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Symptom Improvement of ulceRative colitis after an Induction dose of UStekinumab in Japanese clinical practice (SIRIUS), measured using patient-reported outcomes: a prospective observational study

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ABSTRACT

Introduction Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease of the large intestine. Ustekinumab is a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23 and has proven efficacy in inducing and maintaining remission in adult patients with moderate-to-severe UC. In the Symptom Improvement of ulceRative colitis after an Induction dose of Ustekinumab study, we will document the initial treatment response (daily patient-reported outcomes for 8 weeks from first infusion) and treatment patterns of patients wih UC receiving an induction dose of ustekinumab in the real-world setting in Japan. We will also investigate the relationship between the treatment response at week 8 and early indicators of response and determine patient factors that may define the appropriate dosing interval for maintenance therapy.

Methods and analysis For this single-arm, prospective observational study at 24 centres in Japan with a follow-up period of 16/20 weeks, we aim to recruit 140 patients with moderate-to-severe UC between July 2021 and July 2022. All surveys will be conducted in Japanese and patient-reported outcomes relating to rectal bleeding, stool frequency, abdominal pain, nocturnal diarrhoea, tenesmus and perception of UC symptoms will be recorded using a smartphone application, where the patients can enter their initial response to ustekinumab induction therapy on a daily basis. Dosing intervals and the reasons for selecting this interval, and concomitant medications taken during treatment with ustekinumab will be collected by a physician questionnaire at the end of the study. On completion of primary end point (8-week patient-reported outcomes) data collection, results will be reported sequentially.

Ethics and dissemination The study has been approved by the ethics committee of each facility involved and the Institutional Review Board of the non-profit organisation MINS.

Trial registration number UMIN000043753, NCT04963725.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Symptom Improvement of ulceRative colitis after an Induction dose of Ustekinumab (SIRIUS) study will reflect actual usage of ustekinumab for moderate-to-severe ulcerative colitis (UC) in real-world clinical practice in Japan.
⇒ The SIRIUS study will assess patient-reported outcome (PRO) daily for 8 weeks after the induction of ustekinumab and to explore optimal management in the early phase of UC treatment.
⇒ The PRO questionnaire consists of questions suitable for daily monitoring of UC symptoms, which will allow detailed analysis of changes in symptoms in response to ustekinumab.
⇒ A smartphone application enables real-time tracking of daily conditions without the burden of visits on patients.
⇒ One limitation is that this study assesses only short-term and not long-term outcomes.

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory bowel disease (IBD) that causes mucosal inflammation and may affect any portion of the large bowel continuously from the rectum to the proximal segments of the colon.[1] The resultant natural history of the disease is one of relapsing and remitting mucosal inflammation with a 10-year cumulative risk of surgery of approximately 15%.[2] The incidence and prevalence of UC are increasing globally, including in Japan. Although UC can develop in younger children,[3] the age of onset increases rapidly from the late teens, with the peak occurring in the mid-20s for both men and women.[2]

The symptoms of UC include diarrhoea, rectal bleeding, bowel urgency and

abdominal pain, all of which have a significant impact on patients' daily lives.[4] The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) guidance highlight the importance of symptomatic remission as a short-term treatment goal.[5] In addition, pharmaceutical treatment of UC aims to achieve sustained clinical and endoscopic remission (mucosal healing) and to interrupt the naturally progressive course of the disease that culminates in serious complications and the need for surgical intervention.[2]

The number of drugs available for UC is increasing, and treatment selection is becoming more complicated. Clarification of the efficacy of each formulation in treating clinical symptoms over the course of the disease will lead to more appropriate treatment selection and formulation use. In Japan, the anti-inflammatory compound 5-aminosalicylic acid (5-ASA) is recommended for patients with mild-to-moderate UC.[6] If 5-ASA therapy fails, corticosteroid treatment is recommended, followed by leucocyte apheresis, immunomodulators, calcineurin inhibitors, a Janus kinase inhibitor or biological therapies (infliximab, adalimumab, golimumab, ustekinumab or vedolizumab), if corticosteroid does not provide adequate control or the patient becomes refractory or progresses to severe disease.[6]

Ustekinumab is a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23.[7] A phase III study (UNIFI) including adult patients with moderate-to-severe UC, where biological therapy had failed in approximately half of the patients, showed a significantly higher remission rate at week 8 in patients who received intravenous ustekinumab 6 mg/kg compared with placebo.[8] Furthermore, among patients who achieved remission at week 8 and underwent re-randomisation, a significantly higher percentage of patients assigned to subcutaneous ustekinumab 90 mg treatment every 8 or 12 weeks remained in remission for 44 weeks compared with placebo.[8] Based on these results, ustekinumab was approved in Europe (September 2019), the USA (October 2019) and Japan (March 2020) for the treatment of moderate-to-severe UC in adult patients with inadequate response to conventional therapies.

