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# Using serum ustekinumab levels to predict clinical response in psoriasis: a multicenter prospective observational cohort study

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**Key Points**

**Question:** Can therapeutic drug monitoring for the IL-12/23 inhibitor ustekinumab optimise treatment pathways and outcomes in psoriasis?

**Findings:** Early serum ustekinumab levels predicted subsequent PASI75 response, although this relationship did not hold across other PASI outcomes. Drug immunogenicity appeared low, with anti-drug antibodies detected in only 3.5% of patients.

**Meaning:** This real-world study provides evidence that measurement of early ustekinumab levels could be useful to direct treatment strategy in psoriasis. Adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome.

**Abbreviations**

ADA - Anti-drug antibodies

AIC - Akaike Information Criterion

AU – Arbitrary units

BADBIR - British Association of Dermatologists Biologic Interventions Registry

BMI – Body mass index

BSTOP - Biomarkers of Systemic Treatment Outcomes in Psoriasis

CI - Confidence interval

IL - Interleukin

OR - Odds ratio

PASI - Psoriasis Area and Severity Index

PSORTD – Psoriasis Stratification to Optimise Relevant Therapy (Discovery)

SD – standard deviation

TDM – Therapeutic drug monitoring

TNF - tumour necrosis factor

78 **Abstract**

79 **Importance:** High-cost biologic therapies have transformed the management of immune-
80 mediated inflammatory diseases. To optimise outcomes and reduce costs, dose adjustment
81 informed by circulating drug levels has been shown to be effective in various settings.
82 However, limited evidence exists for this approach with the IL-12/23 inhibitor ustekinumab.

83 **Objective:** To determine the real-world clinical utility of therapeutic drug monitoring in
84 psoriasis for ustekinumab.

85 **Design:** A prospective observational cohort of adults recruited to Biomarkers of Systemic
86 Treatment Outcomes in Psoriasis within the British Association of Dermatologists Biologic
87 and Immunomodulators Register, 2009-2017.

88 **Setting:** Multicenter (n=60) UK and Eire study; dermatology secondary care.

89 **Participants:** Adults with psoriasis, started on ustekinumab with up to one year's follow-up.

90 **Exposure:** Serum ustekinumab level (μg/ml), measured at any point during the dosing cycle
91 using an enzyme-linked immunosorbent assay.

92 **Main Outcomes and Measures:** Disease activity measured using the Psoriasis Area and
93 Severity Index (PASI). Treatment response outcomes were PASI75 (75% reduction in PASI
94 from baseline, primary outcome), PASI90 and absolute PASI≤1.5.

95 **Results:** 491 patients (65.2% male; mean age 45.7 years (sd 12.8)) had ≥1 serum sample
96 (total 853 samples taken 0-56 weeks from start of treatment) and ≥1 PASI score within the
97 first year of treatment. Anti-drug antibodies were detected in only 3.5% of patients. Early
98 drug levels (1-12 weeks after starting treatment) were predictive of PASI75 response 6
99 months after starting treatment (OR 1.38, 95% CI 1.11-1.71) when adjusted for baseline

PASI, age and ustekinumab dose. However, this was not consistent across the other PASI outcomes (PASI90 and PASI≤1.5).

**Conclusions and Relevance:** This real-world study provides evidence that measurement of early serum ustekinumab levels could be useful to direct treatment strategy in psoriasis. Adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome.

## Introduction

Psoriasis is a chronic immune-mediated skin disease affecting at least 2% of the population[1]. Management has been transformed by therapeutic monoclonal antibody biologics, of which the first-line choices are either adalimumab (a tumour necrosis factor [TNF] inhibitor) or ustekinumab (an interleukin [IL]-12/IL-23 inhibitor)[2]. There is wide variation in response to these drugs, with a significant number of patients not responding (primary treatment failure) or losing response over time (secondary treatment failure)[3,4]. Some of this heterogeneity may be explained by differences in the bioavailability and quantity of drug available at the target tissue, which in turn is influenced by adherence, drug dose and pharmacokinetic covariates such as weight and drug immunogenicity (development of anti-drug antibodies [ADA]).

Unlike most other biologics used for inflammatory disease, ustekinumab is dosed according to bodyweight; patients under 100kg are generally given 45mg subcutaneously every 12 weeks, whereas those weighing at least 100kg are given 90mg[5]. Despite this, evidence suggests that ustekinumab dosing is suboptimal in some patients: clinical trial data previously showed that dose escalation increased PASI75 response rates in partial responders (those achieving > or =50% but <75% improvement from baseline PASI)[6], whilst patients with higher baseline body mass index (BMI) have been reported to receive in excess of the recommended cumulative dose over the first year of treatment[7]. Similarly, response rates to ustekinumab in patients weighing 90-100kg have been reported to be significantly lower than in other weight groups, suggesting that the standard 45mg dose is inadequate in patients approaching the 100kg threshold[8]. On the other hand, ustekinumab dosing is likely to be excessive in some patients; a recent phase IIIb study reported that lengthening intervals between ustekinumab doses did not affect maintenance of response[9].

