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Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn's Disease (REMODEL-CD) Clinical Trial

Short Title: REMODEL-CD trial

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Key Words: proactive drug monitoring, therapeutic drug monitoring, pharmacokinetics, anti-TNF

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Abstract

Introduction: The only biologic therapeutic currently approved to treat moderate to severe Crohn's disease in children (<18 years old) are those that antagonize tumor necrosis factor-alpha (anti-TNF). Therefore, it is critically important to develop novel strategies that maximize treatment effectiveness in this population. There is growing evidence that rates of sustained corticosteroid-free clinical remission, endoscopic healing and drug durability considerably improve when patients receive early anti-TNF dose optimizations guided by reactive or proactive therapeutic drug monitoring and pharmacodynamic monitoring. In response, our team has developed a personalized and scalable infliximab dosing intervention that starts with dose selection and continues throughout maintenance to optimize drug exposure. We hypothesize that a precision dosing strategy starting from induction and targeting dose-specific pharmacokinetic and pharmacodynamic endpoints throughout therapy will significantly improve outcomes compared to a conventional dosing strategy. **Methods and analysis**: Conduct a clinical trial to assess rates of deep remission between Crohn's disease patients receiving infliximab with precision dosing vs. conventional care. Subjects (age 6-22 years) will be recruited from 10 medical centers in the United States. Each center has been selected to provide either precision dosing or conventional care dosing. Precision dosing includes the use of a clinical decision support tool (RoadMAB™) from the start of infliximab to achieve specific (personalized) trough concentrations and specific pharmacodynamic targets (at dose3, 4 and 6). Conventional care includes the use of a modified infliximab starting dose (5 or 7.5 mg/kg based on the pre-treatment serum albumin) with a goal to achieve maintenance trough concentrations of 5-10 µg/mL. The primary endpoint is year1 deep remission defined as a combination of clinical remission (pediatric Crohn's disease activity index<10 [child] or a Crohn's disease activity index<150 [adults]), off prednisone >8weeks and endoscopic remission (simple endoscopic severity-Crohn's disease≤2). **Ethics and dissemination**: The trial is registered at ClinicalTrials.gov (NCT05660746).

Strengths and Limitations of this Study

- Performing a pragmatic clinical trial enrolling subjects 6-22 years old across 10 medical centers with deep remission assessed by colonoscopy after one year of infliximab
- Intervention arm includes the use of infliximab dose optimization from the first dose and continued throughout therapy based on specific pharmacokinetic (proactive TDM) and pharmacodynamic targets
- The interventional arm will use a novel precision dosing platform (RoadMAB™) throughout the trial that is scalable for use in real-world clinical practice
- All enrolled subjects will be provided with infliximab (in-kind support) from Janssen Scientific Affairs (drug-only) and therapeutic drug monitoring at no cost
- Gradual real-world clinical practice changes of using infliximab optimization during induction (doses 5-10 mg/kg) and the routine use of proactive TDM limit a true control cohort of using only 5 mg/kg and reactive TDM

Introduction

Crohn's disease (CD) is a chronic illness that results in intestinal inflammation and unwanted gastrointestinal symptoms. The only biologic (monoclonal antibody) therapeutics approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for moderate to severe CD in children (<18 years old) are those that antagonize tumor necrosis factor-alpha (anti-TNF). Initial response rate to labeled infliximab (anti-TNF) dosing ranges from 70-80%, however, only about half of infliximab exposed patients will achieve clinical remission and less than 40% will achieve endoscopic healing after one year of therapy.[1-3] The estimated 5-year sustained benefit from infliximab in real-world practice is about 40-60%.[4, 5]

In children, it is clear that use of labeled (standard) anti-TNF dosing regimens often lead to significant under-exposure and that a "one-size-fits-all" approach is outdated.[6] In fact, children receiving the standard (5 mg/kg) starting dose during induction has led to a significant rate (36-60%) of infliximab concentrations below the maintenance infliximab cTrough target (5-10 μg/mL) for luminal CD.[2, 7, 8]

Several studies have shown that rates of sustained corticosteroid-free clinical remission are improved when patients receive anti-TNF dose optimizations following reactive or proactive therapeutic drug monitoring (TDM).[9-12] There is growing evidence that anti-TNF dose optimizations during induction and following pharmacodynamic (PD) monitoring will lead to improved rates of clinical remission, endoscopic healing (EH), and lower rates of immunogencity.[6, 13] Therefore, given the limited therapeutic options for children with moderate to severe CD, there is a critical unmet need for the development of a personalized and scalable anti-TNF dosing intervention used from drug start and continued throughout maintenance therapy to optimize drug exposure and decrease immunogenicity with a long-term goal to improve rates of EH and drug durability.

In a prior prospective, real-world investigation, our team developed a population pharmacokinetic (PK) model for children and young adults receiving infliximab for moderate to severe CD.[2] In this study, we identified five covariates of infliximab clearance that significantly improved the prediction accuracy of our PK model with less unexplained variability in comparison to previous models.[2] This discovery also led to the development of a clinical-decision support tool (RoadMAB™) that performs

bedside model-informed precision dosing (MIPD) to optimize drug exposure for the individual patient.[2, 14] The RoadMAB™ platform performs Bayesian PK estimation using the published population PK model and the five covariates of infliximab clearance including the patient's weight (kg), serum albumin, erythrocyte sedimentation rate (ESR), neutrophil CD64 (nCD64), and antibodies to infliximab (ATI) to simulate the recommended (and user-selected) infliximab regimens. In addition to displaying the predicted trough concentrations (cTrough) throughout induction, RoadMAB™ incorporates measured infliximab concentrations collected at any timepoint during an interval to further update the platform and guide the future dosing regimen.

As noted, separate randomized controlled trials have demonstrated effectiveness of anti-TNF dose optimization using either PD targets (c-reactive protein [CRP] and/or fecal calprotectin [fCal]), proactive TDM, or a clinical decision support tool during maintenance therapy.[11, 13, 15] While these individual strategies improved rates of clinical remission and EH in their respective trials, it is currently unknown if a pragmatic anti-TNF dosing strategy that combines MIPD from induction, proactive TDM and repeated PD assessments to inform dose optimizations as a singular, novel strategy will result in superior clinical and endoscopic outcomes vs. the current dosing strategy that largely relies on TDM during maintenance and a "trial and error" approach to dose optimizations (conventional care). Therefore, our team has designed a pragmatic clinical trial that unifies proven anti-TNF dosing strategies to increase the rates of deep remission (EH and clinical remission). Furthermore, this study will provide invaluable data regarding whether MIPD of infliximab with a precision dosing platform is feasible, safe, and more effective at inducing EH in order to modernize future use of biologics.

The central hypothesis is that the hybrid precision dosing approach (intervention arm) of combining MIPD at the start of infliximab induction with proactive TDM and routine PD monitoring will improve rates of deep remission compared to the current methods of infliximab dose selection and use of proactive TDM prior to the first maintenance dose (control arm). To test this hypothesis, we will conduct a pragmatic clinical trial among CD subjects and assess rates of deep remission following one year of infliximab therapy between both arms.

Methods and Analysis

Study design and population

The REMODEL-CD study is an open-label, pragmatic clinical trial to assess the superior infliximab dosing strategy to achieve deep remission (clinical remission and EH) after one year of infliximab. All subjects will be recruited from 10 medical centers within the ImproveCareNow learning health network. Five centers will prescribe infliximab using the precision dosing strategy (interventional arm) and five centers will prescribe infliximab according to the conventional dosing strategy (control arm). Study eligibility is listed in Table1. The specific dosing strategy (treatment arm) has been assigned at the center-level to assure that all treating physicians have been properly informed and trained on the dosing intervention at their respective center. Subjects meeting eligibility criteria will be recruited prior to the start of infliximab.

Study outcomes

The primary outcome is deep remission that is defined as clinical remission (an inactive disease activity index and off prednisone >8 weeks) and EH (simplified endoscopic score-CD [SES-CD≤2]) at year 1.[3, 13] As both children and adults will be enrolled, the disease activity index for subjects 6-17 years old is assessed with the pediatric CD activity index (PCDAI) while the CD activity index (CDAI) will be used for subjects ≥18 years old. In order to assess for EH, all enrolled subjects remaining on infliximab >42 weeks will undergo a standard of care, follow up ileocolonoscopy with central readers blinded to the subject, treatment arm, center, and the endoscopic report. As noted, EH is assessed by the SES-CD while the Simplified Endoscopic Mucosal Assessment for CD (SEMA-CD) will be scored as an exploratory measure.[16, 17] Deep remission has been chosen as the primary endpoint as it was identified as a major long-term therapeutic goal by the STRIDE-II consortium.[18] Key secondary endpoints (Table2) will also include assessments of immunogenicity (ATI), patient reported outcomes (PRO), quality of life assessments,[19-21] and growth restoration in Tanner I-III children consistent with other STRIDE-II highlighted outcome measures.[18]

Interventions

All 10 centers participating in the REMODEL-CD trial currently utilize the ImproveCareNow Model IBD Care guidelines to manage CD patients starting infliximab. These guidelines recommend

physicians use the FDA/EMA approved starting dose of 5 mg/kg (rounding up the nearest 100 mg) but also acknowledge that higher starting doses can be considered in more severe or extensive disease. In addition, it is recommended that a cTrough be obtained prior to the first maintenance dose (proactive TDM) or with disease activity (reactive TDM) and to target a minimum cTrough of 5 µg/mL during the maintenance phase. Once enrolled, all subjects will receive infliximab at their center at no cost from the in-kind (drug-only) support from Janssen Scientific Affairs, LLC. Both treatment arms will receive the standard induction regimen (infusions at 0, 2 and 6 weeks) with maintenance infusions varying between 4-8 weeks for both groups. As a pragmatic study, all dosing and management decisions will be made by the subject's treating physician.

Conventional Care (control arm)

The FDA and EMA approved infliximab induction dose is 5 mg/kg occurring at weeks 0, 2 and 6. Consistent with conventional dosing at the participating centers, treating physicians will choose a starting dose between 5-7.5 mg/kg based on the patient's serum albumin at the time of screening. As CD severity is often subjective, we chose to use the patient's serum albumin to base the starting dose as it provides a more objective marker of CD severity and it has been found to be a consistent biomarker of infliximab clearance in multiple pediatric PK studies.[2, 22, 23] The protocol recommends that subjects with a serum albumin <3 gm/dL receive 7.5 mg/kg and subjects with a serum albumin ≥3 gm/dL receive 5 mg/kg. Once the starting dose has been selected, the subject will receive the same dose (in mg) throughout induction (dose1, dose2 and dose3). As is routine practice, calculated doses of ≥20 mg over a 100 mg increment will be increased up to the nearest 100 mg to minimize drug waste as vials are supplied in 100 mg increments. Rounding to the nearest 100 mg will not be done if the rounding of the induction doses would cause the patient to receive a dose >7.5 mg/kg. Therefore, these subjects will receive the exact flat dose (7.5 mg/kg) ordered by the treating physician in accordance with the study protocol.

All subjects in the conventional care arm will undergo proactive TDM (Esoterix, LabCorp specialty lab, Calabasas, CA) prior to receiving dose4 (~week14, cTrough). The treating physician will then interpret these results and prescribe future infliximab doses between 5-10 mg/kg with a dosing interval between 4-8 weeks to achieve or maintain a cTrough target of 5-10 µg/mL.

Importantly, the dose will not be rounded to the nearest 100 mg if rounding would result in a maintenance dose >10 mg/kg in this arm. Therefore, these subjects will receive the exact flat dose (10 mg/kg). As this is a pragmatic dosing arm, no dose reductions or intensifications will be study mandated. During the study, the treating physician can obtain one reactive TDM during maintenance if there is a concern for active CD. If ATI are discovered during any TDM, the subsequent dosing regimen (including the possible addition of methotrexate) is at the discretion of the treating physician and will not be considered a treatment failure unless infliximab is discontinued. The use of MIPD programs, PK software or other commercially available TDM modeling services to inform dosing regimens is not permitted in this arm.

Precision Care (interventional arm)

The precision care arm includes the use of the RoadMAB™ platform to inform the first starting dose during induction and assess for opportunities to dose optimize during maintenance based on three strict Checkpoints (Supplemental Figure1). Checkpoint1 (dose3) includes a cTrough target while Checkpoint2 (dose4) and Checkpoint3 (dose6) include both a cTrough and PD target, respectively.

Prior to starting infliximab, the treating physician will access the New Start Wizard within the RoadMAB™ precision dosing software portal (Figure1) and review the dashboard recommended infliximab starting dose. RoadMAB™ formulates a dosing recommendation based on the predicted infliximab clearance using Bayesian estimation with the Xiong et al. population PK model[2] and is guided by a novel method of disease progression modeling. While RoadMAB™ will display the predicted cTrough at dose2, 3 and 4, the initial target (Checkpoint1) is a cTrough at dose3 (week6) between 18-24 µg/mL (Target1). Infliximab clearance is estimated by the PK model using the subject's current weight (kg), serum albumin (g/dL), ESR (mm/hr.), and nCD64 results. RoadMAB™ will provide a "Model Informed Dosing" (Figure1b) recommendation between 5-12.5 mg/kg (at weeks 0, 2, and 6) to achieve a cTrough (Target1) between 18-24 µg/mL.[23] The treating physician will also have the option of viewing the "Standard Dosing" tab (Figure1c) to preview (as a reference) the predicted cTrough at dose2-4 for the standard FDA/EMA approved dose (5 mg/kg). Within the "Manual Dosing" tab (Figure1d), the physician is also able to interact with RoadMAB™ to review

variable dosing options and the subsequent predicted cTrough. Any deviations from the Model Informed Dosing recommendation will be described in the case report form.

The starting dose will range between 5-12.5 mg/kg with the same rounding principles (to the nearest 100 mg) as described in the conventional care arm. Rounding to the nearest 100 mg will not be done if rounding would result in the subject receiving an induction dose >12.5 mg/kg and therefore, the patient would max at a dose of 12.5 mg/kg.

Prior to dose3 (week6), a cTrough will be obtained. The cTrough along with the subject's weight, albumin, ESR, nCD64 and ATI (ng/mL) will be entered into RoadMAB™ to further guide a maintenance dosing regimen to achieve a cTrough of 5-10 µg/mL at the next infusion (dose4). The treating physician will make the final decision for maintenance dosing (that achieves the cTrough target) as there are multiple choices of modifying the dose alone, interval alone or both dose and interval.

During maintenance, there are two Checkpoints that will require additional review. Both Checkpoints will assess whether the PK and PD targets were met. As adequate drug exposure has been shown to be a key variable in assessing treatment effectiveness, the cTrough target has been prioritized for both Checkpoints and will guide all subsequent dosing recommendations. The PK/PD targets for Checkpoint2 and Checkpoint3 are listed in Table3 and Table4, respectively. Importantly, if either the CRP or fCal is missing, the missing PD biomarker will default to Yes (achieved) with future dosing based on the success or failure of the other PD targets.

Assessing Success or Failure for Checkpoint2 and Checkpoint3

During maintenance, the cTrough target concentration (at dose4 and dose6) is dependent on whether the subject is (1) a PK failure only or (2) PK success with PD failure. Following each infusion, vital subject data (weight, albumin, CRP, ESR, and nCD64) and dose administration (date and time) will be manually entered into the secure RoadMAB™ platform. The treating physician will then access the RoadMAB™ platform to review whether the Checkpoint PK and PD targets were achieved to determine the next optimal dose (mg) and dosing interval (weeks). Infliximab maintenance doses will range between 5-15 mg/kg (rounded to the nearest 100 mg) and infusion

intervals will range between 4-8 weeks. As a precaution, rounding up to the nearest 100 mg vial will not be done if rounding the maintenance dose would result in a single dose >15 mg/kg.

As noted, during maintenance, the PK target takes precedence over the PD assessment. For example, if a cTrough is below target (at dose4 or 6), RoadMAB™ will provide a dosing recommendation to achieve the PK target first (irrespective of the result of the PD target). Once a PK target is achieved, the PD targets are assessed by RoadMAB™ and subsequent dosing recommendations will be presented to the user. Therefore, a PK success with any PD failure (at the two maintenance Checkpoints) is then systematically elevated to a new PK tier. PK tiers range from 5-10 µg/mL (starting maintenance target for all subjects), 10-15 µg/mL and up to 15-20 µg/mL depending on the PD outcomes. To achieve PK and PD success, all PD criteria (disease activity index, CRP and fCal) must be achieved. Supplementary Table1 provides details of the PD failure criteria and the subsequent escalation plan.

Treatment Failure (special circumstances)

Primary infliximab failure can be difficult to define in a real-world, pragmatic study as clinicians often dose escalate infliximab to ensure proper exposure prior to drug discontinuation. In this trial, if any of the following criteria are met, the subject will not continue in the study and will be classified as a primary infliximab non-responder. These primary failure criteria include: (a) receiving the first two doses of infliximab <7 days apart, (b) receiving >3 doses before week6, (c) receiving the third dose <2 weeks after dose2, (d) receiving ≥10 mg/kg during induction (first three doses, in the conventional care arm), (e) receiving >12.5 mg/kg during induction (first three doses, in the precision care arm), (f) continuation of high dose prednisone or prednisolone (at doses >0.5 mg/kg if <40 kg or >20 mg for patients ≥40 kg) beyond week12, (g) use of oral budesonide beyond week16, or (f) starting methotrexate, 6-mercaptopurine or azathioprine prior to receiving infliximab dose4. Criteria for secondary nonresponse or study withdrawal during maintenance are listed in Supplementary Table2.

In order to manage any ATI (lower limit of detection is 22 ng/mL with the Esoterix, LabCorp assay), RoadMAB™ will provide a dose optimization strategy (as ATI is a covariate of drug clearance in the PK model) and display the predicted cTrough for the next two infusions. The addition of methotrexate (to reduce immunogenicity or improve exposure) is at the discretion of the treating

physician. Similarly, the addition of methotrexate during maintenance phase for a cTrough persistently below the 5-10 μg/mL is at the discretion of the treating physician and will not be considered a treatment failure.

During the trial, both treatment arms can perform reactive TDM during maintenance, however, use of reactive TDM on ≥2 occasions will be recorded as a deviation in both arms. As is standard in clinical care, any subject receiving a dose optimization will have repeat TDM performed prior to the second new dose. Similar to the conventional care arm, dose reduction or interval lengthening is not mandated in the trial but the treating physician is encouraged to discuss the risks and benefits for any subject with a persistently elevated cTrough.

Adverse Event Monitoring

The trial team at each center will be responsible for detecting, documenting, and reporting events that meet the definition of adverse events including all serious adverse events and adverse events of special interest. Per protocol, the subject will be monitored until the event resolves, stabilizes, or is reasonably explained. The team will be responsible to determine if the adverse event was related to the study device, a procedure, or infliximab while considering pre-existing conditions or concomitant medications. Adverse events will be reported in a timely manner to the medical monitor, the study Data Safety Monitoring Board, the principal investigator, the FDA, the Sponsor and Janssen Scientific Affairs, LLC.

