the Italian Group for the study of Inflammatory Bowel Disease

**Study title: Upadacitinib: Personalized Goals for Remission and Disease Evaluation in Patients with Crohn's Disease.**

**Study Acronym: UPGRADE-CD**

**Protocol version: 1.0** **Date: 08/01/25**

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

## ROLES AND RESPONSIBILITIES

| | |
|---|---|
| **Principal Investigator** | Name Surname: Brigida Barberio<br>Phone: 0498212893<br>e-mail: brigida.barberio@unipd.it |
| **Co-PI** | Name Surname: Edoardo Savarino<br>Phone: 0498217749<br>e-mail: edoardo.savarino@unipd.it |
| **Sponsor:** | IGIBD<br>e-mail: ctm@igibd.it |
| **Study Coordinator:** | Name Surname: Greta Lorenzon<br>Phone: 0498218717<br>e-mail: greta.lorenzon@unipd.it |

**Title: UPGRADE-CD: Upadacitinib: Personalized Goals for Remission and Disease Evaluation in Patients with Crohn's Disease.**

**Abstract** Crohn's Disease (CD) poses significant challenges due to its unpredictable course and severe complications, such as frequent hospitalizations and surgeries. Effective early management is essential to prevent disease progression and reduce reliance on corticosteroids. This study evaluates Upadacitinib, a selective JAK1 inhibitor, for CD management. The primary objectives are to measure the percentage of participants achieving clinical remission using the Harvey-Bradshaw Index (HBI) and endoscopic response at 12 months. Secondary objectives include assessing clinical response, steroid-free remission, deep remission, endoscopic remission, transmural healing, radiologic response, fistula healing, and resolution of extra-intestinal manifestations (EIMs) at 3, 6, and 12 months. The study will also evaluate changes in CRP and fecal calprotectin levels and identify predictors of deep remission. Conducted as a multicenter, observational study starting in December 2024, the research will track CD patients on upadacitinib for up to 12 months, collecting data on HBI scores, fecal calprotectin, CRP levels, endoscopic findings, radiologic assessments, fistula outcomes, and hospitalization rates.Statistical analyses will determine the drug's efficacy and identify predictors of treatment response. This study aims to provide real-world evidence on upadacitinib's effectiveness, refine treatment strategies, and enhance patient care, ultimately improving outcomes and quality of life for individuals with CD.

## State of the Art and Scientific Rationale

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease characterized by persistent inflammation in the gastrointestinal tract [1]. This condition significantly impacts patients' quality of life due to its association with severe complications, including frequent hospitalizations, surgical interventions, an increased risk of colorectal cancer, and overall disability [1]. Effective management of CD is crucial, particularly when initiated early in the disease course, to mitigate the risk of relapses and serious complications [2]. Current treatment strategies for CD include a range of medications, from corticosteroids and immunosuppressants to biologics and small molecules targeting specific inflammatory

pathways [3]. However, despite the availability of these treatments, randomized clinical trials (RCTs) have revealed that only about half of the patients achieve clinical remission [4]. Furthermore, the efficacy of these treatments often declines over time, with many patients experiencing a relapse within a year of initiating therapy [4]. This underscores the need for ongoing research and novel therapeutic approaches to better manage the disease. Recent advancements in understanding the pathophysiology of CD have highlighted the role of the Janus kinases (JAK)-STAT signaling pathway in mediating inflammation [5–7]. The JAK family, comprising JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), is instrumental in transmitting signals from various cytokine receptors through the STAT pathway. This signaling cascade plays a critical role in regulating T-cell proliferation, differentiation, and B-cell activation, all of which contribute to the inflammatory process observed in CD [8]. Key cytokines involved in this pathway, such as IL-6, IL-12, and IL-23, are known to drive disease activity in CD. In this context, upadacitinib, a selective JAK1 inhibitor, has emerged as a promising therapeutic agent for treating moderate to severe CD [9]. Upadacitinib received marketing authorization based on robust evidence from clinical trials, including the pivotal 12-week induction studies U-EXCEED and U-EXCEL, and the 52-week maintenance study U-ENDURE [9]. These trials demonstrated that upadacitinib effectively induced and maintained clinical remission in patients with moderate to severe active CD. The phase 3 RCTs for upadacitinib established its efficacy in achieving clinical remission and endoscopic improvement, and other crucial endpoints [9]. The results highlighted that upadacitinib not only improved clinical outcomes but also offered sustained benefits over a 52-week period.