Taken together, these findings suggest that individualized dose optimization and therapeutic drug monitoring (TDM) of ustekinumab may have clinical utility.

Although several ustekinumab assays are commercially available in both the USA and Europe[10-15], serum ustekinumab levels are not yet widely used in clinical practice. This is partly due to limited evidence for TDM of this drug, in contrast to the strong correlation described between TNF inhibitor serum levels, ADA and treatment response across multiple immune-mediated inflammatory diseases[16-20]. Indeed, reports on the relationship between ustekinumab level and response have been inconclusive[21-25], with basic parameter requirements for TDM (eg. therapeutic range, target drug level) yet to be established in the context of psoriasis.

Since the first step towards defining such parameters is to determine the relationship between drug levels and outcome, we investigated this using a real-world bioresource from a large multicenter cohort study BSTOP (Biomarkers of Systemic Treatment Outcomes in Psoriasis) within the UK pharmacovigilance registry BADBIR (British Association of Dermatologists Biologic and Immunomodulators Register). Specifically, we aimed to (1) explore the relationship between drug level and response on the same day the drug level was taken, and (2) explore the relationship between early drug level and response at 6 months, since maximum clinical utility may lie in the ability to predict outcome and modify therapy prior to clinical relapse.

## Materials and methods

### Ethics approval

This study was conducted in accordance with the 2008 Declaration of Helsinki. Two studies provided samples and data: BSTOP (ethics approval code 11/H0802/7), and its nested study Psoriasis Stratification to Optimise Relevant Therapy Discovery (PSORTD, ethics approval code 14/LO/1685).

### Patients and setting

As described previously[20], BSTOP is a prospective multicenter (n=60) observational study, established in 2011 to identify markers of outcomes to systemic therapies in psoriasis. All UK adults fulfilling BSTOP inclusion criteria[26] and enrolled onto BADBIR[27] were invited to participate. Clinical response was assessed longitudinally using the Psoriasis Area and Severity Index (PASI). The current analysis includes patients on ustekinumab monotherapy, with $\geq$1 serum sample and $\geq$1 recorded PASI within the first year of treatment (Figure 1).

### Drug level and ADA measurements

Venous blood was collected during clinic reviews, centrifuged for 10 minutes (2000g) and serum aliquots frozen (-80°C). In this pragmatic study, samples were not collected from every patient at every timepoint; most were taken without reference to treatment administration. Samples within the first year of treatment were sent to Sanquin for measurement if ustekinumab levels and ADA. The ustekinumab level assay was an enzyme-linked immunosorbent assay similar to a previously developed adalimumab assay[28], but using IL-12 to capture ustekinumab, with rabbit anti-ustekinumab for detection (lower limit of detection 0.02µg/mL). ADA were measured using a previously described radioimmunoassay[29], with minor modifications (ADA positive cutoff >12 arbitrary units [AU]/ml). Specifically, 1µl serum diluted in freeze medium was incubated with Sepharose-

immobilized protein A in the presence of 1ng/test biotin-conjugated ustekinumab $F(ab)_2$. Non-bound serum components were removed by washing; 50µl $^{125}$I-labelled streptavidin was added in 500µl phosphate buffered saline-albumin tween (0.3% bovine serum albumin, 0.01M ethylenediaminetetraacetic acid, 0.004% tween-20, 0.05% NaN3). After incubation and washing, radioactivity was measured using a gamma counter. Assay results were converted to AU/ml calculated from a 2-fold serially diluted calibration curve of a polyclonal ustekinumab-specific rabbit anti-idiotype[30]. This assay format has limited drug-tolerance[31], but was previously shown to have better correlation with clinical response versus drug-tolerant alternatives in rheumatoid arthritis patients on adalimumab[32].

**Outcome measures**

Primary treatment response was defined as achieving a 75% reduction in PASI from baseline (PASI75), with baseline PASI defined as the most recent PASI recorded prior to the date of the first drug dose within the preceding 6 months[3,33]. Secondary outcomes were: i) PASI90 (90% PASI reduction from baseline) ii) PASI$\leq$1.5 (absolute PASI$\leq$1.5, which approximates to PASI90, personal communication Nina Wilson).

