The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.
The YODA Project
Research Proposal Review - Final
(Protocol #: 2014-0287 )

Reviewers:
☒ Nihar Desai
☒ Cary Gross
☒ Harlan Krumholz
☒ Richard Lehman
☒ Joseph Ross

Review Questions:

1. Is the scientific purpose of the research proposal clearly described?  
   Yes

2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?  
   Yes

3. Can the proposed research be reasonably addressed using the requested data?  
   Yes, or it's highly likely

4. Recommendation for this data request:  
   Approve

Comments:

No additional comments.
Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.
The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2014-0287)

Reviewers:
- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

1. Is the scientific purpose of the research proposal clearly described?  
   Decision: No

2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?  
   Decision: Yes

3. Can the proposed research be reasonably addressed using the requested data?  
   Decision: Unsure, further clarification from requestor is needed

4. Recommendation for this data request: Not Approve

Comments:

We found the Methods used to describe your proposed research to be unclear. Specifically, it would be helpful to clarify how you will construct the model (including the independent and dependent variables and if/how you plan to validate the model). The YODA Project has updated the Research Methods section of the data request form to promote greater clarity.
YODA Project Protocol #: 2014-0287

Associated Trial(s):
A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
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What type of data are you looking for?:
Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title:
Post hoc analysis of the ACT-1 & ACT-2 trials to develop a dosing calculator for infliximab for patients with ulcerative colitis

Narrative Summary:
Anti-tumor necrosis factor (anti-TNF) therapy with monoclonal antibodies such as infliximab (Remicade®) has revolutionized the treatment of patients with inflammatory bowel diseases. Unfortunately 30% of the patients do not respond to anti-TNF therapy and of those initially responding, the risk for loss of response to the drug was reported to be as high as 40% when treated according to the standard dosing regimen. This can be attributed to suboptimal dosing and the development of antibodies towards the drug. A more rational way of dosing based on the exposure in the individual patient might overcome some of these challenges and prove to be more efficacious.

Scientific Abstract:
Background: The population pharmacokinetics (PK) of infliximab and the exposure-response relationship was described in patients with ulcerative colitis (UC). Given this causal relationship between infliximab concentrations and efficacy outcomes such as response, remission and mucosal healing, the use of therapeutic drug monitoring (TDM) was advocated as an approach to optimize infliximab therapy in patients with UC.

Objective: To develop a calculator based on infliximab PK to optimize dosing in patients with UC and to conduct an in silico study based on a subset of patients of the ACT-1 and ACT-2 studies that evaluates how the dose should theoretically be adapted to achieve a predefined infliximab concentration at a certain time point that correlates with an efficacy outcome.

Study Design: Retrospective in silico study, translating pharmacokinetics and pharmacodynamics into a clinically applicable calculator.

Participants: Subset of patients of the ACT-1 (NCT00036439) and ACT-2 (NCT00096655) clinical trials.

Main Outcome Measure(s): A dosing calculator will be developed so that a better prediction of the optimal dose for each individual patient can be achieved. This calculator will be tested in silico using a subset of patients of the ACT-1 and ACT-2 studies.

Statistical Analysis: Using Nonmem® (Icon Development Solutions, Dublin, Ireland) software, the base PK model of infliximab for UC will be used together with Bayesian averaging, Bayesian updating and Bayesian forecasting techniques to develop the patient-specific dosing regimens.
Brief Project Background and Statement of Project Significance:
The population pharmacokinetics (PK) of infliximab was previously described in subjects with ankylosing spondylitis [1], ulcerative colitis (UC) [2] and Crohn’s disease (CD) [3]. Recently, the exposure-response relationship was described in subjects with CD [4] and UC [5]. Given this causal relationship between infliximab concentrations and efficacy outcomes such as response, remission and mucosal healing, the use of therapeutic drug monitoring (TDM) was advocated as an approach to optimize infliximab therapy in patients with inflammatory bowel disease (IBD) [6].

However, the high unexplained variability of infliximab PK in currently available population PK models makes it difficult to generate precise individual PK parameters which could introduce some challenges to the application of TDM in practice. It is therefore desirable to refine the existing population PK models to improve the precision of infliximab PK parameters in UC patients.

