USBIOS Study

Switching from UStekinumab originator to BIOSimilar in Crohn's disease: The USBIOS Study, an IG-IBD study

PROTOCOLLO PRINCIPALE

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Promotore: IGIBD Italian Group for the study of Inflammatory Bowel Disease

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INTRODUCTION

Crohn's disease (CD) is a chronic disease, with progressive damage to the gastrointestinal tract, which affects the quality of life of patients. The introduction of biological therapy in the treatment of CD has led to great benefits and a growing number of drug classes are now available.

Ustekinumab (originator Stelara®) is a monoclonal antibody directed to the p40 subunit of interleukin-12 and interleukin-23, able to induce and maintain remission in CD with a good safety profile in patients with inadequate response, loss of response or intolerant to either conventional therapy or anti-TNF or with contraindications to these therapies.

Although being very effective and improving the quality of life, biological therapy demands an increasing cost on national health systems.

For this reason, biosimilars (of anti-TNF so far) have been approved and are now of widespread use in clinical practice.

In July 2024 Ustekinumab originator patent is going to expire. There are currently many biosimilars under study, such as SB17 (Jeong H, Kang T, Lee J, Im S. Comparison of SB17 and reference ustekinumab in healthy adults: A randomized, double-blind, single-dose, phase I study. Int J Clin Pharmacol Ther. 2024 May;62(5):231-240), CT-P43 (Papp KA, Lebwohl MG, Thaçi D, et al. Efficacy and Safety of Candidate Biosimilar CT-P43 Versus Originator Ustekinumab in Moderate to Severe Plaque Psoriasis: 28-Week Results of a Randomised, Active-Controlled, Double-Blind, Phase III Study. BioDrugs. 2024;38(1):121-131.), and ABP 654 (Cantin G, Liu Q, Shah B, et al. Analytical and Functional Similarity

of the Biosimilar Candidate ABP 654 to Ustekinumab Reference Product. Drugs R D. 2023;23(4):421-438). So far, the European Medicines Agency (EMA) has approved biosimilar AVT04 (Uzpruvo®) for psoriatic arthritis, plaque psoriasis, and Crohn's disease.

NEEDS THAT THE PROJECT INTENDS TO SATISFY

No study has been published yet about the effectiveness and safety of switching from ustekinumab originator to its biosimilar/biosimilars approved in Italy in a cohort of CD patients in real-life settings.

MAIN OBJECTIVES OF THE PROJECT

The aim of this study will be to assess the effectiveness and safety of switching from ustekinumab originator to its biosimilar/biosimilars in patients affected from CD in clinical remission in a large, real-life cohort of Italian patients.

The switch from originator to biosimilar ustekinumab will be defined as successful in patients not experiencing a disease flare (HBI ≤ 5) or needing systemic steroids or stopping biosimilar/biosimilars during the 6 months of follow-up after the switch. The following variables will be evaluated for failure of the switch: age at T0, smoking habit at T0, sex, disease extension, CD phenotype, previous anti-TNF treatment, previous vedolizumab treatment, duration of ustekinumab originator therapy, C-reactive protein (CRP, mg/L) at T0, calprotectin (µg/g) at T0, HBI at T0, immunosuppressants therapy at T0. In addition, secondary endpoints will include: rate of ustekinumab biosimilar/ biosimilars discontinuation; switch back to originator; biochemical remission (CRP < 5 mg/L, calprotectin < 250 µg/g); not increase of bowel wall thickness assessed with intestinal ultrasound (if available); not inferiority of biosimilar/ biosimilars compared to control group that maintains originator in terms of overall remission (if available).

ESTIMATED TIME FOR THE REALIZATION OF THE PROJECT

The recruitment of the patients will start from August 1st, 2024 and will finish of August 31st, 2025. The last day of follow-up for the last recruited patient will be on February 28th, 2026.

EXPECTED ACTIVITY

Once approved by the Ethic Committee of the coordinator centre and satellite centres, the data collection can start. A shared database will be created. After the deadline of 02/2026, available data will undergo to statistical analysis, as already described below.

METHODS

The USBIOS study is an observational, prospective, multicentre, spontaneous, and not financially supported study on patients affected from CD that switch from ustekinumab originator to biosimilar/biosimilars approved in Italy.

