



ALMA MATER STUDIORUM  
UNIVERSITÀ DI BOLOGNA

## ARCHIVIO ISTITUZIONALE DELLA RICERCA

### Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Adalimumab Clearance, rather than Trough Level, May Have Greatest Relevance to Crohn's Disease  
Therapeutic Outcomes Assessed Clinically and Endoscopically

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Wright, E.K., Chaparro, M., Gionchetti, P., Hamilton, A.L., Schulberg, J., Gisbert, J.P., et al. (2024).  
Adalimumab Clearance, rather than Trough Level, May Have Greatest Relevance to Crohn's Disease  
Therapeutic Outcomes Assessed Clinically and Endoscopically. JOURNAL OF CROHN'S AND COLITIS, 18(2),  
212-222 [10.1093/ecco-jcc/jjad140].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/955347> since: 2024-02-02

*Published:*

DOI: <http://doi.org/10.1093/ecco-jcc/jjad140>

*Terms of use:*

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are  
specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).  
When citing, please refer to the published version.

(Article begins on next page)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## **Adalimumab Clearance, rather than Trough Level, May Have Greatest Relevance to Crohn's Disease Therapeutic Outcomes Assessed Clinically and Endoscopically**

Emily K. Wright<sup>1,6</sup>, Maria Chaparro<sup>2</sup>, Paolo Gionchetti<sup>3</sup>, Amy L. Hamilton<sup>1,6</sup>, Julien Schulberg<sup>1,4,6</sup>,  
Javier P. Gisbert<sup>2</sup>, Maria Chiara Valerii<sup>3</sup>, Fernando Rizzello<sup>3</sup>, Peter De Cruz<sup>4,6</sup>, John C. Panetta<sup>5</sup>, Annelie  
Everts van der wind<sup>7</sup>, Michael A. Kamm<sup>1,6</sup> and Thierry Dervieux<sup>7</sup>

<sup>1</sup> St Vincent's Hospital, Melbourne, Australia; <sup>2</sup>Hospital Universitario de La Princesa, IIS-Princesa,  
UAM and CIBEREHD, Madrid, Spain; <sup>3</sup>University of Bologna, Bologna, Italy; <sup>4</sup>Austin Health,  
Melbourne, Australia; <sup>5</sup>St Jude Children's Research Hospital, Memphis TN, USA; <sup>6</sup>The University of  
Melbourne, Melbourne, Australia; <sup>7</sup>Prometheus Laboratories San Diego, CA, USA.

**Short Title:** Adalimumab Clearance and therapeutic outcome

**Correspondence:**

Thierry Dervieux PharmD, PhD.

Research and Development

Prometheus Laboratories, San Diego CA

Email: [tdervieux@prometheuslabs.com](mailto:tdervieux@prometheuslabs.com)

Michael A Kamm

St Vincent's Hospital

Victoria Parade, Fitzroy 3065

Melbourne, AUSTRALIA

Email: [mkamm@unimelb.edu.au](mailto:mkamm@unimelb.edu.au)

1  
2  
3 **ABSTRACT**  
4  
5  
6

7 **Objective:** We postulated that Adalimumab (ADA) drug clearance (CL) may be a more critical  
8 determinant of therapeutic outcome than ADA concentration. This was tested in Crohn's disease (CD)  
9 patients undergoing ADA maintenance treatment.  
10  
11

12 **Methods:** CD patients from 4 cohorts received ADA induction and started maintenance. Therapeutic  
13 outcomes consisted of endoscopic remission (ER), sustained C-reactive protein (CRP) based clinical  
14 remission (defined as CRP levels below 3 mg/L in the absence of symptoms) and fecal calprotectin (FC)  
15 levels below 100µg/g. Serum Albumin, ADA concentrations and anti-drug antibody status were  
16 determined using immunochemistry and homogenous mobility shift assay, respectively. CL was  
17 determined using nonlinear mixed effect model with Bayesian priors. Statistical analysis consisted of  
18 Mann-Whitney test, logistic regression with calculation of odds ratio. Repeated event analysis was  
19 conducted using nonlinear mixed effect model.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29

30 **Results:** In 219 patients enrolled (median age 40 years, 45% females), median CL was lower in ER as  
31 compared to active endoscopic disease status (median 0.247 L/day vs 0.326 L/day, respectively)  
32 (p=0.004). There was no significant difference in ADA concentrations between patients in endoscopic  
33 remission compared to recurrence (median 9.3 µg/mL vs 11.7 µg/mL respectively) (p=0.201). Sustained  
34 CRP-based clinical remission and FC levels below 100µg/g were generally associated with lower CL and  
35 higher ADA concentrations. Repeated event analysis confirmed those findings with better performances  
36 of CL than concentrations in associating with ER and other outcomes.  
37  
38  
39  
40  
41  
42  
43  
44

45 **Conclusion:** Lower ADA Clearance is associated with an improved clinical outcome for patients with  
46 Crohn's disease and may be a superior pharmacokinetic measure than concentrations.  
47  
48  
49  
50  
51

52 **Key words:** Crohn's disease; Adalimumab, pharmacokinetics, Clearance  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Therapeutic drug monitoring (TDM) is now routine for many patients with CD receiving anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) therapies and helps direct and improve drug management<sup>1</sup>. The measurement of adalimumab (ADA, a monoclonal antibody targeting TNF- $\alpha$ ) blood concentration can inform clinicians of the potential need for dose escalation to achieve exposure commensurate with disease control and provide reassurance regarding the absence of immune tolerance and formation of antibodies to adalimumab (ATA).

In order to maximize the clinical yield associated with ADA and availability to neutralize the inflammatory burden present, gastroenterologists have endorsed the TDM of ADA, reactively, in the face of inadequate disease control,<sup>2, 3</sup> or proactively with maintenance of ADA concentration above a minimal effective concentration, associated with enhanced drug tolerance and sustained disease control<sup>4, 5</sup>. Reactive or proactive; the decision to increase or decrease the dose intensity requires careful implementation to maintain exposure above the desired concentration. To that end, model informed precision guided dosing (MIPD) tools that employ clinical PK coupled with machine learning have recently demonstrated their value in assisting with the achievement of desired exposure<sup>6</sup>, with the potential to also fine tune the therapeutic window between minimal effective concentration and potential overexposure where side effects may occur<sup>7</sup>.

These MIPD tools are now implemented in clinical practice<sup>8</sup> and have demonstrated value in anti-TNF treatment.<sup>9</sup> Both retrospective and prospective clinical utility studies support the value of this approach to improve outcomes<sup>6, 10</sup>. Machine learning based tools now allow the determination of CL, a key predictive factor of pharmacokinetic (PK) origin that accelerates in the presence of immunization against the drug<sup>11</sup> and increasing inflammatory burden<sup>12</sup>. As such, this PK outcome measure which represents the monoclonal antibody containing volume available in the central compartment for pharmacological effect may perform equally well or better than ADA concentration in associating with outcome. This hypothesis was tested in this report.

