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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

2.0 SYNOPSIS

Sponsor: Takeda Biopharmaceuticals India Pvt. Ltd.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Kynteles 300 mg injection	Volume:	
Name of Active Ingredient: Vedolizumab	Page:	

Study Title: A Multicenter, Single-arm, Open-label, Phase 4 Study to Evaluate the Safety and Efficacy of Vedolizumab in Indian Patients With Ulcerative Colitis and Crohn's Disease

Investigators and Study Centers:

The study was conducted at 17 centers across India. The details are provided in Table S.a.

Table S.a Investigators and Centers Details

S. No.	Center No.	Principal Investigator	Address
1	*	Dr.	India.
2		Dr.	India.
3		Dr.	India.
4		Dr.	India.
5		Dr.	, India.
6		Dr.	India.
7		Dr.	India.
8		Dr.	India.
9		Dr.	India.
10		Dr.	India.
11		Dr.	India.
12		Dr.	India.

13	[redacted]	Dr. [redacted]	[redacted] India.
14	[redacted]	Dr. [redacted]	[redacted] India.
15	[redacted]	Dr. [redacted]	[redacted] India.
16	[redacted]	Dr. [redacted]	[redacted] India.
17	[redacted]	Dr. [redacted]	[redacted] India.
18	[redacted]	Dr. [redacted]	[redacted] India.

***Site [redacted] did not recruit any patients and the study was conducted across 17 centers.**

Publication (reference): None

Enrollment Period: 29 December 2021 to 15 September 2022

Date of first patient enrolment: 29 December 2021

Date of last patient last visit: 02 February 2024

Study Phase: Phase 4

Objectives:

Primary Objective

To assess the safety of vedolizumab intravenous (IV) in patients with Ulcerative Colitis (UC) or Crohn's Disease (CD) in India.

Secondary Objective

To assess the efficacy of vedolizumab IV in patients with UC or CD in India.

Methodology:

This was an open-label, single-arm, prospective, Phase 4 study conducted at 17 sites in India to evaluate the safety and efficacy of vedolizumab 300 mg IV infusion in patients with moderately to severely active UC or CD.

A total of 150 patients with moderately to severely active UC or CD who demonstrated inadequate response to, loss of response to, or intolerance to either conventional therapy or tumor necrosis factor-alpha (TNF-α) antagonist were planned to be enrolled in this study. At least 30% of the total recruited patients were required in each UC or CD group.

The total duration of the study for each patient was up to 74 weeks, consisting of a 4-week screening period (Days -28 to -1), a 46-week treatment period, and a 16-week (ie, 5 vedolizumab half-lives) safety follow-up period after the last dose of study drug. Additionally, patients were required to participate in a long-term follow-up safety survey through a telephonic visit at 6 months after the last dose of the study drug ie, 8 weeks after the 16-week follow-up visit.

Patients who met all the inclusion criteria and none of the exclusion criteria were administered with vedolizumab 300 mg IV at the site. Patients were required to visit the site for dosing at Weeks 0 (Day 1), 2, 6, 10 (CD-patients who did not show a response received a dose at Week 10), 14, 22, 30, 38, and at Week 46.

Patients were evaluated for safety and efficacy from initiation of vedolizumab until 46 weeks (the treatment period), or until discontinuation of vedolizumab, whichever occurred earlier. All patients were observed further for safety assessments for 16 weeks after the study treatment period or discontinuation of vedolizumab for post-treatment adverse event (AE) monitoring.

In addition, information was collected on events such as infections resulting in hospitalizations, cancer, UC- or CD-related surgeries, and development of progressive multifocal leukoencephalopathy (PML) during the long-term follow-up safety survey through the telephonic visit at 6 months after the last dose ie, 8 weeks after the 16-week follow-up visit.

Number of Patients (Planned and Analyzed):

Planned: 150 patients (at least 30% of the total in each UC and CD group)

Analyzed: 150 patients (102 in UC and 48 in CD group)

Diagnosis and Criteria for Inclusion:

Main Inclusion Criteria

- Adult patients aged 18 to 65 years both inclusive.
- Patients who were diagnosed with moderately to severely active UC or CD for at least 3 months prior to screening with a Full Mayo Score of 6-12 for UC or a Harvey Bradshaw Index (HBI) score of ≥8 for CD at the time of enrollment.
- Patients who demonstrated an inadequate response to, loss of response to, or intolerance to either conventional therapy or TNF-α antagonist.

