Clinical Development

DEB025/Alisporivir

Clinical Trial Protocol CDEB025A2312

A multi-centre 3-year follow-up study to assess the durability of sustained virologic response in Alisporivir-treated chronic Hepatitis C patients

Authors: Scherrer Rebecca, Orsenigo Roberto, Wu Min, Avila Claudio

Document type: Clinical Trial Protocol

EUDRACT number: 2011-006131-38

Version number: Original Protocol

Development phase: III

Release date: 31-Jan-2012

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed without the consent of Novartis
NCDS Template Version 21 Sep-2011

This document (090095a883ba0dc0 in docbase CREDI_BS) has been digitally signed with external signatures using Entrust PKI. Signatures manifested as of 2/1/2012 4:53:06 PM, signing status at this time: Completed (1 of 1 signatures) Approved for report publication by Scherrer Rebecca in Basel at Wed, Feb 01, 2012 17:51:28 CET
Table of contents

Table of contents ............................................................................................................. 2
List of tables ................................................................................................................ ... 4
List of figures ................................................................................................................. ... 4
List of abbreviations ....................................................................................................... 5
Glossary of terms .......................................................................................................... 6
Protocol synopsis ............................................................................................................. 7

1 Introduction .................................................................................................................. 9
  1.1 Background .......................................................................................................... 9
  1.2 Purpose .............................................................................................................. 10

2 Study objectives .......................................................................................................... 10
  2.1 Primary objective ............................................................................................... 10
  2.2 Secondary objectives ......................................................................................... 10

3 Investigational plan .................................................................................................. 10
  3.1 Study design ...................................................................................................... 10
  3.2 Rationale of study design ................................................................................... 11
  3.3 Rationale of dose/regimen, duration of treatment .............................................. 11
  3.4 Rationale for choice of comparator .................................................................... 11
  3.5 Purpose and timing of interim analyses/design adaptations ................................ 11
  3.6 Risks and benefits .............................................................................................. 11

4 Population ................................................................................................................... 12
  4.1 Inclusion criteria ................................................................................................ 12
  4.2 Exclusion criteria ............................................................................................... 12

5 Patient Management .................................................................................................. 12
  5.1 Treatment .......................................................................................................... 12
  5.2 Relapsed or re-infected patients ......................................................................... 12
    5.2.1 Premature patient withdrawal ...................................................................... 13
    5.2.2 Study completion and post-study treatment .............................................. 13
    5.2.3 Early study termination .............................................................................. 13

6 Visit schedule and assessments .................................................................................. 14
  6.1 Information to be collected at visit 1 ................................................................. 15
  6.2 Patient demographics/other baseline characteristics ........................................ 15
    6.2.1 Demographic Information .......................................................................... 15
    6.2.2 Baseline Characteristics .............................................................................. 15
    6.2.3 Medical History ......................................................................................... 15
    6.2.4 Liver Fibrosis Evaluation .......................................................................... 15
    6.2.5 Ultrasound evaluation ................................................................................. 15
6.2.6 Other baseline characteristics ............................................................. 16

6.3 Efficacy ............................................................................................................. 16
6.3.1 HCV RNA Viral Load ....................................................................... 16
6.3.2 Alanine-aminotransferase (ALT) ........................................................ 16
6.3.3 HCV sequencing ................................................................................ 16
6.3.4 Genotyping and sub-typing .............................................................. 16
6.3.5 Appropriateness of efficacy assessments ............................................ 16

6.4 Safety ................................................................................................................ 17
6.4.1 Physical examination ......................................................................... 17
6.4.2 Vital signs .......................................................................................... 17
6.4.3 Height and weight .............................................................................. 17
6.4.4 Laboratory evaluations ....................................................................... 17
6.4.5 FibroTest® and elastography ............................................................. 17
6.4.6 Ultrasound ......................................................................................... 18
6.4.7 Laboratory evaluations ....................................................................... 18
6.4.8 Appropriateness of safety measurements ............................................ 19

6.5 Other assessments .............................................................................................. 19

7 Safety monitoring .......................................................................................................... 19
7.1 Adverse events................................................................................................... 19
7.2 Serious adverse event reporting .......................................................................... 21
7.3 Pregnancy reporting ........................................................................................... 22

8 Data review and database management ........................................................................ 22
8.1 Site monitoring .................................................................................................. 22
8.2 Data collection ................................................................................................... 22
8.3 Database management and quality control ......................................................... 23

