Real-world multicentre observational study including population pharmacokinetic modelling to evaluate the exposure–response relationship of vedolizumab in inflammatory bowel disease: ERELATE Study

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Summary

Background: ERELATE was a phase 4, multinational, retrospective, observational study.
Aim: To evaluate the relationship between intravenous vedolizumab exposure and treatment outcomes over 52 weeks in adults with ulcerative colitis (UC) or Crohn’s disease (CD).
Methods: Real-world data from patients with UC or CD treated with intravenous vedolizumab in nine centres in six countries were collected retrospectively. Treatment outcomes were collected at Weeks 14, 26 and 52. An established population pharmacokinetic model (incorporating observed vedolizumab concentrations based on a Bayesian approach) was used to predict individual vedolizumab exposure. Vedolizumab exposure–response relationship was evaluated overall, by indication and based on baseline characteristics.
1 | INTRODUCTION

Up to one-third of patients with inflammatory bowel disease (IBD) do not respond to tumour necrosis factor alpha (TNF) antagonists, and many who respond to initial treatment lose response over time.\(^1-3\) Non-response and loss of response to these agents may be secondary to inadequate drug exposure caused by inter- and intra-patient variability in clearance, from multiple potential mechanisms including variable expression of antigen targets, non-linear clearance secondary to target-mediated elimination or immunogenicity.\(^4-7\)

Vedolizumab (Entyvio; Takeda) is a gut-selective humanised monoclonal antibody that targets the \(\alpha_4\beta_7\) integrin. It is approved for inducing and maintaining clinical response and remission in adults with moderate-to-severe ulcerative colitis (UC) and Crohn’s disease (CD) with an inadequate response or intolerance to TNF antagonists, immunosuppressives or corticosteroids.\(^8\)

Therapeutic drug monitoring (TDM) by determining drug concentrations and anti-drug antibodies (ADAs) during biologic therapy has been used to optimise dosing and treatment outcomes, notably in patients experiencing non-response or loss of response.\(^9\) TDM enables guided dosing and individualised therapy, optimising potential response to therapy, and is well characterised for TNF antagonist therapy for IBD.\(^9\) Guidelines on TDM for TNF antagonist therapy in IBD recommend measuring serum drug and ADA concentrations following loss of response to therapy.\(^9\) However, data on TDM for newer biologics including vedolizumab are limited.\(^9,10\) Post hoc analyses of the GEMINI program phase 3 trials showed a positive exposure–response relationship between serum vedolizumab concentrations and treatment outcomes during induction\(^11\) such that following stratification by concentration quartiles, patients with UC in higher quartiles showed higher rates of clinical response vs those in lower quartiles.\(^12\)

Exposure threshold concentrations associated with therapeutic outcomes have not yet been well defined for vedolizumab. Although emerging real-world data further support a role for reactive TDM during vedolizumab therapy,\(^13-20\) additional evidence is needed to support implementation in routine clinical practice and for further evaluation of vedolizumab drug concentrations, along with a range of different therapeutic outcomes. The population pharmacokinetic (PK) model from the phase 3 GEMINI program demonstrated an apparent positive exposure–response relationship for vedolizumab. Body weight and serum albumin concentrations were identified as two key covariates explaining the majority of inter-patient variability, and were predictive factors of clearance.\(^21\)

The primary objective of the study was to evaluate vedolizumab exposure–response relationship in a real-world population of patients treated for UC or CD. Secondary objectives were to evaluate clinical and endoscopic endpoints and remission following vedolizumab therapy, delineate vedolizumab exposure thresholds associated with treatment outcomes and explore the relationship between vedolizumab exposure and response on the basis of baseline patient demographics and disease characteristics in the real-world setting.

2 | METHODS

2.1 | Study design

ERELATE (Evaluation of the Exposure-Response Relationship of Vedolizumab in Inflammatory Bowel Disease: A Pooled Multi-Center Observational Cohort Analysis of Real World Clinical and Modeled Pharmacological Data) was a multinational, retrospective cohort study conducted at nine study centres across six countries (Belgium, Canada, France, Israel, Spain and the United States). Patients with UC or CD were treated with intravenous (IV) vedolizumab according to local prescribing patterns and their physician’s best clinical judgement between 5 June 2014 and 29 December 2019; data were collected between 5 June 2014 and 29 December 2019. This was a non-interventional/observational study, and no treatments/pharmacotherapy were instructed by the study protocol. All patients
contributing retrospective data to this study received vedolizumab according to local prescribing patterns and their physician’s clinical judgement. The study aimed to enrol a cohort of ~800–1000 patients; the sample size was not prespecified, nor based on statistical considerations. Data were collected specifically for this study and extracted from electronic medical records and/or other established databases at participating study sites.