Statistical analysis

Our study design including the use of a precision dosing platform to optimize infliximab doses during induction in children is novel. Therefore, the expected rates of deep remission with this strategy are currently unknown. In order to develop our sample size calculation, we likened the precision dosing arm (interventional) to subjects within the SONIC study that found 63% of CD subjects who received combination of infliximab and azathioprine (within 18 months of diagnosis) achieved deep remission at week26.[24] The control arm subject would be most similar to those who participated in the CALM and TAILORIX clinical trials, where rates of year 1 deep remission was achieved in 23-36.9% and 27-33% (variation by treatment arm), respectively.[13, 25] Furthermore, preliminary review of children within the ImproveCareNow learning health network, indicated an

intra-class correlation (ICC) of 0.02 for clinical remission outcomes. Therefore, based on an anticipated 36.9% deep remission rate in the control arm and 63% deep remission rate in the interventional arm, we determined 140 subjects (70 in each arm) would provide 80% power to detect a clinically meaningful absolute difference of at least 25% between the two treatment arms (alpha 0.05), assuming an ICC of 0.02. As study attrition is estimated at 5% and primary nonresponse is estimated at 12-15%[1], the final sample size was increased to 180 subjects (90 in each arm).

Generalized linear mixed models with a logit link will be used to compare rates of deep remission between the two arms. Our team will individually assess both the intention-to-treat and per protocol populations with the per protocol population to include all enrolled subjects who received scheduled infliximab for at least 42 weeks while the intention-to-treat population will include all enrolled subjects who received at least one maintenance infliximab infusion (4 doses). Fidelity will be assessed to avoid a type III error. We will assess whether core components of each intervention were conducted at the critical timepoints for precision dosing (pre-treatment, doses3, 4 and 6) and for conventional care (dose4) as noted in the study design. There is a planned interim analysis after the first 40 patients in the precision dosing arm complete one year of infliximab.

Ethics and Dissemination

The REMODEL-CD trial is registered at ClinicalTrials.gov (NCT05660746). The clinical trial has received Institutional Review Board approval at Cincinnati Children's Hospital Medical Center and Reliance agreements will be completed at all participating centers before subject enrollment. Parental consent will be required for all children <18 years of age while adults ≥18 years of age will provide consent before any study procedures are started. Prior to submission of this trial for funding, our study team met with parents of children with CD and adult patients with CD to discuss the study hypothesis and study protocol. These individuals were key in refining the inclusion criteria, the interventions, methods to enhance study retention and the plans for dissemination. Following completion of the trial, the results will comply with the Consolidated Standards of Reporting Trials (CONSORT) and sent for peer review to inform whether precision dosing of infliximab is feasible, safe, and more effective at inducing endoscopic healing and clinical remission then conventional care.

Discussion

Suboptimal inflammatory control of pediatric CD increases the likelihood of irreversible intestinal damage and CD-related complications.[26, 27] Innovative clinical trials using novel approaches to maximize the current FDA/EMA approved biologics in pediatric CD are needed as anti-TNF dose optimization strategies informed by proactive TDM in children[9, 11] and PD control in adult CD[13] have been associated with improved outcomes. Dose optimization in children is particularly important as several studies have shown that anti-TNF clearance is significantly elevated in young patients (<10 years old), those with extensive disease (ileocolonic) or a high inflammatory burden and most children will require a dose modification during therapy as they continue to grow.[2, 11, 28] Therefore, subjects enrolled in the precision care arm will receive dose optimization (based on pre-treatment biomarkers of drug clearance) from the start of infliximab with the maintenance regimen (dose and/or frequency) based entirely on achieving specific cTrough and PD targets.

While there is debate whether proactive TDM and PD monitoring will improve near and long-term outcomes, anti-TNF dose optimization in clinical practice in children and young adults is common. Therefore, our team has designed a clinical trial that is both practical and based on key, objective procedures used in prior clinical trials (CALM, PRECISION, and PAILOT).[11, 13, 15] Specifically, in the PAILOT clinical trial, subjects were randomized to receive adalimumab dose optimization using either a reactive or proactive TDM approach (following successful induction).[11] Assa et al. found CD patients in the proactive TDM arm (targeting a cTrough >5 µg/mL during maintenance) resulted in higher rates of corticosteroid-free sustained clinical remission.[11] The PRECISION trial randomized adults with IBD receiving maintenance infliximab to model-informed dosing or standard of care dosing.[15] After one year, subjects receiving model-informed dosing (with a dose calculator similar to RoadMAB™) to maintain a minimal cTrough (3 µg/mL) had significantly lower rates of loss of response and a lower median fCal after one year.[15]

There are a variety of reasons as to why the prior proactive TDM clinical trials in adults with IBD (TAXIT[29], TAILORIX[25] or SERENE-CD[30]) failed to demonstrate significant improvement compared to the respective control group. Key limitations to these prior studies include delaying the intervention until maintenance, only including adults with IBD, and use of a low cTarget (3 µg/mL for infliximab

or 5 µg/mL for adalimumab). Therefore, we have designed a trial that will enroll children to receive dose optimization during induction with an intensifying cTrough strategy that starts at 5-10 µg/mL and escalates based on success or failure of key PD biomarkers at specific, early stages of treatment.

While this will be one of the first studies to use a precision dosing support tool to dose optimize infliximab in pediatric CD, several studies in renal transplantation and other chronic conditions have demonstrated the value of using PK software (decision support tools) to guide dose selection, obtain targeted immunosuppressive drug concentrations and achieve superior outcomes.[15, 31, 32] Therefore, while the rate of deep remission at year 1 is the primary outcome, we will also be assessing the useability, fidelity, safety and effectiveness of the RoadMAB™ software platform in real-world clinical practice.

In summary, the current "one-size-fits-all" with labeled anti-TNF dosing often leads to suboptimal drug exposure, poor gut healing and increased burdens on the patient and family. In this trial, our global aim is to conduct the first clinical trial to evaluate the rate of deep remission in children and young adults who have been recently diagnosed with CD and set to receive infliximab using a combination of MIPD, PD control, and proactive TDM throughout induction and maintenance.

Authors' contributions

PM: Concept & design, initial draft and revising manuscript, final manuscript approval, and responsible for the study funding as the principal investigator.

RJC: Literature review and manuscript revision.

NZ: Literature review, developed both the sample size calculation and statistical analysis plan, and manuscript revision.

TM: Developed statistical analysis plan, performed literature review and manuscript revision.

AAV: Concept& design, manuscript revision for intellectual content, study mentoring and manuscript revision.

All authors approved the final version of the manuscript including the authorship list.

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Competing interests statement

Phillip Minar and Alexander Vinks are inventors of the RoadMAB™ dosing platform. Janssen Scientific Affairs, LLC has reviewed and approved the study protocol.

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Table1. REMODEL-CD Eligibility Criteria

Inclusion Criteria	• Written informed consent from the patient (≥18 years old) or from parent/legal guardian if patient is <18 years old
	• Written informed assent from patient when age appropriate
	• Diagnosis of Crohn's disease within the last 90 days (luminal-only or luminal with perianal Crohn's without a need for systemic antibiotics in the last 7 days)
	• ≥6 years to ≤22 years of age, anti-TNF naïve and starting infliximab (or an infliximab biosimilar)
	• Clinical activity and luminal inflammation, defined by both (1) and (2)
	  • (1) PCDAI>10 (<18 years old) or CDAI >150 (≥18 years old) in last 60 days
	  • (2) SES-CD>6 (or a report of large intestinal ulcerations) or a fecal calprotectin ≥250 µg/g within last 60 days
	• C-reactive protein >1.0 mg/dL in last 30 days and/or fecal calprotectin ≥250 µg/g within last 60 days
	• Negative TB (tuberculosis) interferon-gamma release test and a negative urine pregnancy test (if menstruation has started)

Exclusion Criteria	• Diagnosis of ulcerative colitis or inflammatory bowel disease-unspecified • Prior use of anti-TNF therapy (*infliximab, adalimumab, certolizumab pegol, or golimumab*) • Internal (abdominal/pelvic) penetrating fistula(e) in last 180 days • Intra-abdominal abscess/phlegmon/inflammatory mass in the last 180 days • Active perianal abscess (receiving oral antibiotics for <7 days) • Intestinal stricture (luminal narrowing with pre-stenotic dilation >3mm) and surgery planned in next 90 days • *Clostridium difficile* infection or other intestinal infection in the last 1-week or a severe infection in last 90 days. Severe infection is defined as requiring hospitalization for treatment or a vancomycin taper. • Current hospitalization for complications of severe Crohn's disease • Planned use of methotrexate or 6-mercaptopurine (azathioprine) during induction • Current ileostomy, colostomy, ileoanal pouch, and/or previous extensive small bowel resection (>35 cm) • History of autoimmune hepatitis, primary sclerosing cholangitis, thyroiditis, or juvenile idiopathic arthritis • Treatment with another investigational drug in last 4 weeks • History of malignancy (including lymphoma or leukemia) • History of histoplasmosis, human immunodeficiency virus (HIV), an immunodeficiency syndrome, a central nervous system demyelinating disease or receiving intravenous antibiotics in last 14 days for any infection • Currently pregnant, breast feeding or plans to become pregnant in the next 1 year • Inability or failure to provide informed assent/consent • Any developmental disabilities that would impede providing assent/consent

Table2. Key Secondary Outcome Measures

Name of Outcome	Specific measure to be used	Time point(s)
Rate of Clinical Response	Decrease from baseline PCDAI of at least 12.5 points & total PCDAI<30 or a total PCDAI<10 (child).[1] Reduction of CDAI>70 from baseline or CDAI<150 (adult).[33]	Weeks14 and 52
Time to and Rate of Steroid-free Clinical Remission	(1) PCDAI<10 (child) or CDAI<150 (adult) and (2) off prednisone/budesonide for ≥4 weeks[1, 13]	Weeks14-52
Rate of Sustained Steroid-free Clinical Remission	(1) PCDAI<10 (child) or CDAI<150 (adult) at dose5 to week52 and (2) off prednisone/budesonide from dose5 to week52	Week~22-52
Rate of Steroid-free Clinical Remission – biomarker composite	(1) PCDAI<10 (child) or CDAI<150 (adult), (2) off prednisone/budesonide for ≥4 weeks, (3) CRP ≤0.5 mg/dL and (4) fecal calprotectin ≤250 µg/g[13]	Weeks14 and 52
Rate of Endoscopic Healing	SES-CD ≤2[24]	Week52
Rate of Complete Endoscopic Healing	SES-CD=0	Week52
Rate of Bias and Precision	Model predicted vs. actual infliximab concentration. Bias: mean predictive error (MPE). Precision: root mean squared error (RMSE)	All infusions
Time to and Rate of IBD-related events	Events: surgery, hospitalization, perianal or internal fistula, intestinal stricture, start of oral/IV prednisone or presence of antibody to infliximab >200 ng/mL[34]	Week0-52
Rate of Growth Restoration	In Tanner stage I-III subjects: height velocity (z-score) by gender[35] and change from baseline weight (kg) by gender and age group[18]	Week0-52
Rate of PRO2 Response	>50% improvement in stool frequency and abdominal pain from baseline[18]	Week4, 14, 26 and 52
Rate of PRO2 Remission	Stool frequency ≤3.0 and abdominal pain ≤1.0 (from baseline)[36]	Week4, 14, 26 and 52
Quality of Life Assessment before/after treatment	IMPACT-III (child)[19, 20] or Short IBD Questionnaire (adult)[21] compared to baseline	Week52
Time to and Rate of Adverse events	Includes Serious Adverse Events and Adverse events	Week0-52

PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; SES-CD, simple endoscopic score-Crohn's disease.

Table3: Checkpoint2 (dose4) Pharmacokinetic and Pharmacodynamic Targets

Pharmacokinetic	Infliximab trough concentration 5-10 µg/mL
Pharmacodynamic	(1) Disease activity score + Child: PCDAI decrease of at least 12.5 points from baseline and a total PCDAI<30 OR a total PCDAI<10 Adult: delta CDAI >70 from baseline OR a CDAI<150 (2) CRP ≥50% change from baseline CRP OR a CRP ≤0.5 mg/dL + (3) Fecal calprotectin ≥50% change from baseline OR a fecal calprotectin ≤250 µg/g

PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein.

Table4: Checkpoint3 (dose6) Pharmacokinetic and Pharmacodynamic Targets

Pharmacokinetic	Infliximab trough concentration 5-15 µg/mL (varies from 5-10 or 10-15 µg/mL depending on whether Target2 trough concentration was achieved)
Pharmacodynamic	(1) Disease activity score + Child: PCDAI <10 Adult: CDAI <150 (2) CRP ≤0.5 mg/dL (or CRP ≤5 g/dL) + (3) Fecal calprotectin ≤250 µg/g

PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein.

Figure1. The RoadMABTM New Start Wizard will launch prior to the first dose. Pre-treatment biomarkers including weight, albumin, erythrocyte sedimentation rate and neutrophil CD64 are entered into the table. The Wizard uses dynamic disease progression modeling along with the population pharmacokinetic model to simulate a dosing regimen to achieve the (A) dose3 (week6) target concentration of 18-24 µg/mL. The default tab is (B) model-informed dosing, however the user can also toggle through (C) standard dosing and (D) manual dosing. (E) The predicted concentration over time curve is shown and based on the selected starting dose.

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Supplementary Table1: Specific Pharmacodynamic (PD) Treatment Failure Criteria and the Target Escalation Plan

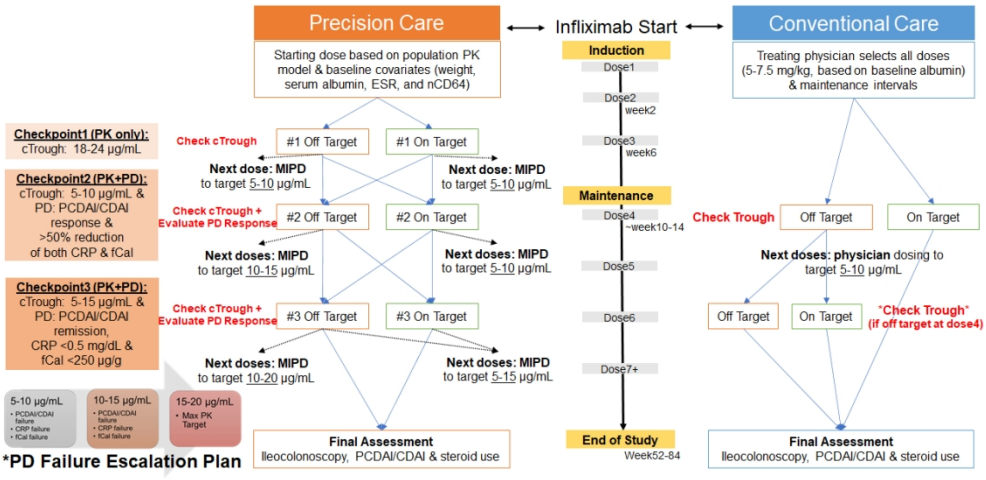
Specific PD Target	Timing by infusion (~week)	PCDAI/CDAI cut-points	(and/or) CRP cut-points	(and/or) fecal calprotectin cut-points
Checkpoint 2	Dose4 (~week10-14)	delta PCDAI<12.5 or a PCDAI>30 (child) delta CDAI<70 (adult)	<50% change from baseline	<50% change from baseline
Checkpoint 3	Dose6 (~week26)	PCDAI≥10 CDAI≥150	>0.5 g/dL	>250 µg/g
PD Target Failure for *any 2 consecutive* infusions after (dose6)		PCDAI≥30 CDAI>220	≥1 g/dL	---
PD Target Failure for any *single* infusion after dose6				>500 µg/g
Target Escalation plan*	PD Failure1: New PK target = 10-15 µg/mL		PD Failure2: New PK target = 15-20 µg/mL (max)	

*The trough concentration is the primary target, therefore, pharmacodynamic targets are only instituted if the prior trough concentration was within the target. PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; PK, pharmacokinetic.

Supplementary Table2. Criteria for Secondary Nonresponse and Study Withdrawal

Secondary Nonresponse (may remain in the trial)	• Remaining on prednisone/prednisolone or oral budesonide for >14 weeks after week20 (corticosteroid restarts) or remaining on prednisone/prednisolone or oral budesonide after week44
Secondary Nonresponse (meet study withdrawal criteria)	• Subjects in the conventional care arm receiving >10 mg/kg infliximab and/or <25 days apart between infusions during maintenance. • Subjects in the precision care arm receiving >12.5 mg/kg infliximab during induction (first 3 doses) • Subjects in the precision care arm receiving >15 mg/kg infliximab and/or <25 days apart between infusions during maintenance. • Subjects who have a Crohn's disease-related surgery • Subjects who develop an intra-abdominal abscess or inflammatory mass • Subjects diagnosed with a bacterial infection requiring intravenous antibiotics or hospitalization (related to the infection) • Subjects who discontinuation of infliximab before week42 (either initiated by the subject or treating physician) • Any plan to start another biologic (anti-integrin, anti-cytokine), small molecule (any JAK inhibitor or sphingosine-1-phosphage inhibitor) or 6-mercaptopurine (including Imuran or azathioprine) during the trial • Anaphylaxis (hypersensitivity reaction) during/after an infusion that is deemed by the provider, medical monitor or principal investigator to be unsafe to attempt a subsequent future infusion

Supplementary Figure1: The REMODEL-CD Clinical Trial Overview. The trial includes two arms, the precision care (interventional) and conventional care (control). The conventional care arm will receive starting doses of 5-7.5 mg/kg (based on pre-treatment serum albumin) and one proactive therapeutic drug monitoring (TDM) at dose4. The starting dose in the precision care arm will vary between 5-12.5 mg/kg and is based on predicted (baseline) infliximab clearance and a target trough concentration (cTrough) of 18-24 µg/mL at dose3. Following induction, two additional Checkpoints will be assessed for Pharmacokinetic (PK) and Pharmacodynamic (PD) targets. Infliximab optimization during maintenance is dependent on whether the PK, PD or both PK/PD targets have been met. As noted, the PK target is the first priority before assessing the PD targets and escalating the target concentration to the next tier. ESR, erythrocyte sedimentation rate; nCD64, neutrophil CD64; PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; fCal, fecal calprotectin; MIPD, model-informed precision dosing.



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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1

Roles and responsibilities: sponsor and funder	#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	15
Roles and responsibilities: committees	#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)	15
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	6-10
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	6
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)	19
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11
Interventions: modifications	#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)	10-11

Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
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	6, 20
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)	Suppl.Figure2
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	11-12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
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	n/a
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	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#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	11-12
Data collection plan: retention	#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	n/a
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	n/a
Statistics: outcomes	#20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring: formal committee	#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	11
Data monitoring: interim analysis	#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	12

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	11
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	12
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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: trial results	#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	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

BMJ Open

Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn's Disease (REMODEL-CD): Study Protocol for a Multicenter, Open-label, Pragmatic Clinical Trial in the United States

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Paediatrics, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, Clinical Trial, Inflammatory bowel disease < GASTROENTEROLOGY, Paediatric gastroenterology < GASTROENTEROLOGY

Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn's Disease (REMODEL-CD): Study Protocol for a Multicenter, Open-label, Pragmatic Clinical Trial in the United States

Short Title: REMODEL-CD trial

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Disclosure Statement: Janssen Scientific Affairs, LLC is providing drug-only (infliximab) support for all enrolled subjects. Esoterix, LabCorp specialty lab, Calabasas, CA is providing therapeutic drug monitoring at a reduced cost to the investigators.

