BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057656
Article Type:	Protocol
Date Submitted by the Author:	22-Sep-2021
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Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, CLINICAL PHARMACOLOGY, IMMUNOLOGY

Proactive infliximab optimization using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease: study protocol for a randomized, controlled, multi-center, open-label study (the OPTIMIZE Trial)

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Word count: 3,820

Key words: Inflammatory bowel disease; Crohn's disease; infliximab; therapeutic drug monitoring; pharmacokinetic dashboard.

ABSTRACT

Introduction: Preliminary data indicates that proactive therapeutic drug monitoring (TDM) is associated with better outcomes compared to 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 randomized, controlled, multicenter, open-label trial is to evaluate the efficacy and safety of a proactive TDM combined PK dashboard-driven infliximab dosing compared to standard of care (SOC) dosing in patients with moderate to severely active CD.

Methods and analysis: Eligible adolescent and adult (age ≥16 to 80 years) patients with moderately to severely active CD will be randomized 1:1 to receive either infliximab monotherapy with proactive TDM using a PK dashboard (iDose™, Projections Research Inc.) 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 endpoints, such as endoscopic and biological remission, durability of response, and CD-related surgery and hospitalization.

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: ClinicalTrials.gov identifier: NCT04835506 (registered on 5th April 2021).

Protocol version: #02, 07 July 2021

Strengths and limitations of this study

- This is an investigator-initiated multicenter, open-label, randomized controlled trial evaluating, the efficacy of proactive therapeutic drug monitoring of infliximab starting early during the induction phase combined with a pharmacokinetic dashboard (iDose™), compared to standard of care dosing in patients with moderate to severe Crohn's disease.
- The standard of care arm represents the real-world use of infliximab and is either combination infliximab therapy with an immunomodulator (thiopurines or methotrexate) or monotherapy at the discretion of the treating physician according to their usual clinical practice.
- Due to the study design, blinding of investigators and subjects to the treatment assignment will not be feasible. However, outcome assessment will be conducted by independent, blinded assessors where possible.
- Strengths of the study include randomization stratified by concomitant corticosteroid use and prior biologic failure; central reading for scoring endoscopic disease activity; central laboratory results for high sensitivity C-reactive protein, albumin, infliximab concentrations and antibodies to infliximab levels; centralized iDose™ predictions provided by study personnel not involved in in the care of the study participants; and evaluation of objective outcome measures, such as endoscopic and biological remission, as secondary outcomes

INTRODUCTION

Crohn's disease (CD) is a life-long chronic inflammatory bowel disease (IBD) characterized by transmural inflammation of the intestine.[1] CD is a global disease in the 21st century with increasing incidence in newly industrialized countries.[2] One of the most effective therapies to treat patients with moderate to severe CD is the antitumor 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 endpoint), 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 prioritized over efficacy.[9, 10]

Up to 30% of patients do not respond to IFX induction therapy (primary nonresponse [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, characterized 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 favorable 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 optimization to achieve a threshold drug concentration during maintenance therapy compared to empiric dose escalation and/or reactive TDM is associated with better long-term outcomes including longer drug persistence, reduced risk of relapse, and fewer hospitalizations 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 μg/mL for Week 2 and > 10-20 μg/mL for Week 6) are associated with better short and long-term outcomes.[13] Proactive TDM can also support the practice of IFX optimized 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]

IFX dosing by weight only (i.e., mg/kg) may not be adequate for many patients as inter-individual 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.[27-31] Dosing

calculators account for these individual factors and improve the precision of dosing towards better personalized medicine. These systems have already been validated, and personalized dosing has shown clinical benefit in patients with IBD.[30-37] The iDose™ (Projections Research, Inc., Phoenixville, PA) dashboard is a clinical decision support tool that uses Bayesian updates to visualize and forecast a patients' PK profile and the timing and dose of infusions to ensure therapeutic concentrations of IFX are maintained and thus optimize 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 personalized dosing schedule intended to achieve trough concentrations that have been associated with remission. A single-arm dashboard-guided dosing pilot study showed that iDose™ is not only feasible in the real-world setting but also confirmed that approximately 80% of patients need a higher IFX induction dose than the standard dosing regimen.[30] The PRECISION (Dashboard-driven vs. conventional dosing of IFX in IBD patients) trial showed a clinical benefit from personalized 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).[33]

Study aim and objectives

The aim of the OPTIMIZE study 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 endpoints of the OPTIMIZE trial are described in **Table 1**.

METHODS AND ANALYSIS

Study design and population

The OPTIMIZE study is a randomized, controlled, multicenter, open-label study. The study will be conducted in approximately 20 sites across United States. It is anticipated that the first patient will be enrolled in October 2021 and the last patient's follow up will 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 **Table 2**.

Recruitment

Study sites have been assessed for feasibility and are highly experienced, high-volume care centers 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.

