PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Minar, Phillip; Colman, Ruben J.; Zhang, Nanhua; Mizuno, Tomoyuki; Vinks, Alexander

VERSION 1 – REVIEW

REVIEWER	Aloi, Marina University of Rome La Sapienza
REVIEW RETURNED	25-Oct-2023

GENERAL COMMENTS	The protocol is well-structured and addresses a very important question. The calculated sample sample is sufficient to address the study's questions.

REVIEWER	de Ridder, Lissy Erasmus MC Sophia Children Hospital, Paediatric gastroenterology
REVIEW RETURNED	01-Nov-2023

GENERAL COMMENTS	This is a very interesting and valuable study, assessing whether precision dosing of infliximab will result in higher rates of deep remission in children and adults with Crohn's disease compared to labelled dosing. Please see below some comments to improve the manuscript. Abstract: Please mention the amount of inclusions of the study in the abstract. Introduction: • In the introduction it should be stated what labelled infliximab dosing is. • I would suggest to rephrase 'sustained benefit'. What kind of benefit? • There are several cited studies performed in adults or regarding adalimumab. I would suggest to clarify this when referring to a specific publication. • I would suggest to mention in the introduction what the ImproveCareNow Model IBD Care guidelines recommend regarding IFX dosing (i.e. when is it recommended to start 10mg/kg, or shortening of interval?). Please add a reference for this guideline. Additionally, is anything mentioned in the guidelines about advised co-medication when starting IFX?

	Methods: • Is the primary outcome not met in case infliximab is discontinued do pharmacokinetic or –dynamic responses <42 weeks? Why are only patients who received at least one maintenance dose included in the intention-to-treat analysis, and not all patients who are included? • I would suggest to shortly describe the study population (i.e. patients with Crohn's disease, diagnosis <90 days and age), and refer for details to Table 1. • I would suggest to change 'Study eligibility' to patient eligibility for the study. • If patients have perianal disease, is cTrough target also 5-10 µg/mL (and not higher)? • On what guidelines/references is the target cTrough of dose3 based in the intervention arm? • '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.' -> for the conventional arm: if the cTrough is too low, are there any recommendations in the guidelines on whether to change interval to 6 or 4 weeks, or increase dose, or is this up to the discretion of the treating physician? • 'Furthermore, preliminary review of children within the ImproveCareNow learning health network, indicated an intra-class correlation (ICC) of 0.02 for clinical remission outcomes.' Which clinical outcomes are meant? PCDAI/PUCAI, or the clinical remission outcome as defined in this study? • Why was a generalized linear mixed effect model with logit link chosen to analyse the primary outcome? To the best of my knowledge, such a model is primarily used when there are repeated measurements. As I understand from this data the primary outcome is no repeated measurement as it is assessed only at 1 year. Is it true the generalized linear mixed model takes into account repeated measurements, and if yes, why did authors choose to use a generalized linear mixed model, and not for example a logistic regression? • '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.' ¬-> so does this repeat TDM then count as reactive or proactive TDM? How are patients analysed when there is such a protocol deviation? • I would suggest to report all checkpoints and cTroughs of both conventional and intervention arm in 1 table. Table5: is it correct cTrough is 5-15 µg/mL (and not 5-20 as seems to be stated in text?) Maybe supplementary Table 1 could also be incorporated in such a table, so all information on checkpoints/targets is provide in one overview. • In patients <18 years, I assume parents, but also patients, need to give consent? • Supplementary Figure 1; instead of text Off target or On target, I would consider to put the cTrough in this graph (for example <18 ug/ml or >18 ug/ml at week 6) if that is feasible. General comments: Sometimes the text is somewhat hard to read, due to for example long sentences or overlap within the text. For example (where it is

