized workflow enabling reproducibility in metagenomics research. *GigaScience* 2018;7:1–9.
- Lu J, Rincon N, Wood DE *et al.* Metagenome analysis using the Kraken software suite. *Nature Protocols* 2022;17:2815–39.
- Beghini F, McIver LJ, Blanco-Míguez A *et al.* Integrating taxonomic, functional, and strain-level profiling of diverse microbial communities with bioBakery 3. *eLife* 2021;10:e65088.
- Symmons D, Silman A. The norfolk arthritis register (NOAR). *Clin Exp Rheumatol* 2003;21:S94–9.
- McMurdie PJ, Holmes S. phyloseq: an R package for reproducible interactive analysis and graphics of microbiome census data. *PLoS ONE* 2013;8:e61217.
- Dixon P. VEGAN, a package of R functions for community ecology. *Journal of Vegetation Science* 2003;14:927–30.
- Smirnova E, Huzurbazar S, Jafari F. PERfect: PERmutation Filtering test for microbiome data. *Biostatistics* 2019;20:615–31.
- Law CW, Chen Y, Shi W, Smyth GK. voom: precision weights unlock linear model analysis tools for RNA-seq read counts. *Genome Biol* 2014;15:R29.
- Ritchie ME, Phipson B, Wu D *et al.* limma powers differential expression analyses for RNA-seq and microarray studies. *Nucleic Acids Res* 2015;43:e47.
- Chen L, Reeve J, Zhang L *et al.* GMPR: a robust normalization method for zero-inflated count data with application to microbiome sequencing data. *PeerJ* 2018;6:e4600.
- Lê Cao K-A, Boitard S, Besse P. Sparse PLS discriminant analysis: biologically relevant feature selection and graphical displays for multiclass problems. *BMC Bioinformatics* 2011;12:253.
- Zhao Y, Cheng M, Zou L *et al.* Hidden link in gut-joint axis: gut microbes promote rheumatoid arthritis at early stage by enhancing ascorbate degradation. *Gut* 2022;71:1041–3.
- Esberg A, Johansson L, Johansson I, Dahlqvist SR. Oral microbiota identifies patients in early onset rheumatoid arthritis. *Microorganisms* 2021;9:1657.
- Tett A, Pasolli E, Masetti G, Ercolini D, Segata N. *Prevotella* diversity, niches and interactions with the human host. *Nat Rev Microbiol* 2021;19:585–99.
- Wells PM, Williams FMK, Matey-Hernandez ML, Menni C, Steves CJ. 'RA and the microbiome: do host genetic factors provide the link?' *J Autoimmun* 2019;99:104–15.
- Alpizar-Rodriguez D, Lesker TR, Gronow A *et al.* *Prevotella copri* in individuals at risk for rheumatoid arthritis. *Ann Rheum Dis* 2019;78:590–3.
- Tett A, Huang KD, Asnicar F *et al.* The *Prevotella copri* complex comprises four distinct clades underrepresented in westernized populations. *Cell Host Microbe* 2019;26:666–79.
- De Filippis F, Pasolli E, Tett A *et al.* Distinct genetic and functional traits of human intestinal *Prevotella copri* strains are associated with different habitual diets. *Cell Host Microbe* 2019;25:444–53.

34. Nii T, Maeda Y, Motooka D *et al*. Genomic repertoires linked with pathogenic potency of arthritogenic *Prevotella copri* isolated from the gut of patients with rheumatoid arthritis. *Ann Rheum Dis* 2023;82:621–9.
35. Fuggle NR, Smith TO, Kaul A, Sofat N. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. *Front Immunol* 2016;7:80.
36. Kitamoto S, Nagao-Kitamoto H, Hein R, Schmidt TM, Kamada N. The bacterial connection between the oral cavity and the gut diseases. *J Dent Res* 2020;99:1021–9.
37. Cook GS, Costerton JW, Lamont RJ. Biofilm formation by *Porphyromonas gingivalis* and *Streptococcus gordonii*. *J Periodontal Res* 1998;33:323–7.
38. Berthelot J-M, Lioté F, Sibia J. Methotrexate also improves rheumatoid arthritis through correction of microbiota dysbiosis. *Joint Bone Spine* 2023;90:105602.
39. de Arruda AA, Correa JD, Singh Y *et al*. Methotrexate promotes recovery of arthritis-induced alveolar bone loss and modifies the composition of the oral-gut microbiota. *Anaerobe* 2022;75:102577.

# Biologics may be **less effective** in patients who are **overweight**<sup>1,2</sup>



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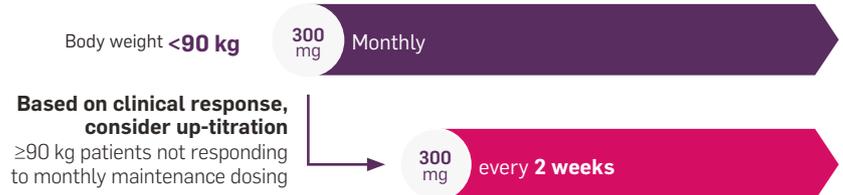
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Adapted from Cosentyx<sup>®</sup> (secukinumab) SmPC.<sup>4,5</sup>

\*For adult patients with PsA and concomitant moderate to severe PsO, the recommended dose of Cosentyx is 300 mg with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by **monthly maintenance dosing**. Based on clinical response, a maintenance dose of 300 mg **Q2W** may provide additional benefit for patients with a body weight of **90 kg or higher**.<sup>4,5</sup>

Cosentyx is indicated for the 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 adult patients (alone or in combination with methotrexate) 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 moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic therapy; 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 and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.<sup>4,5</sup>

PsA, psoriatic arthritis; PsO, plaque psoriasis; Q2W, every 2 weeks.

**References:** **1.** Warren RB, et al. *J Invest Dermatol* 2015;135:2632–2640; **2.** Warren RB, et al. *Br J Dermatol* 2019;180(5):1069–1076; **3.** Office for Health Improvement and Disparities. Obesity profile: short statistical commentary May 2024. Available at: <https://www.gov.uk/government/statistics/update-to-the-obesity-profile-on-fingertips/obesity-profile-short-statistical-commentary-may-2024> [Accessed August 2024]; **4.** Cosentyx<sup>®</sup> (secukinumab) GB Summary of Product Characteristics; **5.** Cosentyx<sup>®</sup> (secukinumab) NI Summary of Product Characteristics.

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at [www.novartis.com/report](http://www.novartis.com/report), or alternatively email [medinfo.uk@novartis.com](mailto:medinfo.uk@novartis.com) or call 01276 698370

## **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  $\geq$  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-TNF $\alpha$  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  $\geq$  50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. **Hidradenitis suppurativa:**

## **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  $\geq$  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-TNF $\alpha$  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  $\geq$  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 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

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 ( $\geq$ 1/10):** Upper respiratory tract infection. **Common ( $\geq$ 1/100 to <1/10):** Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. **Uncommon ( $\geq$ 1/1,000 to <1/100):** Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. **Rare ( $\geq$ 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 x1 £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:**

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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 ( $\geq$ 1/10):** Upper respiratory tract infection. **Common ( $\geq$ 1/100 to <1/10):** Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. **Uncommon ( $\geq$ 1/1,000 to <1/100):** Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. **Rare ( $\geq$ 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 x1 £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**

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