AUTONOME PROVINZ BOZEN – SÜDTIROL | PROVINCIA AUTONOMA DI BOLZANO – ALTO ADIGE
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GESUNDHEITSBEZIRK BOZEN *Krankenhausbereich* | COMPRENSORIO SANITARIO DI BOLZANO *Area Ospedaliera*

IGIBD the Italian Group for the study of Inflammatory Bowel Disease

Study title: effectiveness and safety of upadacitinib in patients with ulcerative colitis: a real-life, multicenter, IG-IBD study

Study acronym: UPAREAL-UC

Protocol version: v. 3.0 12.11.2023

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AUTHORIZATIONS AND SIGNATURES

Effectiveness and safety of Upadacitinib in patients with ulcerative colitis: a real-life, multicenter, IG-IBD 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

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Signature _____ Date

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BACKGROUND AND RATIONALE

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting the colon and rectum. Despite the availability of multiple therapeutic options for patients with UC, achieving short-

term and long-term disease control remains challenging, and symptoms negatively impact on patients' quality of life (QOL) *(1,2).* Indeed, approximately two-thirds of patients fail to obtain or maintain remission after 1 year even with the use of current biologics agents. Janus kinase (JAK) pathways regulate immune signaling and are implicated in IBD pathogenesis *(3).* Upadacitinib (UPA) is an oral, selective, small molecule JAK inhibitor engineered to have preferential inhibitory effects for JAK1 that has recently received approval in Italy for the treatment of UC. UPA selectivity might allow the evaluation of higher doses, potentially providing greater efficacy without increasing some of the reported safety issues associated with JAK2 and JAK3 inhibition. The efficacy of UPA is supported by phase 2 *(4)* and phase 3 *(5)* explanatory trial.

In a phase 2 *(4)* dose-ranging, placebo-controlled induction study, patients with moderately to severely active ulcerative colitis received UPA at the following doses: 7,5 mg, 15 mg, 30 mg, and 45 mg once daily. UPA 45 mg once daily showed an optimal benefit–risk profile with the highest efficacy rates and no clinically relevant increase in safety events compared with lower doses and was therefore selected for the phase 3 induction dose. Considering a potentially more favorable long-term safety profile, two doses (15 mg and 30 mg once daily) lower than the induction dose were selected as the phase 3 maintenance doses; both doses also showed superior efficacy versus placebo in the phase 2b study.

In the induction analysis of a phase 3 trial *(5)*, the primary endpoint, clinical remission at week 8, was achieved by 26-33% of patients receiving UPA versus 4-5% of patients receiving placebo (both p<0,0001).

Moreover, in the maintenance analysis of the same trial, the primary endpoint defined as clinical remission at week 52, was achieved by 42% of patients receiving UPA 15 mg once daily, and 52% patients receiving UPA 30 mg once daily, and 12% of patients receiving placebo (p<0,0001).

At present, the efficacy and safety data of UPA come mostly from clinical trials. Few real-world experiences *(6,7)* are available in the literature and one report is a multicenter case series from our center that is planned to be presented during the upcoming XIV IGIBD national congress. As stated in drug data sheet *(8)*, UPA is indicated in the treatment of adult patients with moderate to severe active ulcerative colitis (evaluated with Mayo Score – disease activity index *(9)*) who have had an inadequate response, have lost the response or are intolerant to conventional therapy or a

biological agent. UPA is available in three doses 45,30 and 15 mg. Patients receive 45 mg orally every day for 8 or 16 weeks (depending on clinical judgment and according to risk-benefit evaluation) as induction therapy. At the end of induction period, patients in clinical remission will receive UPA 15mg or 30mg (depending on clinical judgment and according to risk-benefit evaluation) every day as maintenance therapy.

According to reported adverse events in both registrative trials *(4,5)*, serious adverse events and adverse events leading to discontinuation of treatment were less frequent in the UPA 45 mg group than in the placebo group (serious adverse events 3% vs 5-6%; adverse events leading to discontinuation 2% vs 5-9%).

