2. ABSTRACT

Full Study Title: Retrospective observational study on the effect of vedolizumab treatment on patients with inflammatory bowel disease and extraintestinal manifestations. The EMOTIVE study			
Phase:	Post-marketing/Phase IV	**Type:**	Observational
Number of Patients: 99		**Duration of Patient Participation**: 12 Months	
Number of Study Centres: The study was conducted from 16 sites in 5 countries (Israel [n=5], Switzerland [n=4], Denmark [n=2], Belgium [n=3] and Netherlands [n=2])		**Duration of Study**: 35 months	

Background and Rationale:

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is regarded as a systemic disorder not limited to the gastrointestinal tract, because many patients develop extraintestinal symptoms. There is a broad range of extraintestinal manifestations (EIMs) such as musculoskeletal, metabolic bone disease, mucocutaneous, ocular, hepatobiliary, vascular, or haematologic. EIM's may occur with or without a link to disease activity and affect about 50% of IBD patients over the course of their disease.

In the past three decades, the tumour necrosis factor-α (TNF-α) antagonist have revolutionised the treatment strategy in patients with IBD, including the management of patients with EIMs, which often share a pathogenic TNF-α dependent mechanism with IBD.

Vedolizumab (VDZ), a humanised monoclonal antibody that specifically recognises the α4β7 heterodimer, selectively blocks gut lymphocyte trafficking and has been an addition to the treatment armamentarium for IBD patients since 2014.

The current European Crohn's and Colitis Organisation (ECCO) guidelines (2017 and 2020) recommend VDZ for the treatment of UC and CD after conventional or anti-TNF failure.

A few studies have evaluated the efficacy of VDZ in the management of EIMs in IBD patients, showing more frequent resolution of EIMs among patients treated with VDZ compared to placebo. However, most of these studies had a small number of patients with active EIMs at baseline and were not primarily

aimed to study the effectiveness of VDZ on EIM. Thus, the evidence on the effectiveness of VDZ on EIMs in IBD patients is still scarce. Currently, more and more real-world cohort studies on VDZ are conducted which either include patients with EIM or are even focused on this subgroup of IBD patient.

Rationale:

Due to the gut-specific mechanism of action of VDZ, its effectiveness in the management of EIMs in IBD patients has remained a matter of evaluation. Evidence in this subpopulation of IBD patients is still relatively scarce. Therefore, real-world cohort studies specifically aimed at investigating the effectiveness of VDZ on EIM in IBD patients is of interest.

Thus, the aim of this retrospective observational study was to assess EIM resolution, clinical effectiveness, and safety in a cohort of patients with moderate to severe CD or UC and EIMs treated with VDZ under routine clinical practice.

Objectives:

Primary Objective:

To describe the percentage of patients treated with VDZ experiencing resolution of EIMs within 6 months post-treatment initiation.

Secondary Objectives:

- To describe the course and outcome of EIMs within 6 and 12-months post VDZ treatment initiation in terms of response to therapy
- To describe the time to resolution of EIMs post VDZ treatment initiation
- To describe the real-world clinical effectiveness of VDZ therapy in IBD at 14 weeks (post induction), 6 months and 12 months post-treatment initiation in this population
- To describe the percentage of patients treated with VDZ experiencing resolution of EIMs within 12 months post-treatment initiation
- To describe the percentage of patients treated with VDZ experiencing resolution of gut related EIMs within 6- and 12-months post-treatment initiation
- To describe treatment persistence rate with VDZ at 12-months post-treatment initiation
- To describe the safety events occurring during treatment with VDZ
- To describe the new-onset EIM conditions (chronic and acute) during the post-index event period, treatment and evolution

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Study Design: This was a non-interventional retrospective multi-national, multi-centre medical chart review study of patients with IBD and EIMs who initiated treatment with VDZ at minimum 6 months before chart abstraction initiation (Eligibility Period).

Index Date was defined as the date when VDZ treatment was initiated. Data collection spanned over two main periods anchored to the date of index event:

- **Pre-index event period**: Began on the date of diagnosis of UC/CD and ended one day prior to the date of index VDZ treatment initiation during the Eligibility Period
- **Post-index event period/follow-up period**: Began on the date of index VDZ treatment initiation during the Eligibility Period and ended at the date of chart abstraction initiation, lost to follow-up or death, whichever occurred earlier

Study Population:

The study population consisted of adult patients with IBD and EIMs who initiated treatment with VDZ during the defined Eligibility Period.