9 Data analysis ................................................................................................................. 23
9.1 Analysis sets ...................................................................................................... 23
9.2 Patient demographics and other baseline characteristics ..................................... 23
9.3 Treatments ......................................................................................................... 23
9.4 Analysis of the primary and key secondary variable(s) ....................................... 24
  9.4.1 Variable(s) ......................................................................................... 24
  9.4.2 Statistical model, hypothesis, and method of analysis ................................ 24
  9.4.3 Handling of missing values/censoring/discontinuations .......................... 24
  9.4.4 Supportive Analyses ........................................................................ 24
9.5 Analysis of secondary variables ......................................................................... 25
  9.5.1 Efficacy variables .............................................................................. 25
  9.5.2 Safety variables ................................................................................. 25
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.6</td>
<td>Interim analyses</td>
<td>26</td>
</tr>
<tr>
<td>9.7</td>
<td>Sample size calculation</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>Ethical considerations</td>
<td>26</td>
</tr>
<tr>
<td>10.1</td>
<td>Regulatory and ethical compliance</td>
<td>26</td>
</tr>
<tr>
<td>10.2</td>
<td>Informed consent procedures</td>
<td>26</td>
</tr>
<tr>
<td>10.3</td>
<td>Responsibilities of the investigator and IRB/IEC</td>
<td>26</td>
</tr>
<tr>
<td>10.4</td>
<td>Publication of study protocol and results</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>Protocol adherence</td>
<td>27</td>
</tr>
<tr>
<td>11.1</td>
<td>Protocol Amendments</td>
<td>27</td>
</tr>
<tr>
<td>12</td>
<td>References</td>
<td>28</td>
</tr>
<tr>
<td>13</td>
<td>Appendices</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Appendix 1: Clinically notable laboratory values and vital signs</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Appendix 2: Sample log</td>
<td>28</td>
</tr>
</tbody>
</table>

**List of tables**

- **Table 1-1**  
  Alisporivir studies as feeder studies ............................................. 9
- **Table 6-1**  
  Assessment schedule ......................................................................... 14
- **Table 13-1**  
  Sample Numbering ............................................................................. 28

**List of figures**

- **Figure 3-1**  
  Study design .......................................................................................... 11
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AFP</td>
<td>Alfa-FetoProtein</td>
</tr>
<tr>
<td>ALT</td>
<td>ALanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>ASpartate aminotransferase</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report/Record Form (paper or electronic)</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>DMID</td>
<td>Division of Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>DS&amp;E</td>
<td>Drug Safety &amp; Epidemiology</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IN</td>
<td>Investigator Notification</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate DeHydrogenase</td>
</tr>
<tr>
<td>LOCF</td>
<td>last observation carried forward</td>
</tr>
<tr>
<td>LOD</td>
<td>Limit Of Detection</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit Of Quantification</td>
</tr>
<tr>
<td>peg-IFNα</td>
<td>pegylated InterFeroN alfa</td>
</tr>
<tr>
<td>RBV</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>RNA</td>
<td>RiboNucleid Acid</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>SVR</td>
<td>Sustained Virologic Response</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-Stimulating Hormone</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell count</td>
</tr>
</tbody>
</table>
### Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td>A procedure used to generate data required by the study</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)</td>
</tr>
<tr>
<td>LOD</td>
<td>Level of detection. The assay used in this study has a reported LOD of 10 IU/ml (1 log10).</td>
</tr>
<tr>
<td>LOQ</td>
<td>Level of quantification, The assay used in this study has a reported LOQ of 25 IU/ml (1.398 log10)</td>
</tr>
<tr>
<td>SVR12</td>
<td>&quot;Sustained Virologic Response at week 12 FU&quot;: HCV RNA undetectable (by limit of detection) 12 weeks after end of treatment</td>
</tr>
<tr>
<td>SVR24 (= SVR)</td>
<td>&quot;Sustained Virologic Response at week 24 FU&quot;: HCV RNA undetectable (by limit of detection) 24 weeks after end of treatment</td>
</tr>
<tr>
<td>Subject Number</td>
<td>A number assigned to each patient who enrolls into the study</td>
</tr>
<tr>
<td>Premature patient withdrawal</td>
<td>Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)</td>
</tr>
<tr>
<td>Re-infection</td>
<td>At any time after SVR24, patients have detectable HCV RNA and a different viral genotype as reported in the feeder study.</td>
</tr>
<tr>
<td>Relapse</td>
<td>At any time after SVR24, patients have detectable HCV RNA and the same viral genotype as reported in the feeder study.</td>
</tr>
<tr>
<td>Stop study participation</td>
<td>Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later</td>
</tr>
<tr>
<td>Variable</td>
<td>Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points</td>
</tr>
</tbody>
</table>
Protocol synopsis

Title of study: A multi-centre 3-year follow-up study to assess the durability of sustained virologic response in Alisporivir-treated chronic Hepatitis C patients

Purpose and rationale: The purpose of this study is to follow patients from the feeder studies who have achieved SVR 24 to assess the durability of sustained virologic response, and to assess the changes in liver function and safety over time. Data from this study is aimed at supporting the registration submission of alisporivir-containing treatment as a treatment with long-term sustained virologic response and no long-term safety concerns.

