END OF TRIAL REPORT TO REC AND MHRA

Study Title: A clinical study to evaluate the biological effects of administering rimantadine in patients with hepatitis C virus (HCV) infection alongside standard combination therapy with pegylated interferon and ribavirin (HepRiACT)

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REC Ref: 11/YH/0343

Sponsor's Protocol Code No: CO11/9730

Chief Investigators: Dr. Mark Aldersley and Dr. Lynsey Corless

Scientific lead Investigator: Dr. Stephen Griffin

Sponsor: National Health Service

List of Principal Investigators and Sites	**Leeds Teaching Hospitals NHS Trust** Dr. Mark Aldersley and Dr. Lynsey Corless Department of Hepatology, St James's University Hospital, Leeds
List of Publications (or plans for publications) including those for patients (if applicable)	No publications to date
Duration of Study (date first patient was entered to date of last follow up)	Trial opened to recruitment: 10/05/2012 Date first patient entered: 09/07/2012 Date of last patient follow up: 01/06/2014
Phase of Study	Biological endpoint study with a licensed product to assess efficacy at currently prescribed doses, but for a new indication
Study Objectives	Primary Endpoint: Detection of genomic sequence alterations in patients receiving rimantadine. Secondary Endpoint: Preliminary information on variations in treatment response, toxicity data for this new combination of therapies
Methods	Trial Design: This is an open-label, single centre study of rimantadine given orally to patients with HCV infection alongside standard combination therapy with pegylated IFN and ribavirin. In order to confirm that the genomic changes are specific to rimantadine therapy, a retrospective analysis of a matched anonymised cohort of stored historical HCV treatment samples will also be

	undertaken. The CTIMP, Rimantadine, will be prescribed at a dose of 100 mg twice daily for the first 12 weeks of the standard 24 or 48 week combination therapy regimen. Combination therapy comprises pegylated interferon and ribavirin given for 24 weeks in genotype 3 infection, and 48 weeks in genotype 1 infection. Clinical assessment and blood samples for virus genomic sequence analysis and routine clinical data will be collected at multiple time-points throughout the trial (12 visits in total for those with genotype 3 infection, and 18 visits for those with genotype 1 infection). Viral genomic analysis will be conducted on anonymised samples at our laboratory within the University of Leeds.
No. of Patients (planned and analysed)	11 patients were planned for recruitment. 8 patients were recruited to the trial. Recruitment ceased on expiration of project funding (funding was received via the Leeds CRUK centre grant and ended when this central grant was renewed).
Main inclusion/exclusion criteria	Inclusion Criteria Each patient MUST: • Have a diagnosis of HCV infection, genotype 1 or 3 • Be eligible for standard combination therapy with pegylated interferon and ribavirin • Be at least 18 but no more than 65 years of age • Have signed an informed consent indicating that the patient is aware of the infectious nature of their disease and have been informed of the procedures of the protocol, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts • Be willing and able to comply with scheduled visits, the treatment plan, and laboratory tests • Have no contraindications to receiving rimantadine therapy • Have blood results within defined acceptable haematological and biochemical parameters (haemoglobin >10 g/dl, platelet count >150 x 10^9/L, bilirubin <25 mmol/L, albumin >35 g/L, creatinine <150 mmol/L) Exclusion Criteria No patient may: • Have dementia or altered mental status that would prohibit informed consent • Have previously received treatment for HCV infection • Have any condition, which would deem the patient ineligible for combination therapy with pegylated interferon or ribavirin.

	This includes pregnancy, significant cardiac, renal or autoimmune disease, severe depression or psychosis, and previous organ transplantation • Cirrhosis or liver failure as evidenced by clinical (cutaneous stigmata of chronic liver disease, ascites, encephalopathy), ultrasonic (cirrhotic appearance of liver, ascites) or biochemical (platelet count >150 x 10^9/L, bilirubin <25 mmol/L, albumin >35 g/L) evidence • Any condition which would preclude the use of rimantadine. This comprises significant renal impairment (creatinine >150), pregnancy, breastfeeding, epilepsy or history of unexplained seizures • Have any other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Chief Investigators, would make the patient inappropriate for this study. This includes the presence of end stage liver disease (cirrhosis), and HIV infection.
Investigational Medicinal Product(s) **Dose, Mode of Administration and Batch Number(s)**	Test Product: Rimantadine hydrochloride is supplied in 50 mg film-coated tablets, intended for oral administration and tablets are stored at room temperature. Rimantadine will be provided to the Chief Investigators in tablet form by the hospital pharmacy. Labels will indicate the product, lot number and dose. Rimantadine is supplied by the Ambe Medical group (MHRA approved). Administration: Rimantadine will be prescribed at a dose of 100 mg twice daily (200 mg total, 4x 50 mg Rimantin tablets) for the first 12 weeks of the standard 24 or 48week combination therapy regimen. Tablets will be taken at the same time as ribavirin (morning and evening).
Duration of Treatment	12 weeks of CTIMP alongside standard treatment, followed by further 12 or 36 weeks of standard treatment alone dependent upon HCV genotype.
Criteria for Evaluation (Efficacy and Safety)	Clinical assessment and routine haematological and biochemical monitoring will be performed at each visit, and a record made of any adverse events or adverse reactions. The primary endpoint (changes in genomic sequence) will be analysed via genetic sequencing of patient blood samples collected at visits 1, 2, 3, 4, 5, 7, 12 (genotype 3 only), 16 (genotype 1 only) and 18 (genotype 1

	only). The size of the trial does not allow statistically significant conclusions to be drawn regarding whether addition of rimantadine affects treatment response in patients with HCV treated with combination therapy. However, treatment response rates will be collated.
Statistical Methods	The study is descriptive in nature and is not designed to provide analytical results regarding treatment response. The sample size is based on clinical and regulatory considerations and has no formal statistical basis. 10 patients will receive rimantadine in addition to standard combination therapy with pegylated IFN and ribavirin. To demonstrate that the virus genome changes detected are a specific effect of rimantadine therapy, we will perform a retrospective analysis of an age/sex/genotype matched cohort of 10, using historical blood samples stored by the hospital virology department from patients who were undergoing standard HCV therapy. This data will be anonymised after the initial analysis in the hospital virology laboratory. Descriptive statistics will be used to summarise all baseline patient characteristics, treatment administration and safety variables. All patients will be included in the safety analysis.
Summary (Efficacy results, Safety results and Conclusions)	This trial has reported no serious adverse events or suspected unexpected serious adverse events. There were no patient withdrawals due to safety concerns or adverse events. No safety changes were made to the trial protocol and no new information regarding safety, efficacy, or adverse events related to rimantadine have come to light. No differences were seen in efficacy in patients treated with rimantadine alongside standard of care therapy, but the trial was not an endpoint of the trial. Genomic sequence analysis is ongoing (this analysis was planned to take at least 2 years following collection of all clinical data). Results of the laboratory analysis will be published in peer-reviewed journals and at academic conferences.

Authorised by: Lynsey Corless

Signature:

Date: 17/05/2015