


BMJ Open Proactive infliximab optimisation using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease: study protocol for a randomised, controlled, multicentre, open-label study (the OPTIMIZE trial)

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ABSTRACT

Introduction Preliminary data indicates that proactive therapeutic drug monitoring (TDM) is associated with better outcomes compared with empiric dose escalation and/or reactive TDM, and that pharmacokinetic (PK) modelling can improve the precision of individual dosing schedules in Crohn's disease (CD). However, there are no data regarding the utility of a proactive TDM combined PK-dashboard starting early during the induction phase, when disease activity and drug clearance are greatest. The aim of this randomised, controlled, multicentre, open-label trial is to evaluate the efficacy and safety of a proactive TDM combined PK dashboard-driven infliximab dosing compared with standard of care (SOC) dosing in patients with moderately to severely active CD.

Methods and analysis Eligible adolescent and adult (aged ≥16–80 years) patients with moderately to severely active CD will be randomised 1:1 to receive either infliximab monotherapy with proactive TDM using a PK dashboard (iDose, Projections Research) or SOC infliximab therapy, with or without a concomitant immunomodulator (IMM) (thiopurine or methotrexate) at the discretion of the investigator. The primary outcome of the study is the proportion of subjects with sustained corticosteroid-free clinical remission and no need for rescue therapy from week 14 throughout week 52. Rescue therapy is defined as any IFX dose escalation other than what is forecasted by iDose either done empirically or based on reactive TDM; addition of an IMM after week 2; reintroduction of corticosteroids after initial tapering; switch to another biologic or need for CD-related surgery. The secondary outcomes will include both efficacy and safety end points, such as endoscopic and biological remission, durability of response and CD-related surgery and hospitalisation.

Ethics and dissemination The protocol has been approved by the Institutional Review Board Committee of the Beth Israel Deaconess Medical Center (IRB#:2021P000391). Results will be disseminated in peer-reviewed journals and presented at scientific meetings.
Trial registration number NCT04835506.

Strengths and limitations of this study

- This is an investigator-initiated, multicentre, randomised controlled trial assessing the role of early proactive therapeutic drug monitoring based on a PK-dashboard in patients with Crohn's disease.
- A strength of the study is the use of a central lab for evaluation of infliximab concentrations and high-sensitivity C-reactive protein, albumin and antibodies to infliximab levels.
- An advantage of the study is the use of central reading for scoring endoscopic disease activity.
- Objective efficacy measures such as biological and endoscopic remission are included as secondary outcomes of the study.
- A limitation of the study is that blinding of investigators and subjects to the treatment assignment is not feasible.

INTRODUCTION

Crohn's disease (CD) is a life-long chronic inflammatory bowel disease (IBD) characterised by transmural inflammation of the intestine.¹ CD is a global disease in the 21st century with increasing incidence in newly industrialised countries.² One of the most effective therapies to treat patients with moderate-to-severe CD is the anti-tumour necrosis factor (anti-TNF) agent infliximab (IFX), either as monotherapy or as a combination therapy with an immunomodulator (IMM), such as thiopurines or methotrexate.^{3–5} The SONIC (The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) trial showed that of 169 patients receiving IFX combination therapy with azathioprine, 96 (56.8%) were in corticosteroid (CS)-free

clinical remission at week 26 (the primary end point), compared with 75 of 169 patients (44.4%) receiving IFX alone ($p=0.02$).⁴ Although more effective, combination therapy is associated with more serious adverse events (SAEs), such as serious opportunistic infections and cancers,^{6,7} as well as potential treatment adherence issues.⁸ Consequently, many patients and physicians choose to use IFX alone as safety is often prioritised over efficacy.^{9,10}

Up to 30% of patients do not respond to IFX induction therapy (primary non-response (PNR)), and up to 50% of initial responders lose response over time (secondary loss of response (SLR)).¹¹ Reactive therapeutic drug monitoring (TDM) helps to explain and better manage these patients with lack or loss of response to IFX. In many cases, the lack or loss of response is due to pharmacokinetic (PK) issues, characterised by low drug concentrations with or without development of antibodies to IFX (ATI).^{12,13} Unfortunately, reactive TDM or empiric dose escalation is often too late for patients who do not either respond to IFX induction therapy or lose response during maintenance. This reactive approach results in many patients losing IFX as a therapeutic option.^{14–17} Multiple studies have shown that higher IFX concentrations during both induction and maintenance is associated with favourable therapeutic outcomes and, furthermore, that ATI result in low drug concentrations, PNR and SLR.^{18–23} The prospective PANTS (Personalising anti-TNF therapy in CD) study showed that low IFX concentration at week 14 was independently associated with PNR at week 14 and non-remission at week 54.¹⁹ The optimal week 14 IFX concentration associated with remission at weeks 14 and 52 was 7 mg/L, while suboptimal IFX concentrations were associated with the development of ATI. Exposure-outcome relationship studies also show that higher IFX concentrations are likely required to achieve more stringent therapeutic outcomes.²⁰