The most frequently reported adverse events in the maintenance part of the trial were nasopharyngitis (12-15%], creatine phosphokinase elevation (5-6%), arthralgia (6-10%) and upper respiratory tract infection (4-6%). Events of cancer, adjudicated major adverse cardiac events, or venous thromboembolism were reported infrequently. There were no treatment-related deaths.

Despite the drug presents an adequate safety profile, careful analysis of indications and contraindications must therefore be carried out by medical personnel before starting the drug.

AIM OF THE STUDY

The usefulness of real-life studies is already well clarified. A real-life multicenter study is therefore essential to assess the effectiveness and safety of this drug in our daily clinical practice outside the context of clinical trials. With our prospective observational study, the first in Italy on UPA in ulcerative colitis, we expect to obtain important observations on the efficacy of this novel therapeutic. By also collecting the adverse effects, a better definition of its safety profile is desirable.

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 the treatment from the EMA approval in March 2023. In detail, the planned study design involves an enrollment phase of about 6 months and then a prospective observational period of about 12 months during which clinical, biochemical, endoscopic, and histological information will be recorded. The number of patients included in the prospective enrollment phase will then be added to the number of patients retrospectively included already on therapy since 01.03.2023. In accordance with this, for patients retrospectively included and therefore already on UPA therapy, clinical and biochemical data will be retrospectively retrieved.

2.PATIENT ENROLLMENT

Inclusion criteria: patients with established diagnosis of UC according to standard criteria *(10)* aged ≥ 18 years receiving UPA for moderately to severely active UC, either experienced or naïve to any advanced therapies (biologics and/or small molecule) currently available will be enrolled. 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 *(11)* for acute severe ulcerative colitis (ASUC) will also be excluded.

3.OUTCOMES

a. PRIMARY OUTCOME

The effectiveness of UPA in patients with ulcerative colitis is evaluated in terms of clinical remission at week 8 (t1), 26 (t3), and 52 (t4) defined as a partial mayo score (PMS) ≤2.

b. SECONDARY OUTCOMES

As secondary outcomes, our study will evaluate:

- Clinical response at week 8 (t1), 16 (t2), 26 (t3), 52 (t4) 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 t4 defined as remission without the need of any kind of systemic steroids

- Biochemical remission at t3 and t4 defined as C-reactive protein < 0.5 mg/dl and fecal calprotectin level < 250 ug/g

- Endoscopic remission at t4 defined as Mayo endoscopic sub score (MES) ≤ 1 *(12)*

- Histological remission at t4 defined as a Nancy index ≤ 1 *(13)*

- Treatment persistency at t4 defined as percentage of patients continuing UPA as maintenance treatment through week 52

c. SAFETY OUTCOMES

Another aspect that will be assessed is the safety profile of the drug during all the period in terms 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)

Since the reporting of adverse events is the responsibility of the prescribing physician of the drug, it will be necessary for the investigating physician of each participating center to provide the report to AIFA.

4.PROCEDURES

To evaluate these outcomes, as previously described, the study involves 5 main evaluation points that are normally part of our clinical practice (see also Flow-Chart file):

T0 (baseline visit): at the beginning of the induction period of UPA treatment, general information regarding the disease will be collected.

T1 (8 weeks): clinical status will be re-evaluated with a telephone consultation and/or clinical examination if an objective examination is needed. At this time, as reported in the drug data sheet, the need for continued induction therapy and drug dosing will be assessed.

T2 (16 weeks): clinical status will be re-evaluated with a telephone consultation and/or clinical examination if an objective examination is needed. At this time, as reported in the drug data sheet, drug dosing will be assessed.

T3 (26 weeks): the clinical status will be re-evaluated with a telephone consultation and/or clinical examination if an objective examination is needed. At this time, as reported in the drug data sheet, drug dosing will be assessed. In addition to the previous evaluation, a C-reactive protein blood sample and fecal collection will be requested for a calprotectin assay.

T4 (52 weeks): the clinical status will be re-evaluated with a telephone consultation and/or clinical examination if an objective examination is needed. At this time, as reported in the drug data sheet, drug dosing will be assessed. A C-reactive protein blood sample and fecal collection will be requested for a calprotectin assay. If possible, a colonoscopy with biopsy sampling will be requested.