2.2 | Patients

The study enrolled patients ≥17 years of age diagnosed with UC or CD at study entry who initiated vedolizumab treatment ≥12 months before data extraction. Data on baseline body weight and serum albumin concentrations, as well as dates and dosing information for each vedolizumab treatment, were required. Patients who received vedolizumab treatment within 6 months of the first dose of vedolizumab as part of date of study data extraction were excluded to accurately obtain induction response information.

2.3 | Study assessments and outcomes

Clinical remission, the main clinical outcome for the study, was defined as complete resolution of IBD-related symptoms for UC and CD according to a retrospective local physician global assessment (PGA). If PGA was not available at a time point, a partial Mayo Clinic score of ≤2 with no individual subscore of >1 for patients with UC, and CD activity index (CDAI) ≤150 or Harvey–Bradshaw Index ≤4 for patients with CD, was considered. Endoscopic remission was defined as the absence of large ulcers >5 mm in patients with CD and Mayo Clinic endoscopic subscore (MCES) of 0/≤1 in patients with UC, or if data on ulcer were not available at a time point, CD Endoscopic Index of Severity ≤4 or Simple Endoscopic Score for CD total score of <3. Deep remission was defined as a combination of clinical and endoscopic remission (absence of large ulcers >5 mm in patients with CD and MCES of ≤1 in patients with UC); if endoscopic assessment was not available, deep remission was defined as clinical and biologic remission (C-reactive protein <5 mg/L).

The definitions of the efficacy outcomes are shown in Table S1. Clinical outcomes (clinical, deep and endoscopic remission) were assessed at the end of induction (Week 14) and during maintenance therapy (Weeks 26 and 52) (Figure 1).

2.4 | Bayesian-updated population PK modelling of exposure

The PK and induction treatment exposure-response relationship of vedolizumab IV was based on the previously described phase 3 clinical trial data from the GEMINI program. Non-linear mixed effects modelling (NONMEM) software (NONMEM version 7.4.3; ICON plc) was used to predict measures of vedolizumab exposure on the basis of the previously published population PK model. Vedolizumab exposure measures were predicted in individual patients including trough (C_{trough}), intermediate and average (C_{avg}) concentrations throughout follow-up, and clearance at baseline. To produce reliable predictions of exposure measures, individual covariate data (baseline body weight and serum albumin concentrations) and individual dose records were incorporated into the population PK model, which was informed with observed vedolizumab concentrations (if available) using a maximum a posteriori estimation approach, known as Bayesian updating. Any dose escalation in this real-world population would be reflected in increased exposure in this exposure–response analysis. A visual predictive check and goodness-of-fit plots were used to evaluate model performance.

To overcome difficulties with missing data or heterogeneity in vedolizumab serum concentrations across study centres, the exposure–response analysis was performed using predicted serum vedolizumab concentrations derived from the published population PK model.

2.5 | Statistical analyses

2.5.1 | Analysis populations

The full analysis set (FAS) consisted of all enrolled patients with at least one post-baseline data point for at least one treatment outcome, and all dates and dosing information for each reported vedolizumab administration. This population was used to evaluate treatment outcomes. The PK analysis set included all patients in the FAS for whom vedolizumab concentrations could be predicted with the population PK model (excluding patients without baseline body weight and/or baseline serum albumin concentration). This population was used to evaluate vedolizumab exposure measures and the exposure–response relationship.

2.5.2 | Analysis of treatment outcomes

Baseline demographic data (within 4 weeks before start of vedolizumab treatment), treatment information throughout the first year of therapy, disease status at baseline (Week 0) and treatment outcomes at end of induction treatment (Week 14) and during maintenance treatment (Weeks 26 and 52) were pooled and analysed for the FAS. For each efficacy outcome, the number and percentage of patients who achieved the outcome at Weeks 14, 26 and 52 were summarised. Patients who stopped vedolizumab treatment as a result of non-response in induction or loss of response during maintenance were imputed as non-remitters.

2.5.3 | Analysis of vedolizumab exposure measures

Exposure measures (C_{trough}, C_{avg} and clearance) were derived and summarised for subjects of the PK analysis set. Data on serum vedolizumab concentrations derived from the published population PK model. Vedolizumab exposure measures were predicted in individual patients including trough (C_{trough}), intermediate and average (C_{avg}) concentrations throughout follow-up, and clearance at baseline. To produce reliable predictions of exposure measures, individual covariate data (baseline body weight and serum albumin concentrations) and individual dose records were incorporated into the population PK model, which was informed with observed vedolizumab concentrations (if available) using a maximum a posteriori estimation approach, known as Bayesian updating. Any dose escalation in this real-world population would be reflected in increased exposure in this exposure–response analysis. A visual predictive check and goodness-of-fit plots were used to evaluate model performance.
concentrations and the assay used were collected when available from any sampling time point between the start of vedolizumab therapy and Week 52. The lower limit of quantification of locally available assays was recorded for each study centre providing observed PK data. For patients with observed vedolizumab serum concentrations reported for any given time point, the correlation between observed and corresponding predicted serum vedolizumab concentrations at those time points (Weeks 6, 10, 14, 22, and 46 [not shown]) was evaluated using the Spearman test and intra-class correlation (ICC) (one-way, random-effects model). Scatter plots for predicted vs observed concentrations by time point across all time points were generated.