DEB025A2312 follows the recommendations from the current draft regulatory guidelines (FDA 2010, EMA 2011).

Objectives: The primary objective is to assess the durability of sustained virologic response after SVR24 has been achieved in patients treated with alisporivir in a Novartis-sponsored chronic Hepatitis C study

Key secondary objectives:
- To determine whether subsequent detection of HCV RNA in patients who relapse following SVR24, represents the re-emergence of pre-existing virus, the development of resistance mutations, or whether it is due to re-infection
- To assess the impact of successful alisporivir treatment on the change in liver disease over time
- To assess the development of hepatocellular carcinoma (HCC)
- To assess the safety over time of previous alisporivir exposure

Study design: This study is a follow-up study where patients from various Novartis studies (called feeder studies) who were treated with alisporivir and achieved SVR24 enter this study and return to the site for 3 years, with a maximum of 5 visits. No treatment is involved.

Population: The study population will consist of male and female adult (≥ 18 years old) chronic Hepatitis C (genotypes 1-4) infected patients who had received alisporivir and achieved SVR24 in previous Novartis-sponsored studies. Up to 2000 patients are expected to enter the study.

Inclusion/Exclusion criteria:

Key Inclusion Criteria:
- Written informed consent must be obtained before any assessment is performed.
- Males or females aged ≥18
- Have previously completed a Novartis-sponsored hepatitis C study and received alisporivir
- Have achieved SVR24

Key Exclusion Criteria:
- Use of any investigational drugs within 5 half-lives of enrollment, or within 30 days of that medication, whichever is longer.
- Use or planned use to start a new course of hepatitis C therapy

Investigational and reference therapy: None

Efficacy assessments:
- HCV RNA level in serum (IU/mL) at each visit
- ALT level at each visit

Other assessments: None
The primary efficacy variable is the proportion of patients who maintained HCV RNA viral load below lower limit of quantification (LOQ) at each scheduled time points. There is no key secondary variable in this study.

There is no hypothesis testing to be conducted in this study. Number and percentage of patients who maintained HCV RNA<LOQ at each scheduled time points will be summarized by feeder study number and feeder treatment group. Pooled summary will also be provided for various subgroups of patients who were treated with the same alisporivir treatment regimen in the feeder studies.

The assessment of safety will be based on the analyses of AEs, vital signs, and laboratory evaluations. All safety analyses will be performed on the safety set.
1 Introduction

1.1 Background

Alisporivir (also known as DEB025, previously Debio 025) is a cyclophilin (Cyp) inhibitor with a new mechanism of action involving interaction at the host-viral interface; its increased Cyp binding (determinant for antiviral activity) and absence of calcineurin inhibition (determinant for immunosuppressive activity), were obtained via structural modifications of cyclosporin A (CsA). Alisporivir is currently in clinical development for chronic hepatitis C in all genotypes.

The primary goal of chronic hepatitis C treatment is sustained virologic response (SVR24), defined as the achievement of undetectable HCV ribonucleic acid (RNA) measured from serum by a sensitive Polymerase Chain Reaction (PCR) at 24 weeks after the end of treatment. SVR24 was universally accepted as equivalent of cure (Ghany et al 2009) until recently (October 2011) when the FDA presented data on SVR12 (sustained virologic response 12 weeks after end of treatment), suggesting the new endpoint for regulatory approval to be SVR12 rather than SVR24 (Florian et al 2011). Despite SVR12 becoming the primary endpoint for all future studies, SVR24 remains in clinical practice a suitable approach for confirming a patient’s clinical response. The Novartis current and planned studies with alisporivir include the SVR24 as secondary endpoint. This endpoint (SVR24) represents the first timepoint of this study.

At the time the protocol was written Novartis had two ongoing Phase II studies and two ongoing Phase III studies with more studies in planning. All the studies listed in Table 1-1 (the ‘feeder’ studies) provide the basis for this study DEB025A2312. Additional studies could be added to the list below (Table 1-1).