**Statistical methods**

Based on our previous work using adalimumab drug levels[20], we explored the relationship between ustekinumab level and response in two ways. First, we investigated the association between drug levels and response on the same day of the sample; secondly, we investigated whether drug levels sampled early following treatment start, can predict response at 6 months. Two datasets were therefore derived: a dataset comprising samples taken at steady state (≥16 weeks after treatment start), with a corresponding PASI on the same day as the sample date - hereafter referred to as the 'same-day response' dataset; and

198 a dataset comprising samples taken early in the treatment course (1-12 weeks after
199 treatment start), with a corresponding PASI at 6 months (122-243 days after treatment
200 start) - hereafter referred to as the '6-month response' dataset. Analyses for PASI75 and
201 PASI90 responses were restricted to patients with baseline PASI >10 as an accepted criterion
202 for severe disease[34], and to minimize confounding due to pre-biologic treatments. The latter
203 is particularly relevant in this real-world dataset.
204 *Descriptive analysis*
205 A descriptive concentration effect curve was generated to assess whether clinical response
206 plateaus beyond a certain drug level. Boxplots were used to visually compare drug levels by
207 responder group in both the 'same-day response' and '6-month response' datasets.
208 *Logistic regression analysis*
209 We used univariate logistic regression models with the `6-month response' dataset to
210 explore the relationship between early drug levels and treatment response in the presence
211 of other covariates, including those previously identified as predictors of response in the
212 BADBIR cohort (eg. weight, ethnicity, disease/treatment duration, ustekinumab dose,
213 biologic-naïve status)[35]. Given that most samples were not trough levels, we also included
214 time of sample from last ustekinumab dose as a covariate. For continuous covariates, the
215 best-fitting simple non-linear transformation was chosen based on reduction in the Akaike
216 Information Criterion (AIC). Covariates associated with response at significance level $p<0.1$
217 were taken forward to a multivariable logistic regression model. Forward selection
218 techniques were then used, with covariate inclusion based on a significance level of $p<0.05$.
219 Multivariable models were derived for all three PASI outcomes (PASI75, PASI90 and
220 PASI$\leq$1.5). For PASI90 and PASI$\leq$1.5, drug level was included as the first covariate and
221 retained at each stage, despite not being significant on univariate analysis. Pseudo $R^2$ and

AIC were calculated to assess model fit. All analyses were undertaken using Stata version 14[36] on a complete case basis.

## Results

### Patient cohort and baseline characteristics

491 patients on ustekinumab monotherapy had both serum samples and PASI scores available within the first year of treatment (Figure 1, Table 1). The cohort was predominantly male (65.2%), with mean BMI 32.0 (sd 7.3) and mean baseline PASI 13.3 (sd 6.8). 40.9% of patients were biologic-naïve, and 57.4% were on 45mg ustekinumab versus 42.6% on 90mg (Table 1). Patients not providing serum samples were excluded, but their baseline characteristics were similar (eTable 1).

### Response to treatment

70.9% of patients (348/491) achieved PASI75 at some point within a year of starting treatment. PASI75 remains a standard measure of adequate treatment response in UK guidelines[37].

### Drug levels and ADA

Drug levels were sampled according to standard clinical care. Excluding samples taken on the day the first dose was given: the median time from last dose was 28 days (IQR 16-57 days, range 0-98 days, data available on n=515 samples); median drug level was 1.19µg/ml (IQR 0.37-2.86µg/ml, range 0-13.1µg/ml, n=800 samples); ADA were detected in 3.5% (17/490) of patients (on 20 samples taken 29-350 days after starting treatment).

### Relationship between drug level and response

All analyses considered all eligible samples (maximum 4 per patient).

*Descriptive analysis*

A concentration effect curve showed no clear evidence of a relationship between steady state drug levels and same-day absolute PASI (eFigure 1). Median drug level and spread of drug levels were similar between patients recorded to have responded/not responded on the same day as the serum sample was taken ('same-day response' dataset, eFigure 2). However, patients achieving PASI75 at 6 months ('6-month response' dataset) on average had higher early ustekinumab levels (median 2.78µg/ml, IQR 1.78-4.02, range 0.02-9.78) compared to patients not achieving PASI75 (median 1.83µg/ml, IQR 0.96-2.86, range 0.02-9.00, Figure 2), with overlapping ranges between the two groups. A similar pattern was observed for the other two response outcomes PASI90 and PASI≤1.5 (eFigure 3).

To explore the relationship between drug level, response and dose, we split boxplot data by ustekinumab dose 45mg/90mg (Figure 2b). As expected, PASI75 responders had higher median drug levels than non-responders within each dose group. This pattern was also evident for the PASI90 and PASI≤1.5 outcomes (eFigure 4). However, PASI75 non-responders on 90mg ustekinumab had slightly higher median drug levels than non-responders on 45mg, albeit with overlapping ranges and large variability (Figure 2b).

*Logistic regression analysis*

Univariate logistic regression indicated that early drug level was associated with 6-month PASI75 ('6-month response' dataset: OR 1.27, 95% CI 1.04-1.56), but there was no evidence of this relationship for the other two PASI outcomes (eTable 2). Next, multivariable models were derived to explore the relationship between early drug level and 6-month response in the presence of other relevant covariates. The final model for PASI75 included drug dose, baseline PASI and age as well as drug level (OR 1.38, 95% CI 1.11-1.71, Table 2), and shows increasing probability of response with increasing drug level (Figure 3). The model also suggests that patients on the higher ustekinumab dose (90mg) have a lower probability of

response for a given drug level (Figure 3). To explore this finding further, we inspected boxplots of drug levels split by weight and dose (eFigure 5). Despite overlapping ranges, these show slightly lower median drug levels both in patients weighing >100kg, and in patients on the higher ustekinumab dose.