The approved induction dose of ustekinumab in Japan is a single intravenous infusion of 6 mg/kg. Ustekinumab has a longer dosing interval than other IBD drugs, which means that patients visit hospital less frequently. Maintenance therapy begins 8 weeks after the induction dose and consists of subcutaneous ustekinumab 90 mg administered every 12 weeks thereafter. The 12-week maintenance dosing interval may be reduced to 8 weeks by the attending physician if the patient shows reduced response to the treatment.

The detailed remission rate before week 8 was not investigated in the UNIFI study,[8] and there are currently limited data on the early patient-reported outcome (PRO) response to the ustekinumab induction dose. Therefore, we designed the Symptom Improvement of ulceRative colitis after an Induction dose of Ustekinumab in Japanese clinical practice (SIRIUS) study to evaluate the early response to ustekinumab induction therapy in patients with moderate-to-severe UC in the real-world setting in Japan. PROs are an important end point for the assessment of treatment efficacy, and to determine treatment decisions. STRIDE-II guidance recommends at least 50% reduction in PRO2 score (the sum of rectal bleeding and stool frequency scores) and also recommends changing treatment if this objective has not been achieved.[5] In the SIRIUS study, we use a smartphone application to collect data for initial response to the induction therapy with ustekinumab on a daily basis, where patients can enter PROs themselves at home. The aim is to obtain more accurate PRO information than would be obtained during hospital visits, particularly because of the long dosing interval with ustekinumab. This article describes the design and methodology of the SIRIUS study.

METHODS AND ANALYSIS

Study design

The SIRIUS study is a single-arm prospective observational study that is being conducted at 24 centres in Japan. Patient recruitment started in July 2021 and will end in July 2022. The patients will be followed up for 16 or 20 weeks depending on the dosing interval (8 or 12 weeks, respectively). The structure of the study from its initiation to data analysis is shown in figure 1. This study is being conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Medical Research in Humans, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare of Japan and all applicable laws and guidelines. Written informed consent will be obtained from all patients. The study is registered at the University Hospital Medical Information Network Center and at ClinicalTrials.gov registry.

Study objectives

The objectives of this study are to describe treatment response and treatment pattern in the real-world setting among patients with moderate-to-severe UC who are initiating ustekinumab in Japan.

The primary study objective is to evaluate early response to ustekinumab induction therapy in patients with moderate-to-severe UC in the real-world setting in Japan. Secondary objectives are to investigate the relationship between the treatment response at week 8 and early indicators of response, and to describe the ustekinumab treatment pattern for patients initiating ustekinumab for UC in Japan, in particular, the dosing interval for maintenance therapy. Although the dosing interval in maintenance therapy can be reduced from 12 to 8 weeks, the conditions/characteristics of patients who qualify for an interval reduction is currently unknown. If there are a sufficient number of patients in each subgroup receiving maintenance ustekinumab every 8 or 12 weeks, or sufficient variability in independent variables, the study may

