NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: Post-Marketing Observational Cohort Study of Patients With Inflammatory Bowel Disease (IBD) Treated With CT-P13 in Usual Clinical Practice (CONNECT-IBD)

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Keywords: inflammatory bowel disease, CONNECT-IBD, infliximab, Crohn's disease, ulcerative colitis, CT-P13.

Rationale and Background: CT-P13 is an infliximab biosimilar expected to provide similar quality, efficacy, and safety to Remicade® (infliximab, Janssen Biotech, Inc). It was expected that CT-P13 will be considered in varied settings for inflammatory bowel disease (IBD) patients with Crohn's disease (CD) and ulcerative colitis (UC), including biologic naive patients and as an alternative in stable patients receiving Remicade. This abstract describes the final analysis for the, non-interventional, observational cohort study conducted to characterise adult patients with CD and UC in a real-world setting taking CT-P13 as their first biologic or who switched to CT-P13 from stable Remicade in accordance with the locally-approved label.

Research Question and Objectives: The primary objectives were to characterise the population and drug utilisation patterns and to explore the long-term safety profile of CT-P13 for CD or UC in the context of standard of care Remicade. The secondary objective was to assess the effectiveness of CT-P13 in the treatment of patients with CD or UC and the exploratory objective was to evaluate patient-reported outcomes (PROs) including quality of life (QoL), work productivity and healthcare resource utilisation (HRU) in patients treated with CT-P13 for CD or UC.

Study Design: This study was a multi-national, multi-centre, observational cohort study of patients with CD or UC who were treated with CT-P13 (or Remicade for the smaller standard of care cohort). Patients being initiated or treated with Remicade constituted a smaller although substantial standard of care cohort and were expected to provide context for the CT-P13 cohort. The decision to treat with CT-P13 or Remicade was made at the discretion of the physician in accordance with usual care practice independent of and before the decision to enrol patients in the study. In compliance with the observational methodology of the study, there was no study visit mandated. Patient's visit schedules followed local standard of care, typically coinciding with the schedule of infusions of infliximab, with any additional visits at the treating physician's discretion.

Setting: The study took place in countries in which CT-P13 and Remicade were authorised for the treatment of CD and UC. A heterogeneous sample of approximately 150 sites was planned to be recruited in approximately 13 countries. In order to meaningfully describe expected subgroups in the heterogeneous patient population under treatment, approximately 1900 of the patients enrolled were to be included in the CT-P13 cohort. It was expected that

depending on local formulary regulations or institutional policies, there may have been sites that prescribed either Remicade or CT-P13 but not both. Sites that only utilised Remicade were not recruited to participate in the study.

Subjects and Study Size, Including Dropouts: The planned sample size was 2500, with approximately 1900 of the patients enrolled to be included in the CT-P13 cohort and 600 patients in the Remicade cohort. Patients being initiated or treated with Remicade constituted a smaller although substantial standard of care cohort and were expected to provide context for CT-P13.

Variables and Data Sources: Primary outcome variables were patient demographic, clinical and diagnostic characteristics (relevant medical history for CD or UC including prior treatments); CT-P13 treatment, CT-P13 or Remicade switches and reasons for switch, CT-P13 dose frequency, augmentation/reduction and reasons for changes and; co-therapy(ies) for the management of CD or UC. Adverse events (AEs), serious adverse events (SAEs) or adverse events of special interest (AESIs), and events in a special situation (eg, pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure) during patient study participation.

Secondary outcome variables were clinical assessment of CD and UC disease activity (evaluated using the Harvey-Bradshaw Index (HBI) for patients with CD, Partial Mayo Scoring System for patients with UC, Montreal classification index for patients with CD and for patients with UC, and fistula drainage assessment index for patients with CD); laboratory and imaging results related to the treatment or assessment of CD or UC.

Exploratory outcomes variable were QoL as measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ); changes in the work productivity and activity impairment (WPAI) as measured by the WPAI Questionnaire and HRU relating to the management of CD or UC, any SAEs or AESIs.