Preliminary data show that proactive IFX optimisation to achieve a threshold drug concentration during maintenance therapy compared with empiric dose escalation and/or reactive TDM is associated with better long-term outcomes including longer drug persistence, reduced risk of relapse and fewer hospitalisations and surgeries.^{14–17} Of note, none of the studies investigated the role of proactive TDM during the induction phase when the inflammatory burden and drug clearance are highest. Drug concentrations need to be higher during induction and adequate drug concentrations (>15 – 30 $\mu\text{g}/\text{mL}$ for week 2 and >10 – 20 $\mu\text{g}/\text{mL}$ for week 6) are associated with better short-term and long-term outcomes.¹³ Proactive TDM can also support the practice of IFX optimised monotherapy instead of IFX combination therapy with an IMM. Two recent observational studies showed that IFX durability was not different between patients on IFX monotherapy with dosing based on proactive TDM and patients receiving combination therapy.^{24,25} A post hoc analysis of the SONIC trial showed that the superior remission rates with combination IFX and azathioprine

therapy were more related to an effect on IFX concentrations and decreasing ATI than a synergistic effect. Patients receiving IFX monotherapy appeared to do just as well as patients on combination therapy when they achieved the same IFX concentrations.²⁶ Of note, a recent study showed that the impact of thiopurine exposure on immunogenicity to IFX in the setting of IFX concentrations >5 $\mu\text{g}/\text{mL}$ seems negligible.²⁷

IFX dosing by weight only (ie, mg/kg) may not be adequate for many patients as interindividual variability in drug clearance and other factors affecting IFX concentrations and PK are often not accounted for, such as albumin and C reactive protein (CRP) levels.^{28–32} Dosing calculators account for these individual factors and improve the precision of dosing towards better personalised medicine. These systems have already been validated, and personalised dosing has shown clinical benefit in patients with IBD.^{31–38} The iDose (Projections Research, Phoenixville, Pennsylvania, USA) dashboard is a clinical decision support tool that uses Bayesian updates to visualise and forecast a patient's PK profile and the timing and dose of infusions to ensure therapeutic concentrations of IFX are maintained and thus optimise the efficacy of IFX during induction and maintenance. The iDose dashboard accounts for dose, IFX serum concentrations and laboratory values such as albumin and CRP as well as weight to predict a patient's drug clearance and provide a personalised dosing schedule intended to achieve trough concentrations that have been associated with remission. A prospective single-arm dashboard-guided dosing pilot study including both adults and children with IBD showed that iDose is feasible in the real-world setting and confirmed that approximately 80% of patients need a higher IFX induction dose than the standard dosing regimen.³¹ The PRECISION (Precision dosing of infliximab versus conventional dosing of infliximab) trial showed a clinical benefit from personalised dosing in patients with IBD using dashboard-guided dosing (iDose), with a significantly higher proportion of patients maintaining clinical remission after 1 year of treatment compared with patients that continued treatment without proactive adjustments (88% vs 64%, respectively).³⁴

Study aim and objectives

The aim of the OPTIMIZE (Proactive infliximab optimisation using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease) trial is to evaluate whether IFX proactive TDM combined PK dashboard (iDose)-driven dosing is more effective than standard of care (SOC) IFX dosing (with or without a concomitant IMM at the physician's discretion) for the treatment of moderately to severely active CD. The specific objectives and end points of the OPTIMIZE trial are described in table 1.