2.5.4 Analysis of exposure–response relationship

The exposure–response relationship between predicted serum vedolizumab concentrations and observed clinical outcomes (clinical, deep and endoscopic remission) was evaluated at the end of induction (Week 14) and during maintenance therapy (Weeks 26 and 52).

Exploratory evaluations were carried out to graphically evaluate associations between predicted measures of exposure and observed treatment response at various time points. Predicted measures of exposure were correlated with treatment outcomes at Weeks 14, 26 and 52 to determine if there was any prognostic relationship. Furthermore, predicted measures of exposure were compared between patients who achieved and did not achieve the prespecified treatment outcomes. Vedolizumab exposure thresholds associated with treatment outcomes were delineated if an exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident. For each efficacy outcome and time point, the exposure–response relationship was evident.
The number and percentage of patients achieving clinical and deep remission per vedolizumab concentration quartiles (Weeks 14 and 52) were summarised, and trends across the vedolizumab concentration quartiles were evaluated using the one-sided Cochran-Armitage trend test.

The effects of potential covariates for the exposure–response relationship during induction and maintenance therapy were identified by multivariable logistic regression. The predictive model evaluated the dosing regimen (Week 10 dose, yes/no), vedolizumab baseline clearance, vedolizumab concentration and baseline covariates (age, sex, body weight, diagnosis, disease duration, albumin, haematocrit, faecal calprotectin, C-reactive protein, use of concomitant immunosuppressant or corticosteroids, prior TNF antagonist exposure, prior bowel surgery and fistulising disease [CD]).

2.6 | Ethical considerations

The study protocol was approved by the Independent Ethics Committees/Institutional Review Boards of the participating sites and was conducted in accordance with the Declaration of Helsinki, the International Society for Pharmacoepidemiology’s Good Pharmacoepidemiology Practices and any local regulations. If local regulations permitted, a waiver regarding patient consent to the secondary use of existing data was requested and informed consent was therefore not necessary.

3 | RESULTS

3.1 | Study population

A total of 695 patients (UC, n = 304; CD, n = 391) were included in the FAS, of which 658 patients (UC, n = 291; CD, n = 367) were included in the PK analysis for the exposure–response relationship (Table 1). Overall, the majority of the patients were from the United States (39.3%) and Belgium (25.8%). Patients had a median age of 39 years and median disease duration of 9 years. Almost half (47.9%) of the patients were male and 86.9% had received prior TNF antagonist therapy.

Signs and symptoms of active disease (based on the totality of baseline information extracted from medical records) were present in most patients in the UC and CD groups (82.2% [250/304] and 59.6% [233/391], respectively) (Table 1). At the start of vedolizumab treatment in the UC and CD groups, median (interquartile range [IQR]) C-reactive protein concentrations were 5.2 (2.0–16.7) mg/L and 6.4 (2.3–24.3) mg/L, respectively, and more than half of patients had a C-reactive protein concentration ≥5 mg/L in each group (51.9% and 56.8%, respectively). In the CD group, the median (IQR) CDAI score at baseline was 182 (94–238) (n = 92). Baseline disease characteristics of the PK analysis set were similar to the FAS for the UC and CD groups. In the FAS, 92.8% (645/695) of all patients completed induction treatment (Week 14) and 77.3% (537/695) received maintenance vedolizumab treatment until at least Week 46. The most common reason for stopping treatment was no response after induction (8.2% [57/695]).

3.2 | Bayesian-updated population PK model

At least one measured vedolizumab serum concentration was extracted from health records of 126 of 291 patients with UC (43.3%) and 206 of 367 patients with CD (56.1%). The median (IQR) observed $C_{\text{trough}}$ at Weeks 14 (n = 263) and 46 (n = 97) were 17.6 μg/ml (9.7–27.30) and 15.4 μg/ml (8.90–26.54) respectively. Data predicted using the population PK model (developed on the basis of data from the GEMINI studies) were similar to the real-world data, as demonstrated by the visual predictive check for the overall data (Figure S1). Furthermore, goodness-of-fit plots showed consistency between the observed and predicted data, with no observation of abnormal trends in the residuals and conditional weighted residuals with interaction versus time- and population-predicted serum vedolizumab concentrations (data not shown). Together, these results indicate that the population PK model developed on the basis of data from the GEMINI studies is valid to fit these real-world data.