<table>
<thead>
<tr>
<th>Study code</th>
<th>Patient Population</th>
<th>Approx # patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2210</td>
<td>GT 1 non-responder patients</td>
<td>433</td>
</tr>
<tr>
<td>A2211</td>
<td>GT 2/3 naïve patients</td>
<td>340</td>
</tr>
<tr>
<td>A2301</td>
<td>GT 1 naïve patients</td>
<td>1040</td>
</tr>
<tr>
<td>A2303</td>
<td>GT 2/3 naïve patients</td>
<td>800</td>
</tr>
<tr>
<td>A2305</td>
<td>GT 2/3 non-responder</td>
<td>150</td>
</tr>
<tr>
<td>A2306</td>
<td>GT 1 PI-experienced patients</td>
<td>150</td>
</tr>
<tr>
<td>A2307</td>
<td>GT 1 African-American patients</td>
<td>150</td>
</tr>
<tr>
<td>A2314</td>
<td>GT 1/4 naïve patients</td>
<td>100</td>
</tr>
</tbody>
</table>

Although clinically seen, patients who achieved SVR24 are considered cured of infection (Lindsay 2002), there is evidence that serum HCV-RNA may become positive after long-term follow-up (Pawlotsky 2006). There is little data available on long-term follow-up of SVR24. Therefore regulatory authorities (FDA 2010, EMA 2011), have issued draft guidelines recommending that long-term follow-up data be collected from larger phase 2 or phase 3 trials to ensure durability of response, assess changes in liver function over time and any presence and/or persistence of viral mutations in viremic patients. DEB025A2312 is the first study to provide long-term data on alisporivir.
1.2 Purpose

The purpose of this study is to follow patients from the feeder studies who have achieved SVR 24 to assess the durability of sustained virologic response, and to assess the changes in liver function and safety over time. Data from this study is aimed at supporting the registration submission of alisporivir-containing treatment as a treatment with long-term sustained virologic response and no long-term safety concerns.

2 Study objectives

2.1 Primary objective

- To assess the durability of sustained virologic response after SVR24 has been achieved in patients treated with alisporivir in a Novartis-sponsored chronic Hepatitis C study

2.2 Secondary objectives

- To determine whether subsequent detection of HCV RNA in patients who relapse following SVR24, represents the re-emergence of pre-existing virus, the development of resistance mutations, or whether it is due to re-infection
- To assess the impact of successful alisporivir treatment on the change in liver disease over time
- To assess the development of hepatocellular carcinoma (HCC)
- To assess the safety over time of previous alisporivir exposure

3 Investigational plan

3.1 Study design

This study is a follow-up study where patients from various Novartis studies (called feeder studies) who were treated with alisporivir and achieved SVR24 enter this study and return to the site for 3 years, with a maximum of 5 visits. No treatment is involved.
3.2 Rationale of study design
The design of the study follows EMA and FDA guidance (FDA 2010, EMA 2011) and follows standard of care for the long-term follow-up of previously treated HCV patients. For new therapies, the pattern of relapse following undetectable viremia at the end of treatment is unknown, therefore Health authorities are requesting long-term follow-up in a subset of patients included in preliminary trials. The data generated from these long-term follow-up studies will provide confirmation whether SVR24 is a reliable predictor of long-term hepatitis C cure.

3.3 Rationale of dose/regimen, duration of treatment
This section is not applicable, as no drug is administered in this study.

3.4 Rationale for choice of comparator
This section is not applicable, as no drug is administered in this study.

3.5 Purpose and timing of interim analyses/design adaptations
The interim analyses are planned to allow for efficacy and safety data to be submitted to Health Authorities, other institutions or for internal Novartis use when requested. The first interim analysis will occur at least 1 year after study has started. There will be approximately up to 5 interim analyses.

3.6 Risks and benefits
The risk to subjects in this trial is minimized by the fact that there is no drug given to subjects. The schedule of assessment is aligned to standard of care of long-term follow-up of subjects achieving SVR24. The only invasive test is the blood sample which is also done in normal routine clinical practice for monitoring these subjects. Additional examinations (i.e. fibroscan, ultrasound) are not invasive, are part of routine clinical practice in a subset of patients (i.e. cirrhotic patients) and do not put the subject at risk.
The benefit of the study to the subjects is that they will be monitored regularly and should there be any clinically significant event it can be detected early.

