Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for asunaprevir

Proprietary Product Name: Sunvepra

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

First round evaluation: 29 October 2014

Second round evaluation: 13 February 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

Most common abbreviations used

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASV	asunaprevir (BMS-650032)
AUC	area under the plasma concentration-time curve
BD	twice daily
BMI	body mass index
BOC	boceprevir
Cavgss	steady state average concentration
CRF	case record form
cEVR	complete early virologic response
CHC	chronic hepatitis C
CI(s)	confidence interval(s)
CSR	clinical study report
DAAs	direct acting antivirals
DCV	daclatasvir (BMS-790052)
EOT	end of treatment
EOTR	end of treatment response
E-R	exposure-response
eRVR	extended rapid virologic response
EU	European Union
EVR	early virologic response
GT	genotype
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon

Abbreviation	Meaning
IFNα	interferon alfa
IFNβ	interferon beta
ITT	intent-to-treat
LLOQ (LOQ)	lower limit of quantitation
NA	Not applicable
NS3	non-structural protein 3
NS5A	non-structural protein 5A
PBO	placebo
PD	pharmacodynamic
PDR	protocol-defined response
pegIFNα/RBV	peginterferon alfa plus ribavirin
PK	pharmacokinetics
PKVC	pharmacokinetic viral kinetic analysis
PPK	population pharmacokinetics analysis
QD	once daily
QW	weekly
RAV	resistance-associated variant
RBV	ribavirin
RCI	replication complex inhibitor
RNA	ribonucleic acid
RVR	rapid virologic response
SC	subcutaneous
SMV	simeprevir
SNP	single nucleotide polymorphisms
SOF	sofosbuvir
SVR	sustained virologic response
SVR4, 12, 24, 36, 48	sustained virologic response at follow-up Week 4, 12, 24, 36, 48

Abbreviation	Meaning
TD	target detected
TND	target not detected
TVR	telaprevir
VBT	virologic breakthrough

1. Introduction

This is a full submission to register the new chemical entity asunaprevir.

Asunaprevir (ASV) is a direct-acting antiviral agent (DAA) that is a selective inhibitor of the hepatitis C virus (HCV) non-structural protein 3 (NS3) protease and subsequently viral ribonucleic acid (RNA) replication with genotype (GT) 1 and 4 coverage.

The proposed indication is:

> Sunvepra (asunaprevir) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis) in combination with:
>
> - Daklinza, an NS5A replication complex inhibitor, for patients with HCV genotype 1b infection (See Clinical Trials and Dosage and Administration)
> - Daklinza, peginterferon alfa, and ribavirin for patients with HCV genotype 1 or 4 infection (see Clinical Trials and Dosage and Administration)

The submission proposes registration of the following dosage form and strength:

- Oval, opaque white to pale yellow, soft gelatin capsules imprinted with BMS in black on one line and 711 in black on second line, filled with clear solution containing 100 mg of asunaprevir.

1.1. Guidance

The TGA has adopted the following European Medicines Agency guidelines which are relevant to the submission:

- Guideline on pharmacokinetic studies in man[5].
- Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function[6].
- Concept paper on the need for revision of the note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function[7].
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function[8].
- Guideline on the investigation of drug interactions [9].
- Guideline on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs [10].
- Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C[11].

In addition, US Food and Drug Administration guidance is noted:

- Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment[12].

1.2. Related submissions

As ASV is indicated in combination with other medications the following submissions are related:

- DCV: currently under evaluation.
- Interferon (IFN) α and RBV have been approved as both single agents and as combination therapy for the treatment of CHC C in patients previously untreated and in those who have relapsed following IFNα monotherapy.

- Other DAAs approved for marketing in Australia: TVP, BOC, SOF and SMV.

1.3. Clinical rationale

Approximately 150 to 160 million people worldwide are chronically infected with HCV. The majority of infected individuals progress to chronic hepatitis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

Chronic hepatitis C (CHC) infection is associated with variable degrees of hepatic inflammation and progression of fibrosis. Liver disease progression takes place over several decades, and is accelerated in the presence of co-factors such as alcohol consumption, diabetes mellitus, old age, HIV co-infection, or hepatotropic virus co-infection. Between 10-40% of patients with CHC will develop cirrhosis depending on the presence of these co-factors. Deaths, related to the complications of cirrhosis, occur at an incidence of approximately 4% per year, and HCC occurs in this population at an estimated incidence of 1-5% per year. Given that HCC often goes undiagnosed until late into the disease, once diagnosed with HCC, patients have an approximate 33% probability of death during the first year.

Various HCV genotypes (GT) have been described that respond differently to current treatment regimens. HCV GT-1 (subtypes 1a and 1b) is the most prevalent worldwide with a higher prevalence of GT-1a in the United States and GT-1b in Europe. GT-3 is the second most prevalent GT in some European countries and India, and is associated with an increased likelihood of developing hepatic complications, from steatosis to HCC. Due to the migration from North-East and Sub-Saharan Africa, HCV GT-4 accounts for up to 19% of cases in Mediterranean countries and in 5-8% in Central and Western European countries. GT-2 is found in clusters in the Mediterranean region, while GT-5 and GT-6 are more rarely found in Europe.

Comment: There is no discussion of the prevalence of genotypes in Australia in the application but in a reference quoted in the Risk Management Plan (RMP) and supported by a publication not provided in the submission it is estimated that in Australia, approximately 32 to 35% of people with hepatitis C have subtype GT-3 (mostly being GT-3a), 15 to 35% have GT-1a, 15 to 23% have GT-1b and 7 to 9.3%, have GT-2, 5.5% have GT-4 and 1.7% have GT-6.[a,b]

Peginterferon alfa in combination with ribavirin (pegIFNα/RBV) was the traditional well accepted standard of care for the treatment of CHC until 2011. This treatment regimen is administered for either 48 weeks (GT-1, -4, -5, -6) or for 24 weeks (GT-2 and -3), inducing sustained virologic response at 24 weeks (SVR24) rates of 42% to 46% in patients with HCV GT-1 and GT-4, and 76% and 82% in patients with GT-2 and GT-3 infections.

In recent years the introduction of DAAs, which target specific viral enzymes, have improved patient outcomes.[c,d] In 2011, 2 DAA agents, the HCV NS3/4A protease inhibitors telaprevir (TVR) and boceprevir (BOC), added on to pegIFNα/RBV were approved in the United States (US) and European Union (EU). These DAA/ pegIFNα/RBV regimens were then considered the standard of care for treating CHC patients in the EU, US, Japan and other regions.

Comment: Boceprevir (BOC) and telaprevir (TVR) have been approved for marketing in Australia and were entered into the Australia Register of Therapeutic Goods (ARTG) in January 2012 and March 2013 respectively.

Recently, other agents including sofosbuvir (Sovaldi) (SOF), a nucleoside NS5B polymerase inhibitor, and simeprevir (Olysio) (SMV), an NS3/4A protease inhibitor, have been approved in the US offering new treatment options to patients with CHC.

Comment: SOF and SMV were approved in Australia in June and July 2014 respectively.

[a] Dore G.J., Law M., MacDonald M. et al. Epidemiology of Hepatitis C virus infection in Australia. *Journal of Clinical Virology* 2003; 26(2):171-84.
[b] Kaba S., Dutta U, Byth K., Crewe E. B., Khan M, H., Coverdale S. A., Lin R., Liddle C., and Farrell C. Molecular Epidemiology of Hepatitis C in Australia. Journal of Gastroepidemiology and Hepatology 1998; 13: 914-920
[c] Chan J. Hepatitis C. *Disease-a-Month*; 2014; 60: 201-212.
[d] Kohli A, Shaffer A, Sherman A et al. Treatment of Hepatitis C - A Systematic Review. *JAMA*. 2014. 312: (6): 631-640.

The introduction of these newer options has provided an improvement over the use of IFN-based therapies alone for patients with GT-1. However, there is still a need for improved efficacy in HCV GT-1 patients, particularly in patients with limited response to pegIFNα/RBV or in patients who are intolerant or ineligible for IFN based therapy, and for patients who have failed current protease inhibitor therapies.

Treatment duration with pegIFNα/RBV can be long (24 to 48 weeks) depending on the GT, and because pegIFNα requires parenteral administration, treatment adherence, compliance, and complications arising from injections can be a challenge.

Side effects associated with pegIFNα/RBV include flu-like symptoms (chills, pyrexia, myalgia, fatigue), psychiatric disorders (depression, irritability, anxiety), and haematologic abnormalities (anaemia and neutropenia). TVR and BOC are associated with serious dermatologic side effects (rash and/or pruritus) and additional decreases in haemoglobin and absolute neutrophils when combined with pegIFNα/RBV, compared to IFN-based therapy alone. SMV treatment is associated with increased rates of hyperbilirubinaemia and photosensitivity.

Despite the treatment advancement with the first generation DAAs and recently approved DAAs, there is still an unmet medical need for new therapeutic agents that are more effective, pangenotypic, less toxic than INF- and RBV-based therapies and less complex with simpler administration, monitoring and management of adverse events to ensure the most optimal combination of DAAs are available to patients. Currently, there is a need for improved therapies in subjects who have failed TVR- and BOC-regimens as well as INF ineligible/intolerant patients and non-responders to pegIFNα/RBV.

Asunaprevir (ASV) has shown additive to synergistic interactions in combination with DCV with no cross resistance between the two agents. This data supports the combination therapy of DCV and ASV in HCV infected patients.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

Of particular note, the efficacy studies for the requested regimens of combination therapy were all common to the DCV submission and have been assessed in the DCV clinical evaluation report. They are cross referenced to that report and only brief summaries are provided in this report.

The clinical studies contained in Module 5 of the submission are as follows:

- 3 bioavailability studies that examined bioequivalence between various formulations and the effect of food;
- 1 absolute bioavailability study;
- 6 ascending dose studies examining pharmacokinetics (PK) and initial tolerability. Four were conducted in healthy subjects and two in subjects with chronic HCV infection.
- 1 mass balance study;
- 2 studies in special populations (1 in hepatic impairment and 1 in renal impairment);
- 12 interaction studies;
- 4 studies examining population PK and population PK/exposure-response;
- 1 pharmacodynamic (PD) study examining effects on QT interval.
- 1 efficacy/safety study not provided in the DCV dossier

Also, Integrated Summaries of Efficacy and Safety have been submitted in Module 5 in place of Summary of Clinical Efficacy, and Summary of Clinical Safety in Module 2 but the documents are titled Summary of Clinical Efficacy and Summary of Clinical Safety.

2.2. Paediatric data

The submission did not include paediatric data.

The sponsor states that there is an agreed Paediatric Plan in the USA. No date for submission of a Paediatric Assessment is provided. There is a waiver for submission of a Paediatric Assessment for children under the age of 3 as they will not benefit significantly from the therapy due to the higher spontaneous resolution of HCV infection in children than in adults and that HCV infection is milder within this age group (milder liver inflammation, less frequent cirrhosis, lower viral load and shorter duration of infection).

2.3. Good clinical practice

The study reports all state that the studies were conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

All protocols were reviewed by appropriate ethics committees and patients signed appropriate informed consent prior to any study procedures.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each PK topic.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	AI447-001	*
	- Multi-dose	AI447-003	*
		AI447-005	*
	Bioequivalence† - Single dose	AI447-008	*
		AI447-024	*
	Absolute bioavailability	AI447-027	*
	Food effect	AI447-024	
		AI447-043	*

PK topic	Subtopic	Study ID	*
	Mass balance	AI447-010	*
PK in special populations	Target population § - Single dose	AI447-002	*
	- Multi-dose	AI447-004	*
	Hepatic impairment	AI447-012	*
	Renal impairment	AI447-033	*
Genetic/gender-related PK	Caucasian versus Chinese subjects	AI447-030	*
PK interactions (with ASV)	Midazolam	AI447-007	*
	Ketoconazole	AI447-014	*
	Rosuvastatin	AI447-015	*
	Rifampicin	AI447-018	*
	Norgestimate and Ethinyl oestradiol	AI447-019	*
	Metabolic probe cocktail	AI447-020	*
	Digoxin	AI447-021	*
	Escitalopram and Sertraline	AI447-032	*
	Methadone	AI447-038	*
Population PK analyses	Population PK (ASV)	-	*
	Exposure-response for efficacy and safety (DCV+ASV)	-	*

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of these PK studies had deficiencies that excluded their results from consideration. The submission included some other early phase studies, which have not been reviewed in this report. These studies have been reviewed and summarised as part of the clinical evaluation of early phase studies for DCV. These studies are listed in Table 2.

Table 2: Pharmacokinetic studies submitted but not reviewed in this report.

Study ID	Subtopic(s)
AI444-003	Multiple dosing of DCV in healthy subjects
AI444-012	Interaction study between DCV and rifampicin
AI447-009	Interaction study between ASV and DCV
AI447-039	Interaction study between AS+DCV combination and oral contraceptive
AI447-040	Interaction study between AS+DCV combination and digoxin
930077408	Exposure-response analysis for efficacy for AS+DCV combination
930077407	Exposure-response analysis for safety for AS+DCV combination

4. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies unless otherwise stated.

4.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2. The drug has a molecular weight of 748.29. It is practically insoluble in water at pH values up to 6.8. Alterations in gastric pH would therefore not be expected to alter solubility or systemic exposure. It is highly soluble in lipid vehicles. It has a pKa value of 4.85. It is a chiral molecule with five chiral centres but the drug substance is manufactured as a single enantiomer.

4.2. Pharmacokinetics in healthy subjects

4.2.1. Absorption: Sites and mechanisms of absorption

Absorption of ASV was rapid with maximum concentrations being reached within 1.5 – 4.0 hours following administration of the proposed softgel capsule formulation. After multiple dosing with the proposed regimen of 100 mg BD (with the proposed softgel capsule formulation) in 16 healthy Caucasian subjects, C_{max} was 192 ng/mL, and $AUC_{(0\text{-}12)}$ was 625 ng.h/mL. ASV is a substrate for the efflux transporter P-glycoprotein. There were no clinical data examining site or mechanism of absorption.

4.2.2. Bioavailability

4.2.2.1. Absolute bioavailability

Absolute bioavailability was estimated to be **9.3%**, with the proposed softgel capsule formulation.