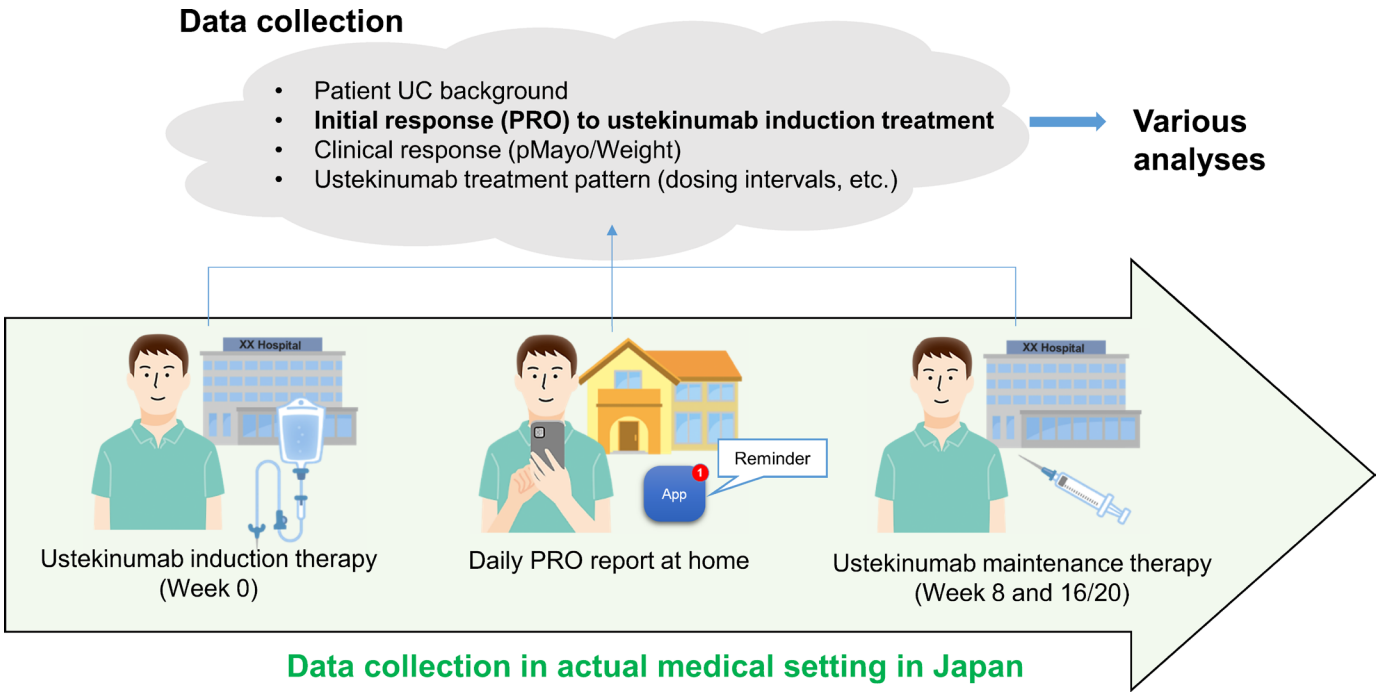

Figure 1 Data collection in actual medical setting in Japan and analysis of results. pMayo, partial Mayo score; PRO, patient-reported outcome; UC, ulcerative colitis.

also explore differences in, or predictors of, induction treatment response and maintenance therapy dose interval.

We hypothesised that there may be a relationship between early remission and late response; therefore, we expect that evaluating early response could give us valuable information that will help with making decisions about the appropriate dosing interval during maintenance therapy. The results of the Japanese population in the UNIFI will be also examined to provide a meaningful description of the categorical relationship between early response and efficacy (secondary objective) at week 8.

Study population and sample size

To be included in the study, patients must meet the following criteria: a definitive diagnosis of UC, as defined in accordance with the standard diagnostic criteria[6]; age ≥16 years; moderate-to-severe UC (partial Mayo (pMayo) score 5–9 points) as determined by the attending physician; inadequate response to, or poor tolerance of previous therapy for UC; able to provide signed informed consent for participation in the study by the patient or a legal representative (in patients aged 16–19 years) according to each institutional/hospital regulation and ability to read, understand and enter evaluation metrics for the PRO questionnaire using a smartphone/tablet.

Patients will be excluded if they have previously received ustekinumab (including use in clinical studies); have severe, widespread colitis with imminent risk of colectomy; a history of stoma or fistula; a history of extensive colectomy (eg, residual colon <30 cm); presence of fulminant colitis and currently hospitalised for worsening UC-related symptoms (not excluded if hospitalised for receipt of the first dose of ustekinumab); received 3 months of systemic biological therapy for other indications (eg, Crohn's disease, psoriasis, rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis); received an investigational drug (including investigational vaccines) or who used an invasive medical device within 3 months before the start of the study or during the baseline data collection period and currently enrolled in intervention trials or other observational studies sponsored by Janssen Pharmaceutical (including postmarketing surveillance).

The target number of participants is 140. Data of Japanese patients in the UNIFI study (data on file) were collated with the analysis plan of this study, and power calculations were performed. Since Japanese patients were large enough to detect the relationship between rectal bleeding at week 2 and symptomatic remission at week 8 in the UNIFI study (data on file), we proposed a sample size of 140, taking into account potential discontinuations or incomplete data, as well as real-world ustekinumab prescription patterns in Japan.