The safety analysis set (SAS) was defined as all patients who received at least 1 dose of study drug during the study observation period. The full analysis set (FAS) was defined as all patients who received at least 1 dose of study drug during the study observation period and had at least 1 postdose assessment of any of the effectiveness endpoints. The primary endpoints were evaluated using SAS and the secondary endpoints and the exploratory endpoints were evaluated using FAS.

Case report forms (CRFs) were designed to gather the data needed for the study that were collected as part of standard of care. Patients completed a set of PRO instruments on paper during their standard of care visits at enrolment and then approximately every 3 months (based on the visit that was closest in time to 3 months after the last visit) thereafter. Patient's medical record information, any relevant diagnostic reports, and the paper-based PROs and patient-reported HRU survey were the source documents for study data collection.

Results:

Primary Outcome Results:

Disposition and Demographic Characteristics: A total of 2565 patients were enrolled; of which 1694 had CD, 870 had UC and 1 patient had a missing diagnosis. Out of the 2565 patients enrolled, 22 (0.8%) patients were not treated (18 [1.0%] with CD and 3 [0.3%] with UC). All the 2543 (99.1%) patients treated were included in the SAS and 2535 (98.8%) patients were included in FAS. Out of the total patients treated; 1522 (59.3%) patients were treated with CT-P13, 494 (19.2%) patients were treated Remicade; 358 (13.9%) patients switched from Remicade to CT-P13, 67 (2.6%) patients switched from CT-P13 to Remicade and 102 (3.9%) patients switched the study drug multiple times.

A total of 592 (38.9%), 107 (29.9%), 117 (23.7%), 11 (16.4%), and 21 (20.6%) patients discontinued from treatment phase of the study in the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment groups, respectively. During the follow-up phase, 395 (26.0%), 67 (18.7%), 98 (19.8%), 7 (10.4%), and 14 (13.7%) patients discontinued the study in the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment groups, respectively.

The majority of patients were White and non-smokers without medical history of cancer, fistulating disease, stoma or surgery for CD or UC. The majority of patients (94%) in the Remicade treatment group were already documented prior infliximab at the time of study enrollment. Approximately 30% of patients in the CT-P13 treatment group were infliximab naive at the time of study enrollment.

Drug Utilisation Pattern: More than 45% of patients in all the treatment groups had an infusion frequency of once every 8 weeks, as reported at baseline; 804 (52.8%), 198 (55.3%), 247 (50.0%), 42 (62.6%), 47 (46.0%) patients in the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment group, respectively.

Duration of Drug Exposure During the Observation Period: In the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment group, the median (range) duration from first treatment to study completion or treatment discontinuation was 14.0 (0, 27.6) months, 19.6 (0, 25.3) months, 17.7 (0, 24.5) months, 16.6 (2.1, 23.8) months and 20.1 (6.15, 25.2) months, respectively.

Treatment interruptions were reported in 301 (19.8%), 61 (17.0%), 63 (12.8%), 4 (6%), and 18 (17.6%) patients in the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment group, respectively.

Safety Endpoints: The percentage of patients who experienced treatment-emergent adverse events (TEAEs) was balanced between the CD and UC disease groups (601/1676 [35.9%] patients for CD versus (vs) 328/867 [37.8%] patients for UC).

A higher percentage of patients experienced TEAEs that were considered treatment-related in the UC disease group compared to the CD disease group (228/867 [26.3%] patients for UC vs 302/1676 [18.0%] patients for CD). The majority of patients experienced TEAEs which were of mild to moderate severity for all the treatment groups and by disease type.

The percentage of patients experienced treatment-emergent SAEs and TEAE of special interest (TEAESI) was high in the CD disease group compared to the UC disease group (272/1676 [16.2%] patients with CD vs 109/867 [12.6%] patients with UC and 202/1676 [12.1%] patients with CD vs 92/867 [10.6%] patients with UC). In total 294/2543 (11.6%) patients had at least 1 TEAESI. In the CD disease group; 202/1676 (12.1%) patients had at least 1 TEAESI while in the UC disease group 92/867 (10.6%) patients had at least 1 TEAESI.