Main Exclusion Criteria

- Any evidence of an active infection during Screening.
- Patients who received any biologics within 60 days (or 5-half-lives of the drug) of enrollment.
- Patients who had prior exposure to vedolizumab, natalizumab, efalizumab, or rituximab.

Investigational Product, Dose, and Mode of Administration:

Study Drug: Vedolizumab IV

Dose:

Induction Phase: 300 mg at Weeks 0 (Day 1), 2, and 6

Maintenance Phase: 300 mg at Weeks 14, 22, 30, 38, and 46

No dose modifications were allowed during the study.

Note:

Patients with CD who did not show a response received a dose (300 mg IV) at Week 10.
Patients who showed a decrease in response received a 4 weekly vedolizumab 300 mg IV.

Route of Administration: Intravenous

Reference Product(s), Dose and Mode of Administration, Lot Number:

Not applicable

Duration of Treatment: 46 weeks

Criteria for Evaluation:

The planned primary and secondary outcome measures of the study were:

Primary Endpoint

- Incidence of AEs, serious AEs (SAEs), AEs of special interest (AESIs), adverse drug reactions (ADRs), and unexpected ADRs.

ADR was defined as AE for which there was at least a reasonable suspicion of a causal relationship between an AE and the study treatment.

Secondary Endpoints

- Proportion of patients with clinical response at Weeks 14, 30, and 46 in UC and CD groups.
- Proportion of patients with clinical remission at Weeks 14, 30, and 46 in UC and CD groups.
- Proportion of patients with vedolizumab discontinuation in UC and CD groups.
- Proportion of patients with mucosal healing/endoscopic response at Week 46 in UC and CD groups.
- Change in the patient-reported Quality of Life (Short Inflammatory Bowel Disease Questionnaire [SIBDQ]) from baseline to Weeks 14, 30, and 46.

Statistical Methods:

Primary safety endpoints: All safety analyses were performed for the safety analysis set (SAS). The number and percentage of patients with AE, treatment-emergent AEs (TEAEs; defined as any AEs, occurring at or after the initial administration of study drug or the AE that had worsened since baseline), ADR, AEs leading to discontinuation, AESIs, and SAEs that occurred on or after the first dose date and up to 6 months after the last dose date of the study drug, were summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 system organ class (SOC), high-level term (HLT), and preferred term (PT) overall, by severity, and by relationship to study drug. No statistical inference was performed on AEs.

Exposure-adjusted incidence rates (EAIR) and 95% confidence intervals (CIs) were calculated by Poisson method for each safety endpoint based on the total number of incident events and person-time at risk.

Secondary efficacy endpoints: All efficacy analyses were performed for the SAS and per-protocol analysis set (PPAS). The binary efficacy endpoints were summarized using number and percentage at each visit by UC and CD groups and 95% CIs by the exact Clopper-Pearson method were provided. Drop-outs/missing data for binary efficacy endpoints were considered as non-responders, no other imputation method was used in this study.

For the continuous efficacy endpoint (ie, SIBDQ), the patients-reported quality of life (QoL) score of actual, change from baseline and percentage change from baseline were summarized descriptively by using number of non-missing observations (n), mean, standard deviations (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum value at each visit by UC and CD groups.

Results:

Patient Disposition: A total of 215 patients were screened in the study; of these, 151 patients met the eligibility criteria. As the target study sample size was 150, 1 patient was not enrolled in the study despite being eligible.

Of 150 (69.8%) patients enrolled, 102 (47.4%) were patients with UC and 48 (22.3%) were patients with CD. Of the enrolled patients, 111 patients (51.6%; 76 patients with UC and 35 patients with CD) completed the study and a total of 39 (18.1%) patients were terminated early. The common reasons for discontinuation were voluntary withdrawal (18 [8.4%] patients), pre-treatment event (PTE) or AE (9 [4.2%] patients), lost to follow-up (6 [2.8%] patients), lack of efficacy (5 [2.3%] patients) and 1 subject discontinued the study due to other reason.