## METHODS

In this retrospective analysis, CD patients from 4 different cohorts started subcutaneous ADA treatment with standard induction schedule (160 mg followed by 80 mg and 40 mg every other week) followed by 40 mg every two weeks during maintenance (Cohort 1 through Cohort 3)<sup>13, 14, 15</sup> or on an intensive induction schedule (160 mg weekly for 4 consecutive doses followed by 40 mg every other week) with the potential to increase the dose or frequency based on the presence of inflammation<sup>16</sup> (STRIDENT study). The first cohort (BOLOGNA cohort) was performed in the context of a one-year prospective observational clinical trial aimed at identifying biomarkers, and predictors of a failure response to commonly used biological therapy in patients with Crohn's Disease<sup>13</sup>. The second cohort (PredictCrohn) was a prospective multicenter cohort study in patients naïve to biologics and active luminal disease and followed for 14 weeks<sup>14</sup>. The third cohort (the POCER<sup>15</sup> study) examined a cohort of patients with ileo-colonic CD following intestinal resection of all macroscopic disease, with ADA used post-operatively to prevent recurrence. The fourth cohort (STRIDENT cohort) was from an open-label, single-centre, randomized controlled trial evaluating Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures<sup>16</sup>. Patients from each cohort were followed longitudinally at each visit during their maintenance treatment. Blood specimens were collected periodically during maintenance, serum was isolated and stored until analysis. Serum ADA concentrations and antibodies to ADA (ATA) were determined using drug tolerant homogenous mobility shift assay in a clinical laboratory (Prometheus Laboratories, San Diego, CA)<sup>17</sup>. Lower and upper limit of quantification of the drug assay was 1.6 µg/mL and 50 µg/mL, respectively. Cutoff associated with ATA status was 1.7 U/mL. Serum Albumin and C-reactive protein (CRP) were determined using immunochemistry. Fecal calprotectin (FC) was determined using immunoassays with cut off below 100 µg/g consistent with endoscopic remission<sup>18</sup>.

The population PK parameters were estimated from the first cohort<sup>13</sup> and nonlinear mixed effect modeling,

1  
2  
3 (one compartment with linear elimination), with random effects on apparent CL (referred as CL thereafter)  
4 with albumin levels and ATA status as covariates. Apparent volume of distribution was fixed. These  
5 estimates were applied as Bayesian priors to calculate CL in all specimens available. The outcomes  
6 consisted of CRPbased clinical remission status corresponding to CRP levels below 3 mg/L in the absence  
7 of symptoms (Crohn's Disease Activity Index < 150 points) determined at each study visit, and sustained  
8 CRP-based clinical remission throughout maintenance (corresponding to CRP based clinical remission  
9 status achieved at all evaluable time points for a given patient). Endoscopic remission (ER) corresponded  
10 to the Simple Endoscopic Score for CD (SES-CD<3 points) available during treatment in Cohorts 1, 3 and  
11 4 . Statistical analysis consisted of univariate and multivariate logistic regression with odds ratio (OR, with  
12 95% confidence interval and pseudo R<sup>2</sup> calculated and reflective of the proportion of variance explained).  
13 Mann-Whitney test for group comparisons was used in this analysis. Results were expressed as median  
14 with interquartile ranges (IQR), as appropriate. The impact of PK parameters (ADA trough concentrations  
15 and CL estimates) on outcomes was estimated using longitudinal repeated event analysis using non-linear  
16 mixed effects modeling via Monolix (Lixoft, 2021R2). For each model tested the change in objective  
17 function value ( $\Delta$ OFV, as assessed using -2 log likelihood [-2LL] by importance sampling) calculated with  
18 5% level of significance to assess the value of the additional predictor where lower -2LL indicated better  
19 fit and performances in association with outcome.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

## 41 **RESULTS**

42  
43  
44 The patient characteristics (n=219, with a total of 818 study visits and 211 endoscopic assessments during  
45 maintenance) are presented in **Table I**, the parameter estimates for the PK model is presented in **Table S1**.  
46 Population CL determined from Cohort 1 was 0.317 L/day with 8.9 L in the central compartment with  
47 albumin and immunization impacting CL and used as covariate for the calculation of the individual  
48 parameter estimates.  
49  
50  
51  
52  
53

54  
55 Less than half of the patients were in ER (46%). Sustained clinical remission, defined by CRP or FC below  
56  
57  
58  
59  
60

1  
2  
3 100 ug/g, was achieved in 31% and 53%, respectively. Overall, the prevalence of ATA was seen in 10%  
4 (81/818) of the specimens. ATA positive status was associated with lower ADA concentrations than ATA  
5 negative status ( $<1.6 \mu\text{g/mL}$  [IQR:  $<1.6$ - $<1.6$ ] vs  $11.2 \mu\text{g/mL}$  [IQR:  $<7.8$ - $<14.8$ ], respectively) ( $p<0.001$ )  
6 and higher CL ( $1.264 \text{ L/day}$  [IQR:  $0.660$ - $1.580$ ] vs  $0.263 \text{ L/day}$  [IQR:  $0.197$ - $0.373$ ], respectively)  
7 ( $p<0.001$ ). ATA status was associated with a 33.8-fold (95%CI: 18.7 - 61.0) higher likelihood to have ADA  
8 concentration below  $5 \mu\text{g/mL}$ .  
9  
10  
11  
12  
13  
14  
15  
16  
17

18 As presented in **Table II**, lower CL was associated with ER in two of three cohorts tested (all cohorts:  $0.247$   
19  $\text{L/day}$  [IQR:  $0.195$ - $0.340 \text{ L/day}$ ] vs  $0.326 \text{ L/day}$  [IQR:  $0.203$ - $0.730 \text{ L/day}$ ] in the presence and absence of  
20 ER, respectively) ( $p=0.004$ ). There was a non-significant higher ADA concentration in the presence of ER  
21 (median  $9.3 \mu\text{g/mL}$  [IQR: $3.8$ - $14.8 \mu\text{g/mL}$ ] vs  $11.7 \mu\text{g/mL}$  IQR:  $7.9$ - $14.1 \mu\text{g/mL}$ ] in the presence and  
22 absence of ER, respectively) ( $p=0.201$ ), and was statistically significant in cohort 1 ( $p=0.037$ ). Sustained  
23 CRP based clinical remission status and FC below  $100\mu\text{g/g}$  were generally associated with higher ADA  
24 concentration and lower CL in all cohort tested (except that concentration was not associated with FC levels  
25 in cohort 1).  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36

37 Odds ratio analysis with low ( $\leq 5\mu\text{g/mL}$ ), intermediate ( $>5\mu\text{g/mL}$ ), and high ( $>10 \mu\text{g/mL}$ ) ADA levels or  
38 CL ( $<0.318 \text{ L/day}$  and  $<0.8 \text{ L/day}$ ) for each of the outcomes tested confirmed these findings  
39 (**Supplementary Tables S2 through S9**). The proportion of CD who achieved ER by ADA concentration  
40 ( $>5 \mu\text{g/mL}$  and  $>10 \mu\text{g/mL}$ ) and CL ( $<0.8 \text{ L/day}$  and  $<0.318 \text{ L/day}$ ) is presented in **Figure 1**. The  
41 proportions of those who achieved sustained CRP-based clinical remission and FC below  $100\mu\text{g/g}$  are  
42 presented in **Figure 2** and **Figure 3**, respectively. Higher concentrations and lower CL yielded better  
43 disease control.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54 Multivariate analysis with ADA concentrations and CL revealed that ER was associated with CL (each unit  
55  
56  
57  
58  
59  
60

