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Effectiveness of budesonide MMX (Cortiment) for the treatment of mild-to-moderate active ulcerative colitis: study protocol for a prospective multicentre observational cohort study

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ABSTRACT

Introduction: A study has been developed to assess the use and effectiveness of budesonide MMX for mild-to-moderate active ulcerative colitis (UC) in routine clinical practice.

Methods and analysis: A prospective, multicentre, observational, cohort study of 300 patients prescribed budesonide MMX for the treatment of mild-to-moderate active UC will be conducted in Europe, Israel and Canada. Patients will be treated with budesonide MMX9 mg daily for induction of remission for ≤8 weeks. Data on effectiveness, including patient-reported outcomes, tolerability and use will be recorded at the end of treatment and at ≥2 weeks after. The primary outcome (improvement ≥3 point in the clinical subscores of the UC Disease Activity Index score at the end of treatment) will be compared in: patients who receive budesonide MMX added to mesalazine >2 weeks after increased/optimised mesalazine dose for the treatment of flare (late add-on); patients who receive budesonide MMX added to mesalazine ≤2 weeks since mesalazine increased/optimised for the treatment of flare, or without mesalazine dose modification (early add-on); and patients who receive budesonide MMX as monotherapy for the treatment of flare (mono). Propensity scoring will be used to minimise bias and confounding inherent in observational studies.

Ethics and dissemination: First ethical approval: Ethikkommission der Ärztekammer Hamburg (12/22/2015). The results will be published in full.

Discussion: Completion of primary data collection is expected in December 2017. Our results will provide further evidence on the effectiveness of budesonide MMX to support clinicians in their daily practice and inform therapeutic guidelines.

Trial registration number: NCT02586259.

INTRODUCTION

Ulcerative colitis (UC) is a chronic, inflammatory disease of the colon and rectum, characterised by intermittent flares, with diarrhoea, rectal bleeding, urgency and tenesmus, alternating with periods of remission.[1] UC affects over two million people in Europe,[2] presenting a significant burden to society, healthcare resources and expenditure.[3] The symptoms of the disease can have a major impact on patients' quality of life (QoL), affecting their personal life, performance at work and ability to enjoy leisure activities.[4 5] Patients with mild-to-moderate disease can normally be managed in an outpatient setting and do not require hospitalisation. The European Crohn's and Colitis Organisation (ECCO) guidelines recommend that left-sided or extensive mild-to-moderate active UC should initially be treated with an aminosalicylate enema 1 g/day combined with oral mesalazine (5-aminosalicylic acid; 5-ASA) >2 g/day.[6] Systemic corticosteroids, such as prednisolone, are effective for inducing rapid remission in active UC, but the side effects of systemic corticosteroids in particular, limit their short-term and long-term use so they are usually reserved for patients with symptoms of active UC whose disease does not respond to mesalazine.[6 7] The most frequent side effects include mood changes, sleep disturbances, acne, insomnia, moon face, fluid retention, hirsutism, flushing and striae, while the most severe include diabetes, hypertension, osteoporosis, cataracts, and hypothalamopituitary-adrenal suppression.[8 9]

The systemic side effects associated with conventional corticosteroids has led to the development of a corticosteroid with less systemic effects. Budesonide is a synthetic glucocorticosteroid, structurally related to

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prednisolone, but with 15 times greater affinity for the glucocorticoid receptor as well as higher topical activity.[10 11] Budesonide has a low systemic bioavailability (around 10%) due to a high first-pass effect in the liver, therefore, systemic effects with budesonide are significantly less than with conventional corticosteroids.[11] At doses clinically equivalent to systemically acting glucocorticosteroids, budesonide gives significantly less hypothalamic-pituitary-adrenal axis suppression and steroid-associated side effects compared with prednisolone.[12] There are three formulations of budesonide currently available. The two standard formulations (Budenofalk gastroresistant capsules; Dr Falk Pharma GmbH, Germany,[13] and Entocort CR capsules, AstraZeneca, UK,[14]) are both designed to release the drug only at the distal ileum and proximal colon,[13 14] and are therefore not optimal for the treatment of UC. A third formulation, budesonide MMX (Cortiment, Ferring Pharmaceuticals Ltd), is the first glucocorticosteroid designed for topical release to the whole colon using a multimatrix system (MMX);[15] thus, overcoming the limited release of other budesonide formulations for treating UC, especially in the left-sided location. MMX extended-release technology is characterised by a multimatrix structure covered by a gastroresistant coating that dissolves in intestinal fluids having a pH >7.[16] Budesonide MMX is indicated in adults for induction of remission in patients with mild-to-moderate active UC, where mesalazine treatment is not sufficient.[16] The recommended daily dose for induction of remission is one 9 mg tablet in the morning, for up to 8 weeks.[16]

