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TITLE:

PRACTICALITIES OF USING BOCEPREVIR AND EARLY RESPONSE TO TREATMENT: EARLY EXPERIENCE IN THE UK

Summary of Changes

Summary of Changes for Amendment 3

Protocol Section	Change
Front/Title Page	Study title amended.
Protocol Summary	Study title and study duration amended – end date of 30th September 2012 changed to 31st March 2013.
3 Methodology	Study duration amended.
4 Variables and Epidemiological Measurements	4.1 Exposure- study duration amended.

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List of Abbreviations

AE	Adverse Event
AER	Adverse Event Reporting
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
IFN	interferon
IRB	Institutional Review Board
MHRA	Medicines and Healthcare products Regulatory Authority
NICE	National Institute for Health and Clinical Excellence
NSAE	Non-Serious Adverse Event
PEG-IFN	pegylated interferon
PSUR	Periodic Safety Update Report
RBV	ribavirin
RCT	randomised clinical trials
RNA	ribonucleic acid
SAE	Serious Adverse Event
SMC	Scottish Medicines Consortium

List of Definitions

Committee for Medicinal Products for Human Use (CHMP)	European Medicines Agency's committee responsible for elaborating the agency's opinions on all issues regarding medicinal products for human use.
European Medicines Agency (EMA)	European Union agency responsible for the evaluation of medicinal products.
Medicines and Healthcare products Regulatory Agency (MHRA)	UK government agency responsible for ensuring the safety of medicines and medicinal devices granted marketing authorisations within the UK.
National Institute for Health and Clinical Excellence (NICE)	Health authority responsible for publishing guidance on clinical practice and the use of health technologies (medicines, treatments and procedures) within the UK's National Health Service (NHS).
Particular Patient Supply/Named Patient Programme (NPP)	An early-access programme in which a therapeutic intervention is made available to patients, prior to Market Authorisation, based on urgent clinical need.
Scottish Medicines Consortium (SMC)	Scottish-based health authority which reviews all new medicinal products in the UK.

PROTOCOL SUMMARY

Title	Practicalities of using Boceprevir and Early Response to Treatment: Early Experience in the UK.
Vendor/Collaborator	N/A
Rationale	Boceprevir was recently approved by the EMA to treat adults with genotype 1 chronic HCV in combination with PEG-IFN and RBV. In Phase III clinical trials, the new therapy combination significantly increased efficacy compared to PEG-IFN and RBV alone. While the therapy holds promise for HCV patients, relatively little is known of its implementation in the real-life clinical setting. This study will evaluate the real-life clinical use of boceprevir for the management of chronic genotype 1 HCV in the UK, particularly with regard to the turnaround time for viral titres, early efficacy demonstrated at Weeks 4, 8 and 12, and utilisation of the lead-in and adherence to stopping rules.
Primary Objective(s)	Aim 1: How is clinical management of HCV patients on triple therapy with boceprevir being implemented (as determined by time to introduction of boceprevir therapy, PCR assessment and turnaround at Week 4, percentage of patients achieving $\geq$1 $\log_{10}$ viral decline at Week 4, any application of early stopping rules)? Aim 2: What are the early efficacy results being observed in clinical practice (as determined by percentage becoming PCR negative at Weeks 8 and 12 respectively, adjustment of 'Week 8' and 'Week 12' milestones to accommodate lead-in period in excess of 4 weeks, adherence to stipulated futility rules)?
Study Design	This is a retrospective cohort study.
Study Population	HCV G1-infected patients within the UK age 18 years or older initiated on boceprevir combination therapy.
Study Duration	The study duration is from 01 March 2011 to 31st March 2013.

1 BACKGROUND AND RATIONALE

1.1 Background

The hepatitis C virus (HCV) is a single-stranded ribonucleic acid (RNA) virus that invades hepatocytes and replicates within the cytoplasm after entering the host cell. People can contract HCV in a number of ways, including exposure to HCV-infected blood, being born to an HCV-infected mother, sharing an infected needle, having unprotected sex with an infected person, sharing personal items such as a razor or toothbrush with an infected person, or from unsterilised tattooing or piercing tools.