1  
2  
3 change in CL: adjusted OR=0.12 95%CI: 0.02; 0.79; p=0.028) while no association was detectable with  
4  
5 ADA concentrations (p=0.152; **Table 3**). A total of 14.2% (pseudo R<sup>2</sup>=0.142) of the variance in ER could  
6  
7 be explained by CL and concentrations. Similar results were observed with sustained CRP-based clinical  
8  
9 remission and FC below 100µg/g outcome measures with no significance of concentrations after adjusting  
10  
11 for CL and where 41.0% and 12.6% of the variance in these therapeutic outcomes could be explained with  
12  
13 these PK parameters, respectively.  
14  
15

16  
17  
18 Repeated analysis of the probability of ER over the maintenance period was tested using time,  
19  
20 concentration, and CL as regressors, either on their own or in combination. As presented in **Table 4**,  
21  
22 higher concentrations were not associated with ER (estimate: +0.050, relative standard error [RSE]: 68%)  
23  
24 while higher CL (estimate -2.75; RSE=29%) resulted in lower probability of ER, this finding remaining  
25  
26 significant after adjusting for time on treatment. Lower -2LL were achieved with CL than with  
27  
28 concentrations with themselves as regressors (265.5 vs 276.3, ΔOFV = -10.8; p<0.01) and these findings  
29  
30 remained significant after adjusting for time on treatment (260.5 vs 273.0, ΔOFV =-12.5; p<0.05).  
31  
32 Repeated event analysis with CRP-based remission and FC below 100µg/g revealed that higher  
33  
34 concentration and lower CL also associated better probability of having these improved outcomes  
35  
36 (Supplementary Table S13 and S14). The probability of having the therapeutic outcome calculated from  
37  
38 those estimates are summarized in **Figure 4**.  
39  
40  
41  
42

## 43 **DISCUSSION**

44  
45  
46

47  
48 ADA drug CL is a recognised PK parameter, reflective of the volume containing ADA eliminated from the  
49  
50 central compartment as a function of time (expressed as L/day). It is well established that immunization to  
51  
52 ADA and other monoclonal antibodies results in high CL<sup>11</sup> with the consequence of having lesser ADA  
53  
54 available, a condition that worsens with inflammation<sup>19</sup>; and potentially preventable with the concomitant  
55  
56 immunosuppressant<sup>20</sup> or proactive achievement of exposure that promotes tolerance to the antigen fraction  
57  
58  
59  
60

1  
2  
3 itself (CDR3 of the fragment antigen binding domain of the IgG1)<sup>21, 22</sup>. In this report we describe the  
4 associations and performance characteristics of CL alone as well as ADA concentration in four cohorts of  
5 patients starting ADA treatment. All outcomes were collected during maintenance treatment. Endoscopic  
6 assessment ( SES-CD score) was routinely performed with data available longitudinally.  
7  
8  
9

10  
11  
12  
13 Overall, our data support the expert opinion that ADA concentrations have value<sup>1</sup>, based on their association  
14 with outcomes in patients with CD. However, the portion of the clinical picture explained by the  
15 concentrations themselves was modest (with pseudo R<sup>2</sup> consistently below 20% for each of the three  
16 outcomes tested). ADA concentrations above 5 and 10 µg/mL yield several fold higher likelihood of better  
17 outcome than levels < 5 µg/mL. The measurement of concentration is therefore likely to assist with clinical  
18 decision making with respect to treatment and monitoring.  
19  
20  
21  
22  
23  
24  
25  
26  
27

28  
29 The volume containing ADA present in the central compartment and eliminated as function of time, is the  
30 CL. In this study it performed better than concentration alone. Lower CL and better retention of ADA  
31 yielded better endoscopic outcome (median: 0.246 L/day vs 0.320 L/day vs, in the presence and absence of  
32 ER, respectively; **Table 2**), sustained clinical disease control and lower inflammation. Also, for each of the  
33 outcomes tested, multivariate analysis of CL and concentration as independent predictors revealed higher  
34 likelihood of ER, sustained CRP based remission and FC levels below 100 µg/g were all a function of lower  
35 CL, with contribution of concentrations after adjusting with CL. Nonlinear mixed effect modelling of the  
36 longitudinal data also confirmed these findings with lower -2log likelihood for CL than concentration for  
37 each of the outcome tested.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

48  
49  
50 Our data suggests that CL is a predictive PK factor that may assist with optimization of ADA treatment and  
51 potentially other monoclonal antibodies, particularly the anti-TNF agents. The clinician may decide to dose  
52 intensify in the presence of higher CL and lower concentration, or reduce dose intensity in the presence of  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 remission, high concentrations and lower CL. Indeed, in each of the cohorts tested we systematically  
4  
5 observed that in the presence of both lower CL and higher drug concentration disease control was superior  
6  
7 (data not shown).  
8  
9

10  
11 In this work we cannot address the causality of the association with outcomes, but it is tempting to suggest  
12  
13 that two key characteristics converge toward lower CL. Firstly absence of immunization and efficient PK  
14  
15 (reflected by adequate albumin levels) and secondly achievement of sufficient supply of anti-cytokine drug  
16  
17 as a reservoir available for the neutralization of inflammatory burden present. We acknowledge that this  
18  
19 analysis is retrospective and that these findings could be significant by chance, or due to type one error, and  
20  
21 confirmation will be required. However, these data suggest that CL is PK predictive factor in its own right,  
22  
23 potentially outperforming drug concentration.  
24  
25  
26  
27

## 28 **ACKNOWLEDGMENTS**

29  
30  
31

32 We acknowledge Judson McFarland, Michael Schwalbe, and Patty Hughes from management of the clinical  
33  
34 testing at Prometheus Laboratories.  
35

36  
37 Contributions: study design and data collection: all authors; writing of first draft: TD; analysis of PK data:  
38  
39 TD, CP; data interpretation: all authors; approval of final manuscript: all authors.  
40

41 Conflict of interest: TD and AE are employed by Prometheus Laboratories. CP is a consultant for  
42  
43 Prometheus Laboratories.  
44

45 Source of funding: Prometheus Laboratories  
46

47 Data sharing: available upon reasonable request.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Cheifetz AS, Abreu MT, Afif W, et al. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease. *Am J Gastroenterol* 2021.
2. Vande Casteele N, Herfarth H, Katz J, et al. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. *Gastroenterology* 2017;153:835-857 e6.
3. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology* 2017;153:827-834.
4. Assa A, Matar M, Turner D, et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. *Gastroenterology* 2019;157:985-996 e2.
5. Papamichael K, Juncadella A, Wong D, et al. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. *J Crohns Colitis* 2019;13:976-981.
6. Strik AS, Lowenberg M, Mould DR, et al. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. *Scand J Gastroenterol* 2021;56:145-154.
7. Landemaine A, Petitcollin A, Brochard C, et al. Cumulative Exposure to Infliximab, But Not Trough Concentrations, Correlates With Rate of Infection. *Clin Gastroenterol Hepatol* 2021;19:288-295 e4.
8. Primas C, Reinisch W, Panetta JC, et al. Model Informed Precision Dosing Tool Forecasts Trough Infliximab and Associates with Disease Status and Tumor Necrosis Factor-Alpha Levels of Inflammatory Bowel Diseases. *J Clin Med* 2022;11.
9. Dubinsky MC, Phan BL, Singh N, et al. Pharmacokinetic Dashboard-Recommended Dosing Is Different than Standard of Care Dosing in Infliximab-Treated Pediatric IBD Patients. *AAPS J* 2017;19:215-222.
10. Eser A, Primas C, Reinisch S, et al. Prediction of Individual Serum Infliximab Concentrations in Inflammatory Bowel Disease by a Bayesian Dashboard System. *J Clin Pharmacol* 2018;58:790-802.
11. Berends SE, Strik AS, Van Selm JC, et al. Explaining Interpatient Variability in Adalimumab Pharmacokinetics in Patients With Crohn's Disease. *Ther Drug Monit* 2018;40:202-211.
12. Kantasiripitak W, Wang Z, Spriet I, et al. Recent advances in clearance monitoring of monoclonal antibodies in patients with inflammatory bowel diseases. *Expert Rev Clin Pharmacol* 2021;14:1455-1466.
13. Rizzello F, Gionchetti P, Spisni E, et al. Dietary Habits and Nutrient Deficiencies in a Cohort of European Crohn's Disease Adult Patients. *Int J Mol Sci* 2023;24.
14. Chaparro M, Guerra I, Iborra M, et al. Usefulness of monitoring antitumor necrosis factor serum levels during the induction phase in patients with Crohn's disease. *Eur J Gastroenterol Hepatol* 2020;32:588-596.
15. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015;385:1406-17.
16. Schulberg JD, Wright EK, Holt BA, et al. Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures (STRIDENT): an open-label, single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022;7:318-331.
17. Wang SL, Hauenstein S, Ohrmund L, et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 2013;78-79:39-44.