Randomization 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. Randomization will be stratified by concomitant CS use and prior biologic failure. The computer-generated randomized 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 personalized 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 optimization 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, CA) results for high sensitive (hs)-CRP, albumin, IFX, and ATI will not be shared with treating physicians unless specifically requested for the purposes of supporting dose optimization 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 centralized and not involved in providing care to any study participants. A centralized, 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 centers. The iDose™ operator will receive individualized 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 centers 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 centers. 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.

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 (e.g., ileal resection, ileocecal resection, subtotal colectomy, total proctocolectomy, stricturoplasty, diverting stoma, ileostomy, colostomy procedures, or fistula repair) or seton placement for active perianal fistulizing disease.

Secondary outcomes

The secondary outcomes include both efficacy and safety endpoints that are described in detail in **Table 1**.

Intervention

All subjects in both treatment groups will receive IV 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 3**.

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 optimization or reactive TDM driven dose escalation in accordance with their usual practice. Subjects randomized 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.

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 ≥ 17 µg/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 ≥ 10 µg/mL at infusion #4. 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 ≥ 7 µg/mL at each infusion. During maintenance therapy, subjects with 2 consecutive IFX trough concentrations of >15 µg/mL will de-escalate IFX therapy to reach the target concentration threshold of ≥ 7 µg/mL, as guided by the iDose™. Concomitant IMM use is prohibited in subjects randomized to the iDose™-driven IFX group throughout the study. If a subject is using one of these medications at screening and they are randomized to the iDose™ group, they must discontinue at the time of randomization and prior to starting IFX.

Concomitant corticosteroid use

All subjects who are using oral CSs (prednisone or equivalent [≤ 40 mg per day] or budesonide [≤ 9 mg per 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 (i.e., fecal 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 the Simple Endoscopic Score for CD at a central reading center. 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 hospitalizations.

Treatment failure and exiting the study

Regardless of randomization 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 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 Inc.) 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 endpoints. 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. Upon completion of the study an appropriate dataset will be placed in an open repository.

Statistical analyses

Medians (interquartile range) 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 chi-square or the Fisher's exact test, respectively. Corresponding two-sided 95% confidence intervals will be obtained using methods by Zou[38] and Newcombe[39]. All randomized 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 4th 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 includes treatment-related SAEs, CD-related surgeries and hospitalizations, 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 Chi-square test at the 2-sided 5% significance level, a total of 178 participants in a 1:1 randomization 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% confidence interval (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 analyzed for hypothesis-generating purposes. Risk ratios for secondary outcomes will be analyzed 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.[40] Mixed models and weighted generalized estimation equations will be used to analyze secondary outcomes with repeated measures. Ordinal outcome data will be analyzed using nonparametric methods, with treatment effect quantified by the Mann-Whitney probability and associated 95%CIs.[41] 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 post-marketing 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 personalize the delivery of anti-TNF to patients with CD. If PK dashboard-driven proactive IFX optimized monotherapy is superior to the SOC, the paradigm of CD treatment will shift. Monotherapy with IFX using proactive TDM and

optimization using PK modelling will become the favored approach. This paradigm shift may occur even if PK-driven proactive infliximab optimized 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. Furthermore, the use of the dashboard allows for a more individualized, patient-specific, dosing regimen. Through proactive optimization using a PK dashboard to visualize and calculate personalized 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 optimizing 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 hospitalizations and surgeries attributed to treatment failure. 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 centers. Written informed consent will be obtained from all patients and parents/legal guardians of minor patient prior to enrolment. The study is registered at ClinicalTrials.gov (identifier: NCT04835506). 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.

Contributors

Study concept and design: K.P., M.C.D., A.S.C.; study design was developed in collaboration with Alimentiv Inc.; statistical support: GY Z.; manuscript drafting: KP. All authors have made substantial contributions to the study protocol and critically revised the manuscript. K.P., V.J., B.L.C., T.E.R., B.E.S., C.A.S., J.F.V., M.C.D. and A.S.C. are members of the study steering committee. All authors have approved the final manuscript and agree to be accountable for all aspects of the work

Funding: This work is supported by the The Leona M. & Harry B. Helmsley Charitable Trust Grant #2108-04776. The funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. In-kind contributions for protocol writing provided by Alimentiv Inc.

Patient consent for publication: Not required.

