the Italian Group for the study of Inflammatory Bowel Disease

Study title: Effectiveness and safety of switching from a first JAKi to subsquent JAKi in patients with ulcerative colitis: a real-life multicentre cohort study

Study Acronym: JAKi

Protocol version: 2.0 **Date: 16/09/2024**

Sponsor: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

AUTHORIZATIONS AND SIGNATURES

Study Title **Effectiveness and safety of switching from a first JAKi to subsquent JAKi in patients with ulcerative colitis: a real-life multicentre cohort study**

AGREEMENT

This document is confidential and belongs to the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). The information is confidential and is to be used only in connection with matters authorized IG-IBD, and no part of it is to be disclosed to others without prior written permission from the IG-IBD.

This document, however, can be made known to the designated Ethics Committee, or representatives authorized by the Investigator or the Health Authority provided that they are bound to its confidentiality.

The Principal Investigator's signature below confirms his agreement to this protocol and provides the necessary guarantees that:

1.This study will be conducted following all the clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000 with Explanatory note paragraph 29 from Washington 2002 and paragraph 30 from Tokyo 2004) and current legislation regarding clinical studies.

2. No partial or final data (written or verbal) will be published without prior agreement between the Investigator and the IgIBD

PRINCIPAL INVESTIGATOR SIGNATURE

Printed name:

Institution:

Signature _____ Date_____

ROLES AND RESPONSIBILITIES

Principal Investigator	Name Phone: Fax: e-mail:
Sponsor:	Phone: Fax: e-mail:
Study Coordinator:	Name Surname Phone: Fax: e-mail:
Statistician:	Name Surname Phone: Fax: e-mail:

Study Title

Effectiveness and safety of switching from a first JAKi to subsequent JAKi in patients with ulcerative colitis: a real-life multicentre cohort study

Sponsor: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

Principal Investigator: Dott. Marco Mendolaro, S.C. Gastroenterologia – AO Mauriziano, Torino

Protocol version: v 2.0 16/09/2024

Background and rationale

In recent years the therapeutic armentarium for inflammatory bowel disease (IBD) has been expanding, and Janus Kinase inhibitors (JAKi) are a new class of oral therapies for the treatment

of moderate-severe ulcerative colitis (UC). Three JAKi were approved for the treatment of UC in Italy and showed similar efficacy and safety: tofacitinib (an inhibitor of JAK1 and JAK3), and upadacitinib and filgotinib (more selective inhibitors of JAK1). Although there is no evidence that differences in affinity influence response to JAKi, based on previous experience with cycling of TNFi, a second JAKi is often used in case of intolerance or failure to the first JAKi.
There are a few clinical data of comparative effectiveness in real life limited to upadacitinib cohorts of patients previously treated with tofacitinib.

Aims of the study

The main objective of this study is to assess the effectiveness and safety of a second JAKi after a first JAKi treatment failure, in patients with ulcerative colitis.
Secondary objectives will include the analysis of several clinical covariates potentially associated to the outcomes of subsequent JAKi courses, among which response and reason for stopping the first JAKi.

Methods

1. **Study design**

   This is a 12-month observational, multicenter, prospective study. A retrospective part is planned to include patients who have already started a second JAKi less than 12 months before inclusion, after a first line JAKi course.

   Patients are treated and monitored according to usual clinical practice, and drugs are used according to their RCP. The study design includes an enrollment phase and a prospective follow-up observation of 12 months during which clinical, biochemical, endoscopic information will be recorded. Patients included in the prospective-only enrollment will be cumulated to the patients retrospectively included (since the drug became commercially available, e.g. since September 2023). For such patients (retrospectively enrolled and therefore already on therapy), basal clinical, biochemical and endoscopy data will be retrospectively retrieved with chart abstraction.

2. **Patient enrollment**

   Inclusion criteria:

   Every patient with established diagnosis of UC according to standard criteria, aged ≥ 18 years receiving (according to usual clinical practice) a second JAKi after a previously treatment with a first JAKi stopped for intolerance, failure or drug holiday will be eligible. All concomitant therapies will be admitted. These inclusion criteria are equally applied for the retrospective part of the study as stated before.