Recently, the principal investigators Dr. William Sandborn and Dr. Niels Vande Casteele in collaboration with Dr. Joseph Adedokun (employer of Janssen R&D) and in collaboration with Biotech Scientific Affairs, refined the existing PK model of infliximab for UC by incorporating time varying covariate values.

Given that the unexplained BSV of infliximab clearance remains moderately high despite the inclusion of multiple covariates, implementing TDM with infliximab may require a Bayesian approach whereby serum concentrations of infliximab measured after treatment are used to update individual PK parameters. This would allow constructing precise probabilistic models as a utility for physicians to guide dosing in the individual patient.

The results of this scientific exercise would be highly interesting for current clinical practice. Physicians face the challenge of treating patients with moderate to severe UC that do not respond, partially respond or initially respond but later lose response to infliximab. Given the absence of adequate biomarkers that can guide treatment decision and dosing strategies, physicians are often left with a treat-to-symptoms approach which has been shown to be suboptimal, time consuming for the patient and costly. A calculator could help physicians (based on patient- and disease-specific covariates) prior to initiation of infliximab therapy to identify 1) what is the ideal first dose and 2) what exposure over time profile is to be expected after this first dose in a given patient. Upon a consecutive measurement of the serum infliximab concentration in that patient, the model’s prediction can be refined and the physician can choose to adjust the dosing regimen accordingly. This will allow for tighter disease control, which we anticipate, will benefit patient’s short- and long-term clinical outcomes.

In addition of improving standard of care, this approach of dosing based on exposure can also aid in designing future clinical trials for new biologicals or post marketing trials for biologicals that are already on the market.

Specific Aims of the Project:
The main outcome of this project is to develop a calculator that could help clinicians to define the most optimal dosing regimen in an individual patient to target the recently establish exposure-response relationship cut-offs [5]. Imputing baseline covariates of an individual patient into the model will return an initial estimate of the optimal start dose in that particular patient. This first estimate will be further refined by imputing time varying covariates and consecutive measurements of serum infliximab concentrations by Bayesian updating, so that a better
prediction of the optimal dose for each individual patient can be achieved throughout the induction phase.
A secondary outcome will be to test in silico this approach on a subset of patients of the ACT-1 and ACT-2 studies. This exercise will consist of calculating the most optimal start dose in these patients and to update the model using consecutive measurements of serum infliximab concentrations. For example how many patients achieved the target concentration at week 14 and how the calculator would have predicted to change the dose based on the week 8 infliximab concentration in those patients that did not achieve the target concentration at week 14.

What is the purpose of the analysis being proposed?
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Research that confirms or validates previously conducted research on treatment effectiveness

Research Methods:
Using Nonmem® (Icon Development Solutions, Dublin, Ireland) software, the base PK model of infliximab for UC will be used together with Bayesian averaging, Bayesian updating and Bayesian forecasting techniques to develop the patient-specific dosing regimens. Our preference would be to perform this work in close collaboration with Janssen R&D and in particular with Dr. Joseph Adedokun (employer of Janssen R&D) as he has expert knowledge of pharmacokinetics/pharmacodynamics modeling as well as hands-on experience with the datasets. This would allow a rapid initiation of the project, starting immediately from the base PK model of infliximab to construct the calculator. Access to the pharmacological data could be set up through Janssen R&D for the second stage of the proposal where we would do an internal validation of the calculator based on a subset of the ACT-1 and ACT-2 data. However, if such collaboration is not possible, then we are prepared to proceed with the analyses without collaboration.

Project Timeline:
Start date: 1/1/2015 – end date: 31/12/2015. Development of calculator and data analysis: 9 months. Preparation of manuscript: 3 months. Anticipated date manuscript drafted and first submitted for publication: 30/11/2015. Anticipated date results reported back to the YODA Project: 31/12/2015.

Dissemination Plan:
The application of the dosing calculator on a subset of the data from the ACT-1 and ACT-2 trial will be published in a high impact peer-reviewed journal, with a functional calculator provider as a web supplement. Suitable journals for submission of the completed research project: Gastroenterology or Gut.

Bibliography: