

## Title Page

# SYSTEMATIC REVIEW: SAFETY OF VEDOLIZUMAB FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

<b>Journal:</b>	APT
<b>Manuscript ID:</b>	Draft
<b>Article type:</b>	Review
<b>Corresponding Author:</b>	Professor Simon PL Travis Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom Email: <a href="mailto:simon.travis@ndm.ox.ac.uk">simon.travis@ndm.ox.ac.uk</a> Phone: +44 1865 228753
<b>List of Authors:</b>	Bye, William A; Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom  Jairath, Vipul, Departments of Medicine, Epidemiology and Biostatistics, Western University, London, ON, Canada  Travis, Simon P L; Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom
<b>Keywords:</b>	Vedolizumab; safety; inflammatory bowel disease; Crohn's disease; ulcerative colitis
<b>Word count:</b>	3932
<b>Number of tables:</b>	9
<b>Number of figures:</b>	1
<b>Number of references:</b>	68

## Summary

**Background:** Vedolizumab specifically recognizes the  $\alpha 4\beta 7$  integrin and selectively blocks gut lymphocyte trafficking: potentially, it offers gut-specific immunosuppression.

**Aim:** To review the safety of vedolizumab and summarise post-marketing data to assess if any safety concerns that differ from registration trials have emerged.

**Method:** A systematic bibliographic search identified six registration trials and nine cohort studies.

**Results:** Integrated data from registration trials included 2830 vedolizumab-exposed patients (4811 person-years exposure (PYs)) and 513 placebo patients. This reported lower exposure-adjusted incidence rates of infection (63.5/100 PYs; 95% CI 59.6 to 67.3) and serious adverse events (20.0/100 PYs; 95% CI 18.5 to 21.5) compared to placebo (82.9/100 PYs; 95% CI 68.3 to 97.5) and (28.3/100

17 PYs 95% CI 20.6 to 35.9) respectively. Higher, but statistically insignificant rates of enteric infections  
18 occurred in vedolizumab-exposed patients (7.4/100 PYs; 95% CI 6.6 to 8.3) compared to placebo  
19 (6.7 PYs; 95% CI 3.2 to 10.1). Six post-marketing cohort studies (1049 patients, 403 PYs)  
20 demonstrated rates of infection of 8% (82/1049); enteric infection of 2% (21/1049) and adverse events  
21 of 16% (166/1049). Multivariate analysis in one cohort study suggested increased risk of surgical site  
22 infection with perioperative VDZ. Human experience in pregnancy is limited.

23 **Conclusions:** Post-marketing data confirm the excellent safety of vedolizumab observed in  
24 registration trials. The signal of post-operative complications should be interpreted with caution, but  
25 warrants further study. Although comparative studies are needed, Vedolizumab may be a safe  
26 alternative in patients who best avoid systematic immunosuppression, including those predisposed to  
27 infection, malignancy, or the elderly.

28

## 1. Introduction

Vedolizumab (VDZ) potentially provides gut-specific immunosuppression. It recognizes and binds to  $\alpha 4\beta 7$  integrin, a glycoprotein expressed on circulating B and T lymphocytes, inhibiting selective trafficking of gut-homing CD4<sup>+</sup> T lymphocytes through addressin cell adhesion molecule 1 (MaDCAM-1).<sup>1-6</sup> Integrated analysis of registration randomised controlled trials reported by Colombel et al. indicated no greater increase in adverse events or serious adverse events compared to patients treated with placebo, but is this borne out in real-life practice?<sup>7-13</sup> Patients enrolled in randomised trials may not be representative which limits the generalizability of safety findings to the practicing physician in the “real world”.<sup>14</sup> Questions related to safety persist around the mechanism of action and potential complications, including; enteric infections, anastomotic healing after surgery, immunosurveillance for malignancy and neonatal safety in pregnancy in an uncontrolled non-clinical trial environment. By reviewing the data available from post-marketing studies, we assess whether there are any safety signals or differences from the conclusions of Colombel's integrated analysis, which may have emerged since FDA approval in May 2014.

A bibliographic search was performed using the MEDLINE, EMBASE and Cochrane CENTRAL Register of Controlled Trials databases with the key words (vedolizumab OR MLN002) AND (inflammatory bowel disease OR ulcerative colitis OR Crohn) AND (safety OR pregnan\* OR infection OR malignancy OR surgery OR adverse\* OR immunogenicity). The search returned 571 articles, including 6 registration trials (4 randomised controlled trials and 2 open label extension studies), and 9 cohort studies that reported safety outcomes for VDZ.<sup>15-23</sup> Two case reports of interest were included.<sup>24,25</sup> We compare the safety profile established in pooled integrated analysis of all registration studies to those reported in subsequent post-marketing cohort studies in the literature to date to assess the “real world” safety profile of VDZ.

### 1.1 Registration studies

55

56 Six registration studies were used to assess safety of patients exposed to VDZ (see table 1).<sup>8-13</sup> The  
 57 six studies consisted of four phase 3 trials including GEMINI 1,2 and 3 (randomised controlled trials)  
 58 and the GEMINI long-term study (open label) as well as two phase 2 trials. The phase 2 trials included  
 59 the initial dose-ranging study; C13002 (placebo-controlled) and the corresponding long term safety  
 60 extension of the study, C13004 (open label study). Integrating all trials data creates a total safety  
 61 population of 2932 patients. Colombel et al. pooled data from the placebo-controlled trials and long-  
 62 term extension studies, of which 2830 of these patients were exposed to at least one dose of VDZ  
 63 with a combined total of 4811 patient years (PYs). The median exposure for ulcerative colitis (UC)  
 64 patients was 378 days (range 1 – 1977) and 338 for Crohn’s disease (CD) (range 1 – 1927).<sup>7</sup> The  
 65 placebo cohort is constructed using the phase 3 randomised control trials of which 504 patients  
 66 received placebo contributing a total of 214 PYs of placebo exposure. Pooled, integrated analysis  
 67 from Colombel is used as the comparator for the subsequent real world cohort studies identified and  
 68 summarised in this review.

69

## 70 1.2 Cohort studies

71

72 We defined “post marketing” studies as any study published after the FDA approved a licence for  
 73 VDZ in May 2014 and “cohort studies” as those designed to evaluate safety of patients exposed to  
 74 VDZ, either prospectively or retrospectively. Using these definitions 6 studies have reported safety  
 75 outcomes of VDZ-exposed patients (Table 1).<sup>15-20</sup> These studies will henceforth be referred to  
 76 collectively as the “post-marketing cohort studies”. The post-marketing cohort studies provide real  
 77 world data on the safety of VDZ in 1049 exposed patients with 403 patient years’ exposure. Patients  
 78 might have failed multiple therapies, had symptomatic strictures, an ostomy or CD affecting an  
 79 ileoanal pouch. One study established that only 36% of patients would have fulfilled eligibility criteria

80 for a GEMINI trial. A further 3 cohort studies examined post-operative outcomes in patients exposed  
81 to VDZ (see table 1).<sup>21-23</sup>

82

83 **Table 1: Registration and post-marketing cohort studies of vedolizumab safety**

84

## 85 2. Results

86

### 87 2.1 Safety data from registration trials

88

89 Integrated safety analysis of the six registration trials of VDZ, including preliminary data from the  
 90 extension study (GEMINI Long Term Study (LTS)), has demonstrated a safety profile similar to  
 91 placebo.<sup>7</sup> When adjusted for duration of exposure, the incidence rates for all (AE) and serious adverse  
 92 events (SAEs) were lower in patients treated with VDZ compared to those treated with placebo. In  
 93 the safety population, 248 (95% CI 230 to 266 per 100 patient years) and 20 (95% CI 19 to 22) VDZ-  
 94 exposed patients experienced an AE or SAE respectively, compared to 419 (95% CI 359 to 480) and  
 95 28 (95% CI 21 to 36) patients on placebo (Table 2). Frequency of AEs or SAEs was independent of  
 96 duration of exposure to VDZ. Numerically this favours VDZ over placebo, but the studies were not  
 97 powered for difference in side effects.

98

99 **Table 2: Exposure-adjusted incidence rates of adverse events in the safety population of**  
 100 **registration studies**

101

### 102 2.2 Safety data from cohort studies

103

104 Non-infectious adverse events from the six cohort studies are summarised [Table 3]. Although  
 105 absolute numbers are lower in post-marketing studies, likely due to less stringent reporting protocol,  
 106 the data support that VDZ causes no more side effects than placebo. This matters to patients.  
 107 Arthralgia (3%), arthritis (1%) and headache (2%) were the three most frequently reported adverse  
 108 events. Unique non-infectious adverse events that may be of concern in the real world include one  
 109 case of retinal vein occlusion and one case of optic neuritis.<sup>16,18</sup> The patient who developed optic

neuritis had previously failed anti-TNF and natalizumab therapy. Her sight responded to plasmapheresis after failing to respond to steroids and golimumab. There were no cases of demyelination in the GEMINI trials. 9/13 patients who experienced paraesthesia in the Amiot cohort underwent brain magnetic resonance imaging and electromyography analysis, which did not demonstrate any abnormalities.<sup>17</sup> Paraesthesia resolved over time in all patients. Venous thrombosis in atypical vascular beds is a hallmark of prothrombotic disorders such as IBD.

