Sustained Clinical Remission With Vedolizumab in Patients With Moderate-to-Severe Ulcerative Colitis

Brian G. Feagan, MD,[*] Stefan Schreiber, MD, PhD,[†] Douglas C. Wolf, MD,[‡] Jeffrey L. Axler, MD, FRCPC,[§] Arpeat Kaviya, MBChB, MRCP, MFPM,[¶,#] Alexandra James, MSc,[¶] Rebecca I. Curtis, MBBS, MRCGP, FFPM,[¶,#] Parnia Geransar, PhD,[‖] Andreas Stallmach, MD, PhD,[**] Robert Ehehalt, MD, PhD,[††] Bernd Bokemeyer, MD, PhD,[‡‡] Javaria Mona Khalid, PhD,[¶] and Sharon O'Byrne, MB, Bch BAO, MSc, MD[‖,#]

Background: Sustaining clinical remission is an important treatment goal in moderate-to-severe UC. This post hoc exploratory analysis assessed the long-term efficacy of vedolizumab in the subset of patients with UC in the GEMINI 1 study who were in clinical remission by week 14 after 3 induction doses, administered at weeks 0, 2, and 6.

Methods: Sustained clinical remission (primary endpoint) was evaluated using 2 definitions: (1) a partial Mayo Score (pMS) of ≤2 with no subscore >1 and (2) a rectal bleeding subscore (RBS) of 0 throughout weeks 14, 26, 38, and 52.

Results: The proportion of patients in clinical remission at week 14 was significantly higher in patients receiving vedolizumab (n = 620) compared with placebo (n = 149) (pMS: 32.7% vs 20.1% [percentage-point difference (Δ) 12.6%; 95% confidence interval [CI], 5.2–20.0]; RBS: 47.3% vs 28.9% [Δ18.4%; 95% CI, 10.1–26.7]). Of patients in clinical remission at week 14, a significantly higher proportion of vedolizumab-treated patients achieved sustained clinical remission compared with placebo (pMS: 66.5% vs 26.7%; Δ39.8%; 95% CI, 22.7–56.9; RBS: 56.7% vs 20.9%; Δ35.7%; 95% CI, 22.3–49.1). Findings were consistent in tumor necrosis factor (TNF) antagonist-naive and antagonist-failure patients.

Conclusion: Compared with placebo, 35%–40% more patients receiving a full induction course of vedolizumab had sustained clinical remission after 52 weeks of therapy. This result was observed irrespective of TNF antagonist treatment history. Clinical remission at week 14 may therefore be a predictor for sustained clinical remission with vedolizumab.

Key Words: TNF antagonist, remission, ulcerative colitis, vedolizumab

Received for publications June 14, 2018; Editorial Decision September 17, 2018.

From the *Robarts Research Institute, University of Western Ontario, London, Ontario, Canada; †Department of Internal Medicine I, Kiel University, Kiel, Germany; ‡Atlanta Gastroenterology Associates, Atlanta, Georgia, USA; §Toronto Digestive Disease Associates, University of Toronto, Toronto, Ontario, Canada; ¶Takeda International - UK Branch, London, United Kingdom; ‖Takeda Pharmaceuticals International AG, Zurich, Switzerland; **Department of Internal Medicine IV, University Hospital Jena, Friedrich Schiller University of Jena, Jena, Germany; ††Gastroenterology Outpatient Clinic, Heidelberg, Germany; ‡‡Gastroenterology Practice, Minden, Germany

Conflicts of Interest: BGF is a consultant for Abbott/AbbVie, ActoGeniX, Akros, Albireo Pharma, Amgen, AstraZeneca, Avaxia Biologics Inc., Avir Pharma, Axcan, Baxter Healthcare Corp., Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, enGene, Ferring Pharma, Roche/Genentech, gICare Pharma, Gilead, Given Imaging Inc., GSK, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Hakko Kirin Co Ltd, Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nektar, Nestle, Novartis, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, VHsquared Ltd, Warner Chilcott, Wyeth, Zealand, and Zyngenia; BGF has received grant and research support from Abbott/AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen Biotech (Centocor), JnJ/Janssen, Roche/Genentech, Millennium, Pfizer, Receptos, Santarus, Sanofi, Tillotts, and UCB Pharma; BGF is on the board of directors for Robarts Clinical Trials Inc. SS is a consultant for AbbVie, Celltrion, Janssen, Merck, Pfizer, Roche, and Takeda. DCW has received financial support for research from AbbVie, Genentech, Janssen, Takeda, and UCB; DCW has received lecture fees from and and is a consultant for AbbVie, Janssen, Takeda, and UCB. JLA is a consultant for AbbVie, Janssen Pharmaceutical, and Takeda. AK is a former employee of Takeda Development Centre Europe Ltd. AJ is an Employee of Takeda International–UK Branch. RIC is a former employee of Takeda Development Centre Europe Ltd. PG is an employee of Takeda Development Centre Europe Ltd. AS has received financial support for research from AbbVie, Pentax; AS has received lecture fees from AbbVie, Falk Foundation, Janssen, MSD, Mundipharma, and Takeda; AS is a consultant for AbbVie, Astellas, Biogen, Janssen, MSD, Mundipharma, Summit Therapeutics, and Takeda. RE has received lecture fees from AbbVie, Falk, Ferring, Hospira, Janssen, MSD, Pfizer, and Takeda; RE is a consultant for AbbVie, Biogen, Ferring, Janssen, MSD, and Takeda. BB has received financial support for research from AbbVie, Ferring, Given Imaging, Janssen, Takeda, and UCB; BB has received lecture fees from AbbVie, Biogen, Celltrion, Falk, Ferring, HLR, Janssen, Merckle, MSD, Mundipharma, Pfizer, Shield, Takeda, and UCB; BB is a consultant for AbbVie, Biogen, Boehringer, Ferring, Hexal, Hospira, Janssen, Movetis, MSD, Pfizer, Shield, Shire, Takeda, and UCB. JMK is an employee of Takeda International–UK Branch. SOB is a former employee of Takeda Pharmaceuticals International AG. All authors were involved in the interpretation of the data for this work. AJ was the statistician who conducted the analysis of the data. All authors reviewed the drafts of the manuscript and approved the final draft of the manuscript for submission.