4 Population

The study population will consist of male and female adult (≥ 18 years old) chronic Hepatitis C (genotypes 1-4) infected patients who had received alisporivir and achieved SVR24 in previous Novartis-sponsored studies. Up to 2000 patients are expected to enter the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:
1. Written informed consent must be obtained before any assessment is performed.
2. Males or females aged ≥18
3. Have previously completed a Novartis-sponsored hepatitis C study and received alisporivir
4. Have achieved SVR24
5. Are able to comply with the visit schedule

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.
1. Use of any investigational drugs within 5 half-lives of enrollment, or within 30 days of that medication, whichever is longer.
2. Use or planned use to start a new course of hepatitis C therapy

5 Patient Management

5.1 Treatment

There is no investigational treatment given to patients enrolled in this study.

5.2 Relapsed or re-infected patients

Relapsed patients are defined as those patients who, at any time after SVR24, have detectable HCV RNA and the same viral genotype (measured by viral sequencing) as reported in the feeder study.

Re-infected patients are defined as those patients who, at any time after SVR24, have detectable HCV RNA and a different viral genotype (measured by viral sequencing) as reported in the feeder study.

If patients relapse or are re-infected during the study, it is up to the clinical judgement of the investigator to decide whether to re-treat the patient with anti-HCV therapy or not. Should the patient be re-treated, they will be discontinued from the study. If the patient is not re-treated,
the patient should continue in the study and follow the schedule of assessment given in Table 6-1.

5.2.1 Premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient’s premature withdrawal from the study and record this information on the Study Completion CRF.

The investigator withdraws the subject from study under the following circumstances:

- Withdrawal of informed consent
- Use of prohibited treatment defined as any anti-HCV therapy
- Any other protocol deviation that results in a significant risk to the patient’s safety

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

5.2.2 Study completion and post-study treatment

Study completion is defined as all visits being completed within 3 years as defined in the schedule of assessments in Table 6-1.

When subjects enter this study, they are cured from chronic Hepatitis C. No Hepatitis C treatment is given in this study. Most subjects are expected to have sustained virologic response at the end of this study. If a patient becomes re-infected or relapses during the study, it is up to the clinical judgement of the investigator to decide whether to re-treat the patient with anti-HCV therapy or not. Post-study treatment options are outside of the scope of this study and are the responsibility of the investigator. Should the patient be re-treated, they will be discontinued from the study. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.2.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient’s interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.
6 Visit schedule and assessments

The visit schedule is depicted in Table 6-1 listing all of the assessments and indicating with an “x” or “s” when the visits are performed.

Patients should be seen for all visits on the designated week with an allowed “visit window” of five (5) weeks for visits 1 and 2, and eight (8) weeks for visits 3, 4 and 99.

Any repeat procedures should be conducted within 2 weeks of the test being performed (i.e. lab tests).

Patients who discontinue the study should follow the Visit 99/End of Study (EOS) assessment schedule shown in Table 6-1 at the time of their discontinuation.

Table 6-1 Assessment schedule

<table>
<thead>
<tr>
<th>Visit</th>
<th>End of feeder study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>99 /EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>-24</td>
<td>1</td>
<td>24</td>
<td>48</td>
<td>96</td>
<td>120</td>
</tr>
<tr>
<td>Month</td>
<td>-6</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Obtain informed consent</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incl/Excl. Criteria</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Prior) Concomitant Medication</td>
<td>x x x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td>s s s s s s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>x x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrotest®</td>
<td>x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastography (if available)</td>
<td>x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound (liver &amp; spleen)</td>
<td>x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sampling:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology, clinical chemistry, prothrombin time, fibrinogen</td>
<td>x x x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alphafetoprotein</td>
<td>x x x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA viral load</td>
<td>x x x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampling for HCV sequencing</td>
<td>x^2 x^2 x^2 x^2 x^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV genotyping</td>
<td>x^3 x^3 x^3 x^3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>x x x x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Completion form</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

x – data collected in CRF (and source data)
s – data only collected in source data
1 – end of study from feeder study – to have occurred 24 weeks prior to Visit 1
2 – analysis only if relapse/re-infection
3 – HCV genotyping sample will be collected at the visit following confirmation that there’s a re-infection of HCV (additional 1.8 mL plasma to be collected)
6.1 Information to be collected at visit 1

Unlike studies where treatment is given, visit 1 in this study is not a ‘screening visit’ per se, as there is no screening period. As soon as a subject has completed the feeder study, the investigator will inform the subject that there is a follow-up study. If the subject signs the informed consent, the subject is already ‘enrolled’ in the study. All visit 1 CRF pages will be completed. Adverse events occurring after informed consent is signed will be entered on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Patient demographics/other baseline characteristics

All the information listed below will be collected at visit 1 (see Table 6-1).