Table 1 Specific objectives and end points of the OPTIMIZE study

Primary objective	Primary end point	Evaluation time point
To evaluate the efficacy of iDose-driven IFX dosing versus SOC dosing in maintaining sustained CS-free clinical remission	Proportion of subjects with sustained CS-free (no CS use from week 14 through 52) clinical remission (CDAI <150 at weeks 14, 26, 52) and no need for rescue therapy.	Week 14 through 52
Secondary objectives	Secondary end points	Evaluation time point(s)
To evaluate clinical, endoscopic and biologic CD outcomes in subjects that receive iDose-driven IFX dosing versus SOC dosing	1. Proportion of subjects in CS-free clinical remission (CDAI <150 and no use of CS within previous 6 months).	Week 52
	2. Proportion of subjects in deep remission (CDAI <150 and SES-CD ≤4, with no individual subscore >1).	Week 52
	3. Proportion of subjects with a composite biological (hs-CRP <10 mg/L) and endoscopic remission (SES-CD ≤4).	Week 52
	4. Proportion of subjects with sustained CS-free clinical remission (CDAI <150 and no CS use from week 14 through week 52).	Week 52
	5. Proportion of subjects who are primary non-responders (≤70-point decrease in CDAI score and at least one of: hs-CRP ≥10 mg/L, FC >250 µg/g or SES-CD >4; or need for rescue therapy prior to week 14).	Week 14
	6. Proportion of subjects with sustained biological remission (hs-CRP <10 mg/L).	Week 14 through 52
	7. Proportion of subjects with endoscopic remission (SES-CD ≤4, with no individual subscore >1).	Week 52
	8. Proportion of subjects with normalisation of hs-CRP (decrease from ≥10 at baseline to <10 mg/L).	Week 52
	9. hs-CRP change from baseline.	Weeks 14, 26 and 52
	10. Proportion of subjects with an endoscopic response (≥50% decrease from baseline SES-CD score).	Week 52
	11. Proportion of subjects with normalisation of FC (decrease from >250 µg/g at baseline to ≤250 µg/g).	Week 52
	12. FC change from baseline.	Week 52
To evaluate the durability of response in subjects that receive iDose-driven IFX versus SOC dosing	<ul style="list-style-type: none"> ▶ Proportion of subjects exhibiting SLR (CDAI >220 and at least one of: CRP ≥10 mg/L, FC >250 µg/g or SES-CD >4; or need for rescue therapy) during maintenance. ▶ Time to SLR. 	Week 14 through 52
To compare the ATI-free survival of subjects that receive iDose-driven IFX dosing versus SOC dosing	<ul style="list-style-type: none"> ▶ ATI-free survival (proportion of subjects with no ATI). ▶ Proportion of subjects with ATI. ▶ Time to ATI development. 	Week 2 through 52
To evaluate the safety of iDose-driven IFX dosing and SOC dosing	<ul style="list-style-type: none"> ▶ Proportion of subjects with any treatment-related SAE. ▶ Proportion of subjects with CD-related surgery. ▶ Proportion of subjects with CD-related hospitalisation. ▶ Time to CD-related hospitalisation. ▶ Time to CD-related surgery. 	Week 0 through 52

ATI, antibodies to infliximab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CS, corticosteroid; FC, faecal calprotectin; hs-CRP, high-sensitivity C reactive protein; IFX, infliximab; SAE, serious adverse event; SES-CD, Simple Endoscopic Score for Crohn's Disease; SLR, secondary loss of response; SOC, standard of care.

METHODS AND ANALYSIS

Study design and population

The OPTIMIZE study is a randomised controlled, multi-centre, open-label study. The study will be conducted in approximately 20 sites across the USA. The first patient has already been enrolled in November 2021 and the

last patient's follow-up is anticipated to be completed in February 2024. The study design is outlined in [figure 1](#). The study population will consist of patients aged 16–80 years with moderately to severely active CD. Detailed inclusion and exclusion criteria are shown in [Box 1](#).