116

### 117 **Table 3: Non-infectious adverse events in cohort studies**

118

Two deaths were reported in post-marketing studies. One in a 72-year-old woman with CD who developed cytomegalovirus colitis after 14 weeks of VDZ and steroids.<sup>19</sup> She was commenced on oral ganciclovir and continued VDZ before being diagnosed with lymphoma. The second occurred in a 39 year old with no co-morbid conditions.<sup>16</sup> She had complex disease with perianal fistulae, small bowel strictures, enteral fistulae and abscess formation. She had failed to respond to multiple medical therapies and had an extensive surgical history including a diverting ostomy. She underwent a further resection and had an anastomotic leak, dying 72 hours later. 13/2830 deaths occurred in the GEMINI studies.<sup>7</sup>

127

Comparison through network meta-analysis of randomized-controlled trials (RCTs) has been performed for infliximab, adalimumab, golimumab and VDZ to assess safety profile.<sup>26</sup> This is a method for performing indirect comparisons between therapeutic options, in the absence of head-to-head trials. No significant differences were observed (table 4), nor did analysis of individual adverse events. Supporting the findings from RCTs, cumulative real world data on VDZ have not revealed any difference in non-infectious adverse events compared to RCTs.

134

### 135 **Table 4: Results of a comparative analysis of the safety profile of biologics**

### 3. Vedolizumab and infection

Data from phase 2 and 3 trials report fewer than 1% of patients discontinued VDZ due to infection.<sup>7</sup> Adjusted for exposure, the incidence of upper respiratory infection (60% of all infections) was 28.6/100 patient years (PYs) for VDZ compared to 34.7/100 PYs for placebo. All other infections, including abdominal, gastrointestinal and lower respiratory tract infections occurred with similar incidence between VDZ and placebo (see table 5).

#### **Table 5: Exposure-adjusted incidence rates of infections in the overall safety population**

The incidence of serious infection, defined by V.14.0 of the Medical Dictionary for Regulatory Activities (MedDRA)<sup>27</sup> was 4.3/100 PY for VDZ compared to 3.8/100 PY for placebo. Given theoretical concerns of gastrointestinal infection due to gut selectivity of VDZ it was notable that all *Clostridium difficile* infections occurred in VDZ-exposed patients (0.7/100 PYs). Cox proportional hazard modelling demonstrated younger age (HR 0.98, 95% CI 0.97 to 1.00; p=0.0003), concomitant corticosteroid use (HR 1.72, 95% CI 1.30 to 2.28; p=0.0002) and concomitant narcotic analgesics (HR 2.7, 95% CI 2.06 to 3.72; p <0.0001) as risk factors.<sup>7</sup> The reported annual incidence of pneumonia in IBD patients of 138/10,000 is higher than healthy individuals, 76/10,000 (IRR 1.82, 95% CI: 1.75 – 1.88).<sup>28</sup> Post hoc analysis of GEMINI 1, 2 and open-label extension study concluded that VDZ treatment of IBD was not associated with an increased risk of lower respiratory tract infections (LRTI's).<sup>29</sup> Post-marketing VDZ data from the Global Safety Database (May 2014 to May 2016) demonstrated 40 serious and 68 non-serious LRTIs in 46, 978 patient-years of VDZ therapy. 54 of these events were pneumonia occurring at an incidence of 1-report/1000 years of therapy.<sup>30</sup>

#### **Table 6: Exposure-adjusted incidence rates of serious infections in the overall safety population**



162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187

Safety data from real world cohort studies are reassuring (table 7). The total reported infectious complication rate across all cohort studies was 7.8% (n=82/1049). Two case reports of atypical infections whilst on VDZ therapy include one of *Pseudomonas stutzeri* meningitis in a 19-year-old woman with ileocolonic CD refractory to certolizumab, azathioprine and budesonide who received VDZ 6 weeks after her last dose of certolizumab.<sup>24</sup> The other was of *Histoplasmosis* in a 40-year-old woman, also with ileocolonic CD.<sup>19</sup> She presented with sepsis after her second dose of VDZ, 7 weeks after the last adalimumab dose and was on concomitant therapy with subcutaneous methotrexate 25mg weekly.

**Table 7: Post marketing cohort studies: infectious adverse events**

**4. Vedolizumab infusion reactions**

Safety analysis of the randomised controlled trials included 2830 patients with exposure to at least one dose of VDZ and a median exposure of 378 days. Fewer than 5% patients experienced an infusion related reaction (IRR), defined as an adverse event within a day of the infusion.<sup>7</sup> Preliminary data from 2243 patients enrolled in the VDZ extension study (GEMINI Long Term Study (LTS)) report 87 patients (4%) had an IRR. Nausea (n= 14) and headache (n= 10) were the most common. In twelve patients (<1%) the infusion was interrupted or resulted in incomplete dosing because of an IRR and three developed anaphylactoid reactions: one with dyspnoea, bronchospasm and urticaria; another with rash, vomiting and a swollen tongue; and a third had throat tightness and nausea despite prophylactic hydrocortisone. Experience from cohort studies is similar: the rate of IRR's was <2% (14/837 patients). One had an anaphylactic reaction and 2/837 patients stopped VDZ due to the severity of an IRR (please see supplementary material for IRR rate per cohort study).

## 188 5. Vedolizumab and JC virus/progressive multifocal leukoencephalopathy (PML)

189

190 The background to potential concern relates to the original anti-integrin agent, natalizumab. 566 cases  
 191 of PML have occurred in over 138,000 natalizumab-exposed patients, thought to be due to decreased  
 192 immune surveillance of the John Cunningham (JC) virus attributable to blockade of  $\alpha 4\beta 1$  at the blood  
 193 brain barrier.<sup>31</sup> Gut selectivity by VDZ leaves migration of leukocytes to the central nervous system  
 194 unaffected and should mitigate the risk of PML. Nevertheless, the FDA required a “Risk Assessment  
 195 and Minimization for Progressive multifocal leukoencephalopathy” (RAMP) programme for VDZ.  
 196 The program involved education and a screening algorithm to monitor all patients. As of March 2013,  
 197 2913 patients had been subject to the RAMP program, leading to 56 patients undergoing brain MRI  
 198 (UC 15; CD 41) and lumbar puncture in 5 patients (UC 2; CD 3) with PCR of CSF for JC virus.<sup>32</sup>  
 199 No cases of PML have been found during treatment with VDZ and no JCV was detected in CSF, with  
 200 no association between VDZ exposure and JC viremia on analysis of frozen serum from 1700 subjects  
 201 enrolled in 9 VDZ trials collected at 2-month intervals.<sup>33</sup> Spontaneous clearance of viremia occurred  
 202 in the presence of VDZ. Confidence that VDZ is not associated with PML appears justified.

203

## 204 6. Vedolizumab and immunogenicity

205

206 Initial data from GEMINI 1 and GEMINI 2 trials found a low rate of anti-VDZ antibodies (AVAs),  
 207 in 4% (56 of 1434) patients who treated for up to 52 weeks.<sup>7</sup> Of these patients, 9 had AVA-positive  
 208 samples on two or more consecutive visits and 33 developed neutralising antibodies. Patients who  
 209 tested persistently positive for anti-VDZ antibodies had lower drug trough concentrations.<sup>34</sup> In  
 210 patients who experienced an infusion related reaction, 5% (3/61) had 2 or more consecutive AVA  
 211 positive tests. In the combined intention to treat and non-intention to treat VDZ groups, AVAs  
 212 occurred in 3% (5/161) taking concomitant immunomodulators and 4% (51/1273) in those without.

213 <sup>35</sup> However, the assay used in these trials had relatively low sensitivity to detect anti-drug antibodies  
 214 in the presence of detectable drug concentrations, and results of pharmacokinetic studies with drug  
 215 resistant assays indicate that clinical trials are likely underreporting true drug immunogenicity  
 216 incidence rates for VDZ. <sup>36</sup> Notably, the proportion of patients with AVAs in the GEMINI study  
 217 population increased to about 10% following cessation of therapy. <sup>34</sup> On the other hand, patients  
 218 receiving alternate placebo dosing during the maintenance phase had a higher AVA positive rate  
 219 (18%, 44/247) if they were not on concomitant immunomodulators. AVA's were detected in serum  
 220 with high levels of drug present, which limits the sensitivity of AVA detection. <sup>37</sup> Data from GEMINI  
 221 LTS have not demonstrated an increase in AVAs with longer exposure and from a pragmatic, clinical  
 222 point of view the advantage of gut-selective immunosuppression is negated if a patient takes an oral  
 223 immunomodulator.