Competing interests: A.S.C.: reports consultancy fees from Janssen, Abbvie, Artugen, Procise, Prometheus, Arena, Grifols, Bacainn, Bristol Myers Squibb. V.J. has received consulting/advisory board fees from AbbVie, Alimentiv Inc (formerly Robarts Clinical Trials), Arena pharmaceuticals, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genetech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Reistone Biopharma, Roche, Sandoz, Takeda, Teva, Topivert; speaker's fees from, Abbvie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda. C.A.S.: reports

consultancy fees from Abbvie, BMS, Lilly, Janssen, Pfizer, Prometheus, Takeda, Trellus Health; speaker fees for CME activities for Abbvie, Janssen, Pfizer, Takeda; grant support from the Crohn's and Colitis Foundation, Leona M. and Harry B. Helmsley Charitable Trust, Abbvie, Janssen, Pfizer, Takeda; intellectual property owned by MiTest Health, LLC (Software Company) and ColonaryConcepts, LLC; equity interest and co-founder of MiTest Health, LLC and ColonaryConcepts, LLC. K.P. reports lecture fees from Mitsubishi Tanabe Pharma and Physicians Education Resource LLC; consultancy fee from Prometheus Laboratories Inc; and scientific advisory board fees from ProciseDx Inc and Scipher Medicine Corporation. J.F.V.: reports research support from Roche/Genentech, Takeda, Applied Molecular Transport, Celgene/Bristol Myers Squibb, AbbVie, Arena Pharmaceuticals. GY Z.: reports consulting fees from Alimentiv Inc. B.L.C.: reports financial support for advisory boards and consultancy from Abbvie, Celgene-Bristol Myers Squibb, Pfizer, Sublimity Therapeutics, Takeda, TARGET RWE; CME Companies: Cornerstones, Vindico; speaking fees from Abbvie; educational Grant from Pfizer. M.C.D: reports consultancy fees from Abbvie Inc, Arena Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb Company, Cengene Corporation, Eli Lilly and Company, F. Hoffmann-La Roche Ltd, Genentech Inc, Gilead, Janssen Global Services, LLC, Pfizer Inc, Prometheus Biosciences, Takeda Pharmaceuticals USA Inc, UCB SA; research grants from AbbVie Inc, Janssen Global Services, LLC, Pfizer Inc, Prometheus Biosciences; ownership interest (stocks) Trellus Health Inc; and holds licensing fee with Takeda Pharmaceuticals USA Inc. T.E.R. reports speaking fees from Takeda Pharmaceuticals, Janssen, Pfizer, Bristol Myers Squibb; data adjudication committee fees from Ferring / Rebiotix; advisory boards fees from Abbvie, Arena, Boehringer Ingelheim, Bristol Myers Squibb / Celgene, Coral Genomics (and shareholder), Ferring, Genentech / Roche, Gilead, Gossamer, Intercept, Janssen, Lilly, Pfizer, Prometheus, Sanofi, Takeda. B.E.S.: discloses research grants from Takeda, Pfizer, Theravance Biopharma R&D, Janssen;

consulting fees from 4D Pharma, Abivax, Abbvie, Alimentiv, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, Bacainn Therapeutics, Boehringer-Ingelheim, Boston Pharmaceuticals, Bristol-Myers Squibb, Calibr, Capella Bioscience, Celgene, Celltrion Healthcare, ClostraBio, Enthera, F.Hoffmann-La Roche, Ferring, Galapagos, Gilead, Glaxo SmithKline, GossamerBio, Immunic, Index Pharmaceuticals, Innovation Pharmaceuticals, Ironwood Pharmaceuticals, Janssen, Kaleido, Kallyope, Lilly, MiroBio, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka, Palatin Technologies, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Redhill Biopharma, Rheos Medicines, Salix Pharmaceuticals, Seres Therapeutics, Shire, Sienna Biopharmaceuticals, Sun Pharma, Surrozen, Takeda, Target PharmaSolutions, Teva Branded Pharmaceutical Products R&D, Thelium, Theravance Biopharma R&D, TLL Pharma, USWM Enterprises, Ventyx Biosciences, Viela Bio, Vivante Health, Vivelix Pharmaceuticals; and stock for Vivante Health and Ventyx Biosciences.The remaining authors declare no conflict of interest.

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Table 1. Specific objectives and endpoints of the OPTIMIZE study.

Primary Objective	**Primary Endpoint**	**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 Endpoints**	**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 nonresponders (≤ 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 normalization of hs-CRP (decrease from ≥ 10 at baseline to < 10 mg/L)	Week 52
	9. Hs-CRP change from baseline	Week 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 normalization 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.	• Proportion of subjects exhibiting SLR (CDAI > 220 and at least 1 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.	• 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.	• Proportion of subjects with any treatment-related SAE • Proportion of subjects with CD-related surgery • Proportion of subjects with CD-related hospitalization • Time to CD-related hospitalization • 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: fecal calprotectin; hs- CRP: high-sensitivity C-reactive protein; IFX: infliximab; SLR: secondary loss of response; SAE: serious adverse event; SOC: standard of care; SES-CD: Simple Endoscopic Score for Crohn's Disease.

Table 2. Inclusion and exclusion criteria of the OPTIMIZE study.