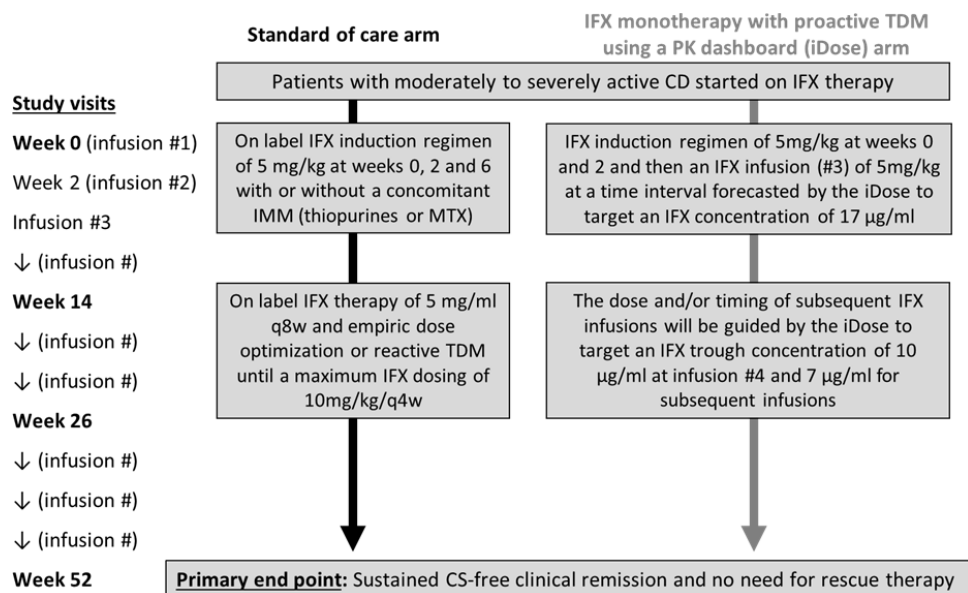


Figure 1 OPTIMIZE trial study design. CD, Crohn's disease; CS, corticosteroid; IMM, immunomodulator; IFX, infliximab; MTX, methotrexate; PK, pharmacokinetic; TDM, therapeutic drug monitoring; w, week.

Recruitment

Study sites have been assessed for feasibility and are highly experienced, high-volume care centres for patients with IBD in a variety of settings. Research staff will leverage current processes to automatically identify members in our target population. Eligible subjects will then be systematically informed about the study and invited to participate.

Randomisation and blinding

All eligible subjects will be randomly assigned in a 1:1 ratio to receive either IFX monotherapy with proactive TDM using the iDose dashboard or SOC IFX therapy, with or without a concomitant IMM at the discretion of the investigator. Randomisation will be stratified by concomitant CS use and prior biologic failure. The computer-generated randomised allocation sequence will be imported into the electronic case report form (eCRF) system after the patient has signed the informed consent form.

Subjects and treating physicians will be aware of the treatment group assignment. The IFX dosing regimen will be personalised for all subjects in this study. This method of dosing is by design for subjects in the iDose group but may also occur in subjects allocated to the SOC regimen if the physician determines that reactive TDM or dose optimisation is required based on the subject's response to IFX. Therefore, blinding of investigators and subjects to the treatment assignment is neither feasible for this study nor important for achieving the study objectives. Independent and blinded assessors will be used in the study, where possible. Central readers for endoscopic disease activity will be blinded to study treatment assignment and laboratory personnel will be blinded. Central laboratory (Prometheus Laboratories, San Diego, California, USA) results for high-sensitivity (hs)-CRP, albumin, IFX and ATI

will not be shared with treating physicians unless specifically requested for the purposes of supporting dose optimisation or reactive TDM in the SOC group. As subjects will be aware that both groups are receiving the same active drug, the recording of subjective patient-reported symptoms is not expected to be systematically biased by knowledge of the group assignment. Furthermore, diary entries will be made at home prior to the visits and consultation with the physician for each treatment. Other efficacy measures in the study include objective measures, such as clinical laboratory and endoscopic assessments, for which blinding of subjects or physicians is not required. Study personnel who perform the iDose predictions will be centralised and not involved in providing care to any study participants. A centralised, trained and experienced operator will be responsible for using the iDose dashboard to provide dosing guidance for all subjects in the iDose group across all study centres. The iDose operator will receive individualised data (including sex, weight, albumin, hs-CRP levels, IMM use, disease activity (based on Crohn's Disease Activity Index (CDAI) score), prior IFX dose, IFX trough concentration and ATI levels) for each subject from the study centres or central laboratory for input into the iDose dashboard, and then communicate the dashboard's dosing guidance for the next infusion back to the study centres. The dosing guidance will include more than one option with different combinations of dose/interval to achieve the target IFX trough concentration prior to the next infusion. The treating physician will review the dosing guidance and select one of the combinations of dose/interval for the next infusion based on their medical judgement and in consultation with the subject. The iDose dashboard operator will not be involved in study subjects' medical care and will only have access to subject data that is required to operate the dashboard.

Box 1 Inclusion and exclusion criteria of the OPTIMIZE study

Inclusion criteria:

1. Males or non-pregnant, non-lactating females aged 16–80 years inclusive.
2. Diagnosis of CD prior to screening using standard endoscopic, histological or radiological criteria. Subjects with patchy colonic inflammation initially diagnosed as indeterminate colitis would meet inclusion criteria, if the investigator feels that the findings are consistent with CD.
3. Moderately to severely active CD, defined by a total CDAI score between 220 and 450 points, and at least one of the following: elevated CRP (>upper limit of normal); elevated FC (>250 µg/g); Simple Endoscopic Score for Crohn's Disease (SES-CD) >6 or SES-CD >3 for isolated ileal disease.
4. Physician intends to prescribe IFX as part of the usual care of the subject.
5. No previous use of IFX.
6. Able to participate fully in all aspects of this clinical trial.
7. Written informed consent must be obtained and documented.