224

## 225 7. Vedolizumab and malignancy

226

227 Malignancy was reported in 18/2830 patients with VDZ exposure compared to 1/504 placebo-  
 228 exposed patients in the registration trials of VDZ: 6/18 amongst the VDZ-exposed patients were  
 229 gastrointestinal malignancies (3 colorectal cancers, 1 hepatic cancer, 1 appendiceal carcinoid and 1  
 230 peritoneal metastases), diagnosed after an average 11.8 year history of IBD and a median 8 (range 2  
 231 – 41) VDZ infusions. <sup>7</sup> All patients had previously received thiopurines and at least one other biologic.  
 232 5/18 were dermatological (2 melanomas, 2 squamous and 1 basal cell carcinoma). Others included 2  
 233 breast cancers, 2 pulmonary, 1 B-cell lymphoma and 2 genitourinary malignancies. Of the 12 non-  
 234 gastrointestinal malignancies, 11/12 patients had received a thiopurine and 9/12 a biologic agent.  
 235 Neoplasms reported after >20 infusions of VDZ included B cell lymphoma, genitourinary, squamous  
 236 cell and hepatocellular carcinoma, none of which suggests a mechanistic signal. Two malignancies  
 237 have been the subject of case reports: a 33-year-old man developed rectal bleeding after his second  
 238 VDZ infusion and found to have a rectal cancer complicating colitis and a 72-year-old woman was

diagnosed with Hodgkin's lymphoma after 14 weeks VDZ, complicated by cytomegalovirus colitis.

<sup>17,19</sup>

Adjusted comparisons between anti-TNF therapy and VDZ using data from registration trials and placebo as the common comparator did not reach significance (OR 0.87; 95% CI 0.26 – 2.88). <sup>38</sup>

Whilst encouraging, these data overall are insufficient to draw firm conclusions about the risk of malignancy on VDZ. A reduction in immunosurveillance as a consequence of leukocyte inhibition remains a theoretical concern for GI malignancies; so long-term safety registries are needed.

## 8. Vedolizumab and peri-operative complications

By inhibiting the migration of leukocytes to sites of inflammation or repair in the gastrointestinal tract VDZ might hypothetically impair wound healing and risk anastomotic leak or infective complications. <sup>39</sup> Leukocytes are intimately involved in the three phases of wound healing: inflammation, tissue formation, and tissue remodelling. <sup>40</sup> The GEMINI trials did not examine surgical outcomes. There are three retrospective, single-centre cohort studies (table 1) on patients who had received at least one infusion of VDZ within 12 weeks prior to surgery. <sup>21-23</sup>

The largest cohort from the Mayo clinic attempted to compare post-operative complications after VDZ exposure with biologic-naïve and anti-TNF-exposed groups (Table 9). <sup>21</sup> Small bowel resection (39%), ileocolic resection (44%) and colectomy (28%) were the most common operations performed amongst all groups. 207 (53%) patients had an anastomosis performed at surgery, including 35/94 in the VDZ group. Pre-operative treatment with VDZ was associated with an increased post-operative complication rate (Table 8), most notably surgical site infection, although the anastomotic leak rate was similar across all groups.

**Table 8:** 30 day complication rate

266

267 Multivariate analysis demonstrated perioperative VDZ increased the risk of surgical site infection 3-  
 268 4 fold (VDZ vs anti-TNF OR 3.6, 95% CI 1.42 to 10.09; VDZ vs no biologics OR 3.8, 95% CI 1.67  
 269 to 9.42). The cohort study by Stringfield et al included 36 operations on 27 patients (27 intra-  
 270 abdominal, 9 perianal) with an overall complication rate of 53%, infectious complications in 44%  
 271 and anastomotic leak rate in 2/13 (15%).<sup>22</sup> Two deaths were reported, secondary to culture-negative  
 272 sepsis, following abdominal surgery. The third study on 15 patients undergoing intra-abdominal  
 273 surgery reported only two post-operative complications (a stitch abscess and ileus requiring hospital  
 274 re-admission).<sup>23</sup> Although these are preliminary data, it does not compare favourably to meta-  
 275 analyses of peri-operative anti-TNF therapy, which reported post-operative infectious complications  
 276 in 15-17%.<sup>41-43</sup> Caution must be exercised in over-interpreting these data due to the retrospective  
 277 nature of studies; nonetheless, this signal requires further study, ideally in prospective studies, with  
 278 propensity matching and adjudication of endpoints.

279

280 9. Vedolizumab in the elderly or young

281

282 Systemic immunosuppression poses a greater risk for those at the extremes of age. A young person  
 283 diagnosed with IBD, faces the possibility of life-long immunosuppression. The absolute risk of  
 284 hepatosplenic T-cell lymphoma after thiopurine therapy with or without anti-TNF may be very  
 285 small, but is a genuine concern for the young patient.<sup>44</sup> For the elderly, immunosenescence  
 286 increases the risk of systemic immunosuppression. VDZ particularly appeals in such patients at risk,  
 287 through avoidance of systemic immunosuppression.

288

289 Post hoc analyses of the GEMINI 1 and 2 trials indicate a good safety profile in older (age 55 years)  
 290 and younger (age <35 years) patients. There were no significant differences in adverse events or  
 291 infections amongst the age groups (table 10).<sup>45,46</sup>

292

293 **Table 9:** Adverse events in GEMINI 1 and 2 by age

294

295 A single, multi-centre, retrospective cohort study has reported on VDZ initiated over age 60 (mean  
 296 67.1) in 29 patients (10 UC and 19 CD).<sup>47</sup> Median treatment duration was 30 weeks. Three patients  
 297 (10%) experienced adverse events including pneumonia, worsening gastrointestinal symptoms and  
 298 flu-like symptoms. The early signal is promising for the safety of VDZ in the elderly.

299 A single-centre, prospective observational cohort study from The Children's Hospital of  
 300 Philadelphia followed 21 young people (16 CD, 3 UC, 2 IBDU), aged 13 to 21 years (age 13–18,  
 301 n=15; age 19–21, n = 6).<sup>48</sup> Adverse events were similar to adult populations, with upper respiratory  
 302 tract infections the most common (See Supplementary material Table 2). Nevertheless, 8/21 (38%)  
 303 experienced 12 serious adverse events that required hospitalization and 2 patients discontinued  
 304 VDZ. Two patients required surgery secondary to disease progression and one developed  
 305 obstructing nephrolithiasis with associated pyonephritis. Interestingly, three patients developed new  
 306 extraintestinal manifestations. Two patients developed erythema nodosum and one developed  
 307 bowel-associated dermatosis-arthritis syndrome. Caution is necessary to avoid over-interpreting  
 308 these data: all patients had severe disease; all were refractory to anti-TNF therapy, steroid  
 309 dependent and without alternative medical options aside from surgery. On the other hand, Cox  
 310 proportional hazards modeling of the 6 VDZ registration trials identified young age as a factor  
 311 independently associated with serious infection in patients with CD.<sup>7</sup> There has been another  
 312 retrospective cohort study of 52 children with CD (58%) or UC (42%) who had almost all failed  
 313 anti-TNF therapy, median age 14.9 (range 7 – 17) years, followed for 30 weeks.<sup>49</sup> No serious  
 314 adverse events were reported.

315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340

# 10. Vedolizumab, pregnancy and lactation safety

Experience of VDZ in pregnancy remains limited. VDZ remains an FDA category B drug, because no fetotoxicity was demonstrated in pre-clinical reproduction studies in New Zealand white rabbits and cynomolgus monkeys at doses up to 25 times the human dose.<sup>50</sup> At doses of 100mg/kg every 2 weeks, levels of VDZ <300mcg/L were detected in milk 1 month post-partum in 3/11 cynomolgus monkeys, although not in animals given 10mg/kg. Human experience is limited to 24 unplanned pregnancies in RCT's of women who had received at least one dose of VDZ.<sup>51</sup> A corpus callosum anomaly occurred in the baby of a 28 year-old healthy volunteer who had received a single dose of VDZ 79 days before the estimated date of conception. 16 pregnancies have been reported in partners of male patients who had received vedolizumab: 9 of these resulted in live births, 2 spontaneous abortions, 2 elective terminations and 3 with no documented outcome.