Demographic Data: Overall, the median age of the patients was 36 years (range: 18.0 to 63.0 years). The median age was 39 years (range: 18.0 to 63.0 years), in patients with UC and 31 years (range: 18.0 to 59.0 years) in patients with CD. The proportion of male patients (83 [55.3%]) was numerically higher when compared to female patients (67 [44.7%]) and the overall median body mass index (BMI) of the patients was 20.41 kg/m^2 (range: 13.0 to 46.3 kg/m^2).

Baseline characteristics: The prior biologics received by the patients included infliximab and adalimumab in a total of 15 (10.0%) patients, including 5 (4.9%) patients from the UC group and 10 (20.58%) patients from the CD

group. Large intestine was the most common disease site reported in majority of patients (140, overall) including all 102 patients in UC and 38 patients in CD. The baseline mean (SD) Full Mayo Score in patients with UC was 8.64 (1.488) and the mean (SD) HBI score in patients with CD was 10.90 (2.469).

Primary Outcome Measure: Safety was the primary objective of the study and the safety results are described below:

- Overall, 83 (55.3%) patients (UC: 54 [52.9%] patients; CD: 29 [60.4%] patients) experienced at least 1 AE, among which 81 (54.0%) patients experienced at least 1 TEAE (UC: 52 [51.0%] patients; CD: 29 [60.4%] patients).
- Overall, the majority of the patients experienced mild AEs (overall: 72 [48.0%] patients; UC: 46 [45.1%] patients; CD: 26 [54.2%] patients), followed by moderate AEs (overall: 12 [8.0%] patients; UC: 7 [6.9%] patients; CD: 5 [10.4%] patients) and severe AEs (3 [2.0%] patients in UC only). These severe AEs included pulmonary tuberculosis, hypertension, and rectal adenocarcinoma. Among these severe AEs, pulmonary tuberculosis and hypertension were considered to be related to the study drug by the Investigator, while rectal adenocarcinoma was considered to be unrelated to the study drug.
- The majority of patients experienced TEAEs that were not related to vedolizumab as determined by the Investigator (overall: 77 [51.3%] patients; UC: 48 [47.1%] patients; CD: 29 [60.4%] patients). At the end of study (EOS), AEs were resolved in most of the patients (overall: 71 [47.3%] patients; UC: 47 [46.1%] patients; CD: 24 [50.0%] patients).
- Overall, the incidence of SAEs was observed in 8 (5.3%) patients (UC: 6 (5.9%) patients and CD: 2 (4.2%) patients). All the SAEs were TESAEs. The most commonly reported criterion for SAE was hospitalization/prolonged hospitalization. These SAEs included small intestinal obstruction (in 2 [1.3%] patients), colitis ulcerative, intestinal obstruction, cholelithiasis, pulmonary tuberculosis, tuberculous pleurisy, and rectal adenocarcinoma, each reported in 1 (0.7%) patient. Among these SAEs, pulmonary tuberculosis, and tuberculous pleurisy were considered to be related to the study drug, while other SAEs were considered to be unrelated to the study drug by the Investigator. Almost all the SAEs except 1 (rectal adenocarcinoma) were resolved at the EOS. The patient reported with rectal adenocarcinoma was withdrawn from the study.
- No cases of PML and death were reported in the study.
- Overall, 5 (3.3%) patients experienced at least 1 ADR (related to study drug as determined by Investigator). All these ADRs were observed in patients with UC. These ADRs included cytomegalovirus infection, pulmonary tuberculosis, tuberculous pleurisy, arthralgia, pruritus, and hypertension (1.0 [1.0%] patient, each). Cytomegalovirus infection, pulmonary tuberculosis, and tuberculous pleurisy were the unexpected ADR reported. None of the patients in the CD group reported any ADR.
- Overall, 4 (2.7%) patients experienced at least 1 AESI. All these AESIs were observed in patients with UC. These AESIs included pulmonary tuberculosis, tuberculous pleurisy, rectal adenocarcinoma, and hypertension (1 [0.7%] patient, each). None of the patients in the CD group reported any AESI.
- The study drug was withdrawn due to AEs in 8 (5.3%) patients (6 [5.9%] patients with UC and 2 [4.2%] patients with CD). The AEs that led to vedolizumab discontinuation included anal fistula, intestinal obstruction, cytomegalovirus infection, fungal skin infection, pulmonary tuberculosis, tuberculous pleurisy, rectal adenocarcinoma, pneumonitis, and hypertension. Of these, the events of cytomegalovirus infection, pulmonary tuberculosis, tuberculous pleurisy, and hypertension were related to the study drug as determined by the Investigator.
- Few patients reported abnormal clinically significant (CS) laboratory values that were reported as AEs. The events include anemia, iron deficiency anemia and hypoproteinaemia, all events were not related to study drug as determined by Investigator. No major CS changes were observed in electrocardiogram