Number of subjects enrolled

At McNemar test, setting a type I error = 0.05, a type II error of 0.2, considering clinically significant a 15% of patient with need of systemic steroid or stop biosimilar during the 6 months of follow up, the power of the study is reached if at least 50 patients are recruited (Ribaldone DG, Parisio L, Variola A, et al. Switching from VEDOlizumab intravenous to subcutaneous formulation in ulcerative colitis patients in clinical remission: The SVEDO Study, an IG-IBD study. Dig

Liver Dis. 2024;56(1):77-82.). We regarded a non-inferiority margin of 15% as appropriate on the basis of the rate of relapse of ustekinumab (Ito, Takahiro et al. Long-Term Clinical Effectiveness of Ustekinumab in Patients With Crohn's Disease: A Retrospective Cohort Study. Crohn's & colitis 360 vol. 2,4 otaa061. 28 Jul. 2020) and according to literature definition of noninferiority (Jørgensen KK et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017 Jun 10;389(10086):2304-2316.).

All patients will be prospectively followed on the outpatient clinics by inflammatory bowel disease expert clinicians with regular appointments. Clinical, biochemical, and endoscopic evaluation will be performed during follow-up at physician's discretion.

Inclusion criteria

- Patients ≥ 18 years of age willing to sign the informed consent
- Patients receiving Ustekinumab as primary indication for active Crohn's disease
- CD in clinical remission (HBI < 5) and not receiving systemic corticosteroids or low absorbable steroids since at least 8 months before the switch from Ustekinumab originator to biosimilar/biosimilars (Ribaldone DG, Parisio L, Variola A, et al. Switching from VEDOlizumab intravenous to subcutaneous formulation in ulcerative colitis patients in clinical remission: The SVEDO Study, an IG-IBD study. Dig Liver Dis. 2024;56(1):77-82; Ribaldone, D. G. et al. Switching from Biosimilar to Biosimilar Adalimumab, Including Multiple Switching, in Crohn's Disease: A Prospective Study. Journal of clinical medicine vol. 10,15 3387. 30 Jul. 2021)
- At least 6 months of follow-up after the switch/enrolment of control group that maintains ustekinumab originator, in order to have recent data in an appropriate time amount to assess biosimilar/biosimilars' effectiveness and safety (Ribaldone DG, Parisio L, Variola A, et al. Switching from VEDOlizumab intravenous to subcutaneous formulation in ulcerative colitis patients in clinical remission: The SVEDO Study, an IG-IBD study. Dig Liver Dis. 2024;56(1):77-82)
- Will of the patient to share their clinical data.

Exclusion criteria

- No clinical data 6 months before the switch, at the switch, 6 months after the switch
- UC/IBD-U diagnosis
- Patients receiving Ustekinumab as primary indication for other diseases (ex. Psoriasis)
- Patients not willing to sign the informed consent
- Patients receiving Ustekinumab (Stelara®) for less than 8 months before the switch/enrolment of control group that maintains ustekinumab originator (T0).

Measures of safety is planned to include clinical and laboratory adverse events. Safety assessment will also include injection reactions.

<u>Data collection</u>

The following data will be collected: switch to biosimilar (yes/continuation of originator), name of Ustekinumab biosimilar, date at switch/enrolment of control group that maintains originator (T0) according to inclusion and

exclusion criteria, age at T0, smoking habit at T0, sex, disease location at T0 (only small bowel/only colon/colon + small bowel/upper digestive tract involved), CD phenotype at T0 (inflammatory/structuring/penetrating), previous anti-TNF, previous vedolizumab, extra-intestinal manifestations at T0, previous IBD-related surgery at T0, history of perianal disease at T0, months of ustekinumab at T0 (at least 8 months), disease duration at T0 (in years), CRP at T0, calprotectin at T0, HBI at T0, immunosuppressants at T0, frequency of administration at T0, intestinal ultrasound within last 6 months at T0 (bowel wall thickness ≤ 3 mm/bowel wall thickness > 3 mm), endoscopy within 6 months at T0 (absence of ulcerations/ulcerations), CRP at 6 months after the switch (T6), calprotectin at T6, HBI at T6, systemic steroids at T6, immunosuppressants at T6, frequency of administration at T6, dose escalation at T6, intestinal ultrasound at T6, if available (unchanged or improved compared to T0/thickness increased more than 1 mm compared to T0), endoscopy at T6, if available (absence of ulcerations/ulcerations), extra-intestinal manifestations at T6, side effects T6 - T0, type of side effects at T6, details on side effects, biosimilar/biosimilars discontinuation within 6 months, reason for biosimilar/biosimilars discontinuation, biosimilar/biosimilars retention at T6, CD-related hospitalization T6 - T0, CD-related intestinal surgery T6 - T0, return to originator and, if return to originator, time of return and if there is clinical remission at T6 without systemic steroids.