Supported by: This study and post hoc analysis were supported by Takeda.

Address correspondence to: Brian G. Feagan, MD, Robarts Clinical Trials, Robarts Research Institute, University of Western Ontario, 100 Perth Dr., London, Ontario, N6A 5K8, Canada. E-mail: bfeagan@robarts.ca.

#Former employee of Takeda

doi: 10.1093/ibd/izy323
Published online 25 October 2018

INTRODUCTION

Ulcerative colitis (UC) is characterized by abdominal pain and bloody diarrhea. Uncontrolled disease activity substantially affects patients' quality of life (QoL), leading to functional impairment, anxiety, and social stigmatization.[1–3] Some patients with severe disease may require hospitalization and, potentially, colectomy.[4] Chronic intestinal inflammation also predisposes patients to colorectal cancer.[5,6] Consequently, UC imposes substantial burdens on patients, society, and healthcare resources.[7–10] The ultimate treatment goal is attaining sustained clinical remission.[11]

Corticosteroids are commonly used to induce clinical remission in patients with moderate-to-severe UC who have failed treatment with 5-aminosalicylates; however, corticosteroids are ineffective as maintenance, and prolonged use is associated with serious side effects.[2] Although tumor necrosis factor (TNF) antagonists have improved UC management, some patients do not respond to induction therapy or lose response during maintenance treatment.[12] Tumor necrosis factor antagonist therapy may also be limited by an increased risk of serious infection.[13] Current clinical evidence on the ability of biologics to sustain UC clinical remission is limited.[14–16]

Vedolizumab is a gut-selective, humanized, immunoglobulin G1 monoclonal antibody that binds to the $\alpha_4\beta_7$ integrin expressed on leukocytes, preventing movement into gut tissue and thereby reducing inflammation.[17,18] International treatment guidelines recommend using vedolizumab for induction and maintenance treatment of adults with moderate-to-severe UC or Crohn's disease who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or a TNF antagonist.[4,19,20] In line with regulatory authority approval, patients with UC or Crohn's disease should receive vedolizumab doses at weeks 0, 2, and 6 before determining whether to continue therapy at week 10 or 14, dependent on label.[19,20]

In this exploratory analysis, we evaluated sustainability of clinical remission with vedolizumab in patients who received 3 induction doses and were in clinical remission by week 14.

MATERIALS AND METHODS

Study Design

This was a post hoc analysis of GEMINI 1 (ClinicalTrials.gov Identifier, NCT00783718), a phase 3 randomized, placebo-controlled trial with separate induction and maintenance phases (details published previously; Fig. 1).[21] Patients who discontinued treatment during maintenance or completed 52 weeks' treatment could enroll in a long-term safety study (GEMINI LTS [ClinicalTrials.gov Identifier, NCT00790933]) with vedolizumab. These studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. Procedures were approved by local institutional review boards or ethics committees; all patients provided informed written consent. All authors had access to the study data and had reviewed and approved the final manuscript.

Treatment Groups

The current analysis investigated 3 treatment groups (Fig. 1): the PLA group (n = 149) comprised patients who received placebo during induction and maintenance phases of GEMINI 1; the VDZ/PLA group (n = 126) comprised patients who responded at week 6 after 2 induction doses of vedolizumab administered at weeks 0 and 2 and were subsequently randomized to placebo for the maintenance phase through week 52; and the combined VDZ group (n = 620) included week 6 responders to vedolizumab randomized to vedolizumab either every 4 or 8 weeks (Q4W or Q8W) or week 6 nonresponders who received open-label vedolizumab (Q4W) in the maintenance phase of GEMINI 1. All patients who discontinued during or completed the maintenance phase were eligible to subsequently enroll into the LTS study.

Endpoints

Sustained clinical remission (primary endpoint) was evaluated using 2 definitions: (1) a partial Mayo Score (pMS) of ≤2 with no subscore >1 and (2) a rectal bleeding subscore (RBS) of 0 throughout weeks 14, 26, 38, and 52 (Fig. 1). The primary endpoint was the proportion of patients who were in clinical remission at week 14 and sustained clinical remission through week 52. The secondary endpoint was the proportion of patients who were in clinical remission before or at week 14 and sustained clinical remission through week 52.

Missing maintenance data for the combined VDZ group were substituted from GEMINI LTS where available. A sensitivity analysis assessed the impact on sustained clinical remission of GEMINI LTS data substitution based on (1) pMS at all study visits but for total MS at week 52 or (2) RBS of 0 for all study visits.

The primary endpoint was assessed in the overall population and according to TNF antagonist treatment history. Tumor necrosis factor antagonist-naive status was determined on assessment at screening (using an interactive voice recording system), and TNF antagonist-failure status was determined on assessment at enrollment (by investigator using the case report form).[21]

Data Collection and Substitution

Some patients who discontinued vedolizumab treatment in the maintenance phase of GEMINI 1 entered the LTS study (PLA 58.4%, VDZ/PLA 54.0%, combined VDZ 27.7%). Data from GEMINI LTS were used to substitute missing GEMINI 1 maintenance data for the combined VDZ treatment group. Data substitution from the GEMINI LTS study was performed for 3.4% (n = 21), 16.3% (n = 101), 18.2% (n = 113), and 16.1%

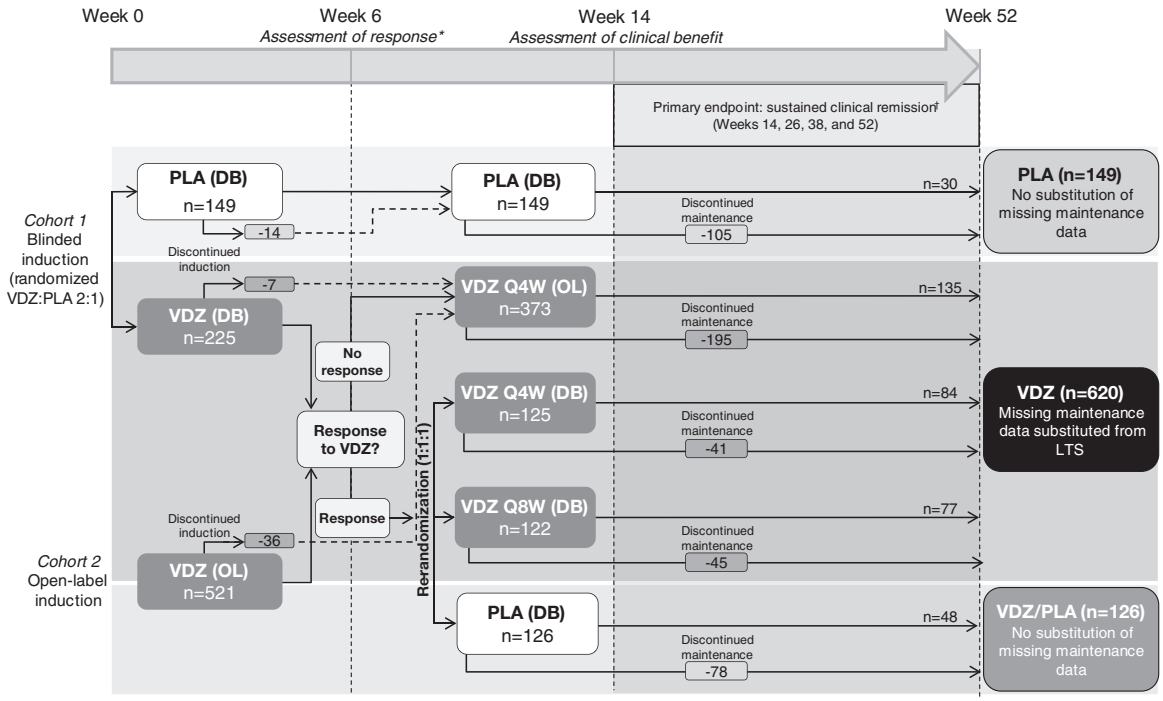

FIGURE 1. Design of GEMINI 1 and patient disposition. GEMINI 1 study design and disposition of patients with moderate-to-severe UC failing conventional therapy.[21] Cohort 1, randomized to double-blind vedolizumab or placebo at weeks 0 and 2; cohort 2 (required to ensure sufficient sample size in maintenance phase) received open-label vedolizumab at weeks 0 and 2. The 2 cohorts were integrated for the maintenance phase (up to week 52) based on clinical response* at week 6. Vedolizumab nonresponders received open-label vedolizumab Q4W, while responders were re-randomized to double-blind vedolizumab Q4W, Q8W, or placebo. Patients discontinuing vedolizumab induction (cohort 1: n = 7; cohort 2: n = 36) or placebo (n = 14) were re-assigned to open-label vedolizumab Q4W maintenance (nonresponder) or to the placebo group, respectively (stippled arrows). *Reduction from baseline in total MS of ≥3 points and ≥30% decrease from baseline, with ≥1-point decrease in RBS or an absolute ≤1-point RBS. †Sustained clinical remission (weeks 14, 26, 38, and 52) assessed according to 2 definitions: (1) pMS ≤2 points and no individual subscore >1 point, and (2) RBS of 0. Data substitution from GEMINI LTS was performed for 3.4% (n = 21), 16.3% (n = 101), 18.2% (n = 113), and 16.1% (n = 100) of the combined VDZ group at weeks 14, 26, 38, and 52, respectively. Abbreviations: DB, double-blind; OL, open-label.