Most people infected with hepatitis initially exhibit no symptoms. However, as the disease progresses, chronic HCV may develop and lead to cirrhosis and end-stage liver disease. If left untreated, cirrhosis can lead to liver damage with complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections, or liver cancer. According to the Health Protection Agency, approximately 216,000 in the United Kingdom have chronic HCV, and it is the leading cause of liver disease in the UK. (HPA) [1]

For the past 20 years, the standard of care for treatment of HCV infection has been a combination of an interferon (IFN) formulation and ribavirin (RBV) for a variable length of time. The clinical goals of anti-HCV therapy are to improve survival, eradicate the virus, and prevent the complications of chronic HCV infection, including cirrhosis and end-stage liver disease. However, lack of access to effective, well-tolerated therapies has serious implications for the burden of HCV. [2] The success of treatment can be affected by demographic and clinical factors, such as Black race and the presence of liver disease and/or diabetes. [3] The most important predictor of sustained virologic response (SVR) is rapid virologic response (RVR).

On the 18th July 2011 the European Medicines Agency (EMA) approved Victrelis (boceprevir) to treat adults with genotype 1 chronic HCV in combination with peginterferon (PEG-IFN) alfa and RBV. Boceprevir is prescribed to patients who have never been treated for HCV, or after unsuccessful treatment with dual therapy.

Previously untreated patients typically receive 4 weeks of PR, then 24 weeks of PR plus boceprevir (28-week total treatment length). However, if patients still have detectable HCV levels at treatment week 8, treatment with boceprevir is extended for a total 32-week three-medicine regimen, followed by 12 weeks of PR treatment only (48-week total treatment length).

Previously treated partial responders and relapsers typically receive 4 weeks of PR, then 32 weeks of PR plus boceprevir, followed by 12 weeks of PR only (48-week total treatment length).

Previously treated null responders and patients with compensated cirrhosis receive a 4-week PR regimen, followed by 44 weeks of boceprevir in combination with PR.

The safety and efficacy of boceprevir was evaluated in two Phase III clinical trials including over 1,300 adult patients. [4,5,6] In both trials, approximately two-thirds of patients receiving boceprevir in combination with PR experienced a sustained virologic response (i.e., HCV was no longer detected in the blood 24 weeks after ceasing treatment), when compared to PR alone.

1.2 Rationale

Viral titres in the Phase III trial programme were assessed by a central pathologist, allowing for accurate and consistent transition from the 4 week PR lead-in period to boceprevir therapy at the beginning of week 5. However, it is acknowledged that the quality and availability of virology laboratory services in clinical practice will vary throughout the UK, and may perhaps impact the length of the lead-in period and subsequent introduction of boceprevir into the treatment regimen. Delaying turnaround time will mean that patients have to take treatment for longer than is necessary, resulting in increased financial impact. In addition to the futility rules at weeks 12 and 24 in the product licence, treatment response at week 4 is a strong predictor of SVR across all disease severities and categories of prior response. Although lead-in is not a stopping rule, it may well be used by clinicians to make decisions about treatment in some patient populations; for example, some clinicians may elect to continue with PR alone following an RVR after the lead-in, or stop treatment if a patient has a poor response after the lead-in coupled with other poor predictors of response.

Stopping rules are essential to prevent patients remaining on drug for longer than is necessary. This minimises the risk of developing resistance, and prevents patients from remaining on treatment that is futile and suffering potential adverse events. Futility rules also enhance the cost-effectiveness of a medication.

The Phase III trials had strict inclusion and exclusion criteria, which may not reflect the real world. In particular, there were low numbers of cirrhotic patients, who tend to respond less well to treatment. Despite this underrepresentation, some of the efficacy data in this population seem promising.
Patients with cirrhosis have a significant unmet need as they tend to be older and have a greater disease burden, and will progress more quickly to disease stages with fewer options for antiviral treatment and reduced chances of success. As a consequence, many clinicians in the UK have prioritised these patients for early treatment with the new protease inhibitors. It is therefore important to evaluate efficacy in a more diverse population than the clinical trial setting can provide.

Merck Sharp & Dohme Corp. proposes to conduct this retrospective study to evaluate the real-life clinical use of boceprevir for the management of chronic genotype 1 HCV in the UK, particularly with regard to the turnaround period from the lead-in to boceprevir introduction, and early efficacy demonstrated at Weeks 4, 8 and 12; and how this may differ from a clinical trial setting.