4.2.2.2. Bioequivalence of clinical trial and market formulations

The softgel capsule formulation is apparently identical to the formulation used in the Phase III studies. Many of the early phase studies were conducted with earlier formulations such as a hard gelatin capsule and a tablet (dry granulated). These early formulations were not bioequivalent to each other. The tablet formulation had significantly lower bioavailability than the proposed softgel capsule formulation.

4.2.2.3. Influence of food

With the softgel capsule formulation proposed for marketing, co-administration with a high fat meal resulted in increased bioavailability (AUC) by approximately 20%, with a 34% increase in C_{max}. T_{max} was reduced by approximately 1.0 hour. In an earlier study, a standard meal increased the AUC for the softgel capsule formulation by 22% and the C_{max} by 31%.

The early tablet formulation was subject to a very large food effect.

Comment: The sponsor is proposing that ASV can be administered with or without food. The early Phase Clinical studies used dosage regimens of up to 600 mg BD, without any major safety issues being apparent. A 20% increase in AUC is therefore unlikely to result in significant increased toxicity. However, the dosage instructions in the PI with respect to co-administration with food should reflect the dosage instructions given to patients in the pivotal efficacy and safety studies.

Dose proportionality

In ascending dose studies, increases in ASV AUC and C_{max} were more than proportional to the increases in dose.

Comment: The sponsor is proposing a fixed dose of 100 mg BD for all subjects, without subsequent titration. There are therefore unlikely to be any clinically significant consequences of the non-linear PK.

4.2.2.4. Bioavailability during multiple-dosing

Repeated twice daily dosing with ASV 100 mg in healthy subjects resulted in accumulation of ASV, with the accumulation index for AUC typically being in the range of 2 to 4. Accumulation index decreased with increasing dose, suggesting auto-induction of metabolism. Steady state (as assessed by trough concentrations) was reached after 7 days.

4.2.2.5. Effect of administration timing

ASV is to be administered twice daily. A comparison between the PK parameters obtained after AM versus PM dosing suggested there was no substantial diurnal variation.

4.2.3. Distribution

4.2.3.1. Volume of distribution

Following IV administration of [^{14}C] ASV, volume of distribution at steady state was estimated to be 194 litres suggesting extensive tissue distribution.

4.2.3.2. Plasma protein binding

In blood samples collected at trough and at T_{max}, protein binding was >99%. The degree of binding was not altered in subjects with hepatic or renal impairment.

4.2.4. Metabolism

The absolute bioavailability of ASV is 9.3%. Only trace amounts of an orally administered dose of ASV are recovered in the urine, with most being recovered in the faeces. According to the sponsor's Summary of Clinical Pharmacology (SCP) in Module 2, most of the drug-related material in faeces is the form of metabolites, with only 7.5% of the dose being unchanged ASV. These data indicate that metabolism is the major route of clearance for ASV.

4.2.4.1. Sites of metabolism and mechanisms / enzyme systems involved

According to the sponsor's SCP in Module 2, in vitro data indicated that metabolism of ASV is primarily mediated by CYP3A4. In clinical interaction studies, co-administration of ASV with agents that inhibited CYP3A4 resulted in increased ASV systemic exposure - for example, ketoconazole and ritonavir. Co-administration of ASV with rifampicin, an agent that induces CYP3A4, resulted in some decrease in ASV systemic exposure.

4.2.4.2. Clearance

Following IV administration of [^{14}C] ASV, total clearance was estimated to be 49.5 L/hr (825 mLs/min).

4.2.4.3. Half-life

Following IV administration of [^{14}C] ASV, half-life was estimated to be 13.7 hours. Following oral administration (of multiple doses of the softgel capsule formulation) at the 100 mg BD dose, mean half-life across studies was 17.7 hours.

4.2.4.4. Metabolites identified in humans

According to the SCP in Module 2, there were 15 metabolites identified in humans. Data regarding the identity of the metabolites was included in Module 4 [nonclinical] of the submission.

4.2.5. Excretion

4.2.5.1. Routes and mechanisms of excretion

Following oral administration of radiolabelled ASV, drug-related material was mainly excreted in faeces (83.96%) with only small amounts (0.24%) in urine. There were no clinical data relating to mechanisms of excretion.

4.2.5.2. Renal clearance

Following oral administration only small amounts of drug-related material are excreted in the urine. Renal clearance of ASV is therefore negligible.

4.2.6. Intra- and inter-individual variability of pharmacokinetics

The sponsor considered intra-subject variability to be low for the softgel capsule formulation, based on C_{max} and AUC values obtained in healthy subjects receiving repeated single doses in bioequivalence studies. Variability was higher for the earlier tablet formulation.

Inter-subject variability was assessed as moderate to high among healthy volunteers, with CV values for AUC and C_{max} being > 50% in most cases.

4.3. Pharmacokinetics in the target population

The 2 early phase studies conducted in subjects with chronic HCV infection (AI447-002 and -004) used early formulations (oral suspension and hard gelatin capsules respectively). It is therefore difficult to compare PK with healthy subjects. According to the Module 2 SCP, comparison of steady-state ASV PK data from subjects with HCV infection from 2 later phase studies (AI447011 [DCV CER [AusPAR for Daklinza Attachment 2]] and AI447016: section *Dosage selection for the pivotal studies* below) demonstrated a 2.3-fold higher C_{max}, a 2.5-fold higher AUC and a 3.1-fold higher C_{min} compared to healthy subjects in studies AI447015 and AI447020 after administration of the 200-mg Phase II tablet under fed conditions.

Greater systemic exposure in HCV subjects may be a result of impairment of hepatic function in these subjects.

4.4. Pharmacokinetics in other special populations

4.4.1. Pharmacokinetics in subjects with impaired hepatic function

Subjects with moderate (Child-Pugh Class B) or severe (Class C) hepatic impairment had markedly increased systemic exposure to ASV compared to healthy volunteers (32-fold increase in AUC for class C and 9.8-fold increase for class B). Subjects with mild (Class A) hepatic impairment did not have increased exposure.

Comment: In the draft PI, ASV is contraindicated in subjects with moderate to severe hepatic impairment. No dosage reduction is recommended for subjects with mild impairment. Based on the data, this approach is appropriate.

4.4.1.1. Pharmacokinetics in subjects with impaired renal function

Patients with end stage renal disease on haemodialysis did not have an increased exposure to ASV based on AUC and C_{min} values. Mean C_{max} values were increased by approximately 25%. No dosage adjustment is recommended in the draft PI for subjects with impaired renal function.

4.4.1.2. Pharmacokinetics according to age

No dedicated studies were conducted examining the effect of age on ASV PK. In a population PK analysis, age was identified as a significant covariate. However, the magnitude of any effect on ASV exposure was small and unlikely to be clinically significant. The mean age of subjects include in the analysis was 55 years (range 18-79). No dosage adjustment is recommended in the draft PI for elderly subjects.

4.4.1.3. Pharmacokinetics according to gender

No dedicated studies were conducted examining the effect of gender on ASV PK. In a population PK analysis, gender was identified as a significant covariate, with females experiencing greater systemic exposure. However, the magnitude of any effect was small and unlikely to be clinically significant.

4.4.1.4. Pharmacokinetics according to race

In a study comparing PK between Caucasian and Chinese subjects, Chinese subjects experienced greater systemic exposure to ASV. With multiple dosing, AUC was increased by 53.9% and Cmax by 89.7%.

In the Module 2 SCP the sponsor presented the results of an integrated analysis of PK data according to race. Compared to White subjects, increased exposure was seen in Indian and Japanese subjects, but not in African-Americans.

4.5. Pharmacokinetic interactions

4.5.1. Effect of other drugs on PK of ASV

The early phase clinical studies that examined the effect of other drugs on ASV PK are summarised:

CYP3A4 inhibitors: Preclinical data suggested that ASV is a substrate for CYP3A4. The early phase clinical studies supported these findings with co-administration of drugs that inhibit CYP3A4 (ketoconazole, ritonavir) causing significant increases in ASV AUC and C_{max}.

Comment: The draft PI states that ASV is contraindicated in patients receiving moderate or strong CYP3A4 inhibitors.

CYP3A4 inducers: Rifampicin, a CYP3A4 inducer, caused a modest reduction in ASV exposure. However the effect of CYP3A4 induction may have been obscured in this study as rifampicin also inhibits the transporter protein OATP -1B1, and this effect would increase ASV exposure (see below).

Comment: The draft PI states that ASV is contraindicated in patients receiving moderate or strong CYP3A4 inducers.

Inhibitors of OATP-1B1: Preclinical data indicated that ASV is a substrate for the transporter proteins OATP-1B1 and OATP-2B1. These agents facilitate the transport of drugs from the hepatic sinusoids in hepatocytes, thereby enabling hepatic clearance. Inhibition of OAT-1B1/2B1 by a single dose of rifampicin resulted in a marked increase in systemic exposure to ASV, supporting the preclinical findings.

Comment: The draft PI states that ASV is contraindicated in patients receiving strong inhibitors of OAT-1B1/2B1.

Other: The draft PI states that no dose adjustment is recommended when ASV is given with peginterferon alfa and ribavirin. There were no early phase clinical studies examining these interactions, and these statements are presumably based on later phase studies.

4.5.2. Effect of ASV on PK of other drugs

The early phase clinical studies that examined the effect of ASV on the PK other drugs were summarised.

CYP3A4 substrates: Preclinical data had suggested that ASV was an inhibitor and inducer of CYP3A4. However, clinical studies indicated that the drug was a weak *inducer* of CYP3A4, causing modest reductions in systemic exposure to CYP3A4 substrates such as midazolam.

PK data also suggested that ASV causes weak auto-induction of its own metabolism via CYP3A4.

CYP2D6 substrates: Preclinical data had suggested that ASV was an inhibitor of CYP2D6. This was confirmed in a clinical study in which ASV treatment was associated with a significant increase in exposure to dextromethorphan, a CYP2D6 substrate.

Comment: The draft PI states that ASV is contraindicated in patients receiving CYP2D6 substrates with a narrow therapeutic range (for example, flecainide). Otherwise, close clinical monitoring and possible reduction in dose for the 2D6 substrate is recommended.

Other CYP450 enzymes: In a clinical study, ASV had no effect on the PK of substrates for 2C9 (losartan), 2C19 (omeprazole), and 1A2 (caffeine).

P-glycoprotein substrates: Preclinical data suggested that ASV inhibited P-gp. This was confirmed in a clinical study where ASV increased digoxin AUC by 30%. The draft PI recommends monitoring of serum digoxin concentrations when co-prescribed with ASV.

OATP and BCRP substrates: In vitro, ASV was an inhibitor of OATP-1B1, -1B3, -2B1 and BCRP. In a clinical study, ASV caused increased systemic exposure to rosuvastatin (an OATP1B1, OATP1B3 and BCRP substrate)

4.6. Evaluator's overall conclusions on pharmacokinetics

The early phase clinical studies have provided sufficient data to adequately describe the PK of ASV. The requirements outlined in the relevant EMA guidelines adopted by the TGA have generally been met. In particular, an extensive program of interaction studies has been conducted, as required by the guideline on DAAs for HCV infection.[9]

5. Pharmacodynamics

Table 3 shows the studies relating to each PD topic and the location of each study summary.

Table 3: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on HCV viral load	AI447-002	*
		AI447-004	*
Secondary Pharmacology	Effect on QT interval	AI447-025	*

* Indicates the primary aim of the study.

None of the studies had deficiencies that excluded their results from consideration.

5.1. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated.

5.1.1. Primary pharmacodynamic effects

In 2 early phase clinical studies in subjects with CHC infection, treatment with ASV monotherapy resulted in significant reductions in HCV RNA loads.

5.1.2. Secondary pharmacodynamic effects

ASV had no significant effect on QT interval or other ECG parameters.

5.2. Evaluator's overall conclusions on pharmacodynamics

The PD data provided were acceptable.

6. Dosage selection for the pivotal studies

6.1. Introduction

ASV was shown to be active as monotherapy. In the Phase I single-ascending dose study (A1447002:). GT-1 subjects with HCV receiving a single dose of ASV 200 mg experienced a mean maximum decline in HCV RNA (log_{10} IU/mL) from baseline of 2.26 in 21.6 hours (mean). In the SCP it is indicated that a dose of 200 mg BD (with the tablet formulation) was chosen for Phase II studies. This was based on an exposure-response analysis of data from the Phase II Study AI447-016. This study also informed the dose to be used in the Phase III studies with DCV and DCV + pegIFNα + RBV. It investigated the safety and efficacy of ASV + PegIFNα + RBV and is summarised and evaluated below.

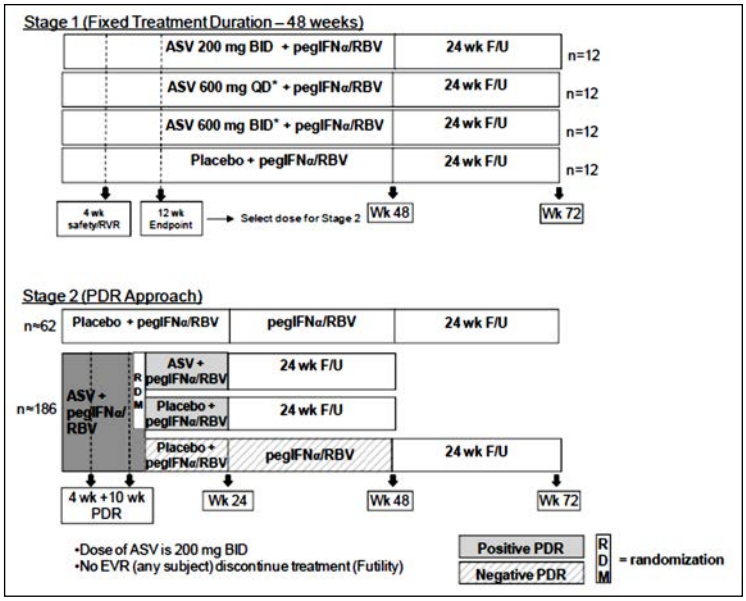
6.2. Study AI447016

6.2.1. Study design, objectives, locations and dates

This was a Phase IIA/2B Study of BMS-650032 in combination with pegIFNα-2A/RBV in treatment-naive subjects with GTs 1 and 4 CHC Infection. It was a comparative, multicentre, 2 stage study conducted for Stage 1 in France (6 sites) and the US (9), and for Stage 2 in Argentina (4 sites), France (6), Germany (4), Ireland (1), Italy (1), Spain (5), United Kingdom (5) and the US (14) from February 2010 to October 2012. It was conducted in 2 stages:

- Stage 1: a double blind, randomised trial of 3 doses of ASV/pegIFNα/RBV versus placebo; subjects were treated for 48 weeks with up to 24 weeks of follow up; this was undertaken to inform dosing in stage 2.
- Stage 2: a double blind, randomised design studying 1 dose of ASV/ pegIFNα/RBV vs placebo for 12 weeks; a second randomisation occurred at Week 12; subjects initially randomised to 200 mg BD ASV who achieved protocol defined response (PDR) were randomised to either receive an additional 12 weeks of triple therapy (ASV/pegIFNα/RBV; 24W ASV group) or an additional 12 weeks of placebo/pegIFNα/RBV (12W ASV plus 12W placebo group).