(n = 100) of the combined VDZ group at weeks 14, 26, 38, and 52, respectively. Substitution was not possible for PLA and VDZ/PLA groups due to there being no placebo arm in the LTS study. Consequently, PLA or VDZ/PLA patients with missing data were not considered in remission. Missing induction data were not substituted.

Statistical Methods

Descriptive statistics were used to summarize baseline demographics and disease characteristics. Proportions of patients and 95% confidence intervals (CIs) for the percentage-point differences (Δ) across the PLA, VDZ/PLA, and combined VDZ groups were described for primary and secondary endpoints.

RESULTS

Demographics and Disease Characteristics

Baseline demographics and disease characteristics were similar across treatment groups (Table 1). The mean age was 40.3 ± 13.1 years, 41% of patients were female, mean pMS was 6.0 ± 1.6, and mean duration of UC was 6.9 ± 6.4 years. Patients in the TNF antagonist-naive subgroup had a shorter mean disease duration (by 1.5 years) compared with those in the TNF antagonist-failure subgroup.

Clinical Remission at Week 14

The proportion of patients in clinical remission at week 14 was significantly greater in the combined VDZ group than in the PLA group: 32.7% vs 20.1% based on pMS (Δ12.6%; 95% CI, 5.2–20.0), and 47.3% vs 28.9% based on RBS (Δ18.4%; 95% CI, 10.1–26.7). The proportion of patients in clinical remission at week 14 in the VDZ/PLA and PLA treatment groups, respectively, was 61.1% vs 20.1% based on pMS (Δ41.0%; 95% CI, 30.3–51.6) and 69.8% vs 28.9% based on RBS (Δ41.0%; 95% CI, 30.2–51.8).

Week 14 clinical remission rates in the week 6 responders within the VDZ group were similar to those in the overall VDZ/PLA group, whereas week 14 rates in the week 6 nonresponders within the VDZ group resembled those in the PLA group. Based on pMS, the week 14 clinical remission rates were 63.4% in week 6 responders in the VDZ group and 61.1% in the overall VDZ/PLA group, who were all week 6 responders. In contrast,

TABLE 1. Patient Demographics and Disease Characteristics

Overall population[a]	PLA n = 149	VDZ/PLA n = 126	Combined VDZ n = 620	Total N = 895
Age (years), mean (SD)	41.2 (12.5)	40.3 (13.9)	40.1 (13.1)	40.3 (13.1)
Female sex, n (%)	57 (38)	57 (45)	256 (41)	370 (41)
BMI (kg/m^2), mean (SD)	24.6 (5.1)	25.8 (6.1)	25.1 (5.6)	25.1 (5.6)
Disease duration (years), mean (SD)	7.1 (7.3)	7.8 (6.9)	6.7 (6.0)	6.9 (6.4)
Total MS, mean (SD)[b]	8.6 (1.7)	8.4 (1.8)	8.6 (1.8)	8.6 (1.8)
pMS, mean (SD)[c]	6.1 (1.5)	5.9 (1.6)	6.0 (1.6)	6.0 (1.6)
Concomitant corticosteroids or immunosuppressants, n (%)	102 (68)	99 (79)	439 (71)	640 (72)
TNF antagonist-naive subgroup[a]	**PLA n = 76**	**VDZ/PLA n = 79**	**Combined VDZ n = 309**	**Total N = 464**
Age (years), mean (SD)	40.5 (11.7)	39.5 (14.2)	40.5 (13.3)	40.3 (13.2)
Female sex, n (%)	29 (38)	34 (43)	134 (43)	197 (42)
BMI (kg/m^2), mean (SD)	24.3 (5.7)	24.9 (5.5)	24.7 (5.9)	24.7 (5.8)
Disease duration (years), mean (SD)	6.1 (6.4)	6.4 (5.6)	6.2 (6.0)	6.2 (6.0)
Total MS, mean (SD)[b]	8.5 (1.5)	8.4 (1.7)	8.5 (1.8)	8.5 (1.7)
pMS, mean (SD)[c]	6.1 (1.3)	6.0 (1.5)	6.0 (1.6)	6.0 (1.5)
Concomitant corticosteroids or immunosuppressants, n (%)	54 (71)	62 (78)	234 (76)	350 (75)
TNF antagonist-failure subgroup[a]	**PLA n = 63**	**VDZ/PLA n = 38**	**Combined VDZ n = 266**	**Total N = 367**
Age (years), mean (SD)	41.8 (13.1)	41.6 (13.4)	39.9 (13.0)	40.4 (13.0)
Female sex, n (%)	28 (44)	17 (45)	115 (43)	160 (44)
BMI (kg/m^2), mean (SD)	25.0 (4.5)	27.4 (7.0)	25.3 (5.5)	25.4 (5.6)
Disease duration (years), mean (SD)	8.0 (7.6)	9.8 (8.4)	7.3 (6.2)	7.7 (6.7)
Total MS, mean (SD)[b]	8.6 (1.9)	8.2 (1.7)	8.7 (1.8)	8.6 (1.8)
pMS, mean (SD)[c]	6.0 (1.7)	5.6 (1.7)	6.1 (1.7)	6.0 (1.7)
Concomitant corticosteroids or immunosuppressants, n (%)	41 (65)	29 (76)	170 (64)	240 (65)