6.2.1 Demographic Information

Subject demographic data to be collected includes: date of birth, sex and race.

6.2.2 Baseline Characteristics

To be able to link the subject data from this study to the feeder study the study code, centre number, subject number and the last visit date (i.e. when SVR24 was achieved) from the feeder study will be recorded in the CRF.

6.2.3 Medical History

Any relevant medical history and/or current medical conditions before obtaining informed consent will be recorded in the Medical History CRF. Significant findings that are observed after the subject has signed the informed consent form and that meet the definition of an AE must also be recorded in the Adverse Events CRF. Whenever possible, diagnoses and not symptoms will be recorded.

There are two medical history pages in this study – one referring to the medical history related to the chronic hepatitis disease and another CRF page related to general medical history. For example, if a subject is cured from HCV in the feeder study, but still has diabetes related to the previous hepatitis C disease, diabetes would be recorded on the hepatitis C related Medical History CRF page.

6.2.4 Liver Fibrosis Evaluation

The following data will be collected for Fibrotest® and elastography method: type of method used, date of assessment, liver fibrosis and cirrhosis result.

6.2.5 Ultrasound evaluation

Ultrasound of the liver and spleen will be assessed at visit 1 as a baseline measure to monitor any changes over time. The following data will be collected: location of ultrasound, date of assessment, overall interpretation and size of the organ.
6.2.6 Other baseline characteristics

Other baseline characteristic data to be collected are: physical exam (recorded as source data), vital signs (height, weight, pulse and blood pressure), general hematology and chemistry blood levels, HCV RNA viral load (and if positive, the sample will be sequenced and if a re-infection is shown another sample will be taken at the following visit to determine the genotype).

6.3 Efficacy

Efficacy variables are described in section 9.4 and section 9.5

6.3.1 HCV RNA Viral Load

The efficacy assessments will be the HCV RNA in serum (IU/ml) at each visit.

The COBAS® TaqMan® HCV Test, v2.0 (Roche Diagnostics) will be used for assessment of HCV viral load. This assay has a reported LOQ of 25 IU/ml (1.398 log10) and LOD of 10 IU/ml (1 log10).

6.3.2 Alanine-aminotransferase (ALT)

Alanine-aminotransferase (ALT) assessments: ALT levels will be assessed at all visits throughout the study as a measure of clinical liver recovery.

6.3.3 HCV sequencing

HCV sequencing will be performed for patients experiencing a relapse or re-infection only if HCV RNA is quantitated at $\geq 1000$ IU/ml (3 log10).

Monitoring of the presence or persistence of resistant mutations will be performed at the time of relapse/re-infection, and other time points if needed by population sequencing or more sensitive clonal sequencing.

6.3.4 Genotyping and sub-typing

If subjects are re-infected, the VERSANT® HCV Genotype 2.0 assay (LiPA) which is based on both, 5’NCR (non-coding region of HCV genome) as well as Core-encoded oligonucleotide probes will be used for HCV genotyping and sub-typing. Samples with inconclusive result from VERSANT® HCV Genotype 2.0 assay (LiPA) will be genotyped by direct sequencing of NS5B. Blood sampling for genotyping and sub-typing will be performed at the following visit after HCV sequencing has shown that a re-infection had occurred.

6.3.5 Appropriateness of efficacy assessments

HCV RNA viral load is a standard measure of efficacy (Ghany et al 2009).

ALT assessment is a recommended standard assessment in HCV trials (Ghany et al 2009).
6.4 Safety

6.4.1 Physical examination

A physical examination of the patient will be performed according to the scheduled defined in Table 6-1.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing the Informed Consent Form must be included in the Medical History screen on the subject’s CRF. Significant findings that occur after the signing the Informed Consent Form which meet the definition of an AE must be recorded in the Adverse Event screen of the subject’s CRF (Section 7).

6.4.2 Vital signs

Vital signs include blood pressure and pulse measurements and will be assessed at every scheduled visit as indicated in Table 6-1. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured with an appropriately sized cuff.

If possible, assessments should be performed by the same qualified study site staff member throughout the study.

6.4.3 Height and weight

Height and weight will be assessed as indicated in Table 6-1. Height in centimeters (cm) or inches (in), and body weight (to the nearest 0.1 kilogram [kg] or pound [lb] in indoor clothing, but without shoes) will be measured. This assessment will be used to calculate Body Mass Index.

6.4.4 Laboratory evaluations

The change in hematology, chemistry, prothrombin time, fibrinogen and alpha-fetoprotein will be assessed at all visits as an overall measure of safety over time.