The correlation analyses between observed and predicted serum vedolizumab concentrations across all time points for the overall population are shown in Figure 2. Individual predicted serum vedolizumab concentrations among patients with UC and CD (PK analysis set) were significantly correlated with observed concentrations across all time points, with a Spearman correlation coefficient of 0.907 (p < 0.0001). In addition, a high ICC coefficient of 0.607 (p = 0.0017) reflected that predicted and observed vedolizumab concentrations for the overall data were clustered across all time points. Correlation coefficients were similar when analysed for UC and CD separately (Figure S2). The product label in Europe allows for an optional Week 10 dose for patients with CD. In total, 34 patients (11.2%) in the UC group and 152 patients (38.9%) in the CD group had a Week 10 dose in their planned regimen. In the CD data set, an early increase in vedolizumab concentrations corresponded with the additional week 10 induction dose.

3.3 | Treatment outcomes

The proportion of patients in the FAS who achieved remission in response to vedolizumab are shown in Figure S3. At Week 52, ~40% of patients with UC or CD were in clinical remission, and endoscopic remission was achieved by 40% and 74% of patients with UC and CD respectively. Approximately 20% of patients with UC or CD attained deep remission by this time. Biologic remission (C-reactive protein <5 mg/L) at Week 52 was achieved by 28% and 21% of patients with UC and CD respectively.
3.4 Exposure–response relationship between predicted vedolizumab C<sub>trough</sub> and observed treatment outcomes

There was a significant difference in median predicted C<sub>trough</sub> (pre-infusion) across most time points (Weeks 6, 10, 14, 22, 46 assessed) in all patients with IBD (UC and CD groups combined) who were remitters relative to non-remitters (P ≤ 0.05) for clinical and deep remission at Weeks 14 and 52 (Figure 3). In addition, these analyses show that higher C<sub>trough</sub> at earlier time points were consistently associated with achieving clinical remission at later time points. Threshold analyses to delineate C<sub>trough</sub> at time points associated with overall clinical remission showed that higher C<sub>trough</sub> (based on Youden index) at earlier time points was associated with clinical remission at later time points (Figure 3A). For example, vedolizumab C<sub>trough</sub> ≥ 31.0 μg/ml at Week 6 and ≥32.1 μg/ml at Week 10 were associated with achieving clinical remission at Week 14. Similarly, C<sub>trough</sub> of 32.0 μg/ml at Week 6, 36.5 μg/ml at Week 10 and 13.6 μg/ml at Week 22 were associated

| TABLE 1 Baseline demographics and disease characteristics of patients with ulcerative colitis or Crohn’s disease (full analysis set) |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Characteristic                                  | UC (n = 304)                                      | CD (n = 391)                                      | Overall (N = 695)                                      |
| Active disease, n (%)                           | 250 (82.2)                                        | 233 (59.6)                                        | 60 (8.6)                                           |
| Country, n (%)                                  |                                                   |                                                   |                                                   |
| France                                          | 23 (7.6)                                          | 37 (9.5)                                          | 60 (8.6)                                           |
| Spain                                           | 26 (8.6)                                          | 30 (7.7)                                          | 56 (8.1)                                           |
| Canada                                          | 4 (1.3)                                           | 3 (0.8)                                           | 7 (1.0)                                            |
| Belgium                                         | 66 (21.7)                                         | 113 (28.9)                                        | 179 (25.8)                                         |
| United States                                   | 135 (44.4)                                        | 138 (35.3)                                        | 273 (39.3)                                         |
| Israel                                          | 50 (16.4)                                         | 70 (17.9)                                         | 120 (17.3)                                         |
| Male, n (%)                                     | 171 (56)                                          | 162 (41)                                          | 333 (48)                                           |
| Current smoker, n (%)                           | 11 (4)                                            | 67 (18)                                           | 78 (12)                                            |
| History of prior surgery, n (%)                 | 38 (16)                                           | 188 (55)                                          | 226 (33)                                           |
| History of prior TNF antagonist therapy, n (%)  | 236 (81)                                          | 348 (91)                                          | 584 (87)                                           |
| Use of concomitant immunosuppressants at baseline, n (%) | 75 (25)                                           | 94 (24)                                           | 169 (24)                                           |
| Use of concomitant corticosteroids at baseline, n (%) | 72 (24)                                           | 82 (21)                                           | 154 (22)                                           |
| Age, years, median (range)                      | 41 (17–83)                                        | 39 (18–88)                                        | 39 (17–88)                                         |
| Body weight, kg, median (range) [n]             | 71.6 (37.5–148.1) [298]                           | 67.6 (38.5–144.2) [377]                           | 69.0 (37.5–148.1) [675]                             |
| Duration of disease, years, median (range) [n]  | 7 (0–37) [299]                                    | 11 (0–48) [369]                                  | 9 (0–48) [668]                                     |
| Baseline albumin, g/L                           |                                                   |                                                   |                                                   |
| n                                               | 291                                               | 367                                               | 658                                                |
| Mean (SD)                                       | 40.5 (5.0)                                        | 40.0 (5.1)                                        | 40.2 (5.0)                                         |
| Median (IQR)                                    | 41.0 (38.0–44.0)                                  | 40.3 (37.0–43.0)                                 | 41.0 (38–43.7)                                     |
| Baseline pMCS                                   |                                                   |                                                   |                                                   |
| n                                               | 122                                               | N/A                                               | 122                                                |
| Mean (SD)                                       | 4.3 (3.0)                                         | 4.3 (3.0)                                         |                                                   |
| Median (IQR)                                    | 5 (2–6)                                           | 5 (2–6)                                           |                                                   |
| Baseline CDAI score                             |                                                   |                                                   |                                                   |
| n                                               | N/A                                               | 92                                                | 92                                                 |
| Mean (SD)                                       | 175.3 (99.6)                                      | 175.3 (99.6)                                      |                                                   |
| Median (IQR)                                    | 182 (92–238)                                      | 182 (94–238)                                      |                                                   |
| Baseline C-reactive protein (mg/L)              |                                                   |                                                   |                                                   |
| n                                               | 208                                               | 301                                               | 509                                                |
| Mean (SD)                                       | 20.4 (49.6)                                       | 42.4 (137.6)                                      | 33.4 (110.9)                                       |
| Median (IQR)                                    | 5.2 (2.0–16.7)                                    | 6.4 (2.3–24.3)                                    | 5.9 (2.0–21.3)                                     |