18. Wright EK, Kamm MA, De Cruz P, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology* 2015;148:938-947 e1.
19. Colman RJ, Xiong Y, Mizuno T, et al. Antibodies-to-infliximab accelerate clearance while dose intensification reverses immunogenicity and recaptures clinical response in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2022;55:593-603.
20. Ungaro RC, Colombel JF, Dubinsky MC, et al. Impact of Thiopurine Exposure on Immunogenicity to Infliximab Is Negligible in the Setting of Elevated Infliximab Concentrations. *Inflamm Bowel Dis* 2022;28:649-651.
21. Spencer EA, Stachelski J, Dervieux T, et al. Failure to Achieve Target Drug Concentrations During Induction and Not HLA-DQA1 \*05 Carriage Is Associated With Antidrug Antibody Formation in Patients With Inflammatory Bowel Disease. *Gastroenterology* 2022;162:1746-1748 e3.
22. Sazonovs A, Kennedy NA, Moutsianas L, et al. HLA-DQA1\*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. *Gastroenterology* 2020;158:189-199.

## TABLES

**Table 1:** Patient Characteristics

	<b>Cohort 1 (BOLOGNA) Italy</b>	<b>Cohort 2 (PredictCrohn) Spain</b>	<b>Cohort 3 (POCER) Australia</b>	<b>Cohort 4 (STRIDENT) Australia</b>	<b>All cohorts</b>
<b>Number of patients</b>	53	60	32	74	219
<b>Age</b>	35 (25-44)	40 (30-49)	39 (29-47)	44 (20-51)	40 (29-48)
<b>Gender (female)</b>	34%	46%	47%	52%	45%
<b>Number of cycles</b>	182	313	115	208	818
<b>Dose per two weeks</b>	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)
<b>Weight (Kg)</b>	70 (62-70)	72 (60-80)	75 (62-70)	78 (66-87)	73 (62-82)
<b>Albumin (g/dL)</b>	4.0 (3.8-4.3)	4.0 (3.6-4.5)	4.1 (3.8-4.3)	3.9 (3.6-4.2)	4.0 (3.7-4.3)
<b>ADA Concentration (µg/mL)</b>	10.0 (5.2-12.8)	10.0 (7.1-14.0)	9.1 (4.7-14.1)	13.2 (8.2-17.7)	10.5 (6.8-14.4)
<b>ADA concentration &gt;5 µg/mL</b>	76% (139/182)	86% (268/313)	72% (83/115)	88% (184/208)	82% (674/818)
<b>ADA &gt;10 µg/mL</b>	49% (90/182)	50% (156/313)	43% (50/115)	65% (135/208)	53% (431/818)
<b>ATA positive (&gt;1.7 U/mL)</b>	15% (28/182)	6% (18/313)	12% (14/115)	10% (21/208)	10% (81/818)
<b>Clearance (L/day)</b>	0.280 (0.220-0.539)	0.279 (0.196-0.420)	0.301 (0.204-0.520)	0.242 (0.174-0.377)	0.273 (0.194-0.434)
<b>SES-CD below 3 points</b>	57% (51/90)	NA	41% (27/66)	36% (20/55)	46% (98/211)
<b>CRP based clinical remission</b>	47% (84/178)	51% (120/236)	54% (43/80)	50% (104/207)	50% (351/701)
<b>Sustained CRP based clinical remission</b>	26% (14/53)	22% (13/60)	41% (13/32)	38% (27/74)	31% (67/219)
<b>Fecal calprotectin below 100 µg/g</b>	38% (45/119)	NA	46% (39/85)	66% (134/204)	53% (218/408)

Results are expressed as median (IQR) as appropriate.

**Table 2: PK variables and Outcomes**

Median ADA concentration and CL are provided (with IQR) for each outcome variable and cohort with p value. Top estimate corresponds to the median and IQR in the absence of the outcome. Bottom estimate corresponds to the median and IQR in the presence of the outcome.

	<b>PK estimate</b>	<b>SES-CD remission (&lt;3 points)</b>	<b>Sustained CRP based clinical remission</b>	<b>FC below 100 µg/g</b>
<b>Cohort 1</b>	Concentration (µg/mL)	6.7 (<1.6-12.8) 11.0 (8.3-12.8) p=0.037	8.5 (3.6-12.5) 12.0 (10.1-14.0) p=0.009	8.5 (3.0-13.4) 10.8 (7.4-12.2) p=0.710
	CL (L/day)	0.490 (0.211-1.240) 0.247 (0.216-0.324) p=0.002	0.325 (0.226-0.699) 0.239 (0.194-0.277) p=0.002	0.339 (0.207-0.829) 0.264 (0.235-0.380) p=0.005
<b>Cohort 2</b>	Concentration (µg/mL)	Not available	9.5 (6.4-13.4) 12.3 (9.4-15.7) p=0.008	Not available
	CL (L/day)	Not available	0.290 (0.206-0.442) 0.231 (0.164-0.303) p<0.001	Not available
<b>Cohort 3</b>	Concentration (µg/mL)	8.6 (4.5-12.6) 10. (5.9-14.2) p=0.735	7.1 (3.1-12.1) 10.6 (8.5-15.0) p=0.003	7.5 (3.7-10.0) 11.5 (5.3-15.0) p=0.017
	CL (L/day)	0.312 (0.241-0.491) 0.256 (0.184-0.435) p=0.190	0.370 (0.223-0.761) 0.255 (0.173-0.319) p<0.001	0.348 (0.265-0.610) 0.252 (0.175-0.470) p=0.033
<b>Cohort 4</b>	Concentration (µg/mL)	13.2 (7.5-17.6) 14.8 (11.2-23.3) p=0.273	10.8 (5.9-15.5) 14.5 (12.1-20.6) p<0.001	9.9 (5.8-15.5) 13.8 (10.0-18.6) p=0.005
	CL (L/day)	0.320 (0.191-0.678) 0.213 (0.171-0.289) p=0.047	0.314 (0.205-0.524) 0.187 (0.143-0.235) p<0.001	0.361 (0.248-0.619) 0.197 (0.154-0.279) p<0.001
<b>All Cohorts</b>	Concentration (µg/mL)	9.3 (3.8-14.8) 11.7 (7.9-14.1) p=0.201	9.4 (5.4-13.6) 12.6 (9.8-15.8) p<0.001	8.6 (4.1-13.5) 12.3 (8.6-15.8) p<0.001
	CL (L/day)	0.326 (0.203-0.730) 0.247 (0.195-0.340) p=0.004	0.311 (0.213-0.552) 0.220 (0.168-0.281) p<0.001	0.353 (0.238-0.670) 0.230 (0.172-0.331) p<0.001

**Table 3: Multivariate logistic regression for outcomes with ADA concentration and CL**

Results are presented for all 4 cohorts combined. **Table S11-S13** provide results by cohort.