As with other immunoglobulin G<sub>1</sub> drugs, placental transfer of VDZ can be expected to increase throughout pregnancy, with the largest transfer in the third trimester. The general strategy for patients on anti-TNF therapy has been to withdraw treatment during the third trimester if disease control allows, minimizing neonatal drug levels. The longer half-life of VDZ (25 days compared to 10 in anti-TNF therapy) may negate this strategy and it is possible that drug clearance may take 6 – 12 months in the babies of mothers who stopped VDZ in the third trimester.<sup>52</sup> This has implications for live rotavirus vaccine, which is given in 2 doses in the early months after birth and poses a risk of active infection or vaccine failure. Careful counseling of women of childbearing age who are treated with VDZ is needed: there is no safety signal from reports to date, but concerns should not be ignored. An FDA observational pregnancy registry has been initiated.

# 11. Vedolizumab and vaccines

341

342 Patients with IBD are at increased risk of infections, secondary to the immune dysregulation of  
343 underlying disease and immunosuppressive therapy. Some of the infections are preventable, but  
344 vaccination rates amongst patients with IBD remain low: 28% for influenza vaccination and 12%  
345 for hepatitis B vaccine. <sup>53-57</sup> In a well-designed demonstration of VDZ gut selectivity, a double-  
346 blinded RCT administered parenteral hepatitis B vaccine and oral cholera vaccine to patients who  
347 received VDZ or placebo. <sup>58</sup> The antibody response to the oral antigen was significantly attenuated,  
348 but the response to parenterally administered antigen was unaffected, consistent with a gut selective  
349 mechanism of action. It means that oral or mucosal administered vaccines cannot be expected to  
350 work during VDZ therapy, although parenteral vaccination will be unaffected. It is also conceivable  
351 that live parenteral vaccines might be safe in patients receiving VDZ. The FDA label states that  
352 patients should only receive live vaccines if the benefits outweigh the risks. <sup>50</sup> One case has been  
353 reported of the safe and successful administration of live measles, mumps and rubella vaccine to a  
354 patient receiving VDZ. <sup>25</sup> An adequate measles antibody index response was demonstrated (from  
355 0.7 (negative) to 2.06 (positive)). Further study is warranted.

356



## 357 CONCLUSIONS

358

### 359 **Figure 1:** Safety profile of Vedolizumab

360

361 Vedolizumab, with its gut specific mode of action appeals as a safe alternative to systemic  
362 immunosuppression and reports from subsequent patient cohorts confirm the favourable safety  
363 profile described in the registration trials of almost 3000 patients. There are two areas that require  
364 further study: an early signal of increased risk of post-operative complications and the risk of  
365 infections in the paediatric population. Such data should not be over-interpreted: patients receiving  
366 VDZ soon after FDA approval are likely to have disease towards the severe end of the spectrum,  
367 often having failed oral immunomodulators and anti-TNF therapy. Further prospective data through  
368 registries are needed to properly appraise the risks. Although no comparative data is yet available,  
369 VDZ may offer a safe alternative to anti-TNF therapy and has an obvious role as the preferred  
370 immunosuppression in some groups with IBD who may benefit most from the lack of systemic  
371 immunosuppression, including patients predisposed to infection, current or past malignancy, or  
372 those at the extreme of age.

373

374 **Disclosures:**

375 Professor Jairath has received scientific advisory board fees from AbbVie, Janssen, Takeda,  
376 Sandoz; speakers fees from Takeda, Janssen, Shire, Ferring.

377 Professor Travis is employed by Oxford University Hospitals NHS Foundation Trust and the  
378 University of Oxford. He has received Grants/Research Support from AbbVie, IOIBD, Lilly, UCB,  
379 Vifor, and Norman Collison Foundation; Consulting Fees from AbbVie, Amgen, Biogen,  
380 Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chemocentryx, Cosmo, Ferring, Giuliani  
381 SpA, GlaxoSmithKline, Janssen, Lilly, MSD, Neovacs, NovoNordisk, Norman Collison  
382 Foundation, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma,  
383 Takeda, Topivert, UCB, VHsquared and Vifor; Speaker fees from AbbVie, Amgen, Biogen,  
384 Ferring, Takeda. No stocks or share options.

385 Dr Bye has no disclosures.

386 **Acknowledgements**

387 Guarantor of the article: Prof. S. Travis

388 Author contributions: Dr Bye wrote the initial draft that was then extensively edited by Professors  
389 Travis and Jairath.

390 All authors approved the final version of the manuscript.

391 **Funding**

392 No funding received.

393 **Competing interests**

394 None.

395 **Provenance and peer review**

396 Not commissioned; externally peer reviewed.

397 **Data sharing statement**

398 Supplementary files and original data are available on request.

399

## **REFERENCES**

1. Soler-Ferran D, Champan T, Yang LL .et al. . The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. *Journal of Pharmacology and Experimental Therapeutics* 2009;330:864-75.
2. Berlin C BE, Briskin MJ, et al. . Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell* 1993;71:185-95.
3. Briskin MJ, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *American Journal of Pathology* 1997;151:97-110.
4. Hesterberg PE W-HD, Briskin MJ, et al. . Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to gut-homing integrin alpha 4 beta 7. *Gastroenterology* 1996;111:1373-80.
5. Picarella D HP, Rottman J, et al. . Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAd-CAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RB<sup>high</sup> CD4<sup>+</sup> cells. *The Journal of Immunology* 1997;158:2099-106.
6. Fedyk ER WT, Yang LL, et al. Exclusive antagonism of the alpha4beta7 integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflammatory Bowel Disease* 2012;18:2109-17.
7. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2016;18:18.
8. Feagan B, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *The New England journal of medicine* 2013;699-710.
9. Parikh A, Fox I, Leach T, et al. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases* 2013;19:1691-9.

- 425 10. Parikh A, Leach T, Wyant T, et al. Vedolizumab for the treatment of active ulcerative colitis:  
426 A randomized controlled phase 2 dose-ranging study. *Inflammatory Bowel Diseases* 2012;1470-9.
- 427 11. Sandborn W, Feagan B, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy  
428 for Crohn's disease. *The New England journal of medicine* 2013;711-21.
- 429 12. Sands B, Feagan B, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients  
430 with Crohn's disease in whom tumor necrosis factor antagonist treatment failed.  
431 *Gastroenterology* 2014;618-27.e3.
- 432 13. Feagan B, Kaser A, Smyth M, Panaccione R, Sankoh S, Abhyankar B. Long-term efficacy of  
433 vedolizumab therapy for patients with ulcerative colitis. *American Journal of Gastroenterology*  
434 2014;109:S477-S8.
- 435 14. Ha C, Ullman TA, Siegal CA, Kornbluth A. Patients enrolled in randomized controlled trials  
436 to not represent the inflammatory bowel disease patient population. *Clinical Gastroenterology and*  
437 *Hepatology* 2012;10:1002-7.
- 438 15. Baumgart DC, Bokemeyer B, Drabik A, et al. Vedolizumab induction therapy for  
439 inflammatory bowel disease in clinical practice - A nationwide consecutive German cohort study.  
440 *Alimentary Pharmacology and Therapeutics* 2016;43:1090-102.
- 441 16. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for  
442 moderate-severe Crohn's disease: Results from the US VICTORY consortium. *American Journal of*  
443 *Gastroenterology* 2016;111:1147-55.
- 444 17. Amiot A, Grimaud JC, Peyrin-Biroulet L, et al. Effectiveness and Safety of Vedolizumab  
445 Induction Therapy for Patients With Inflammatory Bowel Disease. *Clinical Gastroenterology &*  
446 *Hepatology* 2016;22:22.
- 447 18. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of Vedolizumab as Induction Therapy in  
448 Refractory IBD Patients: A Multicenter Cohort. *Inflammatory Bowel Diseases* 2015;21:2879-85.
- 449 19. Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab Effectiveness and Safety Over the First  
450 Year of Use in an IBD Clinical Practice. *Journal of Crohn's & colitis* 2016;10:402-9.