	mentioned twice that target is 18-24): While RoadMABTM 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. RoadMABTM 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 I would suggest to revise the manuscript in order to see which parts can be written more comprehensively.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments:
Comment: The protocol is well-structured and addresses a very important question. The calculated sample size is sufficient to address the study's questions.
Response: Thank you for your time to review our manuscript.
Reviewer 2 Comments:
Comment: This is a very interesting and valuable study, assessing whether precision dosing of infliximab will result in higher rates of deep remission in children and adults with Crohn's disease compared to labelled dosing. Please see below some comments to improve the manuscript.
Response: Thank you for your thorough review of our manuscript and this opportunity to respond to your comments.
Comment: Abstract: Please mention the amount of inclusions of the study in the abstract.
Response: We have added our planned enrollment goal for both arms to the abstract.
Comment: In the introduction it should be stated what labelled infliximab dosing is.
Response: We have updated the introduction to define labelled infliximab dosing (page 4, paragraph 2).
Comment: I would suggest to rephrase 'sustained benefit'. What kind of benefit?
Response: We have corrected this sentence, noting the 5-year durability rate (page 4, paragraph 1).
Comment: There are several cited studies performed in adults or regarding adalimumab. I would suggest to clarify this when referring to a specific publication.
Response: We have made these recommended changes throughout the manuscript. Including page 4 (paragraph 3), page 5 (paragraph 2), and page 12 (paragraph 2).
Comment: I would suggest to mention in the introduction what the ImproveCareNow Model IBD Care guidelines recommend regarding IFX dosing (i.e. when is it recommended to start 10mg/kg, or shortening of interval?). Please add a reference for this guideline. Additionally, is anything mentioned in the guidelines about advised co-medication when starting IFX?
Response: We have provided the web address to the publicly available 2022 ImproveCareNow Model IBD Care guidelines (page 7, paragraph 2, in the Methods section). The model care guidelines do not specifically mention 10 mg/kg starting doses, but rather note that during induction or maintenance that "in the setting of more severe and/or extensive disease including perianal disease, higher starting doses and/or shorter intervals between infusions are often utilized to optimize response and should be considered." Lastly, the 2022 ICN guideline does not provide any formal guidance on combination therapy when starting infliximab.
Comment: Methods: Is the primary outcome not met in case infliximab is discontinued do pharmacokinetic or –dynamic responses <42 weeks? Why are only patients who received at least one maintenance dose included in the intention-to-treat analysis, and not all patients who are included?
Response: If patients discontinue infliximab before week42, they will be considered as a treatment failure for the primary outcome. The stated intention-to-treat was written incorrectly and we have corrected this in the manuscript (page 12, paragraph 3). It should have stated those who completed the first induction dose.