The rationale behind treatment with budesonide MMX is to maximise anti-inflammatory activity while minimising systemic side effects. Two pivotal phase III studies, CORE (Colonic Release Budesonide) I and II, were conducted to evaluate the efficacy, tolerability and safety of budesonide MMX9 mg as monotherapy (without concomitant treatment with mesalazine) for inducing remission in mild-to-moderate UC.[17 18] The primary efficacy end point in both studies was combined clinical and endoscopic remission at Week 8, defined as UC Disease Activity Index (UCDAI) score ≤1 with a score of 0 for rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and a ≥1-point reduction in endoscopic index score from baseline. Secondary end points were clinical improvement, defined as a ≥3-point improvement in the UCDAI score from baseline to Week 8, and endoscopic improvement, defined as a ≥1-point reduction in the endoscopy subscore of the UCDAI from baseline to Week 8.[17 18] The results were consistent across the two studies, and in a pooled analysis of data from both studies, the combined clinical and endoscopic remission rates were significantly greater than placebo (6.2%) for the budesonide MMX9 mg group (17.7%; p=0.0002).[19] Compared with placebo, budesonide MMX9 mg also improved the rates of symptom resolution (26.3% vs 14.3%; p=0.0015) and mucosal healing (27.6% vs 17.1; p=0.0092%).[19]

A further phase IIIb study (CONTRIBUTE) compared budesonide MMX with placebo as add-on therapy to oral mesalazine monotherapy in patients with UC.[20] In this phase IIIb clinical study, patients inadequately controlled after at least 6 weeks of mesalazine ≥2.4 g/day were randomised to add once-daily budesonide MMX9 mg or placebo to their existing mesalazine treatment for 8 weeks. The primary and secondary efficacy end points were similar to those used in the CORE studies.[17 18 20] A greater percentage of budesonide MMX-treated patients than placebo-treated patients achieved a score of 0 (20% vs 12.3%, p=0.0248), indicative of endoscopic remission. Budesonide MMX also induced histological healing in a greater percentage of patients than placebo (27% vs 17.5%, p=0.0155).[20] In a pooled analysis of safety data from five clinical studies, budesonide MMX administered for up to 8 weeks demonstrated a favourable safety and tolerability profile for the induction of remission in patients with mild-to-moderate active UC.[21] Budesonide MMX9 mg was associated with normal mean cortisol concentrations at final visit and an adverse event (AE) incidence comparable with placebo.[21]

Budesonide MMX has been demonstrated in randomised controlled trials (RCTs) to be efficacious therapy for mild-to-moderate active UC and is associated with few adverse effects.[17–19] How the efficacy of inflammatory bowel disease (IBD) therapies in RCTs translates into effectiveness in clinical practice is of crucial importance, since it is recognised that patients included in RCTs are not representative of a real-life IBD setting, and parameters at baseline may be different compared with those for patients in real life.[22 23] Where budesonide MMX fits in the UC treatment paradigm—as starting therapy or after oral mesalazine has failed—also requires further definition. Furthermore, in the case of add-on therapy, at what stage should budesonide MMX be given? The current ECCO guidelines recommend waiting for 6 weeks before stepping up to corticosteroids, although ECCO recognises that it is common practice in many European centres to introduce oral steroids at an early stage due to the speed of response they offer.[6] Based on data from the CORE studies,[17 18] and given its favourable safety profile over systemic steroids,[21] it has been suggested that budesonide MMX should be considered as the first-choice corticosteroid in patients not adequately controlled with mesalazine.[24] In future treatment algorithms for UC, budesonide MMX would be ideally situated when mesalazine therapy is not sufficient and before systemic steroids.[24]

More real-world, population-based data, including patient-reported outcomes (PROs), on the clinical effectiveness of budesonide MMX would help to fully define its role in UC. A PRO is 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'.[25] The Food and Drug Administration (FDA) is moving towards PROs as

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an important aspect of assessing disease activity of IBD.[26] PROs are collected via standardised questionnaires designed to measure an explicit concept (construct) such as symptoms, functioning (activity limitations), health status, health-related QoL (HRQoL) or QoL.[27] A study has therefore been developed to assess the use of budesonide MMX in routine clinical practice. With the results, we intend to validate a new treatment algorithm for gastroenterologists that defines the place in therapy of budesonide MMX, and, thereby, to improve the management of UC and the QoL of patients suffering from this chronic disease.

