A Post-Authorisation Safety Study (PASS) Protocol

DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy

Study sites participating in TARGET-HCC may participate in DAA-PASS to investigate the impact of exposure to direct-acting antivirals (DAAs) on early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients following successful HCC treatment interventions.

PASS information

Title	DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy
Protocol version identifier	Version 6.0
Date of last version of protocol	22 November 2021
EU PAS register number	EUPAS22896
Active substance	Refer to Annex 3 for details
Medicinal product	Refer to Annex 3 for details
Product reference	Refer to Annex 3 for details
Procedure number	EMEA/H/C/PSA/J/0028.1
Marketing authorisation holder(s)	Joint DAA-PASS MAHs (refer to Annex 3 for full list)
Joint PASS	Yes

Research question and objectives	DAA-PASS is designed to investigate the question: does DAA therapy for chronic HCV infection increase the risk of early HCC recurrence among a well-characterized group of patients who have received successful HCC treatment interventions, relative to no DAA therapy? The primary objective is to estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort. The secondary objectives are to: A. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort. B. Estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC. C. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC. The exploratory objective is to describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.
Country(-ies) of study	Will include: United States, France, Germany, Italy, and Spain
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	Joint DAA-PASS MAHs (refer to Annex 3 for full list)
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2. LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AESI	Adverse event of special interest
AFP	Alpha-fetoprotein
ANRS	Agence Nationale de Recherche sur le Sida et les hépatites virales
ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical classification system
AUDIT	Alcohol Use Disorders and Identification Test
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence Interval
CT	Computed tomography
DAA	Direct-acting antiviral
DAA-PASS	A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy
DMP	Data management plan
EASL	European Association for the Study of the Liver
EC	Ethics Committee
EEIG	European Economic Interest Grouping
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International conference on harmonization
ICSR	Individual case safety report
IFN	Interferon
IPCW	Inverse-probability of censoring weighted averages
IRB	Institutional review board
ITA.LI.CA	Italian Liver Cancer Group
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
MRI	Magnetic resonance imaging
PASS	Post-authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee

Q	Quarter
RFA	Radiofrequency ablation
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SVR	Sustained virological response
TACE	Transcatheter arterial chemoembolization
TARGET-HCC	A 5-year Longitudinal Observational Study of the Natural History and Management of Patients with Hepatocellular Carcinoma; Clinicaltrials.gov Identifier: NCT02954094
TPS	TARGET PharmaSolutions, Inc.
US	United States
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Responsible Party	Name and Affiliation
Sponsor	TARGET PharmaSolutions, Inc.
MAHs	Joint DAA-PASS MAHs (refer to Annex 3 for full list)
Principal/coordinating investigators	TARGET-HCC Steering Committee Co-chairs • Adrian Di Bisceglie, MD • Anthony El-Khoueiry, MD
Investigators/Study Site Details	Refer to Annex 1

4. ABSTRACT

4.1. Title

DAA-PASS: A post-authorisation safety study of early recurrence of hepatocellular carcinoma in HCV-infected patients after direct-acting antiviral therapy (DAA-PASS Final Draft Version 3.3, dated 06 Jun 2018).

Sponsored and authored by TARGET PharmaSolutions, Inc. (TPS) and conducted on behalf of the Joint DAA-PASS Marketing Authorisation Holders (MAHs).

4.2. Rationale and Background

Recent reports of direct-acting antiviral (DAA) therapy use for chronic hepatitis C after successful treatment of hepatocellular carcinoma (HCC) have raised concerns that DAA therapy is associated with an increased risk of early HCC recurrence. In contrast, other recently reported studies have indicated no increased risk of early HCC recurrence.

As a response to the initial reports, the European Commission, under Article 20 of Regulation No 726/2004, requested a review of DAAs for the treatment of chronic hepatitis C to evaluate the risk of HCC recurrence. The review was carried out by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) and the recommendation was that the DAA MAHs should perform a prospective study to assess the risk of early recurrence of previously treated HCC after DAA therapy for HCV.

Due to the differences in reported results from published studies, the small numbers of patients analyzed, as well as the significant differences in the patient populations and designs in these studies, including differences in methodologies and lack of comparator groups, uncertainty remains about the risk of early HCC recurrence in patients exposed to DAAs relative to those not exposed. Therefore, a larger, controlled study was designed to address these concerns.