6.4.5 FibroTest® and elastography

The FibroTest® (called FibroSure in the US), is a patented biomarker test that uses the results of six blood serum tests to generate a score that is correlated with the degree of liver damage. This will be done at selected visits for all sites. The local laboratory of the site will perform the test. If the test is not available at the local laboratory, the blood sample will be sent to the central laboratory for analysis.

In addition, sites with elastography facilities (i.e. FibroScan®, ARFI (acoustic radiation force impulse imaging) will perform elastography.
The interpretation will be made by a qualified physician and documented in the CRF. The reading will also be documented in the source documents. Clinically significant abnormalities should be recorded on the Medical History/Adverse event CRF page.

### 6.4.6 Ultrasound

Ultrasound of the liver and spleen will be assessed at scheduled visits as a measure to detect HCC, other malignancies and any potential changes in liver disease.

The interpretation will be made by a qualified physician and documented in the CRF. Each ultrasound will be labeled with the study and subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the Medical History/Adverse event CRF page.

The size of the liver and spleen will also be collected to determine whether there’s any suspicion of splenomegaly or hepatomegaly.

### 6.4.7 Laboratory evaluations

The change in hematology, chemistry, prothrombin time, fibrinogen and alpha-fetoprotein will be assessed at all visits as an overall measure of safety over time.

Laboratory evaluations will be assessed as indicated in Table 6-1.

Blood samples for hematology and biochemistry evaluations are to be taken preferably after a 4 hours fast.

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

#### 6.4.7.1 Hematology

Red blood cell (RBC) count, haemoglobin (Hb), haematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), WBC count, differential WBC count, and platelet count will be measured.

#### 6.4.7.2 Biochemistry

Electrolytes (sodium, potassium, calcium, chloride, magnesium, and phosphate), albumin, total protein, glucose, creatinine, calculated creatinine clearance, blood urea nitrogen (BUN), uric acid, alkaline phosphatase, ALT, AST, total and conjugated bilirubin, bile acids, gamma glutamyl transferase (γ-GT), LDH, amylase, lipase, cholesterol (total and HDL), triglycerides, vitamin D (1, 25 Dihydroxy Vitamin D3), TSH, free T3 and T4 will be measured.

#### 6.4.7.3 Coagulation testing

Prothrombin time (PT expressed as INR) and fibrinogen will be measured.
6.4.7.4 Alpha-fetoprotein

Alpha-fetoprotein (AFP) is used to detect hepatocellular carcinoma and will be measured at all visits.

6.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.5 Other assessments

No additional tests will be performed on patients entering into this study.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
• its relationship to the previous study treatment:
  • No relationship
  • Yes investigational treatment eg related to Alisporivir or Boceprevir
  • Yes other study treatment eg related to peg-IFNα or Ribavirin
  • Yes both, and/or indistinguishable
• its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
• whether it constitutes a serious adverse event (SAE)
• whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
• its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria
• is fatal or life-threatening
• results in persistent or significant disability/incapacity
• constitutes a congenital anomaly/birth defect
• requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  • routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  • elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  • treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  • social reasons and respite care in the absence of any deterioration in the patient’s general condition
• is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the previous study treatment the interventions required to treat it, and the outcome.
Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the end of the study must be reported to Novartis within 24 hours of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded on the paper SAE form should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator’s Brochure or Package Insert (new occurrence) and is thought to be related to the previous investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious
Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is in the study must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the previous study treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, and the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.
Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

9 Data analysis

9.1 Analysis sets

**Full Analysis Set (FAS):** The Full Analysis Set comprises all subjects who enrolled into this study and had at least one HCV RNA assessment.

**Safety Set:** The Safety Set includes all subjects who had at least one post-baseline safety observation (AE and/or laboratory assessment).

9.2 Patient demographics and other baseline characteristics

Summary statistics will be provided for patient demographics (age, sex, race, ethnicity, height, weight and BMI) and other baseline disease characteristics such as HCV viral load. Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, and the number of non-missing observations. Categorical data will be displayed via absolute and relative frequencies for each category (including a category labeled as ‘missing’ when appropriate).

9.3 Treatments

There is no treatment in the study.

Prior and concomitant therapies will be listed. The frequency and percentage of patients who used prior or concomitant medication will be summarized by preferred term (WHO Drug).
9.4 Analysis of the primary and key secondary variable(s)

9.4.1 Variable(s)

The primary efficacy variable is the proportion of patients who maintained HCV RNA viral load below lower limit of quantification (LOQ) at each scheduled time points. There is no key secondary variable in this study.

