Supplemental Methods and Results

Research Priority Addressed

The James Lind Alliance supports partnerships between healthcare providers, patients, and patient support organizations to determine priorities for research.[8] This Alliance has identified research priorities in the treatment of patients with inflammatory bowel disease.[9] The consortium used to conduct the current study was built to directly address the top research priority identified ("What is the optimal treatment strategy considering efficacy, safety, and cost-effectiveness in inflammatory bowel disease management?") through the generation of real-world evidence that supports the use and positioning of biologic agents in patients treated in routine practice who are often excluded from traditional clinical trials.[7,9] The specific question being addressed in this proposal was identified to be the highest priority research question for ulcerative colitis (UC) in the current landscape of medical therapeutic options.[9]

We had the a priori hypothesis that vedolizumab is associated with a lower risk of serious infections than TNF-antagonist therapy in UC, and that vedolizumab is superior to TNF-antagonist therapy for achieving clinical remission in UC.[8,9] This hypothesis was derived prior to the completion of the phase 3 head-to-head trial,[6] and it was informed by prior network meta-analyses of phase 3 clinical trials and comparison of point estimates for developing an infectious adverse event or achieving clinical remission with vedolizumab relative to TNF-antagonist therapy.[10-12]

Variables

Data on variables of interest were collected from the sites, including patient characteristics (age at diagnosis, age at biologic initiation, sex, smoking status, body mass index), disease characteristics (prior hospitalizations, extraintestinal manifestations, and phenotype classified according to Montreal subclassifications of E1 through E3), and treatment history (steroids, immunomodulators, and tumor necrosis factor [TNF] antagonists; duration of use; indication for discontinuation; and complications). Variables of interest specific to the use of biologic agents included baseline disease severity or activity (endoscopic, biochemical, or clinical assessments), concomitant treatments (steroids and/or immunomodulators: azathioprine, 6-mercaptopurine, methotrexate), and follow-up assessments (endoscopic or clinical assessments). Steroid dependency or refractoriness was defined as current users of concomitant steroids who had more than 3 courses of steroids in the previous year and had been unable to remain off steroids for >3 months. Age was transformed into a binary variable (>60 years) to classify patients as elderly or non-elderly given the known association between age and risk of adverse events.[19]

Outcome Definitions

Serious infection was defined as any infection occurring after biologic initiation that required antibiotics, antifungals, or antivirals or that resulted in discontinuation of biologic therapy, hospitalization, or death. Serious adverse events were defined as the occurrence of any infectious or noninfectious adverse event after biologic initiation that required antibiotics, antifungals, or antivirals for a documented infection, or resulted in discontinuation of biologic therapy, hospitalization, or death.[19] Exposure to antibiotics, antifungals, and antivirals was used in the definition given the need to use antibiotics, antifungals, and antivirals indicates a need for the provider to intervene to prevent damage which is in accordance with clinical trial definitions for adverse events, and that exposure to antibiotics increases the risk of developing *Clostridium difficile*, and the development of an infection with *Clostridium difficile* in UC patients is more severe and associated with a significant increase in risk for hospitalization, colectomy, and mortality.[21-23]

Clinical remission was defined by complete resolution of diarrhea, rectal bleeding, and urgency as per the European Crohn's and Colitis Organization Consensus definition.[24] Steroid-free remission was assessed only in those patients taking either prednisone or budesonide-MMX at the initiation of biologic therapy, and was defined as achieving clinical remission, tapering off steroids, and the absence of a steroid prescription within the subsequent 1 month of achieving remission. Deep remission was defined as achieving clinical remission (resolution of diarrhea, rectal bleeding, and/or urgency) and endoscopic remission (Mayo endoscopic subscore 0 or 1). The coordinating site used de-identified endoscopy reports to confirm endoscopic Mayo scores, and any discrepancies were resolved through consensus between the study sites and the coordinating site. If patients underwent dose escalation for non-response or partial response they were censored and considered a non-responder to standard of care labeled dosing for vedolizumab or TNF-antagonist therapy.