Key Words: proactive drug monitoring, therapeutic drug monitoring, pharmacokinetics, anti-TNF

Word count: 4049

Abstract

Introduction: The only biologic therapy currently approved to treat moderate to severe Crohn's disease in children (<18 years old) are those that antagonize tumor necrosis factor-alpha (anti-TNF). Therefore, it is critically important to develop novel strategies that maximize treatment effectiveness in this population. There is growing evidence that rates of sustained corticosteroid-free clinical remission, endoscopic healing and drug durability considerably improve when patients receive early anti-TNF dose optimizations guided by reactive or proactive therapeutic drug monitoring and pharmacodynamic monitoring. In response, our team has developed a personalized and scalable infliximab dosing intervention that starts with dose selection and continues throughout maintenance to optimize drug exposure. We hypothesize that a precision dosing strategy starting from induction and targeting dose-specific pharmacokinetic and pharmacodynamic endpoints throughout therapy will significantly improve outcomes compared to a conventional dosing strategy. **Methods and analysis**: Conduct a clinical trial to assess rates of deep remission between Crohn's disease patients receiving infliximab with precision dosing (n=90) vs. conventional care (n=90). Subjects (age 6-22 years) will be recruited from 10 medical centers in the United States. Each center has been selected to provide either precision dosing or conventional care dosing. Precision dosing includes the use of a clinical decision support tool (RoadMAB™) from the start of infliximab to achieve specific (personalized) trough concentrations and specific pharmacodynamic targets (at dose3, 4 and 6). Conventional care includes the use of a modified infliximab starting dose (5 or 7.5 mg/kg based on the pre-treatment serum albumin) with a goal to achieve maintenance trough concentrations of 5-10 µg/mL. The primary endpoint is year1 deep remission defined as a combination of clinical remission (pediatric Crohn's disease activity index<10 [child] or a Crohn's disease activity index<150 [adults]), off prednisone >8weeks and endoscopic remission (simple endoscopic severity-Crohn's disease≤2). **Ethics and dissemination**: The trial is registered at ClinicalTrials.gov (NCT05660746). The study protocol has been approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. Study results will be disseminated in peer-reviewed journals and presented at scientific meetings.

Strengths and Limitations of this Study

- One of the first real-world, multicenter, pragmatic clinical trials in children receiving infliximab for Crohn's disease that includes an objective assessment of intestinal healing (colonoscopy) at the conclusion of the trial
- Intervention arm includes the use of infliximab dose optimization from the first dose and continued throughout therapy based on specific pharmacokinetic (proactive TDM) and pharmacodynamic targets
- The interventional arm will use a novel precision dosing platform (RoadMAB™) throughout the trial that is scalable for use in real-world clinical practice
- The in-kind drug support (infliximab, from Janssen Scientific Affairs) will assure participants receive the physician specified infliximab dosing and minimize any confounding that may have occurred if the study relied on third-party insurance coverage for the proposed dosing regimen
- One limitation is the gradual adoption in real-world clinical practice of using infliximab optimization during induction (doses 5-10 mg/kg) and the routine use of proactive TDM may limit a true control cohort of standard dosing (5 mg/kg) and reactive TDM

Introduction

Crohn's disease (CD) is a chronic illness that results in intestinal inflammation and unwanted gastrointestinal symptoms. The only biologic (monoclonal antibody) therapy approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for moderate to severe CD in children (<18 years old) are those that antagonize tumor necrosis factor-alpha (anti-TNF). Initial response rate to labeled infliximab (anti-TNF) dosing ranges from 70-80%, however, only about half of infliximab exposed patients will achieve clinical remission and less than 40% will achieve endoscopic healing after one year of therapy.[1-3] In real-world practice, the probability of remaining on infliximab for 5-years was shown to be 60%.[4, 5]

In children, use of labeled (standard, 5 mg/kg at 0, 2, 6 and then every 8 weeks) anti-TNF dosing regimens often leads to significant under-exposure and that a "one-size-fits-all" approach is outdated.[6] In fact, children receiving the standard starting dose during induction has led to a significant rate (36-60%) of infliximab concentrations below the maintenance infliximab trough concentration (cTrough) target (5-10 μg/mL) for luminal CD.[2, 7, 8]

Several studies in children and adults have shown that rates of sustained corticosteroid-free clinical remission are improved when patients receive anti-TNF dose (infliximab or adalimumab) optimizations following reactive or proactive therapeutic drug monitoring (TDM).[9-12] There is growing evidence in adults with CD that anti-TNF (adalimumab) dose optimizations during induction and following pharmacodynamic (PD) monitoring will lead to improved rates of clinical remission, endoscopic healing (EH), and lower rates of immunogenicity.[6, 13] Therefore, given the limited therapeutic options for children with moderate to severe CD, there is a critical unmet need for the development of a personalized and scalable anti-TNF dosing intervention applied from drug start, continued throughout maintenance therapy to optimize drug exposure, reduce immunogenicity and improve rates of EH and drug durability.

In a prior prospective, real-world investigation, our team developed a population pharmacokinetic (PK) model for children and young adults receiving infliximab for moderate to severe CD.[2] In this study, we identified five covariates of infliximab clearance that significantly improved the prediction accuracy of our PK model with less unexplained variability in comparison to previous models.[2] This

discovery also led to the development of a clinical-decision support tool (RoadMAB™) that performs bedside model-informed precision dosing (MIPD) to optimize drug exposure for the individual patient.[2, 14] The RoadMAB™ platform performs Bayesian PK estimation to propose up to three treatment regimens using the published population PK model and the five covariates of infliximab clearance. The five biomarkers (covariates) of infliximab clearance are the patient's weight (kg), serum albumin, erythrocyte sedimentation rate (ESR), neutrophil CD64 (nCD64), and antibodies to infliximab (ATI). In addition to displaying the predicted cTrough throughout induction, RoadMAB™ incorporates measured infliximab concentrations collected at any timepoint during an interval to further update the platform and guide the future dosing regimen.

As noted, separate randomized controlled trials in adults and children have demonstrated effectiveness of anti-TNF dose (infliximab and adalimumab) optimization using either PD targets (c-reactive protein [CRP] and/or fecal calprotectin [fCal]), proactive TDM, or a clinical decision support tool during maintenance therapy.[11, 13, 15] While these individual strategies improved rates of clinical remission and EH in their respective trials, it is currently unknown if a pragmatic anti-TNF dosing strategy that combines MIPD from induction, proactive TDM and repeated PD assessments to inform dose optimizations as a singular, novel strategy will result in superior clinical and endoscopic outcomes as compared to the current dosing strategy that largely relies on TDM during maintenance and a "trial and error" approach to dose optimize infliximab (conventional care). Therefore, our team has designed a pragmatic clinical trial that unifies proven infliximab dosing strategies to increase the rates of deep remission (EH and clinical remission). Furthermore, this study will provide invaluable data regarding whether MIPD of infliximab with a precision dosing platform is feasible, safe, more effective at inducing EH and modernize dosing strategies of other biologics.

The central hypothesis is that the hybrid precision dosing approach (intervention arm) of combining MIPD at the start of infliximab induction with proactive TDM and routine PD monitoring will improve rates of deep remission compared to the current approach to infliximab dose selection and use of proactive TDM prior to the first maintenance dose (control arm). To test this hypothesis, we will conduct a multicenter, pragmatic clinical trial among CD subjects and assess rates of deep remission following one year of infliximab therapy between both arms.

Methods and Analysis

Study design and population

The REMODEL-CD study is an open-label, pragmatic clinical trial to assess the superior infliximab dosing strategy to achieve deep remission after one year of infliximab. All subjects will be recruited from 10 medical centers within the ImproveCareNow learning health network. Five centers will prescribe infliximab using the precision dosing strategy (intervention arm) and five centers will prescribe infliximab according to the conventional dosing strategy (control arm). We will enroll newly diagnosed (<90 days) patients (6-22 years old) with moderate to severe luminal CD who are starting infliximab (additional patient eligibility is listed in Table1). The trial start date is July 1, 2023 with an estimated completion date of March 31, 2027. The specific dosing strategy (treatment arm) has been assigned at the center-level to prevent treatment contamination and assure that all treating physicians have been properly informed and trained on the dosing intervention at their respective center. Subjects meeting eligibility criteria will be recruited prior to the start of infliximab.

Study outcomes

The primary outcome is deep remission that is defined as clinical remission (an inactive disease activity index and off prednisone >8 weeks) and EH (simplified endoscopic score-CD [SES-CD≤2]) at year 1.[3, 13] As both children and adults will be enrolled, the disease activity index for subjects 6-17 years old is assessed with the pediatric CD activity index (PCDAI) while the CD activity index (CDAI) will be used for subjects ≥18 years old. In order to assess for EH, all enrolled subjects remaining on infliximab >42 weeks will undergo a standard of care, follow up ileocolonoscopy with central readers blinded to the subject, treatment arm and center, and the endoscopic report. As noted, EH is assessed by the SES-CD while the Simplified Endoscopic Mucosal Assessment for CD (SEMA-CD) will be scored as an exploratory measure.[16, 17] Deep remission has been chosen as the primary endpoint as it was identified as a major long-term therapeutic goal by the STRIDE-II consortium.[18] Key secondary endpoints (Table2) will also include assessments of immunogenicity (ATI), patient reported outcomes (PRO), quality of life assessments,[19-21] and growth restoration in Tanner I-III children consistent with other key STRIDE-II outcome measures.[18]

Interventions

All 10 centers participating in the REMODEL-CD trial currently utilize the ImproveCareNow Model IBD Care guidelines (available at www.improvecarenow.org) to manage CD patients starting infliximab. These guidelines recommend physicians use the FDA/EMA approved starting dose of 5 mg/kg (rounding up the nearest 100 mg) but also acknowledge that higher starting doses can be considered in more severe or extensive disease (including perianal disease). In addition, it is recommended that a cTrough be obtained prior to the first maintenance dose (proactive TDM) and with an acute increase in gastrointestinal symptoms (reactive TDM). The maintenance cTrough target is 5 µg/mL. Once enrolled, all subjects will receive infliximab at their center at no cost from the in-kind (drug-only) support from Janssen Scientific Affairs, LLC. Both treatment arms will receive the standard induction regimen (infusions at 0, 2 and 6 weeks) with maintenance infusions varying between 4-8 weeks for both groups. As a pragmatic study, all dosing and management decisions will be made by the subject's treating physician.

Conventional Care (control arm)

The FDA and EMA approved infliximab induction dose is 5 mg/kg occurring at weeks 0, 2 and 6. In order to ensure the full spectrum of disease severity will be enrolled at these centers, the treating physicians will choose a starting dose between 5-7.5 mg/kg based on the patient's serum albumin (at the time of screening). The patient's baseline serum albumin was chosen to inform the starting dose as it provides a more objective marker of CD severity and it has been found to be a consistent biomarker of infliximab clearance in multiple pediatric PK studies.[2, 7, 22] The protocol recommends that subjects with a serum albumin <3 gm/dL receive 7.5 mg/kg and subjects with a serum albumin ≥3 gm/dL receive 5 mg/kg. Once the starting dose has been selected, the subject will receive the same dose (in mg) throughout induction (dose1, dose2 and dose3). As is routine practice, calculated doses of ≥20 mg over a 100 mg increment will be increased up to the nearest 100 mg to minimize drug waste as vials are supplied in 100 mg increments. Rounding to the nearest 100 mg will not be done if the rounding of the induction doses would cause the patient to receive a dose >7.5 mg/kg.

All subjects in the conventional care arm will undergo proactive TDM (Esoterix, LabCorp specialty lab, Calabasas, CA) prior to receiving dose4 (~week14, cTrough). The treating physician will then interpret these results and prescribe future infliximab doses between 5-10 mg/kg with a

dosing interval between 4-8 weeks to achieve or maintain a cTrough target of 5-10 µg/mL (Table3). Importantly, the dose will not be rounded to the nearest 100 mg if rounding would result in a maintenance dose >10 mg/kg. As this is a pragmatic dosing study, no dose reductions or intensifications will be study mandated. During the study, the treating physician can obtain one reactive TDM during maintenance if there is a concern for active CD. If ATI are discovered during any TDM, the subsequent dosing regimen (including the possible addition of methotrexate) is at the discretion of the treating physician and will not be considered a treatment failure unless infliximab is discontinued. The use of MIPD programs, PK software or other commercially available TDM modeling services to inform dosing regimens are not permitted.

Precision Care (intervention arm)

The precision care arm includes the use of the RoadMAB™ platform to inform the first starting dose during induction and assess for opportunities to dose optimize during maintenance based on three strict Checkpoints (Supplemental Figure1). Checkpoint1 (dose3) includes a cTrough target while Checkpoint2 (dose4) and Checkpoint3 (dose6) include both cTrough and PD targets.

Prior to starting infliximab, the treating physician will access the New Start Wizard within the RoadMAB™ precision dosing software portal (Figure1) and review the dashboard recommended infliximab starting dose. RoadMAB™ formulates a dosing recommendation based on the predicted infliximab clearance using Bayesian estimation with the Xiong et al. population PK model[2] and is guided by a novel method of disease progression modeling. While RoadMAB™ will display the predicted cTrough at dose2, 3 and 4, the initial target (Checkpoint1) is a cTrough at dose3 (week6) between 18-24 µg/mL (Target1).[7]

The RoadMAB™ platform will provide a starting dose ("Model Informed Dosing," Figure1b) between 5-12.5 mg/kg that will attain the aforementioned dose3 cTrough target (Checkpoint1).[7] Starting doses are rounded up to the nearest 100 mg (as described for the conventional care arm) unless rounding would result in a dose >12.5 mg/kg (max induction dose). The model-informed starting dose is generated by estimating infliximab clearance based on the subject's weight (kg), serum albumin (g/dL), ESR (mm/h) and nCD64. The treating physician will also have the option of viewing the "Standard Dosing" tab (Figure1c) to preview (as a reference) the predicted cTrough at

dose2-4 for the standard FDA/EMA approved dose (5 mg/kg). Within the "Manual Dosing" tab (Figure1d), the physician is able to interact with RoadMAB™ to review variable dosing options and the subsequent predicted cTrough. Any deviations from the Model Informed Dosing recommendation will be documented in the case report form.

Prior to dose3 (week6), a cTrough will be obtained. The cTrough along with the subject's weight, albumin, ESR, nCD64 and ATI (ng/mL) will be entered into RoadMAB™ to further guide a maintenance dosing regimen to achieve a cTrough of 5-10 µg/mL at the next infusion (dose4). The treating physician will make the final decision for maintenance dosing as there are multiple strategies to maintain the target, including modifying the dose alone, interval alone or changing both dose and interval.

During maintenance, there are two Checkpoints that will require additional review. Both Checkpoints will assess whether the PK and PD targets were met. As adequate drug exposure has been shown to be a key variable in assessing treatment effectiveness, the cTrough target has been prioritized for both Checkpoints and will guide all subsequent dosing recommendations. The PK/PD targets for Checkpoint2 and Checkpoint3 are listed in Table3. Importantly, if either the CRP or fCal is missing, the missing PD biomarker will default to Yes (achieved) with future dosing based on the success or failure of the other PD targets.

Assessing Success or Failure for Checkpoint2 and Checkpoint3

During maintenance, the cTrough target concentration (at dose4 and dose6) is dependent on whether the subject is (1) a PK failure only or (2) PK success with PD failure. Following each infusion, vital subject data (weight, albumin, CRP, ESR, and nCD64) and dose administration (date and time) will be manually entered into the secure RoadMAB™ platform. The treating physician will then access the RoadMAB™ platform to review whether the Checkpoint PK and PD targets were achieved to determine the next optimal dose (mg) and dosing interval (weeks). Infliximab maintenance doses will range between 5-15 mg/kg (rounded to the nearest 100 mg) and infusion intervals will range between 4-8 weeks. As a precaution, rounding up to the nearest 100 mg vial will not be done if rounding the maintenance dose would result in a single dose >15 mg/kg.

As noted, during maintenance, the PK target takes precedence over the PD assessment. For example, if a cTrough is below target (at dose4 or 6), RoadMAB™ will provide a dosing recommendation to achieve the PK target first (irrespective of the result of the PD target). Once a PK target is achieved, the PD targets are assessed by RoadMAB™ and subsequent dosing recommendations will be presented to the user. Therefore, a PK success with any PD failure (at the two maintenance Checkpoints) is then systematically elevated to a new PK tier. PK tiers range from 5-10 µg/mL (the starting maintenance cTrough target for all subjects), 10-15 µg/mL and up to 15-20 µg/mL depending on the PD outcomes. To achieve PK and PD success, all PD criteria (disease activity index, CRP and fCal) must be achieved. Supplementary Table1 provides details of the PD failure criteria and the subsequent escalation plan.

Treatment Failure (special circumstances for both arms)

Primary infliximab failure can be difficult to define in a real-world, pragmatic study as clinicians often dose escalate infliximab to ensure proper exposure prior to drug discontinuation. In this trial, if any of the following criteria are met, the subject will not continue in the study and will be classified as a primary infliximab non-responder. These primary failure criteria include: (a) receiving the first two doses of infliximab <7 days apart, (b) receiving >3 doses before week6, (c) receiving the third dose <2 weeks after dose2, (d) receiving ≥10 mg/kg during induction (first three doses, in the conventional care arm), (e) receiving >12.5 mg/kg during induction (first three doses, in the precision care arm), (f) continuation of high dose prednisone or prednisolone (at doses >0.5 mg/kg if <40 kg or >20 mg for patients ≥40 kg) beyond week12, (g) use of oral budesonide beyond week16, or (f) starting methotrexate, 6-mercaptopurine or azathioprine prior to receiving infliximab dose4. Criteria for secondary nonresponse or study withdrawal during maintenance are listed in Supplementary Table2.

The management of ATI (lower limit of detection is 22 ng/mL with the Esoterix, LabCorp assay) will vary by the treatment arm. As a pragmatic trial, infliximab optimizations are determined by the treating physician in the conventional care arm while dose optimizations in the precision care arm will be informed by RoadMAB™. For both arms, the addition of methotrexate (to reduce immunogenicity or improve exposure) is at the discretion of the treating physician. Similarly, the addition of

methotrexate during maintenance phase for a cTrough persistently below the 5-10 µg/mL is at the discretion of the treating physician and will not be considered a treatment failure.