The efficacy of oral small molecules in patients with fistulizing CD is still under study [10]. However, data from a subgroup analysis of two phase 3 upadacitinib trials are promising. A significant proportion of patients treated with upadacitinib 45 mg at week 12 showed complete resolution of drainage compared to placebo (47.7% vs 9.1%, $p = 0.002$) [11]. However, this benefit was not sustained during the maintenance period with either upadacitinib 15 mg or 30 mg compared to placebo [12]. A recent systematic review and meta-analysis evaluated the efficacy of pharmacological therapies specifically targeting fistulizing CD, encompassing 38 RCTs that assessed various treatment options. Among the therapies evaluated, oral small molecules, including upadacitinib demonstrated a significant effect on inducing fistula response, with a pooled risk ratio (RR) of 2.56 (95% CI

1.18–5.53), indicating that these agents markedly improve fistula closure rates compared to placebo

Despite the promising results from RCTs, real-world data (RWD) is essential for understanding the effectiveness and safety of upadacitinib in everyday clinical practice and at this moment are rather scarce. A recent real-world effectiveness study involving 93 patients, have shown that while upadacitinib demonstrates high initial treatment persistence and clinical remission rates, outcomes tend to decline over time. Specifically, 87.1% of patients continued treatment at 12 weeks, but this figure dropped to 62.8% by 52 weeks [13]. Similarly, clinical remission rates decreased from 64% to 38% over the same period. Adverse events were reported in 40% of patients, with 12% experiencing serious complications. The rationale for conducting a real-world study on upadacitinib in secondary and tertiary hospitals across Italy is rooted in the need to extend beyond the controlled environment of RCTs to understand the long-term efficacy and safety of this treatment. RCTs provide essential initial evidence, but RWD is crucial for capturing variations in treatment outcomes and adverse events that may not emerge in trial settings. A real-world study will offer insights into upadacitinib's effectiveness across a diverse patient population with varying comorbidities and complex disease presentations. Additionally, it will help reveal how upadacitinib integrates into existing treatment regimens.

## Objectives and Specific Working Hypotheses

### Primary objectives

**1. Percentage of Participants Achieving Clinical Remission per HBI at 12 months**

Clinical remission is defined as a HBI score of less than 5.

**2. Percentage of Participants Achieving Endoscopic Response at 12 months**

Endoscopic response is characterized by a greater than 50% decrease in the Simple Endoscopic Score for Crohn's Disease (SES-CD) from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease

## Secondary objectives

1. **Percentage of Participants Achieving Clinical Response at 3, 6, and 12 months**

   Clinical response is defined as a decrease of at least 3 points in HBI from baseline.
2. **Percentage of Participants with Clinical Remission per HBI at 3 and 6 months**

   Clinical remission is defined as a HBI score of less than 5.
3. **Percentage of Participants with Steroid-Free Clinical Remission at 3, 6, and 12 months**

   This measures participants who were not taking corticosteroids at least 3 months prior to the assessment and achieved clinical remission per HBI (HBI score of less than 5).
4. Endoscopic response is characterized by a greater than 50% decrease in the SES-CD from baseline, or or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease
5. **Percentage of Participants Achieving Endoscopic Remission at 3, 6, and 12 months**

   Endoscopic remission is defined as an SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable
6. **Percentage of Participants Achieving Endoscopic Response at 3 and 6 months**

   Endoscopic response is characterized by a greater than 50% decrease in the SES-CD from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease
7. **Percentage of Participants Achieving Deep Remission at 3, 6, and 12 months**

   Clinical remission is defined as a HBI score of less than 5. Endoscopic remission is defined as an SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable
8. **Percentage of Patients Achieving Steroid-Free Deep Remission at 6 and 12 months**

   This measures participants who discontinued corticosteroid use at least 3 months prior to the assessment and achieved clinical remission based on the HBI combined with endoscopic remission, defined by SES-CD.
9. **Percentage of Participants with Hospitalizations Due to CD By Month 12**

10. **Percentage of Participants with Resolution of Extra-Intestinal Manifestations (EIMs) at 3, 6, and 12 months**

    Resolution is defined as the absence of EIMs for participants who had EIMs at baseline.