- 451 20. Mendoza Ladd AH, Scott FI, Grace R, Bownik H, Lichtenstein GR. Safety of vedolizumab in  
452 inflammatory bowel disease patients: Real world experience from a large university practice.  
453 Gastroenterology 2016;1:S977.
- 454 21. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative Outcomes in Vedolizumab-Treated  
455 Patients Undergoing Abdominal Operations for Inflammatory Bowel Disease. Journal of Crohn's &  
456 colitis 2016;19:19.
- 457 22. Stringfield S, Parry L, Sandborn W, Ramamoorthy S, Eisenstein S. Patients on vedolizumab  
458 have a high rate of postoperative complications. Diseases of the Colon and Rectum 2016;59 (5):e96.
- 459 23. Koh S, Zaghiyan K, Fleshner P. Safety and efficacy of the perioperative use of vedolizumab  
460 in medically refractory IBD patients. Does "gut-specificity" impact surgical morbidity? Diseases of  
461 the Colon and Rectum 2016;59 (5):e96-e7.
- 462 24. Boland BS, Dulaie PS, Chang M et al. . Pseudomonas meningitis during vedolizumab therapy  
463 for Crohn's disease. American Journal of Gastroenterology;110:1631-2.
- 464 25. Wichmann A, Cleveland NK, Rubin DT. Safety and efficacy of live measles vaccine  
465 administered to a crohn's disease patient receiving vedolizumab. American Journal of  
466 Gastroenterology 2016;111:577.
- 467 26. Mocko P, Kawalec P, Pilc A. Safety Profile of Biologic Drugs in the Treatment of  
468 Inflammatory Bowel Diseases: A Systematic Review and Network Meta-analysis of Randomized  
469 Controlled Trials. Clinical Drug Investigation 2016:1-13.
- 470 27. Brown EG WL, Wood S. . The medical dictionary for regulatory activities (MedDRA). Drug  
471 Safety;20:109-17.
- 472 28. Long MD MC, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients  
473 with inflammatory bowel disease. American Journal of Gastroenterology 2013;108:240-8.
- 474 29. Feagan BG BF, Khalid JM, Palo W, Blake A, Shetzine M, Travis SP. Incidence of pneumonia  
475 and other respiratory tract infections with vedolizumab treatment for inflammatory bowel disease:  
476 Clinical trial experience. ECCO Abstract 2017 2016.

- 477 30. Bhayat F BA, Travis SP. Post-marketing experience of vedolizumab in inflammatory bowel  
478 disease: Analysis of pneumonia and other respiratory tract infections. ECCO Abstract 2017 2016.
- 479 31. Biogen. US-TYSABRI-update June 2015 ed. med Info. 2015.
- 480 32. Parikh A, McAuliffe M, Stephens K, et al. Risk assessment and minimization for progressive  
481 multifocal leukoencephalopathy (PML) (RAMP): A program to assess for potential early signs and  
482 symptoms of PML during clinical development of vedolizumab. United European Gastroenterology  
483 Journal 2013;1):A216.
- 484 33. Parikh A, Fedyk E, Clifford D, et al. No association between vedolizumab exposure and serum  
485 JC virus levels. Inflammatory Bowel Diseases 2011;17:S56.
- 486 34. Rosariio MF IM, Catherine; Parikh, Asit; Feagan, Brian; Sandborn, William; Yang, Huyuan;  
487 Wyant, Tim. Pharmacokinetic/Pharmacodynamic Relationship and immunogenicity of Vedolizumab  
488 in Adults with Inflammatory Bowel Disease: Additional Results from GEMINI 1 and 2. Inflammatory  
489 Bowel Disease 2013;19:P-140.
- 490 35. Rosario M, Wyant T, Milch C, et al. Pharmacokinetic and pharmacodynamic relationship and  
491 immunogenicity of vedolizumab in adults with inflammatory bowel disease: Additional results from  
492 the GEMINI 1 and 2 studies. Journal of Crohn's and Colitis 2014;8:S42-S3.
- 493 36. Rosario M WT, Leach T, Sankoh S, Scholz C, Parikh, Fox I, Feagan BG. Vedolizumab  
494 Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability Following Administration of a  
495 Single, Ascending, Intravenous Dose to Healthy Volunteers. Clinical Drug Investigation  
496 2016;36:913-23.
- 497 37. Wyant T EJ, Yang L et al. . Development and validation of receptor occupancy  
498 pharmacodynamic assays used in the clinical development of the monoclonal antibody vedolizumab.  
499 Cytometry Part B Clinical Cytometry 2015;90.
- 500 38. Bonovas S, Fiorino G, Allocca M, et al. Biologic Therapies and Risk of Infection and  
501 Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-  
502 analysis. Clinical Gastroenterology & Hepatology 2016;14:1385-97.e10.

- 503 39. Shirafuji T OT, Sawada T, et al. . The importance of peripheral blood leukocytes and  
504 macrophage infiltration on bronchial wall wound healing in rates treated preoperatively with  
505 anticancer drugs. *Surgery Today* 2001;31:308-16.
- 506 40. Bielecki T DED, Everts PA, Wiczowski A. The role of leukocytes from L-PRP/L-PRF in  
507 wound healing and immune defense: new perspectives. *Current Pharmaceutical Biotechnology*  
508 *Journal* 2012;13:1153-62.
- 509 41. Billioud V FA, Tedesco ED, Colombel JF, Roblin X, Peyrin-Biroulet L. Preoperative use of  
510 anti-TNF therapy and postoperative complications in inflammatory bowel diseases; a meta-analysis.  
511 *Journal of Crohn's & Colitis*;7:853-67.
- 512 42. Kopylov U B-HS, Zmora O, Eliakim R, Katz LH. Anti-tumo necrosis factor and postoperative  
513 complications in Crohn's disease: systematic review and meta-analysis. *Inflammatory Bowel Disease*  
514 2012;18:2404-13.
- 515 43. Yang ZP HL, Wu Q, Wu KC, Fan DM. Preoperative infliximab use and postoperative  
516 complications in Crohn's disease: a systematic review and meta-analysis. *International Journal of*  
517 *Surgery* 2014;12:224-30.
- 518 44. Kotlyar DS OM, Diamond RH, et al. A systematic review of factors that contribute to  
519 hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clinical*  
520 *Gastroenterology & Hepatology* 2011;9:36-41.e1.
- 521 45. Yajnik V, Khan N, Dubinsky M, et al. Efficacy and safety of vedolizumab with advancing  
522 age in patients with Crohn's disease: Results from the GEMINI 2 study. *Journal of Crohn's and Colitis*  
523 2015;9:S244-S5.
- 524 46. Yajnik V, Khan N, Dubinsky M, et al. Efficacy and safety of vedolizumab with advancing  
525 age in patients with ulcerative colitis: Results from the GEMINI 1 study. *Journal of Crohn's &*  
526 *colitis*2015:S363-s4.

- 527 47. Navaneethan U, Kommaraju KK, Edminster T, Zhu X, Wilson K, Glover SC. Efficacy and  
528 safety of vedolizumab in elderly patients with inflammatory bowel disease. *Gastroenterology*  
529 2016;1):S812.
- 530 48. Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab Therapy in Severe Pediatric  
531 Inflammatory Bowel Disease. *Inflammatory Bowel Diseases* 2016;22:2425-31.
- 532 49. Singh N, Rabizadeh S, Jossen J, et al. Multi-Center Experience of Vedolizumab Effectiveness  
533 in Pediatric Inflammatory Bowel Disease. *Inflammatory Bowel Diseases* 2016;22:2121-6.
- 534 50. . at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/125476s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125476s000lbl.pdf) )
- 535 51. Dubinsky M, Mahadevan U, Vermeire S, Abhyankar B, Lasch K. Vedolizumab exposure in  
536 pregnancy: Outcomes from clinical studies in inflammatory bowel disease. *Journal of Crohn's and*  
537 *Colitis* 2015;9:S361-S2.
- 538 52. Bryant RV, Sandborn WJ, Travis SP. Introducing vedolizumab to clinical practice: who,  
539 when, and how? *Journal of Crohn's & colitis* 2015;9:356-66.
- 540 53. Sands BE CC, Katz J, et al. Guidelines for immunizations in patients with inflammatory bowel  
541 disease. *Inflammatory Bowel Diseases* 2004;10:677-92.
- 542 54. Wasan SK BS, Skolnik PR, Farraye FA. A practical guide to vaccinating the inflammatory  
543 bowel disease patient. *American Journal of Gastroenterology* 2010;105:1231-8.
- 544 55. Desalermos AP, et al. . Vaccinating the inflammatory bowel disease patient. Expert review of  
545 *Gastroenterology & Hepatology* 2015;9:91-102.
- 546 56. Loras C SC, Gonzalez- Huix F, et al. Prevalence and factors related to hepatitis B and C in  
547 inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *American Journal of*  
548 *Gastroenterology* 2009;104:57-63.
- 549 57. Melmed GY IA, Papadakis KA, et al. Patients with inflammatory bowel disease are at risk for  
550 vaccine-preventable illnesses. *American Journal of Gastroenterology* 2006;101:1834-40.
- 551 58. Wyant T, Leach T, Sankoh S, et al. Vedolizumab affects antibody responses to immunisation  
552 selectively in the gastrointestinal tract: randomised controlled trial results. *Gut* 2015;64:77-83.