[a]Difference of n = 10, n = 9, and n = 45 between overall population and TNF antagonist subgroups in the PLA, VDZ/PLA, and combined VDZ groups, respectively, is due to (1) analysis not accounting for patients with prior TNF antagonist therapy exposure and no documented failure from the subgroup analysis and (2) differences in use of prior TNF antagonist exposure recorded at screening vs study baseline.
[b]Range 0–12, higher scores indicate worse symptoms/disease severity.
[c]Range 0–9, higher scores indicate worse symptoms/disease severity.

BMI, body mass index; SD, standard deviation.

week 14 clinical remission rates in week 6 nonresponders within the VDZ group (15.0%) were comparable to those in the PLA group (20.1%). Results based on RBS paralleled those based on pMS, with week 14 clinical remission rates in week 6 responders within the VDZ group (73.1%) close to those in the VDZ/PLA group (69.8%), and with the week 14 rates in week 6 nonresponders in the VDZ group (32.3%) also comparable to those in the PLA group (28.9%).

Sustained Clinical Remission from Week 14 to Week 52

Of the patients in clinical remission at week 14, a significantly higher proportion of the combined VDZ treatment group sustained clinical remission (at weeks 14, 26, 38, and 52) compared with the PLA group, as assessed using pMS (66.5% vs 26.7%; Δ39.8%; 95% CI, 22.7–56.9) or RBS (56.7% vs 20.9%; Δ35.7%; 95% CI, 22.3–49.1). There were no significant differences in proportion of patients in sustained clinical remission between the VDZ/PLA and PLA groups, as assessed using pMS (28.6% vs 26.7%; Δ1.9%; 95% CI, –16.9 to 20.7) or RBS (26.1% vs 20.9%; Δ5.2%; 95% CI, –10.0 to 20.4; Fig. 2 and Supplementary Table S1, Supplementary Data Content 1, which shows sustained clinical remission data). Similar findings were observed in the TNF antagonist-naive patient subgroup using both pMS and RBS to characterize sustained clinical remission (Fig. 2). These observations were also replicated in the TNF antagonist-failure patient subgroup using RBS only; a numerically greater proportion in the combined VDZ group

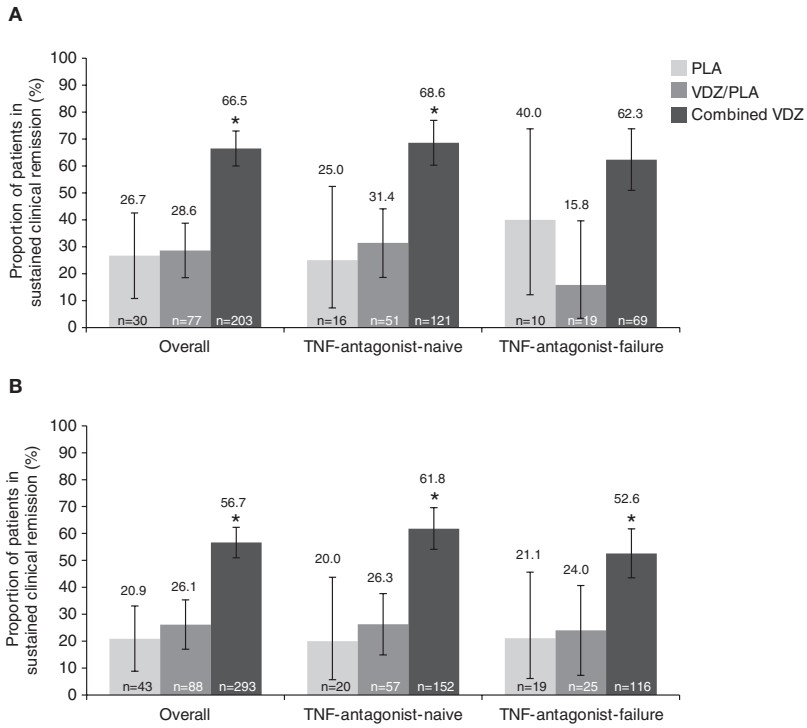

FIGURE 2. Sustained clinical remission based on (A) pMS (≤2 points and no individual subscore >1 point) or (B) RBS of 0 at weeks 14, 26, 38, and 52. Data substitution from the GEMINI LTS study was performed for 3.4% (n = 21), 16.3% (n = 101), 18.2% (n = 113), and 16.1% (n = 100) of the combined VDZ group at weeks 14, 26, 38, and 52, respectively. The n value in each bar indicates patients who were in clinical remission at week 14. *Indicates significance based on the 95% CI for percentage-point difference between combined VDZ and PLA groups.

achieved sustained clinical remission based on the pMS definition, compared with the PLA and VDZ/PLA groups (Fig. 2).