Abbreviations: CD, Crohn’s disease; CDAI, Crohn’s disease activity index; IQR, interquartile range; N/A, not applicable; pMCS, partial Mayo Clinic score; SD, standard deviation; TNF, tumour necrosis factor alpha; UC, ulcerative colitis.

Data are from patients with available information.
In this study population, the exposure–response relationship with respect to endoscopic remission appeared to be stronger in patients with UC vs CD (Figure S5 [UC and CD] and Figure S6 [by disease]). There was no significant evidence for an exposure–response relationship for CD (31 patients at Week 14, and 64 patients at Week 52 had endoscopic outcomes). In patients with UC, an exposure–response relationship was more apparent at Week 14 than at 52, with significant differences in predicted $C_{\text{trough}}$ values between endoscopic remitters and non-remitters in the early weeks of dose initiation (Figure S6). Vedolizumab $C_{\text{trough}} \geq 34.4 \mu g/ml$ at Week 6 or $\geq 31.9 \mu g/ml$ at Week 10 were associated with endoscopic remission at Week 14. Endoscopic remission at Week 52 was only associated with a very early Week 6 threshold concentration of $\geq 32.1 \mu g/ml$, but no threshold concentrations at later time points could be established as being predictive of Week 52 remission.

An exposure–response relationship for biologic remission (defined as C-reactive protein $<5 \text{ mg/L}$, based on significant differences in median $C_{\text{trough}}$, was most evident for early time points (Weeks 6 and 10) and Week 14 remission (Figure S7). Threshold analysis indicated that $C_{\text{trough}} \geq 27.7 \text{ mg/L}$ at Week 6 or $\geq 27.9 \text{ mg/L}$ at Week 10 were associated with biologic remission at Week 14. When examined by indication, there was a significant difference in $C_{\text{trough}}$ between remitters and non-remitters at Week 14 in the UC group, but not in the CD group (Figure S8). Insufficient data were available to conduct analyses using faecal calprotectin as outcome measure.

### 3.5 Characteristics associated with treatment outcomes

 Logistic regression analysis using data from all patients in the PK analysis set (UC and CD combined) identified several factors significantly ($p < 0.10$) associated with achieving remission at Week 14 or 52. Factors associated with clinical remission at Week 52 were older age at baseline (per year), induction period vedolizumab clearance, prior IBD surgery and concomitant immunosuppressant use and albumin concentration at baseline (Table 2A). Factors associated with deep remission at Week 14 were concomitant immunosuppressant use at baseline and prior IBD surgery; at Week 52, deep remission was associated with baseline vedolizumab clearance, concomitant immunosuppressant use at baseline and prior IBD surgery (Table 2B).