Inclusion criteria
1. Males or nonpregnant, nonlactating females aged 16 to 80 years inclusive.
2. Diagnosis of CD prior to screening using standard endoscopic, histologic, or radiologic 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 1 of the following: elevated CRP (> upper limit of normal); elevated FC (> 250 μg/g); 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, ischemic colitis, colonic mucosal dysplasia, or untreated bile acid malabsorption.
3. Current bacterial or parasitic pathogenic enteric infection, according to standard of care assessments, including: C. difficile and tuberculosis; known infection with HBV, HCV 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 1 episode of herpes zoster or any episode of disseminated zoster; any other infection requiring hospitalization or iv antimicrobial therapy within 4 weeks prior to screening.
4. Malignancy or lymphoproliferative disorder other than nonmelanoma 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 enrollment) have been enrolled who have previously failed a biologic.
8. Concomitant use of oral corticosteroid 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, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion 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: fecal 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.

Table 3. 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**	**See note a**	**±7**	**±7**	**±7**	**NA**
Administrative and General Procedures							
Informed consent	X						
Assess inclusion/exclusion	X						
Confirm inclusion/exclusion		X					
Randomization		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 [b]					X	X [b]
Fecal calprotectin	X [b]					X [b]	X [b]
CRP / hs-CRP	X	X	X	X	X	X	X
Hematocrit	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

Note: 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. Abbreviations: 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.

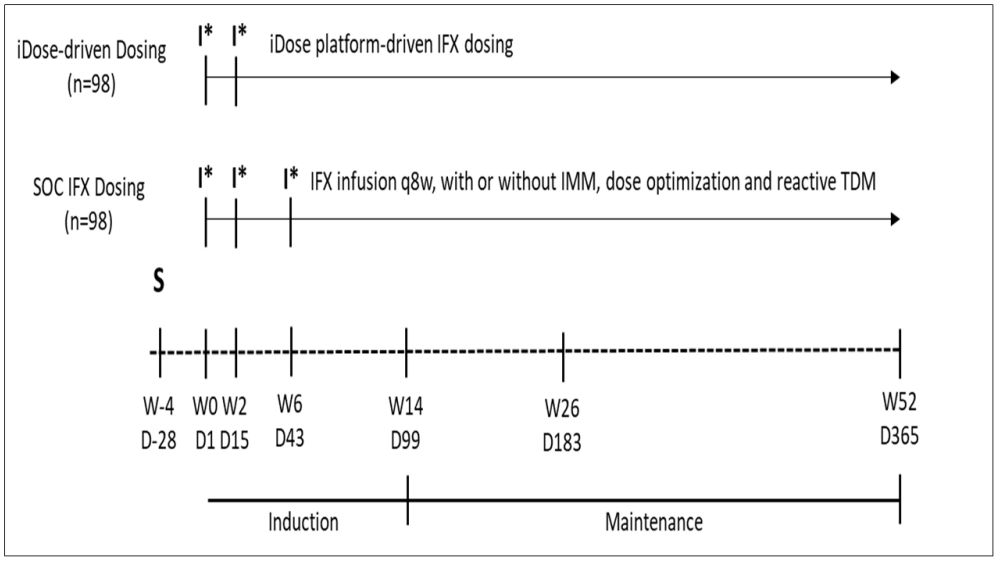
[a] Subjects in both groups will receive infusion #2 at Week 2 (±3 days). Subjects randomized to the standard of care (SOC) group will receive subsequent infusions at Week 6 (±7 days) and every 8 weeks (±7 days) thereafter. Subjects randomized to the iDose™-driven dosing group will receive IFX infusions after Week 2 according to a schedule forecasted by the iDose™ dashboard, with a permitted window of ±7 days of the forecasted date; [b] At the discretion of the treating physician.

Figures

Figure 1 legend: OPTIMIZE Trial Study Design

Figure 1 footnote. Third infusion in iDose™ group will be 5 mg/kg, with timing forecasted by the iDose™ dashboard.

D: Day; I*: infliximab infusion (5 mg/kg of IFX); IFX: infliximab; IMM: immunomodulator; q8w: every 8 weeks; S: screening; SOC: standard of care; TDM: therapeutic drug monitoring; W: Week.