Exclusion criteria:

1. Participants with any of the following CD-related complications: abdominal or pelvic abscess, including perianal; presence of stoma or ostomy; isolated perianal disease; obstructive disease, such as obstructive stricture; short gut syndrome; toxic megacolon or any other complications that might require surgery, or any other manifestation that precludes or confounds the assessment of disease activity (CDAI or SES-CD); total colectomy.
2. History or current diagnosis of ulcerative colitis, indeterminate colitis, microscopic colitis, ischaemic colitis, colonic mucosal dysplasia or untreated bile acid malabsorption.
3. Current bacterial or parasitic pathogenic enteric infection, according to SOC assessments, including: *Clostridium difficile* and tuberculosis; known infection with hepatitis B virus, hepatitis C virus or HIV; sepsis; abscesses. History of the following: opportunistic infection within 6 months prior to screening; any infection requiring antimicrobial therapy within 2 weeks prior to screening; more than one episode of herpes zoster or any episode of disseminated zoster; any other infection requiring hospitalisation or intravenous antimicrobial therapy within 4 weeks prior to screening.
4. Malignancy or lymphoproliferative disorder other than non-melanoma cutaneous malignancies or cervical carcinoma in situ that has been treated with no evidence of recurrence within the last 5 years.
5. Known primary or secondary immunodeficiency.
6. PNR to adalimumab, defined as no objective evidence of clinical benefit after 14 weeks of therapy.
7. Participants with failure to a prior biologic, defined as PNR, SLR or intolerance will be excluded when a maximum of 78 participants (40% of the planned enrolment) have been enrolled who have previously failed a biologic.
8. Concomitant use of oral CS therapy exceeding prednisone 40 mg/day, budesonide 9 mg/day or equivalent.
9. Presence of any medical condition or use of any medication that is a contraindication for IFX use, as outlined on the product label.
10. A concurrent clinically significant, serious, unstable or uncontrolled underlying cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, haematological, coagulation, immunological, endocrine/metabolic or other medical disorder that, in the opinion

Continued

Box 1 Continued

of the investigator, might confound the study results, pose additional risk to the subject or interfere with the subject's ability to participate fully in the study.

11. Pregnant or lactating women to be excluded based on the physician's usual practice for determining pregnancy or lactation status.
12. Known intolerance or hypersensitivity to IFX or other murine proteins.

ATI, antibodies to infliximab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FC, faecal calprotectin; HBV, hepatitis B virus; HCV, hepatitis C virus; hs-CRP, high-sensitivity C reactive protein; IFX, infliximab; PNR, primary non-response; SAE, serious adverse event; SES-CD, Simple Endoscopic Score for Crohn's Disease; SLR, secondary loss of response.

Study outcomes

Primary outcome

The primary outcome of the study is the proportion of subjects with sustained CS-free (no CS use from week 14 through week 52) clinical remission (CDAI <150 at weeks 14, 26, 52) and no need for rescue therapy. Rescue therapy is defined as any IFX dose escalation other than what is forecasted by iDose either done empirically or based on reactive TDM; addition of IMM after week 2; addition of CS after initial tapering; switch to another biologic as decided by the treating physician and need for CD-related surgery including gastrointestinal resection (eg, ileal resection, ileocaecal resection, subtotal colectomy, total proctocolectomy, stricturoplasty, diverting stoma, ileostomy, colostomy procedures or fistula repair) or seton placement for active perianal fistulising disease.

Secondary outcomes

The secondary outcomes include both efficacy and safety end points that are described in detail in [table 1](#).

Intervention

All subjects in both treatment groups will receive intravenous infusions of 5 mg/kg of IFX at weeks 0 and 2 and the third infusion. For both groups, IFX dose can be increased to a maximum of 10 mg/kg at intervals of no less than 4 weeks between infusions. The schedule of enrolment, interventions and assessments is provided in [table 2](#).

Standard of care arm

Subjects in the SOC dosing arm will receive a third intravenous infusion of 5 mg/kg IFX at week 6 and then maintenance therapy with infusions every 8 weeks thereafter. In this group, treating physicians may use empiric dose optimisation or reactive TDM-driven dose escalation in accordance with their usual practice. Subjects randomised to the SOC IFX arm may be prescribed a concomitant IMM (thiopurines or methotrexate) within 2 weeks of starting IFX at the treating physician's discretion.