During the trial, both treatment arms can perform reactive TDM during maintenance. The use of reactive TDM on ≥2 occasions, however, will be recorded as a deviation in both arms. As is standard in clinical care, any subject receiving a dose optimization will have TDM performed prior to the second new dose. For both treatment arms, dose reduction or interval lengthening is not mandated in the trial but the treating physician is encouraged to discuss the risks and benefits for any subject with a persistently elevated cTrough.

Adverse Event Monitoring

The trial team at each center will be responsible for detecting, documenting, and reporting events that meet the definition of adverse events including all serious adverse events and adverse events of special interest. Per protocol, the subject will be monitored until the event resolves, stabilizes, or is reasonably explained. The team will be responsible to determine if the adverse event was related to the study device, a procedure, or infliximab while considering pre-existing conditions or concomitant medications. Adverse events will be reported in a timely manner to the medical monitor, the study Data Safety Monitoring Board, the principal investigator, the FDA, the Sponsor and Janssen Scientific Affairs, LLC.

Statistical analysis

Our study design, including the use of a precision dosing platform to optimize infliximab doses during induction in children is novel. Therefore, the expected rates of deep remission with this strategy are currently unknown. In order to develop our sample size calculation, we likened the precision dosing arm (intervention) to subjects within the SONIC study that found 63% of adults with CD who received combination of infliximab and azathioprine (within 18 months of diagnosis) achieved deep remission at week26.[23] The control arm subjects would be most similar to the adults with CD who participated in the CALM and TAILORIX clinical trials, where rates of year 1 deep remission was achieved in 23-36.9% and 27-33% (variation by treatment arm), respectively.[13, 24] Furthermore, preliminary review of children within the ImproveCareNow learning health network, indicated an intra-class correlation (ICC) of 0.02 for clinical remission outcomes. Therefore, based on

an anticipated 36.9% deep remission rate in the control arm and 63% deep remission rate in the interventional arm, we determined 140 subjects (70 in each arm) would provide 80% power to detect a clinically meaningful absolute difference of at least 25% between the two treatment arms (alpha 0.05), assuming an ICC of 0.02. As study attrition is estimated at 5% and primary nonresponse is estimated at 12-15%[1], the final sample size was increased to 180 subjects (90 in each arm).

Generalized linear mixed models with a logit link will be used to compare rates of deep remission between the two arms. Additionally, center-specific random effect will be included to account for dependence of outcomes from the same center. Our team will individually assess both the intention-to-treat and per protocol populations with the per protocol population to include all enrolled subjects who received scheduled infliximab for at least 42 weeks while the intention-to-treat population will include all enrolled subjects who received at least one infliximab infusion (1 dose). Fidelity will be assessed to avoid a type III error. We will assess whether core components of each intervention were conducted at the critical timepoints for precision dosing (pre-treatment, doses3, 4 and 6) and for conventional care (dose4) as noted in the study design. There is a planned interim analysis after the first 40 patients in the precision dosing arm complete one year of infliximab.

Ethics and Dissemination

The REMODEL-CD trial is registered at ClinicalTrials.gov (NCT05660746). The clinical trial has received Institutional Review Board approval at Cincinnati Children's Hospital Medical Center. The following participating centers have completed the Reliance agreements to participate in the trial: Nationwide Children's Hospital, Rady Children's Hospital San Diego, Medical College of Wisconsin/Children's of Wisconsin, Riley Hospital for Children, Lucile Packard Children's Hospital Stanford, Nemours Children's Health System-Wilmington, Nemours Children's Health System-Jacksonville, and Children's Hospital of Los Angeles. Parental consent will be required for all children <18 years of age while adults ≥18 years of age will provide consent before any study procedures are started. *Patient and public involvement*: Prior to submission of this trial for funding, our study team met with parents of children with CD and adult patients with CD to discuss the study hypothesis and study protocol. These individuals were key in refining the inclusion criteria, the interventions, methods to enhance study retention and the plans for dissemination. Following

completion of the trial, the results will comply with the Consolidated Standards of Reporting Trials (CONSORT) and results disseminated in peer-reviewed journals and presented at scientific meetings to inform whether precision dosing of infliximab is feasible, safe, and more effective at inducing deep remission then conventional care.

Discussion

Suboptimal inflammatory control of pediatric CD increases the likelihood of irreversible intestinal damage and CD-related complications.[25, 26] Innovative clinical trials using novel approaches to maximize the current FDA/EMA approved biologics in pediatric CD are needed as anti-TNF dose optimization strategies informed by proactive TDM in children[9, 11] and PD control in adult CD[13] have been associated with improved outcomes. Dose optimization in children is particularly important as several studies have shown that anti-TNF clearance is significantly elevated in young patients (<10 years old), those with extensive disease (ileocolonic) or a high inflammatory burden.[2, 11, 27] Therefore, subjects enrolled in the precision care arm will receive dose optimization (based on pre-treatment biomarkers of drug clearance) from the start of infliximab with the maintenance regimen (dose and/or frequency) based entirely on achieving specific cTrough and PD targets.

While there is debate whether proactive TDM and PD monitoring will improve near and long-term outcomes, anti-TNF dose optimization in clinical practice in children and young adults is common. Therefore, our team has designed a clinical trial that is both practical and based on key, objective procedures used in prior clinical trials (CALM, PRECISION, and PAILOT).[11, 13, 15] Specifically, in the PAILOT clinical trial, subjects were randomized to receive adalimumab dose optimization using either a reactive or proactive TDM approach (following successful induction).[11] Assa et al. found CD patients in the proactive TDM arm (targeting a cTrough >5 µg/mL during maintenance) resulted in higher rates of corticosteroid-free sustained clinical remission.[11] The PRECISION trial randomized adults with IBD receiving maintenance infliximab to model-informed dosing or standard of care dosing.[15] After one year, subjects receiving model-informed dosing (with a dose calculator similar to RoadMAB™) to maintain a minimal cTrough (3 µg/mL) had significantly lower rates of loss of response and a lower median fCal after one year.[15]

There are a variety of reasons as to why the prior proactive TDM clinical trials in adults with IBD (TAXIT[28], TAILORIX[24] or SERENE-CD[29]) failed to demonstrate significant improvement compared to the respective control group. Key limitations to these prior studies include delaying the intervention until maintenance, only including adults with IBD, and use of a low cTarget (3 µg/mL for infliximab or 5 µg/mL for adalimumab). Therefore, we have designed a trial that will enroll children to receive dose optimization during induction with an intensifying cTrough strategy that starts at 5-10 µg/mL and escalates based on success or failure of key PD biomarkers at specific, early stages of treatment.

While this will be one of the first studies to use a precision dosing support tool to dose optimize infliximab in pediatric CD, several studies in renal transplantation and other chronic conditions have demonstrated superior outcomes using PK software (decision support tools) to guide dose selection and obtain targeted immunosuppressive drug concentrations.[15, 30, 31] Therefore, while the rate of deep remission at year 1 is the primary outcome, we will also be assessing the useability, fidelity, safety and effectiveness of the RoadMAB™ software platform in real-world clinical practice.

In summary, the current "one-size-fits-all" with labeled anti-TNF dosing often leads to suboptimal drug exposure, poor gut healing and increased burdens on the patient and family. In this trial, our global aim is to conduct the first clinical trial to evaluate the rate of deep remission in children and young adults who have been recently diagnosed with CD and receive infliximab using a combination of MIPD, PD control, and proactive TDM throughout induction and maintenance.

Authors' contributions

Study concept and design: PM, AAV; initial draft and revising manuscript: PM, RJC, NZ, TM, AAV; literature review: RJC, NZ, TM; developed both the sample size calculation and statistical analysis plan; NZ, TM, PM; study protocol review and revision: PM, NZ, TM, AAV. All authors approved the final version of the manuscript including the authorship list.

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Competing interests statement

Phillip Minar and Alexander Vinks are inventors of the RoadMAB™ dosing platform. Janssen Scientific Affairs, LLC has reviewed and approved the study protocol.

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Figure1. RoadMAB™ Precision Dosing Platform. The RoadMAB™ New Start Wizard will launch prior to the first dose. Pre-treatment biomarkers including weight, albumin, erythrocyte sedimentation rate and neutrophil CD64, are manually entered into the table prior to launching the platform. The Wizard uses dynamic disease progression modeling along with the population pharmacokinetic model to simulate a dosing regimen to achieve the (A) dose3 (week6) target concentration of 18-24 µg/mL. The default tab is (B) model-informed dosing, however, the user can also toggle through (C) standard dosing and (D) manual dosing to inform the dosing decision. (E) The predicted concentration over time curve is shown and based on the selected starting dose.

Table1. REMODEL-CD Eligibility Criteria

Inclusion Criteria	• Written informed consent from the patient (≥18 years old) or from parent/legal guardian if patient is <18 years old
	• Written informed assent from patient when age appropriate (age of assent is determined by the center)
	• Diagnosis of Crohn's disease within the last 90 days (luminal-only or luminal with perianal Crohn's without a need for systemic antibiotics in the last 7 days)
	• ≥6 years to ≤22 years of age, anti-TNF naïve and starting infliximab (or an infliximab biosimilar)
	• Clinical activity and luminal inflammation, defined by both (1) and (2)
	  • (1) PCDAI>10 (<18 years old) or CDAI >150 (≥18 years old) in last 60 days
	  • (2) SES-CD>6 or SES-CD>3 for isolated ileal disease (or a report of large intestinal ulcerations) or a fecal calprotectin ≥250 µg/g within last 60 days
	• C-reactive protein >1.0 mg/dL in last 30 days and/or fecal calprotectin ≥250 µg/g within last 60 days
	• Negative TB (tuberculosis) interferon-gamma release test and a negative urine pregnancy test (if menstruation has started)

Exclusion Criteria	• Diagnosis of ulcerative colitis or inflammatory bowel disease-unspecified • Prior use of anti-TNF therapy (*infliximab, adalimumab, certolizumab pegol, or golimumab*) • Internal (abdominal/pelvic) penetrating fistula(e) in last 180 days • Intra-abdominal abscess/phlegmon/inflammatory mass in the last 180 days • Active perianal abscess (receiving oral antibiotics for <7 days) • Intestinal stricture (luminal narrowing with pre-stenotic dilation >3mm) and surgery planned in next 90 days • *Clostridium difficile* infection or other intestinal infection in the last 1-week or a severe infection in last 90 days. Severe infection is defined as requiring hospitalization for treatment or a vancomycin taper. • Current hospitalization for complications of severe Crohn's disease • Planned use of methotrexate or 6-mercaptopurine (azathioprine) during induction • Current ileostomy, colostomy, ileoanal pouch, and/or previous extensive small bowel resection (>35 cm) • History of autoimmune hepatitis, primary sclerosing cholangitis, thyroiditis, or juvenile idiopathic arthritis • Treatment with another investigational drug in last 4 weeks • History of malignancy (including lymphoma or leukemia) • History of histoplasmosis, human immunodeficiency virus (HIV), an immunodeficiency syndrome, a central nervous system demyelinating disease or receiving intravenous antibiotics in last 14 days for any infection • Currently pregnant, breast feeding or plans to become pregnant in the next 1 year • Inability or failure to provide informed assent/consent • Any developmental disabilities that would impede providing assent/consent

Table2. Key Secondary Outcome Measures

Name of Outcome	Specific measure to be used	Time point(s)
Rate of Clinical Response	Decrease from baseline PCDAI of at least 12.5 points & total PCDAI<30 or a total PCDAI<10 (child).[1] Reduction of CDAI>70 from baseline or CDAI<150 (adult).[32]	Weeks14 and 52
Time to and Rate of Steroid-free Clinical Remission	(1) PCDAI<10 (child) or CDAI<150 (adult) and (2) off prednisone/budesonide for ≥4 weeks[1, 13]	Weeks14-52
Rate of Sustained Steroid-free Clinical Remission	(1) PCDAI<10 (child) or CDAI<150 (adult) at dose5 to week52 and (2) off prednisone/budesonide from dose5 to week52	Week~22-52
Rate of Steroid-free Clinical Remission – biomarker composite	(1) PCDAI<10 (child) or CDAI<150 (adult), (2) off prednisone/budesonide for ≥4 weeks, (3) CRP ≤0.5 mg/dL and (4) fecal calprotectin ≤250 µg/g[13]	Weeks14 and 52
Rate of Endoscopic Healing	SES-CD ≤2[23]	Week52
Rate of Complete Endoscopic Healing	SES-CD=0	Week52
Rate of Bias and Precision	Model predicted vs. actual infliximab concentration. Bias: mean predictive error (MPE). Precision: root mean squared error (RMSE)	All infusions
Time to and Rate of IBD-related events	Events: surgery, hospitalization, perianal or internal fistula, intestinal stricture, start of oral/IV prednisone or presence of antibody to infliximab >200 ng/mL[33]	Week0-52
Rate of Growth Restoration	In Tanner stage I-III subjects: height velocity (z-score) by gender[34] and change from baseline weight (kg) by gender and age group[18]	Week0-52
Rate of PRO2 Response	>50% improvement in stool frequency and abdominal pain from baseline[18]	Week4, 14, 26 and 52
Rate of PRO2 Remission	Stool frequency ≤3.0 and abdominal pain ≤1.0 (from baseline)[35]	Week4, 14, 26 and 52
Quality of Life Assessment before/after treatment	IMPACT-III (child)[19, 20] or Short IBD Questionnaire (adult)[21] compared to baseline	Week52
Time to and Rate of Adverse events	Includes Serious Adverse Events and Adverse events	Week0-52

PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; SES-CD, simple endoscopic score-Crohn's disease.

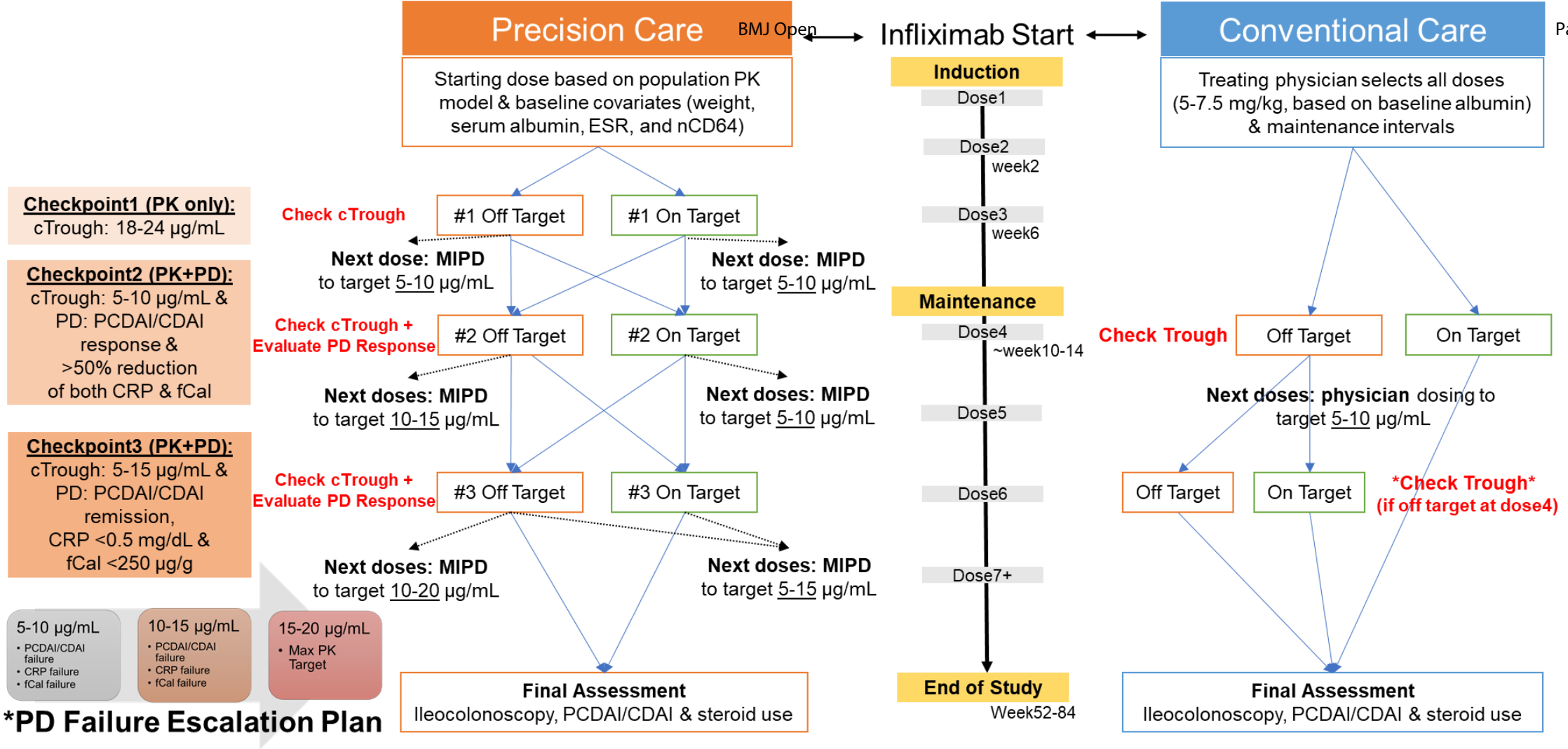
Table3: Pharmacokinetic and Pharmacodynamic Targets by Treatment Arm.

Conventional care arm	
Dose3	Proactive therapeutic drug monitoring is not performed
Dose4	Infliximab trough concentration 5-10 µg/mL
Dose6	Proactive therapeutic drug monitoring is not performed
Precision care arm	
Dose3 (Checkpoint1)	Infliximab trough concentration 18-24 µg/mL
Dose4 (Checkpoint2)	
Pharmacokinetic	Infliximab trough concentration 5-10 µg/mL
Pharmacodynamic	(1) Disease activity score + Child: PCDAI decrease of at least 12.5 points from baseline and a total PCDAI<30 OR a total PCDAI<10 Adult: delta CDAI >70 from baseline OR a CDAI<150 (2) CRP ≥50% change from baseline CRP OR a CRP ≤0.5 mg/dL + (3) Fecal calprotectin ≥50% change from baseline OR a fecal calprotectin ≤250 µg/g
Dose6 (Checkpoint3)	
Pharmacokinetic	Infliximab trough concentration 5-15 µg/mL (varies from 5-10 or 10-15 µg/mL depending on whether Target2 trough concentration was achieved)
Pharmacodynamic	(1) Disease activity score + Child: PCDAI <10 Adult: CDAI <150 (2) CRP ≤0.5 mg/dL (or CRP ≤5 g/dL) + (3) Fecal calprotectin ≤250 µg/g

PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein.

