Analysis of serum proteomics data identifies a quantitative association between beta-defensin 2 at baseline and clinical response to IL-17 blockade in psoriatic arthritis

Mathias Cardner,1,2 Danny Tuckwell,2 Anna Kostikova,2 Pascal Forrer,1 Richard M Siegel,2 Alain Marti,1 Marc Vandemeulebroecke,1,2

ABSTRACT

Objectives Despite several effective targeted therapies, biomarkers that predict whether a patient with psoriatic arthritis (PsA) will respond to a particular treatment are currently lacking.

Methods We analysed proteomics data from serum samples of nearly 2000 patients with PsA in placebo-controlled phase-III clinical trials of the interleukin-17 inhibitor secukinumab. To discover predictive biomarkers of clinical response, we used statistical learning with controlled feature selection. The top candidate was validated using an ELISA and was separately assessed in a trial of almost 800 patients with PsA treated with secukinumab or the tumour necrosis factor inhibitor adalimumab.

Results Serum levels of beta-defensin 2 (BD-2) at baseline were found to be robustly associated with subsequent clinical response (eg, American College of Rheumatology definition of 20%, 50% and 70% improvement) to secukinumab, but not to placebo. This finding was validated in two independent clinical studies not used for discovery. Although BD-2 is known to be associated with psoriasis severity, the predictivity of BD-2 was independent of baseline Psoriasis Area and Severity Index. The association between BD-2 and response to secukinumab was observed as early as 4 weeks and maintained up to 52 weeks. BD-2 was also found to predict response to treatment with adalimumab. Unlike in PsA, BD-2 was not predictive of response to secukinumab in rheumatoid arthritis.

Conclusions In PsA, BD-2 at baseline is quantitatively associated with clinical response to secukinumab. Patients with high levels of BD-2 at baseline reach and sustain higher rates of clinical response after treatment with secukinumab.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disorder affecting the skin, joints and entheses. Important clinical manifestations of PsA include tender and swollen peripheral joints, psoriasis activity on skin and nails, as well as pain, fatigue and impaired quality of life.1 Genetic evidence points to tumour necrosis factor (TNF) and interleukin (IL-)23 and their signalling pathways as molecular drivers of disease, and yet, 4 out of 10 patients have an inadequate clinical response to cytokine inhibitors.2 Across the range of available therapeutics, including disease-modifying antirheumatic drugs, only about 6 out of 10 patients experience a 20% improvement in clinical endpoints, highlighting that there is still a large unmet medical need. This, together with the heterogeneous presentation of PsA, calls for the need to individualise treatments.3

In precision medicine, endotyping refers to the dissection of a disease (or multiple related diseases) into subtypes informed by underlying molecular mechanisms.4 5 When relating molecular read-outs to subsequent
clinical response, prognostic biomarkers forecast clinical outcome regardless of intervention, whereas predictive biomarkers forecast clinical response to treatment. A recent literature review on predictive biomarkers in psoriasis and PsA highlighted the lack of independent validation of reported biomarkers in large cohorts. Secukinumab, a fully human monoclonal antibody that selectively neutralises IL-17A, is approved for treatment of PsA, plaque psoriasis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. The efficacy and safety of secukinumab in PsA have been demonstrated in five placebo-controlled randomised phase-III clinical studies, the FUTURE 1–5 trials. Despite a positive numerical trend, the head-to-head phase-IIIb study EXCEED failed to establish superiority of secukinumab over the TNF inhibitor (TNFi) adalimumab.

To identify biomarkers which predict clinical response to PsA treatment, we performed statistical learning on high-dimensional serum proteomics data at baseline from the FUTURE trials, followed by hypothesis-driven analysis of EXCEED. Discovery of novel protein markers was enabled by SomaScan, a multiplexed assay capable of measuring semiquantitative levels of thousands of proteins in serum or plasma. The top candidate was validated using an ELISA. By comprehensively analysing clinical and proteomics data we were able to identify a putative predictive biomarker of clinical response to secukinumab.

METHODS

We analysed studies with the following ClinicalTrials.gov IDs: the phase-III PsA trials FUTURE 1–5 (NCT01392326, NCT01752634, NCT01989468, NCT02294227, NCT02404350), the phase-IIIb PsA trial EXCEED (NCT02745080) and the phase-III rheumatoid arthritis (RA) trials REASSURE, NURTURE 1 and REASSURE 2 (NCT01377012, NCT01350804, NCT01770379).