Figure 1: Study AI447016. Study design



*Post protocol amendment 06, ASV doses changed to 200 mg BD.

The objectives are those detailed in the CSR addendum which presents the safety, efficacy, and results applicable to the follow-up Week 24 final results in both Phase IIa (Stage 1) and Phase IIb (Stage 2).

6.2.1.1.1. Primary objectives:

- Antiviral activity as determined by the proportion of subjects with GT-1 with extended rapid virologic response (eRVR), defined as undetectable HCV RNA at Weeks 4 and 12 (Stages 1 and 2)
- Antiviral activity, as determined by the proportion of subjects with GT-1 with 24 week sustained virologic response (SVR24), defined as undetectable HCV RNA at follow up Week 24 (Stage 2 only)
- Safety, as measured by the frequency of serious adverse events (SAEs) and discontinuations due to AEs (Stage 1)

6.2.1.1.2. Secondary objectives:

- To assess the proportion of subjects with GT-1 with
  - rapid virologic response (RVR) defined as undetectable HCV RNA at Week 4 (Stage 1)

- complete early virologic response (cEVR) defined as undetectable HCV RNA at Week 12 (Stage 2 only)
- early virologic response (EVR) defined as ≥2 $\log_{10}$ decrease in HCV RNA from baseline or HCV RNA < LOQ at Week 12 (Stage 1)
- 12 week sustained virologic response (SVR12) defined as undetectable HCV RNA at follow up Week 12 (Stage 1 and 2)
- SVR24 (Stage 1 only)

- To describe resistant variants associated with virologic failure (Stage 1 and 2)

6.2.1.1.3. Other outcomes:

- To explore the relationship between antiviral activity endpoints and single nucleotide polymorphisms (SNPs) in genes encoding proteins of the IFNλ family (IL-28A, IL-28B, IL-29)
- To describe the relationship between antiviral activity endpoints and the duration of triple therapy (12W ASV plus 12W placebo versus 24W ASV) for subjects with HCV GT-1 on 24-week ASV regimens (Stage 2 only)
- To evaluate antiviral activity endpoints for subjects with HCV GT-4 (Stage 2 only)
- To describe the PK of ASV, RBV, and pegIFNα (Stage 1 and Stage 2)

6.2.1.1.4. Inclusion and exclusion criteria

Adult men and women aged 18 to 70 years with chronic HCV GT-1 and GT-4 (Stage 2 only) who had not received prior treatment with pegINFα and RBV or other agents with anti-HCV activity, and who did not exhibit human immunodeficiency virus or hepatitis B virus co-infection or advanced liver disease.

6.2.1.2. Study treatments

The dose administered in this study was 200 mg BD using the tablet formulation. The tablet formulation was found to be approximately equal to 100 mg BD of the soft gel capsule in Study AI447-024.

Stage 1: Subjects were initially administered ASV tablets at the following doses: 200 BD, 600 mg BD or 600 mg QD. After a protocol amendment the remaining subjects on treatment who were receiving 600 mg BD or QD had their dose reduced to 200 mg BD. Treatment was for total of 48 weeks.

Stage 2: Subjects were administered ASV 200 mg tablets BD for 48 weeks in addition to:

- PegIFNα: All subjects self-administered 180 mcg/0.5 ml pegIFNα by subcutaneous injection once weekly throughout the entire dosing period. On Day 1, pegIFNα was administered prior to ASV/placebo and RBV
- RBV: All subjects took RBV BD with food. For subjects weighing < 75 kg the total dose was 1000 mg/day and for those weighing ≥ 75 kg the dose was 1200 mg/day. Therefore, subjects took either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) in the morning with food and 600 mg (3 tablets) in the evening with food.

6.2.1.2.1. Efficacy and safety variables and outcomes

The primary efficacy outcomes were the proportion of subjects with eRVR, defined as undetectable at both Week 4 and 12 and the SVR24. Other efficacy outcomes included: RVR at Week 4; cEVR at Week 12 and SVR12. The primary safety outcomes were the frequency of AEs and discontinuations due to AEs (Stage 1 and 2). Other safety outcomes included deaths, SAEs, Grade 3 and 4 AEs, Grade 2 to 4 related AEs and Grade 3 to 4 laboratory abnormalities.

6.2.1.2.2. Randomisation and blinding methods

In Stage 1 subjects were randomised 1:1:1:1 to receive the three doses of ASV or placebo. In Stage 2 subjects were randomised 3:1. Randomisation was via an Interactive Voice Response System. Randomised treatment assignment was double-blind and placebo-controlled for ASV.

6.2.1.2.3. Analysis populations

- Treated subjects were randomised subjects who received at least 1 dose of study therapy (ASV, pegIFNα, or RBV). This cohort was used to assess all data domains.
- Follow-up subjects were treated subjects who completed the follow-up period (48-week). This cohort was used to assess safety in follow-up.

6.2.1.2.4. Sample size

The sample size for Stage 1 was not selected on the basis of power, but rather to provide information on the safety and antiviral activity of ASV in combination with pegIFNα/RBV. A target sample size of 12 treated subjects could detect, with 80% probability, a safety event that occurs at an incidence rate of 13%. This was considered acceptable given that in the published 24-week and 48-week pegIFNα/RBV regimens investigated by Hadziyannis et al[13] the study discontinuation rates due to AEs or laboratory abnormalities were 5% and 15%, respectively.

For the efficacy targets, sample sizes of 168 subjects with HCV GT-1 on the ASV treatment regimen and 56 subjects on the placebo regimen provided 87% power to infer that ASV/pegIFNα/RBV is 35% greater than placebo/pegIFNα/RBV, as assessed by the proportion of subjects with eRVR. The eRVR rate for pegIFNα/RBV was expected to be at most 15%.

6.2.1.2.5. Statistical methods

Categorical variables were summarised with counts and percents. Continuous variables were summarised with univariate statistics (for example, mean, median, standard error).

6.2.1.2.6. Participant flow

Table 4A: Study AI447016: Participant flow End of Treatment Period – Stage 1 – treated subjects

	ASV 200 mg BD	ASV 600 mg BD	ASV 600 mg QD	PBO	Total
Subjects	12	12	12	11	47
Subjects completing the period [1] (%)	10 (83.3)	9 (75.0)	10 (83.3)	6 (54.5)	35 (74.5)
Subjects not completing the period [1] (%)	2 (16.7)	3 (25.0)	2 (16.7)	5 (45.5)	12 (25.5)
Reason for not completing the period [1] (%)					
Lack of efficacy	0	0	0	2 (18.2)	2 (4.3)

	ASV 200 mg BD	ASV 600 mg BD	ASV 600 mg QD	PBO	Total
adverse event	0	1 (8.3)	2 (16.7)	1 (9.1)	4 (8.5)
Lost to follow-up	0	1 (8.3)	0	1 (9.1)	2 (4.3)
Poor/non-compliance	0	0	0	1 (9.1)	1 (2.1)
Subject request to discontinue study treatment	2 (16.7)	1 (8.3)	0	0	3 (6.4)
Subjects continuing in the study (%)	11 (91.7)	10 (83.3)	12 (100.0)	9 (81.8)	42 (89.4)
Subjects not continuing in the study (%)	1 (8.3)	2 (16.7)	0	2 (18.2)	5 (10.6)
Reason for not continuing in the study (%)					
Adverse event	0	1 (8.3)	0	0	1 (2.1)
Lost to follow-up	0	1 (8.3)	0	1 (9.1)	2 (4.3)
Poor/non-compliance	0	0	0	1 (9.1)	1 (2.1)
Subject request to discontinue study treatment	1 (8.3)	0	0	0	1 (2.1)

[1] Subjects completing or not completing the on-treatment period; 2 Subjects who continued into or did not continue the follow-up period.

Table 4B: End of treatment period – Stage 2 – Treated subjects

	ASV 200 mg BD	PBO	Total
Subjects	177	61	238
Subjects completing the period [1] (%)	153 (86.4)	41	194

	ASV 200 mg BD	PBO	Total
		(67.2)	(81.5)
Subjects not completing the period [1] (%)	24 (13.6)	20 (32.8)	44 (18.5)
Reason for not completing the period [1] (%)			
Lack of efficacy	7 (4.0)	11 (18.0)	18 (7.6)
Adverse event	10 (5.7)	3 (4.9)	13 (5.5)
Subject withdrew consent	2 (1.1)	1 (1.6)	3 (1.3)
Death	1 (0.6)	0	1 (0.4)
Lost to follow-up	1(0.6)	1 (1.6)	2 (0.8)
Subject no longer meets study criteria	1 (0.6)	0	1 (0.4)
Subject request to discontinue study treatment	1 (0.6)	1 (1.6)	2 (0.8)
Other	1 (0.6)	1 (1.6)	2 (0.8)
Completed 24-week treament period only	0	2 (3.3)	2 (0.8)
Subjects continuing in the study [2] (%)	172 (97.2)	57 (93.4)	229 (96.2)
Subjects not continuing in the study (%) [2]	5 (2.8)	4 (6.6)	9 (3.8)
Reason for not continuing in the study (%) [2]			
Lack of efficacy	1 (0.6)	1 (1.6)	2 (0.8)
Subject withdrew consent	2 (1.1)	1 (1.6)	3 (1.3)
Lost to follow up	1 (0.6)	1 (1.6)	2 (0.8)
Other	1 (0.6)	1 (1.6)	2 (0.8)

[1] Subjects completing or not completing the on-treatment period; [2] Subjects who continued into or did not continue the follow-up period.

Table 4C: End of treatment period – Stage 2 – Genotype 1

	ASV 200 mg BD	PBO	Total
Subjects	159	54	213
Subjects completing the period [1] (%)	137 (86.2)	37 (68.5)	174 (81.7)
Subjects not completing the period [1] (%)	22 (13.8)	17 (31.5)	39 (18.3)
Reason for not completing the period [1] (%)			
Lack of efficacy	6 (3.8)	9 (16.7)	15 (7.0)
Adverse event	9 (5.7)	3 (5.6)	12 (5.6)
Subject withdrew consent	2 (1.3)	1 (1.9)	3 (1.4)
Death	1 (0.6)	0	1 (0.5)
Lost to follow-up	1 (0.6)	1 (19)	2 (0.9)
Subject no longer meets study criteria	1 (0.6)	0	1 (0.5)
Subject request to discontinue study treatment	1 (0.6)	1 (1.9)	2 (0.9)
Other	1 (0.6)	1 (1.9)	2 (0.9)
Completed 24-wk trt period only	0	1 (1.9)	1 (0.5)
Subjects continuing in the study [2] (%)	154 (96.9)	50 (92.6)	204 (95.8)
Subjects not continuing in the study (%) [2]	5 (3.1)	4 (7.4)	9 (4.2)
Reason for not continuing in the study (%) [2]			
Lack of efficacy	1 (0.6)	1 (1.9)	2 (0.9)
Subject withdrew consent	2 (1.3)	1 (1.9)	3 (1.4)
Lost to follow up	1 (0.6)	1 (1.9)	2 (0.9)
Other	1 (0.6)	1 (1.9)	2 (0.9)

[1] Subjects completing or not completing the on-treatment period; [2] Subjects who continued into or did not continue the follow-up period.

Table 4D: End of treatment period – Stage 2 – Genotype 4

	ASV 200 mg BD	PBO	Total
Subjects	18	7	25
Subjects completing the period [1] (%)	16 (88.9)	4 (57.1)	20 (80.0)
Subjects not completing the period [1] (%)	2 (11.1)	3 (42.9)	5 (20.0)
Reason for not completing the period (%)			
Lack of efficacy	1 (5.6)	2 (28.6)	3 (12.0)
Adverse event	1 (5.6)	0	1 (4.0)
Completed 24-wk treatment period only	0	1 (14.3)	1 (4.0)
Subjects continuing in the study [2] (%)	18 (100.0)	7 (100.0)	25 (100.0)
Subjects not continuing in the study [2] (%)	0	0	0

[1] Subjects completing or not completing the on-treatment period; [2] Subjects who continued into or did not continue the follow-up period.

6.2.1.2.7. Major protocol violations/deviations

In Stage 1, 4 subjects had dose interruptions of ASV or pegIFNα for 1 to 41 days. In 1 subject this was due to AE of low absolute neutrophil count. In Stage 2 a total of 42 subjects: [ASV group: 30 (16.9%), Placebo (pegIFNα/RBV only) group: 12 (19.7%)] had protocol violations mostly due to taking prohibited concomitant medications. Overall, the protocol deviations were not major in nature and were not considered to have had a significant effect on the study results or conclusions.

6.2.1.2.8. Baseline data

In Stage 1 the demographic and HCV disease characteristics were balanced between the ASV and placebo groups.

In Stage 2 the majority of subjects (64.3%) were male (111/177 ASV group, and 42/61 placebo group). The mean age for all subjects was 47.7 years and 95.8% of subjects were aged 21 to < 65 years (168/177 ASV group and 60/61 placebo group). Most treated subjects were White (83.6%), and 8.4% were Black/African American.