- 553 59. Rutgeerts P SW, Feagan BG, et al. Infliximab for induction and maintenance therapy for  
554 ulcerative colitis. *New England Journal of Medicine* 2005;23:2462-76.
- 555 60. Hanauer S FB, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the  
556 ACCENT I randomised trial. *The Lancet* 2002;9317:1541-9.
- 557 61. Sands BE AF, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's  
558 disease. *New England Journal of Medicine* 2004;350:876-85.
- 559 62. Jiang XL CH, Gao J, Fan H. Low-dose infliximab for induction and maintenance treatment in  
560 chinese patients with moderate to severe active ulcerative colitis. *Journal of Clinical Gastroenterology*  
561 2015;49:582-8.
- 562 63. Sandborn WJ vAG, Reinisch W, et al. Adalimumab induces and maintains clinical remission  
563 in patients with moderate- to-severe ulcerative colitis. *Gastroenterology* 2012;142:257-65.
- 564 64. Colombel JF SW, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and  
565 remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52-65.
- 566 65. Sandborn WJ HS, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's  
567 disease: results of the CLASSIC II trial. *Gut* 2007;56:1232-9.
- 568 66. Suzuki Y MS, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with  
569 moderately to severely active ulcerative colitis. *Journal of gastroenterology* 2014;49:283-94.
- 570 67. Watanabe M HT, Lomax KG, et al. Adalimumab for the induction and maintenance of clinical  
571 remission in Japanese patients with Crohn's disease. *Journal of Crohn's & colitis* 2012:160-73.
- 572 68. Sandborn WJ FB, Marano C, et al. Subcutaneous golimumab maintains clinical response in  
573 patients with moderate-to severe ulcerative colitis. *Gastroenterology* 2014;146:96-109.

574

575 **Figures**

576 **Figure 1: Safety profile of Vedolizumab**

577

578

579

580

581

582

Encouraging safety aspects	Further evidence required	Early signals to watch
<p>Early post-marketing data supports appealing registration trial safety data of VDZ for the following aspects</p> <ul style="list-style-type: none"> <li>- Adverse events and serious adverse events</li> <li>- Systemic infectious complications (eg pneumonia)</li> <li>- Gastrointestinal infections</li> <li>- Infusion-related reactions</li> <li>- Use in the elderly</li> </ul>	<p>Scarce data for VDZ appear promising but needs further evidence for the following safety aspects</p> <ul style="list-style-type: none"> <li>- Use in pregnancy and lactation</li> <li>- Concomitant use of live vaccines</li> <li>- Low rates of immunogenicity</li> </ul>	<p>Early signals for risk in the following sub groups</p> <ul style="list-style-type: none"> <li>- Peri-operative complication rates</li> <li>- Use in the paediatric population</li> </ul> <p>Although data to be interpreted with caution due to skewed cohorts, non-controlled trials and small sample sizes. Further accumulation of evidence is necessary</p> <p>Enteric infections (despite post - marketing data to date)</p>
<p>No cases of PML have been reported although monitoring and databases must be maintained</p>	<p>Theoretical benefits persist although longer duration patient-year exposure and data need to be acquired</p> <ul style="list-style-type: none"> <li>- Malignancy risk</li> </ul>	

## TABLES

**Table 1: Registration and post-marketing cohort studies of vedolizumab safety**

Trial	Design	Patients	CD/UC	Trial/Study notes	Duration
Registration trials					
Parikh et al. (2012) C13002 NCT01177228	RCT Phase 2	47	UC Mild	Disease beyond rectum Age 18 - 70	253 days
GEMINI 1 Feagan et al. (2013) NCT00783718	RCT Phase 3	895	UC Mod to severe	< 50% previous exposure to anti- TNFs Age 18 - 80	Induction 6 weeks Maintenance 46 weeks
GEMINI 2 Sandborn et al. (2013) NCT00783692	RCT Phase 3	1115	CD CDAI 220-450	< 50% previous exposure to anti- TNFs Age 18 - 80	Induction 6 weeks Maintenance 46 weeks
GEMINI 3 Sands et al. (2014) NCT01224171	RCT Phase 3	416	CD CDAI 220-450	Inadequate or loss of response to, or intolerance to CS, IS and/or anti-TNFs within 5 years	10 weeks
Registration - Open-label extension studies					
Parikh et al. (2013) C13004 NCT00619489	Open-label Phase 2	72	CD and UC	Rollover patients from study C13002 (n = 34). VDZ-naïve patients. Partial mayo 2 – 7 (UC) or CDAI 220 – 450 (CD)	78 weeks
Feagan et al; Hanauer et al. (2014) GEMINI LTS NCT00790933	Open-label Phase 3 (in progress)	2243	CD and UC	Rollover patients from c13004 (n=37), GEMINI 1 (n=675), GEMINI 2 (n=726), GEMINI 3 (n=384). VDZ naïve. Partial mayo 3 – 9 (UC), HBI 8 – 18 (CD)	46 + months
Cohort studies - General Safety Data					
Baumgart et al. (2016)	Multicentre Prospective cohort	212	97 CD 115 UC	5% CD naïve 24% UC naïve	14 weeks
Dulai et al. (2016)	Multicentre Retrospective cohort	212	212 CD	10% naïve	Median follow up 39 weeks (25 – 53)
Amiot et al. (2016)	Multicentre Prospective cohort	294	173 CD 121 UC	1% CD naïve 2% UC naïve	14 weeks
Shelton et al. (2016)	Multicentre	172	107 CD 59 UC	77% failed >2 TNF CD 62% failed >2 TNF UC	14 weeks

	Prospective cohort		6 IBDU		
Vivio et al. (2016)	Single centre Prospective cohort	51	30 CD 21 UC	3% CD naïve 24% UC naïve	14 weeks
Mendoza et al. (2016)	Single centre Retrospective cohort	108	N/R	N/R, although all patients who experienced adverse events were TNF - exposed	Mean follow up 23 weeks
Cohort studies - Surgical Safety data					
Lightner et al (2016)	Mayo clinic Retrospective	94	71 CD 22 UC 1 IBDU	All intra-abdominal operations	4 weeks
Stringfield et al (2016)	Single centre Retrospective	26	N/R	36 operations in total 27 intra-abdominal, 9 ano-rectal	N/R
Koh et al. (2016)	Single centre Retrospective	15	8 CD 6 UC 1 IBDU	15 intra-abdominal	30 days

N/R – Not reported

**Table 2. Exposure-adjusted incidence rates of adverse events in the safety population of registration studies**

Adverse Event	Placebo n= 504	No. of patients with event/100 PY (95% CI)	Vedolizumab n = 2830	No. of patients with event/100 PY (95% CI)
	No of patients with event		No of patients with event	
Any AE	355	419.4 (359.3 to 479.5)	2549	247.8 (229.8 to 265.8)
Any SAE	56	28.3 (20.6 to 35.9)	842	20.0 (18.5 to 21.5)
<u>Common AEs (&gt; 10 patients with events/100 PY in any patient group)</u>				
Nasopharyngitis	29	14.1 (8.8 to 19.3)	541	13.5 (12.3 to 14.7)
Abdominal pain	41	20.7 (14.3 to 27.1)	505	12.1 (11.0 to 13.2)
Headache	47	23.7 (16.7 to 30.8)	471	11.5 (10.4 to 12.6)
Arthralgia	39	19.3 (13.2 to 25.4)	465	11.2 (10.1 to 12.3)
Upper respiratory tract infection	24	11.6 (6.9 to 16.3)	334	7.7 (6.8 to 8.5)
Nausea	27	13.2 (8.1 to 18.3)	325	7.4 (6.6 to 8.3)
Pyrexia	35	17.0 (11.3 to 22.8)	310	7.0 (6.2 to 7.8)
Vomiting	21	10.1 (5.8 to 14.5)	228	5.0 (4.4 to 5.7)
Anaemia	21	10.2 (5.8 to 14.6)	189	4.1 (3.5 to 4.7)
Exacerbation of CD	57	47.3 (34.4 to 60.2)	N/A	N/A
Exacerbation of UC	29	38.2 (24.2 to 52.1)	N/A	N/A

