1. ABSTRACT

<table>
<tr><td colspan="4">Full Study Title: A Retrospective Observational Study to describe the Effectiveness and Safety of Vedolizumab With or Without Budesonide Induction Therapy Among Patients With Moderate to Severe Crohn’s Disease</td></tr>
<tr><td>Phase:</td><td>Post-marketing/Phase IV</td><td>Type:</td><td>Observational</td></tr>
<tr><td colspan="2">Number of Patients:
Targeted: 200
Actual: 123</td><td colspan="2">Duration of Patient Participation:
01 January 2015 - 31 January 2019</td></tr>
<tr><td colspan="2">Number of Study Centres:
Targeted: 21
Actual: 11</td><td colspan="2">Duration of Study:
August 2019 – December 2020</td></tr>
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Background and Rationale:

Crohn's disease (CD) is an idiopathic inflammatory disorder. It is influenced by genetics, the environment, and immunologic milieu. The incidence of this disease is increasing and treatment options are always evolving. The goal of medical therapy is to induce remission with medications, followed by the administration of maintenance medications to prevent a relapse of the disease. It is very important to understand the relationship between induction of remission and maintenance of remission, as there exists an overlap of medications used to induce and maintain remission. Generally, physicians first direct treatment to induce a remission that involves relief of symptoms and mucosal healing of the lining of the colon and then provide long-term treatment to maintain the remission. Treatment for CD depends on the location and severity of the disease, complications, and response to previous medical treatment when treated for recurring symptoms. The pharmacologic treatment of CD involves a wide array of agents with varying indications and mechanisms of action. These therapeutic agents can be classified into 5 groups namely: aminosalicylates, corticosteroids, immunosuppressive agents (e.g. azathioprine, 6-MP), biologic (antibody) agents, and antibiotics. Corticosteroids are used for the induction of remission, and should not be used to maintain remission, as they cannot help in mucosal healing and there is a major concern for the long-term side adverse effects of the use of steroids. Biologic therapies such as anti-TNF agents, VDZ or ustekinumab are indicated and recommended by the ECCO guidelines, for patients with moderately to severely active CD who are dependent or refractory to oral steroids and/or refractory to immunomodulators such as azathioprine or 6-MP as well as previous biologic therapies. Budesonide is a second-generation steroid which has selective localised effect, mainly on the terminal ileum and the right colon (proximal); and thus, leads to minimal systemic exposure and thus reduced risk of corticosteroid-related side effects. VDZ is a humanized monoclonal antibody, which binds α4β7 integrin heterodimer and subsequently blocks the interaction of α4β7 integrin with MAdCAM-1 which prevents leukocyte migration into affected tissue.

Currently, there is limited data on the combination of VDZ with any other medical therapies to induce a response or remission in patients with CD. Most of the data did not explore a 'de-novo' combination but included subpopulations of patients that were on either steroids and/or

other immunosuppressive therapies and VDZ was added due to ongoing active disease despite the therapy with steroids and/or immunosuppressives. Furthermore, given the fact that both budesonide and VDZ have a localized gut-selective effect, such a combination was hypothesized to potentially increase overall response rates and/or time to response in CD patients without systemic immunosuppressive side effects of other combinations such as systemically active corticosteroids or immunosuppressives.

The aim of this study was therefore to assess the real-world effectiveness and safety as well as the description of CD patient profiles following induction therapy using VDZ in combination with budesonide or VDZ as a montherapy.

Objectives:

Primary objectives

The primary objective of the present study was to assess the effectiveness in terms of the Crohn's Disease Activity Index (CDAI) patient-reported symptoms: abdominal pain (AP) and/or loose stool frequency (LSF) during induction therapy (baseline through to Week 14) in CD patients with moderately to severely active CD treated with either a combination of VDZ with budesonide or VDZ monotherapy.

Secondary objectives

1. To assess effectiveness in terms of AP and/or LSF at Weeks 2, 6 and 10 (or closest available prior to these timepoints) of an induction therapy using VDZ with budesonide or the VDZ monotherapy among patients with moderately to severely active CD.
2. To assess the time to clinical remission based on AP and/or LSF in moderately to severely active CD patients initiating induction therapy with VDZ and budesonide in combination or VDZ as a monotherapy.
3. To assess the safety profile through Week 14 of an induction therapy in patients on VDZ with budesonide or VDZ monotherapy in terms of the incidence and characteristics of AEs.
4. To describe the time to budesonide withdrawal (and reasons) through Week 14 among patients with moderately to severely active CD who received budesonide as part of the induction combination therapy with VDZ.
5. To describe the time to VDZ withdrawal (and reasons) through Week 14 among all patients initiating VDZ induction therapy with and without budesonide.
6. To compare clinical, biochemical and endoscopic assessment outcomes and previous treatment patterns for moderately to severely active CD patients treated with VDZ in combination with budesonide and those treated with VDZ monotherapy.