As was noted by the PRAC in the 30 Nov 2017 Final Assessment Report as part of the initial assessment of the protocol (EMA procedure: EMEA/H/C/PSP/J/0056.2), a depletion of the

patient pool was identified early as a significant risk for this study. With the current widespread availability and increasing utilization of DAAs within the 5 countries with active DAA-PASS sites as well as worldwide, the population of patients who are naïve to DAA treatment for HCV prior to HCC treatment has dramatically diminished compared to the original enrollment projections provided in the original DAA-PASS protocol.

Although investigators continue to indicate that the population of patients who meet entry criteria is increasingly difficult to find, a number of actions were taken to attempt to increase enrollment. In April 2019 a site survey was conducted, in part, to better understand enrollment challenges. Sites reiterated that patients with HCC and HCV most often present for HCC treatment after having already been treated with a DAA, and as current practice guidelines generally recommend routine screening for patients with HCC risk factors, the likelihood of HCV being undiagnosed and untreated in HCC patients is very low.

Additional steps taken to address the low enrollment rate include the following: 1) creation of a DAA-PASS Advisory Committee; 2) customized site engagement and enrollment plans and enrollment mediation activities; 3) site re-education and motivational visits; 4) identification of potential additional sites willing to consider participation within active countries; 5) conduct of a DAA-PASS Investigator meeting; and 6) revision to the Informed Consent Form to minimize time burden on site staff and study participants.

Although implementation of these enrollment remediation efforts was initiated in 2019, overall the monthly screening and enrollment rates have decreased or have remained unchanged over the course of the year, likely reflecting the lack of the available eligible patient population. Thus, revisions to the current protocol reflect that of a convenience sample.

Since the population of HCC treated patients who have not been treated with DAAs for HCV has decreased dramatically, so as to make the original sample size needed for this study unobtainable, greater reliance on currently available and retrospective data is required. Fortunately, many manuscripts with such data have been published since the start of DAA-PASS.

4.3. Research Question and Objectives

DAA-PASS is designed to investigate the question: does DAA therapy for chronic HCV infection increase the risk of early HCC recurrence among a well-characterized group of patients who have received successful HCC treatment interventions, relative to no DAA therapy?

Primary Objective	Primary Endpoint
Estimate the risk of early HCC recurrence (within the follow up period after the first HCC free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.	Time to recurrence of HCC (from radiological confirmation of the absence of detectable disease following HCC treatment intervention) associated with DAA therapy exposure relative to no DAA therapy exposure in the prospective DAA-PASS cohort.

Secondary Objective	Secondary Endpoint
A. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.	A. Number of events (early HCC recurrence) associated with DAA therapy exposure relative to no DAA therapy exposure, in the prospective DAA-PASS cohort.
B. Estimate the risk of early HCC recurrence (within the follow up period after the first HCC free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.	B. Time to recurrence of HCC (from radiological confirmation of the absence of detectable disease following HCC treatment intervention) associated with DAA therapy exposure from the prospective DAA-PASS cohort relative to no DAA therapy exposure including the historical cohort.
C. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.	C. Number of events (early HCC recurrence) associated with DAA therapy exposure from the prospective DAA-PASS cohort relative to no DAA therapy exposure including the historical cohort.
Exploratory Objective	
Describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.	

4.4. Study Design

This prospective, observational study will estimate the risk of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC using a prospective cohort from TARGET-HCC.

DAA-PASS will include a prospective cohort and data from a historical cohort.

For the purposes of data analysis in DAA-PASS, the following definitions will be used:

- **Enrollment/Baseline**: the date of the **first HCC-free** (radiological) **image**
- **Successful treatment of HCC**: no evidence of enhancing liver lesions and no extrahepatic lesions consistent with new or persistent HCC on radiological imaging after HCC treatment intervention
- **First HCC-free image (Index Date)**: the first radiological image that showed confirmation of **successful treatment of HCC**
- **Follow-up**: from Enrollment/Baseline up to 24 months

- **HCC recurrence**: evidence of enhancing liver lesions or extrahepatic lesions consistent with recurrence or new HCC on radiological imaging after **successful treatment of HCC**
- **Early HCC recurrence**: **HCC recurrence** within the follow up period after **the first HCC-free image**

Prospective Cohort

The prospective DAA-PASS cohort will include the following periods:

- Screening (participants identified in TARGET-HCC who fulfil the screening criteria)
- Enrollment/Baseline (participants with their first HCC-free image who fulfil the enrollment criteria)
- Follow-up (up to 24 months from Enrollment/Baseline)

During the follow-up period, which has a cutoff date of June 2021, participants will be managed per local standard of care which includes follow-up imaging according to guidelines established by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL): AASLD Guidelines for the Treatment of Hepatocellular Carcinoma and EASL–European Organization for the Research and Treatment of Cancer (EORTC) Clinical Practice Guidelines: Management of Hepatocellular Carcinoma.