### 4 DISCUSSION

This study is the largest exposure–response analysis of real-world vedolizumab data to date. Results from this real-world study provide valuable new insights into the association between PK parameters and short- and long-term treatment outcomes. The results also strengthen observations from the GEMINI trials, including validating the application of population PK modelling with Bayesian updating to evaluate exposure–response relationships in a real-world population. Historically, exposure–response relationship studies...
based on real-world data mainly used observed $C_{\text{trough}}$, which, owing to the sparsity of data, can limit measures of drug exposure and necessitate the use of site-specific time points. In contrast, population PK models can provide insights into the exposure–response relationship between vedolizumab and clinically important disease outcomes in the setting of large inter-patient disparity. The large size of the ERELATE cohort and the representation of daily clinical practice from different parts of the world contributed to a better estimate and confidence of the actual threshold values for vedolizumab exposure–response relationship. Although not prospective,
the identified threshold levels for most clinical endpoints in the current study suggest that TDM may be useful for vedolizumab. The value of ERELATE is that it applies commonly defined evaluation in a large cohort and therefore mitigates the lack of prospectively designed study. Taken together, the approach of population PK modelling with Bayesian updating in the current study allows to reduce the impact of missing PK data and provides accurate determination of PK parameters threshold levels.

The baseline characteristics of the ERELATE study population were mostly similar, with only a few exceptions, to those of the GEMINI controlled trials. The ERELATE study population was a more diverse IBD population than the GEMINI program, including...
patients with a broader range of disease severity, medical and surgical history, concomitant medications and dosing regimens. In particular, one-third of patients did not have active disease when vedolizumab treatment was initiated, whereas all patients in the GEMINI studies had moderately to severely active disease. In patients with CD, mean (standard deviation) baseline CDAI score was lower in ERELEATE (175.2 [99.6]) vs GEMINI 2 and 3 (324 [69] and 303.3 [55.0] respectively). Less severe disease may have contributed to fewer endoscopy being performed, which impacted our ability to evaluate this endpoint.

The previously developed population PK model was able to fit real-world vedolizumab concentrations without needing refinement of the model. Bayesian updating with observed serum concentrations allowed evaluation of the exposure–response analyses of pooled multicentre real-world data, despite the use of different assays to measure vedolizumab concentrations, as demonstrated
by a strong correlation between observed and predicted serum vedolizumab concentrations. Furthermore, the approach allowed for a more robust exposure–response analysis vs using only observed concentrations, which were available for few patients, typically only at $C_{\text{trough}}$, and not at all time points. Using a population PK approach to predict exposure in all patients at all time points during therapy allowed for the evaluation of a wider range of exposure measures including $C_{\text{trough}}$, $C_{\text{avg}}$, AUC and baseline vedolizumab clearance, as opposed to prior exposure–response analyses that only evaluated $C_{\text{trough}}$. Together, this approach of pooling data and then predicting concentrations using a population PK model with Bayesian updating allows for evaluation of the exposure–response relationship over a meta-analysis or review of individual centre studies, which we propose could be used as a method for other compounds as well.

The rate of clinical remission (40%) at Week 52 of vedolizumab treatment was comparable to other real-world data reported in the literature.\textsuperscript{13-20,27} Positive exposure–response relationship between serum vedolizumab concentrations and treatment outcomes were observed for UC and CD; however, these associations were more pronounced for UC than CD. This finding may be because the outcomes measured were different between the two diseases and perhaps more readily defined for UC. Higher drug concentrations were associated with better treatment outcomes in remitters vs non-remitters. $C_{\text{trough}}$ thresholds of $\geq 31.0 \mu g/ml$ at Week 6 and $\geq 32.1 \mu g/ml$ at Week 10 were associated with achieving clinical remission at Week 14; patients above these thresholds would be more likely to achieve clinical remission. Early exposure was associated with clinical remission and deep remission at the end of induction (Week 14) and during maintenance in UC and CD. For deep remission, a similar

| Variable | Effect estimate | $p$ value |
|----------|----------------|-----------|
| (A) Clinical remission | | |
| Week 14 (remission, $n=215$; non-remission, $n=236$) | | |
| Predicted VDZ concentration (Week 14 per 10 mg/L) | 0.3189 | 0.0001 |
| Disease type, UC vs CD | 0.3577 | 0.0022 |
| Concomitant immunosuppressant used | -0.8659 | <0.0001 |
| Prior TNF antagonist treatment | 0.5987 | 0.0746 |
| Any prior IBD surgery | -0.3370 | 0.0035 |
| | | |
| Week 52 (remission, $n=131$; non-remission, $n=213$) | | |
| Albumin baseline (per 1 g/L) | -0.0436 | 0.0982 |
| VDZ clearance (per 0.01L/day) | -0.1030 | 0.0006 |
| Age (per 1 year) | -0.0173 | 0.0214 |
| Concomitant immunosuppressant used | -0.4215 | 0.0019 |
| Any prior IBD surgery | -0.3357 | 0.0110 |
| | | |
| Week 52 (remission, $n=119$; non-remission, $n=266$) | | |
| Predicted VDZ concentration (Week 14 per 10 mg/L) | 0.3092 | 0.0016 |
| Disease type, UC vs CD | 0.2305 | 0.0675 |
| Concomitant immunosuppressant used | 0.4010 | 0.0037 |
| Any prior IBD surgery | -0.4031 | 0.0333 |
| Any prior IBD surgery | -0.3628 | 0.0088 |

Note: Factors analysed included VDZ dosing regimen (for models after Week 14), predicted VDZ trough concentration at the time point, VDZ clearance and the baseline covariates age (continuous and categorised), sex, body weight, disease duration, albumin, use of concomitant immunosuppressants, use of corticosteroids, prior TNF antagonist exposure, prior IBD surgery, disease extent for UC and location of involvement, behaviour and fistulising disease for CD. If an additional analysis pooled over disease type was performed, then the disease type (UC or CD) was also included as factor.