Table 2 Time and events schedule

Study period	Screening	Baseline	Treatment period				UNS
Week	-4 to 0	0	Infusion visits†	14	26	52/EOS	NA
Permitted interval (days)	-28 to 0	0		±7	±7	±7	NA
Administrative and general procedures							
Informed consent	X						
Assess inclusion/exclusion	X						
Confirm inclusion/exclusion		X					
Randomisation		X					
Demographics	X						
Medical/Surgical history	X						
Concomitant medications	X	X	X	X	X	X	X
Physical exam	X	X		X	X	X	X
Dispense subject diary	X						
Review compliance with subject diary		X	X	X	X	X	X
Schedule return visit	X	X	X	X	X		
Efficacy and safety assessments							
CDAI	X	X		X	X	X	
Ileocolonoscopy (SES-CD)	X*					X	X*
Faecal calprotectin	X*					X*	X*
CRP/hs-CRP	X	X	X	X	X	X	X
Haematocrit	X	X		X	X	X	X
Albumin		X	X	X	X	X	X
AEs and SAEs	X	X	X	X	X	X	X
Treatment and related procedures							
Body weight	X	X	X	X	X	X	X
IFX infusion		X	X				
IFX and ATI concentrations			X	X	X	X	X

Procedures performed as part of usual care and the physician's decision to initiate IFX treatment are not listed unless they are part of the data collection required for this study.

*Subjects in both groups will receive infusion #2 at week 2 (±3 days). Subjects randomised to the standard of care group will receive subsequent infusions at week 6 (±7 days) and every 8 weeks (±7 days) thereafter. Subjects randomised to the iDose-driven dosing group will receive IFX infusions after week 2 according to a schedule forecasted by the iDose dashboard, with a permitted window of ±7 days of the forecasted date.

†At the discretion of the treating physician.

AE, adverse event; ATI, antibodies to infliximab; CDAI, Crohn's Disease Activity Index; EOS, end of study; hs-CRP, high-sensitivity C reactive protein; IFX, infliximab; NA, not applicable; SAE, serious adverse event; SES-CD, Simple Endoscopic Score for Crohn's Disease; UNS, unscheduled.

Proactive TDM iDose dosing arm

Using data and labs collected the previous infusion the dashboard will forecast an IFX dosing interval that targets an IFX trough concentration of $\geq 17 \mu\text{g/mL}$ at infusion #3; for infusion #3, a dose of 5 mg/kg will be used. After infusion #3, the dashboard will forecast a combination of dosing intervals and infusion doses that target an IFX trough concentration of $\geq 10 \mu\text{g/mL}$ at infusion #4. These cut-offs have been previously used in a prospective study by Dubinsky *et al.*³¹ For subsequent infusions (infusion #5 and later infusion), the dashboard will forecast a combination of dosing intervals and infusion doses that target a trough concentration of $\geq 7 \mu\text{g/mL}$ at each

infusion. During maintenance therapy, subjects with two consecutive IFX trough concentrations of $> 15 \mu\text{g/mL}$ will de-escalate IFX therapy to reach the target concentration threshold of $\geq 7 \mu\text{g/mL}$, as guided by the iDose. Concomitant IMM use is prohibited in subjects randomised to the iDose-driven IFX group throughout the study. If a subject is using one of these medications at screening and they are randomised to the iDose group, they must discontinue at the time of randomisation and prior to starting IFX. IFX concentrations and ATI levels will be measured using a drug-tolerant homogenous mobility shift assay (HMSA) (Prometheus Laboratories) as previously described.³⁹ The results of the HMSA will be available within five business

days in contrast to a point-of-care (POC) assay that results would be available within minutes allowing a more timely dose adjustment as previously used for proactive TDM.⁴⁰ However, a POC assay for this study was not selected as these assays are still not widely available and there may be discrepancies in drug concentrations and ATI titres compared with the commonly used standard IFX assays.⁴¹

Concomitant corticosteroid use

All subjects who are using oral CSs (prednisone or equivalent (≤ 40 mg/day) or budesonide (≤ 9 mg/day)) will undergo tapering and discontinuation of the CS during the induction treatment period. If symptoms worsen during tapering, the CS dose can be increased to the previous level for 1 week before reinitiating the dose taper. If the second attempt at tapering is not successful, subjects may remain in the study if they continue to be prescribed IFX, do not require another medication prohibited by the study or complete the study to week 52.