Drug level was non-significant for the PASI90 and PASI≤1.5 outcomes, even taking into account other covariates. Furthermore, significant covariates were not consistent across the three models for different PASI outcomes within the 6-month response dataset. Finally, we performed a sensitivity analysis by fitting the final model for PASI75 to very early trough samples (21-28 days after treatment start). Despite smaller sample size and greater uncertainty around estimates, a similar relationship between drug level and response was seen (OR 1.31, 95% CI 1.24-11.08, eTable 3).

## Discussion

### Key findings

In the largest study to date of ustekinumab drug level monitoring in psoriasis, we report evidence that early ustekinumab levels were significantly associated with 6-month PASI75 response. This finding has particular clinical and practical relevance, because assays to measure serum ustekinumab levels are already commercially available in both the USA and Europe[10-15].

We also report a low rate (3.5%) of detectable ADA to ustekinumab within the first year of treatment, compared to the previously reported rate of 37.5% in a cohort of patients on adalimumab derived from the same UK study[20]. It is possible that this differential drug immunogenicity accounts, at least partially, for significantly higher rates of drug survival (length of time from initiation to discontinuation) on ustekinumab compared to adalimumab[3].

The finding that the higher ustekinumab dose is associated with a lower probability of response is perhaps surprising. One possible explanation is that patients on the higher dose exhibit characteristics predictive of poor response, that have not been accounted for in our model. An alternative explanation may be that a double dose of ustekinumab (90mg as opposed to 45mg) fails to adequately compensate for the increased volume of distribution in some people of higher bodyweight; indeed, we noted that median drug levels were slightly lower both in patients on the higher ustekinumab dose and in patients weighing >100kg.

Our dataset should allow for stable estimation of comparable numbers (4-5) of covariates[38] in each of the analyses for early drug level versus the three different PASI outcomes. However, we were unable to demonstrate a link between early drug level and

the other PASI outcomes, nor between steady state drug levels and same-day response. It is therefore possible that the association between early drug level and PASI75 is due to a spurious p value or statistical artefact. This contrasts with our findings for adalimumab, where the same statistical approach showed that both early and steady state drug levels were significantly associated with all PASI outcomes. A fundamental explanation for this may lie in differing mechanisms of biologic action: adalimumab directly inhibits the inflammatory effector cytokine TNF, whereas ustekinumab inhibits IL-12 and IL-23 – the latter being a master regulator of pathogenic T helper 17 cell development[39]. Just as the underlying biological impact is more complex for ustekinumab, it may be that the relationship between drug level and response is correspondingly convoluted.

**Existing literature**

Other studies in this area are few in number, generally limited to descriptive or empirical analyses investigating the relationship between ustekinumab level and response, and report mixed results. The most recent study in psoriasis included prospective follow-up of only 27 patients, but reported similar findings to us, in that very early drug levels (Week 6) were inversely correlated with subsequent response (Week 12). However, in line with our data, no relationship was detected between drug levels taken later (in this case at Week 12) and same-day response[25].

The largest study in psoriasis reported significantly lower drug levels and PASI50 response rates in patients with detectable ADA compared to those without[23]. Finally, in a Dutch cohort of 41 psoriasis patients there was no correlation between ustekinumab level and response; 7% (3/41) of patients developed ADA[24].

Larger-scale studies have been conducted in the context of inflammatory bowel disease. Indeed, it is possible that variability in the amount of drug lost via the inflamed gut means

that some patients are less able to achieve adequate serum concentrations, meaning that TDM may have greater utility in this setting. An analysis of Phase 3 trial data (n = 1154) reported positive association of drug levels with clinical and endoscopic improvement, and inverse correlation with C-reactive protein level. Only 2% of patients developed ADA[21].

**Strengths and limitations**

A strength of this study is high external validity, since more than 50% of all UK psoriasis patients on biologics are registered on BADBIR, and 95% of UK dermatology centers prescribing biologics for psoriasis contribute data to BADBIR. Our findings highlight the potential clinical utility of this easily measurable early biomarker in optimizing subsequent response. They also serve as a call to action for both industry and academia to develop cost-effective and widely available assays, and to further validate the role of TDM in clinical practice.

One limitation is that out of 491 patients with both a serum sample and PASI within a year of treatment, the 'same-day response' and '6-month response' datasets included 148 and 85 patients respectively. Figure 1 shows the drop-off in patient numbers at each stage of filtering.

A second limitation relates to the difficulty in accounting for the complex relationship between drug level and response using a standard logistic regression modelling approach. This has been successfully used in other settings, notably to define a therapeutic range and target drug level for adalimumab[20]. However, it is possible that ustekinumab's extended dosing interval compared to adalimumab may pose a particular hindrance in this context, as a single or small number of drug levels may represent a relatively poor measure of total drug exposure. This issue may have been exacerbated by pragmatic serum sampling and PASI assessment at routine clinical visits, as opposed to having samples and PASIs only

during trough periods. To partially address this, we accounted for the timing of samples by including time from last ustekinumab dose as a covariate in modelling, but this did not remain in the final multivariable models after the forward selection process. Finally, the validity of our findings is limited to within one year of start of treatment, since this was the selected cohort duration.