A higher percentage of patients discontinued treatment and the study due to AEs in the UC disease group compared to the CD disease group (210/867 [24.2%] patients with UC vs 254/1676 [15.2%] patients with CD discontinued treatment due to AEs and 44/867 [5.1%] patients with UC vs 47/1676 [2.8%] patients with CD discontinued study due to AEs). The majority of study drug discontinuations were due to AEs of drug ineffective, hypersensitivity and infusion related reaction.

There were 7 deaths reported in the study (4 patients in the CT-P13 treatment group, 2 patients in the Remicade dose group and 1 patient in the switched from Remicade dose group). Out of the 7 deaths; 6 were in the CD disease group.

Secondary Outcome Results (Effectiveness Analysis):

Clinical Assessment of Disease Activity: At Month 6, 870/1516 (57.4%), 261/358 (72.9%), 312/492 (63.4%), 51/67 (76.1%) and 70/102 (68.6%) patients reported remission in the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment group, respectively. A total of 166/1516 (10.9%), 19/358 (5.3%), 23/492 (4.7%), 3/67 (4.5%) and 4 /102 (3.9%) patients reported relapse at Month 6; in the CT P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment group, respectively.

At Month 24, 386/1516 (25.5%), 148/358 (41.3%), 184/492 (37.4%), 23/67 (34.3%) and 39/102 (38.2%) patients reported remission in the CT-P13, switched from Remicade to CT-P13, Remicade, switched from CT-P13 to Remicade and multiple switchers treatment groups, respectively. A total of 38/1516 (2.5%), 9/358 (2.5%), 7/492 (1.4%), 1/67 (1.5%), and 4/102 (3.9%) patients reported relapse at Month 24; in the CT P13, switched from Remicade to CT-P13, Remicade, switched from CT P13 to Remicade and multiple switchers treatment group, respectively.

The percentage of patients with remission and relapse at Months 6, 12, 18 and 24 for each treatment group were consistent with historical data for infliximab.

Crohn's Disease Activity (Harvey-Bradshaw Index): The percentage of patients in clinical remission at baseline was higher for both the CT-P13 and Remicade treatment groups (62.5%

and 70.7%) for CD patients when compared to the percentage of patients with disease activity. For the CT-P13 treatment group, at least 50% of patients achieved clinical remission and improvement measured by disease activity at Month 6 and 12 and at least 40% in Month 18 and for the Remicade treatment group, at least 45% of patients achieved clinical remission and improvement measured by disease activity at Month 6, 12 and 18.

Ulcerative Colitis Activity (Partial Mayo Scoring System): The percentage of patients in clinical remission at baseline was lower (30.9%) in the CT-P13 and was higher (57.6%) in the Remicade treatment group for UC patients when compared to the percentage of patients with disease activity. For the CT-P13 treatment group, at least 50% of patients achieved clinical remission and improvement measured by disease activity at Month 6 and 12 and at least 40% in Month 18 and for the Remicade treatment group, at least 45% of patients achieved clinical remission and improvement measured by disease activity at Month 6, 12 and 18.

Montreal Classification Index for CD: The extent of disease activity for patients with CD was evaluated by the Montreal classification index. Improvements in disease location, including perianal disease, and disease behavior was observed over time across treatment groups. Overall, the improvement in disease activity for CD patients was observed in the majority of post-baseline timepoints for each treatment group.

Montreal Classification Index for UC: The extent and severity of disease activity for patients with UC was evaluated by the Montreal classification index. The majority of patients were classified with more extensive UC (E3) and with mild or moderate severity at baseline. Improvements in extent of disease and severity by Montreal classification were observed over time across treatment groups.

Fistula Drainage Assessment Index for CD: The fistula drainage assessment index was used to assess the improvement or remission of the disease activity of CD with a history of fistulating disease.

Laboratory Results Related to the Treatment or Assessment of CD or UC: Laboratory evaluations of C-reactive protein (CRP) and fecal calprotectin for the FAS were performed at baseline and at 6, 12, 18 and, 24 months postdose. The mean (standard deviation [SD]) change from baseline for both CRP and fecal calprotectin for all IBD patients improved for the majority of treatment groups at Month 6, 12, 18 and 24, respectively.