   Exclusion criteria:

   Patients unwilling or unable to give informed consent to the study. Patients meeting criteria for acute severe ulcerative colitis (ASUC) will also be excluded. History of Crohn's Disease (CD) or IBD-U. Presence of ostomy. Second JAKi started for an indication different from UC (inactive disease at second/third JAKi start, e.g. for Rheumatologic / Dermatologic manifestation).

3. **Endpoints**

   Primary endpoints:

- Treatment persistency at week 52 (t3) defined as percentage of patients continuing second JAKi as maintenance treatment through week 52 (ITT and LOCF analysis)
- Safety up to week 52 (any AEs / SAEs / AEs of special interest)

Secondary endpoints:

- Clinical remission after JAKi switch at week 8 (t1), 26 (t2), and 52 (t3) defined as a partial mayo score (PMS) ≤2.
- Clinical response at week 8 (t1), 26 (t2), and 52 (t3) defined as a decrease in PMS of ≥3 points and ≥30% from baseline, plus either a decrease in the rectal bleeding sub score of ≥1 point or an absolute rectal bleeding sub score of 0 or 1.
- Steroid-free clinical remission at t3 defined as remission without the need of any kind of systemic steroids
- Endoscopic remission at t3 defined as Mayo endoscopic sub-score (MES) ≤1
- Biochemical remission (CRP and/or fecal calprotectin) at t2 and t3 defined as C-reactive protein <5 mg/l and fecal calprotectin level < 250 ug/g
- Colectomy rates

Secondary endpoints (prospective phase):

- Resolution of bowel urgency (quantitative assessment with NRS score) recorded at week 8 (t1), 26 (t2), and 52 (t3)
- Improvement of quality of life (QoL) assessment with IBDQ at week 26 (t2) and 52 (t3)

Safety outcomes:

Specific reporting of:

- Any adverse events
- Serious adverse events are defined as any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent disability according to European Medicines Agency definition
- There will be a focus on opportunistic Infections (principally Herpes Zoster infections), thrombo-embolic events and major adverse cardiovascular events (MACE)

4. Study assessments and procedures

- T0 (baseline visit): at the beginning of the induction period of the second or third JAKi treatment, general information regarding the patient and the disease will be collected (or retrospectively abstracted): gender, age, weight, smoking status, disease duration, disease extent (according the Montreal Classification for UC), disease activity by Partial Mayo Score Index (PMS), endoscopy activity (evaluated with a colonoscopy or rectosigmoidoscopyperformed within 3 months before the beginning of the second JAKi), concomitant EIMs, FC and CRP levels, bowel urgency (quantitative assessment with NRS score in prospective phase), QoL (assessment with IBDQ in prospective phase), previous and concomitant UC treatments, concomitant steroid treatment, first JAKi stopped and second JAKi started, reason for stopping the first JAKi (primary failure/secondary failure/intolerance), possible Herpes Zoster vaccination (type of vaccine/date of vaccination/completion of vaccination schedule)
- T1 (week 8 ± 2 weeks): clinical status will be re-evaluated with clinical examination (as per usual clinical practice) if an objective examination is needed (or data will be retrospectively abstracted). Assessment of bowel urgency with NRS score (prospective-only enrollment). At this time the need for continued induction therapy and drug dosing will be assessed.

- T2 (week 26 ± 4 weeks): the clinical status will be re-evaluated with clinical examination if an objective examination is needed (or data will be abstracted). Assessment of bowel urgency with NRS score and QoL with IBDQ (prospective-only enrollment). FC and/or CRP levels will be recorded as per clinical practice. Drug dosing will be assessed. Concomitant steroid therapy will be recorded.
- T3 (week 52 ± 4 weeks): the clinical status will be re-evaluated with clinical examination if an objective examination is needed (as per usual clinical practice). Assessment of bowel urgency with NRS score and QoL with IBDQ (prospective-only enrollment). FC and/or CRP levels will be recorded. If an endoscopy evaluation (with colonoscopy or rectosigmoidoscopy) was/will be carried out as per usual clinical practice, data will be reported. Concomitant steroid therapy will be recorded.