	<b>PK estimate</b>	<b>Adjusted OR per unit change</b>	<b>P value</b>	<b>Pseudo R<sup>2</sup></b>
<b>ER</b>	Concentration (µg/mL)	0.96 (0.92,1.01)	0.152	0.142
	CL (L/day)	0.12 (0.02,0.79)	0.028	
<b>Sustained CRP based remission</b>	Concentration (µg/mL)	0.98 (0.95,1.01)	0.238	0.410
	CL (L/day)	0.02 (0,0.07)	<0.001	
<b>FC below 100µg/g</b>	Concentration (µg/mL)	1.02 (0.98,1.05)	0.333	0.126
	CL (L/day)	0.24 (0.11,0.52)	<0.001	

**Table 4: Repeated event analysis with ER**

Estimates are provided with relative standard error (<50% indicates significant association).

	<b>Time only</b>	<b>Conc. only</b>	<b>CL only</b>	<b>Time and concentrations</b>	<b>Time and CL</b>
Population	0.88 (62%)	-1.05 (49%)	0.81 (52%)	1.19 (53%)	2.84 (22%)
Time regressor (wks)	-0.024 (40%)†	NA	NA	-0.037 (28%)†	-0.037 (30%)†
PK regressor	NA	+0.050 (68%)	-2.75 (29%)†	+0.033 (106%)	-2.81 (34%)†
-2LL	273.1	276.3	265.5	273.0	260.5

†<50% is significant regressor; NA: not applicable. -2LL: -2 log likelihood.

## FIGURES

### **Figure 1: ADA concentration and CL in association with ER**

ER was defined as SES-CD score below 3 points.

Top panel: Overall, ADA concentration  $>5 \mu\text{g/mL}$ , and  $>10 \mu\text{g/mL}$  associated with 2.6-fold (95%CI: 1.3-5.2) ( $p=0.007$ ; pseudo  $R^2=0.047$ ) and 2.1-fold (95%CI: 1.2-3.7) ( $p=0.008$ ; pseudo  $R^2=0.040$ ) higher likelihood of ER respectively (**Table S2**).

Bottom panel: Overall, CL  $<0.318 \text{ L/day}$ , and  $<0.8 \text{ L/day}$  associated with 2.5-fold (95%CI: 1.4-4.4) ( $p=0.002$ ; pseudo  $R^2=0.058$ ) and 3.0-fold (95%CI: 1.3-6.7) ( $p=0.008$ ; pseudo  $R^2=0.047$ ) higher likelihood of ER, respectively (**Table S3**).

### **Figure 2 ADA PK parameter and sustained CRP based remission.**

Top panel: Overall, ADA concentration  $>5 \mu\text{g/mL}$ , and  $>10 \mu\text{g/mL}$  associated with 9.7-fold (95%CI: 2.3-41.7) ( $p<0.001$ ; pseudo  $R^2=0.181$ ) and 4.5-fold (95%CI: 2.3-8.9) ( $p<0.001$ ; pseudo  $R^2=0.146$ ) higher likelihood of sustained CRP based clinical remission, respectively (**Table S4**).

Bottom panel: Overall, CL  $<0.318 \text{ L/day}$ , and  $<0.318 \text{ L/day}$  associated with 6.5-fold (95%CI: 2.9-14.4) ( $p<0.001$ ; pseudo  $R^2=0.197$ ) and 10.6-fold (95%CI: 1.4-80.4) ( $p<0.001$ ; pseudo  $R^2=0.133$ ) higher likelihood of sustained CRP based clinical remission (**Table S5**).

### **Figure 3 ADA concentration and CL in association with FC below $100\mu\text{g/g}$**

Top panel: Overall, ADA concentration  $>5 \mu\text{g/mL}$ , and  $>10 \mu\text{g/mL}$  associated with 3.3-fold (95%CI: 2.0-5.7) ( $p<0.001$ ; pseudo  $R^2=0.064$ ) and 3.2-fold (95%CI: 2.2-4.9) ( $p<0.001$ ; pseudo  $R^2=0.094$ ) higher likelihood of FC below  $100\mu\text{g/g}$ , respectively (**Table S6**).

Bottom panel: Overall, CL  $<0.318 \text{ L/day}$ , and  $<0.318 \text{ L/day}$  associated with 3.2-fold (95%CI: 2.1-4.9) ( $p<0.001$ ; pseudo  $R^2=0.093$ ) and 4.1-fold (95%CI: 2.1-7.9) ( $p<0.001$ ; pseudo  $R^2=0.062$ ) higher likelihood of FC below  $100\mu\text{g/g}$ , respectively (**Table S7**).

### **Figure 4 Probability of achieving outcome by ADA concentration and CL**

All estimates are provided in **Table 4** (ER) and **supplementary Table 13 and 14** (CRP based clinical remission and FC below  $100\mu\text{g/g}$ , respectively). Estimates from the nonlinear mixed effect model of the outcome in relation to the PK parameter is provided with relative standard error expressed as % ( $<50\%$  indicates significance); -2 log likelihood (-2LL) is also reported.

Panel A: probability of SESC-CD below 3 points and CL (estimate=-2.75 [RSE: 29%]; -2LL: 265.5); Panel B: probability of CRP based clinical remission and CL (estimate=-5.04 [RSE: 24%]; ); Panel C: probability of FC below  $100 \text{ ug/g}$  and CL (estimate=-1.57 [RSE: 52%]; -2LL: 193.2); Panel D: probability of SESC-CD below 3 points and concentration estimate=0.050 [RSE: 68%]; -2LL: 276.3); Panel E: probability of CRP based clinical remission and concentration (estimate=0.10 [RSE: 38%]; -2LL: 237.9); Panel F: probability of FC below  $100 \text{ ug/g}$  and concentration (estimate=0.210 [RSE:32%]; -2LL: 193.2).

SUPPLEMENTARY MATERIALS

Table S1 Parameter Estimates nonlinear mixed effect model and Bayesian prior.