Handling Missing Data for Outcome Assessments

All patients received follow-up assessments for safety outcomes. A single patient had missing data for the assessment of clinical remission and was not included in the comparative effectiveness estimates. A follow-up assessment for endoscopic remission was performed in 59% of vedolizumab-treated patients and 69% of TNF-antagonist–treated patients (P = .007). Patients who did not undergo a follow-up assessment for endoscopic remission had less baseline inflammation as measured by baseline C-reactive protein (CRP) and baseline endoscopy (**Supplemental Table S1**). Comparative effectiveness outcomes including endoscopic remission in the definition were therefore limited to patients with documented baseline moderate-severe endoscopic inflammation (Mayo endoscopic subscore 2 or 3) within 4 weeks of starting vedolizumab or TNF-antagonist therapy to account for this differential attrition rate and the impact of missing data on comparative estimates.

Power Calculation for Safety Outcomes

In this observational nonrandomised cohort study, we used the observed event rates in the control group (TNF-antagonist−treated UC patients) to determine power calculations for unweighted comparisons of safety outcomes using the methodology described by Cohen et al.[25] For serious infections and serious adverse events we would need an observed event rate of 5% and 11%, respectively, in the vedolizumab-treatment group to be powered for the comparison.

Propensity Score Model and Statistical Analyses

The final set of variables used for the clinical remission propensity score model included age at initiation (>60 years), disease extent (left-sided colitis E1 or E2, or pancolitis E3), clinical disease severity (severe vs non-severe based on the physician global assessment), UC-related hospitalization within the preceding 1 year, prior TNF-antagonist exposure, baseline steroid dependency or refractoriness, concomitant steroid use, or concomitant immunomodulator use. Baseline CRP, albumin, and body mass index were not included because >25% of the cohort had missing baseline data for these variables. Post hoc assessment of these variables revealed that they had no prognostic significance for the primary treatment outcomes (clinical remission or serious infection), and therefore were unlikely to create an unmeasured confounder bias on the comparative estimates.

Comparative effectiveness between vedolizumab and TNF-antagonist therapy for the primary analysis and all subgroup or sensitivity analyses for effectiveness was done using the Cox-proportional hazard competing risk model. Colectomy is a preference sensitive decision and therefore variation is likely to have occurred as to when a patient may consider surgery and when a provider may offer surgery, creating a one-way competing risk for allowing treatment to take effect and observing clinical remission or treatment-related safety events. Furthermore, a larger proportion of the vedolizumab-treated UC patients had multiple prior TNF-antagonist exposures, and vedolizumab represented last-line biologic therapy in these patients prior to surgery. It was

further hypothesized that lack of availability for additional biologic therapy could therefore lead to surgery more often and earlier in the treatment course in the vedolizumab group. Therefore, this differential risk for surgery between the vedolizumab- and TNF-antagonist–treatment groups was accounted for by using a competing risk model with surgery functioning as a non-fatal competing risk.

Baseline Demographics

The median number of follow-up visits was comparable between the vedolizumab- (median number of visits 2, interquartile range [IQR] 1-3) and TNF-antagonist (median number of visits 2, IQR 1-3)–treated patients. The median duration of follow-up was comparable between the vedolizumab- (276 days, IQR 143-418) and TNF-antagonist (349 days, IQR 137-581)–treated patients. Vedolizumab-treated patients with UC were more often steroid refractory or dependent (48% vs 31%) and more often had prior TNF-antagonist exposure (69% vs 40%) or prior TNF-antagonist failure (57% vs 23%) than TNF-antagonist–treated patients. Among patients on concomitant steroids at baseline, the median dose was comparable between vedolizumab-treated (28 mg) and TNF-antagonist−treated (32 mg) patients.

Looking specifically at the TNF-antagonist−naïve patients, UC patients treated with vedolizumab were more often female (60% vs 49%), had less often been hospitalized within the previous year (25% vs 38%), and less often had severe endoscopic disease activity at baseline (21% vs 42%) compared to the TNF-antagonist−treated UC patients (**Supplemental Tables S2 and S3**).