Ethical considerations

The study will be approved by the ethical committee of the proposing centre and then by the ethical committees of all the satellite centres.

Statistical Analysis

Descriptive statistics will be used to characterize the patient population. Results will be provided as mean and standard deviation or median and interquartile range (according to normal distribution at D'Agostino-Pearson test) for continuous variables and as frequencies and percentages for categorical variables. The influence of risk factors on the outcome will be analysed with logistic regression analysis (backward stepwise selection; cut-off for continuous variable will be chosen according to Youden index). The HBI, CRP, calprotectin value at T0 will be compared with their values at T6 with Paired sample t -test according to distribution of the values. A p-value of < 0.05 will be considered to be statistically significant. Statistical analyses will be performed using the IBM SPSS Statistics v25 (IBM Corporation).

Patient's consent

Only patients who will give their free and informed consent by signing on the appropriate form will be enrolled in the study. Before signing, patients will have received from the principal investigator and co-investigators all the information regarding:

- the purpose of the study
- the duration of their participation
- the clinical procedures to which they will be subjected
- the benefits, foreseeable risks, disadvantages that could derive from participation in the study
- the confidential nature of their personal data
- the voluntary nature of their participation

- the possibility of withdrawing consent at any time, without this implying any consequence on their normal therapeutic process.

Safety assessment and side effects

No risks or side effects are anticipated.

Risk / benefit ratio

This study does not present significant risks and side effects for the patient's health. However, this study will provide, for the first time in literature, data about efficacy and safety of switching from Ustekinumab originator (Stelara®) to biosimilar/biosimilars approved in Italy in patients treated at least for 8 months with ustekinumab originator and in clinical remission.

If the obtained data from this study will be similar to those ones achieved on studies about switching from anti-TNF originator to biosimilars (e.g. Ribaldone, D. G. et al. Effectiveness and safety of adalimumab biosimilar ABP 501 in Crohn's disease: An observational study. Rev. Esp. Enfermedades Dig. 112, 195–200 (2020); Macaluso, F. S. et al. The SPOSIB SB2 Sicilian Cohort: Safety and Effectiveness of Infliximab Biosimilar SB2 in Inflammatory Bowel Diseases, including Multiple Switches. Inflamm. Bowel Dis. 27, 182–189 (2021); Ribaldone, D. G. et al. Switching from Biosimilar to Biosimilar Adalimumab, Including Multiple Switching, in Crohn's Disease: A Prospective Study. Journal of clinical medicine vol. 10,15 3387. 30 Jul. 2021), we expect an important economic advantage for national health systems without loss of effectiveness or increase of side effects for patients.

Criteria for leaving the study

Patients can withdraw their consent to the study at any time, without this in any way affecting the subsequent treatments that may be necessary for the pathology from which they are suffering.

Measures for the protection of the rights of the person

The nature, purpose, and meaning of the study will be explained to the patient in a comprehensive and understandable way. They must express a favourable opinion on participation by signing an acceptance model. They will be entitled to withdraw from participation in the study at any time.

Patient data will be collected and stored in an "anonymous" manner, meaning that each patient will be assigned an identification code known only to the researchers, doctors and nurses involved in the project. The code key will be stored in a protected environment following the laws on the protection of privacy and personal data protection (Pursuant to EU Regulation 2016/679 General Data Protection Regulation (GDPR) concerning the protection of individuals with regard to the processing of personal data, as well as the free circulation of such data (hereinafter GDPR EU 2016/679)).

ADDITIONAL COSTS

None.

EFFECTIVENESS OF THE ACTIVITY

The parameters that will allow to evaluate the effectiveness of the proposed activity are:

- reach an enrolment of at least 50 patients at the end of 12 months from the beginning of the work;
- publish the results in international scientific journals indexed on recognized databases (e.g. PubMed), disseminate the results of this study at national and international conferences (IG-IBD, ECCO, UEGW).

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