METHODS AND ANALYSIS

Study objectives

The primary objective is to assess the effectiveness of budesonide MMX. Secondary objectives are to assess the tolerability of budesonide MMX in a real-life setting and to determine how budesonide MMX is prescribed and used by gastroenterologists in routine clinical practice (as monotherapy or add-on therapy to mesalazine, and the timeframe for add-on therapy).

Study design

This is a prospective, multicentre, multinational, observational, cohort study, which does not require any changes in the current clinical management of patients with UC by the treating clinician (figure 1). The ClinicalTrials.gov identifier is NCT02586259.

Participating centres

It is anticipated that 50–100 centres in Europe, Israel and Canada will enrol patients, primarily from gastroenterology outpatient departments.

Study population

Patients from different countries will be enrolled by gastroenterologists based in clinics, hospitals and specialised centres. Patients can be included if they meet all the following inclusion criteria:

1. are aged ≥18 years;
2. are seen in the outpatient department;
3. have been prescribed budesonide MMX for the treatment of mild-to-moderate active UC;
4. have received adequate information regarding this non-interventional study and are able to understand and voluntarily sign the Informed Consent form.

Patients will be excluded if they meet any of the following criteria:

1. have severe active/fulminant UC;
2. are being treated with antibiotics or corticosteroids for the current flare;
3. have had a total/subtotal colectomy;
4. are hypersensitive to the active substance, lecithin (derived soya oil, peanut oil) or to any of the excipients;
5. are enrolled and involved in an interventional study;
6. are considered inappropriate by the investigators to participate in the study.

Study outline

Eligible patients will be recruited at the outpatient department of each participating centre. Patient enrolment will be agreed after the treatment decision is made. Patients will be treated according to routine clinical practice and budesonide MMX will be prescribed in accordance with the terms of the country marketing authorisation. The recommended dose of budesonide MMX for induction of remission is one 9 mg tablet daily in the morning, for up to 8 weeks.[16] The clinician will decide if and how the dose should be reduced, and the duration of the tapering-off period, if required. These data will be collected throughout the tapering-off period until treatment has been discontinued or after a 6-month tapering-off period (whichever occurs earlier).

Data collection and monitoring

Eligible patients will be seen at the outpatient department of each participating centre at baseline (Day 1), at the end of induction treatment (daily), and at follow-up ≥2 weeks after the end of the last treatment dose (table 1). On Day 1, data, as recommended by current ECCO guidelines,[2] will be collected by the investigator or from the patient's medical record. Patients will be given the option to fill in the questionnaires (SIBDQ, WPAI) on Day 1 and at the end of the induction treatment (daily) visit (SIBDQ, WPAI, treatment satisfaction scale), approximately 4–8 weeks after the investigator has decided to treat the patient with budesonide MMX to induce remission. An electronic case report form (eCRF) will be used to capture data. During these contacts, the clinician will also evaluate the information reported in the patient's weekly diary (if any), and will capture the data on the appropriate eCRF.

At the end of induction treatment (daily), the clinician will capture the following data: symptoms and severity of flare; AEs reported by patients (event name, seriousness, start date, stop date, causality and outcome); status of budesonide MMX treatment, and status of other treatments (mesalazine, other corticosteroids, immunosuppressive drug or biologics, and non-UC-related concomitant treatments). Depending on routine clinical practice at the participating centre, the clinician will also perform a faecal calprotectin test and evaluate the patient's UCDAI endoscopic subscore. Two weeks after the end of the last treatment dose (or up to a maximum of 6 months for a prolonged tapering-off period), the clinician will assess flare activity and any switch to other drugs, (eg, corticosteroids, immunosuppressive drug or biologics (type of therapy, start date, dose and regimen)) if any, and any AEs reported by the patient (event, seriousness, start date, stop date, causality and outcome). At the time of completion of follow-up or early discontinuation, the date will be recorded. In