Exploratory objectives

1. To assess the effectiveness in terms of change in physician assessment of disease activity, change in CDAI, change in Harvey Bradshaw Index (HBI), clinical response and clinical remission according to CDAI and HBI scores at Weeks 2, 6, 10 and 14 of

an induction therapy with VDZ in combination with budesonide or VDZ monotherapy (if available).

2. To assess any changes in laboratory assessments measures (i.e., liver enzyme elevation, haemoglobin, faecal Calprotectin [fCal] and C reactive protein [CRP]), and endoscopic findings through Week 14 (or closest available prior to this timepoint) of an induction therapy of VDZ in combination with budesonide or VDZ monotherapy among patients with moderately to severely active CD (if available).
3. To describe the patient profile characteristics, effectiveness in terms of AP and/or LSF and safety in terms of AEs based on the dose of budesonide received during induction therapy.
4. To describe the safety profile depending on the induction regimen of VDZ received during induction therapy.

Study Design:

This was a retrospective, multi-national, multi-centre, medical chart review study in moderately to severely active CD patients who initiated VDZ induction therapy with VDZ in combination with budesonide or VDZ monotherapy between 01 Jan 2015 and 31 Jan 2019 inclusive (Eligibility Period).

Index Date was defined as the date of VDZ induction therapy (with or without budesonide) initiation. Data collection spanned 2 main periods anchored to the date of index event:

- **Pre-index Event Period**: Began on the date of diagnosis of CD and ended one day prior to the date of Index date.
- **Post-index Event Period**: Starting one day after the Index Date and ending at 14 weeks after Index Date, death or lost to follow-up, whichever came first.

Follow-up Period: From the Index Date to 14 weeks after the Index Date.

The study was planned to be conducted in 21 sites distributed across 3 countries (Belgium, Switzerland, and Israel).

Study Population: The study population consisted of adult patients (≥18 years of age) with moderately to severely active CD who were not previously treated with VDZ and had initiated VDZ monotherapy or VDZ in combination with budesonide for at least one week during the defined Eligibility Period between 01 Jan 2015 and 31 Jan 2019. Study patients had active disease at the time of VDZ initiation: reporting at least a moderate AP (AP ≥2) and/or mean daily LSF ≥4 for the previous 7 days.

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 (Medical Dictionary for Regulatory Activities [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 with SAS® Enterprise Guide 7.13. Descriptive statistics was used to summarise patient characteristics, clinical disease presentation, therapeutic regimens, and clinical outcomes (mean, standard deviation [SD], minimum, maximum, median, 25th and 75th percentile for continuous variables; count and proportion for categorical variables). A logistic regression model was used to identify the main factors associated with the decision to prescribe VDZ with budesonide vs VDZ monotherapy. The mean percentage change in AP and/or LSF from baseline through Week 14 + 3 was calculated for each treatment group. These study outcomes were assessed using the post-index visit closest to the Week 14 (allowing a maximum of 17 weeks after baseline visit).

Kaplan-Meier (KM) curves were used for descriptive time-to-event analyses (time to budesonide or VDZ discontinuation and time to clinical remission). For patients who did not complete the 14-week induction therapy or for whom treatment was changed (i.e., VDZ and or budesonide are discontinued, or another drug is added to the treatment originally prescribed at Week 0), the reason for treatment change was described and they were considered as treatment failure.

Results:

The study was conducted at 11 sites distributed across 3 countries (Belgium, Switzerland and Israel). A total of 123 patients (50 patients in VDZ with budesonide group and 73 patients in the VDZ monotherapy group) were included in the all patients enrolled set (ENR) and analysed in the study.

Sociodemographic Characteristics:

A total of 71 female patients (57.7%) and 52 male patients (42.3%) were enrolled in the study. Overall, the mean (SD) age of patients in the study was 44.2 (15.8) years. The mean (SD) body mass index (BMI) of patients was 24.3 (4.5) kg/m^2. The number and percentage of female patients were slightly higher in VDZ with budesonide group (32 females [64.0%]), compared to the VDZ monotherapy group (39 females [53.4%]). Age and BMI were similar in both the treatment groups.