**Conclusion**

Despite the complexities outlined above, we did find a significant association between early drug levels ($\leq$12 weeks) and 6-month PASI75 response. This suggests that adequate drug exposure early in the treatment cycle may be particularly important in determining clinical outcome on ustekinumab. However, our statistical approach did not take into account patient-level pharmacokinetic parameters such as volume of distribution and clearance, nor potential differences in the evolution of PASI over time versus changing drug levels. Therefore, future work should focus on pharmacokinetic-pharmacodynamic modelling of the whole timecourse of response to ustekinumab[40]. This may be of particular relevance for biologics with more upstream targets, such as differentiation pathway cytokines as opposed to effector cytokines. Further investigation to confirm the clinical utility of TDM of ustekinumab and other biologics is a key step towards personalisation of treatment regimens across multiple immune-mediated inflammatory diseases.

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**Conflicts of interest**

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537 ***Table 1. Summary statistics for the full cohort, 'same-day response' dataset and '6-month***

538 ***response' dataset***

539

| | **Full cohort** (n= 491 patients, 853 samples) | | **'Same-day response' dataset** (n= 148 patients, 175 samples) | | **'6-month response' dataset** (n= 85 patients, 119 samples) | |
|---|---|---|---|---|---|---|
| **Covariate** | **Mean (sd)** | **Complete data n (%)** | **Mean (sd)** | **Complete data n (%)** | **Mean (sd)** | **Complete data n (%)** |
| Baseline PASI | 13.3 (6.8) | 452 (92.1) | 16.6 (5.2) | 148 (100) | 16.3 (5.5) | 85 (100) |
| Height (cm) | 172.2 (10.3) | 463 (94.3) | 172.4 (10.5) | 140 (94.6) | 172.1 (10.5) | 81 (95.3) |
| Weight (kg) | 94.7 (22.7) | 435 (88.6) | 96.1 (23.7) | 140 (94.6) | 94.2 (22.9) | 80 (94.1) |
| Waist (cm) | 105.8 (16.8) | 420 (85.5) | 106.5 (17.4) | 131 (88.5) | 105.2 (15.7) | 77 (90.6) |
| BMI ($kg/m^2$) | 32.0 (7.3) | 427 (87.0) | 32.3 (7.7) | 136 (91.9) | 31.7 (7.6) | 78 (91.8) |
| Age (years) | 45.7 (12.8) | 491 (100) | 45.2 (13.1) | 148 (100) | 48.7 (13.3) | 85 (100) |
| Disease duration (years) | 23.3 (13.1) | 464 (94.5) | 23.1 (13.1) | 142 (95.9) | 23.4 (13.0) | 82 (96.5) |
| | **n (%)** | | **n (%)** | | **n (%)** | |
| Ethnicity – white | 421 | 491 | 123 | 148 | 70 | 85 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (85.7) | (100) | (83.1) | (100) | (82.4) | (100) |
| Gender - male | 320 (65.2) | 491 (100) | 99 (66.9) | 148 (100) | 59 (69.4) | 85 (100) |
| Inflammatory arthritis | 101 (23.5) | 430 (87.6) | 26 (18.8) | 138 (93.2) | 24 (30.4) | 79 (92.9) |
| Ever smoked | 289 (61.2) | 472 (96.1) | 81 (55.9) | 145 (98.0) | 51 (61.5) | 83 (97.6) |
| Palm psoriasis | 93 (21.1) | 441 (89.8) | 30 (21.6) | 139 (93.9) | 19 (24.1) | 79 (92.9) |
| Biologic naive | 201 (40.9) | 491 (100) | 64 (43.2) | 148 (100) | 37 (43.5) | 85 (100) |
| Dose 45mg<br><br>90mg | 282 (57.4)<br><br>209 (42.6) | 491 (100) | 82 (55.4)<br><br>66 (55.6) | 148 (100) | 48 (56.5)<br><br>37 (43.5) | 85 (100) |

Summaries for the 'same-day response and '6-month response' datasets are restricted to patients with baseline PASI > 10.