Patient and public involvement

There was no active patient involvement in our retrospective analyses of the above clinical trials. We restricted all analyses to patients with active informed consent.

Protein assays

Serum samples were taken from patients at baseline, that is, immediately before the initiation of treatment with secukinumab or placebo. The samples were assayed using the SomaScan platform, which employs slow off-rate modified aptamers (SOMAmers) to profile thousands of proteins. The SOMAmers are ultimately hybridised to DNA microarrays and abundance is measured in terms of relative fluorescent units (RFUs). The SomaScan data consisted of semiquantitative measurements of 4785 SOMAmers. Known batch effects stemming from microarray plates were removed using an empirical Bayes method. This was done jointly for the FUTURE studies, but separately for the EXCEED study, due to differing SomaScan platform versions: 3 and 4.1, respectively.

For targeted quantification of the novel biomarker, an ELISA was used to measure protein concentration in serum samples.

Clinical features and endpoints

In the FUTURE trials, patients were randomised to treatment arms (placebo or secukinumab at 75 mg, 150 mg or 300 mg) stratified by prior exposure (naïve or inadequate responder) to TNFi. The treatment arm (by dose level) and TNFi status, along with concomitant use of methotrexate (yes/no), were included as categorical variables in our statistical models. Subject weight was modelled as a continuous covariate. In the active arms, patients received or self-administered subcutaneous secukinumab every 4 weeks. In addition, FUTURE 2–5 prescribed subcutaneous secukinumab or placebo loading doses at weeks 1, 2 and 3, whereas FUTURE 1 prescribed intravenous loading doses (10 mg/kg) at weeks 0, 2 and 4. Therefore we included an indicator variable identifying patients in the intravenous-loading secukinumab regimen. In the remainder of this manuscript, we refer to the features described in this paragraph as ‘key clinical features’.

All explanatory variables pertained to baseline, whereas we modelled clinical response at week 16. This allowed us to include the placebo arms, which until that point had not yet switched onto secukinumab treatment. In line with the primary endpoint of the clinical trials, we mainly considered clinical response in terms of the American College of Rheumatology (ACR) definition of 20% improvement (ACR20). Patients were considered ACR20 responders if exhibiting at least 20% improvement from baseline in the number of swollen and tender joints as well as at least three of the following five metrics: patient’s assessment of pain, patient’s or physician’s global assessment of disease activity, health assessment questionnaire score and levels of high-sensitivity C-reactive protein (hsCRP) or erythrocyte sedimentation rate (ESR). ACR50 and ACR70 were defined analogously.

Choice of training/test data

Before analysing any data, we set aside FUTURE 2 as a hold-out test set which was not used for discovery of candidate predictive biomarkers. We chose FUTURE 2 because of its size (amounting to roughly 20% of all patients in the FUTURE trials) and because its arms were representative of all administered secukinumab dose levels. FUTURE 1, 3, 4 and 5 were used as a pooled training set for model fitting and variable selection. After identifying biomarkers and tuning model parameters based on the training set, we predicted expected responses in the test set and compared the predictions to the observed clinical responses. Similarly, we performed hypothesis testing only in FUTURE 2, thereby enabling valid statistical inference and assessing replicability in an independent cohort.
Statistical model and learning

We used penalised linear regression to model relationships between clinical response (dependent variable) and baseline abundance of proteins (independent variables) as measured by SomaScan in terms of RFUs on a logarithmic scale. In addition, the above-defined key clinical features were included as main effects to account for their associations with clinical response. Each protein was modelled both as a main effect and in interaction with an indicator variable of secukinumab treatment. Thus, the main effects modelled prognostic biomarkers and the interaction terms captured predictive biomarkers.