Clinical Characteristics:

Overall, in over half of the patients (56.1%, n=69) no chronic comorbidities were reported. Among the patients with reported chronic comorbidities, the most frequently reported (in >10% of patients) among VDZ monotherapy group were as follows: hypertension (9 patients [27.3%]), rheumatic disease and gastric or peptic ulcers, reported in 5 patients (15.2%) each, diabetes and hypo/hyperthyroidism, reported in 4 patients (12.1%) each, and 'other' comorbidities were reported in 13 patients (39.4%). Among patients in the combination group (VDZ with budesonide), the most frequently reported (>10% of patients) chronic comorbidities were as follows: rheumatic disease (5 patients [23.8%]), depression (4 patients [19.0%]), hypertension, other skin disorder than those described in the list and gastric or peptic ulcers , reported in 3 patients (14.3%) each, and other comorbidities were reported in 13 patients (61.9%). The mean (SD) of the Charlson Comorbidity Index was 1.0 (1.8) in the overall population and was similar in both treatment groups, but the profile of reported comorbidities was slightly different according to the treatment group.

the majority of CD patients (102 [82.9%]) had a disease duration ≥2 years and the proportion of patients with a CD disease duration ≥2 years was higher in the VDZ monotherapy group (64 patients [87.7%]) compared to the combination group (38 patients [76.0%]).

At the index date, disease location according to Montreal classification was as follows; L1 terminal ileum 55 patients (51.9%], L2 colonic CD 18 patients (17.0%) and L3 ileocolonic CD 28 patients (26.4%). The most commonly (70 patients [66.0%]) reported disease behaviour was B1 (non-stricturing, non-penetrating), Physician rated disease activity at diagnosis revealed that 30 patients (24.4%) had moderate, 11 patients (8.9%) had severe and 9 patients (7.3%) had mild disease activity.

Various laboratory assessment parameters were available at index date. Faecal calprotectin was only available for 28 patients, and 22 of these patients (23.2%) had faecal calprotectin values >250 µg/g. In the VDZ monotherapy group there was a higher proportion and percentage of patients with faecal calprotectin values >250 µg/g than in the combination group (18 patients [29.5%] vs 4 patients [11.8%], respectively). Overall, a total of 27 patients (22.0%) presented with an extra-intestinal manifestations (EIMs) at index date. The most common EIMs at index date were arthralgia; 17 patients (63.0%), followed by peripheral spondylarthritis; 4 patients (14.8%), axial spondylarthritis; 4 patients (14.8%) and erythema nodosum; 3 patients (11.1%) patients. Overall, only 4 patients (3.3%) presented with perianal fistula at index date.

Prior and current therapies at index date:

The most common prior treatments received by patients for CD between the timepoint of diagnosis until 12 months prior to index date were immunomodulators; 86 (76.8%) patients (51 patients [73.9%] in the VDZ monotherapy group and 35 patients [81.4%] in the VDZ with budesonide group), followed by anti-TNFs agents; 79 (70.5%) patients (48 patients [69.6%] in the VDZ monotherapy group and 31 patients [72.1%] in the VDZ with budesonide group) and systemic corticosteroids; 73 (65.2%) patients (45 patients [65.2%] in the VDZ monotherapy group and 28 patients [65.1%] in the VDZ with budesonide group).

The most common type of prior surgery reported in patients with CD was ileocolonic resection with ileocolonic anastomosis (38 patients [64.4%]); reported in 24 patients (64.9%) in the VDZ monotherapy group and 14 patients (63.6%) in the VDZ with budesonide group.

The most common IBD-related treatments received by CD patients immediately preceding VDZ initiation were anti-TNFs agents, prescribed to 50 (59.5%) patients (32 patients [58.2%]

in the VDZ monotherapy group and 18 patients [62.1%] in the VDZ with budesonide group) and systemic corticosteroids received by 8 patients 9.5% (6 patients [10.9%] in the VDZ monotherapy group and 2 patients [6.9%] in the VDZ with budesonide group).

Adalimumab was the most common biologic received by a total of 40 patients (47.6%) within the 12 months prior to the index date (22 patients [40.0%] in the VDZ monotherapy group and 18 patients [62.1%] in the VDZ with budesonide group) followed by infliximab, received by 23 (27.4%) patients (19 patients [34.5%] in the VDZ monotherapy group and 4 patients [13.8%] in the VDZ with budesonide group). The most common reason for adalimumab discontinuation was lack of effectiveness for the management of CD which was observed in 33 patients (82.5%) followed by AEs, which were observed in 7 patients (17.5%). Similar trends for the reasons of discontinuation were observed across treatment groups.