Exploratory Outcome Results:

Quality of Life Measured by Short Inflammatory Bowel Disease Questionnaire: The mean SIBDQ score change from baseline in the CT-P13 group increased by (mean change ±SD): 1.98±10.9, 3.06±11.8, 4.88±11.6 and 5.01±12.3 at Month 6, 12, 18 and 24, respectively. The mean SIBDQ score change from baseline in the Remicade treatment group decreased by (mean change ±SD): -0.56±8.7 at Month 6 and an increased by 0.37±9.0 at Month 12, 0.61±9.3 at Month 18 and 0.98±9.5 at Month 24.

Work Productivity and Activity Impairment Questionnaire: WPAI was assessed based on the 4 components, time missed from work (absenteeism), impairment while working (presenteeism), overall work impairment, and impairment of daily activities (activity impairment). For those employed, the WPAI questionnaire was used to assess absenteeism, presenteeism and overall work impairment and, for all patients, activity impairment. The mean (SD) change from baseline for all the components of WPAI for all IBD patients improved for the majority of the treatment groups at Month 6, 12, 18 and 24, respectively.

Discussion:

The aim of this study was to assess the long-term safety and effectiveness of CT-P13 in the context of standard of care utilisation of Remicade, in the treatment of patients with CD or UC in real-world clinical practice. Population characteristics and prior biologic therapy analyses indicated differences between the CT-P13 and the Remicade treatment groups. The majority of patients (94%) in the Remicade treatment group had received prior Remicade (infliximab) at the time of study enrollment while in the CT-P13 treatment group, approximately 30% of the patients were infliximab naive and 19.2% of patients were biologic naive at the time of study enrollment.

The duration of drug exposure during the observation period was expected for each treatment group.

Safety profiles (including SAEs and AESIs) for each treatment group were consistent with the expected safety profile of infliximab and did not identify significant new safety information to change the benefit-risk profile of CT-P13. The rates observed for all AESIs for each treatment group were expected based on Remicade summary of product characteristics and Remsima/Inflectra Risk Management Plan.

Differences in baseline remission status between the CT-P13 and Remicade treatment groups were observed by disease type; however, the effectiveness endpoint results for each treatment group were also consistent with prior reports of Remicade. For the CT-P13 treatment group, the percentage of patients in clinical remission at baseline was higher (62.5%) for CD patients based on HBI and lower (30.9%) for UC patients based on Partial Mayo score when compared to the percentage of patients with disease activity.

Improvements of disease locations and behavior of disease for CD patients, as well as, for extent and severity of disease for UC patients were observed over time based on Montreal classification. The exploratory endpoints results demonstrated that treatment with CT-P13 showed improvement in quality of life based on SIBDQ and work-related outcomes based on WPAI. Additionally, available data for the clinical assessments of disease activity, and laboratory results indicated improvement over time with treatment of CT-P13.

Recognising that this was a non-interventional, observational study, there were some limitations or potential biases inherent in this study design: survivor bias, selection bias and the risk of systematic longer follow-up period in the Remicade treatment group (given the higher probability of current use). Additionally, due to the observational nature of this study, limited details were captured in the CRF, including many details related to AEs.

For patients who switched therapies, the timing of switch may have occurred during the actual study period; thus, confounding the interpretation for the drug utilization, safety and effectiveness endpoints. Given the historic availability of Remicade safety and effectiveness information, the observation groups in the study might have included different numbers of patients. Therefore, the estimation of the true incidence of AEs is supported by different statistical powers, according to those subgroup sizes. The width of the confidence intervals around the estimated incidence rates might differ between subgroups (wider with Remicade).

Consequently, the findings could be difficult to compare or the comparison might not be clinically meaningful. Events might occur in within 1 treatment group, but the comparison group might be too small to determine if the differences across the subgroups (CD vs UC) were significant. Historically available information for Remicade is utilised to provide additional context. However, the findings from this study were descriptive and not inferential in nature, due to the study nature and design.

Marketing Authorization Holder: Europe MA EEIG

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