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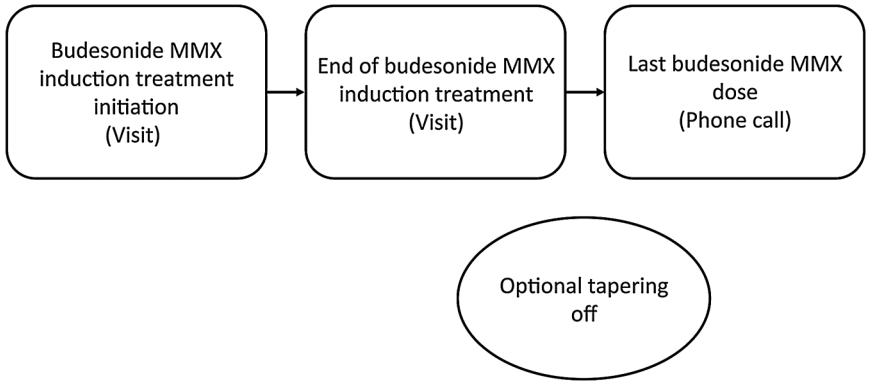


Figure 1 Study design flow chart design: prospective, observational, cohort study. This study does not require any changes in the standard clinical management of patients with UC by the treating clinician. MMX, multimatrix; UC, ulcerative colitis.

the case of early discontinuation, the reason for discontinuation will also be recorded.

Effectiveness end points

Primary effectiveness end point. The primary effectiveness end point will be the clinical benefit seen in a real-life setting, defined as the percentage of patients with clinical improvement ≥3 points in the UCDAI clinical subscore (stool frequency, rectal bleeding, Physician's Global Assessment) at the end of treatment.

Secondary effectiveness end points. Secondary effectiveness end points will be the percentage of patients with clinical remission, defined as a UCDAI clinical subscore ≤1 at the end of treatment; the percentage of patients with symptom resolution (rectal bleeding=0+stool frequency ≤1) at the end of treatment, and the percentage of patients with full symptom resolution (rectal bleeding=0 +stool frequency=0) at the end of treatment. PROs will be used as secondary end points and will include time to symptom resolution (rectal bleeding, stool frequency, urgency); change in QoL, assessed using the Short Inflammatory Bowel Disease Quality of Life (SIBDQ) questionnaire at the end of treatment;[28] change in health economic parameters, assessed using the Work Productivity and Activity Impairment (WPAI) at the end of treatment;[29 30] and treatment satisfaction evaluation at the end of treatment, assessed using an analogue scale where 0=totally unsatisfied and 10=very satisfied.[31] Faecal calprotectin, as well as endoscopies, will be tested at the beginning and end of treatment at the discretion of the individual clinician. In the subpopulation in which a faecal calprotectin test is performed, the percentage of patients with faecal calprotectin within normal range at the end of treatment will be assessed. In the subpopulation in which endoscopies are performed at the beginning and end of treatment, the percentage of patients with endoscopic healing (UCDAI endoscopic subscore=0) and the percentage of patients in remission (UCDAI endoscopic subscore ≤1) at the end of treatment will be assessed.

Tolerability end point

The secondary end point will be the tolerability of budesonide MMX in a real-life setting. Safety assessments will include AE and adverse drug reaction reporting. All AEs will be coded according to the Medical Dictionary for Regulatory Activities.

Statistical analysis

Sample size was calculated on the percentage of patients with clinical improvement ≥3 points in the clinical subscores of UCDAI score at the end of the induction treatment (once daily budesonide MMX9 mg tablet). A sample size of 300 evaluable patients will allow estimation of the two-sided 95% CI with a width equal to 11.0% of the clinical benefit when the expected percentage is equal to 38% based on the Phase III trials data. The Clopper-Pearson's formula was used for the computation.

Descriptive analyses will be carried out using the tools available within standard spreadsheet and database packages. Continuous variables will be summarised using the number of patients, mean, SD, minimum, first quartile, median, third quartile and maximum. For categorical variables, data will be summarised by the number and percentage of patients in each category. Incidence percentages will be calculated. When summarising categorical variables, if there are any missing responses, these will be shown as a separate category. When summarising continuous variables, the number of non-missing observations will be displayed. All withdrawals after enrolment will be summarised by time of, and reason for, discontinuation.