The number of patients that received treatment with anti-TNFs at any time between CD diagnosis and index date was 65 (52.5%), 43 patients (58.9%) in the VDZ monotherapy group and 22 patients (44.0%) in the VDZ with budesonide group.

At index date, a total of 81 patients (65.9%) received 300 mg VDZ by intravenous infusion at 0, 2, 6, 10 and 14 weeks (46 patients [63.0%] in the VDZ monotherapy group and 35 patients [70.0%] in the VDZ with budesonide group); and a total of 41 patients (33.3%) overall received 300 mg VDZ by intravenous infusion at 0, 2, 6 and 14 weeks (27 patients [37.0%] in the VDZ monotherapy group and 14 patients [28.0%] in the VDZ with budesonide group). VDZ treatment discontinuation prior to Week 14 was only reported in 2 patients (1.6%) of the overall population of which, 1 patient in the VDZ monotherapy group discontinued VDZ due to lack of effectiveness for the management of CD and the other patient in the VDZ with budesonide group discontinued VDZ treatment due to an AE. Budesonide discontinuation was reported for 34 patients (68.0%) in the VDZ with budesonide group. The most common reason for discontinuation was classical tapering schedule for budesonide (29 patients [85.3%]).

Univariable and Multivariable Logistic Regression Analysis:

The univariable and multivariable logistic regression analysis were performed to identify the main factors associated with the decision to prescribe VDZ in combination with budesonide

(VDZ monotherapy used as reference). Univariable logistic regression analysis results showed that the use of VDZ in combination with budesonide was less common in patients whose weight was in the range of 60-74 kg range compared to low weight patients (OR=0.31; 95% CI: 0.11-0.89), in patients with a CD disease duration of >2 years (OR=0.45; 95% CI: 0.17-1.16), and in patients who had received 1 prior biologic treatment versus biologic treatment naïve patients (OR=0.40; 95% CI: 0.16-0.98). Weight was used as a factor, in analysis instead of BMI as height data was not available for all patients. Combining all these potential predictors, the multivariable regression analysis showed that patients whose weight was in the range of 60-74 kg range were less frequently prescribed VDZ in combination with budesonide (OR=0.28; 95% CI: 0.09-0.91). The result regarding the use of 1 prior biologic drug compared with no prior use of biologic treatment was close to reaching statistical significance (OR=0.39; 95% CI: 0.15-1.03).

Effectiveness at Week 14:

The mean percentage change in AP and LSF from baseline to Week 14 according to treatment received at index date was measured, showing a reduction in AP and LSF. The mean (SD) percentage change in AP from baseline to 14 weeks in the overall study population was -39.8 (27.5) % and was similar across the treatment groups. The mean (SD) percentage change in the LSF from baseline to 14 weeks in the overall patients study population was -48.3 (69.1) % and was slightly higher in the VDZ with budesonide group (-49.6 [71.4] %) compared to the VDZ monotherapy (-47.5 [68.2] %).

Effectiveness at Weeks 2, 6 and 10:

Overall, the mean (SD) percentage change in AP from baseline to 2, 6 and 10 weeks was -16.9 (26.3) %, -29.9 (30.5) % and -35.6 (31.2) %, respectively. The reduction in mean (SD) percentage change in AP from baseline to Week 2 in the VDZ monotherapy group (-19.5 [27.9] %) was higher than the VDZ with budesonide group (-11.7 [22.4] %). The mean (SD) percentage change in AP from baseline to 6 weeks was also higher in the VDZ monotherapy group (-35.2 [28.1] %) compared to the VDZ with budesonide group (-21.6 [32.7] %). Change in AP observed from baseline to 10 weeks was similar in both treatment groups.

The mean (SD) percentage change in LSF from baseline to 2, 6 and 10 weeks in overall sample was reported as -14.7 (60.7) %, -19.1 (80.0) % and -28.9 (81.9) %, respectively. The mean (SD) percentage change observed in LSF from baseline to 2 weeks was higher in the VDZ with budesonide group (-28.5 [44.2] %) compared to the VDZ monotherapy (-8.2 [66.8] %). However, the mean (SD) percentage change in LSF from baseline to 6 weeks was higher in the VDZ monotherapy group (-22.7 [72.6] %) compared to -12.6 (93.3) % in the VDZ with budesonide group. The change observed in LSF at Week 10 was similar in both treatment groups.

