The following page contains the final YODA Project review approving this proposal.
The YODA Project
Research Proposal Review - Final
(Protocol #: 2016-0738 )

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: Yes

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: Yes, or it's highly likely

4. Recommendation for this data request:  
   Decision: 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 #: 2016-0738)

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:

1. What additional data will be used (the "existing real-life HCV-4 cohorts")?
2. The purpose of the study is to use pooled estimates to better understand efficacy and safety of Sofosbuvir + Simeprevir +/- ribavirin, but what efficacy data is available from the existing real-life cohorts? What safety data? What covariates of interest (since the stated goal is to use logistic regression methods to identify patient predictors of efficacy and safety, such as within demographic sub-groups)?
3. Right now, without knowing which data sources will be merged in, it's not possible for the proposal to clearly prespecify the outcomes of interest and the analytic approach.
4. Second, and related to this, the statistical analysis plan is not sufficiently explained - more detail is provided in the statistical analysis section of the scientific abstract (please define F4, is this Fibrosis staging or HCV genotype 4?) than in the main text of the proposal.
5. Third, one point of clarity, the covariates of interest section suggested that HCV genotype (4a or not) would be examined, but I had thought all patients had been diagnosed with HCV4 - is this for patients will multiple HCV genotypes?
6. The investigators propose to pool data from several cohorts. They name 6 countries - are there 6 distinct cohorts? Roughly how many people are in these cohorts? How many of them have received Sofosbuvir and Simeprevir?
7. How do they propose to use the RCT data obtained from the Osiris trial to inform their analysis of the observational cohorts?
8. The investigators should clarify whether they are aiming to assess effectiveness (i.e. comparison with a comparison to an untreated group) or to assess outcomes among a treated cohort. Some of the language implies a comparative effectiveness aim but this does not seem to be the goal.
Principal Investigator

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2016-0738

General Information

Key Personnel (in addition to PI):  
First Name: Christophe  
Last name: Moreno  
Degree: MD, PhD  
Primary Affiliation: CUB Hôpital Erasme, 808 route de Lennik, 1070 Brussels, Belgium

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

-certification_of_interest_form_yoda_morenopdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s):  
NCT02278419 - A Phase 2a, Partly Randomized, Open-label Trial to Investigate the Efficacy and Safety of an 8 or 12-Week Treatment Regimen of Simeprevir in Combination With Sofosbuvir in Treatment-Naïve and Experienced Subjects With Chronic Genotype 4 He

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Efficacy and safety of Sofosbuvir and Simeprevir for the Treatment of Chronic Hepatitis C genotype 4: a pooled
analysis of existing data

Narrative Summary:
Simeprevir has antiviral activity against genotype 1 and 4. Results from the RESTORE trial, evaluating Simeprevir in combination with Pegylated Interferon and ribavirin, has shown a high efficacy and a favorable tolerance profile in G4 infected patients.

Sofosbuvir is approved for the treatment of HCV, and has pangenotypic activity. The combination of Sofosbuvir and Simeprevir has been evaluated in phase 3 trials and in real-life in HCV patients infected by genotype 1. The combination of Sofosbuvir and Simeprevir is approved in Europe for HCV-1 and -4 patients. However, efficacy data in HCV-4 patients are scarce. The aim is to pool existing data on this combination in HCV-4 patients.

Scientific Abstract:
Background: Data on efficacy and safety with Sofosbuvir + Simeprevir with or without ribavirin in HCV patients infected by genotype 4 are scarce (HCV-4)
Objective: To pool existing data from existing real-life existing cohorts and clinical trial (Osiris study)
Study design: analysis of data in HCV-4 patients coming from real life existing cohorts (Belgium, France, Saoudi Arabia, Italy, Qatar, Germany) and Osiris trial, with the aim to study the impact of fibrosis stage, use of ribavirin and other predictive factors on SVR and safety
Participants: HCV-4 patients from real-life cohorts (Belgium, France, Saoudi Arabia, Italy, Qatar, Germany) and Osiris trial (patients treated with 12 weeks)
Main outcome measures: SVR 12, occurrence of SAEs
Statistical analysis: To compare SVR 12 between patients receiving or not ribavirin, between F4 and non-F4 patients, and to identify other predictive factors of SVR12 by logistic regression