Assessments

Clinical disease activity will be monitored throughout treatment with CDAI assessments. In addition, the study will collect results of tests performed as part of usual care to monitor patient responses to treatment, including endoscopic and biologic markers (ie, faecal calprotectin and hs-CRP) of disease activity. Endoscopic outcomes will be evaluated at week 52 (and other time points, if performed by the physician for usual care of the subject) with SES-CD at a central reading centre. All subjects will be monitored for safety throughout the study, with specific collection of data on any treatment-related SAEs, CD-related surgeries or CD-related hospitalisations.

Treatment failure and exiting the study

Regardless of randomisation assignment, any subject who requires additional therapy to manage signs and symptoms of CD, in the medical judgement of the investigator, will receive appropriate therapy at any time during the study in accordance with the investigator's usual practice. Subjects who require rescue or add-on therapy will continue in the study and complete all follow-up assessments. However, if the subject requires alternative therapy and discontinues IFX because of a disease flare, then the subject should complete the end of study (week 52) procedures and discontinue the study. Subjects should be discontinued from IFX therapy if it is deemed in the best interests of the subject based on the investigator's medical judgement. If IFX is stopped due to a SAE, the participant will be followed to the resolution or stabilisation of the event. A participant may withdraw from the study at any time at his/her own request.

Patient and public involvement in research

Interviews with patients and caregivers at Mount Sinai Hospital that were enrolled in a pilot study using iDose as part of a single arm intervention were conducted to obtain feedback on the study outcomes. Patient input was also sought at local Crohn's and Colitis Foundation

symposiums in the various New York Chapters as well as the Springfield Massachusetts annual symposium to obtain feedback on the key barriers to the early adoption of IFX and helped shape the comparator arm. Focus groups at Dartmouth Hitchcock Medical Center were also engaged to discuss research-specific questions focused on study design. Patients and caregivers at Beth Israel Deaconess and Mount Sinai Medical Center reviewed the protocol to ensure that it was addressing key outcomes and provided feedback on feasibility and protocol design.

Data collection, monitoring and management

A web-based eCRF software solution (TrialStat Solutions) will be used to collect study data. Patients will receive a study ID number at enrolment and all data will be entered and stored linked to this study ID number. Data will be stored during the study period and 15 years thereafter. A Data Monitoring Committee (DMC) will assess the study progress, safety data and, if needed, critical efficacy end points. Safety data will include listings of SAEs, CRP values and reasons for early withdrawal from the study. The DMC will review data after 50, 100, 150 and all 196 subjects have completed the trial and provide recommendations regarding study modification, continuation or termination and if additional safety monitoring procedures are required. The DMC consists of four members who are not part of the study team; three IBD experts with experience in clinical trials and one biostatistician employed at the primary site. On completion of the study, an appropriate dataset will be placed in an open repository.

Statistical analyses

Medians (IQR) and frequency/percentages will be reported for continuous and categorical demographic data as well as baseline characteristics, respectively. Continuous and categorical variables will be compared between groups using the Mann-Whitney U test and the χ^2 or the Fisher's exact test, respectively. Corresponding two-sided 95% CIs will be obtained using methods by Zou⁴² and Newcombe.⁴³ All randomised subjects will be included in the intent-to-treat (ITT) analysis set. Subjects who received at least one IFX dosing predicted by iDose will be defined as the modified ITT set (mITT). All ITT subjects who do not have any major deviations from protocol will be included in the per-protocol (PP) analysis set. For the iDose group, subjects must receive at least the fourth infusion according to the iDose forecast without deviation to be considered evaluable in the PP analysis set. All subjects who received at least one IFX infusion will be included in the safety analysis set. Safety data for this study include treatment-related SAEs, CD-related surgeries and hospitalisations and clinical laboratory data. Multiple linear regression (with backward elimination at $p < 0.1$) analyses will be conducted to explore association between independent factors and these secondary outcomes. No imputation of values of missing efficacy or safety data will be performed.

Sample size determination

The sample size of this exploratory trial was determined by assuming that 25% of subjects in the SOC group will achieve the primary outcome of sustained CS-free clinical remission, without need for rescue therapy, while the iDose-guided IFX will have 45% for the outcome. Based on χ^2 test at the two-sided 5% significance level, a total of 178 participants in a 1:1 randomisation would have 80% power. To account for an approximately 10% dropout rate, the study needs to recruit 196 subjects.

Primary outcome analysis

The primary outcome will be evaluated with the Cochran-Mantel-Haenszel method, adjusting for stratification factors. The effect of iDose over SOC will be quantified using the common risk ratio and associated 95% CI based on the Cochran-Mantel-Haenszel method. Primary efficacy analyses will be based on the ITT analysis set, and the mITT and PP analysis sets will be used for confirmatory purposes of the primary outcome. All subjects who withdraw from the study for any reason will be considered treatment failures in the primary analysis.