Comment: I would suggest to shortly describe the study population (i.e. patients with Crohn's disease, diagnosis <90 days and age), and refer for details to Table 1.
Response: Agree, we have made these updates (page 6, paragraph 2).
Comment: I would suggest to change 'Study eligibility' to patient eligibility for the study.
Response: We have made this change (page 6, paragraph 2).
Comment: If patients have perianal disease, is cTrough target also 5-10 µg/mL (and not higher)?
Response: Correct, we have not mandated a trough target for perianal disease. As a pragmatic trial, the treating physician in either treatment arm can make this adjustment in trough target as long as they follow the guidelines for max dose in their respective treatment arm.
Comment: On what guidelines/references is the target cTrough of dose3 based in the intervention arm?
Response: The cTrough target at dose3 is referenced on page 9, paragraph 1 and 2 and is based on the target (>18 µg/mL) established by Clarkston et al. JPGN 2019 to achieve a maintenance target of at least 5 µg/mL (reference #7).
Comment: '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.' -> for the conventional arm: if the cTrough is too low, are there any recommendations in the guidelines on whether to change interval to 6 or 4 weeks, or increase dose, or is this up to the discretion of the treating physician?
Response: As a pragmatic study, dose adjustment has been left to the discretion of the treating physician and is line with the ImproveCareNow IBD guidelines that note "if the measured trough is below the desired therapeutic range, consider increasing the dose and/or decreasing the interval between infusions."
Comment: Furthermore, preliminary review of children within the ImproveCareNow learning health network, indicated an intra-class correlation (ICC) of 0.02 for clinical remission outcomes.' Which clinical outcomes are meant? PCDAI/PUCAI, or the clinical remission outcome as defined in this study?
Response: The expected rate of deep remission in children receiving optimized infliximab regimens is largely unknown as this is one of the first studies to assess this outcome using the planned precision dosing intervention. Therefore, the sample size was estimated from the rates of deep remission in adult CD trials and children in clinical remission in the ICN network (based on the physician global assessment).
Comment: Why was a generalized linear mixed effect model with logit link chosen to analyse the primary outcome? To the best of my knowledge, such a model is primarily used when there are repeated measurements. As I understand from this data the primary outcome is no repeated measurement as it is assessed only at 1 year. Is it true the generalized linear mixed model takes into account repeated measurements, and if yes, why did authors choose to use a generalized linear mixed model, and not for example a logistic regression?
Response: The generalized linear mixed effects model is used to account for potential dependence of outcomes from the same site; our previous analysis indicated that the intra-class correlation was around .02, and we want to make sure that we account for such correlation in our analyses. We have added this clarification in the manuscript (page 12, paragraph 3).
Comment: '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.' ¬-> so does this repeat TDM then count as reactive or proactive TDM? How are patients analysed when there is such a protocol deviation?
Response: The repeat TDM that follows a dose optimization will not be regarded as reactive TDM as it is generally recommended to repeat TDM in 2-3 doses after a dose modification. Patients in either arm with ≥2 reactive TDM will be analyzed as a treatment failure (per protocol).
Comment: I would suggest to report all checkpoints and cTroughs of both conventional and intervention arm in 1 table. Table5: is it correct cTrough is 5-15 µg/mL (and not 5-20 as seems to be

stated in text?) Maybe supplementary Table 1 could also be incorporated in such a table, so all information on checkpoints/targets is provide in one overview.
Response: Thank you for this suggestion. We have combined Table3 and Table4 into one table (Table3, updated text as well on page 10, paragraph 1). The cTrough range is between 5-15 µg/mL for the first 6 doses, but could be escalated to 15-20 µg/mL depending on whether the subject achieves the PD targets at dose4 and dose6. Therefore, the text is correct. We feel the Supplementary Table1 is best kept as a separate table to avoid additional confusion.
Comment: In patients <18 years, I assume parents, but also patients, need to give consent?
Response: Correct, written informed consent from a parent or legal guardian is required for patients <18 years old. For patients <18 years old, written informed assent will be required. However, each individual center sets the age that assent must be obtained. Therefore, we updated Table1 to state that “written informed assent from patient when age appropriate (age of assent is determined by the center).”
Comment: Supplementary Figure 1; instead of text Off target or On target, I would consider to put the cTrough in this graph (for example <18 ug/ml or >18 ug/ml at week 6) if that is feasible.
Response: As the off/on target includes both PK and PD outcomes at Checkpoints 2 and 3, this would not be feasible to just add the PK target as suggested.
Comment: General comments: Sometimes the text is somewhat hard to read, due to for example long sentences or overlap within the text. For example (where it is mentioned twice that target is 18-24): While RoadMABTM 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. RoadMABTM 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. I would suggest to revise the manuscript in order to see which parts can be written more comprehensively.
Response: We want to thank the reviewer for this opportunity to enhance our manuscript. We have reviewed the entire manuscript as suggested and made significant improvements in our sentence structure. Those edits can be found in our tracked changes document on the following pages (paragraph): page 4, paragraph 3; page5, paragraph 1 and 2; page 7, paragraph 2 and 3; page 8, paragraph 1 and 2; page 9, paragraph 2 and 4; page 11, paragraph 2 and 3; page 14, paragraph 1 and 4 and page 15, paragraph 1 and 2.

VERSION 2 – REVIEW

REVIEWER	de Ridder, Lissy Erasmus MC Sophia Children Hospital, Paediatric gastroenterology
REVIEW RETURNED	30-Dec-2023

GENERAL COMMENTS	Thank you very much for the thorough revision, I do not have any comments anymore.