Outcome measures and survey items

The primary outcome measures are the percentage of participants with a rectal bleeding score of 0 (no blood seen) and the percentage of participants with a stool frequency score of 0 or 1 (where 0=normal number of stools and 1=1 to 2 stools more than normal) up to week 8 (figure 2, tables 1 and 2).

Secondary end points include change from baseline in calculated pMayo score,[9] rectal bleeding score and stool frequency score at week 8 and week 16 or 20; percentage of participants with a reduction in rectal bleeding score ≥1 from baseline and percentage of participants

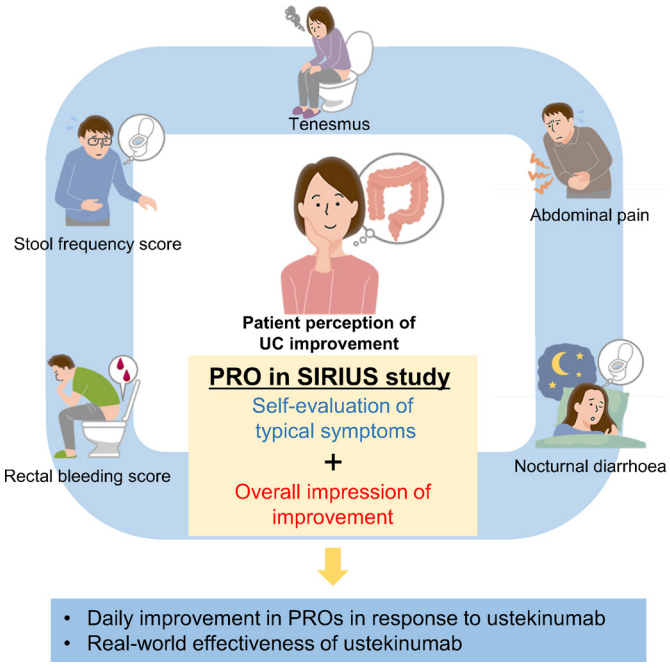

Figure 2 Surveys completed using smartphone application and PROs. PRO, patient-reported outcome; SIRIUS, Symptom Improvement of ulceRative colitis after an Induction dose of Ustekinumab; UC, ulcerative colitis.

with reduction in stool frequency score of ≥1 from baseline up to week 8; change from baseline in abdominal pain through week 8; percentage of participants with presence of nocturnal diarrhoea, presence of tenesmus and with a perceived improvement in UC up to week 8.

All surveys are conducted in Japanese. Where available, information relating to patient characteristics, disease history and previous and current treatments are to be documented at the baseline visit only. Data related to patients' history will be collected from their medical records or through discussion with the patient (table 1). We will also include information about any specific therapy used for the treatment of UC prior to (or at) the baseline visit that the patient has been deemed to be inadequately responding to, or intolerant of, that led to the decision to initiate ustekinumab. Using a smartphone application (Medidata), patients will complete the PRO survey questions, including rectal bleeding and stool frequency, abdominal pain, presence of tenesmus, awakenings due to nocturnal diarrhoea and perceived improvement in UC symptoms, which will be recorded daily for 8 weeks. Rectal bleeding and stool frequency will also be recorded at week 16 or 20 (figure 3). Remission is defined as a stool frequency score of 0 or 1 and a rectal bleeding score of 0 (table 2). Body weight, blood data and pMayo score will be recorded at the time of ustekinumab intravenous injection (baseline), at the time of ustekinumab subcutaneous injection (week 8 and week 16 or 20) and during visits for purposes other than ustekinumab administration between day 7 and 34 after the ustekinumab induction dose (figure 3).

Dosing intervals (choice between 8 and 12 weeks) and the reason for selecting this interval will be collected by physician questionnaire after the end of the study. As this is an 8-week study, we do not anticipate many changes to