545 ***Table 2. Final multivariable models for predicting 6-month response***

546

| | Covariate | Coefficient (s.e) | OR (95% CI) | P value | Pseudo $R^2$ | Number of samples | Number of responders (% of samples) |
|---|---|---|---|---|---|---|---|
| **PASI75** | Drug level (µg/ml) | 0.32 (0.11) | 1.38 (1.11, 1.71) | 0.004 | 0.18 | 119 | 73 (61.3) |
| | Baseline PASI | 0.10 (0.04) | 1.10 (1.01, 1.20) | 0.03 | | | |
| | Age (years) | 0.04 (0.02) | 1.04 (1.00, 1.07) | 0.03 | | | |
| | Dose 90 mg | -1.43 (0.44) | 0.24 (0.10, 0.56) | 0.001 | | | |
| **PASI90** | Drug level (µg/ml) | 0.14 (0.09) | 1.15 (0.97, 1.38) | 0.1 | 0.10 | 115 | 45 (39.1) |
| | Baseline PASI | 0.10 (0.04) | 1.11 (1.02, 1.20) | 0.01 | | | |
| | Disease duration (years) | 0.04 (0.02) | 1.04 (1.01, 1.08) | 0.009 | | | |
| **PASI≤1.5** | Drug level (µg/ml) | 0.11 (0.08) | 1.12 (0.96, 1.30) | 0.2 | 0.06 | 186 | 58 (31.2) |
| | Biologic naïve | 0.92 (0.33) | 2.51 (1.31, 4.81) | 0.006 | | | |
| | Ever smoked | -0.70 (0.34) | 0.50 (0.26, 0.96) | 0.04 | | | |

***FIGURE TITLES AND LEGENDS***

***Figure 1. Flow diagram of patients included in the study***

***Figure 2. Boxplots comparing early drug levels by 6-month PASI75 response***

***a. Split by response only***

n = 46 and 73 samples in each group respectively. On each boxplot: middle line is the median, circles are the means, ends of boxes are the lower and upper quartiles, solid dots are outliers (values more than or equal to 1.5 times the interquartile range from the lower and upper quartiles), whiskers show the minimum and maximum values (unless there are outliers, in which case they are 1.5 times the interquartile range from the lower and upper quartiles).

***b. Split by response and by ustekinumab dose***

n = 18, 50, 28, 23 samples in each group respectively. The red boxes correspond to 45mg and the blue boxes correspond to 90mg. On each boxplot: middle line is the median, circles are the means, ends of boxes are the lower and upper quartiles, solid dots are outliers (values more than or equal to 1.5 times the interquartile range from the lower and upper quartiles), whiskers show the minimum and maximum values (unless there are outliers, in which case they are 1.5 times the interquartile range from the lower and upper quartiles).

***Figure 3. Probability of 6-month PASI75 response based on early drug level, split by ustekinumab dose***

Probability of response is split by ustekinumab dose (45 mg in blue, 90 mg in red). Solid lines plot the marginal predicted probability of response; dashed lines are 95% confidence intervals.

726 patients
on ustekinumab monotherapy providing serum samples

491 patients
with both a serum sample and recorded PASI ≤12 months from treatment start

252 patients
with samples taken at steady state
(≥16 weeks after treatment start)