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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	All WHO Trial Registration Data requirements are met with the trial's registration in the ClinicalTrials.gov. (page 4)
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18, 19
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14, 17, 19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
	6b	Explanation for choice of comparators	6-8
Objectives	7	Specific objectives or hypotheses	8, 11, Table 1
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9-14
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9 (The list of sites will be available at clinical ClinicalTrials.gov)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11, 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13-15

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-13, Table 2
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 11, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, Table 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15, 16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9, 10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9, 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9, 10

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14, 15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14, 15

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14, 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 14, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18, 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not provided as the document has an extensive length. It can be provided upon request.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19-21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Not provided as the document has an extensive length. It can be provided upon request.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided as the document has an extensive length. It can be provided upon request.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not provided as the document has an extensive length. It can be provided upon request.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Proactive infliximab optimization using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease: study protocol for a randomized, controlled, multi-center, open-label study (the OPTIMIZE Trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057656.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Feb-2022
Complete List of Authors:	Papamichael, Konstantinos; Beth Israel Deaconess Medical Center, Jairath, Vipul; Alimentiv Inc; Western University Zou, Guangyong ; Alimentiv Inc; Western University Cohen, Benjamin; Cleveland Clinic Ritter, Timothy; GI Alliance Sands, Bruce; Mount Sinai Health System, Siegel, Corey; Dartmouth-Hitchcock Medical Center, Section of Gastroenterology and Hepatology Valentine, JF; The University of Utah School of Medicine Smith, Michelle; Alimentiv Inc Vande Casteele, Niels; University of California San Diego, Department of Medicine Dubinsky, Marla; Mount Sinai School of Medicine, Cheifetz, AS; Beth Israel Deaconess Medical Center,
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, CLINICAL PHARMACOLOGY, IMMUNOLOGY

Proactive infliximab optimization using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease: study protocol for a randomized, controlled, multi-center, open-label study (the OPTIMIZE Trial)

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Word count: 3,993

Key words: Inflammatory bowel disease; Crohn's disease; infliximab; therapeutic drug monitoring; pharmacokinetic dashboard.

ABSTRACT

Introduction: Preliminary data indicates that proactive therapeutic drug monitoring (TDM) is associated with better outcomes compared to 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 randomized, controlled, multicenter, open-label trial is to evaluate the efficacy and safety of a proactive TDM combined PK dashboard-driven infliximab dosing compared to standard of care (SOC) dosing in patients with moderate to severely active CD.

Methods and analysis: Eligible adolescent and adult (age ≥16 to 80 years) patients with moderately to severely active CD will be randomized 1:1 to receive either infliximab monotherapy with proactive TDM using a PK dashboard (iDose™, Projections Research Inc.) 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 endpoints, such as endoscopic and biological remission, durability of response, and CD-related surgery and hospitalization.

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: ClinicalTrials.gov identifier: NCT04835506 (registered on 5th April 2021).

Protocol version: #02, 07 July 2021

Strengths and limitations of this study

- This is an investigator-initiated, multicenter, 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 CRP, 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) characterized by transmural inflammation of the intestine.[1] CD is a global disease in the 21st century with increasing incidence in newly industrialized countries.[2] One of the most effective therapies to treat patients with moderate to severe CD is the antitumor 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 endpoint), 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 prioritized over efficacy.[9, 10]

Up to 30% of patients do not respond to IFX induction therapy (primary nonresponse [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, characterized 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 favorable 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 optimization to achieve a threshold drug concentration during maintenance therapy compared to empiric dose escalation and/or reactive TDM is associated with better long-term outcomes including longer drug persistence, reduced risk of relapse, and fewer hospitalizations 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 µg/mL for week 2 and > 10-20 µg/mL for week 6) are associated with better short and long-term outcomes.[13] Proactive TDM can also support the practice of IFX optimized 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 infliximab in the setting of infliximab concentrations more than 5 µg/mL seems negligible.[27]

IFX dosing by weight only (i.e., mg/kg) may not be adequate for many patients as inter-individual 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 personalized medicine. These systems have already been validated, and personalized dosing has shown clinical benefit in patients with IBD.[31-38] The iDose™ (Projections Research, Inc., Phoenixville, PA) dashboard is a clinical decision support tool that uses Bayesian updates to visualize and forecast a patients' PK profile and the timing and dose of infusions to ensure therapeutic concentrations of IFX are maintained and thus optimize 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 personalized 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 not only feasible in the real-world setting but also confirmed that approximately 80% of patients need a higher IFX induction dose than the standard dosing regimen.[31] The PRECISION (Dashboard-driven vs. conventional dosing of IFX in IBD patients) trial showed a clinical benefit from personalized 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 study 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 endpoints of the OPTIMIZE trial are described in **Table 1**.

METHODS AND ANALYSIS

Study design and population

The OPTIMIZE study is a randomized controlled, multicenter, open-label study. The study will be conducted in approximately 20 sites across United States. 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 **Table 2**.

Recruitment

Study sites have been assessed for feasibility and are highly experienced, high-volume care centers 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.

Randomization 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. Randomization will be stratified by concomitant CS use and prior biologic failure. The computer-generated randomized 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 personalized 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 optimization 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, CA) results for high sensitive (hs)-CRP, albumin, IFX, and ATI will not be shared with treating physicians unless specifically requested for the purposes of supporting dose optimization 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 centralized and not involved in providing care to any study participants. A centralized, 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 centers. The iDose™ operator will receive individualized 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 centers 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 centers. 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.