Parameter	Estimate	Definition
CL/F_pop (L/day)	0.317	Population apparent CL
V/F_pop (L)	8.9	Population apparent V1
Ka (day <sup>-1</sup> )	0.2	Absorption constant
Omega CL	0.501	Inter-patient variability on CL (SD)
beta_CI_ATA_1	0.806	Covariate estimate ATA status on CI
beta_CI_logtALB	-2.2	Covariate estimate ALB on C
a	1	additive error model

Table S2 OR for ER and ADA concentration above cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	>5 µg/mL	3.74 (1.39,10.05)	0.007	0.095
	>10 µg/mL	3.27 (1.37,7.82)	0.006	0.097
Cohort 3	>5 µg/mL	1.56 (0.5,4.83)	0.445	0.012
	>10 µg/mL	1.92 (0.71,5.22)	0.197	0.031
Cohort 4	>5 µg/mL	Infinite	--	--
	>10 µg/mL	1.83 (0.5,6.78)	0.364	0.022
All	>5 µg/mL	2.58 (1.29,5.17)	0.007	0.047
	>10 µg/mL	2.11 (1.21,3.68)	0.008	0.040

Table S3 OR for ER and CL below cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	<0.318 L/day	3.78 (1.55,9.24)	0.003	0.114
	<0.8 L/day	3.33 (1.12,9.91)	0.030	0.066
Cohort 3	<0.318 L/day	1.02 (0.38,2.73)	0.964	<0.01
	<0.8 L/day	2.73 (0.52,1.85)	0.234	0.036
Cohort 4	<0.318 L/day	4.24 (1.18,14.33)	0.027	0.134
	<0.8 L/day	4.75 (0.54,41.8)	0.160	0.085
All	<0.318 L/day	2.48 (1.41,4.36)	0.002	0.058
	<0.8 L/day	2.96 (1.31,6.67)	0.006	0.047

Table S4 OR for sustained CRP based clinical remission and ADA above cutoffs.

	<b>Cutoff</b>	<b>OR</b>	<b>P value</b>	<b>Pseudo R2</b>
<b>Cohort 1</b>	>5 µg/mL	5.78 (0.68,49.33)	0.054	0.150
	>10 µg/mL	7.33 (1.74,30.94)	0.003	0.233
<b>Cohort 2</b>	>5 µg/mL	Infinite	--	--
	>10 µg/mL	4.07 (0.81,20.45)	0.058	0.124
<b>Cohort 3</b>	>5 µg/mL	13.33 (1.43,123.94)	0.005	0.322
	>10 µg/mL	4.48 (0.99,20.35)	0.052	0.145
<b>Cohort 4</b>	>5 µg/mL	Infinite	--	--
	>10 µg/mL	5.51 (1.65,18.4)	0.006	0.172
<b>All</b>	>5 µg/mL	9.72 (2.27,41.73)	0.002	0.181
	>10 µg/mL	4.55 (2.33,8.9)	<0.001	0.146

Table S5 OR for sustained CRP based clinical remission and CL below cutoffs.

	<b>Cutoff</b>	<b>OR</b>	<b>P value</b>	<b>Pseudo R2</b>
<b>Cohort 1</b>	<0.318 L/day	4.75 (1.14,19.73)	0.032	0.158
	<0.8 L/day	3.90 (0.45,34.02)	0.218	0.081
<b>Cohort2</b>	<0.318 L/day	6.80 (0.81,56.93)	0.077	0.192
	<0.8 L/day		--	--
<b>Cohort 3</b>	<0.318 L/day	7.22 (1.44,36.22)	0.016	0.235
	<0.8 L/day	Infinite	--	--
<b>Cohort 4</b>	<0.318 L/day	17.64 (2.2,141.28)	<0.001	0.334
	<0.8 L/day	Infinite	NA	NA
<b>All</b>	<0.318 L/day	6.46 (2.89,14.45)	<0.001	0.197
	<0.8 L/day	10.58 (1.39,80.36)	0.023	0.133

Table S6 OR for FC below 100 ug/g and ADA concentration above cutoffs.

	<b>Cutoff</b>	<b>OR</b>	<b>P value</b>	<b>Pseudo R2</b>
<b>Cohort 1</b>	>5 µg/mL	4.92 (1.58,15.33)	0.002	0.123
	>10 µg/mL	1.9 (0.9,4.02)	0.092	0.030
<b>Cohort 3</b>	>5 µg/mL	1.55 (0.6,3.96)	0.363	0.012
	>10 µg/mL	4.57 (1.8,11.6)	<0.001	0.146
<b>Cohort 4</b>	>5 µg/mL	3.47 (1.42,8.5)	0.006	0.045
	>10 µg/mL	3.11 (1.69,5.73)	<0.001	0.081
<b>All</b>	>5 µg/mL	3.37 (1.97,5.75)	<0.001	0.064
	>10 µg/mL	3.24 (2.16,4.87)	<0.001	0.094

Table S7 OR for FC below 100 ug/g and CL below cutoffs.

	<b>Cutoff</b>	<b>OR</b>	<b>P value</b>	<b>Pseudo R2</b>
<b>Cohort 1</b>	<0.318 L/day	2.35 (1.09,5.08)	0.027	0.053
	<0.8 L/day	4.84 (1.34,17.43)	0.006	0.103
<b>Cohort 3</b>	<0.318 L/day	1.68 (0.71,3.98)	0.234	0.020
	<0.8 L/day	5.14 (1.05,25.1)	0.022	0.091
<b>Cohort 4</b>	<0.318 L/day	4.83 (2.58,9.04)	<0.001	0.145
	<0.8 L/day	2.62 (0.99,6.99)	0.053	0.223
<b>All</b>	<0.318 L/day	3.25 (2.15,4.9)	<0.001	0.093
	<0.8 L/day	4.07 (2.10,7.90)	<0.001	0.062

Table S8 OR for CRP based clinical remission and ADA concentration above cutoffs.

	<b>Cutoff</b>	<b>OR</b>	<b>P value</b>	<b>Pseudo R2</b>
<b>Cohort 1</b>	>5 µg/mL	8.44 (3.34,21.34)	<0.01	0.203
	>10 µg/mL	3.02 (1.64,5.56)	<0.01	0.085
<b>Cohort2</b>	>5 µg/mL	2.15 (1.03,4.46)	0.036	0.023
	>10 µg/mL	1.98 (1.18,3.33)	0.009	0.034
<b>Cohort 3</b>	>5 µg/mL	5.43 (1.93,15.28)	0.001	0.162
	>10 µg/mL	3.80 (1.42,10.17)	0.006	0.114
<b>Cohort 4</b>	>5 µg/mL	6.02 (1.98,18.32)	0.002	0.092
	>10 µg/mL	3.32 (1.82,6.07)	<0.001	0.091
<b>All</b>	>5 µg/mL	4.28 (2.76,6.65)	<0.001	0.089
	>10 µg/mL	2.62 (1.93,3.55)	<0.001	0.066

Table S9 OR for CRP based clinical remission and CL below cutoffs.