237 patients
with PASI on same date as sample taken

148 patients
with baseline PASI >10

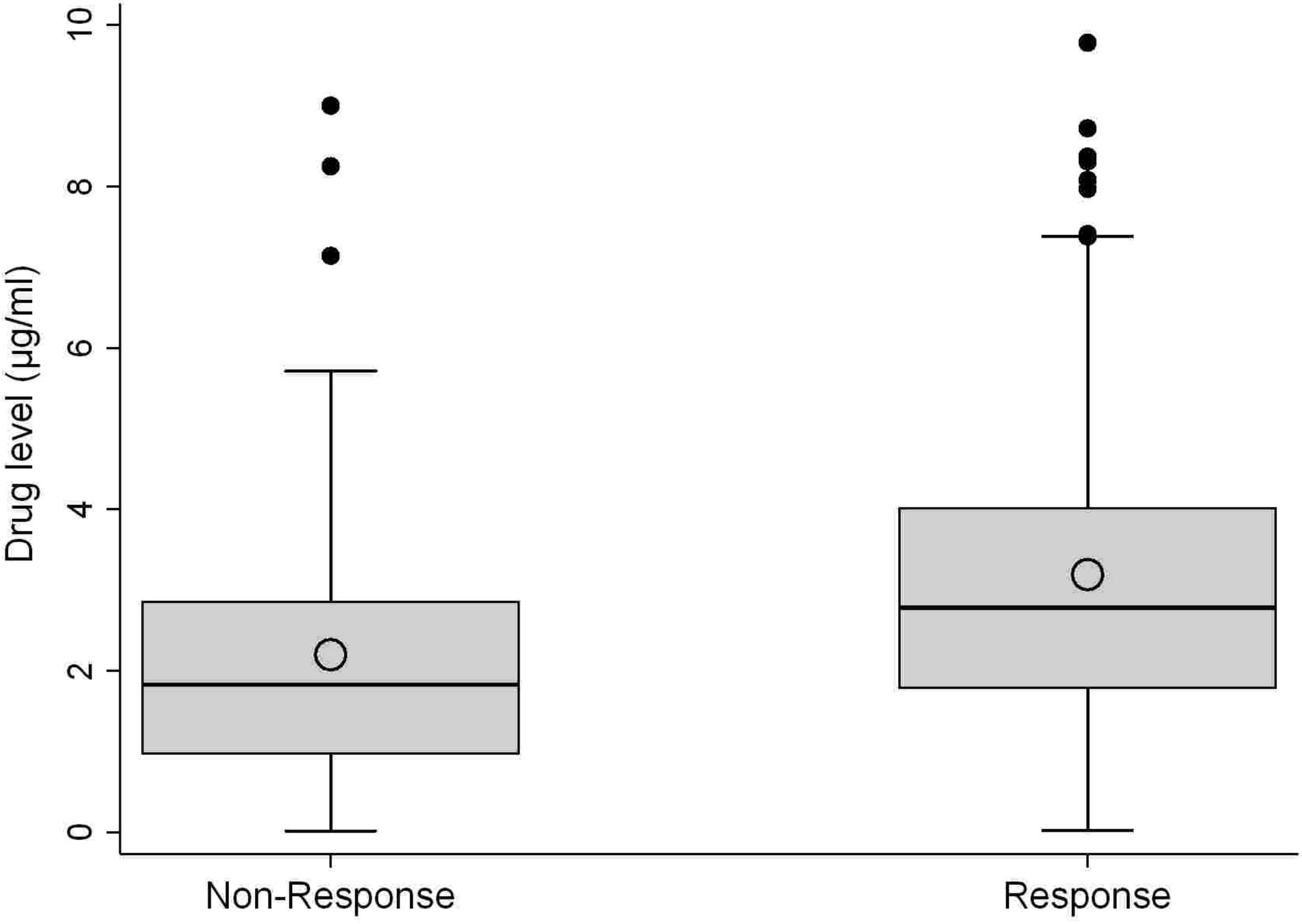
**'Same-day response' dataset**

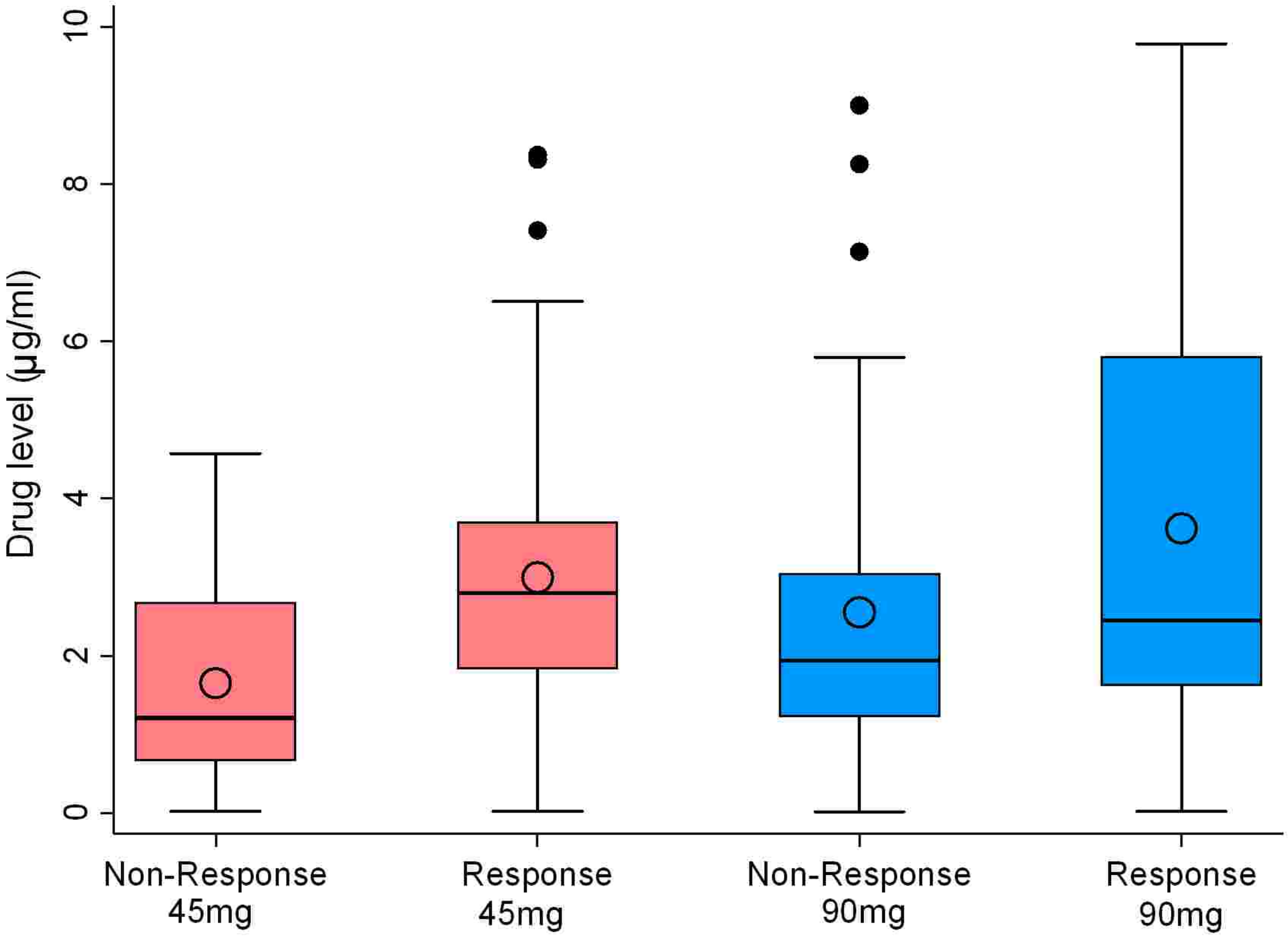
248 patients
with samples taken early
(1-12 weeks after treatment start)