Statistical analyses will be performed using the SAS System V.9.4. A two-tailed $p<0.05$ will be considered statistically significant. Analyses will be presented with 95% CIs. Association between the response and clinical variables (with variables with a $p<0.20$ in univariate analysis) will also be tested using logistic regression analysis. Odds ratios with 95% CIs will be derived from the logistic model. To evaluate effectiveness, the primary outcome (improvement ≥3 point in the clinical subscores of the UCDAI score at the end of treatment) will be compared in patients who will receive budesonide MMX added to mesalazine at least 14 days (>2 weeks) after increased/optimised mesalazine dose for the treatment of flare (late add-on) (Cohort 1) (figure 2); patients who will receive budesonide MMX added to mesalazine within

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Table 1 Data collection

Visit	1	2	3
Time	Day 1*	End of induction treatment (daily)*	≥2 weeks after end of last treatment dose
Informed consent†	x		
Inclusion/exclusion criteria	x		
Demographics	x		
Concomitant diseases	x		
UC history	x		
Current flare activity	x	x	
Concomitant treatments	x	x	x
Effectiveness assessments (UCDAI clinical subscore)	x	x	
WPAI questionnaire‡	x	x	
SIBDQ questionnaire‡	x	x	
Treatment satisfaction scale		x	
Tolerability		x	x
Patient weekly diary§	x	x	
Fecal calprotectin¶	x	x	
UCDAI endoscopy subscore¶	x	x	

*Visits will be made in accordance with routine clinical practice, and budesonide MMX treatment must be prescribed in the usual manner in accordance with the terms of the marketing authorisation of each participating country.
†Written informed consent must be obtained prior to any study-related data collection.
‡Depending on country regulations for non-interventional study and on local clinical practice.
§The investigator will also offer the patient a weekly diary. If she/he wishes to complete this, the diary will be provided at inclusion, and the patient will be requested to return the diary to the physician at the end of daily treatment visit, whenever this occurs. The diary will be completed with information related to the last 3 days of the week.
¶Optional: to be collected, if available, because it is considered by the clinician as routine clinical practice.
SIBDQ, Short Inflammatory Bowel Disease Quality of Life; UC, ulcerative colitis; UCDAI, UC Disease Activity Index; WPAI, Work Productivity and Activity Impairment.

14 days (≤2 weeks) since mesalazine increased/optimised for the treatment of flare, or without mesalazine dose modification (early add-on) (Cohort 2) (figure 2); and patients who will receive budesonide MMX as monotherapy for the treatment of flare (mono) (Cohort 3) (figure 3). Matching will be based on the propensity score method, which attempts to balance the treatment groups so as to reduce bias of treatment selection.[32 33] The propensity score estimates the probability, using logistic regression, of receiving a particular treatment conditioned on the individual's baseline characteristics. The rationale behind propensity scores is to allow design and analysis of an observational (non-randomised) study so that it mimics particular characteristics of a RCT.

ETHICS AND DISSEMINATION

Ethics

The study will be conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The protocol has been approved by an independent ethics committee. The first ethics committee approval was: Approval Number: 12/22/2015; Board Name: Ethikkommission der Ärztekammer Hamburg. The regulatory permission to perform the study will be obtained in accordance with applicable national regulatory requirements. All ethical and regulatory approvals for the particular country will be available before the study is initiated. Consent from all patients will also be obtained from the participating centres. Patients prescribed budesonide MMX for the treatment of mild-to-moderate active UC will be counselled, and written informed consent will be obtained from all patients if the inclusion criteria are met. For patients not qualified to give their legal consent, written informed consent will be obtained from the guardian, in accordance with national/local regulations. If such patients can understand the risks and benefits of the study, they will also be informed, and will provide their written consent.

Patient safety

AEs will be reported as per the national safety reporting requirements of each participating country. Depending on national regulations, all non-serious AEs or only budesonide MMX-related non-serious AEs, spontaneously notified by the patients or observed/recorded by the investigator during the whole study period (from the signature of the informed consent until the end of the study) will be recorded by the investigator in a specific AE page of the eCRF. All serious AEs will be recorded regardless of relationship with the medicinal product. The investigator will be responsible for ensuring that any AE recorded in the eCRF (either observed by the investigator or reported by the patient) will also be recorded in the patient's medical record. All AEs will be reported to ethics committees, National Health Authority and investigators, depending on the national requirement of each country participating in the study.