(ECG). In terms of vital signs, 2 (1.3%) patients experienced hypertension and the event of pyrexia were reported in 14 (9.3%) patients. All the events of pyrexia were resolved at the EOS.

Secondary Outcome Measures: Efficacy was the secondary objective of the study and the efficacy results are described below:

Clinical response and clinical remission were assessed in 136 patients (UC: 91 and CD: 45) at Week 14, 123 patients (UC: 81 and CD: 42) at Week 30, and 120 patients (UC: 82 and CD: 38) at Week 46.

- Clinical response: In the UC population, clinical response was achieved by 56 (54.9%) patients at Week 14, 64 (62.7%) patients at Week 30, and 75 (73.5%) patients at Week 46. In the CD population, the response was achieved by 35 (72.9%) patients at Week 14, 34 (70.8%) patients at Week 30, and 33 (68.8%) patients at Week 46.

- Clinical remission: In the UC population, clinical remission was observed in 40 (39.2%) patients at Week 14, 44 (43.1%) patients at Week 30, and 53 (52.0%) patients at Week 46. In the CD population, the remission was observed in 23 (47.9%) patients at Week 14, 22 (45.8%) patients at Week 30, and 27 (56.3%) patients at Week 46.

- Vedolizumab discontinuation: A total of 39 (26.0%) patients discontinued vedolizumab. Of these, 26 (25.5%) patients belonged to the UC group and 13 (27.1%) patients belonged to the CD group.

- The reason for vedolizumab treatment discontinuation included voluntary withdrawal (18 patients) followed by PTE or AE (9 patients), lost to follow-up (6 patients), lack of efficacy (5 patients), and other reason (1 patient).

- Mucosal healing/Endoscopic response: By Week 46, endoscopy was an optional procedure so, the mucosal healing/endoscopic response assessment was done only in a total of 42 patients (UC: 32 and CD: 10). Overall, 27 (18.0%) patients showed mucosal healing; of which 23 (22.5%) patients belonged to UC group and 4 (8.3%) patients belonged to CD group. Endoscopic response was observed in a total of 28 (18.7%) patients; 22 (21.6%) in UC group and 6 (12.5%) in CD group. As the proportion was calculated considering the full SAS population and drop-outs/missing values were imputed as non-responders, this impacts the proportion rate.

- Patient-reported Quality of Life (SIBDQ): The QoL of patients was assessed by SIBDQ score after completion of 14, 30, and 46 weeks of vedolizumab treatment. At Week 14, Week 30 and Week 46, the score was recorded in 136 patients (UC: 91 and CD: 45), 123 patients (UC: 81 and CD: 42), and 118 patients (UC: 81 and CD: 37), respectively. In the UC population, the median absolute change from baseline in SIBDQ score was 5.00 (range: -20 to 42) at Week 14, 12.00 (range: -12 to 48) at Week 30, and 13.00 (range: -12 to 45) at Week 46. In the CD population, the median absolute change from baseline in the SIBDQ scores was 5.00 (range: -19 to 36) at Week 14, 6.50 (range: -26 to 36) at Week 30, and 13.00 (range: -32 to 44) at Week 46.

Conclusion: The study results showed that the safety profile of vedolizumab 300 mg IV administration in patients with UC and CD was generally similar and consistent with previous clinical trials and real-world studies of vedolizumab. No new significant safety findings were identified in this study. Therefore, treatment with vedolizumab can be considered safe, with manageable AEs.

The efficacy data of vedolizumab 300 mg in patients with UC and CD demonstrated efficacy in improving the clinical condition and QoL of the patients who were non-responsive to available conventional therapies and/or TNF-α antagonists with minimum serious adverse effects.

Overall, vedolizumab represents a valuable treatment option for managing UC and CD, with benefits in clinical outcomes and patient's QoL.

Final Date: 04 October 2024