Looking specifically at the TNF-antagonist−exposed patients, UC patients treated with vedolizumab were more comparable to the TNF-antagonist−treated patients in baseline demographics, with the exception of the vedolizumab-treated patients being more often steroid dependent at baseline (49% vs 21%) (**Supplemental Tables S2 and S3**).

Supplemental Table 1: Differences in Baseline Characteristics Between Patients Who Did and Those Who Did Not Have a Follow-up Assessment for Endoscopic Remission

	Had follow-up assessment for endoscopic remission	**No follow-up assessment for endoscopic remission**	*P*-value
Age at biologic	n = 455	n = 267	
	41.23 (16.62)	40.53 (16.75)	.586
Age at diagnosis	n = 455	n = 267	
	32.49 (15.29)	32.37 (16.08)	.921
Sex (female)	n = 455	n = 267	
Female	224 (49.2%)	137 (51.3%)	.644
Male	231 (50.8%)	130 (48.7%)	
BMI	n = 424	n = 253	
	25.65 (6.46)	25.51 (5.64)	.763
Smoking status	n = 455	n = 267	
Current	14 (3.1%)	9 (3.4%)	.948
Former	120 (26.4%)	68 (25.5%)	
Never	321 (70.5%)	190 (71.2%)	
Disease duration	n = 455	n = 267	
	8.75 (9.12)	8.16 (8.71)	.396
Ever hospitalized?	n = 455	n = 267	
Never	217 (47.7%)	125 (46.8%)	.844
Yes (in the last year)	124 (27.3%)	78 (29.2%)	
Yes (not in the last year)	114 (25.1%)	64 (24.0%)	
CRP	n = 356	n = 193	
	11.66 (30.85)	6.74 (15.19)	.013
Albumin	n = 391	n = 236	
	3.89 (0.56)	3.90 (0.61)	.749
Rheumatic EIM (Yes/No)	n = 455	n = 267	
No	386 (84.8%)	215 (80.5%)	.163
Yes	69 (15.2%)	52 (19.5%)	
Ophthalmologic EIM (Yes/No)	n = 455	n = 267	
No	448 (98.5%)	266 (99.6%)	.283
Yes	7 (1.5%)	1 (0.4%)	
Dermatologic EIM (Yes/No)	n = 455	n = 267	
No	437 (96.0%)	257 (96.3%)	1.000
Yes	18 (4.0%)	10 (3.7%)	
Hepatic EIM (Yes/No)	n = 455	n = 267	
No	436 (95.8%)	258 (96.6%)	.733
Yes	19 (4.2%)	9 (3.4%)	
Disease extent	n = 454	n = 265	
E1	19 (4.2%)	14 (5.3%)	.707
E2	164 (36.1%)	90 (34.0%)	
E3	271 (59.7%)	161 (60.8%)	
Disease severity	n = 455	n = 267	
Mild	42 (9.2%)	23 (8.6%)	.057
Moderate	232 (51.0%)	160 (59.9%)	
Severe	181 (39.8%)	84 (31.5%)	
Endoscopic severity	n = 345	n = 207	

Mild	51 (14.8%)	21 (10.1%)	.031
Moderate	137 (39.7%)	105 (50.7%)	
Severe	157 (45.5%)	81 (39.1%)	
Combo. IM (Yes/No)	n = 455	n = 267	
No	266 (58.5%)	193 (72.3%)	<.001
Yes	189 (41.5%)	74 (27.7%)	
Combo. steroids (Yes/No)	n = 455	n = 267	
No	212 (46.6%)	122 (45.7%)	.875
Yes	243 (53.4%)	145 (54.3%)	
Steroid dependency (Yes/No)	n = 455	n = 267	
No	270 (59.3%)	153 (57.3%)	.647
Yes	185 (40.7%)	114 (42.7%)	
TNF antagonist exposed (Yes/No)	n = 455	n = 267	
No	195 (42.9%)	108 (40.4%)	.579
Yes	260 (57.1%)	159 (59.6%)	
Number TNF antagonist exposed	n = 455	n = 267	
0	195 (42.9%)	108 (40.4%)	.930
1	186 (40.9%)	115 (43.1%)	
2	65 (14.3%)	39 (14.6%)	
3	9 (2.0%)	5 (1.9%)	
TNF antagonist failure (Yes/No)	n = 455	n = 267	
No	246 (54.1%)	155 (58.1%)	.336
Yes	209 (45.9%)	112 (41.9%)	
Ever PNR TNF antagonist? (Yes/No)	n = 260	n = 159	
No	185 (71.2%)	110 (69.2%)	.750
Yes	75 (28.8%)	49 (30.8%)	
TNF antagonist vs VDZ	n = 455	n = 267	
Anti-TNF	187 (41.1%)	81 (30.3%)	.005
Vedolizumab	268 (58.9%)	186 (69.7%)	
Infliximab vs VDZ	n = 392	n = 227	
Infliximab	124 (31.6%)	41 (18.1%)	<.001
Vedolizumab	268 (68.4%)	186 (81.9%)	
Subcutaneous TNF Antagonist vs VDZ	n = 331	n = 226	
Subcutaneous anti-TNF	63 (19.0%)	40 (17.7%)	.774
Vedolizumab	268 (81.0%)	186 (82.3%)	