Upon completion of or early discontinuation from DAA-PASS, participants will continue to be followed in the TARGET-HCC study.

Historical Cohort

As part of Secondary Objectives B and C, data from the prospective DAA-PASS cohort will be integrated with data from a historical cohort of patients with active HCV infection who were successfully treated for previous HCC. The Italian Liver Cancer Group (ITA.LI.CA) study cohort has been identified as a source of historical cohort data for this analysis.

Additionally, a descriptive analysis for the Exploratory Objective will be performed to characterize the cumulative risk of HCC recurrence in the ITA.LI.CA study cohort only.

4.5. Population

Prospective Cohort

The prospective DAA-PASS cohort will include a subset of HCV RNA positive participants in the TARGET-HCC study who meet entry criteria including hepatitis C (with no prior history of DAA therapy) and newly diagnosed Barcelona Clinic Liver Cancer (BCLC) Stage A HCC. Participants will be enrolled in the countries participating in TARGET-HCC which will include the United States (US), France, Germany, Italy, and Spain.

Historical Cohort

The historical cohort will be derived from the ITA.LI.CA database, which includes data on all consecutive patients with HCC who were managed within participating centers in Italy. The historical cohort will include patients from the ITA.LI.CA database who have active HCV infection who were not treated for HCV (IFN-based or DAA-based regimens) during the follow-up period, with initial HCC diagnosis BCLC Stage A, and subsequent successful treatment of HCC with curative therapy.

4.6. Variables

The prospective DAA-PASS cohort will include information on participant demographics, laboratory values, medical history events, concomitant medication use (including hepatotoxic medications), alcohol use, staging of liver disease and HCC, HCC treatment intervention(s) and response, tumor assessments, additional liver imaging information, prior HCV treatment, and DAA therapy. Variables included in any models will be the last values collected from the time of initial HCC diagnosis through the first HCC-free image.

The historical cohort will include similar data extracted from the ITA.LI.CA database, as available.

4.7. Data Sources

Data for the prospective DAA-PASS cohort will be obtained through abstraction of the participant medical record into the TARGET-HCC database. For selected sites outside of the US, the abstraction will be performed by study site personnel (or designee) while for sites in the US, electronic copies of the participant information will be uploaded for abstraction or imported electronically. Imaging data will be abstracted from local radiological reports. Imaging information will be collected from initial HCC diagnosis through study follow-up (up to 24 months after the first HCC-free image).

Data for the historical cohort will come from the ITA.LI.CA database; data were abstracted from medical records at the time of initial HCC diagnosis and treatment; subsequent data abstractions were performed at the time of any HCC recurrence event.

4.8. Study Size

Initially a sample size of 600 enrolled participants was planned for the prospective DAA-PASS cohort to capture an expected 122 HCC recurrence events through the 24 months of follow-up based on a 15% annual recurrence rate or 195 expected HCC recurrence events based on a 25% annual recurrence rate. Due to enrollment challenges, convenience sample sizes between 40 and 70 participants are expected. Based on a meta-analysis from 3 US and European sites[8,1], the 1-year HCC recurrence rate is estimated as 35%. Thus, example confidence bounds using the 35% 1-year HCC recurrence rate follow. Assuming the DAA HR is equal to 1.0, a sample size of 70 participants with an HCC recurrence rate of 35% per 12 months will provide two-sided 95% confidence bounds of 0.46 to 2.82. Hence, the convenience sample size of 70 will distinguish from a HR of 3.0 if there is no additional HCC recurrence risk related to DAA exposure. A

sample size of 60 participants with an HCC recurrence rate of 35% per 12 months will provide two-sided 95% confidence bounds of 0.43 to 3.10, and no upper confidence bound is calculable with sample size less than or equal to 50 participants.