	<b>Cutoff</b>	<b>OR</b>	<b>P value</b>	<b>Pseudo R2</b>
<b>Cohort 1</b>	<0.318 L/day	3.43 (1.83,6.43)	<0.001	0.102
	<0.8 L/day	9.37 (3.15,27.99)	<0.001	0.191
<b>Cohort 2</b>	<0.318 L/day	1.75 (1.03,2.96)	0.039	0.022
	<0.8 L/day	3.68 (1.30,10.4)	0.008	0.040
<b>Cohort 3</b>	<0.318 L/day	4.56 (1.76,11.82)	0.001	0.150
	<0.8 L/day	28.64 (3.55,231.27)	<0.001	0.357
<b>Cohort 4</b>	<0.318 L/day	5.86 (3.07,11.21)	<0.001	0.178
	<0.8 L/day	5.74 (1.61,20.58)	0.002	0.069
<b>All</b>	<0.318 L/day	3.13 (2.28,4.29)	<0.001	0.087
	<0.8 L/day	7.21 (3.92,13.26)	<0.001	0.116

**Table S10** Multivariate analysis for ER with ADA concentration and CL

	PK estimate	Adjusted OR per unit change	P value	Pseudo R <sup>2</sup>
<b>Cohort 1</b>	ADA concentration (µg/mL)	0.95 (0.84,1.09)	0.468	0.138
	Clearance (L/day)	0.12 (0.02,0.79)	0.028	
<b>Cohort 3</b>	ADA concentration (µg/mL)	0.93 (0.8,1.07)	0.314	0.100
	Clearance (L/day)	0.13 (0.01,2.22)	0.158	
<b>Cohort 4</b>	ADA concentration (µg/mL)	0.99 (0.92,1.06)	0.885	0.431
	Clearance (L/day)	0 (0,0.02)	0.018	

**Table S11** Multivariate analysis for FC below 100µg/g with ADA concentration and CL

	PK estimate	Adjusted OR per unit change	P value	Pseudo R <sup>2</sup>
<b>Cohort 1</b>	ADA concentration (µg/mL)	0.89 (0.77,1.03)	0.118	0.280
	Clearance (L/day)	0.06 (0.01,0.52)	0.012	
<b>Cohort 3</b>	ADA concentration (µg/mL)	1.07 (0.95,1.2)	0.254	0.091
	Clearance (L/day)	0.54 (0.07,4.16)	0.558	
<b>Cohort 4</b>	ADA concentration (µg/mL)	1.02 (0.97,1.07)	0.378	0.109
	Clearance (L/day)	0.27 (0.09,0.82)	0.020	
	<b>Clearance (L/day)</b>	<b>0.24 (0.11,0.52)</b>	<b>&lt;0.001</b>	

**Table S12** Multivariate analysis for sustained CRP remission with ADA concentration and CL

	PK estimate	Adjusted OR per unit change	P value	Pseudo R <sup>2</sup>
<b>Cohort 1</b>	ADA concentration (µg/mL)	0.98 (0.92,1.05)	0.579	0.169
	Clearance (L/day)	0.14 (0.03,0.66)	0.112	
<b>Cohort 2</b>	ADA concentration (µg/mL)	0.93 (0.85,1.03)	0.162	0.446
	Clearance (L/day)	0.03 (0,0.25)	0.006	
<b>Cohort 3</b>	ADA concentration (µg/mL)	0.81 (0.68,0.97)	0.034	0.787
	Clearance (L/day)	0 (0.01,0.02)	0.001	
<b>Cohort 4</b>	ADA concentration (µg/mL)	0.97 (0.92,1.02)	0.277	0.807
	Clearance (L/day)	0 (0,0.02)	<0.001	
	<b>Clearance (L/day)</b>	<b>0.02 (0.01,0.07)</b>	<b>&lt;0.001</b>	

**Table S13: Repeated event analysis with CRP based clinical remission status.**

Estimates are provided with relative standard error (<50% indicates significant association).

	<b>Time only</b>	<b>Conc. only</b>	<b>CL only</b>	<b>Time and concentrations</b>	<b>Time and CL</b>
Population	-0.32 (206%)	-0.95 (54%)	2.33 (24%)	-1.06 (62%)	2.77 (39%)
Time regressor (wks)	-0.010 (118%)	NA	NA	-0.002 (705%)	-0.003 (410%)
PK regressor	NA	0.10 (38%)†	-5.04 (24%)†	+0.1 (53%)	-5.64 (32%)†
-2LL	272.0	265.8	237.9	265.9	239.1

†<50% is significant regressor; NA: not applicable. -2LL: -2 log likelihood.

**Table S14: Repeated event analysis with FC levels below 100µg/g.**

Estimates are provided with relative standard error (<50% indicates significant association).

	<b>Time only</b>	<b>Conc. only</b>	<b>CL only</b>	<b>Time and concentrations</b>	<b>Time and CL</b>
Population	1.26 (59%)	-1.32 (91%)	1.20 (49%)	3.23 (50%)	10.74 (18%)
Time regressor (wks)	-0.017 (102%)	NA	NA	-0.082 (41%)†	-0.082 (31%)†
PK regressor	NA	+0.210 (32%)†	-1.57 (52%)	+0.18 (78%)	-7.2 (21%)†
-2LL	196.9	203.3	193.2	197.9	202.7

†<50% is significant regressor; NA: not applicable. -2LL: -2 log likelihood.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