11. **Percentage of Patients Achieving Transmural Healing at 3, 6 and 12 months**

    Transmural healing is assessed via CT scan, MRI enterography, or intestinal ultrasound, defined as a bowel wall thickness (BWT) ≤ 3 mm with normal parietal contrast enhancement or color Doppler signal (CDS), or absence of hyperemia.

12. **Percentage of Patients Showing Response to Radiological Exams at 3, 6 and 12 months**

    Response is defined as a decrease in BWT by 25% from baseline or by 2.0 mm, or greater than 1.0 mm with a decrease in parietal contrast enhancement or in CDS assessed by the modified Limberg score of one grade.

13. **Percentage of patients with external closure of fistula openings at 3, 6, and 12 months among those with fistula openings at baseline.**

    This endpoint measures the proportion of patients with external closure of fistula openings at 3, 6, and 12 months among those who had fistula openings at baseline.

14. **Percentage of patients with complete resolution of draining at 3, 6, and 12 months among those with fistula draining at baseline under gentle compression.**

    This endpoint evaluates the percentage of patients who achieve complete resolution of drainage from fistulas at **3, 6, and 12 months** among those with fistulas draining at baseline under gentle compression.

    Fistulas will be categorized as follows:

    - **Draining Enterocutaneous Fistulas:** Classified as draining when there is observable drainage upon gentle compression.

    **- Rectovaginal Fistulas:** Classified as draining based on either the presence of drainage during physical examination or relevant clinical symptoms (e.g., passage of rectal material or flatus from the vagina).

15. **Percentage of patients with ≥ 50% reduction in draining at 3, 6, and 12 months among those with fistula draining at baseline under gentle compression.**
16. **Change in C-Reactive Protein (CRP) at 3, 6 and 12 months.**

17. **Change in Fecal calprotectin at 3, 6 and 12 months.**
18. **Identification of Clinical, Endoscopic, or Radiologic Predictors of Deep Remission at 12 months** .
19. **Comparison Between the Efficacy Of Upadacitinib, as Assessed According to The Primary Endpoint Of The Study, When Used As Second, Third Or Fourth Line of Biological Treatment.**
20. **Number of Participants with Adverse Events (AEs) .**

## Methodology

### Study design

#### Overall study design

This multicenter, prospective and retrospective observational study will include patients who meet the specified inclusion and exclusion criteria. We will enroll consecutive patients with CD who have started treatment with Upadacitinib, starting from December 2024.

#### Study duration and milestones

The study will last 12 months from the first patient enrolled, for patient recruitment. Each subject will participate for a maximum of 12 months.

### Methods: Participants, interventions and outcomes

#### Eligibility criteria

#### Inclusion criteria

The participants must fulfill the following criteria for participating in the study:

- **Age:** At least 18 years old.
- **Diagnosis:** A confirmed diagnosis of CD according to the ECCO guidelines, established at least 3 months [14] prior to study enrollment.
- **Prior Treatment:** Documented failure or intolerance to at least one of the following treatments:
    - Oral corticosteroids
    - Azathioprine or 6-mercaptopurine
- **Current Treatment:** Initiation of Upadacitinib therapy for CD based on clinical practice indications (primary loss of response, secondary loss of response, or intolerance to previous therapy).

- **Informed Consent:** Willingness to provide written informed consent to participate in the study.

### Exclusion criteria

1. Age < 18 years.
2. Patients with diagnosis of indeterminate IBD or Ulcerative Colitis.
3. Refusal to sign written informed consent certifying the willingness of the subject to participateto the study.

**a. Treatment dosage:**

**Updacitinib Treatment:**

- **Induction Phase:**

- **Dosage**: 45 mg
- **Frequency**: Once daily
- **Duration**: 12 weeks
    - **Maintenance Phase:**
- **Standard Dosage**: 15 mg once daily
- **Alternative Dosage**: 30 mg once daily (considered for patients with refractory, severe, or extensive disease)

**b. Criteria for Modifying or Discontinuing Treatment**

**Modification Criteria:**

- AEs: Consider dose adjustments or discontinuation if significant AEs occur, such as severe infections, leukopenia, anemia, hyperlipidemia, or elevated liver enzymes. In case of severe renal impairment (eGFR 15 to <30 mL/min/ 1.73 $m^2$), mild or moderate hepatic impairment (Child-Pugh A or B), and strong CYP3A4 inhibitors: induction dose of 30 mg once daily for 8 weeks; maintenance dose of 15 mg once daily.
- Disease Progression: Modify treatment if there is notable worsening of CD symptoms or complications.