The historical cohort will include approximately 400 patients from the ITA.LI.CA database who have HCV and were diagnosed with HCC after 2007 (when the database began to capture follow-up clinical and imaging data), successfully treated for BCLC Stage A HCC with curative therapy, and not treated with DAAs for their HCV infection after HCC diagnosis.

4.9. Data Analysis

The primary objective of DAA-PASS is to estimate the risk of early recurrence of HCC (within the follow up period after the first HCC-free image) associated with all-oral DAA therapy exposure relative to no DAA therapy exposure in the prospective DAA-PASS cohort. The planned analyses will use a Cox proportional hazards model with DAA exposure included in the model as a time-dependent variable.

The secondary objectives of DAA-PASS are to:

A. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.

B. Estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.

C. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.

For Secondary Objectives B and C, data from the prospective DAA-PASS cohort will be integrated with data from a historical cohort of HCV infected patients who have no DAA exposure and have been successfully treated for previous HCC, to enable adjustment for potential confounding factors and other variables that may differ in their distribution between the prospective and historical patients.

Descriptive statistical methods for interval-scale measures will include tabulation of count, mean, standard deviation, median, and range. For categorical measures with fixed levels the number of participants will be displayed along with percentages based on participants with available results. Medical events of interest and concomitant medication data will be displayed based on the number of participants presenting with an event along with percentages based on an appropriate denominator. Cumulative events and event-free survival rates will be provided. HCC recurrence status can only be evaluated when imaging for HCC is completed. For these

data, methods designed to handle interval censoring will be utilized. In addition, if applicable, the cumulative number of participants ongoing or censored by time will be provided.

Descriptive summaries of baseline information, such as disease characteristics and HCC treatment interventions, will be tabulated.

The Exploratory Objective of DAA-PASS is to describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone. Estimates of cumulative incidence will be provided for 3, 6, 9, 12, 18, and 24 months.

4.10. Milestones

Milestone	Planned Date
Start of data collection	1Q2018
End of data collection	2Q2021
Registration in the EU PAS register	19 April 2018
Final report of study results	4Q2021*

*Date of Submission

5. AMENDMENTS AND UPDATES

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	08 Feb 2018	4.1, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 7.3, 8, 9.1.1, 9.2, 9.2.2.2, 9.2.7, 9.3, 9.4, 9.5.1, 9.6, 9.7, 9.7.1, 9.7.2, 9.7.5, 9.7.7.2, 9.7.7.3, 9.7.10, 9.9, 9.9.2	Amendment	• Address PRAC comments • Add additional information regarding the historical cohort • Correct minor inconsistencies
2	08 May 2018	4.1, 4.3, 4.4, 4.6, 4.10, 5, 6, 8, 9.1.1, 9.3, 9.7.2, 9.7.3, 9.7.7.2, 9.7.7.3, 9.7.8, 9.7.10, 9.7.11	Amendment	• Address PRAC comments • Administrative changes
3	29 May 2018	4.4, 4.9, 5, 7.3, 9.1.1, 9.7	Amendment	• Address PRAC comments
4	06 Jun 2018	4, 5	Amendment	• Address PRAC comment
5	24 Mar 2020	4.5, 9.2.1, 9.2.8, Annex 3	Amendment	• Address PRAC request following submission of the interim progress report and to revise the sample size
6	09 Jun 2020	4, 5, 6, 7.2, 9.5, 9.7	Amendment	• Sample size adjustment

6. MILESTONES

Milestone	Planned Date
Start of data collection	1Q2018
End of data collection	2Q2021
Registration in the EU PAS register	19 April 2018
Final report of study results	4Q2021*

*Date of Submission

7. RATIONALE AND BACKGROUND

7.1. DAA-PASS

DAA-PASS is a prospective, observational study that will estimate the risk of early hepatocellular carcinoma (HCC) recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy relative to no DAA therapy during routine clinical care of HCV-infected patients with previous successfully treated HCC.

Participants in TARGET-HCC will be offered participation in the prospective DAA-PASS cohort if they meet certain criteria (e.g., Barcelona Clinic Liver Cancer [BCLC] Stage A, HCV-positive, DAA-naïve) detailed in Section 9.2.2.