5. Statistical plan

Exploratory analyses will be carried out. Continuous variables are going to be reported as median with 95% confidence intervals (95%CI), while categorical variables as frequence and percentage. The Chi-square, or Fisher's exact test when appropriate, and the Mann-Whitney test will be used for categorical and continuous variables, respectively. The rate of therapy discontinuation over time will be calculated separately for each treatment group by computing the Kaplan Meier survival curves, under intention to treat (ITT) and last observation carry forward (LOCF) assumptions. The effectiveness of the second JAKi by clinical remission in the two groups (PMS <2 vs PMS>2) is calculated by Chi-square or Fisher's exact test at week 8 (T1), week 26 (T2), week 52 (T2). An univariate analysis and then eventually a multivariate analysis will be performed in order to identify predictor factors of response. P-values less than 0.05 will be considered to be statistically significant.

The focus of the study is mainly on exploratory description of the outcomes of subsequent JAKi courses after a first course, with no pre-specified subgroup analysis or possibility to compare to previous external cohorts. Nonetheless the goal is to enroll, within one year, 150 to 200 patients for main effectiveness measures to be correctly evaluated and to guarantee a minimal sample size for subgroups comparisons.

6. Ethical considerations

The study will be conducted in accordance with the Standards of Good Clinical Practice, with the ethical principles deriving from the Helsinki Declaration and the current legislation on observational studies. The observational study and the related documentation will be presented to the competent Ethical Committee.

7. Data management and protection

All records identifying the patient will be kept confidential and, to the extent permitted by applicable laws and regulations, will not be made publicly available. The PI, co-investigators, and personnel involved in the trial will comply with the GCP principles regarding the storage, processing, and dissemination of sensitive data. Patient names will be kept confidential. Only the patient number will be recorded in the electronic Case Report Form (eCRF) using the IGIBD RedCap

system. Study findings stored on a computer will adhere to local data protection laws. Patients will be informed in writing that representatives of the sponsor, Institutional Ethics Committee (IEC), or Regulatory Authorities may inspect their medical records to verify the collected information. All personal information made available for inspection will be handled with the utmost confidentiality and in accordance with local data protection laws. Patients will also be informed that non-identifiable information regarding the study will be posted on clinicaltrials.gov. If the results of the trial are published, the patient's identity will remain confidential. The investigators will maintain a list to enable the identification of patient records. Data storage will be under the responsibility of the PI.

References

- Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcer- ative colitis: results from the phase 3, multicentre, double-blind, randomised trials. *Lancet.* 2022;399(10341):2113-2128
- Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376:1723–1736
- Feagan BG, Danese S, Loftus EV Jr, et al.. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet* 2021;397:2372–84
- Leo Boneschansker, Ashwin N. Ananthakrishnan. Comparative Effectiveness of Upadacitinib and Tofacitinib in Inducing Remission in Ulcerative Colitis: Real-World Data. Clinical Gastroenterology and Hepatology 2023;21:2427–2429
- C. Radia , R. George. JAK inhibitor safety in Inflammatory Bowel Disease: real-world data comparing the effect of JAK inhibitors on blood parameters and their clinical significance. *Journal of Crohn's and Colitis*, Volume 18, Issue Supplement_1, January 2024
- Shuhei Hosomi. Efficacy of Upadacitinib As a Second-line JAK Inhibitor in Ulcerative Colitis: A Case Series. July 2024 Internal Medicine 63(13)
- Dubinsky MC, Shan M, Delbecque L, et al.. Psychometric evaluation of the Urgency NRS as a new patient-reported

outcome measure for patients with ulcerative colitis. *J Patient Reported Outcomes* 2022;6(1):1–15

- Yarlas A., Maher S., Bayliss M., Lovley A., Cappelleri J.C., Bushmakin A.G., DiBonaventura M.D. The Inflammatory Bowel Disease Questionnaire in Randomized Controlled Trials of Treatment for Ulcerative Colitis: Systematic Review and Meta-Analysis. *J. Patient-Cent. Res. Rev.* 2020;7:189–205. doi: 10.17294/2330-0698.1722