Values are mean (SD) or n (%).

BMI, body mass index; CRP, C-reactive protein; EIM, extraintestinal manifestation; IM, immunomodulator; PNR, primary nonresponse; SD, standard deviation; TNF, tumor necrosis factor; VDZ, vedolizumab.

Supplemental Table 2: Baseline Characteristics of Vedolizumab-Treated UC Patients Stratified by Prior Anti-TNF Exposure

	Prior anti-TNF exposure No (n = 143)	**Prior anti-TNF exposure Yes (n = 311)**
Age (biol.)	42.80 (18.85)	41.75 (16.30)
Age (Dx)	33.79 (17.09)	32.22 (15.30)
Sex (female)	86 (60.1%)	140 (45.0%)
BMI	25.77 (6.20)	25.75 (5.83)
Smoking status		
Current	4 (2.8%)	7 (2.3%)
Former	43 (30.1%)	70 (22.5%)
Never	96 (67.1%)	234 (75.2%)
Disease duration	6 (11.5)	6 (10)
Ever hospitalized?		
Never	77 (53.8%)	136 (43.7%)
Yes (in the last year)	36 (25.2%)	78 (25.1%)
Yes (not in the last year)	30 (21.0%)	97 (31.2%)
CRP	1 (4.1)	2.4 (7.89)
Albumin	3.99 (0.46)	3.88 (0.58)
Rheumatic EIM (Yes)	19 (13.3%)	60 (19.3%)
Ophthal EIM (Yes)	0 (0.0%)	3 (1.0%)
Derm EIM (Yes)	5 (3.5%)	12 (3.9%)
Hepatic EIM (Yes)	7 (4.9%)	13 (4.2%)
Disease extent		
E1	8 (5.6%)	14 (4.5%)
E2	61 (42.7%)	100 (32.3%)
E3	74 (51.7%)	196 (63.2%)
Disease severity		
Mild	20 (14.0%)	32 (10.3%)
Moderate	93 (65.0%)	160 (51.4%)
Severe	30 (21.0%)	119 (38.3%)
Endoscopic severity		
Mild	11 (10.6%)	37 (14.9%)
Moderate	66 (63.5%)	100 (40.3%)
Severe	27 (26.0%)	111 (44.8%)
Combo. IM (Yes)	33 (23.1%)	116 (37.3%)
Combo. steroids (Yes)	74 (51.7%)	169 (54.3%)
Steroid dependency (Yes)	64 (44.8%)	152 (48.9%)

Biol, Biologic; Dx, Diagnosis; BMI, body mass index; CRP, C-reactive protein; Dx, diagnosis; EIM, extraintestinal manifestation; IM, immunomodulator; TNF, tumor necrosis factor.