2 OBJECTIVES AND HYPOTHESES

2.1 Primary Objective(s) & Hypothesis(es)

The nature of this study is purely descriptive, and as such no formal hypotheses will be tested. Using data collated from patients identified both from within and outside the particular patient supply programme, we will explore how clinical management of HCV patients on triple therapy with boceprevir is being implemented in the UK, outside of the clinical trial setting. Specific project objectives are as follows:

Aim 1: How is clinical management of HCV patients on triple therapy with boceprevir being implemented, as determined by:

- time to introduction of boceprevir therapy,
- PCR assessment conducted at Week 4 and subsequent turnaround time,
- percentage of patients achieving $\geq$1 $\log_{10}$ viral decline at Week 4 (as determined by the viral titre after the lead-in period compared with the baseline titre), and
- any application of early stopping rules due to poor treatment response at Week 4.

Aim 2: -To estimate the proportion of subjects with early virologic responses (e.g. PCR negative at Weeks 8 and 12) – this will be determined by the detection limit of the PCR assays used by centres

-To estimate the proportion of subjects adhering to futility rules (patients who discontinue all treatment at Week 12 due to insufficient viral decay)

3 METHODOLOGY

3.1 Summary of Study Design

This is a retrospective cohort study designed to explore the practicalities of introducing boceprevir to treatment regimens in real-life clinical practice, and the utilisation of the PR lead-in as a potential stopping rule in those patients deemed unlikely to respond well to triple therapy. In addition, the proportion of patients demonstrating early antiviral efficacy with triple therapy (as per the Week 8 and Week 12 milestones) will be identified.

The initial study period will be from March 1st, 2011 to 31st March, 2013. Since this study is retrospective and follows the outcomes of routinely administered patient care within a specified duration, the size of the cohort will depend upon the number of patients initiated on boceprevir combination therapy within the study period.

3.2 Study Population

The study will consist of HCV G1-infected patients age 18 years or older, who were initiated on a boceprevir-based regimen in the UK between 1st March 2011and 31st March 2013.

A particular patient supply programme (or Named Patient Programme; NPP) was launched in March 2011 in the UK to enable physicians to access boceprevir for previously treated chronic genotype 1 hepatitis C patients, where previous therapy had failed, and with an urgent need for treatment, prior to boceprevir receiving a product licence in the EU. On July 18, 2011, the EMA approved boceprevir for use in combination with PEG-IFN alfa and RBV for the treatment of chronic HCV infections. The study period proposed for this study will therefore include both patients treated within the NPP setting, and those treated following the product launch.

(There were inclusion and exclusion criteria for patients to receive boceprevir within the Named Patient setting. See Appendices 9.2 and 9.3)

4 VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposure

This study will utilise an inception cohort (new users) design, and will include patients with an intent-to-receive-treatment with boceprevir-based regimens. Patients treated with boceprevir will be identified by the administering clinicians within the treatment centres. For study inclusion, each patient must have:

1. first written prescription for boceprevir combination therapy betweenMarch 1, 2011 and 31st March, 2013; and
2. ≥12 weeks of treatment data available unless they have discontinued treatment earlier; these patients will also be recorded in the dataset. Patients yet to complete 12 weeks' treatment by the study close date that have not had their treatment discontinued by their clinician, will not be included within this study.

For each patient, the date of the first written prescription for boceprevir between March 1, 2011and 31st March 2013will be identified as the index date.
Exposure to boceprevir will follow an as-treated approach, where exposure will begin at the index prescription date and end at the date indicated by the administering clinician.

4.2 Outcomes

The primary outcome of interest is the time to introduction of boceprevir therapy as determined by PCR assessment conducted at Week 4 and subsequent turnaround time, percentage of patients achieving ≥1 $\log_{10}$ viral decline at Week 4 (as determined by the viral titre after the lead-in period compared with the baseline titre), and application of early stopping rules due to poor treatment response at Week 4. The date that the lead-in with PR is initiated will be captured, along with the total length, in days, of this lead-in period. The HCV viral load at therapy initiation and after the lead-in will also be recorded, as this will determine whether or not patients achieve a ≥1 $\log_{10}$ decline in viral titres during the lead-in. In order to further define this, the type of PCR assay used by each centre, along with the turnaround time in days for samples (from the date the samples are submitted for analysis to the date the results are received by the treating centre), will also be recorded. Early cessation of treatment, and the reason(s) why, will be described in the study spreadsheet.