In the overall population, sensitivity analysis of sustained clinical remission excluding GEMINI LTS data was consistent with results observed when LTS study data were included in the analysis (Supplementary Fig. S1, Supplementary Data Content 2, which shows sustained clinical remission data for the overall population). While in the sensitivity analysis, the proportion of patients in the combined VDZ group who achieved sustained clinical remission was reduced, and this proportion was still significantly higher than in the PLA group (pMS: 42.3% vs 23.3%; Δ19.0%; 95% CI, 2.4–35.6) (RBS: 38.5% vs 16.3%; Δ22.3%; 95% CI, 9.9–34.6; Supplementary Fig. S1, Supplementary Data Content 2). The proportion of patients in sustained clinical remission also remained similar in the VDZ/PLA and PLA groups (pMS: 18.2% vs 23.3%; Δ–5.2%; 95% CI, –22.6 to 12.3) (RBS: 19.3% vs 16.3%; Δ3.0%; 95% CI, –10.7 to 16.8).

Within each treatment group, a proportion of patients entered clinical remission before week 14 and sustained this through week 52, according to both pMS and RBS definitions (Supplementary Fig. S2, Supplementary Data Content 3). Between week 0 and 14, there was a cumulative increase in number of patients entering into clinical remission. This increase was more pronounced in the combined VDZ group than in the VDZ/PLA or PLA groups (Supplementary Fig. S2, Supplementary Data Content 3). This was observed in the overall population and the TNF antagonist subgroups.

DISCUSSION

An unmet need in managing moderate-to-severe UC is sustaining clinical remission. Patients who achieve this outcome should benefit from improved QoL, reduced exposure to corticosteroids, and decreased risk of disease-related complications.[1,2,7,10] Accordingly, the definition of "clinical remission" deserves careful consideration. Historically, pivotal clinical trials have used cross-sectional assessments of clinical remission at a given timepoint, giving rise to assessments of remission maintenance at 1 year of treatment.[22,23] Some clinical trials have evaluated the more rigorous outcome of durable or sustained remission, with longitudinal assessment of 2 timepoints at the end of induction therapy (after 4–12 weeks) and at the end of maintenance therapy (after 24–54 weeks).[15,16,21]

Sustained clinical remission analyses in this study were based on clinical remission after completion of induction treatment (3 doses) at week 14.[19,20] Using pMS and RBS definitions, 32.7% and 47.3% of patients on vedolizumab and 20.1% and 28.9% of patients on placebo, respectively, were in clinical remission after a full induction course. Among patients achieving clinical remission at week 14, 66.5% on vedolizumab

and 26.7% on placebo achieved sustained clinical remission using the pMS definition. Furthermore, most of these patients entered clinical remission before week 14 and sustained clinical remission through week 52 using the pMS or RBS definition for sustained clinical remission.

Where available, additional data on clinical remission in patients in the combined VDZ group who withdrew from the 52-week maintenance study but continued treatment in GEMINI LTS were included. This approach was intended to help optimize the analysis by using all available data. In the analyses where missing data were not substituted with GEMINI LTS data for patients in the combined VDZ group after withdrawal from the maintenance phase, these patients were all simply considered as nonremitters from that point onward. Where such patients with available GEMINI LTS data were included in the analysis, some patients were found to have continued to experience clinical remission. This resulted in higher estimates of sustained clinical remission in the combined VDZ group with GEMINI LTS substitution than in those without substitution, although the overall treatment effect observed between treatment groups remained consistent compared with placebo using both approaches.

Our findings inform clinical practice in that they support recommendations of regulatory authorities that the full 3-dose induction course of vedolizumab should be completed before clinical benefit is assessed at week 10 or 14.[19,20] Given the refractory nature of the GEMINI 1 population, with ~40% having failed TNF antagonist treatment (from among the 50% who were previously treated), the high rates of success after induction therapy allow patients the opportunity to experience efficacy and safety benefits of long-term treatment with vedolizumab.[21] It is noteworthy that an interim analysis of GEMINI LTS data showed long-term clinical benefits of vedolizumab treatment for up to 5 years in patients with early response to the drug: 90% (57 of 63) of GEMINI 1 patients who responded at week 6 and were on long-term treatment at week 248 experienced clinical remission (pMS definition).[24] GEMINI LTS is a long-term, noncomparative safety study that was not designed or powered to evaluate treatment effectiveness. As expected for a 5-year analysis of an ongoing LTS study, patient numbers at the last available study assessment were low.[24]

In an analysis of TNF antagonist-naive vs TNF antagonist-failure subgroups, sustained clinical remission was achieved by >60% on vedolizumab vs 25% to 40% on placebo (pMS definition) and 50% to 60% on vedolizumab vs 20% on placebo (RBS definition). Therefore, sustained clinical remission was observed irrespective of TNF antagonist treatment history.