Clinical Remission:

Clinical remission was defined based on a composite score of 2 symptoms reported by the patients: AP (≤1) and LSF (≤3). A total of 50 out of 70 patients treated with VDZ monotherapy (71.4%) and 34 out of 50 patients treated with VDZ with budesonide (68.0%) achieved clinical remission based on AP and LSF. Median time to clinical remission over time was slightly higher in the VDZ with budesonide group (95 days with 95% CI: 70.0-98.0) compared to the VDZ monotherapy group (91 days with 95% CI: 70.0-98.0).

Clinical, Biochemical and Endoscopic Assessments Outcomes:

At the end of this induction therapy, lesions were reported in the rectum and ileum in 1 patient (50%) in the VDZ monotherapy group. The type of lesions included presence of inflammation without ulceration, deep ulceration and superficial ulceration which was reported in 1 patient (50%) each, in the VDZ monotherapy group

Time to Budesonide Withdrawal:

In the analysis of time to budesonide withdrawal, a total of 49 patients were included. The number of events (budesonide discontinuations) captured in VDZ with budesonide was 33 (37.3%) and 16 patients (32.7%) were being censored due to continuation with budesonide treatment at end of data collection. The median time to budesonide withdrawal was estimated at 91 days with the 95% CI between 72.0-100.0.

Safety:

Overall, a total of 30 patients (24.4%) reported at least one AE over a period of 14 weeks. The most commonly reported AEs as per system organ class (SOC) included gastrointestinal disorders (12 patients [40.0%]) followed by infections and infestations SOC (10 patients [33.3%]). The AE with highest frequency under gastrointestinal disorders was worsening of CD and was reported by 3 patients (50%) in the VDZ monotherapy group. Majority of patients (25 [83.3%]) recovered from AEs in the study. The AE presented by 4 patients (13.3%) were severe.

Overall, a total of 9 patients (7.3%) in the study reported serious adverse events (SAEs). The most commonly reported SOC with SAEs was infections and infestations (5 patients [55.6%]) followed by gastrointestinal disorders (3 patients [33.3%]). All 3 patients reported worsening of CD under gastrointestinal disorders SOC. Two patients (22.2%) experienced at least one severe SAE. A total of 7 patients (77.8%) were reported to have recovered from SAEs. AE profile was also assessed in patients stratified by budesonide dose (≥9 mg) and VDZ regimen.

Discussion and Conclusions: The current study allowed to describe the profile of patients with moderately to severely CD treated with VDZ monotherapy or VDZ with budesonide, in terms of clinical practice. The study showed that a high percentage of patients had prior use of anti-TNF before VDZ initiation in both the treatment groups. There were differences in number of patients in different variables e.g., the number of female patients were higher in VDZ in combination with budesonide group compared to VDZ monotherapy group and the number of patients with hypertension were higher in VDZ monotherapy group compared to VDZ in combination with budesonide group, but the study did not allow to identify clinical drivers (i.e., disease location) for the use of combination therapy of VDZ with budesonide. Effectiveness was assessed in the study in terms of change in AP and LSF symptoms. The reduction in symptoms was reported at different timepoints in both study groups. The reduction in the mean (SD) percentage change in AP presented by patients from baseline to Week 14 was similar in both VDZ monotherapy group (-39.7 [29.2]) and the VDZ with budesonide group (-40.0 [25.2]). On the other hand, mean (SD) percentage change observed in the LSF from baseline to 14 weeks was slightly higher in the VDZ with budesonide group (-49.6 [71.4] %) compared to the VDZ monotherapy group (-47.5 [68.2] %). The patients in both study groups achieved high remission rates at 14 weeks, which are comparable to those reported in prior real-world studies for VDZ treatment. The current study has several limitations that must be considered in order to generalize the study results, but nonetheless, provides relevant information, especially in the subgroup of patients treated with VDZ and budesonide due to the existing data gap. The study provides a base for the conduct of further prospective studies in larger populations that could confirm and substantiate the findings of this study.

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), International Society for Pharmacoepidemiology GPP guideline and any local regulations. Special attention was to be paid to data protection, following the European Union directive on data protection (95/46/EC). Takeda and IQVIA ensured that the protocol, any amendments and the patient information sheet/informed consent form (ICF) were submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements. Takeda was responsible for meeting the International Conference on Harmonisation requirement for yearly updates to the IECs/IRBs, if applicable. According to applicable regulations, IQVIA or the Site Study Responsible notified or obtained approval from the relevant IEC/IRB for the protocol, any amendments and the patient information sheet/ICF.

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).