Efficacy outcomes will be measured by HCV RNA levels at Weeks 8 and 12 respectively; or 4 and 8 weeks post lead-in respectively in those instances where the lead-in exceeds the usual 4 weeks. Application of stopping rules at the nominal Week 12 will also be captured.

4.3 Variables

The following variables will be used as confounders or risk factors for HCV-RNA positive laboratory test outcomes.

- **Gender:** Gender will be captured in the dataset. Subjects with undefined gender will be removed from the study sample.
- **Race:** Race will be captured in the dataset as reported by the treatment centres.
- **Year of birth:** Year of birth will be recorded in the dataset for all patients.
- **Fibroscan:** Baseline FibroScan results will be recorded in the dataset for patients either instead of, or in addition to, biopsy results where these are additionally conducted. Subjects without either a baseline FibroScan or biopsy result will be removed from the study sample
- **Biopsy METAVIR score:** Baseline liver biopsy results will be recorded in the dataset for patients either instead of, or in addition to, FibroScan test results where these are additionally conducted. Subjects without either a baseline FibroScan or biopsy result will be removed from the study sample.
- **HCV genotype:** HCV genotype will be recorded in the dataset. Subjects with unstated genotype will be removed from the sample.
- **Result of last treatment:** The outcome of any previous HCV treatment; either relapse, partial or null response, or naïve for those who have not received prior HCV treatment, will be captured in the dataset. Subjects with undefined prior response will remain within the study sample.
- **HIV/HCV co-infection status:** HIV/HCV co-infection status, positive or negative, will be recorded for each patient. Subjects with unknown co-infection status will remain within the study sample.
- **PCR assay used:** The name and type of the PCR assay used by each treatment centre will be captured, along with the limit of detection of the assay (see below). This is one piece of information that will be used to help determine factors affecting turnaround times for viral loads.
- **Limit of detection of PCR assay:** The limit of detection for each type of PCR assay used (see above) will be recorded in the dataset. As the assays and detection limits may vary among centres and from the boceprevir clinical trials, there is a possibility that the cut-off points at which patients are declared to be undetectable may vary between centres.
- **Pre-treatment HCV titre:** HCV titre prior to commencement of the PR lead-in will be recorded in the dataset. This will be used to determine the degree of viral decline during the lead-in period.
- **HCV RNA at end of lead-in:** HCV-RNA level at the end of each patient's lead-in period will be recorded. This will be used to determine whether or not patients have achieved a 1 $\log_{10}$ drop between their pre-treatment titre and the end of the lead-in period.
- **Length of lead-in period (if not 4 weeks):** The number of days elapsed on PR treatment will be recorded for instances where the PR lead-in exceeds 4 weeks, possibly due to the PCR turnaround time (this will be recorded as a separate variable discussed below).
- **PCR assay turnaround time (days):** The time elapsed from the blood sample being submitted for PCR testing to the day the result is returned to the treatment centre will be recorded in the dataset.
- **Treatment continued (Y/N):** The decision on whether or not treatment is continued after the lead-in by introducing boceprevir, will be recorded in the dataset.

- **Reason for treatment discontinuation:** The reason for a patient not being commenced on boceprevir following the PR lead-in period will be recorded.
- **HCV RNA at Week 8:** Patients' viral titres at Week 8 will be recorded in order to assess early treatment efficacy. In those cases where the PR lead-in exceeds 4 weeks, Week 8 will be interpreted as the first 4 weeks of boceprevir as part of triple therapy.
- **HCV RNA at Week 12:** Patients' viral titres at Week 12 will be recorded in order to assess early treatment efficacy. In those cases where the PR lead-in exceeds 4 weeks, Week 12 will be interpreted as the first 8 weeks of boceprevir as part of triple therapy. Viral titres at Week 12 will also be used to define patients as having met the futility rules within the UK licence for boceprevir.
- **Stopping rule applied:** For patients with viral titres meeting the definition of treatment futility, the decision to stop or continue treatment will be recorded here.
- **Patient stopped at any point other than post lead-in or Week 12:** In those instances where patients are discontinued at timepoints other than after the lead-in (nominally Week 4) or Week 12 (the first futility rule milestone), the week of treatment discontinuation and the reason will be recorded.