When modelling clinical endpoints with a dichotomous outcome (ie, ACR20, ACR50 and ACR70), we used logistic regression through the implementation in R V.4.0.5.19 For swollen/tender joint counts, we used logistic regression through the implementation of main effects modelled prognostic biomarkers and the indicator variable of secukinumab treatment. Thus, the modelled both as a main effect and interaction with an indicator variable of secukinumab treatment. This finding was replicated in the test set FUTURE 2 (n=310), where baseline abundance of BD-2 was significantly and positively associated with ACR20 response in the treatment arms, but not in the placebo arm (figure 1B). Compared with a clinical model consisting of the above-defined key clinical features, the addition of BD-2 improved predictive power at secukinumab by increasing the area under the ROC curve by 11 percentage points (figure 1C). Importantly, patients with above-median levels of BD-2 at baseline had higher response rates already after 4 weeks of secukinumab treatment, and this trend continued consistently for at least 1 year. In the placebo arms no such trend was visible in the training set. In the test set the numerical trend was inverted, though CIs largely overlapped (figure 1D). As expected, BD-2 did not facilitate response prediction in the placebo arm (online supplemental figure 1).

ORs of response above versus below a biomarker cut-off

After determining a threshold value for a given protein, we computed odds ratios (ORs) using simple logistic regression. This was done separately per treatment (placebo/secukinumab) and TNFi status (naïve/inadequate responder) to allow for differences between the resulting four strata. Within each stratum, the dependent variable was a dichotomised clinical response (eg, ACR20) and the independent variable was an indicator signifying whether the protein’s baseline level exceeded the threshold. The estimated effect size of the non-intercept term, along with its confidence interval (CI) and statistical significance, corresponded to the log OR of clinical response above vs below the threshold. We reported these estimates on a linear scale to aid interpretation.

Descriptive statistics

All figures were created using ggplot2 V.3.3.5,27 and CIs for means were computed using the basic non-parametric bootstrap.

RESULTS

We analysed clinical and SomaScan data from 1989 patients treated with secukinumab or placebo across the FUTURE 1–5 studies to find protein biomarkers whose baseline abundance predict clinical response to secukinumab at 16 weeks. Using regularised regression, we jointly modelled the prognostic and predictive effects of all 4785 SOMAmers on ACR20 response while controlling for the above-defined key clinical features. We used stability selection to generate candidate biomarkers while tolerating at most one false positive; that is, at most one candidate was expected not to replicate beyond the training set. Stability selection found three features associated with clinical response after 16 weeks of treatment (figure 1A).

Hypothesis testing in the test set

Candidate biomarkers were assessed using Wilcoxon’s rank-sum test (two-tailed) in the test set. To assess how a given protein improved predictive performance over a benchmark, we used the training data to fit a clinical model consisting of the above-defined key clinical features (treatment, weight, TNFi exposure, methotrexate use). This model was then augmented by the given candidate biomarker as a main and treatment-interaction effect. Receiver operating characteristic (ROC) curves were used to visualise true and false-positive rates as a function of predicted probability of response. The area under the ROC curve was used to evaluate predictive performance.

Finding a biomarker cut-off enriching treatment response

To determine thresholds enriching for clinical response, we fitted a classification tree using rpart V.4.1–15,25 based on the key clinical features along with a given candidate biomarker. The complexity of the tree was tuned to maximise sensitivity through leave-one-out cross-validation using caret V.6.0–90,26

Strikingly, we found that more liberal models containing up to eight additional proteins, optimally chosen using cross-validation (online supplemental figure 2), did not significantly outperform the predictive advantage of BD-2 alone (encoded by the gene DEFB4A). Similarly, the alternative method random forest yielded the same qualitative result, namely that BD-2 was the top candidate biomarker (online supplemental figure 4).

In the secukinumab arms, baseline BD-2 also improved prediction of ACR50 and ACR70 response (online supplemental figure 3) as well as numerical changes in swollen/tender joint counts, DAS28CRP, physician’s/patient’s global assessment of disease activity and PsA-related pain score (online supplemental figure 5). Furthermore, secukinumab-treated patients with above-median levels of BD-2 at baseline exhibited higher clinical improvement longitudinally in quality-of-life metrics (online supplemental figure 6).

In the literature, BD-2 is known as a marker of IL-17 pathway activity in psoriatic disease. Indeed, in the FUTURE trials, BD-2 was correlated with the Psoriasis Area and Severity Index (PASI) at baseline.
when controlling for PASI, BD-2 was not significantly correlated with baseline disease components (such as swollen/tender joint counts and hsCRP) except for ESR. Nor was BD-2 significantly correlated with quality-of-life scores or DAS28 at baseline (online supplemental figure 7).