6.2.1.3. Results for the efficacy outcomes

6.2.1.3.1. Stage 1

Based on modified intention-to-treat (mITT) analyses for Stage 1:

- ASV at 200 mg BD, 600 mg BD, and 600 mg QD in combination with pegIFNα/RBV demonstrated rapid antiviral activity.
- A high proportion of subjects who received 200 mg BD, 600 mg BD, and 600 mg QD achieved eRVR and were treated with only 24 weeks of therapy. All subjects in the 600-mg QD ASV/pegIFNα/RBV group who achieved eRVR subsequently achieved the numerically highest SVR24 rate of all ASV/pegIFNα/RBV groups.
- The SVR24 rate for subjects who received 200 mg BD, 600 mg BD, or 600 mg QD (ASV/pegIFNα/RBV) groups was numerically higher than the SVR24 rates for subjects administered pegIFNα/RBV therapy alone. Most virologic failures in the ASV-treated subjects were due to relapse.
- More subjects administered pegIFNα/RBV therapy alone experienced virologic failure than subjects during ASV therapy in combination with pegIFNα/RBV.
- Although small numbers of subjects were included in Stage 1, differences were noted among subjects with CC versus CT/TT (GT-1 and -4) genotype for placebo (pegIFNα/RBV only) but not for ASV/pegIFNα/RBV.

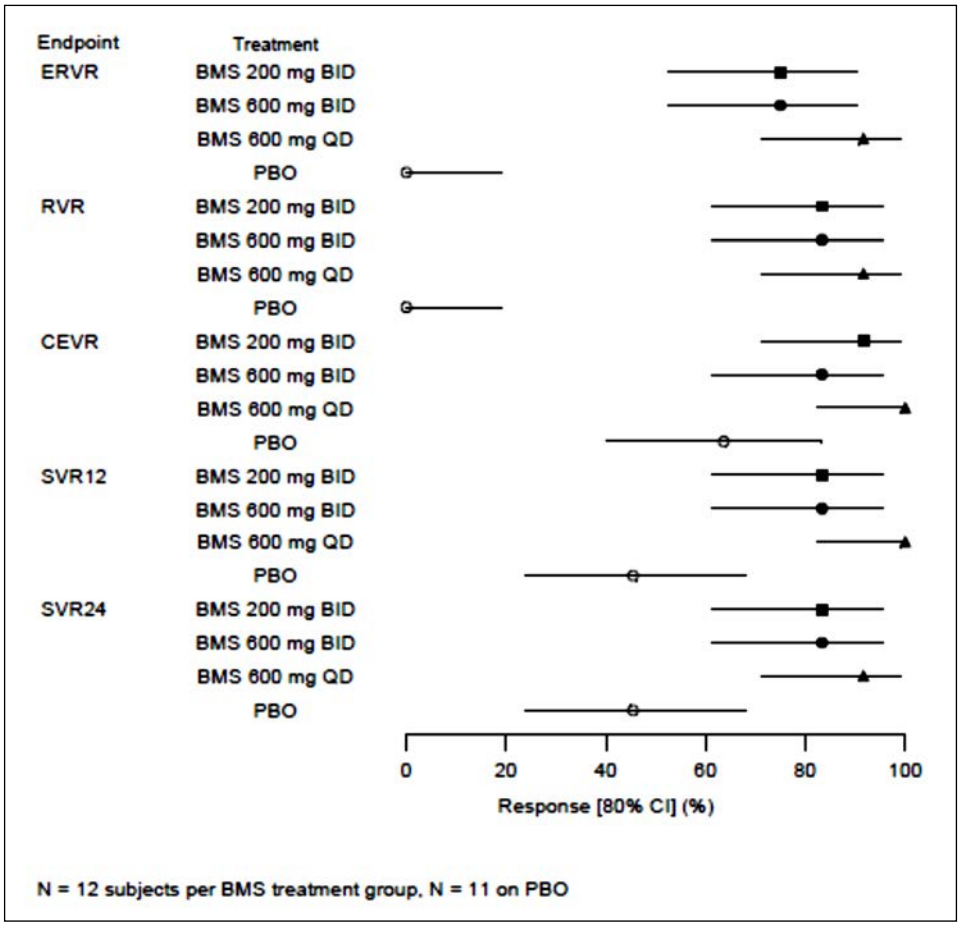
Table 5: Study AI447016: Summary of Primary and Secondary Efficacy Endpoints, Stage 1 Modified Intent-to-Treat Analysis, Roche Assay - Treated Subjects with Genotype-1

	Number of Subjects (%)			
	200 mg BD ASV (N = 12)	600 mg BD ASV (N = 12)	600 mg QD ASV (N = 12)	Placebo (N = 11)
Primary Antiviral Endpoint				
eRVR Responder (%)	9/12 (75.0)	9/12 (75.0)	11/12 (91.7)	0/11
80% CI	(52.5, 90.4)	(52.5, 90.4)	(71.3, 99.1)	(0.0, 18.9)
Secondary Antiviral Endpoint				
RVR Responder (%)	10/12 (83.3)	10/12 (83.3)	11/12 (91.7)	0/11
80% CI	(61.4, 95.5)	(61.4, 95.5)	(71.3, 99.1)	(0.0, 18.9)
EVR Responder (%)	12/12 (100.0)	11/12 (91.7)	12/12 (100.0)	11/11 (100.0)
80% CI	(82.5, 100.0)	(71.3, 99.1)	(82.5, 100.0)	(81.1, 100.0)

	Number of Subjects (%)			
	200 mg BD ASV (N = 12)	600 mg BD ASV (N = 12)	600 mg QD ASV (N = 12)	Placebo (N = 11)
cEVR Responder (%)	11/12 (91.7)	10/12 (83.3)	12/12 (100.0)	7/11 (63.6)
80% CI	(71.3, 99.1)	(61.4, 95.5)	(82.5, 100.0)	(40.1, 83.1)
EOTR Responder (%)	11/12 (91.7)	11/12 (91.7)	11/12 (91.7)	6/11 (54.5)
80% CI	(71.3, 99.1)	(71.3, 99.1)	(71.3, 99.1)	(31.8, 75.9)
SVR4 Responder (%)	11/12 (91.7)	9/12 (75.0)	10/12 (83.3)	
80% CI	(71.3, 99.1)	(52.5, 90.4)	(61.4, 95.5)	(24.1, 68.2)
SVR12 Responder (%)	10/12 (83.3)	10/12 (83.3)	12/12 (100.0)	5/11 (45.5)
80% CI	(61.4, 95.5)	(61.4, 95.5)	(82.5, 100.0)	(24.1, 68.2)
SVR24 Responder (%)	10/12 (83.3)	10/12 (83.3)	11/12 (91.7)	5/11 (45.5)
80% CI	(61.4, 95.5)	(61.4, 95.5)	(71.3, 99.1)	(24.1, 68.2)
Virologic Failure [a] (Treated Subjects)	3 (25.0)	2 (16.7)	3 (25.0)	7 (63.6)
Virologic failure, on-treatment	1 (8.3)	1 (8.3)	1 (8.3)	5 (45.5)
Relapse	2 (16.7)	1 (8.3)	2 (16.7)	2 (18.2)

a Virologic failure is defined as 1) virologic breakthrough, 2) < 1 log10 decrease in HCV RNA from baseline at Week 4 of treatment, 3) failure to achieve EVR, 4) detectable HCV RNA at Week 12 and HCV RNA ≥ LOQ at Week 24 of treatment, 5) detectable HCV RNA at End of Treatment (EOT) including early discontinuation, or 6) relapse, categorised by the earliest virologic failure event in the study.

Figure 2: Study AI447016: Undetectable HCV RNA Endpoints, Stage 1 - Modified ITT - Treated Subjects



6.2.1.3.2. Stage 2

Genotype I group

In subjects with GT-1, virologic response rates during treatment and SVR rates during follow-up in the ASV group (ASV/pegIFNα/RBV) were numerically higher than those in the placebo (pegIFNα/RBV only) group:

- Subjects with GT-1 exhibited greater early virology response than placebo in inducing eRVR. Extended RVR rates were numerically higher in the ASV treatment groups (66.7%) compared with the placebo group (5.6%).
- The rates for SVR24 were also numerically higher for the ASV group (63.5%) compared with the placebo group (44.4%).

ASV-treated subjects who achieved a PDR (HCV RNA < LOQ at Week 4 and undetectable HCV RNA at Week 10) in both of these groups had a 66.7% to 73.1% chance of achieving SVR24. The 12W plus 12W placebo group demonstrated a slightly higher response (73.1%) at SVR24 than the 24W ASV group (66.7%).

Concordance (defined as [number of responders at both time points + number of non-responders at both time points] divided by total number of subjects with non-missing data at both time points) between SVR12 with SVR24 for subjects with GT-1, based on the criteria HCV RNA < LLOQ, target not detected (TND) or target detected (TD), was 97.1% and 97.6% in the ASV and placebo groups, respectively.

Virologic failure on-treatment was more frequent in the placebo group (12 [22.2%]) than the ASV group (16 [10.1%] subjects). Virologic failures on-treatment in the ASV group included virologic breakthrough (VBT) (6.3%) or detectable HCV RNA at end of treatment (EOT) (3.8%).

In the placebo group, virologic failure was due to < 1 $\log_{10}$ HCV RNA decrease from baseline at Week 4 (11.1%), failure to achieve EVR (5.6%), or detectable HCV RNA at Week 12 and HCV RNA ≥ LOQ at Week 24 (5.6%). A greater number of subjects (14 [53.8%]) in the 12W ASV plus 36W placebo group had virologic failure than the 24W ASV and 12W ASV plus 12W placebo groups (17 [25.8%] and 17 [25.4%], respectively).

Based on the SVR24 outcomes analysis, 58 (36.5%) subjects in the ASV group and 30 (55.6%) in the placebo group had virologic failure. Relapse rates (among subjects who had HCV RNA < LLOQ, TND at EOT) were 18.4% (26/141) in the ASV group and 30.2% (13/43) in the placebo group. In Stage 2, 6.3% (10/159) subjects had VBT in the ASV group; no subject in the placebo group had VBT.

ASV demonstrated efficacy in all subgroups of subjects with GT-1:

- SVR24 rates were higher in subjects without baseline cirrhosis compared with subjects with baseline cirrhosis
- SVR24 rates were higher in subjects with GT-1b compared with GT-1a

The results for GT-1 are presented in the table below.

Table 6: Study AI447016: Summary of primary and secondary efficacy endpoints – Stage 2: MITT analysis: Treated subjects – GT-1

	Number of Subjects (%)					
	Genotype-1		Genotype-1a		Genotype-1b	
	200 ASV (N = 159)	Placebo (N = 54)	200 ASV (N = 94)	Placebo (N = 28)	200 ASV (N = 63)	Placebo (N = 25)
Primary Antiviral Endpoint						
eRVR Responder (%)	106/159 (66.7)	3/54 (5.6)	56/94 (59.6)	1/28 (3.6)	48/63 (76.2)	2/25 (8.0)
80% CI	(61.9, 71.5)	(1.6, 9.6)	(53.1, 66.1)	(0.0, 8.1)	(69.3, 83.1)	(1.0, 15.0)
Secondary Antiviral Endpoint						
RVR Responder (%)	118/159 (74.2) [b]	3/54 (5.6)	65/94 (69.1)	1/28 (3.6)	51/63 (81.0) [b]	2/25 (8.0)
80% CI	(69.8, 78.7)	(1.6, 9.6)	(63.0, 75.3)	(0.0, 8.1)	(74.6, 87.3)	(1.0, 15.0)
cEVR Responder (%)	135/159 (84.9) [b]	28/54 (51.9)	76/94 (80.9)	14/28 (50.0)	57/63 (90.5) [b]	14/25 (56.0)
80% CI	(81.3, 88.5)	(43.1, 60.6)	(75.7, 86.1)	(37.9, 62.1)	(85.7, 95.2)	(43.3, 68.7)
PDR Responder (%)	139/159 (87.4)	8/54 (14.8)	80/94 (85.1)	4/28 (14.3)	57/63 (90.5) [b]	4/25 (16.0)
80% CI	(84.1, 90.8)	(8.6, 21.0)	(80.4, 89.8)	(5.8, 22.8)	(85.7, 95.2)	(6.6, 25.4)
EOTR Responder (%)	141/159	43/54	81/94	22/28 (78.6)	58/63	20/25 (80.0)

	Number of Subjects (%)					
	Genotype-1		Genotype-1a		Genotype-1b	
	200 ASV (N = 159)	Placebo (N = 54)	200 ASV (N = 94)	Placebo (N = 28)	200 ASV (N = 63)	Placebo (N = 25)
	(88.7)	(79.6)	(86.2)		(92.1) [b]	
80% CI	(85.5, 91.9)	(72.6, 86.7)	(81.6, 90.7)	(68.6, 88.5)	(87.7, 96.4)	(69.7, 90.3)
SVR4Responder (%)	120/159 (75.5) [b,]	30/54 (55.6)	66/94 (70.2) [c]	14/28 (50.0)	52/63 (82.5) [b]	16/25 (64.0)
80% CI	(71.1, 79.8)	(46.9, 64.2)	(64.2, 76.3)	(37.9, 62.1)	(76.4, 88.7)	(51.7, 76.3)
SVR12Responder (%)	114/159 (71.7)	28/54 (51.9)	66/94 (70.2)	14/28 (50.0)	46/63 (73.0)	14/25 (56.0)
80% CI	(67.1, 76.3)	(43.1, 60.6)	(64.2, 76.3)	(37.9, 62.1)	(65.8, 80.2)	(43.3, 68.7)
SVR24 [e] Responder (%)	101/159 (63.5) [b,c]	24/54 (44.4)	55/94 (58.5)	10/28 (35.7)	45/63 (71.4)[b]	14/25 (56.0)
80% CI	(58.6, 68.4)	(35.8, 53.1)	(52.0, 65.0)	(24.1, 47.3)	(64.1, 78.7)	(43.3, 68.7)
Virologic Failure [f] (Treated Subjects)	48 (30.2)	27 (50.0)	30 (31.9)	16 (57.1)	17 (27.0)	10 (40.0)
Virologic failure, on-treatment	16 (10.1)	12 (22.0)	13 (13.8)	6 (21.4)	3 (4.8)	6 (24.0)
VBT	10 (6.3)	0	8 (8.5)	0	2 (3.2)	0
Relapse [g]	32 (20.1)	15 (27.8)	17 (18.1)	10 (35.7)	14 (22.2)	4 (16.0)

	Number of Subjects (%)					
	Genotype-1		Genotype-1a		Genotype-1b	
	200 ASV (N = 159)	Placebo (N = 54)	200 ASV (N = 94)	Placebo (N = 28)	200 ASV (N = 63)	Placebo (N = 25)
Relapse Rate [h]	32/141 (22.7)	15/43 (34.9)	17/81 (21.0)	10/22 (45.5)	14/58 (24.1)	4/20 (20.0)

a One genotype missing; b After database lock, 1 subject was identified as a potential eRVR, RVR, cEVR, PDR, EOTR, SVR4, SVR12, and SVR24 responder; c After database lock, 1 subject was identified as a potential SVR4, SVR12, and SVR24 responder; d The numerator is based on subjects meeting the response criteria; e The numerator is based on subjects meeting the response criteria; The denominator is based on all treated subjects; f Virologic failure is defined as 1) virologic breakthrough, 2) < 1 log10 decrease in HCV RNA from baseline at Week 4 of treatment, 3) failure to achieve EVR, 4) detectable HCV RNA at Week 12 and HCV RNA □LOQ at Week 24 of treatment, 5) detectable HCV RNA at EOT including early discontinuation, or 6) relapse, categorised by the earliest virologic failure event in the study; g Based on all treated subjects (modified ITT approach) as the denominator; h Based on the number of subjects with HCV RNA < LLOQ, TND at EOT as the denominator

Genotype 4 group

In subjects with GT-4, virologic response rates during treatment and SVR rates during follow-up in the ASV group (ASV/pegIFNα/RBV) were higher than in the placebo (pegIFNα/RBV only) group:

- Subjects with GT-4 exhibited greater early virology response than placebo in inducing eRVR. Extended RVR rates were numerically higher in the ASV treatment groups (88.9%) compared with the placebo group (0%)
- The rates for SVR24 were also numerically higher for the ASV group (88.9%) compared with the placebo group (42.9%)

Concordance between SVR12 with SVR24 for subjects with GT-4 (based on the criteria HCV RNA < LLOQ, TND or TD) was 100.0% in both ASV and placebo groups, respectively.