Previous studies with TNF antagonists in moderate-to-severe UC have sustained clinical remission (defined as MS ≤2 and no individual subscore >1). Sustained clinical remission (assessed at weeks 8, 30, and 54) was reported in 19.8% and 20.5% of TNF antagonist-naive patients receiving 5 and 10 mg/kg of infliximab, respectively, compared with 6.6% of patients on placebo ($P = 0.002$ for both groups).[15] Low proportions of patients with sustained clinical remission (assessed at weeks 8 and 52) were also reported with adalimumab in TNF antagonist-naive (10.7%) and TNF antagonist-exposed (5.1%) patient subgroups and were not significantly greater than the proportion observed with placebo.[22] In another study, among responders to induction therapy, fewer than one third (27.8%) of TNF antagonist-naive patients receiving golimumab achieved sustained clinical remission (assessed at weeks 30 and 54) compared with 15.6% on placebo ($P = 0.004$).[16] While higher absolute rates of sustained clinical remission were reported with vedolizumab in the present study than have been reported with TNF antagonists, the magnitude of the treatment effect appears to be generally consistent across studies (with rates on active treatment approximately 2-fold higher than those on placebo). It is important to note that direct comparison of these results across studies of different agents is not feasible because of substantial differences in study design, study endpoints, and patient populations.

Some direct comparisons of durability of clinical response have been reported previously. A recent network meta-analysis comparing the efficacy of biologics in phase 3 clinical studies concluded that vedolizumab demonstrated greater durable clinical response (defined as clinical response at both start and end of maintenance) compared with infliximab (odds ratio [OR] 3.18; 95% CI, 1.14–9.20), golimumab (OR 2.33; 95% CI, 1.04–5.41), or adalimumab (OR 3.96; 95% CI, 1.67–9.84), irrespective of prior TNF antagonist exposure and after adjusting for differences in study design.[25] Notably, mucosal healing, which has been associated with sustained clinical remission, was reported at a significantly higher rate in vedolizumab-treated patients with prior TNF antagonist exposure than in adalimumab-treated patients (OR 6.72; 95% CI, 1.36–41.0).

Based on the limited availability of datasets, this post hoc analysis with vedolizumab is the only report of evidence for a sustained long-term treatment benefit in both TNF antagonist-naive and antagonist-failure patients. No standardized definition of sustained clinical remission exists in the published literature. This analysis used pMS of ≤2 with no individual subscore >1 or RBS of 0 at 4 distinct timepoints—more rigorous definitions than used in previous studies. Nevertheless, RBS has been shown to be a good surrogate for endoscopic subscore.[26] Indeed, this analysis could be used as a new benchmark for future studies assessing sustained clinical remission.

Definitions of clinical remission that were used in this analysis are broadly in line with the recommendations in the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) guidelines for the clinical targets of no rectal bleeding and normalization of bowel habit.[11] However, STRIDE also recommends including an MS endoscopic subscore of 0 or 1 in the definition of remission. In GEMINI 1, endoscopy

was performed at weeks 0, 6, and 52; therefore, data were not available to assess endoscopic subscore throughout the maintenance phase. The MS and pMS measures have been shown to have a high degree of correlation (Spearman correlation coefficient = 0.97).[27] Consequently, pMS is a useful tool for long-term studies in which repeated, noninvasive assessments of disease activity are desired. Moreover, current FDA guidance recommends that the definition of clinical remission includes an RBS of 0.[28] Compared with endoscopic measures, RBS is a simple, objective, noninvasive marker of clinical remission,[11,28] which can easily be followed over a long period of time. In this post hoc analysis, evaluation of sustained clinical remission based on an RBS of 0 provided similar outcomes to the pMS definition.

Although not analyzed in the present study, vedolizumab therapy may also offer better tolerability compared with agents that cause systemic immunosuppression, such as TNF antagonists, which are associated with an increased risk of serious infection.[13,15] Recent analysis (cutoff date: September 30, 2016) of data from up to 72,140 patient-years of vedolizumab exposure in patients with inflammatory bowel disease indicated a favorable safety profile.[29]

Our study has several strengths, including a relatively large sample size and consistent findings across 2 definitions of sustained clinical remission. Limitations include those associated with the nature of post hoc analyses and potential bias based on the composition of the treatment groups, which differed from the original randomized design of the GEMINI 1 trial.[21] The combined VDZ treatment group comprised both patients who did and did not respond to vedolizumab by week 6 and, thus, is not as select a group as that reported in the maintenance study.[21] One potential source of bias comes from the missing data for the PLA and VDZ/PLA groups, which could not be substituted from GEMINI LTS because all patients in the LTS study received vedolizumab. This limitation was addressed by conducting a sensitivity analysis; results were consistent with findings for the primary endpoint. Finally, the relatively small number of patients available for subgroup analysis, particularly for the TNF antagonist subgroups, precluded formal statistical testing. Therefore, results should be interpreted with caution.