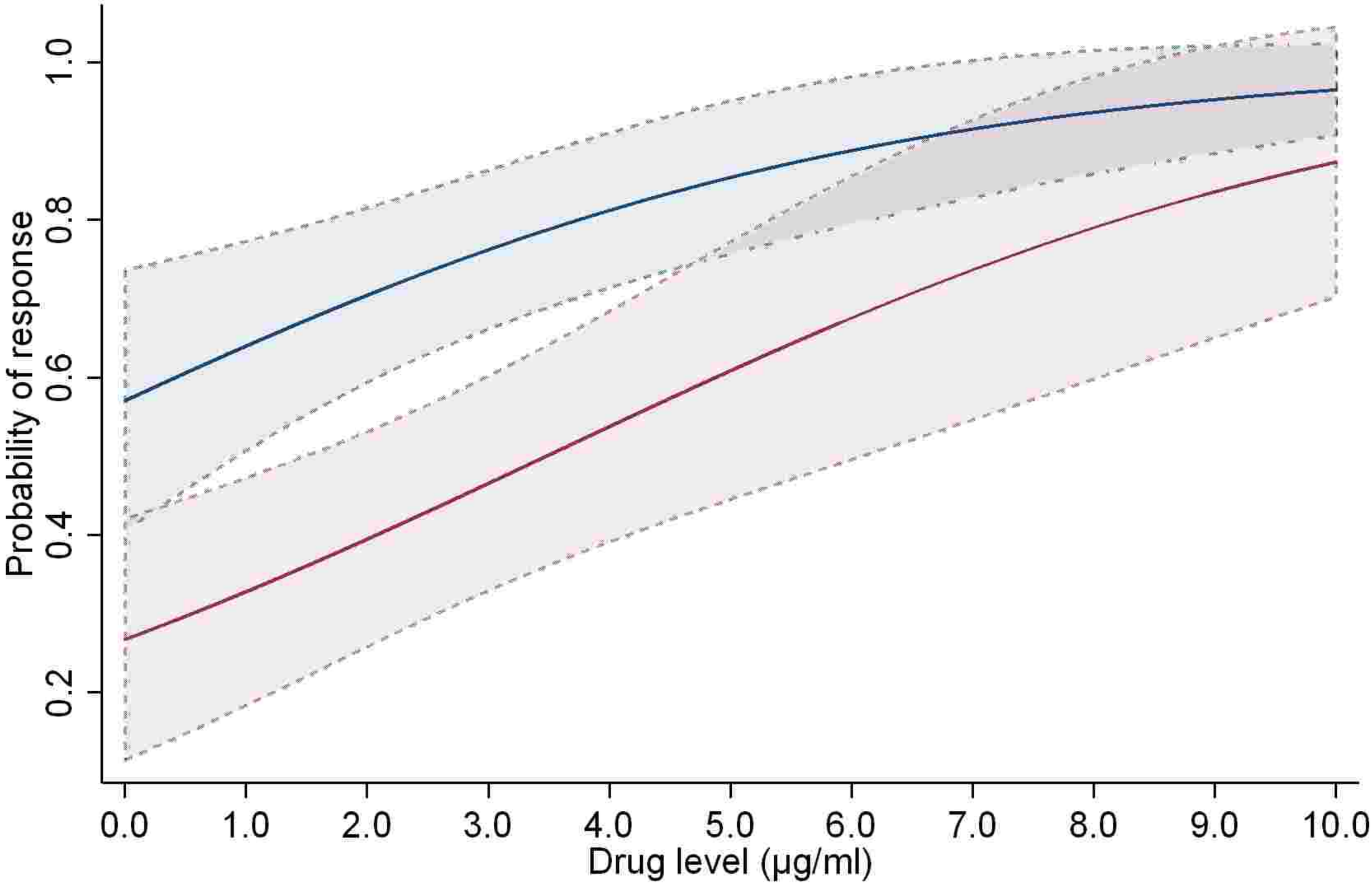
144 patients
with PASI at 6 months
(122-243 days after treatment start)

85 patients
with baseline PASI >10

**'6-month response' dataset**


Drug level (µg/ml)
0
2
4
6
8
10
Non-Response
Response


Drug level (µg/ml)
0
2
4
6
8
10
Non-Response
45mg
Response
45mg
Non-Response
90mg
Response
90mg


Probability of response
0.2
0.4
0.6
0.8
1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
Drug level (µg/ml)