Secondary outcomes analyses

Secondary outcomes will be analysed for hypothesis-generating purposes. Risk ratios for secondary outcomes will be analysed using the Cochran-Mantel-Haenszel method, adjusting for categorical prognostic factors. The modified Poisson regression model will be used when both categorical and continuous prognostic factors need to be adjusted.⁴⁴ Mixed models and weighted generalised estimation equations will be used to analyse secondary outcomes with repeated measures. Ordinal outcome data will be analysed using non-parametric methods, with treatment effect quantified by the Mann-Whitney probability and associated 95% CIs.⁴² Secondary time-to-event outcomes will be depicted using the Kaplan-Meier curve (with log-rank test) and treatment effect will be estimated using the Cox regression model analysis. Multivariable regression analyses will be performed to determine the independent effects of variables associated with study outcomes, using backward elimination with $p < 0.1$ as the selection criterion.

Adverse event monitoring

All AEs, including SAEs experienced by the participant between the signing of the informed consent and discontinuation of IFX or study completion will be recorded in the participant's medical records. All treatment-related (IFX and IMM, if applicable) SAEs and CD-related events of greater intensity, frequency or duration than expected for the individual participant, and is considered related to treatment, will be recorded in the eCRF including date of onset, description, severity (mild, moderate, severe), time course, duration, outcome and relationship of the adverse event to study procedures (possible, probable or definite), if known, and any action(s) taken. SAEs are any adverse events that result in death, are life-threatening,

require hospitalisation or cause significant disability or incapacity. As only approved treatments for CD are being used in this study, all unexpected SAEs and adverse drug reactions will be reported to the respective manufacturers as per local postmarketing safety reporting requirements. An unexpected event is one that is not reported in the IFX product labelling. All AEs will be monitored to determine the outcome or until the physician considers it medically justifiable to terminate follow-up. All SAEs will be monitored until resolved or until the SAE is clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

DISCUSSION

The results of OPTIMIZE trial will help to personalise the delivery of anti-TNF to patients with CD. If PK dashboard-driven proactive IFX optimised monotherapy is superior to the SOC, the paradigm of CD treatment will shift. Monotherapy with IFX using proactive TDM and optimisation using PK modelling will become the favoured approach. This paradigm shift may occur even if PK-driven proactive IFX optimised monotherapy only proves to be as effective as IFX combination therapy with an IMM, as patients and physicians will be able to achieve the desired clinical outcomes without the added safety concerns of infection and malignancy from an additional IMM. This therapeutic approach could also be applied in patients with increased IFX clearance, such as the paediatric IBD population and patients with ulcerative colitis, as well as in patients prone to develop ATI, such as those carrying the HLA-DQA1*05 allele.⁴⁵⁻⁴⁷ A post hoc analysis of a recent prospective study demonstrated that in an adult and paediatric cohort of patients with IBD optimised IFX monotherapy based on a PK dashboard-guided proactive TDM starting early during the induction phase the HLA-DQA1*05 risk variant carriage did not impact development of ATI nor drug durability.⁴⁸

Furthermore, the use of the dashboard allows for a more individualised, patient-specific, dosing regimen. Through proactive optimisation using a PK dashboard to visualise and calculate personalised PK profiles for patients, providers will be able to discuss available permutations of IFX dosing regimens feasible to achieve and maintain target therapeutic IFX concentrations for patients. Consequently, in working with providers to select a dose/dosing interval, patients gain an opportunity to have shared decision-making in their treatment plan that is best suited to accomplish their desired outcomes.

Moreover, the approach to treating CD will be focused on optimising the IFX dosing at the height of the inflammatory burden (when more drug is needed) and possibly de-escalating in maintenance, which could result in lower costs. This will also happen by decreasing hospitalisations and surgeries attributed to treatment failure. In a recent systematic review regarding IBD, the TDM-guided strategies compared with standard treatment without TDM were consistently found to be cost saving or cost-effective.⁴⁹

This study has high potential to improve the quality of the evidence available to help patients and relevant stakeholders make informed health decisions and improve how a patient feels and functions.

Ethics and dissemination

The protocol has been approved by the Institutional Review Board Committee of the Beth Israel Deaconess Medical Center (IRB#: 2021P000391) and is pending at the other participating centres. Written informed consent will be obtained from all patients and parents/legal guardians of minor patient prior to enrolment. The sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB approval prior to implementation. Results will be disseminated in peer-reviewed journals and presented at scientific meetings.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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