Table 1 Survey items

Category	Item (questionnaire)
Items completed by physicians (timing of assessment)	
Patient characteristics (baseline)	Age (years); sex; body weight (kg); smoking history (never, past, current); family history of inflammatory bowel disease; cancer history (never, past, current); extraintestinal complications (never, past, current).
UC diagnosis and history (baseline)	Date of initial UC diagnosis; prior UC surgery; previous indicators of severe disease; hospital admission in last 12 months for UC exacerbations or complications; Mayo endoscopy score and UC classification based on extent of disease (only if endoscopy undertaken in last 12 months); previous therapy(ies) for UC; list of all treatment types previously used for UC (including apheresis but excluding over-the-counter treatments), at any time before baseline.
Prior therapy (baseline)	Treatment type and name of the 'prior therapy'; date of last dose of the 'prior therapy'; duration of the 'prior therapy' from initiation up to date of cessation or study baseline (whichever is later); only if the 'prior therapy' is a corticosteroid, the most recent dosage of the 'prior therapy' (dose, frequency, route); whether the 'prior therapy' is being continued (ie, supplemented with ustekinumab) or has been discontinued; reason for discontinuation or supplementation of that 'prior therapy' (inadequate response, intolerance).
Symptom evaluation (baseline and postbaseline visits)	pMayo score; body weight (kg); blood data (if any).
Treatment pattern of ustekinumab maintenance therapy (all postbaseline visits)	Dosing interval (selection of once every 8 weeks and once every 12 weeks) and the reason for selecting this interval; concomitant medications taken during treatment of UC with ustekinumab.
Items reported by patients (timing)	
Patient-reported outcomes (daily for 8 weeks)	Rectal bleeding and stool frequency (as assessed by the pMayo score)—primary end point; abdominal pain (NRS scale); presence or absence of tenesmus; any awakening due to nocturnal diarrhoea; evaluation of perception of UC symptoms (NRS scale).

NRS, numerical rating scale; pMayo, partial Mayo; UC, ulcerative colitis.

Table 2 Definition of scores in symptomatic evaluations

pMayo* components			
Score	Rectal bleeding†	Stool frequency‡	Physician's global assessment§
0	No blood seen	Normal no. of stools for this patient	Normal
1	Streaks of blood with stool less than half the time	One to two stools more than normal	Mild disease
2	Obvious blood with stool most of the time	Three to four stools more than normal	Moderate disease
3	Blood alone passes	Five or more stools more than normal	Severe disease
NRS§ components			
Score	Abdominal pain¶		Perception of UC improvement**
0	No pain		Completely better (no UC symptoms)
5	Moderate pain		Starting condition (condition immediately before ustekinumab induction)
10	Worst pain		Poor condition (lots of UC symptoms)
Closed question components			
Tenesmus††			Yes/No‡‡
Nocturnal awakenings§§			Yes/No§§

*pMayo score=rectal bleeding+stool frequency+physician's assessment.[9]
†The daily bleeding score represents the most severe bleeding of the day.
‡Each patient serves as his/her own control to establish the degree of abnormality in stool frequency.
§The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being and other observations, such as physical findings and the patient's performance status.
¶NRS is a 11-point numeric scale to measure the pain intensity in adults.[14]
**The abdominal pain score represents the most severe pain of the day.
††The status immediately before ustekinumab induction is reflected as a score of 5 (baseline); improvement is shown by a score of <5 and worsening by a score of >5; a score of 0 indicates that UC is not present. The patient enters the overall status of the day.
‡‡The subject has an urge to defecate but has no bowel movement, has little bowel movements or has only mucous stools.
§§Counts if the subject experiences at least one symptom during the day.
¶¶Waking up during the night to defecate.
NRS, numerical rating scale; pMayo, partial Mayo; UC, ulcerative colitis.

medication during the study; therefore, information on concomitant medication will be collected by physicians at baseline and during the poststudy survey.

Data management

The study uses an electronic data collection system, accessible only to appropriately trained investigators, to register patients, collect questionnaire responses and create a database. The investigator is responsible for the quality of the data. If there is any inconsistency in PRO inputs or a query arises, the investigator will notify the physician and the concerned patient. Since this is an observational study, physicians are not directly involved with collection of the PRO data.

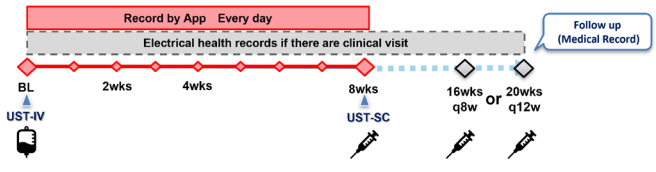

Figure 3 Dosing regimen of UST in adults with moderate-to-severe ulcerative colitis. BL, baseline; IV, intravenous; q8w or q12w, every 8 or 12 weeks; SC, subcutaneous; UST, ustekinumab.