Figure 1 - RoadMABTM Precision Dosing Platform

403x254mm (72 x 72 DPI)



Supplementary Figure1: The REMODEL-CD Clinical Trial Overview. The trial includes two arms, the precision care (interventional) and conventional care (control). The conventional care arm will receive starting doses of 5-7.5 mg/kg (based on pre-treatment serum albumin) and one proactive therapeutic drug monitoring (TDM) at dose4. The starting dose in the precision care arm will vary between 5-12.5 mg/kg and is based on predicted (baseline) infliximab clearance and a target trough concentration (cTrough) of 18-24 µg/mL at dose3. Following induction, two additional Checkpoints will be assessed for Pharmacokinetic (PK) and Pharmacodynamic (PD) targets. Infliximab optimization during maintenance is dependent on whether the PK, PD or both PK/PD targets have been met. As noted, the PK target is the first priority before assessing the PD targets and escalating the target concentration to the next tier. ESR, erythrocyte sedimentation rate; nCD64, neutrophil CD64; PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; fCal, fecal calprotectin; MIPD, model-informed precision dosing.

Supplementary Table1: Specific Pharmacodynamic (PD) Treatment Failure Criteria and the Target Escalation Plan

Specific PD Target	Timing by infusion (~week)	PCDAI/CDAI cut-points	(and/or) CRP cut-points	(and/or) fecal calprotectin cut-points
Checkpoint 2	Dose4 (~week10-14)	delta PCDAI<12.5 or a PCDAI>30 (child) delta CDAI<70 (adult)	<50% change from baseline	<50% change from baseline
Checkpoint 3	Dose6 (~week26)	PCDAI≥10 CDAI≥150	>0.5 g/dL	>250 µg/g
PD Target Failure for *any 2 consecutive* infusions after (dose6)		PCDAI≥30 CDAI>220	≥1 g/dL	---
PD Target Failure for any *single* infusion after dose6				>500 µg/g
Target Escalation plan*	PD Failure1: New PK target = 10-15 µg/mL		PD Failure2: New PK target = 15-20 µg/mL (max)	

*The trough concentration is the primary target, therefore, pharmacodynamic targets are only instituted if the prior trough concentration was within the target. PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; PK, pharmacokinetic.

Supplementary Table2. Criteria for Secondary Nonresponse and Study Withdrawal

Secondary Nonresponse (may remain in the trial)	• Remaining on prednisone/prednisolone or oral budesonide for >14 weeks after week20 (corticosteroid restarts) or remaining on prednisone/prednisolone or oral budesonide after week44
Secondary Nonresponse (meet study withdrawal criteria)	• Subjects in the conventional care arm receiving >10 mg/kg infliximab and/or <25 days apart between infusions during maintenance. • Subjects in the precision care arm receiving >12.5 mg/kg infliximab during induction (first 3 doses) • Subjects in the precision care arm receiving >15 mg/kg infliximab and/or <25 days apart between infusions during maintenance. • Subjects who have a Crohn's disease-related surgery • Subjects who develop an intra-abdominal abscess or inflammatory mass • Subjects diagnosed with a bacterial infection requiring intravenous antibiotics or hospitalization (related to the infection) • Subjects who discontinuation of infliximab before week42 (either initiated by the subject or treating physician) • Any plan to start another biologic (anti-integrin, anti-cytokine), small molecule (any JAK inhibitor or sphingosine-1-phosphage inhibitor) or 6-mercaptopurine (including Imuran or azathioprine) during the trial • Anaphylaxis (hypersensitivity reaction) during/after an infusion that is deemed by the provider, medical monitor or principal investigator to be unsafe to attempt a subsequent future infusion

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1

Roles and responsibilities: sponsor and funder	#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	15
Roles and responsibilities: committees	#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)	15
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	6-10
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	6
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)	19
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11
Interventions: modifications	#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)	10-11

Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
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	6, 20
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)	Suppl.Figure2
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	11-12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
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	n/a
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	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#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	11-12
Data collection plan: retention	#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	n/a
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	n/a
Statistics: outcomes	#20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring: formal committee	#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	11
Data monitoring: interim analysis	#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	12

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	11
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	12
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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: trial results	#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	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

BMJ Open

Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn's Disease (REMODEL-CD): Study Protocol for a Multicenter, Open-label, Pragmatic Clinical Trial in the United States

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Secondary Subject Heading:	Paediatrics, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, Clinical Trial, Inflammatory bowel disease < GASTROENTEROLOGY, Paediatric gastroenterology < GASTROENTEROLOGY

Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn's Disease (REMODEL-CD): Study Protocol for a Multicenter, Open-label, Pragmatic Clinical Trial in the United States

Short Title: REMODEL-CD trial

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Disclosure Statement: Janssen Scientific Affairs, LLC is providing drug-only (infliximab) support for all enrolled patients. Esoterix, LabCorp specialty lab, Calabasas, CA is providing therapeutic drug monitoring at a reduced cost to the investigators.

Key Words: proactive drug monitoring, therapeutic drug monitoring, pharmacokinetics, anti-TNF

Word count: 4057

Abstract

Introduction: The only biologic therapy currently approved to treat moderate to severe Crohn's disease in children (<18 years old) are those that antagonize tumor necrosis factor-alpha (anti-TNF). Therefore, it is critically important to develop novel strategies that maximize treatment effectiveness in this population. There is growing evidence that rates of sustained corticosteroid-free clinical remission, endoscopic healing and drug durability considerably improve when patients receive early anti-TNF dose optimizations guided by reactive or proactive therapeutic drug monitoring and pharmacodynamic monitoring. In response, our team has developed a personalized and scalable infliximab dosing intervention that starts with dose selection and continues throughout maintenance to optimize drug exposure. We hypothesize that a precision dosing strategy starting from induction and targeting dose-specific pharmacokinetic and pharmacodynamic endpoints throughout therapy will significantly improve outcomes compared to a conventional dosing strategy. **Methods and analysis**: Conduct a clinical trial to assess rates of deep remission between Crohn's disease patients receiving infliximab with precision dosing (n=90) vs. conventional care (n=90). Patients (age 6-22 years) will be recruited from 10 medical centers in the United States. Each center has been selected to provide either precision dosing or conventional care dosing. Precision dosing includes the use of a clinical decision support tool (RoadMAB™) from the start of infliximab to achieve specific (personalized) trough concentrations and specific pharmacodynamic targets (at dose3, 4 and 6). Conventional care includes the use of a modified infliximab starting dose (5 or 7.5 mg/kg based on the pre-treatment serum albumin) with a goal to achieve maintenance trough concentrations of 5-10 µg/mL. The primary endpoint is year1 deep remission defined as a combination of clinical remission (pediatric Crohn's disease activity index<10 [child] or a Crohn's disease activity index<150 [adults]), off prednisone >8weeks and endoscopic remission (simple endoscopic severity-Crohn's disease≤2). **Ethics and dissemination**: The trial is registered at ClinicalTrials.gov (NCT05660746). The study protocol has been approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. Study results will be disseminated in peer-reviewed journals and presented at scientific meetings.

Strengths and Limitations of this Study

- One of the first real-world, multicenter, pragmatic clinical trials in children receiving infliximab for Crohn's disease that includes an objective assessment of intestinal healing (colonoscopy) at the conclusion of the trial
- Intervention arm includes the use of infliximab dose optimization from the first dose and continued throughout therapy based on specific pharmacokinetic (proactive TDM) and pharmacodynamic targets
- The interventional arm will use a novel precision dosing platform (RoadMAB™) throughout the trial that is scalable for use in real-world clinical practice
- The in-kind drug support (infliximab, from Janssen Scientific Affairs) will assure participants receive the physician specified infliximab dosing and minimize any confounding that may have occurred if the study relied on third-party insurance coverage for the proposed dosing regimen
- One limitation is the gradual adoption in real-world clinical practice of using infliximab optimization during induction (doses 5-10 mg/kg) and the routine use of proactive TDM may limit a true control cohort of standard dosing (5 mg/kg) and reactive TDM

Introduction

Crohn's disease (CD) is a chronic illness that results in intestinal inflammation and unwanted gastrointestinal symptoms. The only biologic (monoclonal antibody) therapy approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for moderate to severe CD in children (<18 years old) are those that antagonize tumor necrosis factor-alpha (anti-TNF). Initial response rate to labeled infliximab (anti-TNF) dosing ranges from 70-80%, however, only about half of infliximab exposed patients will achieve clinical remission and less than 40% will achieve endoscopic healing after one year of therapy.[1-3] In real-world practice, the probability of remaining on infliximab for 5-years was shown to be 60%.[4, 5]

In children, use of labeled (standard, 5 mg/kg at 0, 2, 6 and then every 8 weeks) anti-TNF dosing regimens often leads to significant under-exposure and that a "one-size-fits-all" approach is outdated.[6] In fact, children receiving the standard starting dose during induction has led to a significant rate (36-60%) of infliximab concentrations below the maintenance infliximab trough concentration (cTrough) target (5-10 μg/mL) for luminal CD.[2, 7, 8]

Several studies in children and adults have shown that rates of sustained corticosteroid-free clinical remission are improved when patients receive anti-TNF dose (infliximab or adalimumab) optimizations following reactive or proactive therapeutic drug monitoring (TDM).[9-12] There is growing evidence in adults with CD that anti-TNF (adalimumab) dose optimizations during induction and following pharmacodynamic (PD) monitoring will lead to improved rates of clinical remission, endoscopic healing (EH), and lower rates of immunogenicity.[6, 13] Therefore, given the limited therapeutic options for children with moderate to severe CD, there is a critical unmet need for the development of a personalized and scalable anti-TNF dosing intervention applied from drug start, continued throughout maintenance therapy to optimize drug exposure, reduce immunogenicity and improve rates of EH and drug durability.

In a prior prospective, real-world investigation, our team developed a population pharmacokinetic (PK) model for children and young adults receiving infliximab for moderate to severe CD.[2] In this study, we identified five covariates of infliximab clearance that significantly improved the prediction accuracy of our PK model with less unexplained variability in comparison to previous models.[2] This

discovery also led to the development of a clinical-decision support tool (RoadMAB™) that performs bedside model-informed precision dosing (MIPD) to optimize drug exposure for the individual patient.[2, 14] The RoadMAB™ platform performs Bayesian PK estimation to propose up to three treatment regimens using the published population PK model and the five covariates of infliximab clearance. The five biomarkers (covariates) of infliximab clearance are the patient's weight (kg), serum albumin, erythrocyte sedimentation rate (ESR), neutrophil CD64 (nCD64), and antibodies to infliximab (ATI). In addition to displaying the predicted cTrough throughout induction, RoadMAB™ incorporates measured infliximab concentrations collected at any timepoint during an interval to further update the platform and guide the future dosing regimen.

As noted, separate randomized controlled trials in adults and children have demonstrated effectiveness of anti-TNF dose (infliximab and adalimumab) optimization using either PD targets (c-reactive protein [CRP] and/or fecal calprotectin [fCal]), proactive TDM, or a clinical decision support tool during maintenance therapy.[11, 13, 15] While these individual strategies improved rates of clinical remission and EH in their respective trials, it is currently unknown if a pragmatic anti-TNF dosing strategy that combines MIPD from induction, proactive TDM and repeated PD assessments to inform dose optimizations as a singular, novel strategy will result in superior clinical and endoscopic outcomes as compared to the current dosing strategy that largely relies on TDM during maintenance and a "trial and error" approach to dose optimize infliximab (conventional care). Therefore, our team has designed a pragmatic clinical trial that unifies proven infliximab dosing strategies to increase the rates of deep remission (EH and clinical remission). Furthermore, this study will provide invaluable data regarding whether MIPD of infliximab with a precision dosing platform is feasible, safe, more effective at inducing EH and modernize dosing strategies of other biologics.

The central hypothesis is that the hybrid precision dosing approach (intervention arm) of combining MIPD at the start of infliximab induction with proactive TDM and routine PD monitoring will improve rates of deep remission compared to the current approach to infliximab dose selection and use of proactive TDM prior to the first maintenance dose (control arm). To test this hypothesis, we will conduct a multicenter, pragmatic clinical trial among patients with CD and assess rates of deep remission following one year of infliximab therapy between both arms.

Methods and Analysis

Study design and population

The REMODEL-CD study is an open-label, pragmatic clinical trial to assess the superior infliximab dosing strategy to achieve deep remission after one year of infliximab. All patients will be recruited from 10 medical centers within the ImproveCareNow learning health network. Five centers will prescribe infliximab using the precision dosing strategy (intervention arm) and five centers will prescribe infliximab according to the conventional dosing strategy (control arm). We will enroll newly diagnosed (<90 days) patients (6-22 years old) with moderate to severe luminal CD who are starting infliximab (additional patient eligibility is listed in Table1). The trial start date is July 1, 2023 with an estimated completion date of March 31, 2027. The specific dosing strategy (treatment arm) has been assigned at the center-level to prevent treatment contamination and assure that all treating physicians have been properly informed and trained on the dosing intervention at their respective center. Patients meeting eligibility criteria will be recruited prior to the start of infliximab.

Study outcomes

The primary outcome is deep remission that is defined as clinical remission (an inactive disease activity index and off prednisone >8 weeks) and EH (simplified endoscopic score-CD [SES-CD≤2]) at year 1.[3, 13] As both children and adults will be enrolled, the disease activity index for patients 6-17 years old is assessed with the pediatric CD activity index (PCDAI) while the CD activity index (CDAI) will be used for patients ≥18 years old. In order to assess for EH, all enrolled patients remaining on infliximab >42 weeks will undergo a standard of care, follow up ileocolonoscopy with central readers blinded to the patient, treatment arm and center, and the endoscopic report. As noted, EH is assessed by the SES-CD while the Simplified Endoscopic Mucosal Assessment for CD (SEMA-CD) will be scored as an exploratory measure.[16, 17] Deep remission has been chosen as the primary endpoint as it was identified as a major long-term therapeutic goal by the STRIDE-II consortium.[18] Key secondary endpoints (Table2) will also include assessments of immunogenicity (ATI), patient reported outcomes (PRO), quality of life assessments,[19-21] and growth restoration in Tanner I-III children consistent with other key STRIDE-II outcome measures.[18]

Interventions

All 10 centers participating in the REMODEL-CD trial currently utilize the ImproveCareNow Model IBD Care guidelines (available at www.improvecarenow.org) to manage CD patients starting infliximab. These guidelines recommend physicians use the FDA/EMA approved starting dose of 5 mg/kg (rounding up the nearest 100 mg) but also acknowledge that higher starting doses can be considered in more severe or extensive disease (including perianal disease). In addition, it is recommended that a cTrough be obtained prior to the first maintenance dose (proactive TDM) and with an acute increase in gastrointestinal symptoms (reactive TDM). The maintenance cTrough target is 5 µg/mL. Once enrolled, all patients will receive infliximab at their center at no cost from the in-kind (drug-only) support from Janssen Scientific Affairs, LLC. Both treatment arms will receive the standard induction regimen (infusions at 0, 2 and 6 weeks) with maintenance infusions varying between 4-8 weeks for both groups. As a pragmatic study, all dosing and management decisions will be made by the patient's treating physician.

Conventional Care (control arm)

The FDA and EMA approved infliximab induction dose is 5 mg/kg occurring at weeks 0, 2 and 6. In order to ensure the full spectrum of disease severity will be enrolled at these centers, the treating physicians will choose a starting dose between 5-7.5 mg/kg based on the patient's serum albumin (at the time of screening). The patient's baseline serum albumin was chosen to inform the starting dose as it provides a more objective marker of CD severity and it has been found to be a consistent biomarker of infliximab clearance in multiple pediatric PK studies.[2, 7, 22] The protocol recommends that patients with a serum albumin <3 gm/dL receive 7.5 mg/kg and patients with a serum albumin ≥3 gm/dL receive 5 mg/kg. Once the starting dose has been selected, the patient will receive the same dose (in mg) throughout induction (dose1, dose2 and dose3). As is routine practice, calculated doses of ≥20 mg over a 100 mg increment will be increased up to the nearest 100 mg to minimize drug waste as vials are supplied in 100 mg increments. Rounding to the nearest 100 mg will not be done if the rounding of the induction doses would cause the patient to receive a dose >7.5 mg/kg.

All patients in the conventional care arm will undergo proactive TDM (Esoterix, LabCorp specialty lab, Calabasas, CA) prior to receiving dose4 (~week14, cTrough). The treating physician will then interpret these results and prescribe future infliximab doses between 5-10 mg/kg with a

dosing interval between 4-8 weeks to achieve or maintain a cTrough target of 5-10 µg/mL (Table3). Importantly, the dose will not be rounded to the nearest 100 mg if rounding would result in a maintenance dose >10 mg/kg. As this is a pragmatic dosing study, no dose reductions or intensifications will be study mandated. During the study, the treating physician can obtain one reactive TDM during maintenance if there is a concern for active CD. If ATI are discovered during any TDM, the subsequent dosing regimen (including the possible addition of methotrexate) is at the discretion of the treating physician and will not be considered a treatment failure unless infliximab is discontinued. The use of MIPD programs, PK software or other commercially available TDM modeling services to inform dosing regimens are not permitted.

Precision Care (intervention arm)

The precision care arm includes the use of the RoadMAB™ platform to inform the first starting dose during induction and assess for opportunities to dose optimize during maintenance based on three strict Checkpoints (Supplemental Figure1). Checkpoint1 (dose3) includes a cTrough target while Checkpoint2 (dose4) and Checkpoint3 (dose6) include both cTrough and PD targets.

Prior to starting infliximab, the treating physician will access the New Start Wizard within the RoadMAB™ precision dosing software portal (Figure1) and review the dashboard recommended infliximab starting dose. RoadMAB™ formulates a dosing recommendation based on the predicted infliximab clearance using Bayesian estimation with the Xiong et al. population PK model[2] and is guided by a novel method of disease progression modeling. While RoadMAB™ will display the predicted cTrough at dose2, 3 and 4, the initial target (Checkpoint1) is a cTrough at dose3 (week6) between 18-24 µg/mL (Target1).[7]

The RoadMAB™ platform will provide a starting dose ("Model Informed Dosing," Figure1b) between 5-12.5 mg/kg that will attain the aforementioned dose3 cTrough target (Checkpoint1).[7] Starting doses are rounded up to the nearest 100 mg (as described for the conventional care arm) unless rounding would result in a dose >12.5 mg/kg (max induction dose). The model-informed starting dose is generated by estimating infliximab clearance based on the patient's weight (kg), serum albumin (g/dL), ESR (mm/h) and nCD64. The treating physician will also have the option of viewing the "Standard Dosing" tab (Figure1c) to preview (as a reference) the predicted cTrough at dose2-4 for

the standard FDA/EMA approved dose (5 mg/kg). Within the "Manual Dosing" tab (Figure1d), the physician is able to interact with RoadMAB™ to review variable dosing options and the subsequent predicted cTrough. Any deviations from the Model Informed Dosing recommendation will be documented in the case report form.

Prior to dose3 (week6), a cTrough will be obtained. The cTrough along with the patient's weight, albumin, ESR, nCD64 and ATI (ng/mL) will be entered into RoadMAB™ to further guide a maintenance dosing regimen to achieve a cTrough of 5-10 µg/mL at the next infusion (dose4). The treating physician will make the final decision for maintenance dosing as there are multiple strategies to maintain the target, including modifying the dose alone, interval alone or changing both dose and interval.