Virologic failure on-treatment was more frequent in the placebo group (4 [57.1%]) compared with the ASV group (2 [11.1%]) for subjects with GT-4. Both virologic failures on-treatment in the ASV group were detectable HCV RNA at EOT; in the placebo group, virologic failure was due to virologic breakthrough (14.3%), < 1 $\log_{10}$ HCV RNA decrease from baseline at Week 4 (28.6%), or detectable HCV RNA at Week 12 and HCV RNA ≥ LOQ at Week 24 (14.3%).

The results for GT-4 are presented in the table below.

Table 7: Study AI447016: Summary of primary and secondary efficacy end points – Stage 2: mITT analysis – Treated subjects with GT-4

	Number of Subjects (%)	
	200 ASV (N = 18)	Placebo (N = 7)
Primary Antiviral Endpoint		
eRVR Responder (%)	16/18 (88.9)	0/7
80% CI	(79.4, 98.4)	(0.0, 0.0)
Secondary Antiviral Endpoint		
RVR Responder (%)	17/18 (94.4)	1/7 (14.3)
80% CI	(87.5, 100.0)	(0.0, 31.2)
cEVR Responder (%)	17/18 (94.4)	1/7 (14.3)
80% CI	(87.5, 100.0)	(0.0, 31.2)
PDR Responder (%)	15/18 (83.3)	1/7 (14.3)
80% CI	(72.1, 94.6)	(0.0, 31.2)
EOTR Responder (%)	16/18 (88.9)	4/7 (57.1)
80% CI	(79.4, 98.4)	(33.2, 81.1)
SVR4Responder (%)	15/18 (83.3)	3/7 (42.9)

	Number of Subjects (%)	
	200 ASV (N = 18)	Placebo (N = 7)
80% CI	(72.1, 94.6)	(18.9, 66.8)
SVR12 [a] Responder (%)	14/18 (77.8)	2/7 (28.6)
80% CI	(65.2, 90.3)	(6.7, 50.5)
SVR24 [b] Responder (%)	16/18 (88.9)	3/7 (42.9)
80% CI	(79.4, 98.4)	(18.9, 66.8)
Virologic Failure [c] (Treated Subjects)	3 (16.7)	5 (71.4)
Virologic failure, on-treatment	2 (11.1)	4 (57.1)
VBT	0	1 (14.3)
Relapse	1 (5.6)	1 (14.3)
Relapse Rate	1/16 (6.3)	1/4 (25.0)

a The numerator is based on subjects meeting the response criteria; b The numerator is based on subjects meeting the response criteria. The denominator is based on all treated subjects; c Virologic failure is defined as 1) virologic breakthrough, 2) < 1 log10 decrease in HCV. RNA from baseline at Week 4 of treatment, 3) failure to achieve EVR, 4) detectable HCV RNA at Week 12 and HCV RNA ≥ LOQ at Week 24 of treatment, 5) detectable HCV RNA at EOT including early discontinuation, or 6) relapse, categorised by the earliest virologic failure event in the study; d Based on all treated subjects (modified ITT approach) as the denominator; e Based on the number of subjects with HCV RNA < LLOQ, TND at EOT as the denominator

6.2.2. Results for the safety outcomes

6.2.2.1. Stage 1

6.2.2.1.1. Adverse events

On-treatment AEs (all grades) were reported in 100% of subjects in each treatment group in Stage 1. The most frequently (≥ 35% in any group) reported AEs in all treatment groups were fatigue, diarrhoea, headache, influenza like illness, nausea, asthenia, dyspnoea, dry skin, alopecia, insomnia, irritability, alopecia, and arthralgia. Most AEs were Grade 1 or 2 in intensity; no Grade 4 AEs were reported in Stage 1.

Table 8: Study AI447016: Summary of safety on treatment – Stage 1 – treated subjects

ResultsSummary	Number (%) of Subjects			
	200-mg BD ASV (N = 12)	600-mg BD ASV (N = 12)	600-mg QD ASV (N = 12)	Placebo (N = 11)
Deaths	0	0	0	0

ResultsSummary	Number (%) of Subjects			
	200-mg BD ASV (N = 12)	600-mg BD ASV (N = 12)	600-mg QD ASV (N = 12)	Placebo (N = 11)
SAEs on-treatment	2 (16.7)	1 (8.3)	2 (16.7)	0
AEs leading to discontinuation of study drugs	0	1 (8.3)	2 (16.7)	1 (9.1)
Overall AEs on-treatment	12 (100.0)	12 (100.0)	12 (100.0)	11 (100.0)
AEs most frequently reported (≥ 35% in any group)				
Fatigue	6 (50.0)	5 (41.7)	10 (83.3)	5 (45.5)
Diarrhoea	6 (50.0)	6 (50.0)	6 (50.0)	1 (9.1)
Headache	5 (41.7)	3 (25.0)	5 (41.7)	6 (54.5)
Influenza Like Illness	4 (33.3)	3 (25.0)	7 (58.3)	5 (45.5)
Nausea	3 (25.0)	6 (50.0)	4 (33.3)	2 (18.2)
Asthenia	5 (41.7)	4 (33.3)	1 (8.3)	4 (36.4)
Dry Skin	4 (33.3)	2 (16.7)	6 (50.0)	1 (9.1)
Dyspnoea	4 (33.3)	1 (8.3)	5 (41.7)	3 (27.3)
Insomnia	7 (58.3)	2 (16.7)	1 (8.3)	1 (9.1)
Irritability	4 (33.3)	1 (8.3)	2 (16.7)	4 (36.4)
Alopecia	5 (41.7)	2 (16.7)	0	3 (27.3)
Arthralgia	2 (16.7)	1 (8.3)	1 (8.3)	4 (36.4)
AEs; Grade 3 to 4	1 (8.3)	2 (16.7)	4 (33.3)	3 (27.3)
Laboratory abnormalities, Grade 3 to 4				
Neutrophils + bands	3 (25.0)	4 (33.3)	4 (33.3)	2 (18.2)
WBC	0	2 (16.7)	3 (25.0)	1 (9.1)
Lymphocytes	1(8.3)	1(8.3)	3(25.0)	0
ALT	0	1 (8.3)	2 (16.7)	0

ResultsSummary	Number (%) of Subjects			
	200-mg BD ASV (N = 12)	600-mg BD ASV (N = 12)	600-mg QD ASV (N = 12)	Placebo (N = 11)
AST	0	1 (8.3)	2 (16.7)	0
Haemoglobin	0	0	2 (16.7)	1 (9.1)
TBIL	1 (8.3)	1 (8.3)	1 (8.3)	0
Lipase	0	1 (8.3)	0	0
Platelets	0	0	1 (8.3)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; WBC, white blood cell.

6.2.2.1.2. Serious adverse events

- Deaths: There were no deaths reported in Stage 1.
- Other SAEs: 5 subjects reported SAEs, 2 (16.7%) subjects each in the ASV 200 mg BD and ASV 600 mg QD groups and 1 in the ASV 600 mg BD group. No SAEs led to discontinuation of study therapy.

Table 9: Study AI447016: Other serious adverse events. Stage 1 – enrolled subjects

Treatment Group	Preferred Term/Intensity	Relationship to Study Therapy [a]	Onset and Duration	
200-mg BD ASV 54 year old White male	Adenocarcinoma/ Grade 3	Not related	Onset: OT Week 32 Duration: 266 days	Study drug not interrupted, treatment required
50 year old White male	Abdominal Pain/Grade 2	Not related	Onset: OT Week 1 Duration: 8 days	Study drug not interrupted, treatment required
600-mg BD ASV 54 year old Black female	Goitre/Grade 2	Not related	Onset: OT Week 48 Duration: 56 days	Study drug not interrupted, treatment required
600-mg QD ASV 69 year old White male	Hepatocellular injury/Grade 3	Related	Onset: OT Week 6 Duration: 42 days	Study drug not interrupted, treatment not required

Treatment Group	Preferred Term/Intensity	Relationship to Study Therapy [a]	Onset and Duration	
31 year old Black male	Appendicitis/ Grade 3	Not related	Onset: OT Week 24 Duration: 6 days	Study drug interrupted, treatment required

a A determination of relatedness indicates that at least 1 of the 3 drugs (ASV, pegIFNα, or RBV) was considered related to the event; relationship to study therapy as judged by the investigator

6.2.2.1.3. Discontinuations due to AEs

Four subjects discontinued all study drugs (ASV/placebo, pegIFNα, and RBV) due to influenza like illness (1 subject in the 600-mg BD ASV group), asthenia (1 subject in the placebo group), hepatic enzyme increased (1 subject in the 600-mg QD ASV group), and VIIth nerve paralysis (1 subject in the 600-mg QD ASV group).

6.2.2.1.4. Laboratory test abnormalities

The most frequent on-treatment (regardless of baseline or end of treatment toxicity grade) laboratory abnormalities were hematologic and hepatic abnormalities. Grade 3 to 4 anaemia was not reported in any subjects in the 200-mg BD ASV and 600-mg BD ASV groups and in 2 (16.7%), and 1 (9.1%) subjects in the 600-mg QD ASV groups, and placebo group, respectively. No subject in Stage 1 discontinued study drugs due to an anaemia event.

Elevations of alanine aminotransferase (ALT) and total bilirubin (TBIL) were observed in Stage 1 of this study.

- ALT elevations were observed more frequently in the ASV regimen compared with placebo. Overall, Grade 3 to 4 ALT abnormalities through Week 12 were reported for 3 subjects: 1 in the 600-mg BD ASV and 2 in the 600-mg QD ASV groups.
- Grade 3 to 4 TBIL was reported for 1 subject each in the 3 ASV treatment groups (200-mg BD, 600-mg BD, and 600-mg QD).
- After discontinuing therapy, liver function test (LFT) abnormalities returned to normal. In subjects who did not complete the full duration of assigned ASV/placebo dosing, elevated LFTs returned to normal despite continued dosing with pegIFNα/RBV. Subjects that discontinued all study medications also returned to normal.

6.2.2.2. Stage 2

6.2.2.2.1. Adverse events

The most frequently (≥ 35% in any group) reported AEs in all treatment groups were headache, fatigue, asthenia, decreased appetite, and influenza like illness. In the small subgroup with baseline cirrhosis, the frequencies of SAEs, AEs leading to discontinuation, and Grade 3 to 4 AEs were slightly higher compared with the large subgroup of subjects without baseline cirrhosis.

Table 3: Study AI447016: Summary of safety on treatment – Stage 2 – treated subjects

Results Summary	Number (%) of Subjects	
	200 ASV (N = 176)	Placebo (N = 61)
Deaths	2	0
SAEs on-treatment	14 (7.9)	3 (4.9)
AEs leading to discontinuation of study drugs	10 (5.6)	3 (4.9)
Overall AEs on-treatment	173 (97.7)	57 (93.4)
AEs most frequently reported (≥ 35% in any group)		
Headache	66 (37.3)	26 (42.6)
Fatigue	62 (35.0)	26 (42.6)
Asthenia	63 (35.6)	17 (27.9)
Decreased Appetite	43 (24.3)	22 (36.1)
Influenza Like Illness	37 (20.9)	23 (37.7)
AEs: Grade 3 to 4	46 (26.0)	15 (24.6)
Laboratory abnormalities: Grade 3 to 4		
Neutrophils + bands	50 (28.4)	18 (29.5)
WBC	16 (9.1)	9 (14.8)
AST	19 (10.8)	1 (1.6)
ALT	17 (9.7)	1 (1.6)
Lymphocytes	16 (9.1)	5 (8.2)
Haemoglobin	8 (4.5)	3 (4.9)
Platelets	6 (3.4)	3 (4.9)
Lipase	5 (2.8)	0
TBIL	2 (1.1)	2 (3.3)

6.2.2.2.2. Serious adverse events

Deaths: 2 subjects died in the ASV 200 mg BD group, 1 subject on Day 177 on-treatment and 1 subject on Day 254 during follow-up. Both events were not judged by the investigators as related to study therapy:

- A 53 year old White female without baseline cirrhosis treated with ASV 200 mg/pegIFNα/RBV died on Day 177 on-treatment from an event of septic shock associated to Staphylococcus bacteraemia at Day 169 on therapy
- A 41 year old White male without baseline cirrhosis treated with ASV 200 mg/pegIFNα/RBV died on Day 254 during follow-up from multiorgan failure of unknown cause. Past history included cholecystectomy, gastritis and gastroesophagic reflux, and hiatal hernia

Other SAEs: 14 subjects in the 200 ASV group and 3 subjects in the placebo group reported SAEs.