Statistical analysis

This is an exploratory study to describe the initial use of ustekinumab in patients with UC in clinical practice in Japan, and has no prespecified hypotheses. The PRO database will be locked after the last patient has completed the PRO data collection. Logistic regression analysis will be used to assess the relationship between clinical response at each week and clinical remission status at week 8.

Patient and public involvement statement

Patients were not involved in the development of the study design, but we integrated patients' opinions on the

specifications of the smartphone application for PRO data collection.

ETHICS AND DISSEMINATION

The study is funded by Janssen Pharmaceutical (Tokyo, Japan). It has been approved by the ethics committee of each facility involved and the non-profit organisation MINS Institutional Review Board. A steering committee has been established that consists of medical specialists who will conduct the study, and representatives of cooperative research institutes. The results will be compiled and subsequently submitted to journals for publication.

DISCUSSION

This is the first study to evaluate early response to ustekinumab (ie, during 8 weeks after induction therapy). We expect this would be achieved by evaluating the effect of ustekinumab on PROs, using a smartphone application to collect the information from each participating patient. In this study, PRO2 (rectal bleeding and stool frequency scores) is used to monitor the early response of patients wih UC to ustekinumab therapy. It is recommended by STRIDE-II because of its strong correlation with endoscopic healing.[5] PROs are also reported to correlate with patient well-being, and the use of PROs to monitor treatment effect can fill the gap between the patients' and physicians' perception of medical conditions.[10] The PROs in patients receiving vedolizumab for the treatment of UC and Crohn's disease were monitored at 2, 4 and 6 weeks after the start of treatment, and significant improvements in symptoms were observed as early as 2 weeks after the initial vedolizumab infusion.[11] Daily monitoring of PROs for 15 days has been reported in a study evaluating the effect of tofacitinib on UC symptoms.[12] Significant improvements in symptoms were seen within 3 days of starting treatment with tofacitinib compared with placebo. This study with tofacitinib showed that treatment efficacy after 8 weeks of treatment induction could be predicted using a short-term PRO assessment. A reduction of ≥1 point in stool frequency subscore from baseline had a positive predictive value of 79.3% for the association of response at day 3 with that of day 15, which means that 79.3% of patients with response at day 3 are predicted to maintain response through day 15.[12] Based on these data with other biologicals, we anticipate that the early PRO response to ustekinumab can also be used to predict later treatment efficacy, confirming this is a key goal of the SIRIUS study. Moreover, as the current study is a prospective real-world study in a heterogeneous group of patients, it has an advantage over the PROs with vedolizumab and tofacitinib that were obtained from post hoc analyses of clinical trial data.

Various methods are in use for the collection of PRO data. In the study with tofacitinib, an interactive voice recording system was used for daily recording of PRO data.[12] In this study, a smartphone application is being used to collect daily PRO data from patients. Another clinical study, YOu and Ulcerative colitis: Registry and Social network (), is using a similar digital application to investigate the effects of lifestyle, psychosocial factors, PRO, admission rates and colorectal resection rates in Japanese patients wih UC.[13]

The SIRIUS study has various strengths. It reflects the actual usage of ustekinumab and treatment trend of moderate-to-severe UC in real-world clinical practice in Japan. The patients can report their daily perception of improvement in disease severity through their smartphones and need not visit the outpatient clinic regularly nor do they need to undergo frequent endoscopic examinations. The limitations of the study are its small patient population and the short-term follow-up, as long-term remission is not a study objective. Moreover, that the rate of filling out forms may decrease over time due to familiarity with the smartphone. In addition, a decline in adherence due to a change in model, crisis malfunctions, etc may affect the response rate.

This will be the first study to record daily PROs for 8 weeks, with a goal of characterising the early response to ustekinumab in patients with UC. By clarifying the correlation between patient background and clinical symptoms related to the initial response to ustekinumab, we hope that ustekinumab will become a more acceptable therapeutic drug. The results of the study may enable us to establish which circumstances the patient considers necessary to monitor versus those that do not need monitoring. We anticipate that the SIRIUS study findings will help physicians to understand the early changes in symptoms that patients with mild-to-moderate UC may expect during treatment with ustekinumab, and may help them plan maintenance ustekinumab treatment regimens that are tailored to each individual patient's condition and disease status.

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Contributors All authors participated in the interpretation of study results, and in the drafting, critical revision and approval of the final version of the manuscript. KM, KN, SN, YM and TH were involved in the study design. KM and TH are investigators and will collect the data in the study.

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