5 STUDY PROCEDURES

5.1 General Informed Consent

Centres eligible for inclusion will have at least four patients who they intent to treat with a boceprevir-based regimen. Selection of the individual patients will be at the discretion of the centres themselves, but they must have a minimum of 12 weeks' treatment data available unless they have discontinued treatment earlier; these patients will also be recorded in the dataset.

A separate electronic Excel spreadsheet will be provided for each centre to enter their data for their patients. The spreadsheet will be structured to prevent the collection, use, or transmittal of individual identifiable data. Selected study centres will conduct their own chart review for this purpose – MSD personnel will not come into contact with source data for any patient. Institutional Review Board (IRB) approval to conduct this study is, therefore, not required.

6 SAFETY REPORTING AND RELATED PROCEDURES

6.1 Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or who undergoes a protocol-specified procedure and which does not necessarily have to have a causal relationship with this treatment or procedure. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal l product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

6.2 Definition of Serious Adverse Event

"Serious Adverse Event" (SAE) means an adverse event which is fatal or life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalisation, prolongation of existing inpatient hospitalisation, or is a congenital anomaly/birth defect, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalisation may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalisation.

6.2.1 Other Relevant Safety Information

The following events are considered important safety information and should be collected/reported using the same timeframes and reporting methods as SAEs:

- Exposure of product during pregnancy or lactation
- Lack of effect

6.3 Definition of Attributed Adverse Event

An attributed adverse event is an adverse event that is felt to be causally related to a Sponsor's product. During studies with direct patient contact (visits), the assessment of causality will be determined by an investigator who is a qualified physician according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of attribution to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; and the AE is more likely explained by the Sponsor's product than by another cause. In studies without direct patient contact, the assessment of causality would be determined by a notation of attribution in medical records. Attribution can be assigned by the investigator or the Sponsor. Examples include a drug-induced rash that an investigator attributes to a specific product, or a clinical notation that a product was discontinued because it caused insomnia.

6.4 Adverse Event Reporting

Although adverse events are not actively solicited in this non-interventional database study, there are certain circumstances in which individual Serious Adverse Events (SAEs), if identified, will be reported. Specifically, in the event that individual records are reviewed and there is a notation in the paper or electronic medical record indicating that a health care provider attributed an SAE to any investigational or marketed product manufactured by Merck the INSTITUTION will complete an Adverse Event report form (attachment) in English and submit it within 24 hours to the Merck Sponsor Contact by Fax (Attention: Drug Surveillance Department, fax number 00 32 240 25990). Merck Sponsor Contact will submit AE form to Merck Global Safety (Outlook email address AER Mailbox) within 2 business days of receipt for reporting to worldwide regulatory agencies as appropriate.

Unless attributed SAEs are identified during review of medical records as described above, there will be no reporting of individual cases to regulatory agencies as part of this non-interventional database study.

Although NSAEs are not actively solicited in this study, if any attributed NSAEs are reported by the investigator, they must be collected for tabulation in interim and/or final study report and submitted to Global Safety within 10 calendar days using the same method as described above for SAEs.

The end of study report, and any interim analysis, will include aggregate listings of all SAEs and any spontaneously reported NSAEs attributable to boceprevir and will be provided to regulatory agencies as required. All interim and final study reports will be included in Periodic Safety Update Reports (PSURs) and/or Development Safety Update Reports (DSURs) until completion of the study as required.

SAEs and spontaneously reported NSAEs attributable to OTHER investigational or marketed products manufactured by Merck will be collected and reported to regulatory agencies as individual cases as required.

7 STATISTICAL ANALYSIS PLAN

7.1 Statistical Methods

7.1.1 Objective 1

To evaluate the implementation of clinical management of HCV patients on triple therapy with boceprevir (as determined by time to introduction of boceprevir therapy, PCR assessment and turnaround at Week 4, percentage of patients achieving ≥1 $\log_{10}$ viral decline at Week 4, any application of early stopping rules).

A descriptive analysis method will be used, based on values entered into the study database. From the PCR samples obtained at the end of the lead-in period it will be possible to calculate the proportions of patients achieving a ≥1$\log_{10}$ decline in viral titre, and conversely, the proportion of poor interferon responders (defined as those who have a <1$\log_{10}$ viral drop). It is from this latter group that the proportion of patients being discontinued early from treatment may be defined.