TARGET-HCC (ClinicalTrials.gov Identifier: NCT02954094)[2] is an ongoing study of the natural history and management of HCC, and is a cooperative consortium of investigators from academic institutions and community-based sites treating patients with HCC. Up to 5000 consecutive, adult patients being treated, managed, or followed for HCC at the study sites are offered participation in TARGET-HCC. Other than requiring consent, there are no other enrollment criteria; therefore, the TARGET-HCC population covers the full staging of HCC disease status from initial diagnosis through end-stage. Participants enrolled in TARGET-HCC consent to the collection of up to 3 years of retrospective medical record data and to prospective follow-up data for up to 5 years. Upon completion of DAA-PASS, participants will continue to be followed in TARGET-HCC.

7.2. Direct-acting Antiviral (DAA) Therapies and HCC Recurrence

Since the approval of direct-acting antiviral (DAA) therapies to treat hepatitis C virus (HCV) infections in 2011, DAA therapy has been incorporated into the treatment paradigm for HCV-positive patients even after successful treatment of HCC. Over 1.5 million patients with chronic HCV infection have been treated with DAA therapy, including patients with advanced HCV disease. In patients with advanced HCV disease, standard of care treatment guidelines recommend treatment with DAA therapies: all treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are

willing to be treated, and who have no contraindications to treatment, must be considered for therapy. Treatment must be considered without delay in patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis. HCC is not a contraindication for HCV treatment (EASL Recommendations on Treatment of Hepatitis C; 2016)[3]. However, the time of HCV treatment after successful HCC treatment is not specified in the guidelines and there is no universally accepted standard for time of HCV treatment initiation. Therefore, it remains important to fully characterize the safety of these DAA regimens in this population and report the impact of DAA therapy on clinical outcomes, including early HCC recurrence.

A report by Reig et al (2016)[4] of a small study of 58 evaluable patients who received DAA therapy after complete response to HCC treatment intervention(s), including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), or resection, concluded that patients treated with DAAs had an unexpected, increased risk of early HCC recurrence (radiologic tumor recurrence in 27.6% (16/58); median follow-up of 5.7 months). The median time from the start of DAA therapy to recurrence was 3.5 months; no control group was included in the study. This study had excluded patients who received interferon (IFN) with their DAA and those with prior liver transplant.

The publication of the Reig study raised the question of an increased risk of HCC recurrence after DAA therapy for HCV for the European Medicines Agency (EMA) and the wider clinical community to consider. As a response to the question, the European Commission, under Article 20 of Regulation No 726/2004, requested a review of DAAs for the treatment of chronic hepatitis C to evaluate the risk of HCC recurrence. The review was carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and the final recommendation was for the Marketing Authorization Holders (MAHs) of DAAs to perform a prospective study to investigate the risk of early recurrence of previously treated HCC after DAA therapy for HCV as summarized in an EMA press release (2016)[5].

Additional studies and letters to the editor have been published both supporting and refuting the findings from the Reig study. A study by Conti et al. (2016)[6] evaluated recurrence of HCC after DAA therapy in 59 cirrhotic patients. During the 24-week follow-up period, 17 (28.8%) patients had recurrence of HCC; and similar to the Reig study, no control group was included in the study.

Conversely, analysis of data from 3 cohorts including patients with chronic hepatitis C who were previously treated for HCC were published by the Agence Nationale de Recherche sur le Sida et les hépatites virales (ANRS) collaborative group (2016)[7]. The cohorts included: HEPATHER with 267 patients (189 patients with DAA therapy and 78 patients with no therapy), CirVir with 79 patients with compensated cirrhosis (13 patients with DAA therapy and 66 with no DAA therapy), and CUPILT with 314 liver transplant recipients for HCC who were subsequently treated with DAAs. There was no increase in HCC recurrence after DAA therapy compared to the non-DAA treated patients in any of the three ANRS cohorts.

In a report from Virlogeux et al (2017)[8], HCC recurrence was evaluated in 68 HCV patients with HCC remission established at least one month subsequent to the end of HCC treatment. Of these patients, 23 were subsequently treated with DAAs and 45 were not treated. The authors reported

11 recurrences of HCC among DAA treated patients and 33 recurrences among untreated patients, favoring DAA therapy (adjusted hazard ratio [HR]: 0.24, 95% confidence interval [CI]: 0.10-0.55).