Inclusion Criteria:

Patient eligibility was determined according to the following criteria prior to entry into the study:

- The patient diagnosed with moderate to severe UC or CD documented on the medical records
- The patient ≥18 years of age at initiation of VDZ (index date)
- The patient presented, at least, one EIM documented on the medical records at maximum 2 months before VDZ treatment initiation and it had not been resolved by the time of initiation
- The patient received at least one dose of VDZ following standard practice for the treatment of IBD, attended at least one visit after induction and follow-up information was available for at least 6 months after VDZ initiation
- The patient, or when applicable, the patient's legally acceptable representative signed and dated a written, informed consent form and any required privacy authorisation prior to the initiation of any study procedures, when required as per local regulations

Exclusion Criteria:

Any patient who met any of the below mentioned criteria did not qualify for entry into the study:

- Index date occurred as part of an interventional clinical trial or patient participated in an interventional clinical trial during the follow-up period
- The patient was diagnosed with indeterminate/an unspecified type of IBD
- The patient initiated VDZ treatment as combination therapy with other biological agents

Patients were allowed to be included only once in the study.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study was the resolution of EIMs (defined as absence of EIM symptoms) within 6 months post-treatment initiation. Secondary endpoints for this study were EIM clinical response at 6 and 12 months after initiation, clinical remission and clinical response at 14 weeks and at 6 and 12 months after initiation, resolution of EIMs within 12 months post-treatment initiation, resolution of gut related EIMs within 6- and 12- months post-treatment initiation, persistence of treatment with VDZ at 12 months after initiation, and adverse events (AEs) during treatment with VDZ.

Data Sources and Measurements:

Site personnel were responsible for entering the data abstracted from the patient medical charts into an electronic data capture platform accessible through an internet connection. The data was stored in a secure data server located in France. Only server administrators were allowed to access to the server and its components.

The patients were identified in the database only by Study ID, Site ID, patient number, year of birth and gender. The coding for medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and AEs /reactions (MedDRA) was followed as per current standard coding instructions.

Statistical Methods:

The statistical analysis was conducted by IQVIA using SAS® statistical software: statistical analysis system (SAS) Enterprise Guide 6.1, SAS version 9.4 or higher; SAS Institute, Inc.; Cary, North Carolina.

The all patients enrolled set (ENR) was the analysis set used in the study and comprises of all patients who provided informed consent for this study and fulfil selection criteria.

Demographic and clinical characteristics of adult patients with IBD and EIMs treated with VDZ were described. The percentage of patients with resolution of EIMs within 6 months post-treatment initiation with VDZ were reported for the overall sample. Analyses were done per type of EIM, where possible, and globally, considering all EIMs together. Patients who discontinued VDZ prior to 6 months post-treatment initiation were included in the analysis of resolution of EIMs (lack of response was assumed). For those patients who did not complete a visit about 6 months post-treatment initiation with VDZ the last available outcome was carried forward to the measure at 6 months. Based on time of EIM resolution reported in clinical charts, a time to event analysis or survival analysis was performed. Kaplan-Meier curves were used to estimate time to EIM resolution per type of EIM, where possible, and globally considering all EIMs together.

Results:

Baseline Characteristics

A total of 99 patients were recruited in this study from 16 sites across 5 countries January 2018 and May 2020 (35 months). Of the total 99 recruited patients, 30 patients (30.3%) each were recruited from Israel and Switzerland; 19 (19.2%) from Denmark, 15 (15.2%) from Belgium and 5 patients (5.1%) were from the Netherlands.