9.4.2 Statistical model, hypothesis, and method of analysis

There is no hypothesis testing to be conducted in this study. Number and percentage of patients who maintained HCV RNA<LOQ at each scheduled time points will be summarized by feeder study number and feeder treatment group. Pooled summary will also be provided for following subgroups of patients who were treated with the same alisporivir treatment regimen in the feeder studies:

- Genotype 1 treatment naïve patients
- Genotype 1 treatment experienced patients
- Genotype 2/3 treatment naïve patients
- Genotype 2/3 treatment experienced patients
- Genotype 4 treatment naïve patients

9.4.3 Handling of missing values/censoring/discontinuations

For summary of HCV RNA assessment as a continuous variable, no imputation will be applied, the summary will be based on observed HCV RNA assessment only.

When impute dichotomous efficacy response based on scheduled HCV RNA assessment (<LOQ vs. >=LOQ), the following rules will apply:

1. The closest unscheduled assessment (when available) will be used when the scheduled assessment is missing. If unscheduled assessment is also not available, go to 2.
2. For missing value at scheduled time points, such as A---missing (X)---B, use the worst HCV RNA assessment of A and B to impute the efficacy response at missing (X). Where A is the closest non-missing HCV RNA value before the missing (X) assessment and B is the closest non-missing HCV RNA value after the missing (X) assessment. When there is no non-missing assessment after missing value (X), missing (X) will not be imputed.

9.4.4 Supportive Analyses

Not applicable
9.5 Analysis of secondary variables

9.5.1 Efficacy variables

- HCV RNA viral load
- The proportion of patients who normalize alanine aminotransferase (ALT)
- The proportion of relapsed patients
- The proportion of re-infected patients

Continuous HCV RNA assessment will be summarized by visit, including number of patients, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum.

The number and percentage of patients who normalize alanine aminotransferase (ALT) at each visit, patients who relapse and patients who are re-infected will be provided.

9.5.2 Safety variables

The assessment of safety will be based on the analyses of AEs, vital signs, and laboratory evaluations. All safety analyses will be performed on the safety set.

Adverse events

AEs will be coded using the MedDRA dictionary and will be summarized by presenting the number and percentage of patients having any AE, having an AE in each system organ class and having each individual AE as reported by preferred term (PT). Furthermore, a summary for SAEs and summaries by severity and relationship to previous study treatment will be presented. Most frequent AEs and previous treatment related AEs will also be provided. All percentages will be based on the number of patients in the safety set. In the summaries, AEs will be counted only once per patient. If a patient reports the same AE more than once, it will be counted with its worst severity and closest relationship to previous study treatment. Only those AEs which began between start and end of study will be summarized. AEs will also be listed by patient.

Patient death due to any cause and patients with AEs leading to study discontinuation will be listed and summarized.

Vital signs

Vital signs will be listed and summarized over time. Changes from baseline will also be summarized. Notable values and changes will be tabulated.

Laboratory evaluations

Summary statistics (mean, median, standard deviation, minimum and maximum) over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline by study visits will also be presented. A frequency table of results of categorical laboratory parameters will be produced. Frequency and percentage of patients with graded laboratory abnormalities (DMID grade) will be presented. Furthermore, lab abnormalities will be analyzed by shift tables and each patient is counted only once with the worst grade in the summary tables. All laboratory data will be listed with abnormal values flagged.
9.6 Interim analyses

There will be approximately 5 interim analyses in the study. The first interim analysis will occur at least after 1-yr data is available from subjects enrolled in this study.

9.7 Sample size calculation

It is estimated that up to 2000 patients may enroll into this study based on the number of patient enrolled or to be enrolled into Novartis sponsored phase II/III studies and the estimated SVR rate. The actual number of subjects entering this study will depend on a) the number of subjects achieving SVR24 from the feeder studies and b) the number of subjects consent to enter this 3-year follow-up study.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient’s representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all
of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.
12 References

EMA (2011) Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C. Draft Guideline Available at:

FDA (2010) Guidance for Industry – Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment. Draft Guidance Available at:


13 Appendices

Appendix 1: Clinically notable laboratory values and vital signs

Please reference the laboratory manual for clinically notable laboratory values.

Appendix 2: Sample log

<table>
<thead>
<tr>
<th>Visit Name/Study Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>99</th>
<th>Un-scheduled</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV sequencing</td>
<td>501</td>
<td>502</td>
<td>503</td>
<td>504</td>
<td>505</td>
<td>1501-1510</td>
</tr>
</tbody>
</table>