To assess the influence of baseline skin involvement when predicting ACR response at week 16, we performed two additional analyses in the test set. First, we fitted a logistic regression model controlling for PASI score at baseline and found that BD-2 remained significantly associated with ACR20 response (online supplemental table 1). Second, we confirmed that BD-2 predicted ACR response in patients with less than 3% body surface area afflicted by psoriasis at baseline (online supplemental figure 8). In contrast, we found no association between baseline BD-2 levels and subsequent PASI75 response (online supplemental figure 9).

Among the other selected features, both of which were prognostic candidates (figure 1A), hypothesis testing confirmed that being naïve to TNFi inhibitors is significantly associated with ACR20 response in the test set (OR=2.21, Fisher’s exact p value=0.002). However, the SOMAmer measuring protein Z-dependent protease inhibitor (encoded by SERPINA10) was not significantly associated with ACR20 (online supplemental figure 10).

The literature suggests that CRP may be a predictive biomarker of clinical response to TNFi. A SOMAmer measuring CRP was included in the SomaScan platform, but it was not chosen by stability selection. By contrast, if including a protocol-embedded assay measuring hsCRP, it was discovered as predictive (online supplemental figure 11) and validated in the test set (online supplemental figure 12). If including baseline hsCRP in the clinical model to predict ACR20 response, then the addition of BD-2 increased the area under the ROC curve by 8 percentage points (online supplemental figure 13). Compared with the 11 percentage points gained when not using hsCRP, this indicates that the predictive signal contained in BD-2 presents a substantial improvement over hsCRP, especially if accepting a sensitivity slightly lower than 75%. However, we decided not to include baseline hsCRP in our models because its per cent change from baseline is one of the ACR criteria, and it therefore influences ACR response by definition.

An ELISA was performed to validate that the SOMAmer faithfully measured BD-2, and to enable determination of a cut-off enriching for secukinumab response. Sera were available from 1648 patients across FUTURE 1, 2, 3 and 5, and concentrations of BD-2 were quantified in these samples. The correlation between the ELISA and SOMAmer measurements of BD-2 was high (Spearman’s rho=85%), though the SOMAmer read-outs were dampened at the extremes (online supplemental figure 14).

The experimentally determined BD-2 concentrations were incorporated, along with the above-defined key clinical features, into a classification tree trained to predict ACR20 response at week 16, while optimising sensitivity (online supplemental figure 15). This model identified the treatment (secukinumab vs placebo) as the most important factor, followed by the baseline concentration of BD-2 (figure 2A). Secukinumab-treated patients with BD-2≥3961 pg/mL (approximately the upper quartile) were classified as responders and exhibited a high response rate of 76%. Conversely, secukinumab-treated patients with BD-2<420.2 pg/mL were classified as non-responders and exhibited a comparatively lower response rate of 39%. Secukinumab-treated patients with BD-2≥420.2 but <3961 pg/mL were classified as responders and exhibited a moderate response rate of 59%. Performance metrics of response prediction in the test set (FUTURE 2) are shown in online supplemental table 2.

The ELISA quantification thus validated the SomaScan-based finding that baseline concentration of BD-2 is associated with higher response rates in patients treated with secukinumab but not placebo. This could also be seen using a sliding threshold over BD-2 levels, which between training and test sets showed consistent trends in the secukinumab but not placebo arms (figure 2B). Note that as the threshold increases, the sample size supporting the curves decreases, resulting in unreliable estimates of response rates. To address this, we compared the numerical ACR score to the baseline BD-2 concentration and found that they were significantly correlated in the secukinumab arms (Spearman’s rho=27%, p value=3.8e−5) but not in the placebo arm (online supplemental figure 16).

Across the study cohorts, marginal associations showed that BD-2 was consistently predictive, and even more so in patients classified as prior TNFi inadequate responders (TNFi-IRs; figure 2C). Indeed, ORs of ACR20 response in secukinumab-treated patients with baseline BD-2≥3961 pg/mL are higher for TNFi-IRs in each study (online supplemental table 3). We observed the same numerical trend for ACR50 and ACR70 response (table 1).