A systematic literature review and meta-analysis was recently published by Cabibbo et al. (2017)[9] evaluating rates of HCC recurrence in untreated HCV-infected patients. From this analysis, pooled estimates of 6-month, 1-year and 2-year recurrence probabilities were 7.4% (95% CI, 4.0-10.0%; range, 0-12.5%), 20% (95% CI: 12.7-27.4%; range, 4.9-62.5%) and 47% (95% CI: 39.5-54.4%; range, 31.8-100%), respectively. The median time to recurrence (95% CI) was estimated as 25.4 months (21.3-29.5 months). The authors noted that, despite the large number of patients (n=712) in the pooled analysis, there was substantial variability in the 95% CI, reflecting the underlying heterogeneity of the recurrence rates between the component studies. This was particularly apparent for the 1- and 2-year rates. In a univariate meta-regression analysis, at the patient level, only serum albumin level was an important predictor and at the study level, duration of follow-up and study design (randomized trial vs. other) were most important. The authors noted that much of the variability in HCC recurrence was not explained by the available predictors. In recent years, additional observational studies with original data and a meta-analysis have been published in English language that evaluated the risk of recurrence of HCC associated with HCV treatment, including DAAs, and this information is summarized in the table below.

Table 1. Published literature on risk of HCC recurrence associated with DAA use in HCV patients

Reference, Year*	Country(ies)	Sample Size	Type of Study
Studies with comparator group(s)			
Singal, 2019[i]	US & Canada; North America	793 patients with HCV-associated HCC, 304 (38.3%) received DAA therapy and 489 (61.7%) untreated	Retrospective study
Singal 2019[ii]	US & Canada; North America	797 patients with HCV-related HCC, 383 (48.1%) received DAA therapy and 414 (51.9%) untreated post HCC complete response	Retrospective study
Cabibbo, 2019[iii]	Italy	102 DAA-treated (DAA group) and 102 DAA-untreated patients (No DAA group) were compared	RESIST-HCV (Rete Sicilia Selezione Terapia HCV) multi-center prospective cohort patients compared with historical untreated ITA.LI.CA. cohort patients
Kuo, 2020[iv]	Taiwan	82 DAA-treated patients, 80 IFN-treated and 160 untreated patients	Retrospective study
Chi, 2019[v]	Taiwan	107 HCV DAA treated patients compared with a historical cohort of 42 HCC patients experienced IFN+RBV	Prospective DAA cohort compared with historical IFN cohort

Reference, Year*	Country(ies)	Sample Size	Type of Study
Teng, 2020[vi]	Taiwan	79 DAA-treated patients, 102 IFN-treated and 120 untreated patients	Retrospective study
Nishibatake Kinoshita, 2019[vii]	Japan	147 DAA-treated patients and 156 IFN-treated patients	Retrospective study
Nagata, 2017[viii]	Japan	60 IFN-treated 83 DAA-treated	Retrospective study
Singh, 2018[ix]	Various	No sample size restrictions on the outcome of recurrent HCC; 12 studies (controlled and uncontrolled) reported on recurrent HCC	Systematic review & meta-analysis
Guarino, 2018[x]	Various	24 studies included; reporting on HCC recurrence after DAAs treatment in patients with previously and successfully treated HCC (liver resection, ablation or trans-catheter arterial chemoembolization — TACE)	Systematic review
Studies without an unexposed or untreated comparator group			
Zou, 2019[xi]	US	264 HCV+ patients with HCV-related HCC who received DAAs following successful treatment for HCC	Retrospective study
Nakano, 2018[xii]	Japan	3012 HCV- infected patients; 459 with prior HCC who were cured with surgery or ablation therapy (curative treatment) before DAAs	Prospective multicenter cohort study
Lleo, 2019[xiii]	Italy	1927 HCV-infected cirrhotic patients treated with DAAs; 161 patients had a prior history of HCC and demonstrated a complete radiologic response prior to starting DAA	Retrospective analysis of prospective multicenter cohort study
Degasperi, 2019[xiv]	Italy	565 HCV-infected cirrhotic (Child-Pugh A or B) treated with DAAs; 60 patients had a prior history of HCC and demonstrated a complete radiologic response prior to starting DAA	Retrospective study

*Refer to Section 13, Table 1 References, for complete references.

The first 2 studies, (1) and (2) in the table, include comparator groups of untreated patents and sample sizes larger than this study. The fourth (4) through eighth (8) studies in the table are controlled by IFN-treated patients. Thus, the published literature has evolved toward answering the research questions posed in this observational study that DAA use was not confirmed to be associated with an increased risk of HCC recurrence compared to untreated HCV and/or treatment with IFN-containing regimens, after adjustment for potential confounders.