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 (e.g., ileal resection, ileocecal resection, subtotal colectomy, total proctocolectomy, stricturoplasty, diverting stoma, ileostomy, colostomy procedures, or fistula repair) or seton placement for active perianal fistulizing disease.

Secondary outcomes

The secondary outcomes include both efficacy and safety endpoints that are described in detail in **Table 1**.

Intervention

All subjects in both treatment groups will receive IV 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 3**.

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 optimization or reactive TDM driven dose escalation in accordance with their usual practice. Subjects randomized 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.

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 ≥ 17 µg/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 ≥ 10 µg/mL at infusion #4. These cut-offs have been previously used in a prospective study by Dubinsky and colleagues.[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 ≥ 7 µg/mL at each infusion. During maintenance therapy, subjects with 2 consecutive IFX trough concentrations of >15 µg/mL will de-escalate IFX therapy to reach the target

concentration threshold of ≥ 7 μg/mL, as guided by the iDose™. Concomitant IMM use is prohibited in subjects randomized to the iDose™-driven IFX group throughout the study. If a subject is using one of these medications at screening and they are randomized to the iDose™ group, they must discontinue at the time of randomization and prior to starting IFX. Infliximab concentrations and ATI levels will be measured using a drug-tolerant homogenous mobility shift assay (HMSA) (Prometheus Laboratories, San Diego, CA) 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 utilized 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 titers compared to the commonly used standard infliximab assays.[41]

Concomitant corticosteroid use

All subjects who are using oral CSs (prednisone or equivalent [≤ 40 mg per day] or budesonide [≤ 9 mg per 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 (i.e., fecal 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 the Simple Endoscopic Score for CD at a central reading center. 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 hospitalizations.

Treatment failure and exiting the study

Regardless of randomization 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 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 Inc.) 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 endpoints. 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. Upon completion of the study an appropriate dataset will be placed in an open repository.

Statistical analyses

Medians (interquartile range) 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 chi-square or the Fisher's exact test, respectively. Corresponding two-sided 95% confidence intervals will be obtained using methods by Zou[42] and Newcombe.[43] All randomized 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 4th 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 includes treatment-related SAEs, CD-related surgeries and hospitalizations, 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 Chi-square test at the 2-sided 5% significance level, a total of 178 participants in a 1:1 randomization 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% confidence interval (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 analyzed for hypothesis-generating purposes. Risk ratios for secondary outcomes will be analyzed 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 generalized estimation equations will be used to analyze secondary outcomes with repeated measures. Ordinal outcome data will be analyzed using nonparametric methods, with treatment effect quantified by the Mann-Whitney probability and associated 95%CIs.[45] 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 post-marketing 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 personalize the delivery of anti-TNF to patients with CD. If PK dashboard-driven proactive IFX optimized monotherapy is superior to the SOC, the paradigm of CD treatment will shift. Monotherapy with IFX using proactive TDM and optimization using PK modelling will become the favored approach. This paradigm shift may occur even if PK-driven proactive infliximab optimized 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 infliximab clearance, such as the pediatric IBD population and patients with UC, as well as in patients prone to develop ATI, such as those carrying the HLA-DQA1*05 allele.[46-48] A post-hoc analysis of a recent prospective study demonstrated that in an adult and pediatric cohort of patients with IBD optimized infliximab 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.[49]

Furthermore, the use of the dashboard allows for a more individualized, patient-specific, dosing regimen. Through proactive optimization using a PK dashboard to visualize and calculate personalized 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 optimizing 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 hospitalizations and surgeries attributed to treatment failure. In a recent systematic review regarding IBD the TDM-guided strategies compared to standard treatment without TDM were consistently found to be cost saving or cost-effective.[50]

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 centers. Written informed consent will be obtained from all patients and parents/legal guardians of minor patient prior to enrolment. The study is registered at ClinicalTrials.gov (identifier: NCT04835506). 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.

Contributors

Study concept and design: K.P., M.C.D., A.S.C.; study design was developed in collaboration with Alimentiv Inc.; statistical support: GY Z.; manuscript drafting: K.P; study protocol and manuscript critical revision: K.P., V.J., B.L.C., T.E.R., B.E.S., C.A.S., J.F.V. N.V.C., M.C.D., A.S.C. Members of the study steering committee: A.S.C. K.P., V.J., B.L.C., T.E.R., B.E.S., C.A.S., J.F.V., M.C.D., A.S.C. All authors have approved the final manuscript and agree to be accountable for all aspects of the work.

Funding: This work is supported by the The Leona M. & Harry B. Helmsley Charitable Trust Grant #2108-04776. The funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. In-kind contributions for protocol writing provided by Alimentiv Inc.

Patient consent for publication: Not required.

Data Availability Statement: De-identified participant data and trial-level data will be available on reasonable request. This data will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement.