Table 11: Study AI447016: Other SAEs, on treatment period, Stage 2 – enrolled subjects

Subject Age/Race/ Gender	Preferred Term/Intensity	Relation-ship to Study Therapy [a]	Onset and Duration	Notes
200 ASV Group				
51 year old White male	Haematemesis/Grade 4 Melaena/Grade 4	Not related	Onset: OT Week 10 Duration: 38 hours	Study drug interrupted, treatment required
	Upper Gastrointestinal Haemorrhage/Grade 4	Not related	Onset: OT Week 10 Duration: 5 days	Study drug interrupted, treatment required
29 year old White male	ALT Increased/Grade 4	Related	Onset: OT Week 10 Duration: 70 days	peg/RBV continued, ASV discontinued, treatment required
29 year old White male	Neutrophil Count Decreased/Grade 4	Related	Onset: OT Week 16 Duration: continuing	Study drug interrupted, treatment required
42 year old Black female	Abdominal Pain Upper/ Grade 3 Asthenia/Grade 3	Not related	Onset: OT Week 6 Duration: 14 days	Study drug not interrupted, treatment required

Subject Age/Race/ Gender	Preferred Term/Intensity	Relation-ship to Study Therapy [a]	Onset and Duration	Notes
40 year old White female	Acute Psychosis [b] /Grade 2	Related	Onset: OT Week 2 Duration: continuing	Study drug discontinued, treatment required
57 year old White female	Epistaxis/Grade 3	Not related	Onset: OT Week 10 Duration: 48 hours	Study drug interrupted, treatment required
45 year old White male	Chest Pain/Grade 1 Syncope/ Grade 1	Not related	Onset: OT Week 16 Duration: 3 days	Study drug not interrupted, treatment not required
55 year old White female	Bacteraemia/Grade 3 Pyelonephritis/Grade 3 Nephrolithiasis/Grade 3	Related	Onset: OT Week 16 Duration: 6 days	Study drug not interrupted, treatment required
50 year old White male	Urinary Tract Infection/Grade 1	Not related	Onset: OT Week 32 Duration: 2 days	Study drug not interrupted, treatment required
29 year old Egyptian male	Suicide Attempt [b] /Grade 4	Related	Onset: OT Week 4 Duration: 6 days	Study drug discontinued, treatment required
63 year old White male	Dizziness/Grade 3	Not related	Onset: OT Week 6 Duration: 4 days	Study drug not interrupted, treatment required
53 year old White female	Gastritis/Grade 2	Not related	Onset: OT Week 16 Duration: 18.7 hours	Study drug not interrupted, treatment required
55 year old White	Sepsis/Grade 4 Septic Shock/Grade	Not	Onset: OT	Study drug interrupted,

Subject Age/Race/ Gender	Preferred Term/Intensity	Relation-ship to Study Therapy [a]	Onset and Duration	Notes
female	4	related	Week 24 Duration: 5 days	treatment required
53 year old White female	Hyperbilirubinaemia [b]/ Grade 3 ALT Increased [b]/Grade 3 AST Increased [b] /Grade 4	Related	Onset: OT Week 10 Duration: 4 days	Study drug discontinued, treatment not required
Placebo Group				
50 year old White male	Bile Duct Obstruction/Grade 3	Not related	Onset: OT Week 20 Duration: 13 days	Study drug not interrupted, treatment required
48 year old White male	Intervertebral Disc Protrusion/ Grade 3	Not related	Onset: OT Week 48 Duration: 82 days	Study drug not interrupted, treatment required
57 year old White female	Abdominal Pain/Grade 2 Vomiting/Grade 2 Musculoskeletal Pain/ Grade 2	Not related	Onset: OT Week 16 Duration: 2 days	Study drug interrupted, treatment required

a A determination of relatedness indicates that at least 1 of the 3 drugs (ASV, pegIFNα, or RBV) was considered related to the event; relationship to study therapy as judged by the investigator b AE leading to discontinuation.

6.2.2.2.3. Discontinuations due to AEs

13 subjects discontinued (any) study therapy due to AEs, with 12 discontinuing all study drugs (ASV/placebo, pegIFNα, and RBV). AEs leading to discontinuation were reported in a slightly higher proportion of subjects in the ASV group than the placebo group (5.6% vs 4.9%). The types of AEs leading to discontinuation were generally similar across the treatment groups. Each AE leading to discontinuation was reported by 1 subject in either group, except rash (2 subjects [1.1%] in the ASV group).

6.2.2.2.4. Laboratory test abnormalities

The most frequent Grade 3 to 4 laboratory abnormality was neutropenia (28.4% in the ASV/pegIFNα/RBV group versus 29.5% in the placebo group) an expected event with pegIFNα/RBV and balanced across treatment regimens. Most laboratory abnormalities were

Grade 1 to 2 in intensity. No Grade 4 anaemia events were reported in any treatment group and no subject in Stage 2 discontinued study drugs due to an anaemia event.

Elevations of ALT and TBIL were observed in Stage 2:

- Alanine aminotransferase elevations were observed more frequently in the ASV regimen compared with placebo. 72 subjects in the ASV group had normal baseline ALT levels; 21 subsequently had Grade 1 to 2 ALT, and 8 subsequently had Grade 3 to 4 ALT on study. 29 subjects in the placebo group had normal baseline ALT levels; 8 subsequently had on-study Grade 1 to 2 ALT. Overall, Grade 3 to 4 ALT abnormalities on-treatment were reported for 18 subjects: 17 in the ASV group and 1 in the placebo group.
- Grade 3 to 4 TBIL was reported for 2 subjects in the ASV and placebo groups, respectively.
- After discontinuing therapy, LFT abnormalities returned to normal. In subjects who did not complete the full duration of assigned ASV or placebo dosing, elevated LFTs returned to normal despite continued dosing with pegIFNα/RBV. Subjects that discontinued all study medications also returned to normal.

6.3. Discussion: Dosage selection for the pivotal studies

In the DCV/ASV Phase II studies (AI447011: DCV CER: sections 7.1.4 and 7.3.2 and AI447017: DCV CER [AusPAR for Daklinza), the following ASV doses were tested: 200 mg QD (AI447011 only), 200 mg BD, and 600 mg BD. In Study AI447016 presented above in non-Japanese subjects, ASV 200 mg BD, ASV 600 mg QD, and ASV 600 mg BD doses were evaluated. All 3 studies (AI447011, AI447016, and AI447017) were conducted using the tablet formulation of ASV.

Although all Phase II ASV doses (200-mg QD to 600-mg BD of the tablet formulation) were generally well tolerated, a trend in the frequency and magnitude of ALT and AST elevations was observed at ASV doses > 200 mg BD of the tablet formulation and this trend was associated with greater plasma exposure of ASV in an initial exposure-safety assessment conducted using data from the Stage 1 portion of Study AI447016**.** The analysis demonstrated a higher probability of Grade 2 or higher ALT (and AST) elevations with higher plasma exposures of ASV, as measured by AUC.

The dose of 200 mg BD of the tablet formulation was selected as the ASV dose in all on-going and future Phase II studies. The prediction that ASV 200 mg tablet BD offered the best balance of safety and antiviral activity was confirmed by the observed LFT data and high response rates in Phase II studies. The safety and efficacy for DCV/ASV in Japanese subjects in Phase II was comparable, with a similar benefit-risk profile, despite the differences in ASV plasma exposures between Japanese and non-Japanese subjects. No dose adjustment was needed in Japanese subjects.

A 100 mg BD soft gel capsule formulation of ASV was selected as the Phase III formulation based on the results from a relative bioavailability study that indicated the bioavailability for the soft gel capsule formulation was approximately 2 fold higher compared with the ASV Phase II tablet administered with food (Study AI447043). Moreover, the soft gel capsule formulation mitigated the significant food effect observed with the Phase II tablet. Based on these data, the soft gel capsule at a dose of ASV 100 mg BD administered either with or without meals was expected to approximate the AUC of the ASV 200 mg Phase II tablet administered with food in Phase II studies; and, using the prior exposure-response assessments, it was concluded that there would be no meaningful alterations in the antiviral activity or safety profile of ASV at the 100-mg BD dose of soft gel capsule without regard to food.

7. Clinical efficacy

7.1. Treatment of HCV – ASV combined with DCV

Two pivotal and 2 supportive studies were included for this indication. These have been evaluated in the DCV clinical evaluation report. Brief summaries are provided here.

7.1.1. Pivotal efficacy studies

Study **AI447028** (DCV CER [see AusPAR for Daklinza Attachment 2), was a randomised, multicentre, parallel group study with 3 cohorts of subjects with HCV GT-1b infection. The study included treatment naïve subjects (N=203), prior pegIFNα/RBV non-responders (null and partial responders, N=205) and IFN intolerant/ineligible subjects (N=235). Overall 206/643 (32.0%) had compensated cirrhosis at baseline. Subjects in the treatment naïve cohort were randomised 2:1 to receive DCV 60 mg QD and ASV soft gel capsule 100 mg BD for 24 weeks and then followed for 24 weeks post treatment or placebo for 12 weeks (and then enrolled into another study of DCV/ASV open label for 24 weeks). There was no randomisation of the other 2 cohorts (all subjects received DCV 60 mg QD and ASV 100 mg BD).

Study **AI447026** (DCV CER [see AusPAR for Daklinza Attachment 2) was an open label study in 2 groups of Japanese subjects with HCV GT-1b infection. The study included prior pegIFNα/RBV or IFNβ/RBV non-responders (null and partial responders N=87) or IFN intolerant/ineligible subjects (N=135). Overall, 22/222 (9.9%) subjects had compensated cirrhosis at baseline. All subjects were treated with DCV/ASV therapy (DCV 60 mg QD and ASV 100 mg soft gel capsule BD) for 24 weeks and followed for 24 weeks post treatment.

7.1.2. Supportive efficacy studies

Study **AI447017** (see AusPAR for Daklinza Attachment 2) was an open label study in Japanese subjects with HCV GT-1 infection. The study included pegIFNα/RBV prior null responders (N=21) and IFN intolerant/ineligible subjects (N=22). Subjects with baseline cirrhosis were excluded. All subjects received DCV 60 mg QD and ASV 600 mg or 200 mg tablets BD for 24 weeks. Subjects with virologic failure were followed for 48 weeks post treatment and all other subjects were followed for 24 weeks post treatment.

Study **AI447011** (see AusPAR for Daklinza Attachment 2) included groups who received DCV/ASV or QUAD (DCV+ASV+ pegIFNα/RBV) regimens. It was an open label study in pegIFNα/RBV prior null responders (N=122) with HCV GT-1a or 1b. Subjects with cirrhosis were excluded. In the DCV/ASV group, 49 subjects received DCV 60 mg and ASV 600 mg tablet BD (N=11) or 200 mg tablet BD (N=18) or 200 mg tablet QD (N=20). The treatment period was 24 weeks and subjects were then followed for 48 weeks post treatment.

Table 12: Efficacy of DCV/ASV by population - GT-1 and GT-1a and GT-1b

Endpoint [b]	Virologic Response: Number of Subjects (%) [95% CI [a]]			
	Pivotal AI447028 [c]	Pivotal AI447026 [c]	Supportive AI447017 [d, e]	Supportive AI447011 [d, f]
Treatment naïve				
SVR12	184/205 (90.6) [86.6, 94.6]	NA	NA	NA

Endpoint [b]	Virologic Response: Number of Subjects (%) [95% CI [a]]			
	Pivotal AI447028 [c]	Pivotal AI447026 [c]	Supportive AI447017 [d, e]	Supportive AI447011 [d, f]
SVR24	155/203 (76.4) [f]	NA	NA	NA
RVR	168/203 (82.8)	NA	NA	NA
cEVR	191/203 (94.1)	NA	NA	NA
EOTR	189/203 (93.1)	NA	NA	NA
SVR4	181/203 (89.2)	NA	NA	NA
Ineligible/intolerants				
SVR12	194/235 (82.6) [77.7 , 87.4]	119/135 (88.1) [82.7 , 93.6]	14/22 (63.6) [43.5, 83.7]	
SVR24	168/235 (71.5) [g]	118/135 (87.4)	14/22 (63.6)	NA
RVR	159/235 (67.7)	114/135 (84.4)	19/22 (86.4)	NA
cEVR	205/235 (87.2)	125/135 (92.6)	20/22 (90.9)	NA
EOTR	204/235 (86.8)	129/135 (95.6)	19/22 (86.4)	NA
SVR4	198/235 (84.3)	126/135 (93.3)	15/22 (68.2)	NA
Prior non-responders				
SVR12	169/205 (82.4) [77.2 , 87.6]	70/87 (80.5) [72.1, 88.8]	10/11 (90.9) (73.9, 100.0]	15/18 (83.3) [66.1 , 100]
SVR24	152/205 (74.1) [f]	70/87 (80.5)	10/11 (90.9)	16/18 (88.9)

Endpoint [b]	Virologic Response: Number of Subjects (%) [95% CI [a]]			
	Pivotal AI447028 [c]	Pivotal AI447026 [c]	Supportive AI447017 [d, e]	Supportive AI447011 [d, f]
RVR	150/205 (73.2)	53/87 (60.9)	7/11 (63.6)	12/18 (66.7)
cEVR	182/205 (88.8)	77/87 (88.5)	10/11 (90.9)	16/18 (88.9)
EOTR	174/205 (84.9)	76/87 (87.4)	10/11 (90.9)	15/18 (83.3)
SVR4	168/205 (82.0)	81/87 (81.6)	10/11 (90.9)	16/18 (88.9)

a Confidence intervals presented for planned analyses; b On-treatment virologic rates; c Included null and partial responders (all subjects infected with GT-1b); d Includes null responders only; e Subjects in Cohort 2 (prior null responders; N = 11) and Cohort 3/4 (ineligible-naïve/intolerants; N = 22) treated in Expansion Phase of study for 24 weeks at recommended dose; f Subjects in Cohort 1A (prior null responders, N = 18) treated in Expansion Phase of study for 24 weeks at recommended dose; g AI447028 CSR completed for primary endpoint (SVR12). SVR24 rates are based on database as of 22-Nov-2013 in which 83 subjects remained in follow-up.

7.2. Treatment of HCV: ASV+DCV+pegIFNα/RBV: QUAD regimen

7.2.1. Pivotal studies

Study **AI447029** (see AusPAR for Daklinza Attachment 2) was an open label, multicentre study in prior pegIFNα/RBV non responders (null and partial responders) with HCV GT-1 (N=353) or GT-4 (N=44). Overall, 90/397 (22.2%) subjects had compensated cirrhosis at baseline. All subjects were treated with DCV 60 mg QD and ASV 100 mg soft gel capsule BD and pegIFNα/RBV for 24 weeks and then followed for 24 weeks post treatment.