7.1.2 Objective 2

To assess the early efficacy results being observed in clinical practice (as determined by percentage becoming PCR negative at Weeks 8 and 12 respectively, adjustment of 'Week 8' and 'Week 12' milestones to accommodate lead-in period in excess of 4 weeks, adherence to stipulated futility rules).

A descriptive analysis method will be used. PCR values presented for patients at Weeks 8 and 12 will be used to calculate the proportion of patients meeting the license definitions of undetectability or futility (Week 12 only) respectively.

7.2 Bias

Lack of treatment group randomisation in retrospective studies can lead to bias due to confounding variables. [7, 8] Residual confounding could occur for unknown risk factors in this study as well.

If factors associated with referral differ between those who receive combination boceprevir therapy and those who do not, then the resulting effect measure could differ from the true estimate. Retrospective studies are prone to spurious associations attributed to this type of bias.

7.2.2 Limitations

This study has a number of limitations that potentially affect the validity or interpretation of the results. Limitations most pertinent to the analysis described in this protocol are as follows:

Threats to internal validity include the loss to follow-up and confounding issues addressed in section 6.2 (Bias).

Although boceprevir was made available for compassionate use throughout the UK between March and August 2011, and has been licensed since July 2011, adoption of this therapy into

clinical practice has been sporadic throughout the UK. Therefore, the proposed sample collection window of 18 months may not reflect experience of clinicians from all parts of the UK.

The patient population in this study will be a heterogeneous one, particularly as some patients in this study will be receiving boceprevir on a compassionate use basis, and others would have been prescribed the drug post-license.

The reduced probability of achieving an SVR with a <1 $\log_{10}$ viral drop after the lead-in may be used by some clinicians as an additional futility rule. Patients may also be discontinued from therapy at other timepoints for varying reasons. Therefore, it may be that the patients in this sample will have been exposed to treatment for varying lengths of time, and some might not have been initiated on boceprevir at all.

Patients receiving boceprevir through the Compassionate Use programme were required to have clinically defined bridging fibrosis or cirrhosis of the liver, as per METAVIR grading (F3 or F4). However, the methods used to define this will vary between centres, as some will use liver biopsy while others will use FibroScan imaging. In some cases, misleading assessments could lead to patients with milder fibrosis (e.g. METAVIR F2 or below) entering the Compassionate Use pathway.

It is also likely that the PCR assays used in treatment centres throughout the UK will have widely varying limits of detection, resulting in wide heterogeneity of standards used to assess undetectable HCV virus in patients.

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 Confidentiality

8.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

8.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

8.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

8.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

8.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant health authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

8.4 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

8.5 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

9 LIST OF REFERENCES

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[5] Poordad F, McCone J, Bacon B, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, et al. Boceprevir for untreated chronic HCV type 1 infection. *N Eng J Med*. 2011;364:1195-206.

[6] Bacon BR, Gordon SC, Lawitz F, Marecllin P, Vierling JM, Zeuzem S, Poordad F, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Eng J Med.* 2011;364:1207-17.

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[8] Normanda SLT , Landruma MB, Guadagnolia E, Ayaniana JZ, Ryand TJ, Cleary PD, McNeila BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: A matched analysis using propensity scores. *J Clin Epidemiol.* 2001;54:387–398.

10 APPENDIX

10.1 Table Shells

10.2 Inclusion Criteria

To be eligible for the Named Patient Programme, patients were required to:

1. be age ≥18 years on the index date;
2. be both able and willing to provide signed informed consent;
3. have documented chronic HCV genotype 1 infection (no mixed genotypes);
4. have bridging fibrosis or cirrhosis
5. previous failure of a minimum of 12 weeks' treatment with interferon/ribavirin (without any dose reduction); and
6. meet all criteria for use of PEG-IFN and RBV defined in product labels.

10.3 Exclusion Criteria

Patients were excluded from the Named Patient Programme if they had:

1. prior utilisation of any NS3/4A protease inhibitor (i.e., boceprevir, telaprevir, narlaprevir);
2. evidence of decompensated cirrhosis (including ascites, variceal bleeding, exclusionary haematologic and biochemical criteria (haemoglobin <12g/dL for females and <13g/dL for males, neutrophils <1500mm3 (black patients <1200mm3), platelets <100,000mm3);
3. organ transplant other than cornea or hair; and
4. co-infection with hepatitis B virus (HBsAg positive).

11 SIGNATURES

Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE
_____	_____	_____