Having established that in PsA, BD-2 predicts clinical response to secukinumab but not placebo, we investigated whether BD-2 also predicts clinical response to TNFi treatment. The EXCEED study compared secukinumab versus adalimumab treatment over 52 weeks in patients with PsA naïve to TNFi. We analysed clinical and SomaScan data in 787 patients with PsA from this study: 395 treated with adalimumab and 394 with secukinumab. We found that patients with an above-median level of BD-2 at baseline had higher rates of ACR20 response in both secukinumab and adalimumab (figure 3A). This indicates that BD-2 is a predictive biomarker not only for anti–IL-17A treatment but also for TNF inhibition. We noted that ACR response data were missing at a higher rate in the adalimumab arm (online supplemental table 4), leading to more prevalent non-responder imputation. To address this, we performed an additional analysis by employing non-responder imputation only for patients who discontinued the study due to a lack of efficacy. For all other patients, missing ACR response data was simply
omitted. We also changed the order of hierarchy to compare treatment arms within BD-2 cohorts. The result does not indicate any significant difference in efficacy between treatment arms (online supplemental figure 17).

To determine whether BD-2 is predictive in other forms of inflammatory arthritis, we analysed SomaScan data from three placebo-controlled phase-III studies assessing secukinumab treatment in a total of 851 patients with active RA. Based on data from 563 patients in the secukinumab arms, we saw no evidence of BD-2 being predictive of clinical response in RA (figure 3B). We also investigated whether BD-2 predicts clinical response to secukinumab in psoriasis, but the results were inconclusive, partly due to small sample sizes (data not shown).

**DISCUSSION**

We performed a data-driven search for predictive biomarkers among thousands of prespecified proteins measured using the SomaScan platform in serum across five phase-III clinical trials of PsA, and found that baseline
levels of BD-2 were significantly associated with clinical response to secukinumab. This finding was confirmed in two studies not used for its discovery, namely FUTURE 2 and EXCEED, and the initial SomaScan results were validated by ELISA, with a cut-off optimised for differentiating between ACR20 responders and non-responders. We found that the chance of ACR20 response to secukinumab increased gradually with the baseline concentration of BD-2, whereby patients with low, medium and high levels exhibited response rates of 39%, 59% and 76%, respectively. While baseline BD-2 levels in serum could in principle be used as a tool to enrich for response, their use in clinical practice would need to be evaluated further.

We separately analysed the numeric endpoints which constitute the ACR criteria, and found that BD-2 was the top candidate for all except hsCRP and ESR. Here, we chose to focus on ACR20 partly because it was the primary endpoint in the clinical trials under investigation, but also because this threshold was low enough to be reached by a moderate proportion of patients treated with placebo. This allowed us to differentiate between prognostic and predictive biomarkers, during both the discovery and validation phase. In the placebo arms there was no consistent

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Reported in parenthesis are 95% CIs along with asterisks indicating p values below 0.05 (*), 0.01 (**) and 0.001 (**). Statistics are based on 1648 patients across FUTURE 1, 2, 3 and 5.

ACR20, American College of Rheumatology definition of 20% improvement; BD-2, beta-defensin 2; TNFi, tumour necrosis factor inhibitor.

Figure 3 Longitudinal ACR20 response rates in patients with above/below median baseline BD-2 levels as measured by SomaScan. Shaded bands show 95% CIs. (A) Clinical response to secukinumab or adalimumab by baseline BD-2 levels, in the EXCEED study in PsA. Sample size n=787 (394 in the secukinumab arm and 393 in the adalimumab arm). (B) Clinical response to secukinumab in rheumatoid arthritis by baseline BD-2 levels (studies REASSURE, NURTURE 1, and REASSURE 2). Sample size n=563. ACR20, American College of Rheumatology definition of 20% improvement; BD-2, beta-defensin 2; PsA, psoriatic arthritis.
evidence of an association between baseline BD-2 and clinical response, leading us to conclude that BD-2 is a predictive rather than a prognostic biomarker. This finding applied to the ACR response criteria (20, 50 and 70), swollen and tender joint counts, as well as a broad array of endpoints including patient-reported outcomes of pain, disease activity and quality of life. The predictive signal was observed regardless of prior TNFi exposure, though it was more pronounced in patients with prior inadequate clinical response to TNFi. For TNFi-naïve patients, those with high BD-2 levels at baseline had about double the odds of clinical response (ACR20, ACR50 and ACR70) compared with patients with low BD-2 levels. By contrast, in the TNFi-IR cohort, patients with high BD-2 levels exhibited ORs of response ranging from 3.3 to 2.4 for ACR20 through ACR70. This suggests that BD-2 may identify patients with an IL-17-driven disease endotype, who would be more likely to feature in the TNFi-IR group since they have previously failed to respond to TNFi.