7.2.2. Supportive study

In Study A**I447011** (see AusPAR for Daklinza Attachment 2) the QUAD therapy group comprised 51 subjects who received DCV 60 mg QD QUAD therapy comprising ASV 600 mg tablet BD (N=10) or ASV 200 mg tablet BD (N=20) or ASV 200 mg QD (N=21). The treatment period was 24 weeks and subjects were then followed for 48 weeks post treatment.

Table 13: Efficacy of DCV QUAD regimen by genotype and population

Endpoint	Virologic Response: N (%) [95% CI] [a]	
Non-responders - GT-1	AI447029 (N = 354)	AI447011 (n=20)
SVR12 [b]	330/354 (93.2) [90.6, 95.8]	19/20 (95.0)
SVR24	313/354 (88.4)	18/20 (90.0)

Endpoint	Virologic Response: N (%) [95% CI] [a]	
RVR	292/354 (82.5)	15/20 (75.0)
cEVR	337/354 (95.2)	19/20 (95.0)
EOTR	337/354 (95.2)	18/20 (90.0)
SVR4	334/354 (94.4)	19/20 (95.0)
Non-responders - GT-4	(N = 44)	NA
SVR12 [b]	44/44 (100.0) [100.0, 100.0]	NA
SVR24	42/44 (95.5)	NA
RVR	36/44 (81.8)	NA
cEVR	44/44 (100.0)	NA
EOTR	43/44 (97.7)	NA
SVR4	44/44 (100.0)	NA

Note: Recommended dose represents DCV 60 mg QD and the ASV exposure achieved by using either 200 mg BD tablets or 100 mg. BD soft gel capsules. a RVR, cEVR, EOTR: HCV RNA <LLOQ TND; SVR4, SVR12 and SVR24: HCV RNA <LLOQ TD or TND. Confidence intervals presented for planned analyses. b SVR12 defined as HCV RNA < LLOQ (TD or TND) at follow-up Week 12. Missing follow-up Week 12 HCV RNA imputed using the next available measurement.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled analyses or meta-analyses were provided.

See Section 8.1 and evaluation of DCV (AusPAR for Daklinza Attachment 2) for summary of results for combinations with DCV.

7.4. Evaluator's conclusions on clinical efficacy for combination therapy with DCV

See evaluation of DCV (AusPAR for Daklinza Attachment 2) for summary of results for combinations with DCV.

As ASV is requested to be used only in combination with DCV, the approval of ASV is dependent on the approval of DCV.

For the ASV/DCV regimen and the QUAD regimen the duration of treatment requested is 24 weeks which matches the treatment period in the studies.

7.4.1. ASV/DCV regimen

The SVR12 rates achieved with the DCV/ASV therapy in treatment-naïve HCV GT-1b-infected subjects were 90.6% (95% CI: 86.6, 94.6). This is similar to the SVR rates in patients who were IFN/RBV-based therapy intolerant/ineligible GT-1b in AI447028: 82.6% (95% CI: 77.7, 87.4),

AI447026: 88.1% (95% CI: 82.7, 93.6) and AI447017: 63.6% (95% CI: 43.5, 83.7)(see AusPAR for Daklinza Attachment 2 *Efficacy*).

The SVR12 rates achieved with the DCV/ASV therapy in HCV GT-1b-infected prior non-responders were 82.4% (95% CI: 77.2, 87.6) in Study AI447028, 80.5% (95% CI: 72.1, 88.8) in AI447026, and 83.3% (95% CI: 66.1, 100.0) in AI447011 (see AusPAR for Daklinza Attachment 2 *Efficacy*).

Further:

- In GT-1b prior null responders, the SVR12 rates were 82.4% in AI447028, 81.3% in AI447026 and 83.3% in AI447011 (see AusPAR for Daklinza Attachment 2 *Efficacy*).
- In GT-1b prior partial responders, the SVR12 rates were 82.1% in AI447028 and 77.8% in AI447026 (see AusPAR for Daklinza Attachment 2 *Efficacy*).

Overall, in DCV/ASV-treated subjects, SVR12 rates were comparable across all subgroups of baseline host factors including age (<65 and ≥65 years), gender, cirrhosis status, IL-28B polymorphism, prior treatment history (null or partial response to HCV therapy, or IFN/RBV-based therapy intolerant/ineligible) and viral factors (such as viral load). The rates of VBT were low (4-13%).

7.4.2. QUAD regimen

The SVR12 rates achieved with DCV Quad therapy in:

- GT-1 prior non-responders were 330/354, 93.2% (95% CI: 90.6, 95.8) in AI447029 and 19/20, 95.0% (95% CI: 81.9, 99.5) in AI447011 (see AusPAR for Daklinza Attachment 2 *Efficacy*):
- GT-1 prior null responders, the SVR12 rates were 93.6% in AI447029 to 95.0% in AI447011 (see AusPAR for Daklinza Attachment 2 *Efficacy*)
- GT-1 prior partial responders, the SVR12 rate was 91.7% in AI447029 (see AusPAR for Daklinza Attachment 2 *Efficacy*)
- GT-4 prior non-responders, the SVR12 rate was 44/44, 100.0% (95% CI: 100.0, 100.0) in AI447029 (see AusPAR for Daklinza Attachment 2 *Efficacy.*)

SVR12 rates with DCV QUAD therapy were consistently high across all host factor subgroups (including age, gender, cirrhosis status, IL-28B polymorphism, prior null or partial response to HCV therapy) and viral factors (such as viral load). SVR12 rates with DCV QUAD therapy were minimally affected by baseline NS5A-L31, NS5A-Y93H, and NS3-R155 polymorphisms and not affected by NS3-D168 polymorphisms.

8. Clinical safety

Except for Study AI447016 (the ASV/PegIFNα/RBV combination) the major studies for safety always included ASV used in combination with DCV the safety of ASV and are covered in the DCV evaluation report. The following provides a brief summary of information in the DCV evaluation report. There is also summary information from Study AI447016 which is presented in more detail in *Dosage selection for the pivotal studies* above.

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General AEs were collected at each study visit either by spontaneously reports by the subject or elicited during open-ended questioning, examination or evaluation of a subject.
- AEs of particular interest, including haematological events (especially pancytopenia and neutropenia), LFTs (especially ALT and AST), gastrointestinal events, rash and hypersensitivity, were assessed by conducting specific searches of the AE database.
- Laboratory tests, including standard haematology and clinical chemistry were performed at each study visit.
- ECG, vital signs and physical examination were conducted pre and post treatment and at specified study visits.

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

See separate clinical pharmacology evaluation report.

8.1.4. Other studies evaluable for safety

See section *Dosage selection for the pivotal studies* for details of Study AI447016.

8.2. Pivotal study that assessed safety as a primary outcome

Not applicable.

8.3. Patient exposure

Table 14: Summary of subjects treated with ASV combination regimens at the recommended dose (100 mg capsule BD or 200 mg tablet BD)

	Number of Subjects			
Study Number	DCV/ASV	DCV Quad	ASV/pegIFNα/RBV	Total ASV
Pivotal Studies				
AI447028	645	---	---	645
AI447026	222	---	---	222
AI447029	---	398	---	398
Supportive Studies				
AI447011	18	20	---	38
AI447017	33	---	---	33
Other Studies				
AI447016	---	---	189	189
Total	918	418	189	1,525

Safety data from DCV 60 mg QD in combination with a dose of ASV other than ASV 100 mg BD softgel capsule or ASV 200 mg BD (i.e., ASV at 600 mg BD and ASV at 200 mg QD) are not integrated in the overall by-regimen safety analyses; however, these data are summarised by cohort in this SCS.

Table 15A: Exposure to asunaprevir in clinical studies according to dose and duration DCV/ASV regimen

Study	DCV median dose (range)	ASV median dose (range)	Median duration (weeks)
AI447028 and AI447026	60 mg (51.1 - 80.5 mg)	200 mg* (157.0 - 210.7 mg)	24 (0.3 - 28.7)
AI447017 and AI447011	60 mg (57.0 - 60.0 mg)	400 mg* (346.4 - 400.0 mg)	24 (0.3 - 28.7)

* In studies AI447028 and AI447026 ASV soft gel capsules were used. In studies AI447017 and AI447011 ASV tablets were used – doses are stated to be comparable.

Table 15B: DCV Quad regimen

Study	DCV median dose (range)	ASV median dose (range)	PegIFNα median dose (range)	RBV median dose* (range)	Median duration (Weeks)
AI447029	60 mg (48.6 - 64.9 mg)	200 mg* (100.0 - 203.0 mg)	180 µg (73.8 - 187.5)	1056.7 mg (422.2 - 1200.0)	24.0 (4.0 - 25.0)
AI447011 (Group B1)	60.0 mg (55.5 - 65.9)	400.0 mg† (359.3 - 400.0)	180.0 µg (144.4 - 180.0)	1098.2 mg (717.9 - 1207.1)	23.9 (23.7 - 24.1)

* Capsule formulation. † Tablet formulation

Table 15C:ASV/IFN/RBV regimen

Study	ASV median dose (range)	PegIFNα median dose (range)	RBV median dose* (range)	Median duration (Weeks)
AI447016	400.0 mg* (272.9 - 536.5)	180 µg (105.0 - 187.5)	1084.0 mg (533.7 - 1285.7)	24.0 (0.1 - 68.0)

* Tablet formulation. Studies AI447028, AI447026, AI447029, AI447011 and AI447017: DCV CER (see AusPAR for Daklinza Attachment 2). Study AI447016: section *Dosage selection for the pivotal studies* above

8.4. Summary of safety by dosing regimen

8.4.1. DCV/ASV regimen

- No deaths were reported while taking the DCV/ASV regimen.
- The frequency of treatment related SAEs was low (9 subjects, 1%). Pyrexia (3 subjects, 0.3%) and increased ALT (2 subjects, 0.2%) were the only treatment related SAEs reported in > 1 subject.
- AEs led to discontinuation in 23 (2.5%) subjects and included 6 (2.9%) treatment naïve, 5 (1.6%) non-responder and 12 (3.1%) intolerant/ineligible subjects. AEs leading to discontinuations in > 1 subject were increased ALT (15, 1.6%), increased AST (12, 1.3%), increased bilirubin (3, 0.3%) and increased transaminases (2, 0.2%).
- Most subjects reported an AE (89.6%). The most frequently reported were fatigue, diarrhoea, nasopharyngitis, headache and nausea. Grade 3/4 AEs were reported in 10.2% of subjects.
- 50 (5.4%) subjects reported Grade 3/4 treatment related AEs. The most frequently reported were increased ALT (2.8%) and increased AST (1.9%). The median time to ALT/ASV elevations was approximately 13 weeks.
- 3 cases met the laboratory criteria for pDILI but one subject did not meet the clinical criteria for pDILI due to baseline Gilbert's syndrome.
- Within the treatment naïve cohort the safety profile was similar between those who received DSV/ASV and those who received the placebo control.

8.4.2. DCV QUAD regimen

The safety profile of the DCV Quad regimen (DCV/ASV in combination with pegIFNα/RBV) in HCV GT 1 or 4 subjects who failed previous IFN/RBV-based therapy, was similar to that reported historically with pegIFNα/RBV alone (that is, Grade 3-4 haematologic abnormalities), with the exception of similar elevated transaminase levels as observed in the other ASV studies.

- No deaths were reported on treatment. One death was reported during the follow up Week 12 due to an SAE of Grade 4 pneumonia, which was judged by the investigator as not related to study drug.
- The frequency of treatment related SAEs was low (2.3% in Study AI447029 and 5% in Study AI447011 [see AusPAR for Daklinza Attachment 2 *Efficacy*]). Anaemia was the only treatment related SAE reported in more than 1 subject.
- AEs led to discontinuations in 18 (4.5%) subjects in Study AI447029 and none in Study AI447011 (see AusPAR for Daklinza Attachment 2 *Efficacy*). 7 subjects discontinued due to skin and subcutaneous tissue disorders although none were reported as serious. 1 subject discontinued to the an AE of increased hepatic enzymes.
- The most commonly reported AEs were fatigue, headache, pruritus, asthenia, flu-like symptoms, insomnia, rash, anaemia, cough, dry skin, diarrhoea, nausea, alopecia, irritability, pyrexia, myalgia, neutropenia, dyspnoea, decreased appetite and arthralgia.
- The most frequently reported on treatment Grade 3/4 laboratory abnormalities were haematologic. In the few on treatment Grade 3/4 ALT/AST elevations the median time to onset was approximately 8 weeks and the median time to reversal was approximately 3-4 weeks. 1 subject treated in Study AI447011 met the laboratory criteria for pDILI (see AusPAR for Daklinza Attachment 2 *Efficacy*).

8.4.3. ASV/IFNα/RBV

- 2 subjects died: 1 during the treatment period of sepsis and septic shock due to unknown causes and 1 during the follow up due to multi-organ failure, both judged not related to study drug.
- SAEs were reported in 16 (8.5%) subjects on ASV/IFNα/RBV and 3 (4.2%) on placebo/ IFNα/RBV: those reported by more than 1 patient were increased ALT (2 subjects in ASV/IFNα/RBV) and abdominal pain (1 subjects in each group).
- AEs leading to discontinuation of study drugs were reported in 10 (5.3%) subjects on ASV/IFNα/RBV and 4 (5.6%) on placebo/IFNα/RBV. AEs leading to discontinuation of study drugs were generally similar across the treatments with only rash (ASV/IFNα/RBV) being reported by more than 1 subject.
- The most frequently reported AEs were headache, fatigue, asthenia, decreased appetite, flu-like symptoms, pruritus, insomnia, and rash.
- Grade 3/4 elevations in ALT and AST occurred in 17 (9.0%) and 19 (10.1%) subjects respectively in the ASV/IFNα/RBV vs 1 subject in the placebo/IFNα/RBV group.
- ALT/ASV levels increased in about 10% of subjects approximately 10.5 weeks of treatment and all showed improvement after ASV was either discontinued or interrupted. The median time from elevation to reversal was approximately 2.5 weeks. 16 subjects had reversal of their ALT/AST levels by end of treatment.
- No subject met the pDILI definition and there were no additional signs of liver decompensation associated with Grade 3 or 4 ALT elevations.