**Discontinuation Criteria:**

- Lack of Efficacy: Discontinue if there is no clinical response after the extended induction phase or during maintenance.
- Severe AEs: Discontinue if the patient experiences severe or life-threatening adverse effects.
- Patient Withdrawal: Discontinue if the patient chooses to withdraw from the study.

## Participant timeline

- Enrollment: December 2024 to December 2025.
- Treatment Period: Maximum of 12 months for each participant.
- Assessments:
  - Baseline: At enrollment.
  - Follow-up Visits: At 3, 6 and 12 months.
  - Data Collection: Regular intervals as specified above, including laboratory tests, endoscopic evaluations, and clinical assessments.

## Sample size

In designing our study, due to scarcity of evidence, we utilized insights from the U-ENDURE trial, which demonstrated the efficacy of upadacitinib in achieving both CDAI clinical remission and endoscopic response [9]. Our sample size calculations were based

on anticipated remission rates of 27.6% for the 15-mg upadacitinib group and 40.1% for the 30-mg upadacitinib group, compared to 7.3% for the placebo. For endoscopic response, similar parameters were used, with 27.6% and 40.1% rates for the upadacitinib groups, respectively, versus 7.3% for placebo. We determined the need of approximately 60 participants per group, totaling 120, would be needed to achieve 80% power with an alpha of 0.05.

### Data collection and management

Data for this study will be extracted from the electronic archives of all participating centers. To ensure data integrity and anonymity, each patient will be assigned a unique identification number. This process will prevent duplicate entries and maintain confidentiality. All collected data will be systematically entered into an electronic case report form (RedCap), adhering to stringent Italian privacy regulations.

**Data Collection Time Points:**

- **T0 (Week 0):** Induction of therapy
- **T1 (Week 12):** 12 weeks post-initiation of therapy
- **T2 (Month 6):** 6 months post-initiation of therapy
- **T3 (Month 12):** 12 months post-initiation of therapy

At each designated time point, the following clinical data will be collected:

- **Clinical Data:**
    - Calculation of the HBI
    - The number of draining and non-draining enterocutaneous (perianal and
    - abdominal) and rectovaginal fistulas should be recorded, including the number of fistulas draining upon gentle compression. Enterocutaneous fistulas will be considered draining when there is drainage upon gentle compression, and rectovaginal fistulas will be considered draining based on either presence of drainage on physical examination or presence of relevant symptoms (e.g., passage of rectal material or flatus from the vagina).
- **Laboratory Tests:**
    - Fecal calprotectin

    - C-Reactive Protein (CRP)
- **Endoscopic and Radiological Monitoring:**
    - Ileocolonoscopy
    - Ultrasound, MRI or CT-scan

For participants who exit the study or interrupt treatment, data collected up to the point of exit will include:

- **Reason for Withdrawal:** To analyse potential impacts on study results and assess patterns of discontinuation.
- **Last Available Data:** To ensure the completeness of the dataset and include the most recent information in the final analysis.

Data collected at the various timepoints are shown in Table 1.

| Time Point | Clinical Data | Laboratory Tests | Endoscopic & Radiological Monitoring | Other Data |
|---|---|---|---|---|
| **T0 (Week 0)** | - HBI Calculation<br>- Fistula assessment (draining/non-draining)<br>- EIMs assessment<br>- Concomitant treatments (including steroids) | - CRP<br>- Fecal calprotectin | - Ileocolonoscopy (SES-CD)<br>- Ultrasound, MRI, or CT scan (for transmural healing and BWT)<br>- Radiological exam | |
| **T1 (Week 12)** | - HBI Calculation<br>- Fistula assessment<br>- EIMs assessment<br>- Steroid-free status assessment<br>- Concomitant treatments | - CRP<br>- Fecal calprotectin | - Ultrasound, MRI, or CT scan (BWT and transmural healing)<br>- Radiological exam | - Hospitalizations due to CD<br>- Adverse Events (AEs) reporting |