Abbreviations: CD, Crohn’s disease; IBD, inflammatory bowel disease; TNF, tumour necrosis factor alpha; UC, ulcerative colitis; VDZ, vedolizumab.
exposure–response relationship was observed for UC and CD. The absence of significant evidence for an exposure–response relationship endoscopy outcome for CD may be attributed to the limited number of patients for whom endoscopic outcomes were available, as well as the comparatively lower proportion of patients with CD with active disease at baseline vs patients with UC.

Further evidence of the vedolizumab exposure–response relationship was shown in the quartile analysis of various exposure measures. Lower vedolizumab clearance and higher drug exposure ($C_{avg}$, $C_{trough}$) were associated with higher rates of remission. A ceiling effect was observed for certain time points and outcomes. The practical clinical implications of this are that one may be able to predict patient vedolizumab concentration on the basis of baseline albumin, body weight and dosing regimen before initiation of therapy. Furthermore, comparisons of exposures with different formulations could potentially be improved when $C_{avg}$ is used to evaluate exposure–response relationship. For example, in the comparison of subcutaneous vs IV formulations of vedolizumab, where $C_{avg}$ is generally comparable but $C_{trough}$ is higher with subcutaneous vedolizumab because of its higher dosing frequency, albeit with a lower dose.

Multiple demographic and disease characteristics and exposure measures were significantly associated with achieving treatment outcomes using a multivariable analysis. Interestingly, vedolizumab concentrations were predictive of clinical and deep remission outcomes at Week 14, whereas baseline clearance was the most common measure of exposure found to be a predictor of clinical and deep remission outcomes at Week 52, thus underscoring the importance of drug exposure found to be a predictor of clinical and deep remission outcomes. This relationship is stronger when evaluated in more demanding treatment outcomes in both UC and CD.

In conclusion, this study provides informative new real-world data demonstrating a positive exposure–response relationship for vedolizumab for UC and CD, whereby lower vedolizumab clearance and higher drug exposure in the early phases of treatment (i.e. induction) are positively associated with better long-term treatment outcomes. This relationship is stronger when evaluated in more demanding treatment outcomes in both UC and CD.

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AUTHOR CONTRIBUTIONS

Niels Vande Casteele: Conceptualization (equal); formal analysis (equal); research support (equal); writing – original draft (equal); writing – review and editing (equal). William J Sandborn: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Brian G Feagan: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Séverine Vermeire: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Parambir S. Dulai: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Andres Yarur: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Xavier Robin: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). S Benhorin: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Maria Rosario: Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). Teresa Osborn: Conceptualization (equal); formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). Julian Panés: Investigation (equal); writing – original draft (equal); writing – review and editing (equal). Dirk Lindner: Formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). Christian Aghotom: Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan and individual patients’ data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymisation. Data are available upon request via application at https://search.vivli.org.