Brief Project Background and Statement of Project Significance:
Chronic hepatitis C virus infection affects over 180 million individuals worldwide. The risk of developing cirrhosis and hepatocellular carcinoma as well as progression to liver failure remains a large global health burden. HCV exhibits great genetic diversity particularly among genotype 4, which accounts for 20% of all HCV cases worldwide. HCV genotype 4 infection is most prevalent in the Middle East and sub-Saharan Africa, accounting for over half of all cases reported in Saudi Arabia and Syria as well as 90% of HCV infections in Egypt. Though this genotype was once largely isolated to these regions, with global migration it is now increasingly seen in parts of Europe. The marked genetic variability of HCV genotype 4 infection includes 17 confirmed subtypes, with subtype 4a predominately seen in Egypt, while Saudi Arabia and parts of Europe have high rates of subtypes 4a, 4c, and 4d. In the era of potent and well tolerated direct-acting antiviral agents, current treatment guidelines for HCV genotype 4 infection from the European Association for the Study of the Liver include several different direct-acting antiviral combinations, with or without ribavirin, for either 12 or 24 weeks. Though these available treatments provide high efficacy and improved safety over pegylated Interferon/ribavirin, their use is based on a limited number of clinical trials with small sample sizes, particularly small numbers of patients with cirrhosis.

Simeprevir is a second generation DAA (NS3/4a inhibitor), with potent antiviral activity against genotype 1 and 4. Results from the RESTORE trial, evaluating Simeprevir in combination with Pegylated Interferon and ribavirin, has shown a high efficacy and a favorable tolerance profile in HCV-4 patients. Those results are comparable to those reported for genotype 1.

Sofosbuvir is a nucleotide polymerase inhibitor approved for the treatment of HCV, with a pangenotypic activity. The combination of Sofosbuvir and Simeprevir has been evaluated in phase 3 trials and in real-life in HCV patients infected by genotype 1. The combination of Sofosbuvir and Simeprevir is approved in Europe for HCV-1 and HCV-4 patients. However, efficacy data in HCV-4 patients are scarce and no phase 3 clinical trial supporting this recommendation has been performed.

Specific Aims of the Project:
The aim of the present project is to pool data from Osiris study and existing real-life HCV-4 cohorts in order to study efficacy and safety of Sofosbuvir + Simeprevir +/- ribavirin in a large sample size of patients, with different fibrosis stages, ethnicity, subgenotypes...
The study will study the effect of fibrosis stage and ribavirin use on SVR12, and will study predictive factors of SVR12 in HCV-4 patients.

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources
Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Inclusion criteria:
chronic HCV-4 patients treated with SOF-SMV +/- RBV for 12 weeks or more

Exclusion criteria:
post-Liver transplant patients
HCV-4 patients co-infected by other HCV genotypes

Data source:
Information on fibrosis stage, treatment history, liver function, use of ribavirin, treatment duration, demographics will be collected

Main Outcome Measure and how it will be categorized/defined for your study:
Primary outcome: SVR12, defined by HCV RNA < LLQ &e weeks after the end of treatment

Secondary outcomes: Serious adverse events, evolution of liver function at the end and 12 weeks after therapy

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The following variables as predictor of SVR12 will be studied:
ribavirin use or not
presence of Cirrhosis or not
Demographics: BMI, ethnicity, subgenotype (4a or not), baseline liver function (platelet count, albumin level, bilirubin level, MELD score, Child-Pugh score)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
HCV RNA at week 4 (when available) and treatment duration (12 vs 24 weeks) as predictor of SVR 12

Statistical Analysis Plan:
Descriptive analysis of the pooled cohorts
Multivariable analysis of predictive factors of SVR12

Project Timeline:
Project start date: data collection will start on March 1, 2016
Analysis completion date: june 2016
An abstract will be submitted at AASLD 2016, submission around june 2016
First manuscript draft for publication: november 2016

Dissemination Plan:
international journal in Hepatology: Liver international as a target

Bibliography:


Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo PA, et al. Effectiveness of simprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. Gastroenterology 2015 Oct 21 (Epub ahead of print)