During maintenance, there are two Checkpoints that will require additional review. Both Checkpoints will assess whether the PK and PD targets were met. As adequate drug exposure has been shown to be a key variable in assessing treatment effectiveness, the cTrough target has been prioritized for both Checkpoints and will guide all subsequent dosing recommendations. The PK/PD targets for Checkpoint2 and Checkpoint3 are listed in Table3. Importantly, if either the CRP or fCal is missing, the missing PD biomarker will default to Yes (achieved) with future dosing based on the success or failure of the other PD targets.

Assessing Success or Failure for Checkpoint2 and Checkpoint3

During maintenance, the cTrough target concentration (at dose4 and dose6) is dependent on whether the patient is (1) a PK failure only or (2) PK success with PD failure. Following each infusion, vital patient data (weight, albumin, CRP, ESR, and nCD64) and dose administration (date and time) will be manually entered into the secure RoadMAB™ platform. The treating physician will then access the RoadMAB™ platform to review whether the Checkpoint PK and PD targets were achieved to determine the next optimal dose (mg) and dosing interval (weeks). Infliximab maintenance doses will range between 5-15 mg/kg (rounded to the nearest 100 mg) and infusion intervals will range between 4-8 weeks. As a precaution, rounding up to the nearest 100 mg vial will not be done if rounding the maintenance dose would result in a single dose >15 mg/kg.

As noted, during maintenance, the PK target takes precedence over the PD assessment. For example, if a cTrough is below target (at dose4 or 6), RoadMAB™ will provide a dosing recommendation to achieve the PK target first (irrespective of the result of the PD target). Once a PK target is achieved, the PD targets are assessed by RoadMAB™ and subsequent dosing recommendations will be presented to the user. Therefore, a PK success with any PD failure (at the two maintenance Checkpoints) is then systematically elevated to a new PK tier. PK tiers range from 5-10 µg/mL (the starting maintenance cTrough target for all patients), 10-15 µg/mL and up to 15-20 µg/mL depending on the PD outcomes. To achieve PK and PD success, all PD criteria (disease activity index, CRP and fCal) must be achieved. Supplementary Table1 provides details of the PD failure criteria and the subsequent escalation plan.

Treatment Failure (special circumstances for both arms)

Primary infliximab failure can be difficult to define in a real-world, pragmatic study as clinicians often dose escalate infliximab to ensure proper exposure prior to drug discontinuation. In this trial, if any of the following criteria are met, the patient will not continue in the study and will be classified as a primary infliximab non-responder. These primary failure criteria include: (a) receiving the first two doses of infliximab <7 days apart, (b) receiving >3 doses before week6, (c) receiving the third dose <2 weeks after dose2, (d) receiving ≥10 mg/kg during induction (first three doses, in the conventional care arm), (e) receiving >12.5 mg/kg during induction (first three doses, in the precision care arm), (f) continuation of high dose prednisone or prednisolone (at doses >0.5 mg/kg if <40 kg or >20 mg for patients ≥40 kg) beyond week12, (g) use of oral budesonide beyond week16, or (f) starting methotrexate, 6-mercaptopurine or azathioprine prior to receiving infliximab dose4. Criteria for secondary nonresponse or study withdrawal during maintenance are listed in Supplementary Table2.

The management of ATI (lower limit of detection is 22 ng/mL with the Esoterix, LabCorp assay) will vary by the treatment arm. As a pragmatic trial, infliximab optimizations are determined by the treating physician in the conventional care arm while dose optimizations in the precision care arm will be informed by RoadMAB™. For both arms, the addition of methotrexate (to reduce immunogenicity or improve exposure) is at the discretion of the treating physician. Similarly, the addition of

methotrexate during maintenance phase for a cTrough persistently below the 5-10 µg/mL is at the discretion of the treating physician and will not be considered a treatment failure.

During the trial, both treatment arms can perform reactive TDM during maintenance. The use of reactive TDM on ≥2 occasions, however, will be recorded as a deviation in both arms. As is standard in clinical care, any patient receiving a dose optimization will have TDM performed prior to the second new dose. For both treatment arms, dose reduction or interval lengthening is not mandated in the trial but the treating physician is encouraged to discuss the risks and benefits for any patient with a persistently elevated cTrough.

Adverse Event Monitoring

The trial team at each center will be responsible for detecting, documenting, and reporting events that meet the definition of adverse events including all serious adverse events and adverse events of special interest. Per protocol, the patient will be monitored until the event resolves, stabilizes, or is reasonably explained. The team will be responsible to determine if the adverse event was related to the study device, a procedure, or infliximab while considering pre-existing conditions or concomitant medications. Adverse events will be reported in a timely manner to the medical monitor, the study Data Safety Monitoring Board, the principal investigator, the FDA, the Sponsor and Janssen Scientific Affairs, LLC.

Statistical analysis

Our study design, including the use of a precision dosing platform to optimize infliximab doses during induction in children is novel. Therefore, the expected rates of deep remission with this strategy are currently unknown. In order to develop our sample size calculation, we likened the precision dosing arm (intervention) to patients within the SONIC study that found 63% of adults with CD who received combination of infliximab and azathioprine (within 18 months of diagnosis) achieved deep remission at week26.[23] The control arm patients would be most similar to the adults with CD who participated in the CALM and TAILORIX clinical trials, where rates of year 1 deep remission was achieved in 23-36.9% and 27-33% (variation by treatment arm), respectively.[13, 24] Furthermore, preliminary review of children within the ImproveCareNow learning health network, indicated an intra-class correlation (ICC) of 0.02 for clinical remission outcomes. Therefore, based on

an anticipated 36.9% deep remission rate in the control arm and 63% deep remission rate in the interventional arm, we determined 140 patients (70 in each arm) would provide 80% power to detect a clinically meaningful absolute difference of at least 25% between the two treatment arms (alpha 0.05), assuming an ICC of 0.02. As study attrition is estimated at 5% and primary nonresponse is estimated at 12-15%[1], the final sample size was increased to 180 patients (90 in each arm).

Generalized linear mixed models with a logit link will be used to compare rates of deep remission between the two arms. Additionally, center-specific random effect will be included to account for dependence of outcomes from the same center. Our team will individually assess both the intention-to-treat and per protocol populations with the per protocol population to include all enrolled patients who received scheduled infliximab for at least 42 weeks while the intention-to-treat population will include all enrolled patients who received at least one infliximab infusion (1 dose). Fidelity will be assessed to avoid a type III error. We will assess whether core components of each intervention were conducted at the critical timepoints for precision dosing (pre-treatment, doses3, 4 and 6) and for conventional care (dose4) as noted in the study design. There is a planned interim analysis after the first 40 patients in the precision dosing arm complete one year of infliximab.

Ethics and Dissemination

The REMODEL-CD trial is registered at ClinicalTrials.gov (NCT05660746). The clinical trial has received Institutional Review Board approval at Cincinnati Children's Hospital Medical Center. The following participating centers have completed the Reliance agreements to participate in the trial: Nationwide Children's Hospital, Rady Children's Hospital San Diego, Medical College of Wisconsin/Children's of Wisconsin, Riley Hospital for Children, Lucile Packard Children's Hospital Stanford, Nemours Children's Health System-Wilmington, Nemours Children's Health System-Jacksonville, Cleveland Clinic Children's Hospital and Children's Hospital of Los Angeles. Parental consent will be required for all children <18 years of age while adults ≥18 years of age will provide consent before any study procedures are started (model consent is included in the Supplemental Materials). *Patient and public involvement*: Prior to submission of this trial for funding, our study team met with parents of children with CD and adult patients with CD to discuss the study hypothesis and study protocol. These individuals were key in refining the inclusion criteria, the interventions,

methods to enhance study retention and the plans for dissemination. Following completion of the trial, the results will comply with the Consolidated Standards of Reporting Trials (CONSORT) and results disseminated in peer-reviewed journals and presented at scientific meetings to inform whether precision dosing of infliximab is feasible, safe, and more effective at inducing deep remission then conventional care.

Discussion

Suboptimal inflammatory control of pediatric CD increases the likelihood of irreversible intestinal damage and CD-related complications.[25, 26] Innovative clinical trials using novel approaches to maximize the current FDA/EMA approved biologics in pediatric CD are needed as anti-TNF dose optimization strategies informed by proactive TDM in children[9, 11] and PD control in adult CD[13] have been associated with improved outcomes. Dose optimization in children is particularly important as several studies have shown that anti-TNF clearance is significantly elevated in young patients (<10 years old), those with extensive disease (ileocolonic) or a high inflammatory burden.[2, 11, 27] Therefore, patients enrolled in the precision care arm will receive dose optimization (based on pre-treatment biomarkers of drug clearance) from the start of infliximab with the maintenance regimen (dose and/or frequency) based entirely on achieving specific cTrough and PD targets.

While there is debate whether proactive TDM and PD monitoring will improve near and long-term outcomes, anti-TNF dose optimization in clinical practice in children and young adults is common. Therefore, our team has designed a clinical trial that is both practical and based on key, objective procedures used in prior clinical trials (CALM, PRECISION, and PAILOT).[11, 13, 15] Specifically, in the PAILOT clinical trial, patients were randomized to receive adalimumab dose optimization using either a reactive or proactive TDM approach (following successful induction).[11] Assa et al. found CD patients in the proactive TDM arm (targeting a cTrough >5 µg/mL during maintenance) resulted in higher rates of corticosteroid-free sustained clinical remission.[11] The PRECISION trial randomized adults with IBD receiving maintenance infliximab to model-informed dosing or standard of care dosing.[15] After one year, patients receiving model-informed dosing (with a dose calculator similar to RoadMAB™) to maintain a minimal cTrough (3 µg/mL) had significantly lower rates of loss of response and a lower median fCal after one year.[15]

There are a variety of reasons as to why the prior proactive TDM clinical trials in adults with IBD (TAXIT[28], TAILORIX[24] or SERENE-CD[29]) failed to demonstrate significant improvement compared to the respective control group. Key limitations to these prior studies include delaying the intervention until maintenance, only including adults with IBD, and use of a low cTarget (3 µg/mL for infliximab or 5 µg/mL for adalimumab). Therefore, we have designed a trial that will enroll children to receive dose optimization during induction with an intensifying cTrough strategy that starts at 5-10 µg/mL and escalates based on success or failure of key PD biomarkers at specific, early stages of treatment.

While this will be one of the first studies to use a precision dosing support tool to dose optimize infliximab in pediatric CD, several studies in renal transplantation and other chronic conditions have demonstrated superior outcomes using PK software (decision support tools) to guide dose selection and obtain targeted immunosuppressive drug concentrations.[15, 30, 31] Therefore, while the rate of deep remission at year 1 is the primary outcome, we will also be assessing the useability, fidelity, safety and effectiveness of the RoadMAB™ software platform in real-world clinical practice.

In summary, the current "one-size-fits-all" with labeled anti-TNF dosing often leads to suboptimal drug exposure, poor gut healing and increased burdens on the patient and family. In this trial, our global aim is to conduct the first clinical trial to evaluate the rate of deep remission in children and young adults who have been recently diagnosed with CD and receive infliximab using a combination of MIPD, PD control, and proactive TDM throughout induction and maintenance.

Authors' contributions

Study concept and design: PM, AAV; initial draft and revising manuscript: PM, RJC, NZ, TM, AAV; literature review: RJC, NZ, TM; developed both the sample size calculation and statistical analysis plan; NZ, TM, PM; study protocol review and revision: PM, NZ, TM, AAV. All authors approved the final version of the manuscript including the authorship list.

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Competing interests statement

Phillip Minar and Alexander Vinks are inventors of the RoadMAB™ dosing platform. Janssen Scientific Affairs, LLC has reviewed and approved the study protocol.

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Figure1. RoadMAB™ Precision Dosing Platform. The RoadMAB™ New Start Wizard will launch prior to the first dose. Pre-treatment biomarkers including weight, albumin, erythrocyte sedimentation rate and neutrophil CD64, are manually entered into the table prior to launching the platform. The Wizard uses dynamic disease progression modeling along with the population pharmacokinetic model to simulate a dosing regimen to achieve the (A) dose3 (week6) target concentration of 18-24 µg/mL. The default tab is (B) model-informed dosing, however, the user can also toggle through (C) standard dosing and (D) manual dosing to inform the dosing decision. (E) The predicted concentration over time curve is shown and based on the selected starting dose.

Table1. REMODEL-CD Eligibility Criteria

Inclusion Criteria	• Written informed consent from the patient (≥18 years old) or from parent/legal guardian if patient is <18 years old
	• Written informed assent from patient when age appropriate
	• Diagnosis of Crohn's disease within the last 90 days (luminal-only or luminal with a perianal fistula or abscess treated with antibiotics for at least 7 days)
	• ≥6 years to ≤22 years of age, anti-TNF naïve and starting infliximab
	• Clinical activity and luminal inflammation, defined by both (1) and (2)
	  • (1) PCDAI>10 (<18 years old) or CDAI >150 (≥18 years old) in last 60 days before the decision to start infliximab
	  • (2) SES-CD>6 or SES-CD>3 for isolated ileal disease (or a report of large intestinal ulcerations) within the last 60 days or a fecal calprotectin >250 µg/g within last 75 days prior to screening
	• C-reactive protein >1.0 mg/dL in last 30 days and/or fecal calprotectin >250 µg/g within last 75 days prior to screening
	• Negative TB (tuberculosis) interferon-gamma release test and a negative urine pregnancy test for female patients (if menstruation has started)

Exclusion Criteria	• Diagnosis of ulcerative colitis or inflammatory bowel disease-unspecified • Prior use of anti-TNF therapy (*infliximab, adalimumab, certolizumab pegol, or golimumab*) • Internal (abdominal/pelvic) penetrating fistula(e) in last 180 days • Intra-abdominal abscess/phlegmon/inflammatory mass in the last 180 days • Active perianal abscess (receiving oral antibiotics for <7 days) • Intestinal stricture (luminal narrowing with pre-stenotic dilation >3 cm) and surgery planned in next 90 days • Have tested positive for Clostridium difficile toxin (stool assay) or other intestinal pathogens within 14 days of screening unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen. • Current hospitalization for complications of severe Crohn's disease • Planned use of methotrexate or 6-mercaptopurine (azathioprine) during the induction (first 3 doses of infliximab) phase • Current ileostomy, colostomy, ileoanal pouch, and/or previous extensive small bowel resection (>35 cm) or any Crohn's disease surgery planned within the next 90 days • History of autoimmune hepatitis, primary sclerosing cholangitis, thyroiditis, or juvenile idiopathic arthritis • Treatment with another investigational drug in last four weeks • History of malignancy (including lymphoma or leukemia) • Currently receiving treatment for histoplasmosis • History of TB, human immunodeficiency virus (HIV), an immunodeficiency syndrome, a central nervous system demyelinating disease, history of heart failure or receiving intravenous antibiotics in last 14 days for any infection • Currently pregnant, breast feeding or plans to become pregnant in the next 1 year • Inability or failure to provide informed assent/consent • Any developmental disabilities that would impede providing assent/consent

Table2. Key Secondary Outcome Measures

Name of Outcome	Specific measure to be used	Time point(s)
Rate of Steroid-free Clinical Remission	PCDAI<10 (child) or CDAI<150 (adult) and off prednisone/budesonide for ≥4 weeks	Week14 and Week52
Rate of Clinical Response	Decrease from baseline PCDAI of at least 12.5 points & total PCDAI<30 or a total PCDAI<10 (child)[1] or a reduction of CDAI>70 from baseline or CDAI<150 (adult).[32]	Week14 and Week52
Rate of Primary Clinical Nonresponse	On prednisone >16 consecutive weeks from start of infliximab or a PCDAI>30 or CDAI>220 for first four infusions	Week16
Rate of Primary Biologic Nonresponse	Failure to improve baseline fecal calprotectin by >100 µg/g (limited to patients with a baseline fecal calprotectin >250 µg/g) or Failure to improve baseline c-reactive protein ≥0.5 mg/dL (limited to patients with a baseline c-reactive protein >1.0 mg/dL)	Week16
Rate of Sustained Steroid-free Clinical Remission	PCDAI<10 (child) or CDAI<150 (adult) at dose5 to week52 and off prednisone/budesonide from week22-52	Weeks22-Week52
Rate of Steroid-free Clinical Remission – biomarker composite	PCDAI<10 (child) or CDAI<150 (adult), off prednisone/budesonide for ≥4 weeks, CRP ≤0.5 mg/dL and fecal calprotectin ≤250 µg/g[13]	Weeks14 and Week 52
Rate of Endoscopic Healing	SES-CD ≤2[23]	Week52
Rate of Complete Endoscopic Healing	SES-CD=0	Week52
Rate of Endoscopic Remission	SES-CD<4	Week52
Rate of Mucosal Healing	SES-CD≤2 and Ileal Global Histologic Activity Score (GHAS)/Colon Global Histologic Activity Score (CGHAS)≤2	Week52
PK Model Bias	Model predicted vs. actual infliximab concentration. Bias: mean predictive error (MPE)	Week0-Week52
PK Model Precision	Model predicted vs. actual infliximab concentration Precision: root mean squared error (RMSE)	Week0 - Week52
Rate of IBD-related event - Fistula	Occurrence of fistula	Week0-Week52
Rate of IBD related – Hospitalization	Occurrence of Crohn's disease related hospitalization	Week0-Week52
Rate of IBD related – Surgery	Occurrence of Crohn's disease related Surgery	Week0-Week52
Rate of IBD related – Intestinal stricture	Occurrence of Crohn's disease related intestinal stricture	Week0-Week52
Rate of IBD related – Starting corticosteroids	Occurrence of patients starting a corticosteroid after week20	Week0-Week52
Rate of IBD related – Antibodies to infliximab	Occurrence of antibodies to infliximab defined as >200 ng/mL	Week0-Week52
Rate of Growth Restoration – Weight change	In Tanner stage I-III patients: change from baseline weight (kg) by gender and age group[18]	Week14-Week52
Rate of Growth Restoration – Height velocity	In Tanner stage I-III patients: change in height velocity (z-score) by gender[18]	Week14-Week52
PK of infliximab in pediatric patients	Measured infliximab clearance at baseline and at week52	Week0-Week52
Correlation between infliximab induction exposure and endoscopic remission	The correlation analysis to be performed for the total area under the curve (infliximab exposure, µg*h/mL from week0-week14) and patients achieving endoscopic remission. Endoscopic remission is defined as a SES-CD ≤2.	Exposure: Week0-Week14 Efficacy: Week52
Correlation between infliximab induction exposure and deep remission	The correlation analysis to be performed for the total area under the curve (infliximab exposure, µg*h/mL from week0-week14) and patients in deep remission. Deep	Exposure: Week0-Week14

	remission is defined as a PCDAI<10 (child) or CDAI<150 (adult), off prednisone/budesonide for >8 weeks and a SES-CD≤2.	Efficacy Week52
Rate of PRO2 Response	>50% improvement in total score from baseline [18]	Week6, 14, 26 and 52
Rate of PRO2 Remission	Stool frequency ≤3.0 and abdominal pain ≤1.0 (from baseline)[33]	Week6, 14, 26 and 52
Quality of Life & Disability – IMAPCT-III score	Total IMPACT-III (child) score [19, 20]	Week52
Quality of Life & Disability – IBD Disk score	Total IBD Disk (without sexual function assessment) score	Week52
Quality of Life & Disability – Short IBD score	Total Short IBD Questionnaire (adult) score	Week52
Process Evaluation – Usability of Decision Support Tool	Total System Usability Scare score	Week0-Week52
Rate of Adverse Events	Number of Adverse Events	Week0-Week52
Rate of Serious Adverse Events	Number of Serious Adverse Events	Week0-Week52

IBD, inflammatory bowel disease; PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; SES-CD, simple endoscopic score-Crohn's disease.