Of the total 99 patients recruited in this study with IBD diagnosis, a greater number of patients had CD (N = 55; 55.6%) compared to UC (N = 44; 44.4%). Most of the patients recruited (93.8%; n = 91/99) were Caucasians (CD: 90.7% [n = 49/55]; UC: 97.7% [n = 42/44]) and the mean (SD) age of the overall population was 44 (14.7) years. The mean (SD) age of patients with CD was 45.6 (13.5) years and that of patients with UC was 42.0 (15.9) years. Overall, the proportion of female patients (64.6%; n = 64/99) was 1.8 times more than that of male patients (35.4%; n = 35/99) and it was similar across CD and UC groups. The mean body mass index (BMI) of the overall population (n = 85), was 24.1 (SD = 5.3; range = 15.4-50.0) kg/m^2. More than half of the patients (54.1%; n = 46/99) belonged to the normal BMI category. The BMI distribution was similar across the CD and UC patient groups.

Only about 20% of the patients (19.3%; n = 17/88) were reported as current smokers at index date (CD: 27.1%; n = 13/48; UC: 10.0%; n = 4/40). About one-fourth of patients were former smokers (25.0%; n = 22/88), with the majority (23.3%; n = 20/88) of them smoking for a span of more than a year. Nearly half of the patients were either occasional drinkers (49.4%; n = 39/79) or non-drinkers (48.1%; n = 38/79). A similar pattern of alcohol consumption was reported among CD and UC patient groups. Over 60% (65.6%; n = 61/93) of the patients were employed at index date.

The physician's assessment of disease severity was moderate or severe, in nearly 60% (58.9%; n = 33/56) and 20% (17.9%; n = 10/56) of patients, respectively. About half (51.5%; n = 51/99) of the patients did not have any chronic comorbidities; while the most frequent comorbidities affecting from 5% to 10% of patients were diabetes, hypertension, renal disease, and rheumatic disease. At index date, mean (SD) for Charlson comorbidity index score was 0.7 (2.0) for overall population, Harvey-Bradshaw Index (HBI) score for CD patients was 10.2 (4.1) and Partial Mayo Score (PMS) for patients with UC diagnosis was 5.8 (2.0).

The EIMs of articular manifestations was most frequently reported at index date, which included arthralgia (69.7%; n = 69/99), peripheral spondyloarthritis (21.2%; n = 21/99), axial spondyloarthritis

(10.1%; n = 10/99). Other EIMs reported less frequently included, erythema nodosum (7.1%; n = 7/99), primary sclerosing cholangitis (PSC) (6.1%; n = 6/99), oral aphthous ulcers (3%; n = 3/99) and uveitis (1%; n = 1/99). None of the patients had Sweet's syndrome, pyoderma gangrenosum or episcleritis reported at index date.

Prior to index date, the most frequent biological drug therapy included, infliximab (63.6%; n = 63/99) and adalimumab (32.3%; n = 32/99). Golimumab (6.1%; n = 6/99), certolizumab pegol (6.1%; n = 6/99), ustekinumab (5.1%; n = 5/99) and 'Other' (1.0%; n = 1/99) were also reported. About one-fourth (23.2%; n = 23/99) of the patients were biologic-naïve at the time of VDZ initiation. At index date, corticosteroids (36.4%; n = 36/99) followed by aminosalicylates (18.2%; n = 18/99), azathioprine (6.1%; n = 6/99) and 6-mercaptopurine (4.0%; n = 4/99) was IBD related concomitant non-biological drug therapy received by majority of the patients.

The majority of patients included (70.7%; n=70/99) received an initial administration of VDZ of 300 mg IV at 0, 2 and 6 weeks and then every 8 weeks, whereas one-fourth (23.2%) of the patients received one extra VDZ dose at 10 weeks prior to starting the regular administration during maintenance phase every 8 weeks. Over one-fourth (27.3%; n = 27) of patients reported changes in the VDZ treatment regimen within the 12 months of the follow-up period with a mean (SD) time to first treatment regimen change of 9.7 (6.9) months. The primary changes in treatment regimen included increased dosing frequency in over one-fifth (21.2%; n = 21/99) of the patients and very low percentage of patients with reduced dosing frequency (2.0%; n = 2/99) and increased dose was reported in 2.0% (n = 2/99) of patients. The reason for dose increase or increased dosing frequency was mainly IBD management related (partial treatment response [10.1%; n = 10/99] or lack of effectiveness [9.1%; n = 9/99]). EIM management related dose increase or increased dosing frequency was reported in very low proportion of patients (partial treatment response [2%; n = 2/99] and lack of effectiveness [1%; n = 1/99]).