BD-2 expression is upregulated by IL-17 in keratinocytes and serum BD-2 is highly correlated with IL-17A levels and psoriasis severity. In patients with psoriasis, BD-2 is also considerably downregulated in serum and skin within 8 days of secukinumab treatment. In PsA, by contrast, when controlling for PASI score we found no relationship between BD-2 and clinical arthritis activity at baseline. Importantly, BD-2 remained predictive in patients with less than 3% body surface area (BSA) afflicted by psoriasis, indicating that the predictive performance of BD-2 is not explained by the extent of skin involvement. While BD-2 has been shown to be overexpressed in non-lesional skin of patients with psoriasis, it is possible that patients with PsA with <3% BSA afflicted by psoriasis may still have enough skin lesions to explain the serum levels of BD-2 which we observed in our study. In psoriasis our inconclusive results may be due to small sample sizes, though it may be challenging to leverage BD-2 for response prediction due to the very high baseline levels of BD-2 found in psoriasis relative to PsA, and the high percentage of clinical responders to IL-17 blockade, which makes statistical discrimination between responders and non-responders difficult. Whereas we observed no significant association between baseline BD-2 and PASI75 response in PsA, a recent study in PsA found that baseline levels of BD-2 were also associated with improved PASI75 response to deucravacitinib, an inhibitor of tyrosine kinase 2 which blocks the IL-23 pathway. In PsA, we thus hypothesise that there are certain patients with increased IL-17 pathway activity, indicated by high BD-2 levels, who are more likely to respond to an IL-17 inhibitor. Within inflammatory arthritis, our findings are specific for PsA in that baseline BD-2 was not predictive of response to secukinumab in RA despite a large sample size. This may be due to the smaller percentage of ACR20 responders in RA versus PsA or lower levels of serum BD-2 in RA compared with PsA.

Our analysis of the EXCEED study showed that BD-2 is predictive of clinical response not only to secukinumab but also to adalimumab. This may be explained by the fact that the TNF and IL-17 pathways are tightly related, with synergistic induction of BD-2 and other response genes by TNF and IL-17, in both skin and synovium. Comparing the secukinumab arms of EXCEED and FUTURE 2—both independent test sets with samples sizes of 394 and 232, respectively—the predictive signal of BD-2 was less striking in the former. Since EXCEED enrolled only TNFi-naïve patients, this is in line with our finding that the predictive signal is less pronounced in TNFi-naïve patients. In conclusion, these results suggest that there may be an IL-17–driven endotype of PsA with higher serum BD-2 levels and an elevated response rate to secukinumab, which raises the possibility for further precision medicine approaches for the significant remaining unmet medical need in PsA.

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Contributors EF conceptualised the project and provided supervision jointly with MV. MC devised the statistical frameworks and performed the data analysis. DT preprocessed data and provided regular feedback together with AK. AM and PF enabled the ELISA profiling and provided constructive feedback along with RMS. MC, EF and MV wrote the first draft of the manuscript with substantive revision by RMS. All authors critically read, revised and approved the final manuscript. MC, MV and EF act as guarantors. Non-author contributors: Tong Zhang coordinated the ELISA data transfer from an external vendor to Novartis. Aashil Batavia helped with the revision of the manuscript.

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Competing interests All authors are employees of Novartis AG, except MC who is now employed by AstraZeneca. AK, PF, RMS, AM, MV and EF hold Novartis shares or share options. Unrelated to this work, RMS has acted as a consultant for Boehringer Ingelheim, and PF serves as a guest lecturer for the University of Applied Sciences Northwestern Switzerland.

Patient consent for publication Not applicable.

Ethics approval We retrospectively analysed data from completed clinical studies with the following ClinicalTrials.gov IDs: NCT01392326, NCT01752634, NCT01998468, NCT02294227, NCT02404350, NCT02745080, NCT01377012, NCT01356084, NCT01770379. The original studies were approved by the relevant institutional boards, including the option of additional use of the data. Individual participants could consent to the additional use of their data, and we limited our analyses to participants with active informed consent. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Anonymised clinical data are available upon request through Novartis’ voluntary data sharing process via ClinicalStudyDataRequest.com. The SomaScan data is governed by a partnership agreement between Novartis and SomaLogic, and access by third parties is possible through a Data User Agreement with the Novartis Institutes for BioMedical Research.

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