STATISTICAL PLAN

We estimate a sample size with normal distribution. According to the available literature, about 250 patients are planned to be enrolled.

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are summarized as frequency and percentage. The Chi-square, or Fisher's exact test when

appropriate, and the independent samples T-test are applied for categorical and continuous variables respectively.

The effectiveness of UPA by clinical remission in the two groups (Partial mayo score (PMS) <2 vs PMS>2) is calculated by Chi-square or Fisher's exact test at week 8 (T1), week 16 (T2), week 26 (T3), week 52 (T4).

Another comparison in primary and secondary outcomes is performed by T Student Test (or One Way ANOVA Test with Post Hoc Multiple Comparison LSD Method) in groups of different type of patients (by gender, by range age).

The influence of risk factors on the outcomes is analyzed by multivariate binary logistic regression with Backward Wald method analysis for the effectiveness of UPA rate and with Linear Regression multivariate analysis with Backward method for week 8 (T1), week 16 (T2), week 26 (T3), week 52 (T4). P <0.05 is considered statistically significant.

STUDY TIMELINE

Project start date: 01.12.2023 (and in any case not before approval of the study by the EC)

Completion date of patients' enrollment: 01.06.2024

Data collection completion date: 01.06.2025

Data analysis: after data collection completion 01.07.2025

SUPPORT

IGIBD represents the sponsor for this study. Although there is no direct financial support, IGIBD provides the expertise of a clinical manager and a statistician for data analysis.

ETHICAL AND DATA CONSIDERATIONS

1.ETHICAL COMMITEE

All participating centers will need Ethical Committee's approval before starting with the patients' enrollment.

2.PATIENT PROTECTION

The study coordinator ensures that this study is conducted in accordance with the Helsinki Declaration (amendments of Tokyo, Venice, Hong Kong, Somerset West, Edinburgh, Washington, Tokyo and Seoul) or with Italian laws and regulations.

The protocol was written, and the study will be conducted in accordance with the ICH guidelines for good clinical practice.

The protocol and its annexes are subject to review and approval of the Independent Ethical Committee of competence and each participating center must obtain the approval of the Ethics Committee of its institute.

3.SUBJECT IDENTIFICATION – PERSONAL DATA PROTECTION

All records identifying the subject must remain confidential and, with the limits permitted by applicable laws, are not made available to the public. The patient's name will not be requested or registered by the Data Center. A sequential identified number will be automatically assigned to each patient registered in the study. Patient information or documentation should be considered "anonymous", and as such not subject to privacy laws, only when a "key" that allows patient identification is no longer available.

4.PROCEDURES FOR COLLECTING DATA

All data required by the study will be recorded in a REDCap database. REDCap is a platform residing on a remote server where the anonymized data will be stored.

Each authorized user can access the database via the web with a dedicated username and password. Each center will see and can modify only its cases, while the principal investigator will be able only to see, data entered by each Center. Every access to REDCap is monitored by the system, as well as every variation of the data contained. Patients will be pseudo-anonymized and

identification data will not be included. It will be the principal investigator's responsibility to keep separately a file containing the patient's personal data (and folder number) together with the code assigned by REDCap for subsequent data quality checks.

5.CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

6.DATA SHARING POLICY

The results of this study will be published and/or presented at scientific meetings. Any formal publication of study results will be a collaborative effort between all the Investigators. All manuscripts or abstracts will be reviewed and approved in writing by the Principal Investigator prior to submission. A final integrated clinical/statistical report will be prepared at the end of the study. The papers produced will respect individual participants whose data are shared and will follow the authorship policy of journal. The order in which the authors will be listed in the subtitle will depend on the number of patients enrolled, except for the first 4 names and last name that will be attributed by the Steering Committee. If the number of authors is more than that allowed by the data sharing policy of the journal, the remaining authors will be included inside the term "working group" at the end of the manuscript, so that all investigators/authors will be in any case identified on PubMed. In signing the protocol/protocol amendment(s), every participating Investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved at each site. Information about study subjects will be kept confidential and managed under the applicable laws and regulations. The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

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