<u>EIM Resolution at Month 6 and Month 12</u>

Overall, within 6 months and 12 months after index date, resolution of all EIMs was reported in about one-fifth (19.2%) and one-fourth (25.3%) of patients, respectively. Among the most frequently reported EIMs at index date, i.e. those related to articular manifestations, resolution at 6 and at 12 months was reported for 20.3% and 26.1% of patients with arthralgia, 28.6% and 33.3% of patients with peripheral spondyloarthritis, respectively. Other EIMs resolution at 6 and at 12 months was reported for 42.9% of patients, each with erythema nodosum;16.7% and 33.3% of patients with PSC (resolution defined as

normalisation of liver enzymes), respectively. Oral aphthous ulcers resolution at 12 months was reported in 33.3% of patients. The only patient presenting with uveitis at index date did not resolve neither at 6 nor at 12 months.

The median time to resolution of first EIM from VDZ initiation in both CD and UC was 0.5 months.

New Onset EIM Conditions – Concomitant Medications

For new onset EIMs appearing post-index date most commonly reported concomitant medications were pain killers (13.1%; n = 13/99; mainly COX-2 inhibitors [6.1%; n = 6/99]) followed by methotrexate in 4.0% of the patients.

Real-World Clinical Effectiveness Post VDZ Treatment in IBD

The clinical effectiveness post VDZ treatment initiation was assessed as clinical response and clinical remission at 14 weeks (± 2 weeks), 6 months (± 1 month) and 12 months (± 2 months) was available for 12 patients, 15 patients and 13 patients, respectively. From the available data, the clinical response was achieved at Week 14 (± 2 weeks), at 6 months (± 1 month) and at 12 months (± 2 months) in about one-third (33.3%; n = 4/12), one-fifth (20.0%; n = 3/15) and nearly one-fourth (23.1%; n = 3/13) of the patients, respectively.

Overall, clinical remission (per PMS or HBI score) was achieved at Week 14 (± 2 weeks), at 6 months (± 1 month) and at 12 months (± 2 months) in almost 60% (58.3%; n = 7/12), about half (46.7%; n = 7/15) and 30% (30.8%; n = 4/13) of the patients, respectively.

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Safety Analysis:

The AE data was collected from index date up to 18 weeks post VDZ treatment discontinuation or date of chart abstraction initiation (whichever occurred first). A total of 33 AEs (CD: 21 AEs; UC: 12 AEs) were reported during this study. The most frequently reported AEs were arthralgia (4.0%; n = 4/99). Other AEs reported in ≤2.0% patients included back pain, constipation, eczema, headache, bronchitis, dyspepsia, erythema, gastroenteritis, hypertension, muscular weakness, and paraesthesia. Most of the reported AEs with available data (96.3%; n = 26/27) were reported as non-serious with just one serious AE, pulmonary embolism, reported (3.7%; n = 1/27) in a patient with CD. This serious AE of pulmonary embolism was reported as recovered/resolved and was assessed as not related to VDZ treatment by the Investigator.

Discussion and Conclusions: In conclusion, this real-world multi-centre chart review study demonstrated the effectiveness and safety of VDZ for the management of EIMs in UC and CD patients, specifically showing good response rates in articular manifestations. Further prospective studies in larger populations are needed to confirm these findings.

Ethical and Regulatory Considerations:

This study was conducted in accordance with the approved protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Special attention was to be paid to data protection, following the EU directive on data protection (95/46/EC). The Sponsor and/or the appointed Contract Research Organisation (CRO) ensured that the protocol, any amendments and the patient information sheet/informed consent form were submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements. The Sponsor was responsible for meeting the International Conference on Harmonisation (ICH) requirement for yearly updates to the IECs/IRBs, if applicable.

According to applicable regulations, the appointed CRO or the Site Study Responsible notified or obtained approval from the relevant IEC/IRB for the protocol, any amendments and the patient information sheet/informed consent form.

In the event that a patient's written informed consent was required, the Site Study Responsible gave the patient (and if applicable, parent or legal guardian) oral and written information about the study in a form that the patient (and if applicable, the parent or legal guardian) could understand, and obtain the patient's (and if applicable, the patient's assent and the parent's or legal guardian's) written consent before collection of identifiable patient information (hereinafter referred to as personal data).