7.3. Purpose and rationale

DAA-PASS will investigate early recurrence of HCC in HCV-positive patients who have received successful treatment of HCC, defined as no evidence of HCC by imaging at study baseline; early recurrence will be considered recurrence within the follow up period after the first HCC-free image. DAA-PASS will utilize a prospective cohort design that estimates the risk of HCC recurrence as a time-varying function of all-oral DAA exposure. In the prospective cohort, all participants begin DAA-PASS as DAA-therapy naïve. Participants who subsequently start

DAA therapy during the study may contribute person-time regarding both the exposure to and the absence of exposure to DAA when estimating HCC recurrence risk. Thus, the DAA-treatment variable is time-varying.

DAA-PASS will benefit from prospectively enrolling participants from ongoing TARGET-HCC. DAA-PASS will incorporate the heterogeneity in clinical practice, utilizing the natural variability in DAA therapy initiation times to generate patient follow-up that includes contemporary surveillance of both DAA exposure and absence of exposure to DAA. The study includes a standardized HCC surveillance protocol.

Additionally, prospective enrollment into DAA-PASS will include collection of baseline criteria that will provide a consistent analysis of the population at risk for early HCC recurrence across the study sites. Participants will be enrolled in the study only if they have confirmation of successful treatment of HCC prior to administration of any DAA therapy. The study design allows for collection of additional potential confounding variables that could be included in the analyses.

Analyses for Secondary Objectives B and C will be conducted to estimate the risk and adjusted incidence of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure after integrating data from the prospective DAA-PASS cohort with data from a historical cohort of HCV patients untreated during the follow-up period who have been successfully treated for previous HCC (from the Italian Liver Cancer Group [ITA.LI.CA] study cohort which has been identified as a source of historical cohort data). These historical cohort data will contribute person-time without DAA exposure when estimating HCC recurrence risk.

In total, DAA-PASS was intended to provide a robust evaluation of the research question of whether there is an increased risk of early HCC recurrence among HCV-infected BCLC Stage A patients who have received successful HCC treatment interventions, following DAA therapy exposure relative to no DAA therapy exposure. However, since the population of HCC treated patients who have not been treated with DAAs for HCV has decreased dramatically, so as to make the sample size needed for this study unobtainable, greater reliance on currently available and retrospective data is required. Fortunately, many manuscripts with such data have been published since the start of DAA-PASS.

Additionally, a descriptive analysis for the Exploratory Objective will be performed to characterize the cumulative risk of HCC recurrence in the ITA.LI.CA study cohort only.

8. RESEARCH QUESTION AND OBJECTIVES

DAA-PASS is designed to investigate the question: does DAA therapy for chronic HCV infection increase the risk of early HCC recurrence among a well-characterized group of patients who have received successful HCC treatment interventions, relative to no DAA therapy?

Primary Objective	Primary Endpoint
Estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.	Time to recurrence of HCC (from radiological confirmation of the absence of detectable disease following HCC treatment intervention) associated with DAA therapy exposure relative to no DAA therapy exposure in the prospective DAA-PASS cohort.
Secondary Objectives	**Secondary Endpoint**
A. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.	A. Number of events (early HCC recurrence) associated with DAA therapy exposure relative to no DAA therapy exposure, in the prospective DAA-PASS cohort.
B. Estimate the risk of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.	B. Time to recurrence of HCC (from radiological confirmation of the absence of detectable disease following HCC treatment intervention) associated with DAA therapy exposure from the prospective DAA-PASS cohort relative to no DAA therapy exposure including the historical cohort.
C. Compare the adjusted incidence of early HCC recurrence (within the follow up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure including a historical cohort of HCV patients not exposed to DAA with initial HCC diagnosis and subsequent successful treatment of HCC.	C. Number of events (early HCC recurrence) associated with DAA therapy exposure from the prospective DAA-PASS cohort relative to no DAA therapy exposure including the historical cohort.
Exploratory Objective	
Describe in a non-comparative summary the cumulative risk of HCC recurrence over time for the historical cohort alone.	

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Overall Design

This prospective, observational study will estimate the risk of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC using a prospective cohort from TARGET-HCC.

DAA-PASS will include a prospective cohort and data from a historical cohort.