Competing interests: A.S.C.: reports consultancy fees from Janssen, Abbvie, Artugen, Procise, Prometheus, Arena, Grifols, Bacainn, Bristol Myers Squibb. V.J. has received consulting/advisory board fees from AbbVie, Alimentiv Inc (formerly Robarts Clinical Trials), Arena pharmaceuticals, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genetech, Gilead, Janssen, Merck, Mylan, Pandion,

Pendopharm, Pfizer, Reistone Biopharma, Roche, Sandoz, Takeda, Teva, Topivert; speaker's fees from, Abbvie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda. C.A.S.: reports consultancy fees from Abbvie, BMS, Lilly, Janssen, Pfizer, Prometheus, Takeda, Trellus Health; speaker fees for CME activities for Abbvie, Janssen, Pfizer, Takeda; grant support from the Crohn's and Colitis Foundation, Leona M. and Harry B. Helmsley Charitable Trust, Abbvie, Janssen, Pfizer, Takeda; intellectual property owned by MiTest Health, LLC (Software Company) and ColonaryConcepts, LLC; equity interest and co-founder of MiTest Health, LLC and ColonaryConcepts, LLC. K.P. reports lecture fees from Mitsubishi Tanabe Pharma and Physicians Education Resource LLC; consultancy fee from Prometheus Laboratories Inc; and scientific advisory board fees from ProciseDx Inc and Scipher Medicine Corporation. J.F.V.: reports research support from Roche/Genentech, Takeda, Applied Molecular Transport, Celgene/Bristol Myers Squibb, AbbVie, Arena Pharmaceuticals. GY Z.: reports consulting fees from Alimentiv Inc. B.L.C.: reports financial support for advisory boards and consultancy from Abbvie, Celgene-Bristol Myers Squibb, Pfizer, Sublimity Therapeutics, Takeda, TARGET RWE; CME Companies: Cornerstones, Vindico; speaking fees from Abbvie; educational Grant from Pfizer. M.C.D: reports consultancy fees from Abbvie Inc, Arena Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb Company, Cengene Corporation, Eli Lilly and Company, F. Hoffmann-La Roche Ltd, Genentech Inc, Gilead, Janssen Global Services, LLC, Pfizer Inc, Prometheus Biosciences, Takeda Pharmaceuticals USA Inc, UCB SA; research grants from AbbVie Inc, Janssen Global Services, LLC, Pfizer Inc, Prometheus Biosciences; ownership interest (stocks) Trellus Health Inc; and holds licensing fee with Takeda Pharmaceuticals USA Inc. T.E.R. reports speaking fees from Takeda Pharmaceuticals, Janssen, Pfizer, Bristol Myers Squibb; data adjudication committee fees from Ferring / Rebiotix; advisory boards fees from Abbvie, Arena, Boehringer Ingelheim, Bristol Myers Squibb / Celgene, Coral Genomics (and shareholder), Ferring, Genentech / Roche,

Gilead, Gossamer, Intercept, Janssen, Lilly, Pfizer, Prometheus, Sanofi, Takeda. B.E.S.: discloses research grants from Takeda, Pfizer, Theravance Biopharma R&D, Janssen; consulting fees from 4D Pharma, Abivax, Abbvie, Alimentiv, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, Bacainn Therapeutics, Boehringer-Ingelheim, Boston Pharmaceuticals, Bristol-Myers Squibb, Calibr, Capella Bioscience, Celgene, Celltrion Healthcare, ClostraBio, Enthera, F.Hoffmann-La Roche, Ferring, Galapagos, Gilead, Glaxo SmithKline, GossamerBio, Immunic, Index Pharmaceuticals, Innovation Pharmaceuticals, Ironwood Pharmaceuticals, Janssen, Kaleido, Kallyope, Lilly, MiroBio, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka, Palatin Technologies, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Redhill Biopharma, Rheos Medicines, Salix Pharmaceuticals, Seres Therapeutics, Shire, Sienna Biopharmaceuticals, Sun Pharma, Surrozen, Takeda, Target PharmaSolutions, Teva Branded Pharmaceutical Products R&D, Thelium, Theravance Biopharma R&D, TLL Pharma, USWM Enterprises, Ventyx Biosciences, Viela Bio, Vivante Health, Vivelix Pharmaceuticals; and stock for Vivante Health and Ventyx Biosciences. N.V.C.: received research grants from R-Biopharm, Takeda and UCB; and personal fees from AcelaBio, Alimentiv, Celltrion, ProciseDX, Prometheus, R-Biopharm, Takeda, UCB, Ventyx and Vividion. The remaining authors declare no conflict of interest.

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Table 1. Specific objectives and endpoints of the OPTIMIZE study.

Primary Objective	**Primary Endpoint**	**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 Endpoints**	**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 nonresponders (≤ 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 normalization of hs-CRP (decrease from ≥ 10 at baseline to < 10 mg/L)	Week 52
	9. Hs-CRP change from baseline	Week 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 normalization 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.	• Proportion of subjects exhibiting SLR (CDAI > 220 and at least 1 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.	• 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.	• Proportion of subjects with any treatment-related SAE • Proportion of subjects with CD-related surgery • Proportion of subjects with CD-related hospitalization	Week 0 through 52

	• Time to CD-related hospitalization • Time to CD-related surgery	

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

Table 2. Inclusion and exclusion criteria of the OPTIMIZE study.

Inclusion criteria
1. Males or nonpregnant, nonlactating females aged 16 to 80 years inclusive.
2. Diagnosis of CD prior to screening using standard endoscopic, histologic, or radiologic 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 1 of the following: elevated CRP (> upper limit of normal); elevated FC (> 250 µg/g); 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, ischemic colitis, colonic mucosal dysplasia, or untreated bile acid malabsorption.
3. Current bacterial or parasitic pathogenic enteric infection, according to standard of care assessments, including: C. difficile and tuberculosis; known infection with HBV, HCV 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 1 episode of herpes zoster or any episode of disseminated zoster; any other infection requiring hospitalization or iv antimicrobial therapy within 4 weeks prior to screening.
4. Malignancy or lymphoproliferative disorder other than nonmelanoma 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 enrollment) have been enrolled who have previously failed a biologic.
8. Concomitant use of oral corticosteroid 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, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion 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: fecal 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.

Table 3. 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**	**See note a**	**±7**	**±7**	**±7**	**NA**
Administrative and General Procedures							
Informed consent	X						
Assess inclusion/exclusion	X						
Confirm inclusion/exclusion		X					
Randomization		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 [b]					X	X [b]
Fecal calprotectin	X [b]					X [b]	X [b]
CRP / hs-CRP	X	X	X	X	X	X	X
Hematocrit	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

Note: 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.

Abbreviations: 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.

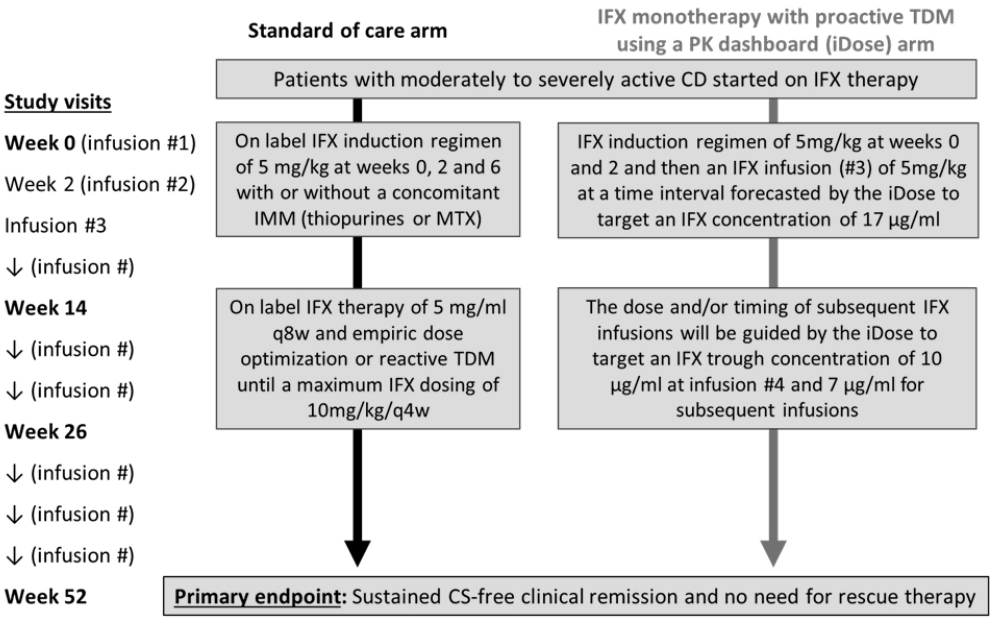
[a]Subjects in both groups will receive infusion #2 at week 2 (±3 days). Subjects randomized to the standard of care (SOC) group will receive subsequent infusions at week 6 (±7 days) and every 8 weeks (±7 days) thereafter. Subjects randomized to the iDose™-driven dosing group will receive IFX infusions after week 2 according to a schedule forecasted by the iDose™ dashboard, with a permitted window of ±7 days of the forecasted date; [b]At the discretion of the treating physician.

Figures

Figure 1 legend: OPTIMIZE Trial Study Design

Figure 1 footnote.

IFX: infliximab; TDM: therapeutic drug monitoring; PK: pharmacokinetic; CD: Crohn's disease; IMM: immunomodulator; MTX: methotrexate; w: week; CS: corticosteroid.



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