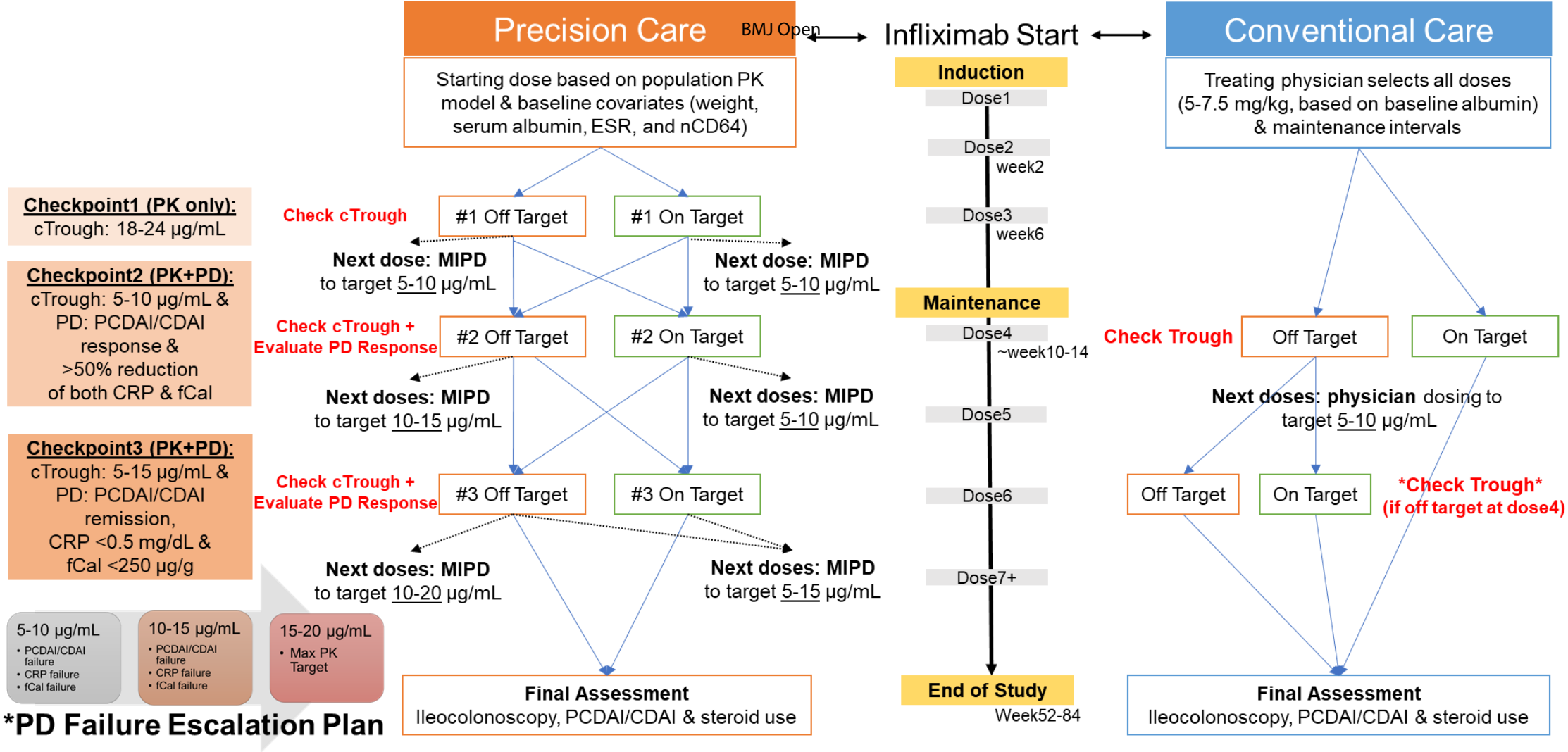
Table3: Pharmacokinetic and Pharmacodynamic Targets by Treatment Arm.

Conventional care arm	
Dose3	Proactive therapeutic drug monitoring is not performed
Dose4	Infliximab trough concentration 5-10 µg/mL
Dose6	Proactive therapeutic drug monitoring is not performed
Precision care arm	
Dose3 (Checkpoint1)	Infliximab trough concentration 18-24 µg/mL
Dose4 (Checkpoint2)	
Pharmacokinetic	Infliximab trough concentration 5-10 µg/mL
Pharmacodynamic	(1) Disease activity score + Child: PCDAI decrease of at least 12.5 points from baseline and a total PCDAI<30 OR a total PCDAI<10 Adult: delta CDAI >70 from baseline OR a CDAI<150 (2) CRP ≥50% change from baseline CRP OR a CRP ≤0.5 mg/dL + (3) Fecal calprotectin ≥50% change from baseline OR a fecal calprotectin ≤250 µg/g
Dose6 (Checkpoint3)	
Pharmacokinetic	Infliximab trough concentration 5-15 µg/mL (varies from 5-10 or 10-15 µg/mL depending on whether Target2 trough concentration was achieved)
Pharmacodynamic	(1) Disease activity score + Child: PCDAI <10 Adult: CDAI <150 (2) CRP ≤0.5 mg/dL (or CRP ≤5 g/dL) + (3) Fecal calprotectin ≤250 µg/g

PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein.

Figure 1 - RoadMABTM Precision Dosing Platform

403x254mm (72 x 72 DPI)



Supplementary Figure1: The REMODEL-CD Clinical Trial Overview. The trial includes two arms, the precision care (interventional) and conventional care (control). The conventional care arm will receive starting doses of 5-7.5 mg/kg (based on pre-treatment serum albumin) and one proactive therapeutic drug monitoring (TDM) at dose4. The starting dose in the precision care arm will vary between 5-12.5 mg/kg and is based on predicted (baseline) infliximab clearance and a target trough concentration (cTrough) of 18-24 µg/mL at dose3. Following induction, two additional Checkpoints will be assessed for Pharmacokinetic (PK) and Pharmacodynamic (PD) targets. Infliximab optimization during maintenance is dependent on whether the PK, PD or both PK/PD targets have been met. As noted, the PK target is the first priority before assessing the PD targets and escalating the target concentration to the next tier. ESR, erythrocyte sedimentation rate; nCD64, neutrophil CD64; PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; fCal, fecal calprotectin; MIPD, model-informed precision dosing.

Supplementary Table1: Specific Pharmacodynamic (PD) Treatment Failure Criteria and the Target Escalation Plan

Specific PD Target	Timing by infusion (~week)	PCDAI/CDAI cut-points	(and/or) CRP cut-points	(and/or) fecal calprotectin cut-points
Checkpoint 2	Dose4 (~week10-14)	delta PCDAI<12.5 or a PCDAI>30 (child) delta CDAI<70 (adult)	<50% change from baseline	<50% change from baseline
Checkpoint 3	Dose6 (~week26)	PCDAI≥10 CDAI≥150	>0.5 g/dL	>250 µg/g
PD Target Failure for *any 2 consecutive* infusions after (dose6)		PCDAI≥30 CDAI>220	≥1 g/dL	---
PD Target Failure for any *single* infusion after dose6				>500 µg/g
Target Escalation plan*	PD Failure1: New PK target = 10-15 µg/mL		PD Failure2: New PK target = 15-20 µg/mL (max)	

*The trough concentration is the primary target, therefore, pharmacodynamic targets are only instituted if the prior trough concentration was within the target. PCDAI, pediatric Crohn's disease activity index; CDAI, Crohn's disease activity index; CRP, c-reactive protein; PK, pharmacokinetic.

Supplementary Table2. Criteria for Secondary Nonresponse and Study Withdrawal

Secondary Nonresponse (may remain in the trial)	• Remaining on prednisone/prednisolone or oral budesonide for >14 weeks after week20 (corticosteroid restarts) or remaining on prednisone/prednisolone or oral budesonide after week44
Secondary Nonresponse (meet study withdrawal criteria)	• Subjects in the conventional care arm receiving >10 mg/kg infliximab and/or <25 days apart between infusions during maintenance. • Subjects in the precision care arm receiving >12.5 mg/kg infliximab during induction (first 3 doses) • Subjects in the precision care arm receiving >15 mg/kg infliximab and/or <25 days apart between infusions during maintenance. • Subjects who have a Crohn's disease-related surgery • Subjects who develop an intra-abdominal abscess or inflammatory mass • Subjects diagnosed with a bacterial infection requiring intravenous antibiotics or hospitalization (related to the infection) • Subjects who discontinuation of infliximab before week42 (either initiated by the subject or treating physician) • Any plan to start another biologic (anti-integrin, anti-cytokine), small molecule (any JAK inhibitor or sphingosine-1-phosphage inhibitor) or 6-mercaptopurine (including Imuran or azathioprine) during the trial • Anaphylaxis (hypersensitivity reaction) during/after an infusion that is deemed by the provider, medical monitor or principal investigator to be unsafe to attempt a subsequent future infusion

Title of research study: ***Precise Infliximab Exposure and Pharmacodynamic Control to Achieve Deep Remission in Pediatric Crohn's Disease***

Key Information:

The following is a short summary of this study to help you decide whether to be a participant in it. More detailed information about the study is listed later in this form. This document does not replace the discussion you should have with the research team about this study including having any questions or concerns answered.

If you are 18 years and older: This is a consent form. It explains this research study. If you decide that you want to be in this research study, then you will sign this form to show that you agree to be part of this study. If you sign this form, you will receive a signed copy of it for your records.

Parental Permission: If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required using a separate form. When we say "you" in this form, we mean you or your child; "we" means the study doctor and other staff.

Investigator:

Contact Info:

Industry Protocol #:
REMODEL-CD

Drug Name:

Infliximab

Funding:

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

In-kind drug-only support: Janssen Scientific Affairs, LLC

Reason for the study:

Approximately 3 million people in the United States are living with inflammatory bowel disease, which includes Crohn's Disease. There are limited treatment options approved for use in children and adults with Crohn's disease. We need better ways to inform decisions on treatment.

We are asking you to be part of this research study because you have been diagnosed with Crohn's Disease and you are going to start treatment with infliximab as part of your routine clinical care.

Infliximab is a FDA-approved drug to treat Crohn's Disease. Currently, standard dosing of infliximab is based only on your weight. However, with standard dosing of infliximab, some patients may not have a complete response or may lose response over time. Several research studies have shown that response to infliximab is improved when levels of infliximab are measured more frequently and when drug levels or other blood tests are within the target range.

The main reason for this research study is to determine if a computer program that calculates an individualized dose based on your blood testing results (precision dosing) can better achieve the best possible response to infliximab compared to standard dosing (conventional dosing). This new method of precision dosing is still experimental while the conventional dosing is already approved by the United States Food and Drug Administration.

If you qualify and decide you want to be in the study, you will come to [Site Name] approximately 9 times over the next year. You will receive infliximab prescribed by your regular doctor. Most of these visits will happen when you get your infliximab infusions. You will be asked to provide blood and stool samples at specific infusions.

Your study site has been assigned to one of two groups: the conventional dosing group, which uses standard dosing based on your weight, *or* the intervention group, which uses the computer program and blood/stool tests to inform your doctor of dosing options. Which group the study site is assigned was chosen by chance, like flipping a coin. You will be told which group your study site has been assigned.

For this study, we will enroll 180 people between 6 and 22 years old with Crohn's Disease.

We expect that you will be in this research study for 12 months.

Procedures:

If you decide to participate in the research study, the following tests and procedures will take place.

Standard Dosing Group:

You will receive standard care of infliximab as ordered by your doctor.

We will:

- Collect information about you
- Measure levels of infliximab in your blood
- Perform other blood and stool tests
- Compare your results to the other group (intervention group)
- Your doctor will likely perform a colonoscopy at the end of the study so we can compare the rate of gut healing across both groups.

Intervention Group:

We will:

- Collect information about you
- Measure levels of infliximab in your blood
- Perform other blood and stool tests
- Enter the results into the computer program.
- Your doctor will likely perform a colonoscopy at the end of the study so we can compare the rate of gut healing across both groups.

Your doctor will use the computer program to inform their decision on your dose and dosing schedule. Your doctor may need to change your infliximab dose or dosing schedule in order to personalize your dosing plan.

Based on prior studies, your doctor may need to prescribe doses that are higher than the standard dosing.

More detailed information about the study procedures can be found under ***"(Detailed Procedures)"***

Risks to Participate:

Like all medicines, infliximab can have side effects. Most side effects are mild to moderate. Some may be serious and may require treatment or additional testing. Side effects may appear up to six months or longer after the last infusion.

The table below shows the most common and most serious side effects that researchers know about. We do not know all of the side effects that may occur.

Possible Infections while on Infliximab (some may be serious)
Viral Infections (affects 10% or more) ○ Common cold ○ Bronchitis (coughing up mucus) Bacterial Infections (occur between 1-10%) ○ Sinus infection ○ Sore throat ○ Pneumonia Tuberculosis (uncommon) Fungal infections (occur between 0.01-0.1%)

Possible Infections while on Infliximab (some may be serious)
Other Side effects of Infliximab ○ Infusion Reactions including Allergic Reactions ○ Lupus-like reactions ○ Antibodies against infliximab ○ Cancer (occur between 0.01-0.1%) ○ Abnormal liver blood tests or liver problems ○ New rash, psoriasis or hair loss ○ Blood problems (low white blood cells) or easy bruising

More detailed information about the risks of this study can be found under ***"(Detailed Risks)"***

Benefits to Participate:

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include improved control of your Crohn's Disease and improved drug durability (longer time on the drug). In addition, you will receive infliximab at no cost during the study for up to 365 days.

This study will provide invaluable data regarding future treatment plans for dosing of infliximab.

Other Options:

Participation in research is completely voluntary. Your decision to participate or not to participate will not affect the care you receive.

Your alternative to participating in this research study is to not participate.

Cost to Participate:

You and your insurance company will be charged for the healthcare services that you would ordinarily be responsible for paying. This includes any additional fees associated with the infusion (such as, but not limited to, facility fees, professional fees and/or laboratory fees). In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay. If your insurance company denies the dose recommended by the computer program, your doctor can appeal.

Payment:

[Sites will alter to conform to their institutions' policies.]

If you agree to take part in this research study, we will pay you for your time and effort (please see the chart below). You will receive payment for this study in the form of a reloadable debit card (Clincard). We will give you a handout that will explain how to use the card. Because you are being paid for your participation, [Site Name] is required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) to track the amount of money that we pay. You will need to complete a Federal W-9 form for this income tax reporting. This form requires your Social Security number. This form will be given to the [Site Name]'s business office. It will not be kept as part of your study chart. If you move, you will need to complete another W-9 with an updated address.

Your information and samples (both identifiable and de-identified) may be used to create products, including some that could be patented/licensed and sold. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

Payment Chart

										Total
Study Activity	**Doses (infusions)**									
	1	2	3	4	5	6	7	8	9	
Questionnaire /Blood sample	$10	$10	$10	$10	$10	$10	$10	$10	$10	$90
Stool sample	$25		$25	$25		$25			$25	$125
Optional Pinch biopsy									$25	$25
Total for participation (*dependent on number of infusions in year1)										**~$240**
*You will receive $10 for each blood sample collected up to 1 year as some patients may require more or less than 9 infliximab doses in one year.										

Additional Study Information:

The following is more detailed information about this study in addition to the Key Information.

If I have Questions or would like to know about:

Who to talk to…	You can call …	At …
• Emergencies • General study questions • Research-related injuries • Any research concerns or complaints	**PI Name:** [Site PI Name]	Phone: [XXX-XXX-XXXX]
• Emergencies • General study questions • Research-related injuries • Any research concerns or complaints	**Lead Study Coordinator:** [Coordinator Name]	Phone: [XXX-XXX-XXXX]
• Your rights as a research participant	**Institutional Review Board** This is a group of scientists and community members who make sure research meets legal and ethical standards.	Phone:

Detailed Procedures:

- Consent- You will need to read and sign this consent form before doing any study procedures. You will get a copy to keep.
- Demographics – We will collect information including your current age, age of diagnosis, gender, race and ethnicity.
- Medical Record Review- We will review your medical records for information on your health, medical and surgical history, and current medications.
- Physical Exam- We will examine your temperature, heart rate, breathing rate, blood pressure, height, weight, and body mass index. We will also perform an abdomen examination and perianal examination (located around the anus, if needed).
- The study staff will ask you about any symptoms you have had since your last visit.

- Questionnaires- You will answer some questions about your stomach pain, stool frequency, and general well-being.
- You will have up to 20 ml (4 teaspoons) of blood collected for research purposes prior to each infusion. In addition, about 5 ml (1 teaspoon) of blood will be collected 30-60 minutes after infusions 1, 3, 4, and 6. We will try to collect the blood sample from your IV so you do not have to have another needle stick. If we are not able to collect a blood sample at that time, you will be given the option to have another needle stick to collect the blood.
- Stool Collection- You will be asked to collect stool samples. You will be provided the kits for collection and mailing. You may also be given the option to perform additional at-home stool testing. This may include the use of a smartphone and a commercially available application that you would install on your smartphone. The study staff will provide additional information about this.
- Pregnancy Test- If you are female and able to get pregnant, you will be asked to give a small sample of urine for a pregnancy test. We will give the results of this test to the parent. If it is positive, you will not be allowed in the study.
- Drug Infusion (first 3 doses) - As part of your normal infusion visits, you will receive infliximab at 0, 2, and 6 weeks. If you are in the intervention group, you may receive doses that are higher than the FDA approved dose.
- Drug infusion (doses 4 - 9) - As part of your normal infusion visits, you will receive infliximab every 4-8 weeks. The dosing schedule and actual dose is variable and based on your site's group assignment. You may require more or less than 9 infliximab doses in one year, regardless of your site's group assignment.
- Drug infusion -You will be monitored for 30 – 60 minutes or longer following your infusion for any infusion-related side effects.
- Approximately 1 year (between 52-84 weeks) after starting treatment, you will likely have a colonoscopy as part of your clinical care.
    - We would like to collect a blood sample and up to 4 intestinal pinch biopsies for this research study. Collection of pinch biopsies is optional. You can indicate your preference on the signature page of this consent.
    - We will capture a video-image of your colonoscopy so the study doctors can review it and give it a score based on the amount of inflammation seen. The video will be labeled with your study ID and stripped of other identifiers.
- The study staff will contact you prior to visits as a reminder of upcoming visits and stool samples.