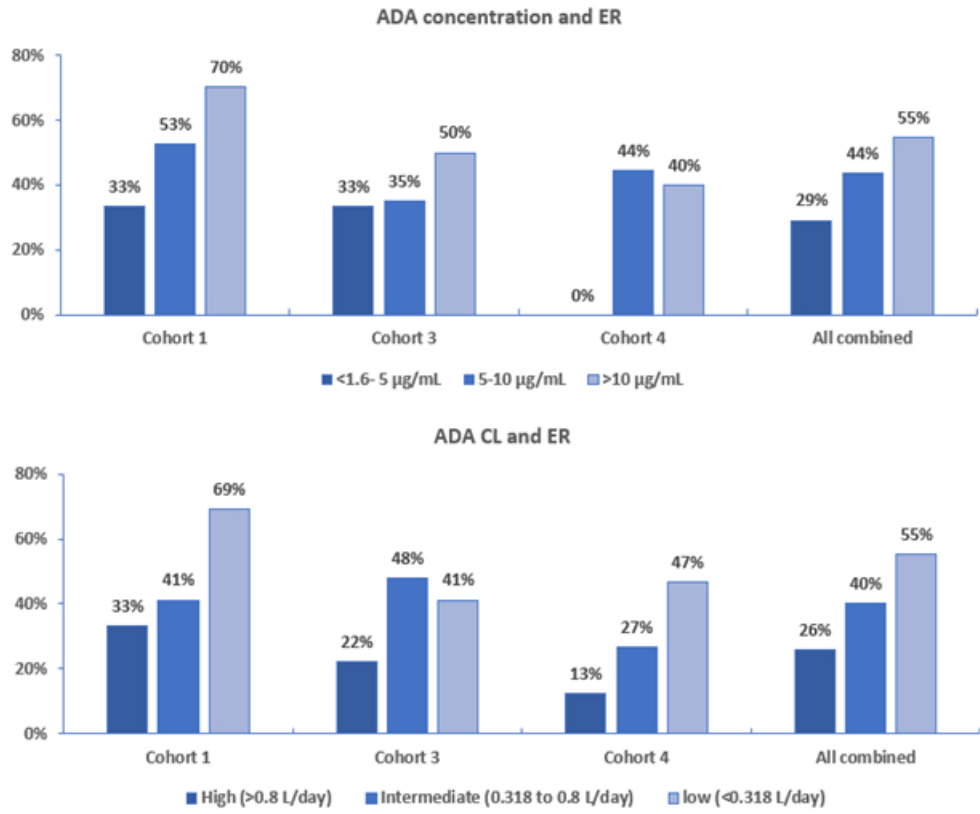


Figure 1

417x343mm (38 x 38 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

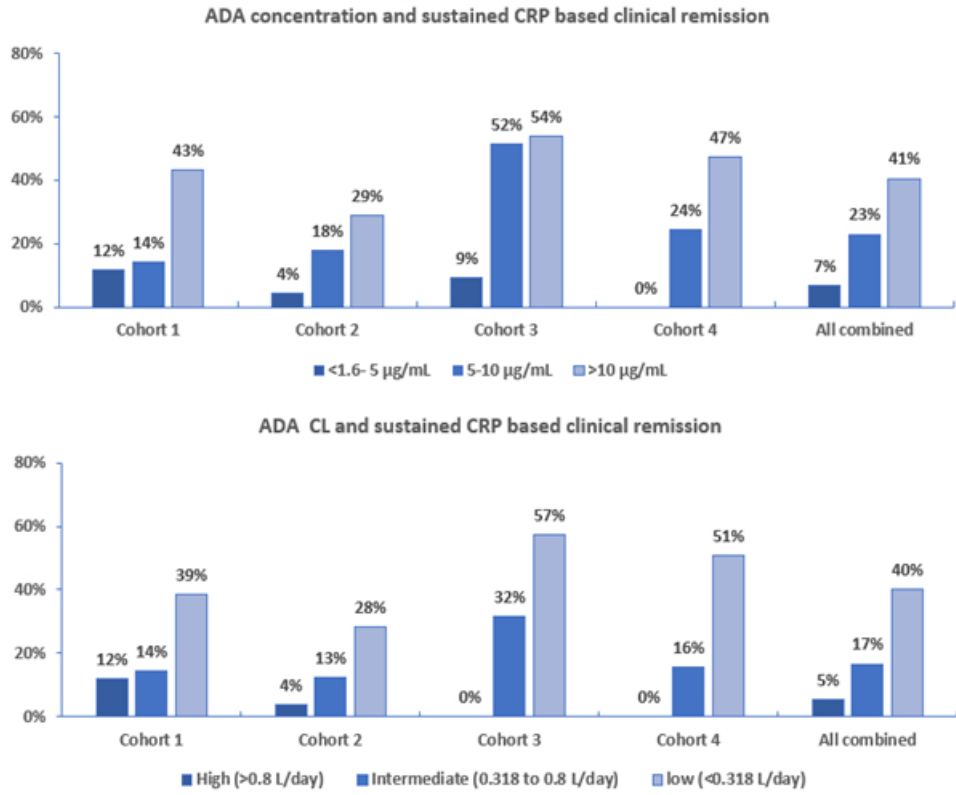


Figure 2

417x341mm (38 x 38 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

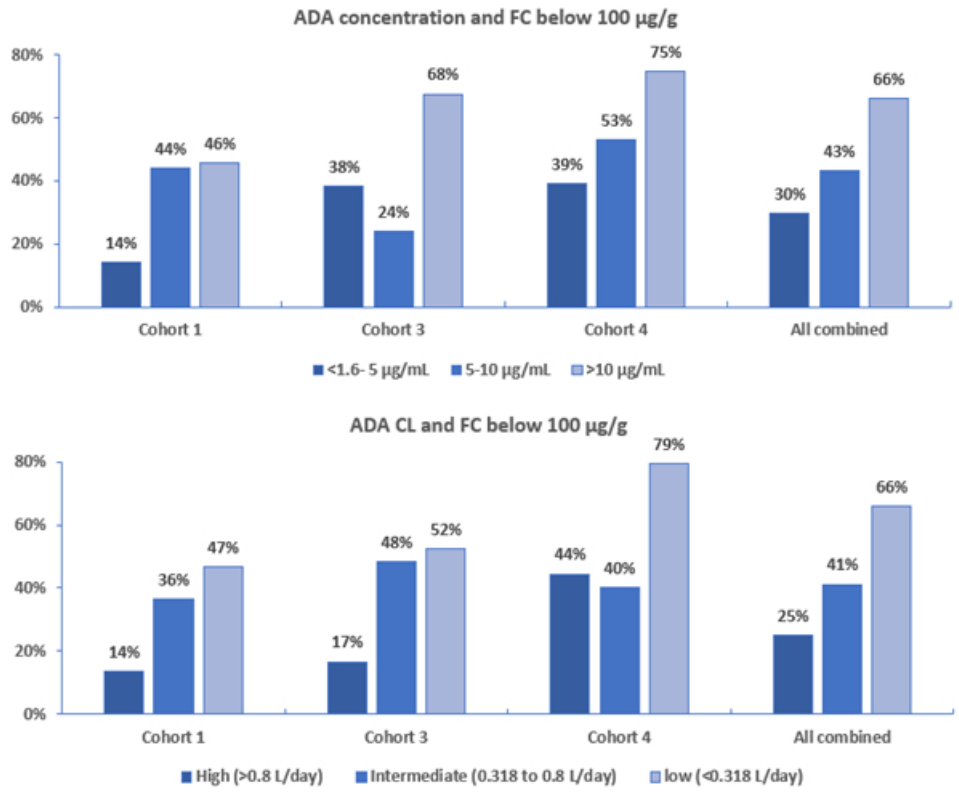


Figure 3

417x337mm (38 x 38 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

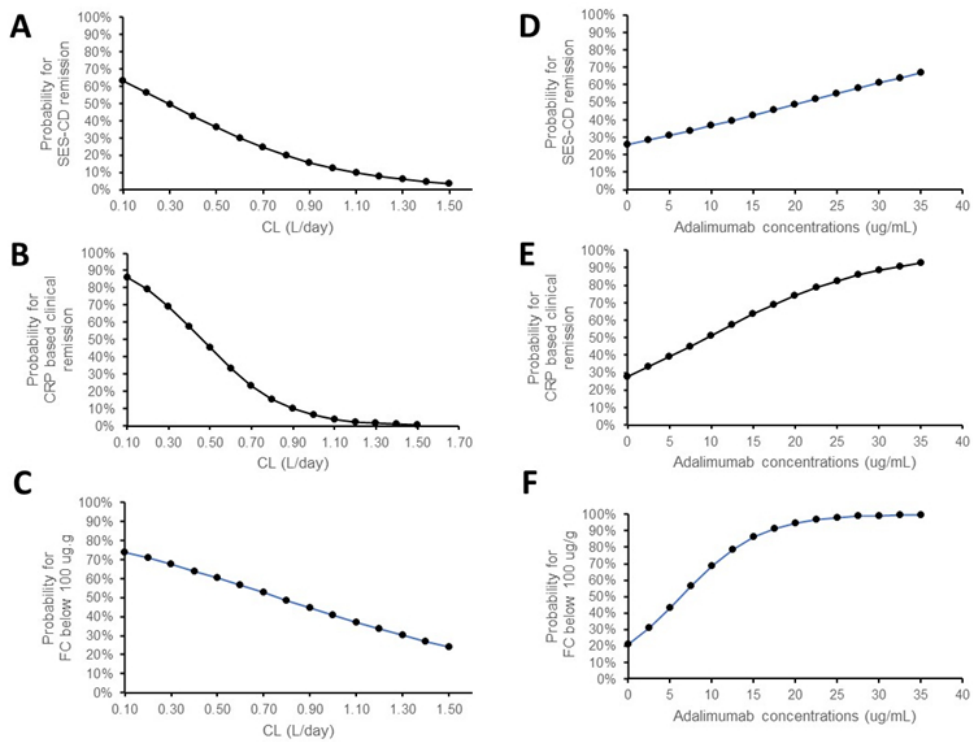


Figure 4

416x312mm (47 x 47 DPI)