8.5. Post-marketing experience

There is no post-marketing experience as the product has not been marketed in any country.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

8.6.1.1. Safety in subjects with cirrhosis

A total of 229 subjects were enrolled with baseline cirrhosis it the DCV/ASV studies, 93 subjects in DCV/ASV Quad regimen studies and 16 in the ASV/peg INF/RBV studies.

- The frequency of SAEs regardless of study drugs was low and similar among subjects with cirrhosis and those without
  - DCV/ASV regimen: 15 (6.6%) with cirrhosis and 41 (6.0%) without cirrhosis
  - DCV/ASV QUAD regimen: 4 (4.3%) with cirrhosis and 18 (5.9%) without cirrhosis
  - ASV/pegIFN/RBV regimen: 3 (18.8%) with cirrhosis and 13 (7.5%) without cirrhosis

8.6.2. Resistance

Genotypic and phenotypic assays were performed in all ASV studies to identify the individual and combinations of substitutions known to confer resistance to specific antiviral agents. The impact to certain baseline NS5A and NS3 polymorphisms and IL-28B (RS12979860) GT on virologic response appeared to be treatment specific. Baseline NS5A polymorphism at L31 and Y93H appeared to be associated with virologic failure in the DCV/ASV therapy in subjects infected with GT-1b, while baseline NS3-D168E appeared to be associated with virologic failure to a lesser extent. The non-CC IL-28B (RS12979860) GT appeared to correlate more with virologic failures in subjects receiving a DAA add on to pegIFNα/RBV therapy. Baseline

polymorphisms had no or minimal impact on SVR in the DCV QUAD regimen (confounded by small numbers of subjects failing treatment).

With the DCV/ASV and the QUAD regimen the majority of subjects with virologic failure who met the criteria for resistance testing had resistance associated substitutions to both DCV and ASV.

Once a subject failed a DCV/ASV regimen. Emergent NS5A RAVs generally persisted in the majority of subjects throughout the duration of the study (follow up Week 48), whereas NS3 RAVs were more likely to be replaced or partially replaced by baseline sequence during this time frame.

8.7. Other safety issues

8.7.1. Safety related to drug-drug interactions and other interactions

See separate clinical pharmacology report.

8.8. Evaluator's overall conclusions on clinical safety

The all-oral therapy of DCV (60 mg QD) in combination with ASV (100 mg BD) has a favourable safety and tolerability profile compared to the currently approved standard therapy regimens in HCV GT-1b subjects who are treatment-naïve, treatment-experienced, or ineligible/intolerant to IFN/RBV-based therapy, including subjects with compensated cirrhosis and the elderly.

The AEs reported for PegIFNα/RBV or TVR or BOC plus pegIFNα/RBV such as haematologic disorders (anaemia, neutropenia and thrombocytopaenia), psychiatric disorders (depression), flu-like symptoms, rash and anorectal disorders) were reported infrequently with the DCV/ASV regimen.

The major AE for the combination is ALT/AST elevations, which appears to be due to both ASV and DCV components. Concurrent (within ±4 weeks of each other) Grade 3/4 ALT and Grade 3/4 AST laboratory abnormalities were reported in 2.9% of DCV/ASV-treated subjects. The events appeared to be easily monitored and readily corrected after cessation of study therapy.

The safety profile of the DCV Quad regimen (DCV/ASV in combination with pegIFNα/RBV) in HCV GT 1 or 4 subjects who failed previous IFN/RBV-based therapy, was similar to that reported historically with pegIFNα/RBV alone (that is, Grade 3-4 haematologic abnormalities and other AEs characteristic of pegIFNα/RBV therapy), with the exception of similar elevated transaminase levels as observed in the other ASV studies.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of asunaprevir in the proposed usage are:

- High rates of SVR12 (and SVR24) in patients infected with HCV GT-1b treated with ASV in combination with DCV treated for 24 weeks:
  - Treatment naïve: 90.6% (184/205)
  - Prior non-responders to pegIFNα or IFNβ/RBV: 80.5% - 90.9%
  - PegIFNα/RBV intolerant/ineligible subjects: 63.6% - 82.6%
- High rates of SVR12 in prior non-responders (partial and null responders) with:

  - GT-1: 93% (330/354) and 95% (19/20)
  - GT-4: 100% (44/44)
- Similar rates were seen across various baseline factors including males and females, patients ≥ 65 and <65 years, with and without cirrhosis and HCV RNA ≥ 800,000 IU/mL and < 800,000 IU/mL and subjects with IL28B and non-CC genotypes
- There were no deaths attributable to ASV and low rates of SAEs, and AEs of increased hepatic transaminases were generally reversible on discontinuation and most patients with increases achieved SVR12

9.2. First round assessment of risks

The risks of asunaprevir in the proposed usage are:

- Increases in hepatic transaminases were reported across all treatment groups
- Increased risk of Grade 3/4 transaminase elevations in combination with DCV

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of asunaprevir, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Based on the clinical efficacy and safety data provided it is recommended that asunaprevir be approved.

11. Clinical questions

Nil.

12. Second round evaluation of clinical data submitted in response to questions

No clinical questions were raised in the first round evaluation. Despite this the sponsor has provided 25 pages of comments on the first round evaluation. Some of the comments are duplicated from those provided for the daclatasvir evaluation (see AusPAR for Daklinza Attachment 2). As these issues were dealt with in that evaluation they have not been repeated in detail here. The sponsor has provided some important new data on the safety of ASV which is relevant to the recommendations in the Product Information.

12.1. Overseas regulatory status

As noted in the daclatasvir evaluation the sponsor withdrew its new drug application for ASV in the USA on 6 October 2014. The decision was not based on any new safety data from the DCV/ASV studies but on a commercial decision that the DCV/ASV regimen would not be competitive in the US marketplace. The sponsor has noted that ASV has been approved in Japan for the treatment of patients with GT-1b CHC with or without compensated cirrhosis, who have failed or are ineligible/intolerant to interferon based therapy. A supplemental application is under review for use in treatment naïve patients.

Applications for the DCV/ASV combination regimen (using the same data package as submitted in Australia) have been submitted to Canada, Taiwan, Korea, Colombia, Chile, Singapore, Russia, Thailand and Israel.

12.2. Safety

The sponsor has provided new information on the safety of ASV in relation to the following:

- A new review of the hepatic safety based on the data in the submission as well as data from studies that were ongoing at the time of the submission
- A new recommendation for ASV dose reduction to once daily dosing for patients with severe renal impairment not receiving haemodialysis based on a new study of a fixed dose combination of DCV/ASV and beclabuvir (Study **AI443110**)

12.2.1. Hepatic safety

Preliminary hepatic safety data are briefly presented for 2 hepatic cases of clinical interest from ongoing studies in the DCV/ASV/BCV (DCV 3DAA) clinical program. The combination regimen includes DCV, a HCV NS5A replication complex inhibitor, ASV, a HCV NS3/4A protease inhibitor, and BCV (BMS-791325), a HCV NS5B thumb 1 nonnucleoside polymerase inhibitor.

Ongoing DCV 3DAA studies include:

- Three global studies conducted in the United States (US), France, Canada, and Australia:
  - **AI443102**: A Phase III, two-cohort (treatment naïve and treatment experienced), open-label two-arm study comparing DCV, ASV, and BCV (DCV/ASV/BCV) administered as a fixed dose combination (FDC) tablet BD versus historical control in 416 randomised subjects with GT-1 HCV infection without cirrhosis. All subjects received DCV/ASV/BCV FDC BD for 12 weeks and were followed for 24 weeks post treatment. GT-1b enrolment was capped at 40%.
  - **AI443113**: A Phase III, two-cohort (treatment naïve and treatment experienced), open-label, four-arm, blinded placebo-controlled RBV study comparing DCV/ASV/BCV FDC BD administered with or without RBV in 202 randomised subjects with GT-1 HCV infection and compensated cirrhosis. All subjects received DCV/ASV/BCV BD with or without RBV for 12 weeks and were followed for 24 weeks post treatment. Enrolment was capped at approximately 40% for GT-1b subjects and at 100 for treatment-experienced subjects.
  - **AI443014**: A Phase II open-label proof of concept study assessing single agent daclatasvir (DCV 60 mg QD or 30 mg BD), in combination with asunaprevir (ASV 200 mg BD), and BMS-791325 75 mg or 150 mg, administered for 12 or 24 weeks in 320 subjects. Subjects had GT-1 (n=299/320) or GT-4 (n=21/320) HCV infection, were treatment-naïve (n=274/320) or null responders to previous pegIFNα/RBV treatment (n=46/320), and were not cirrhotic (n=300/320) or had compensated cirrhosis (n=20/320). All subjects were followed for 48 weeks post treatment.
- One ongoing DCV 3DAA study was conducted in Japan:
  - **AI443117**: A Phase III two-cohort study. Cohort 1 is a double-blind, two-arm comparison of DCV 3DAA for 12 weeks versus DCV/ASV for 24 weeks in treatment-naïve subjects with GT-1b HCV infection (n = 216 planned to be randomized 1:1); GT-1a subjects in Cohort 1 were not randomised but received open-label DCV 3DAA. Cohort 2 is an open-label, single-arm study of DCV 3DAA for 12 weeks in IFN experienced subjects with GT-1a/1b (n = 60) planned). All subjects are to be followed for 24 weeks post treatment. Approximately 20% of compensated cirrhotics were enrolled.

From these ongoing studies2 further cases of pDILI were reported.[5] One patient developed Grade 4 abnormal AST/ALT elevation on Day 43 of treatment but returned to normal with cessation of study drugs. The other patient had study drug ceased on Day 42 when he presented with jaundice and was hospitalised due to hyperbilirubinaemia (Grade 4), AST increased (Grade 4), ALT increased (Grade 4), ALP increased (Grade 1). He experienced clinical signs of hepatic encephalopathy (asterixis) which was resolving but not normal at time of follow up.

The conclusions of the sponsor were:

- *When ASV was combined with DCV ± pegIFNα/RBV), ALT elevations were observed, which are associated with ASV use*
- *In general, these ALT elevations to date have been reversible after study drug has been discontinued*
- *Infrequently, these ALT elevations are associated with increased bilirubin (subjects meeting biochemical criteria for Hy's law or pDILI criteria) without clinical evidence of hepatic decompensation. However, one case of a subject with severe liver injury, who exhibited evidence of hepatic encephalopathy, has been reported among subjects receiving HCV 3DAA (DCV/ASV/BCV); further evaluation of this case is ongoing.*

Given the above, patients receiving DCV/ASV or DCV/ASV/pegIFNα/RBV, should have close monitoring of liver enzymes: at least once every 2 weeks for the initial 12 weeks of treatment, and every 4 weeks thereafter until completion of therapy. Any upward trend in ALT/AST levels warrants more frequent monitoring. If on-treatment elevations in ALT levels 10 times ULN or greater occur, treatment should be discontinued immediately and not be resumed.

It is noted that this recommendation for monitoring is now included in the revised PI.

12.2.2. Renal safety

In the submission and the clinical evaluation report there was no recommendation for dose adjustment in subjects with any degree of renal impairment based on the results of the PK study (**AI447033**) in normal subjects and those with end stage renal disease on dialysis. The sponsor has now provided the synopsis and brief summary of a new study (**AI443110**) of the DCV/ASV/BCV (DCV 3DAA) combination. In this study the effect of renal impairment on the PK of all 3 components was evaluated.

Study **AI443110** was an open label, multi-dose study that assessed the PK of the DCV 3DAA FDC tablet (that is, DCV 30 mg/ASV 200 mg/ BCV 75 mg) administered BD to HCV uninfected subjects with normal renal function and various degrees of renal impairment (normal, mild moderate, severe and ESRD) for 10 to 12 days. The sponsor reports the results as showing:

The PK properties of ASV were studied across a total of 41 subjects with normal renal function (N = 8), mild renal impairment (N = 9), moderate renal impairment (N = 8), severe renal impairment not on haemodialysis (N = 8), and ESRD on haemodialysis (N = 8) groups. Compared with subjects with normal renal function, the Cmax of ASV was estimated to be 29%, 65% and 88% higher, and the AUC of ASV was estimated to be 33%, 76% and 109% higher in subjects with mild, moderate and severe renal impairment, respectively. Asunaprevir unbound Cmax was estimated to be 37%, 87% and 119% higher, and ASV unbound AUC was estimated to be 41%, 99% and 137% higher for subjects with mild, moderate and severe renal impairment, respectively, compared with subjects with normal renal function. Subjects with ESRD requiring haemodialysis had an 11% decrease in ASV Cmax and a 16% decrease in AUC soon after haemodialysis compared with subjects with normal renal function. Asunaprevir unbound Cmax and AUC decreased 2% and 6%, respectively, soon after haemodialysis in subjects with ESRD requiring haemodialysis compared with subjects with normal renal function.

[5] Sponsor clarification: 'There were a total of 2 pDILI cases.'

As a result of this study the sponsor is now recommending that for patients with severe renal impairment (CrCl less than 30 mL/min) who are not receiving haemodialysis, the recommended dose of ASV should be reduced to 100 mg once daily. No dose adjustment of ASV is recommended for those patients with mild or moderate renal impairment (CrCl 30 mL/min or greater) or those receiving haemodialysis.

In light of this new study the sponsor's recommendation for the dose reduction is supported.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly the benefits of asunaprevir are unchanged from those identified in the First round evaluation.

13.2. Second round assessment of benefit-risk balance

No new clinical information was submitted in response to questions. New information was provided on the safety of asunaprevir. After consideration of this new data the risks of asunaprevir are unchanged from those identified in the First round evaluation.

14. Second round recommendation regarding authorisation

Based on the review of the new information provided by the sponsor in response to the First round evaluation the recommendation is unchanged from that stated the First round evaluation, that is, asunaprevir is recommended for approval as requested by the sponsor:

Table 16: Recommended Regimens for Sunvepra 100 mg Twice Daily Combination Therapy

HCV Genotype[a]	Treatment	Duration
Genotype 1b	Sunvepra and Daklinza	24 weeks
Genotype 1 and 4	Sunvepra, Daklinza, peginterferon alfa, and ribavirin	24 weeks

a Treatment-naïve or failed prior treatment with peginterferon alfa/ribavirin

This approval matches the recommended approval for daclatasvir (see AusPAR for Daklinza).

15. References

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