Procedures	Screen	Treatment Period														
Infusion dose number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Final**
Weeks (range)		**0**	**2**	**6**	**10-14**	**14-22**	**18-30**	**22-38**	**26-46**	**30-54**	**34-62**	**38-70**	**42-78**	**42-86**	**50-94**	**52-84**
Ensure you qualify to participate in this study	X	X														
Collect Demographic information	X															
Collect medical and surgical history	X															
Ask about current and past medications	X	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X
Ask about any symptoms you are having or have experienced	X	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X
Receive infliximab infusion		X	X	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X
Collect vital signs (temperature, blood pressure, heart rate, weight and height)	X	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X
Perform physical exam	X				X											X
Perform urine pregnancy test (female participants)	X															
Collect blood sample(s)	X	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X
Collect Stool samples	X			X	X		X									X
Complete questionnaires	X	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X
Research only pinch biopsies and blood sample at colonoscopy																X
*Some patients will have a different number of total doses during the one year study. These data are only collected up through the first year of treatment (first 365 days).																

Change of Mind/Study Withdrawal:

You can leave the research at any time; it will not be held against you.

If you decide to leave the research, contact the investigator so that the investigator can record your reason for withdrawal.

The person in charge of the research study or the sponsor (Cincinnati Children's) can remove you from the research study without your approval. Possible reasons for removal include significant failure to follow study procedures, if the investigator believes it is not in your best interest, or if your disease gets worse and the investigator believes it is best for you to be removed.

If you stop being in the research, data already collected may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

If you stop being in the research, you and your insurance company will be responsible for the cost of infliximab.

Detailed Risks:

Infections

You may have more infections while taking infliximab or if you have an infection it could make it worse. Tell the study doctor if you have a new infection, if an infection keeps coming back, or if you have any signs of infection such as:

• Fever • Chills • Night sweats • Flu-like symptoms • Weight loss • Tiredness • Cold sores	• Headache • Coughing • Coughing up blood • Congestion • Shortness of breath • Chest tightness • Nausea • Vomiting	• Diarrhea • Frequency or burning while peeing • Redness or swelling of limbs, skin or joints • New or worsening of pain in any location

Infections seen with this treatment are colds, bronchitis (coughing up mucus), sinus infections, sore throat, and pneumonia. Those infections caused by viruses occur “very commonly” while those caused by bacteria occur “commonly.”

Some patients have had serious infections while receiving infliximab. Some of the patients have died from these infections.

Tuberculosis is a serious infection that usually develops in the lungs but can also develop in other areas of your body. Tuberculosis has been reported in patients who have received TNF-blockers, and it has been reported uncommonly in patients treated with infliximab. Tuberculosis requires prolonged treatment with specific medication. You may be more likely to develop tuberculosis while on infliximab. If you or any of your family have ever had tuberculosis you should tell your doctor. While in this study, if you come in contact with anyone who has tuberculosis, you should tell your study doctor.

Your study doctor will do a blood test to see if you have come in contact with tuberculosis.

Fungal infections have been reported in patients taking infliximab. Some of these fungal infections, such as histoplasmosis and coccidioidomycosis, occur rarely and can be serious and involve internal organs. You should find out from your study doctor which fungal infections are common where you live or travel, and what symptoms they cause. Tell your study doctor and family physician right away if you develop symptoms of such illnesses.

You should also tell your doctor if you have ever had chickenpox. If while in the study, you come in contact with someone with chickenpox tell your study doctor.

The use of live virus or bacterial vaccines when you are receiving infliximab may result in an infection. You cannot receive a live virus or bacterial vaccine during this study or for 3 months after your last dose of the infliximab. Other types of vaccines are allowed.

Congestive Heart Failure

Patients with congestive heart failure (CHF), a disease where the heart pumping action is weakened, were treated with infliximab in another study. Some of these patients had worsening of their CHF and some died. The risk is unknown. If you have a history of CHF or have received treatment for CHF, you are not allowed to participate in this study.

New cases of heart failure have been reported in patients receiving infliximab. It is not known whether or not these cases are related to infliximab. If you have shortness of breath or swelling in your ankles and/or feet, you must contact your study doctor right away.

Patients treated with infliximab have uncommonly developed worsening CHF or developed CHF for the first time.

Infusion Reactions including Allergic Reactions and Lupus-Like Reactions

Your body might have a reaction during or shortly following an infusion of infliximab into a vein. This is called an infusion reaction. These reactions are usually mild to moderate. They are managed by slowing the infusion or by giving you medication. Any drug may cause an allergic reaction in some patients. A life-threatening allergic reaction called anaphylaxis has occurred uncommonly in patients treated with infliximab.

Symptoms of an infusion reaction or an allergic reaction may include 1 or more of the following:

• Fever • Chills • Hives • Rash • Swelling • Itching	• Headache • Flushing • Nausea • Light-headedness • Chest pain or tightness • Wheezing	• Difficulty breathing or swallowing • Decrease or increase in blood pressure • Anaphylaxis (life-threatening allergic reaction

If the symptoms cannot be managed or become serious or life threatening, the infusion will be stopped and additional treatment will be provided immediately if necessary.

If you have an allergic reaction your regular doctor may give you a medication used to treat allergic symptoms (such as an antihistamine), or to reduce aches, pains, and fever (such as acetaminophen or paracetamol). Antihistamines can make you sleepy, so please use caution when driving a car or operating machinery.

Cases of seizures have also been reported uncommonly. Cases of temporary loss of vision occurring during or within 2 hours of an infliximab infusion have also been reported. Patients have experienced a stroke, heart attack (sometimes resulting in death), or abnormal heart rhythm within 24 hours of the start of their infusion with infliximab.

Another type of reaction is called a delayed hypersensitivity reaction, which as occurred uncommonly in patients treated with infliximab. This reaction can occur 1 to 14 days after the infusion. Symptoms such as fever, rash, muscle aches, and/or joint pain may develop. You should report any of these symptoms to your study doctor right away.

Some patients have developed symptoms or developed abnormal blood tests that look like a disease called lupus. These symptoms may include muscle aches, joint pain, fever, prolonged chest discomfort or pain, rash (including a rash on the cheeks or arms that gets worse in the sun) and shortness of breath. You should report any of these symptoms to your study doctor.

Antibodies against Infliximab

Your body may make antibodies against infliximab. These antibodies might cause an allergic reaction if you receive infliximab in the future.

Cancer

Cancers have been reported in patients who have received infliximab and other TNF-blockers. Lymphoma (a cancer of lymph nodes) has been reported rarely in patients treated with infliximab (affects between 1 and 10 in 10,000 patients). Cases of leukemia (a cancer of the blood) have also been reported in patients taking TNF-blockers. It has been reported rarely in patients treated with infliximab (affects between 1 and 10 in 10,000 patients).

Rarely (between 0.01-0.1%), patients who received infliximab developed skin cancers, including melanoma.

A very aggressive rare type of lymphoma, called hepatosplenic T-cell lymphoma, has been reported in patients treated with TNF-blockers including infliximab. This type of cancer usually causes death. Almost all patients had received azathioprine or 6-mercaptopurine (6-MP) in combination with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis, and most were reported in adolescent or young adult males. Cases of hepatosplenic T-cell lymphoma have also occurred in patients with Crohn's disease and ulcerative colitis receiving azathioprine who were not treated with infliximab. It is unclear what role of infliximab may have in the development of the lymphoma.

Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking infliximab, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.

You should tell your study doctor prior to participating in this study if you have a history of lymphoma or cancer, and if you develop lymphoma or cancer, including skin or cervical cancer, during or after you have participated in this study. You should also regularly discuss cancer screenings with your study doctor, and the impact of life-style choices (for example, smoking) on the risk of developing cancer.

Central Nervous System

Some patients, who have a disease of their nervous system, have reported that this disease got worse. You should tell your doctor if you have a disease of your nervous system. Seizures and multiple sclerosis are examples of nervous system diseases. While in this study, if you are diagnosed with a nervous system disease discontinuation of infliximab should be discussed with your doctor.

Rarely, people who did not have a nervous system disease developed one after taking infliximab. Signs of nervous system disease include:

• changes in your vision • seizures	• numbness or tingling in any part of your body • weakness in your arms and/or legs

Lung

Interstitial lung disease is the name for diseases that inflame or scar the lungs and may cause long term complications. The inflammation and scarring may make it difficult to breathe and get enough oxygen in your blood.

Patients treated with infliximab have rarely developed interstitial lung disease and in some cases, the disease progressed quickly.

Liver

If you currently or at any time in the past have had any liver problems, including hepatitis B, you should tell your doctor. Treatment with TNF-blocking agents such as infliximab may result in a reactivation of the hepatitis B virus in people who have been known to carry this virus. Hepatitis B reactivation has been reported rarely in patients treated with infliximab. You will have a blood test to see if you have hepatitis B prior to treatment with infliximab.

Some patients develop abnormal liver blood tests, often without symptoms. If this happens, your doctor may stop your treatments for a period of time or permanently. In most cases the liver tests return to normal after stopping treatment.

There have been cases where people taking infliximab have developed serious liver problems, resulting in liver transplantation or death. Signs that you could be having a problem include:

• skin and/or eyes turning yellow • dark brown urine • right-sided stomach pain	• nausea • vomiting • loss of appetite • fever • extreme tiredness

Skin

Hair loss has commonly occurred in patients treated with infliximab.

Patients treated with infliximab have commonly developed a worsening of psoriasis or new onset psoriasis, including a type called pustular psoriasis. Symptoms may include dry, red skin with yellow blisters, often on the palms of the hands or soles of the feet, although it can occur elsewhere.

Rarely, a type of rash called vasculitis resulting from inflammation of blood vessels in the skin has occurred in patients treated with infliximab.

Stevens-Johnson syndrome and toxic epidermal necrolysis are two forms of a life-threatening skin condition that have been reported rarely in patients treated with infliximab. Another skin condition called erythema multiforme has been reported rarely in patients treated with infliximab.

A skin condition called linear IgA bullous dermatosis has been very rarely reported in patients treated with infliximab. Rarely, another skin condition called acute generalized exanthematous pustulosis has been reported in patients treated with infliximab.

Rarely, lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes) have occurred in patients treated with TNF-blockers, including infliximab.

Blood Problems

With the use of TNF-blockers, including infliximab, sometimes the body fails to make enough white blood cells that help the body fight infection or fails to make enough red blood cells, resulting in anemia. In some instances, the number of white blood cells was severely decreased. In addition, sometimes the body fails to make enough platelets, the cells that help you stop bleeding. Some patients have died from this failure to produce blood cells. Your study doctor will monitor the results of tests done on your blood during the study. If you develop a fever that does not go away or infection, bruise or bleed very easily, look very pale or become tired easily, tell your study doctor right away.

Other Risks

Rarely, people develop sarcoidosis, a multisystem immune disorder which is characterized by the formation of lesions (granulomas) in body organs that could affect the lungs, lymph nodes, skin, and other body systems.

A serious inflammation of the blood vessels called vasculitis may occur and in severe cases may result in permanent damage of the affected internal body organs. Vasculitis has been reported rarely in patients treated with infliximab.

Rarely, patients treated with infliximab have developed a pericardial effusion which is an abnormal amount of fluid between the heart and the sac around the heart. Hemophagocytic lymphohistiocytosis (HLH), a life-threatening condition, has been very rarely reported in patients treated with infliximab. This condition is identified by fever, enlarged liver or spleen, decreased number of blood cells, and neurological abnormalities.

There may be other discomforts or risks to you from this study that we do not yet know about.

Your study doctor and staff will ask you about any side effects you have at every visit. If you have any problems, you should let the doctor know right away.

Risk of blood collection

When we collect blood from you for this study, you may experience slight pain at the location of the blood draw. Some bleeding, bruising or discoloration of the skin is common at the site after a blood collection. In rare instances, infection at the site may occur. The study doctor will be able to treat any symptoms you may have.

To reduce risks associated with the blood draw, we will try to take the blood sample at the time the IV is placed so you do not have to have another needle stick.

Risk of colonoscopy pinch biopsy

If you agree to additional pinch biopsy samples for research, obtaining the additional intestinal biopsies may not significantly increase the patient's risk of perforation, bleeding, or infection associated with the colonoscopy. As the colonoscopy will be performed at the discretion of your regular doctor, all potential risks of the procedure, including risks of anesthesia will be discussed with you and separate consent documents will be obtained (separate from this research study).

Risk of high doses of infliximab

If you are in the intervention arm, you may receive doses that are higher than the FDA approved dose. These higher doses have been shown to be safe in uncontrolled studies (real world practice).

Risk of loss of confidentiality

Your privacy is of great concern to us. There is a minimal risk of loss of confidentiality and we have taken steps to minimize this risk which include removing all identifiable patient information from biospecimens collection tubes, providing a unique study ID number for each participant, using a secure, password protected electronic data collection database (Medidata Rave®) and secure web portal (RoadMAB™), and storing all study related paper materials in a locked cabinet.

Pregnancy Risks

The effect of infliximab on the ability to have children is unknown. However, we are not fully aware of the effects of the study drug on unborn babies, on human sperm, or pregnant or breastfeeding women. Pregnant women and women making breast milk to feed infants cannot participate in this study. Female patients (if they have had a first menses) must have a urine or blood test when beginning this study that shows they are not pregnant.

It is very important that women taking part in this study do not become pregnant while taking part in this study. It is very important that men taking part in this study do not get a woman pregnant while participating in this study.

During this study and for 6-months after the last dose of infliximab, women of childbearing potential and men must use proven birth control methods (such as avoiding sex, birth control pills or injections, or an intrauterine device). Your study doctor will discuss birth control methods with you.
If you are pregnant, or may become pregnant, treatment with the study drug may lead to new, previously unknown, side effects, and this may involve risks to you and your unborn baby. You will be withdrawn from the study.

If you think that you have become pregnant, have a confirmed pregnancy or may have fathered a child while taking part in the study, you must tell the study doctor immediately. The study doctor will follow your pregnancy to its outcome. You should also notify your childbirth doctor that the mother/father received infliximab.

Infliximab crosses the placenta. If you received infliximab while you were pregnant, your baby may be at a higher risk for getting an infection. It is important that you tell your baby's doctor and other health care professionals that you have received treatment with a study drug before the baby receives any vaccine. A 12-month waiting period following birth is recommended before the administration of a live vaccine (like BCG and rotavirus) to a baby whose mother received infliximab while she was pregnant. Administration of BCG vaccine within 12 months after birth to the baby whose mother received infliximab while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor.

Severely decreased numbers of white blood cells have also been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fever or infections, contact your baby's doctor immediately.

If you are a female study patient, you must agree to not donate eggs (ova, oocytes) during the study and for 6 months after your last dose of study drug.

If you are a male study patient, you must not donate sperm while you are in the study and for 6 months after your last dose of study drug.

If you are a male study patient, and you father a child during your participation in this study, the study doctor will ask for your partner's permission to stay in contact with her throughout the length of the pregnancy.
There may be other risks that we do not know about yet.

Privacy:

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete privacy. Organizations that may inspect and copy your information include the IRB, the Medical Monitor, your doctor, the Food and Drug Administration, National Institutes of Health (NIH), Janssen Scientific Affairs, LLC, and other representatives of this organization.

As approved by the CCHMC Institutional Review Board, de-identified samples will be stored in the Minar Laboratory. These samples could be used to research the causes of Crohn's disease, its complications and other conditions for which individuals with Crohn's disease are at increased risk, and to improve treatment. The Minar laboratory personnel will also be provided with a code-link that will link the biological specimens to each participant, maintaining the blinding.

Samples and/or data collected for or generated from this study could be shared and used for future research. Samples and /or data may be shared with other collaborators at Cincinnati Children's and possibly with outside collaborators, who may be at another institution or for-profit company.

If information that could identify you is removed from your information or samples collected during this research, that information or those samples could be stored and used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

All future researchers will be given the least amount of information needed to meet the goals of their research project. Researchers that use these samples and information must agree to never try to re-identify a participant from a coded dataset. Researchers will only be allowed to use the provided samples and information for approved research purposes. Any researchers planning to do research with information that may identify you will need to have extra review and approval by the Cincinnati Children's Institutional

Review Board (IRB). An IRB is a group of scientists and non-scientists who look at research projects like these and make sure research participants' rights and welfare are protected.

The sponsor (Cincinnati Children's), monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Federal Certificate of Confidentiality:
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

If injured while in the study:

If you believe that you have been injured as a result of this research, you should contact [Site PI Name] as soon as possible to discuss the concerns. Treatment for injuries is available at [Site Name]. If you go to the Emergency Room or to another hospital or doctor, it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

[Site Name] follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

Return of results:

Most tests done on samples or images obtained in research studies are only for research and have no clear meaning for healthcare. At certain time points, you and your treating physician will be made aware of select results of your stool and blood testing and amount of infliximab in your blood and may contact you.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

[Sites may use their own HIPAA language OR use the CCHMC language below]

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?

[Site Name] will need to use and share your PHI as part of this study. This PHI will come from:

- Your [Site Name] medical records
- Your research records

The types of information that will be used and shared from these records include:

- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- Physician reports and video/photo images of a previous recorded colonoscopy

Who will share, receive and/or use your protected health information in this study?

- Staff at [Site Name] and Cincinnati Children's
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor (Cincinnati Children's), Janssen Scientific Affairs, LLC and organizations that the sponsor may use to oversee or conduct the study.
- Government agencies who oversee this study, including the FDA and NIH
- The members of the Cincinnati Children's Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?

People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?

You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?

Your permission will expire at the end of the study.

Will your other medical care be impacted?

By signing this document, you agree to participate in this research study and give permission to [Site Name] to use and share your PHI for the purpose of this research study. If you refuse to sign this document, you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

While you/your child are participating in this research study you may not be able to access some of your/your child's health information that is related to the study. Any request for this information can be fulfilled once the study is completed.

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research, you will document your permission by signature below.

You will receive a copy of this signed document for your records.

Optional procedure:

Indicate if you **AGREE or DO NOT AGREE** to the following optional procedure:

Initials: _____ Yes, I AGREE to the collection of extra gastrointestinal biopsies for research.

Initials: _____ No, I DO NOT AGREE to the collection of extra gastrointestinal biopsies for research.

_____

Printed Name of Research Participant

_____ _____

Signature of Research Participant Indicating Consent Date

_____ _____

Signature of Parent or Legally Authorized Representative* Date

_____

* If signed by a legally authorized representative, a description of such representative's authority must be provided

_____ _____

Signature of Individual Obtaining Consent Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1

Roles and responsibilities: sponsor and funder	#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	15
Roles and responsibilities: committees	#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)	15
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	6-10
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	6
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)	19
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11
Interventions: modifications	#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)	10-11

Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11
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	6, 20
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)	Suppl.Figure2
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	11-12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
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	n/a
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	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#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	11-12
Data collection plan: retention	#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	n/a
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	n/a
Statistics: outcomes	#20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring: formal committee	#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	11
Data monitoring: interim analysis	#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	12

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	11
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	12
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
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: trial results	#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	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a