Dissemination plan

At the end of the study, one or more manuscripts on the full results would be published in peer-reviewed journal(s). Data from individual countries may also be published separately. All study data will be stored on a fully validated, eCRF system held by an independent third-party contract

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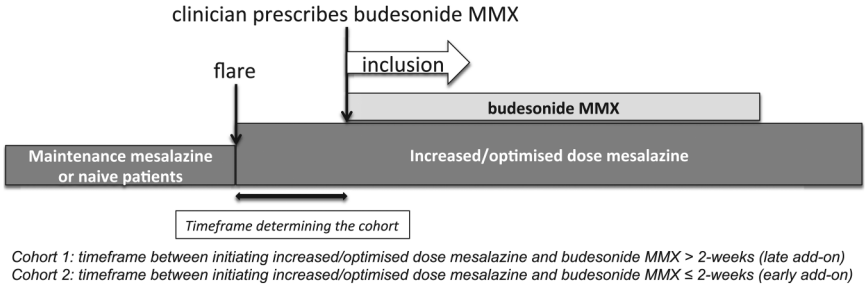


Figure 2 Cohorts 1 and 2: add-on therapy primary outcome: improvement ≥3 point in the clinical subscores of Ulcerative Colitis Disease Activity Index score at the end of treatment. MMX, multimatrix.

research organisation. The investigator will approve/authorise the eCRF entries for each patient. A data management plan will be created before data collection begins, and will describe all functions, processes and specifications for data collection, cleaning and validation. After the study database is declared clean and is released to the statistician, a final copy of the database will be stored at the sponsor.

DISCUSSION

UC is a chronic, idiopathic, inflammatory disorder, which has a significant impact on every aspect of the affected individual's life, and accounts for substantial costs to healthcare systems and society.[2] Corticosteroids are part of the armamentarium for induction of remission in UC and although they may improve symptoms, they have significant adverse effects.[7] Budesonide MMX is a new option for treating mild-to-moderate active UC, providing gastroenterologists with an orally administered alternative to systemic corticosteroids. In RCTs, budesonide MMX was effective, with an AE profile comparable with placebo.[19] Most patients with UC included in RCTs, however, are not representative of a real-life UC setting,[22] which raises questions about the clinical benefit of this treatment in clinical practice. The goal of our study is to understand real-life efficacy of budesonide MMX for inducing remission in mild-to-moderate UC, and to determine how it is prescribed and used by gastroenterologists in routine clinical practice. Whereas efficacy measures how well a treatment works in clinical trials or laboratory studies, treatment effectiveness relates to how well it works in clinical practice.[34] One of the challenges, however, when conducting effectiveness studies, is to distinguish real treatment effects from those caused by bias or confounding. We will address this potential bias by matching patients in the different treatment groups based on a propensity score, a validated method,[23 32 33] and by doing so, we aim to provide valuable information on the therapeutic effects of budesonide MMX in clinical practice. The propensity scoring methodology has been used successfully in a retrospective study of antitumour necrosis factor-α use in paediatric Crohn's disease.[35] As far as we are aware, however, our study represents the first prospective, observational study to measure the clinical effectiveness of an IBD therapy in routine clinical practice using propensity scoring. We anticipate that the innovative methodology of our study will help to inform the design of future real-world studies assessing the effectiveness of IBD therapies.

Patients' involvement in the care they receive is being given greater emphasis, and as a result, PRO measures are becoming increasingly important end points for clinical effectiveness studies.[26] This is particularly the case for products developed to treat chronic, disabling conditions, such as UC, where the intention is not to cure but to induce remission, ameliorate symptoms, facilitate functioning and, ultimately, to improve QoL.[26] PROs can evaluate symptoms, signs, functional status, perceptions, or other aspects, such as tolerability, from the patient's perspective, and complement clinician-reported measures.[36] In our study, PRO data will be