| | | | | |
|---|---|---|---|---|
| | - HBI Calculation | - CRP | - Ultrasound, MRI, or CT scan (BWT and transmural healing) | - Hospitalizations due to CD |
| **T2 (Month 6)** | - Fistula assessment<br>- EIMs assessment<br>- Steroid-free status assessment<br>- Concomitant treatments | - Fecal calprotectin | - Radiological exam | - Adverse Events (AEs) reporting |
| **T3 (Month 12)** | - HBI Calculation<br>- Fistula assessment<br>- EIMs assessment<br>- Steroid-free status assessment<br>- Concomitant treatments | - CRP<br>- Fecal calprotectin | - Ileocolonoscopy (SES-CD)<br>- Ultrasound, MRI, or CT scan (BWT and transmural healing)<br>- Radiological exam | - Hospitalizations due to CD<br>- Adverse Events (AEs) reporting |
| **At Withdrawal** | - Data up to last visit<br>- Reason for withdrawal | - Last available test results | - Last available endoscopy or radiological exam | - Reason for withdrawal<br>- Concomitant treatments<br>- Adverse Events (AEs) reporting |

Table 1. Data Collection Schedule by Time Point

## 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 and initials 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. 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.

### Description of Statistical Data Analysis

The sample will be described using descriptive statistics. Qualitative data will be presented as absolute and relative frequencies, while quantitative variables will be reported as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. The normality of quantitative variables will be assessed using the Shapiro-Wilk test. Missing values (if <5%) will be addressed using multiple imputation methods: Lasso Regression for quantitative data and classification trees for qualitative data.

Baseline differences between groups will be assessed using Chi-squared or Fisher-Freeman-Halton's exact test for qualitative variables, and one-way ANOVA or Kruskal-Wallis test for quantitative data. Pairwise comparisons will be performed using Student’s t-test or Mann-Whitney U test, with adjustments for multiple comparisons using the False Discovery Rate method. Adverse events (AEs) and serious adverse events (SAEs) will be described and compared across different therapy lines using the same inferential tests. Differences in clinical remssion and endoscopic response at 12 months across various biological sequential therapies in second and third-line treatments will be analyzed using Kaplan-Meier survival analysis. The log-rank test will be applied, and cumulative incidence curves will be generated.

Potential predictors of steroid-free clinical remission will be evaluated using Cox proportional hazards regression models. Hazard Ratios (HR) and 95% confidence intervals (CIs) will be reported. The proportionality of hazard functions will be assessed through visual inspection of hazard and Schoenfeld residual plots. If proportionality assumptions are violated, alternative Cox regression models will be fitted.

To evaluate the combined effects of drug and therapy line, multivariable interaction models will be fitted for each predictor, and interaction hazard ratios (HR) will be reported. Coefficients of main effects will be interpreted as HRs for unit increases in predictors within the reference category (first line) for quantitative predictors, or as changes in hazard compared to the reference group for qualitative data. Interaction parameters (IHR) will

reflect differences in HRs due to variations of predictors among different therapy lines, with the first line serving as the reference category. Statistical analyses will be performed using the updated version of R.

## Relevance of the Proposed Study for Advancing Knowledge and Improving Clinical Management of Chronic Inflammatory Bowel Diseases

The proposed study is essential for advancing our understanding and improving the management of CD. CD poses significant challenges due to its unpredictable progression and substantial impact on quality of life. While clinical trials, such as those assessing upadacitinib, provide vital efficacy data, real-world studies are necessary to evaluate how treatments perform across diverse patient populations, including those with comorbidities or who have not responded to previous therapies.

This study will contribute to personalized medicine by identifying key clinical, endoscopic, and radiological predictors of deep remission. By examining a wide range of outcomes—such as steroid-free clinical remission, endoscopic improvements, and radiologic normalization of bowel wall thickness—the research will offer a comprehensive evaluation of upadacitinib's effectiveness. Additionally, the study addresses the challenges of high therapy failure rates and disease progression in CD. It aims to provide valuable insights into alternative treatment options for patients who have not benefited from conventional therapies. The findings will help refine treatment strategies and enhance patient care, ultimately leading to better outcomes and improved quality of life for those living with CD.