In conclusion, this post hoc analysis of GEMINI 1 data demonstrated that a 35%–40% greater proportion of vedolizumab-treated than placebo-treated patients experienced sustained clinical remission from week 14 to 1 year of therapy according to both definitions. These findings support the guidance that the full standard 3-dose induction course of vedolizumab must be completed before a final decision on clinical benefit is assessed at week 10 or 14, dependent on EU or US label.[19,20] These data also provide strong evidence for the long-term benefit conferred by vedolizumab on sustained clinical remission in patients with moderate-to-severe UC, independent of prior TNF antagonist treatment history.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

ACKNOWLEDGMENTS

This study and post hoc analysis were supported by Takeda Pharmaceutical Company Ltd. Medical writing support was provided by Claudia Wiedemann of Chameleon Communications International Ltd, UK (a Healthcare Consultancy Group Company) and sponsored by Takeda Pharmaceutical Company Ltd. Clinical trial registration: ClinicalTrials.gov numbers NCT00783718 and NCT00790933.

REFERENCES

1. Taft TH, Keefer L. A systematic review of disease-related stigmatization in patients living with inflammatory bowel disease. *Clin Exp Gastroenterol.* 2016;9:49–58.
2. Bressler B, Marshall JK, Bernstein CN, et al.; Toronto Ulcerative Colitis Consensus Group. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto Consensus. *Gastroenterology.* 2015;148:1035–1058.e3.
3. Tabatabaeian M, Afshar H, Roohafza HR, et al. Psychological status in Iranian patients with ulcerative colitis and its relation to disease activity and quality of life. *J Res Med Sci.* 2015;20:577–584.
4. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis*. 2017;11:769–784.
5. Scarpa M, Castagliuolo I, Castoro C, et al. Inflammatory colonic carcinogenesis: a review on pathogenesis and immunosurveillance mechanisms in ulcerative colitis. *World J Gastroenterol.* 2014;20:6774–6785.
6. Castaño-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. *Aliment Pharmacol Ther.* 2014;39:645–659.
7. Cohen RD, Yu AP, Wu EQ, et al. Systematic review: the costs of ulcerative colitis in Western countries. *Aliment Pharmacol Ther.* 2010;31:693–707.
8. Kawalec P. Indirect costs of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. A systematic review. *Arch Med Sci.* 2016;12:295–302.
9. Ramos A, Calvet X, Sicilia B, et al. IBD-related work disability in the community: prevalence, severity and predictive factors. A cross-sectional study. *United European Gastroenterol J.* 2015;3:335–342.
10. Rocchi A, Benchimol EI, Bernstein CN, et al. Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol.* 2012;26:811–817.
11. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110:1324–1338.
12. Roda G, Jharap B, Neeraj N, et al. Loss of response to anti-TNFs: definition, epidemiology, and management. *Clin Transl Gastroenterol.* 2016;7:e135.
13. Nyboe Andersen N, Pasternak B, Friis-Møller N, et al. Association between tumour necrosis factor-α inhibitors and risk of serious infections in people with inflammatory bowel disease: nationwide Danish cohort study. *Bmj.* 2015;350:h2809.
14. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. *Ann Intern Med.* 2014;160:704–711.
15. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462–2476.
16. Sandborn WJ, Feagan BG, Marano C, et al.; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2014;146:96–109.e1.
17. Soler D, Chapman 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. *J Pharmacol Exp Ther.* 2009;330:864–875.
18. Fedyk ER, Wyant T, Yang LL, et al. Exclusive antagonism of the α4 β7 integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis.* 2012;18:2107–2119.
19. *Entyvio [package insert]*. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2014.
20. *Entyvio [Summary of Product Characteristics]*. Taastrup, Denmark: Takeda Pharma A/S; 2014.
21. Feagan BG, Rutgeerts P, Sands BE, et al.; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369:699–710.

22. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2012;142:257–265.e1.
23. Reinisch W, Sandborn WJ, Panaccione R, et al. 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. *Inflamm Bowel Dis.* 2013;19:1700–1709.
24. Loftus EV, Colombel JF, Feagan B, et al. Long-term effectiveness and safety of vedolizumab in patients with ulcerative colitis: 5-year cumulative exposure of GEMINI 1 completers rolling into the GEMINI open-label extension study. *Gastroenterology*. 2017;152(suppl 1):S602. Abstract Su1934.
25. Vickers AD, Ainsworth C, Mody R, et al. Systematic review with network meta-analysis: comparative efficacy of biologics in the treatment of moderately to severely active ulcerative colitis. *PLoS One.* 2016;11:e0165435.
26. Colombel JF, Keir ME, Scherl A, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. *Gut.* 2017;66:2063–2068.
27. Dhanda AD, Creed TJ, Greenwood R, et al. Can endoscopy be avoided in the assessment of ulcerative colitis in clinical trials? *Inflamm Bowel Dis.* 2012;18:2056–2062.
28. US Department of Health and Human Services. *Ulcerative Colitis: Clinical Trial Endpoints—Guidance for Industry*. August 2016. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM515143.pdf. Accessed March 20, 2018.
29. Ng SC, Palo W, Blake A, et al. Vedolizumab clinical and post-marketing safety experience of opportunistic infections. *Gastroenterology*. 2017;152(Suppl 1):S575–S576. Abstract Su1865.