Adapted from Colombel et al. (2016) <sup>7</sup>

595 **Table 3: Non-infectious adverse events in cohort studies**

Adverse event	Baumgart	Dulai	Amiot	Shelton	Vivio	Mendoza	Total
Cohort size	n=212	n=212	n=294	n=172	n=51	n=108	n= 1049
Any non-infectious adverse event	73 (34.4%)	8 (3.8%)	61 (20.8%)	14 (8.2%)	4 (7.8%)	6 (5.6%)	166 (15.8%)
<u>Neurological</u>							
Headache	1 (0.5%)	-	16 (5.4%)	-	-	2 (1.9%)	19 (1.8%)
Paresthesia	2 (0.9%)	-	13 (4.4%)	-	-	-	15 (1.4%)
Stroke	-	-	1 (0.3%)	-	-	-	1 (0.1%)
Vertigo	-	-	1 (0.3%)	-	-	-	1 (0.1%)
<u>Dermatological</u>							
Pruritus	1 (0.5%)	-	1 (0.3%)	-	-	-	2 (0.2%)
Acne	15 (7.1%)	-	-	-	-	-	15 (1.4%)
Erythema nodosum	3 (1.4%)	-	-	-	-	-	3 (0.3%)
Pyoderma gangrenosum	-	-	-	1 (0.6%)	-	-	1 (0.1%)
Paradoxical skin manifestation	2 (0.9%)	-	12 (4.1%)	-	1 (2.0%)	2 (1.9%)	17 (1.6%)
Dry skin	3 (1.4%)	-	-	-	-	-	3 (0.3%)
Butterfly rash	-	-	-	2 (1.2%)	-	-	2 (0.3%)
Acute generalized exanthematous pustulosis	2 (0.9%)	-	-	-	-	-	2 (0.2%)
<u>Rheumatological</u>							
Arthralgia	21 (9.9%)	5 (2.4%)	1 (0.3%)	4 (2.3%)	-	1 (0.9%)	32 (3.1%)
Arthritis	13 (6.1%)	-	-	1 (0.6%)	-	-	14 (1.3%)
<u>IBD</u>							
IBD exacerbation	2 (0.9%)	-	12 (4.1%)	3 (1.7%)	-	-	17 (1.6%)
Abdominal pain	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Bowel perforation	-	1 (0.5%)	-	-	-	-	1 (0.1%)
Infusion-related reaction	-	-	2 (0.7%)	1 (0.6%)	2 (3.9%)	-	5 (0.5%)
<u>Ophthalmological</u>							
Optic neuritis	-	1 (0.5%)	-	-	-	-	1 (0.1%)

Retinal vein occlusion	-	-	-	1 (0.6%)	-	-	1 (0.1%)
Conjunctivitis	-	-	-	-	1 (2.0%)	-	1 (0.1%)
<u>Miscellaneous</u>							
Nausea	2 (0.9%)	-	-	1 (0.6%)	-	-	3 (0.3%)
Acute renal failure	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Cough	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Fatigue	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Memory impairment	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Aphthous ulcer	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Deep venous thrombosis	-	-	1 (0.3%)	-	-	-	1 (0.1%)
Liver test abnormalities	-	1 (0.5%)	1 (0.3%)	-	-	1 (0.9%)	2 (0.2%)

596

597

598 **Table 4: Results of a comparative analysis of the safety profile of biologics \***

Outcome	OR (95% CI)		
	ADA vs VDZ	IFX vs VDZ	GLM vs VDV
Any AEs	0.69 (0.07 – 2.76)	1.02 (0.09–12.84)	1.14 (0.10 – 11.93)
SAEs	0.55 (0.19 – 1.44)	0.58 (0.20 – 1.62)	1.22 (0.28 – 5.23)
Infections	1.07 (0.47 – 2.12)	1.06 (0.35 – 3.30)	1.43 (0.49 – 4.25)
Serious infections	0.57 (0.14 – 2.35)	0.53 (0.15 – 2.01)	n/d
Infections requiring antimicrobial treatment	n/d	n/d	n/d
Injection site reaction	0.87 (0.09 – 6.88)	0.57 (0.06 – 4.40)	0.56 (0.03 – 8.98)
<b>By individual adverse event</b>			
Abdominal pain	1.18 (0.21 – 5.82)	0.65 (0.11 – 3.67)	3.11 (0.48 – 21.32)
Arthralgia	1.40 (0.67 – 2.86)	1.18 (0.51 – 2.90)	0.80 (0.32 – 1.98)
Cough	n/d	n/d	1.16 (0.32 – 4.76)
Headache	2.08 (0.63 – 6.70)	0.79 (0.24 – 2.64)	0.90 (0.27 – 3.14)
Nausea	1.32 (0.61 – 2.94)	0.96 (0.38 – 2.42)	n/d
Pharyngitis	n/d	n/d	n/d
Pyrexia	1.11 (0.53 – 2.34)	n/d	n/d
Nasopharyngitis	0.78 (0.11 – 4.01)	0.31 (0.01 – 8.59)	1.22 (0.15 – 9.30)
URTI	0.72 (0.24 – 2.24)	0.55 (0.18 – 1.73)	1.96 (0.50 – 9.27)

599 \*Adapted from Mocko et al. 2016 <sup>26</sup>

600 ADA adalimumab, AE adverse event, CrI credible interval, GLM golimumab, IFX infliximab, n/d no data, OR odds ratio, RCT randomized controlled  
601 trial, SAE serious adverse event, VDZ vedolizumab  
602 Trials – IFX (ACT-1,<sup>59</sup> ACT – 2<sup>59</sup>, ACCENT I<sup>60</sup>, ACCENT II<sup>61, 62</sup>). ADA (ULTRA 2<sup>63</sup>, CHARM<sup>64</sup>, CLASSIC 11<sup>65, 66,67</sup>). Golimumab (PURSUIT –  
603 M<sup>68</sup>). Vedolizumab (GEMINI 1<sup>8</sup>, GEMINI 2<sup>11</sup>)



**Table 5: Exposure-adjusted incidence rates of infections in the overall safety population \***

Adverse Event	Placebo n= 504		Vedolizumab n = 2830	
	No of patients with event	No. of patients with event/100 PY (95% CI)	No of patients with event	No. of patients with event/100 PY (95% CI)
Any infection	139	82.9 (68.3 to 97.5)	1606	63.5 (59.6 to 67.3)
Common infections (>0.5 patient events/100 PY in any patient group)				
<b>Respiratory tract</b>				
Upper	67	34.7 (26.0 to 43.3)	967	28.6 (26.6 to 30.6)
Lower and lung	16	7.7 (3.9 to 11.5)	270	6.1 (5.3 to 6.8) 7.4 (6.6 to 8.3)
<b>Abdominal and GI infections</b>	14	6.7 (3.2 to 10.1)	331	
Gastroenteritis (PT)	3	1.4 (0.0 to 3.0)	183	4.0 (3.4 to 4.6)
Abscess	10	4.7 (1.8 to 7.7)	131	2.8 (2.3 to 3.3)
Anal, rectal and perirectal	8	3.8 (1.1 to 6.4)	96	2.0 (1.6 to 2.4)
Abdominal and intestinal	0	0.0 (0.0 to 1.4)	26	0.5 (0.3 to 0.8)
Abscess, others	2	0.9 (0.0 to 2.2)	12	0.3 (0.1 to 0.4)
<b>Other sites</b>				
Urinary tract	10	4.7 (1.8 to 7.7)	211	4.6 (4.0 to 5.3)
Dental and oral soft tissue	3	1.4 (0.0 to 3.0)	85	1.8 (1.4 to 2.2)
Skin structures and soft tissue	6	2.8 (0.6 to 5.1)	74	1.6 (1.2 to 1.9)
Ear	4	1.9 (0.0 to 3.7)	66	1.4 (1.1 to 1.7)
Eye and eyelid	3	1.4 (0.0 to 3.0)	39	0.8 (0.6 to 1.1)
Infections NEC	3	1.4 (0.0 to 3.0)	96	2.0 (1.6 to 2.5)
Streptococcal	1	0.5 (0.0 to 1.4)	36	0.8 (0.5 to 1.0)
Clostridial	0	0.0 (0.0 to 1.4)	34	0.7 (0.5 to 1.0)
Cellulitis (PT)	4	1.9 (0.0 to 3.7)	29	0.6 (0.4 to 0.8)
Folliculitis (PT)	0	0.0 (0.0 to 1.4)	29	0.6 (0.4 to 0.8)
Female reproductive tract	2	0.9 (0.0 to 2.2)	16	0.3 (0.2 to 0.5)
Sepsis and related terms	2	0.0 (0.0 to 2.2)	12	0.3 (0.1 to 0.4)
<b>Viral</b>				
Influenza	9	4.3 (1.5 to 7.1)	181	4.0 (3.4 to 4.5)
Herpes	9	4.3 (1.5 to 7.1)	118	2.5 (2.1 to 3.0)

---

Herpes zoster (PT)	2	0.9 (0.0 to 2.2)	35	0.7 (0.5 to 1.0)
Viral infections NEC	11	5.2 (2.1 to 8.4)	154	3.3 (2.8 to 3.9)
Candida, tinea and other fungal infections	10	4.8 (1.8 to 7.7)	143	3.1 (2.6 to 3.6)

---

\* Adapted from Colombel et al. (2016) <sup>7</sup>

609 **Table 6: Exposure-adjusted incidence rates of serious infections in the overall safety population**