Supplemental Table 3: Baseline Characteristics of Anti-TNF–Treated UC Patients Stratified by Prior Anti-TNF Exposure

	Prior anti-TNF exposure No (n = 160)	**Prior anti-TNF exposure Yes (n = 108)**
Age (biol.)	39.26 (15.91)	38.85 (15.45)
Age (Dx)	31.83 (15.10)	32.21 (15.07)
Sex (female)	78 (48.8%)	57 (52.8%)
BMI	25.29 (6.67)	25.40 (6.33)
Smoking status		
Current	8 (5.0%)	4 (3.7%)
Former	42 (26.2%)	33 (30.6%)
Never	110 (68.8%)	71 (65.7%)
Disease duration	4 (10)	4 (7)
Ever hospitalized?		
Never	72 (45.0%)	57 (52.8%)
Yes (in the last year)	61 (38.1%)	27 (25.0%)
Yes (not in the last year)	27 (16.9%)	24 (22.2%)
CRP	1.95 (15.375)	0.7 (3.85)
Albumin	3.80 (0.65)	3.92 (0.62)
Rheumatic EIM (Yes)	26 (16.2%)	16 (14.8%)
Ophthal EIM (Yes)	2 (1.2%)	3 (2.8%)
Derm EIM (Yes)	5 (3.1%)	6 (5.6%)
Hepatic EIM (Yes)	4 (2.5%)	4 (3.7%)
Disease extent		
E1	9 (5.7%)	2 (1.9%)
E2	52 (32.9%)	41 (38.0%)
E3	97 (61.4%)	65 (60.2%)
Disease severity		
Mild	4 (2.5%)	9 (8.3%)
Moderate	89 (55.6%)	50 (46.3%)
Severe	67 (41.9%)	49 (45.4%)
Endoscopic severity		
Mild	11 (9.4%)	13 (15.7%)
Moderate	42 (35.9%)	34 (41.0%)
Severe	64 (54.7%)	36 (43.4%)
Combo. IM (Yes)	69 (43.1%)	45 (41.7%)
Combo. steroids (Yes)	84 (52.5%)	61 (56.5%)
Steroid dependency (Yes)	60 (37.5%)	23 (21.3%)

Biol, Biologic; Dx, Diagnosis; BMI, body mass index; CRP, C-reactive protein; Dx, diagnosis; EIM, extraintestinal manifestation; IM, immunomodulator; TNF, tumor necrosis factor.

Supplemental Table 4: Event Rates

	Overall cohort			TNF-antagonist–naïve (VDZ vs. TNF antagonist)	TNF-antagonist–exposed (VDZ vs. TNF antagonist)
	VDZ vs anti-TNF	**VDZ vs IFX**	**VDZ vs SQ TNF antagonist**		
Clinical remission					
	187/453 vs 100/266	187/453 vs 61/163	187/453 vs 39/103	74/143 vs 65/158	113/310 vs 35/108
Deep remission					
	40/169 vs 30/124	40/169 vs 21/86	40/169 vs 9/38	16/44 vs 22/82	24/125 vs 8/42
Steroid-free clinical remission					
	72/243 vs 37/143	72/243 vs 28/97	72/243 vs 9/46	25/74 vs 25/82	47/169 vs 12/61
Steroid-free deep remission					
	24/150 vs 15/92	24/150 vs 11/67	24/150 vs 4/25	9/43 vs 9/57	15/107 vs 6/35
Serious Infection					
	21/453 vs 27/266	21/453 vs 19/163	21/453 vs 8/103	3/143 vs 20/158	18/310 vs 7/108
Serious adverse event					
	26/453 vs 45/266	26/453 vs 31/163	26/453 vs 14/103	3/143 vs 32/158	23/310 vs 13/108
IFX, infliximab; SQ, subcutaneous; TNF, tumor necrosis factor; VDZ, vedolizumab.					