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REFERENCES

1. Mathieu A, Karmiris K, Louis E, et al. Report of the ECCO pathogen- esis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohns Colitis. 2010;4:355–66.
2. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol. 2016;7:e135.
9. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S.
11. Rosario M, French JL, Dirks NL, Sankoh S, Parikh A, Yang H, et al.
10. Ward MG, Sparrow MP, Roblin X. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. Expert Rev Clin Immunol. 2019;15:837–48.
5. Zhao L, Ren TH, Wang DD. Clinical pharmacology considerations in biologics development. Acta Pharmacol Sin. 2012;33:1339–47.
6. Ovacik M, Lin K. Tutorial on monoclonal antibody pharmacokinetics and its considerations in early development. Clin Transl Sci. 2018;11:540–52.
3. Molnár T, Farkas K, Nyári T, Szepes Z, Nagy F, Wittmann T. Frequency and predictors of loss of response to infliximab or adalimumab in Crohn’s disease after one-year treatment period—a single center experience. J Gastrointestin Liver Dis. 2012;21:265–9.
4. Papamichael K, Vogelzang EH, Lambert J, Wolkink G, Cheifetz AS. Therapeutic drug monitoring with biologic agents in inflammatory bowel disease: implications for personalized medicine. BioDrugs. 2019;33:453–68.
7. Lefevre PLC, Shackelton LM, Vande Casteele N. Factors influencing drug disposition of monoclonal antibodies in inflammatory bowel disease: implications for personalized medicine. BioDrugs. 2019;33:453–68.
8. Takeda Pharmaceuticals America, Inc. ENTYvio (vedolizumab, intravenous) prescribing information. https://general.takedapharm.com/ENTYVIOP. Accessed March 2, 2021.
9. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. 2017;153:827–34.
10. Ward MG, Sparrow MP, Roblin X. Therapeutic drug monitoring of vedolizumab in inflammatory bowel disease: current data and future directions. Therap Adv Gastroenterol 2018;11:1756284818772786.
11. Rosario M, French JL, Dirks NL, Sankoh S, Parikh A, Yang H, et al. Exposure-efficacy relationships for vedolizumab induction therapy in patients with ulcerative colitis or Crohn’s disease. J Crohns Colitis. 2017;11:921–29.
12. Osterman MT, Rosario M, Lasch K, Barocas M, Wilbur JD, Dirks NL, et al. Vedolizumab exposure levels and clinical outcomes in ulcerative colitis: determining the potential for dose optimisation. Aliment Pharmacol Ther. 2019;49:408–18.
13. Schreiber S, Dignass A, Peyrin-Biroulet L, Hather G, Demuth D, Mosli M, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. J Gastroenterol. 2018;53:1048–64.
14. Al-Bawardy B, Ramos GP, Willrich MAV, et al. Vedolizumab drug level correlation with clinical remission, biomarker normalization, and mucosal healing in inflammatory bowel disease. Inflamm Bowel Dis. 2019;25:580–6.
15. Dreesen E, Verstockt B, Biais S, de Bruyn M, Compérnelle G, Tops S, et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2018;16:1937–46.e1938.
16. Plevris N, Jenkinson PW, Chuah CS, Lyons M, Merchant LM, Pattenden RJ, et al. Association of trough vedolizumab levels with clinical, biological and endoscopic outcomes during maintenance therapy in inflammatory bowel disease. Frontline Gastroenterol. 2019;11:117–23.
17. Poullon L, Rousseau H, Busby-Venner H, de Carvalho Bittencourt M, Choukour M, Gauchotte G, et al. Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. J Crohns Colitis. 2019;13:970–5.
18. Schulze H, Esters P, Hartmann F, Stein J, Christ C, Zorn M, et al. A prospective cohort study to assess the relevance of vedolizumab drug level monitoring in IBD patients. Scand J Gastroenterol. 2018;53:670–6.
19. Yacoub W, Williet N, Poullon L, di-Bernardo T, de Carvalho Bittencourt M, Nancey S, et al. Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study. Aliment Pharmacol Ther. 2018;47:906–12.
20. Yarur A, Bruss A, Patel A, Beniwal-Patel P, Fox C, Ungaro R, et al. Vedolizumab levels during induction are associated with remission in patients with inflammatory bowel diseases [abstract]. Am J Gastroenterol. 2017;112(Suppl):S533–4.
21. Rosario M, Dirks NL, Gastonguay MB, Fasamade AA, Wyant T, Parikh A, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn’s disease. Aliment Pharmacol Ther. 2015;42:188–202.
22. Sheiner LB, Beal SL. Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci. 1982;71:1344–8.
23. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32–5.
24. Feagan BG, Rutgeerts P, Sande S, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–709.
25. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sande SE, et al. Vedolizumab as induction and maintenance therapy for Crohn’s disease. N Engl J Med. 2013;369:711–21.
26. Sande BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn’s disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147:618–27.e613.
27. Bressler B, Yarur A, Silverberg MS, Bassel M, Bellaguarda E, Fourment C, et al. Vedolizumab and anti-tumour necrosis factor α real-world outcomes in biologic-naïve inflammatory bowel disease patients: results from the EVOLVE study. J Crohns Colitis. 2021;15:1694–706.
28. Sandborn WJ, Baert F, Danese S, Krzna ric Ž, Kobayashi T, Yao X, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. Gastroenterology. 2020;158:562–72.e512.
29. ClinicalTrials.gov. Vedolizumab intravenous (IV) dose optimization in ulcerative colitis (ENTERPRISE). https://www.clinicaltrials.gov/ct2/show/NCT03029143?term=enterpr&draw=2&rank=1. Accessed April 22, 2021.
30. Williet N, Boschetti G, Fovet M, di Bernardo T, Claudez M, Tedesco E, et al. Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases and need for additional doses within 6 months. Clin Gastroenterol Hepatol. 2017;15:1750–7.e1753.
31. Ungar B, Malickova K, Hanžel J, Abu Arisha M, Paul S, Rocha C, et al. Dose-optimization for loss-of-response to vedolizumab—pharmacokinetics and immune mechanisms. J Crohns Colitis. 2021;15:1707–19.

SUPPORTING INFORMATION
Additional supporting information will be found online in the Supporting Information section.

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