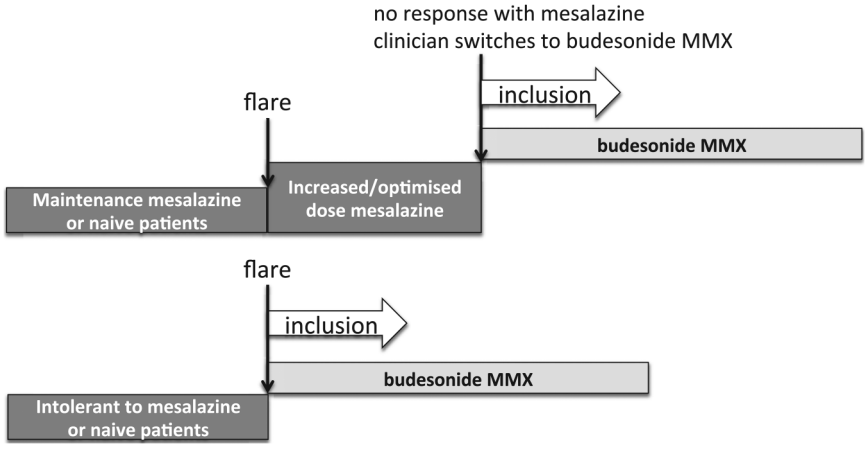


Figure 3 Cohort 3: monotherapy primary outcome: improvement ≥3 point in the clinical subscores of the Ulcerative Colitis Disease Activity Index score at the end of treatment. MMX, multimatrix.

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collected via the SIBDQ, WPAI and treatment satisfaction scale questionnaires, as well as from the patient's weekly diary. To address the potential bias due to PROs, patient weekly diaries and questionnaires will be completed by the patient alone, without any involvement of the investigator. The information provided is in line with current thinking from the FDA on the importance of PROs in assessing disease activity in IBD[25 26] and will help inform clinical care and decision-making.

The results of our study are expected to provide information in the field of UC and further evidence on effectiveness to support clinicians in their daily practice and inform therapeutic guidelines.

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Contributors SD, LP-B, LDA are involved in clinical study design, critical review of the manuscript and final approval of the manuscript; CI is responsible for clinical study design and final approval of the manuscript; GDH, AD, ID, AH, EL, GR are involved in final approval of the manuscript.

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Competing interests SD has served as a speaker, consultant and advisory board member for Schering-Plough, Abbott (AbbVie) Laboratories, Merck and Co, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, α Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson and Johnson. AH has lectured/been on advisory boards for Atlantic, BMS, Falk Pharma, MSD, AbbVie, Takeda, Hospira, Napp Pharmaceuticals, Ferring, Yakult, Pfizer, Janssen, Warner Chillcott, and Genentech. AD has served as a speaker and consultant for Ferring, Falk Pharma, Mundipharma, Hospira, Sandoz, Otsuka, Abbvie, Janssen, Takeda, MSD, Vifor, and Pharmacosmos. EL has received fees for: Educational Grant: MSD, Abbvie; Speaker Fees: Abbvie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, Takeda; Advisory Board: Abbvie, Ferring, MSD, Takeda, Mitsubishi Pharma, Celltrion, Prometheus. GD'H has served as advisor for Abbvie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol Meiers Squibb, Boerhinger Ingelheim, Celgene, Celltrion, Cosmo, Covidien, Ferring, DrFALK Pharma, Engene, Ferring, Galapagos, Gilead, Glaxo Smith Kline, Hospira, Johnson and Johnson, Medimetrics, Millenium/Takeda, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Novonordisk, Pfizer, Prometheus laboratories/Nestle, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant and Vifor, and received speaker fees from Abbvie, Ferring, Johnson and Johnson, MSD, Mundipharma, Norgine, Pfizer, Shire, Millenium/Takeda, Tillotts, and Vifor. ID has served as a speaker and consultant for Ferring, Falk Pharma, Rafa laboratories, Abbvie, Janssen, Takeda, Genentech, Pfizer, Protalix, and Given Imaging. GR has served as a speaker and consultant for Abbvie, Ardeypharm, AstraZeneca, Boehringer, Celgene, Ferring, Falk Pharma, Genentech, Janssen, Novartis, Merck, MSD, Pfizer, Pharmabiome, Roche, Takeda, Tillots, UCB, Vital Solutions, and Vifor, Zeller. LDA is an employee of Ferring. CI has served as biostatistician consultant for Roche, Bayer, Takeda, Bracco Imaging, Chiesi Farmaceutici, Orion Pharma, Gilead, and MolMed. LPB has received consulting fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, and Sandoz; Lecture fees from Merck, Abbvie, Takeda, Janssen, Takeda, Ferring, Norgine, Tillots, Vifor, Therakos, Mitsubishi, and HAC-pharma.

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