Adverse Event	Placebo n= 504		Vedolizumab n = 2830	
	No of patients with event	No. of patients with event/100 PY (95% CI)	No of patients with event	No. of patients with event/100 PY (95% CI)
Any serious infection of infestation	8	3.8 (1.2 to 6.4)	199	4.3 (3.7 to 4.9)
<b>Serious infections of interest</b>				
Gastroenteritis (PT)	0	0.0 (0.0 to 1.4)	17	0.4 (0.2 to 0.5)
Abscess	3	1.4 (0.0 to 3.0)	68	1.4 (1.1 to 1.8)
<i>Clostridial</i> infections	0	0.0 (0.0 to 1.4)	15	0.3 (0.2 to 0.5)
Candida/fungal infection	0	0.0 (0.0 to 1.4)	3	0.1 (0.0 to 0.1)
Sepsis and related terms	2	0.9 (0.0 to 1.4)	11	0.2 (0.1 to 0.4)
Tuberculosis	0	0.0 (0.0 to 1.4)	4	0.1 (0.0 to 0.2)
Cytomegalovirus infections	0	0.0 (0.0 to 1.4)	3	0.1 (0.0 to 1.4)
Meningitis (PT)	0	0.0 (0.0 to 1.4)	1	< 0.1 (0.0 to 0.1)
<i>Salmonella</i> infections	0	0.0 (0.0 to 1.4)	2	< 0.1 (0.0 to 0.1)

610 Adapted from Colombel et al. (2016) <sup>18</sup> Severity of adverse events and infections were defined according to the *Medical dictionary for regulatory*  
611 *Activities (MedDRA)*  
612  
613

614 **Table 7: Post marketing cohort studies: infectious adverse events**  
615

Infection	Baumgart n=212	Dulai n=212	Amiot n=294	Shelton n=172	Vivio n=51	Mendoza n=108	Total n=1049
<b>Any infection</b>	12 (5.7%)	2 (10.0%)	37 (12.6%)	3 (1.74%)	3 (5.9%)	6 (5.6)	82 (7.8%)
<b>Respiratory tract</b>							
Upper	6 (2.8%)	7 (3.3%)	24 (8.2%)	NR	NR	1 (0.9%)	38 (3.6%)
Lower and lung	-	-	-	-	-	-	-
<b>Abdominal and GI infections</b>	2 (0.9%)	8 (3.8%)	5 (1.7%)	3 (1.74%)	1 (2.0%)	2 (1.9%)	21 (2.0%)
Gastroenteritis (PT)		-	1 (<0.1%)	1 (0.58)	-	-	2 (0.2%)
<i>Clostridium difficile</i>	1 (0.5%)	7 (3.3%)	4 (1.4%)	-	-	1 (0.9%)	13 (1.2%)
CMV colitis	-	1 (0.5%)	-	-	1 <sup>^^</sup> (2.0%)	-	2 (0.2%)
Helicobacter gastritis	1 (0.5%)	-	-	-	-	-	1 (0.1%)
Anal abscess	-	-	-	2 <sup>f</sup> (1.2%)	-	-	2 (0.2%)
Abdominal/intestinal abscess	-	-	-	-	-	1 (0.9%)	1 (0.1%)
<b>Other sites</b>							
Urinary tract	-	1 (0.5%)	-	-	-	-	1 (0.1%)
CNS	-	1 <sup>c</sup> (0.5%)	-	-	-	-	1 (0.1%)
Eye and eyelid	-	-	-	-	1 <sup>i</sup> (2.0%)	-	1 (0.1%)
Folliculitis (PT)	-	-	-	-	-	2 (1.9%)	2 (0.2%)
Female reproductive tract	-	2 <sup>d</sup> (0.9%)	-	-	-	-	2 (0.2%)
Sepsis and related terms	-	1 <sup>e</sup> (0.5%)	-	-	1 <sup>g</sup> (2.0%)	1 <sup>j</sup> (0.9%)	3 (0.3%)
<b>Viral</b>							
Influenza viral infections	-	-	3 (1.0%)	-	-	-	3 (0.3%)
Herpes viral infections	2 <sup>a</sup> (0.9%)	1 <sup>b</sup> (0.5%)	-	-	-	-	3 (0.3%)
Candida, tinea and other fungal infections	-	-	-	-	1 <sup>h</sup> (2.0%)	-	1 (0.2%)
<b>Miscellaneous</b>	2 (0.9%)	-	11 (3.7%)	-	-	-	13 (1.2%)

616 a. Oral herpes

617 b. Anogenital HSV infection

618 c. Pseudomonas meningitis

619 d. Labial abscess, fungal rash

620 e. Exploratory laparotomy for anastomosis leak. Developed sepsis, shock, and death 72h later

621 f New onset perianal abscess

622 g. CMV colitis. Patient with CD who had last dose of Infliximab 8 weeks before commencing Vedolizumab. This patient then developed Hodgkin's lymphoma 8 weeks later and prior to starting cancer treatment developed sepsis and acute kidney injury and died.

624 h. *Histoplasma capsulatum*. A diagnosis of disseminated histoplasmosis was confirmed (lung, urine and blood cultures)

625 i. Bacterial conjunctivitis

j. *N. meningitidis* bacteremia**Table 8:** 30 day complication rate \*

		No biological therapy (n = 172)	Anti-TNF inhibitors (n=126)	Vedolizumab (n=94)	p-value
<b>Any</b>	<b>postoperative</b>	57 (33%)	35 (28%)	50 (53%)	<0.01
<b>Non-SSI infections</b>		10 (16%)	6 (5%)	7 (7%)	<0.71
	UTI	5	2	4	<0.49
	Pneumonia	2	1	3	<0.31
	Non-abdominal sepsis	2	2	1	<0.92
	C.diff colitis	0	1	1	<0.44
	Cholangitis	1	0	0	<0.52
<b>All SSIs</b>		22 (13%)	13 (10%)	35 (37%)	<0.01
	sSSIs	11 (6%)	5 (4%)	20 (21%)	<0.01
	dSSIs	11 (6%)	6 (5%)	13 (14%)	<0.03
Anastomotic leak		1 (1%)	4 (3%)	2 (2%)	<0.24
MCS		1 (1%)	1 (1%)	7 (7%)	<0.01
SBO/ileus		20 (12%)	12 (10%)	9 (10%)	<0.79
Readmission		17 (10%)	12 (10%)	15 (16%)	<0.24
ROR		8 (5%)	10 (8%)	8 (9%)	<0.37

\* Adapted from Lightner et al (2016) <sup>17</sup>

SSI = surgical site infection (superficial, deep, anastomotic leak, mucocutaneous separation). Non- SSI infections = pneumonia, *Clostridium difficile* [*C. Diff*], urinary tract infection [UTI], cholangitis, sepsis. sSSI = superficial surgical site infection. dSSI = deep surgical site infection. Anast leak = anastomotic leak. MCS = mucocutaneous separation. ROR = return to the operating room. SBO = small bowel obstruction.

635 **Table 9: Adverse events in GEMINI 1 and 2 by age \***

Event	GEMINI 1 and 2					
	Age < 35 years		Age 35 – 55 years		Age > 55 years	
	PBO	VDZ	PBO	VDZ	PBO	VDZ
	(n=120)	(n=688)	(n=142)	(n=603)	(n=35)	(n=143)
<u>Number of Patients (%)</u>						
Any AE	98 (82)	570 (83)	107 (75)	510 (85)	27 (77)	123 (88)
Any SAE	21 (18)	149 (22)	14 (10)	110 (18)	5 (14)	17 (12)
Infections and infestations (SOC)	44 (37)	301 (44)	45 (32)	260 (43)	14 (40)	61 (43)

636 \* Adopted from Yajnik et al. 2015 <sup>26, 27</sup>

637 AE, adverse event; CD, Crohn's disease; PBO, placebo; SAE, series adverse event, SOC, system organ class; VDZ, vedolizumab

636  
637  
638  
639

## Supplementary Material

**Table 1: IRR in cohort studies**

Study	Patients	IRR (n)	Percentage	Notes
Baumgart	212	N/R	N/R	
Dulai	212	5	2.34 %	3.5 IRR per 1000 infusions
Amiot	294	2	0.68 %	
Shelton	172	1	0.58 %	1 patient ceased VDZ due to IRR
Vivio	51	2	3.92 %	1 fever within 24 hrs, 1 anaphylaxis
Mendoza	108	4	3.70 %	2 headache, 2 hives
Total	837	14	1.67%	

N/R – Not reported, VDZ – Vedolizumab

**Table 2: Adverse and Serious adverse events on Vedolizumab \***

Adverse event (AE)	No.	Serious adverse event (SAE)	No.
Upper respiratory tract infection	5	Dehydration/vomiting	4
Nausea	5	Flare of disease	3
Fatigue	4	Bowel-associated dermatosis-arthritis syndrome	1
Vomiting	4	Synovitis, acne, pustulosis, hyperostosis, osteitis	1
Headache	2	Obstructing nephrolithiasis and pyonephritis	1
Erythema nodosum	2	Diverting ileostomy	1
Nasopharyngitis	2	Colectomy	1
Skin infections	2		
Dizziness	1		

Adapted from Conrad et al. (2016) <sup>48</sup>

1 subject had 3 serious adverse events (SAE), 2 subjects had 2 SAE, and 5 subjects had 1 SAE.