## References


1. Dolinger, M.; Torres, J.; Vermeire, S. Crohn's Disease. *The Lancet* **2024**, *403*, 1177–1191, doi:10.1016/S0140-6736(23)02586-2.
2. Noor, N.M.; Lee, J.C.; Bond, S.; Dowling, F.; Brezina, B.; Patel, K.V.; Ahmad, T.; Banim, P.J.; Berrill, J.W.; Cooney, R.; et al. A Biomarker-Stratified Comparison of Top-down versus Accelerated Step-up Treatment Strategies for Patients with Newly Diagnosed Crohn's Disease (PROFILE): A Multicentre, Open-Label Randomised Controlled Trial. *The Lancet Gastroenterology & Hepatology* **2024**, *0*, doi:10.1016/S2468-1253(24)00034-7.
3. H, G.; S, M.; U, K.; B, V.; M, C.; C, B.; J, W.; M, A.; M, A.; R, A.; et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *Journal of Crohn's & colitis* **2024**, doi:10.1093/ecco-jcc/jjae091.
4. Raine, T.; Danese, S. Breaking Through the Therapeutic Ceiling: What Will It Take? *Gastroenterology* **2022**, *162*, 1507–1511, doi:10.1053/j.gastro.2021.09.078.
5. Kim, J.-W.; Kim, S.-Y. The Era of Janus Kinase Inhibitors for Inflammatory Bowel Disease Treatment. *Int J Mol Sci* **2021**, *22*, 11322, doi:10.3390/ijms222111322.

6. Zhao, M.-Y.; Zhang, W.; Rao, G.-W. Targeting Janus Kinase (JAK) for Fighting Diseases: The Research of JAK Inhibitor Drugs. *Curr Med Chem* **2022**, *29*, 5010–5040, doi:10.2174/1568026622666220307124142.
7. Herrera-deGuise, C.; Serra-Ruiz, X.; Lastiri, E.; Borruel, N. JAK Inhibitors: A New Dawn for Oral Therapies in Inflammatory Bowel Diseases. *Front Med (Lausanne)* **2023**, *10*, 1089099, doi:10.3389/fmed.2023.1089099.
8. Salas, A.; Hernandez-Rocha, C.; Duijvestein, M.; Faubion, W.; McGovern, D.; Vermeire, S.; Vetrano, S.; Vande Casteele, N. JAK-STAT Pathway Targeting for the Treatment of Inflammatory Bowel Disease. *Nat Rev Gastroenterol Hepatol* **2020**, *17*, 323–337, doi:10.1038/s41575-020-0273-0.
9. Loftus, E.V.; Panés, J.; Lacerda, A.P.; Peyrin-Biroulet, L.; D'Haens, G.; Panaccione, R.; Reinisch, W.; Louis, E.; Chen, M.; Nakase, H.; et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* **2023**, *388*, 1966–1980, doi:10.1056/NEJMoa2212728.
10. Shehab, M.; De Marco, D.; Lakatos, P.L.; Bessissow, T. The Potential for Medical Therapies to Address Fistulizing Crohn's Disease: A State-of-the-Art Review. *Expert Opin Biol Ther* **2024**, *24*, 733–746, doi:10.1080/14712598.2024.2383882.
11. Colombel, J.-F.; Lacerda, A.P.; Irving, P.M.; Panaccione, R.; Reinisch, W.; Rieder, F.; Steinlauf, A.; Schwartz, D.; Feng, T.; Dubcenco, E.; et al. Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials. *Clin Gastroenterol Hepatol* **2024**, S1542-3565(24)00860-7, doi:10.1016/j.cgh.2024.08.032.
12. Vuyyuru, S.K.; Solitano, V.; Narula, N.; Lee, M.J.; MacDonald, J.K.; McCurdy, J.D.; Singh, S.; Ma, C.; Jairath, V. Pharmacological Therapies for the Management of Fistulizing Crohn's Disease: A Systematic Review and Meta-Analysis. *Journal of Crohn's and Colitis* **2024**, *18*, 589–603, doi:10.1093/ecco-jcc/jjad185.
13. Elford, A.T.; Bishara, M.; Plevris, N.; Gros, B.; Constantine-Cooke, N.; Goodhand, J.; Kennedy, N.A.; Ahmad, T.; Lees, C.W. Real-World Effectiveness of Upadacitinib in Crohn's Disease: A UK Multicentre Retrospective Cohort Study. *Frontline Gastroenterology* **2024**, *15*, 297–304, doi:10.1136/flgastro-2024-102668.
14. Maaser, C.; Sturm, A.; Vavricka, S.R.; Kucharzik, T.; Fiorino, G.; Annese, V.; Calabrese, E.; Baumgart, D.C.; Bettenworth, D.; Borralho Nunes, P.; et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial Diagnosis, Monitoring of Known IBD, Detection of Complications. *Journal of Crohn's and Colitis* **2019**, *13*, 144-164K, doi:10.1093/ecco-jcc/jjy113.