Supplemental Table 5: Comparative Safety (HR) and Effectiveness (HR) of Vedolizumab vs Tumor Necrosis Factor Antagonists in Ulcerative Colitis

	Overall cohort			TNF-antagonist–naïve	TNF-antagonist–exposed
	VDZ vs anti-TNF	VDZ vs IFX	VDZ vs SQ TNF antagonist		
Clinical remission					
Unweighted	**1.435 (1.118, 1.843)**	**1.410 (1.050, 1.893)**	**1.543 (1.077, 2.212)**	**1.659 (1.180, 2.333)**	**1.644 (1.101, 2.455)**
IPW ATE	**1.651 (1.229, 2.217)**	**1.810 (1.225, 2.675)**	**1.693 (1.091, 2.627)**	**1.676 (1.157, 2.428)**	**1.689 (1.507, 2.700)**
Full match	**2.156 (1.381, 3.366)**	2.161 (0.892, 5.238)	2.091 (0.936, 4.673)	**2.066 (1.299, 3.286)**	**2.282 (1.102, 4.726)**
Deep remission					
Unweighted	1.501 (0.917, 2.457)	1.705 (0.984, 2.956)	1.095 (0.521, 2.302)	**2.157 (1.022, 4.553)**	1.262 (0.553, 2.868)
IPW ATE	1.653 (0.978, 2.794)	**1.914 (1.016, 3.608)**	1.420 (0.739, 2.729)	2.004 (0.938, 4.281)	1.317 (0.707, 2.455)
Full match	**1.878 (1.082, 3.259)**	**3.576 (1.395, 9.169)**	**1.989 (1.055, 3.747)**	**5.244 (1.186, 23.193)**	1.372 (0.667, 2.823)
Steroid-free clinical remission					
Unweighted	**1.541 (1.024, 2.317)**	1.313 (0.839, 2.053)	**2.245 (1.109, 4.546)**	1.386 (0.783, 2.453)	**2.085 (1.087, 3.997)**
IPW ATE	**1.828 (1.135, 2.944)**	**1.786 (1.004, 3.178)**	1.919 (0.852, 4.323)	1.578 (0.844, 2.952)	1.947 (0.955, 3.970)
Full match	**2.268 (1.226, 4.195)**	**2.224 (1.017, 4.866)**	0.845 (0.320, 2.227)	1.844 (0.909, 3.738)	2.238 (0.887, 5.646)
Steroid-free deep remission					
Unweighted	**2.469 (1.209, 5.045)**	**2.363 (1.081, 5.165)**	2.579 (0.757, 8.789)	2.054 (0.738, 5.714)	2.783 (0.969, 7.997)
IPW ATE	**2.819 (1.496, 5.310)**	**2.908 (1.393, 6.070)**	2.286 (0.977, 5.346)	**2.571 (1.008, 6.557)**	**2.754 (1.232, 6.160)**
Full match	**2.718 (1.412, 5.235)**	**3.748 (1.641, 8.562)**	**5.811 (1.916, 17.625)**	**4.203 (1.435, 12.306)**	2.432 (0.932, 6.345)
Serious infection					
Unweighted	1.182 (0.638, 2.188	0.919 (0.476, 1.776	2.448 (0.974, 6.152)	0.355 (0.103, 1.227)	**5.273 (1.728, 16.089**
IPW ATE	1.235 (0.608, 2.511	0.964 (0.413, 2.248)	2.116 (0.776, 5.764)	0.320 (0.078, 1.322)	**4.295 (1.091, 16.897**
Full match	1.481 (0.506, 4.334)	**3.225 (1.027, 10.130)**	2.243 (0.282, 17.833)	0.518 (0.133, 2.019)	3.006 (0.653, 13.839)
Serious adverse event					
Unweighted	0.844 (0.504, 1.414)	0.694 (0.400, 1.206	1.537 (0.741, 3.187	**0.214 (0.064, 0.711)**	**2.646 (1.174, 5.962)**
IPW ATE	0.899 (0.502, 1.612)	0.739 (0.375, 1.456)	1.564 (0.691, 3.540)	**0.192 (0.049, 0.754)**	2.495 (0.988, 6.301)
Full match	0.992 (0.461, 2.135)	1.356 (0.501, 3.673)	2.010 (0.410, 9.857)	**0.227 (0.060, 0.861)**	1.936 (0.733, 5.113)

Bolded numbers are statistically significant. ATE, average treatment effect; IFX, infliximab; IPW, inverse probability weighting; SQ, subcutaneous; TNF, tumor necrosis factor; VD, vedolizumab. Data in parentheses are 95% confidence intervals.