For the purposes of data analysis in DAA-PASS, the following definitions will be used:

- **Enrollment/Baseline**: the date of the **first HCC-free** (radiological) **image**
- **Successful treatment of HCC**: no evidence of enhancing liver lesions and no extrahepatic lesions consistent with new or persistent HCC on radiological imaging (see Section 9.2.9) after HCC treatment intervention
- **First HCC-free image (Index Date)**: the first radiological image (see Section 9.2.9) that showed confirmation of **successful treatment of HCC**
- **Follow-up**: from Enrollment/Baseline up to 24 months
- **HCC recurrence**: evidence of enhancing liver lesions or extrahepatic lesions consistent with recurrence or new HCC on radiological imaging (see Section 9.2.9) after **successful treatment of HCC**
- **Early HCC recurrence**: **HCC recurrence** within the follow up period after **the first HCC-free image**

Prospective Cohort Design

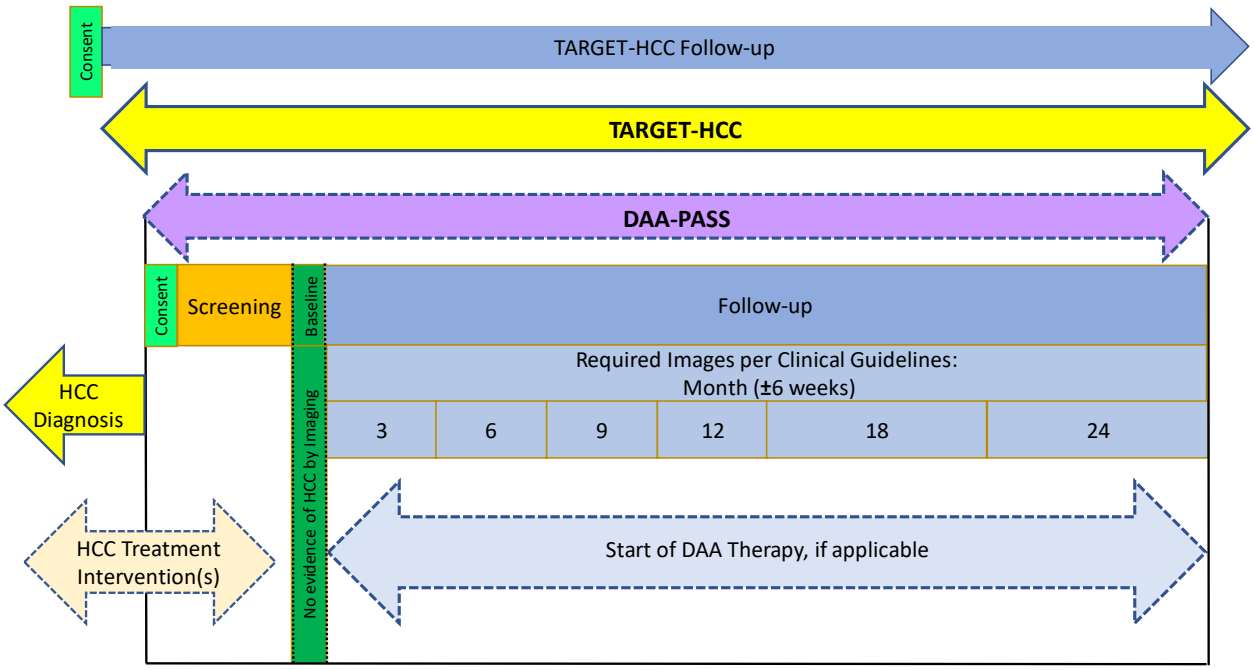
The prospective DAA-PASS cohort will include the following periods:

- Screening (participants identified in TARGET-HCC who fulfil the screening criteria [see Section 9.2.2])
- Enrollment/Baseline (participants with their first HCC-free image who fulfil the enrollment criteria [see Section 9.2.3])
- Follow-up (up to 24 months from Enrollment)

During the follow-up period, participants will be managed per local standard of care which includes follow-up imaging according to guidelines established by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL): AASLD Guidelines for the Treatment of Hepatocellular Carcinoma[10] and EASL–European Organization for the Research and Treatment of Cancer (EORTC) Clinical Practice Guidelines: Management of Hepatocellular Carcinoma[11] (see Section 9.2.9).

Upon completion of or early discontinuation from DAA-PASS, participants will continue to be followed in TARGET-HCC (see Section 9.2.6).

Figure 1. Prospective DAA-PASS Cohort Schema



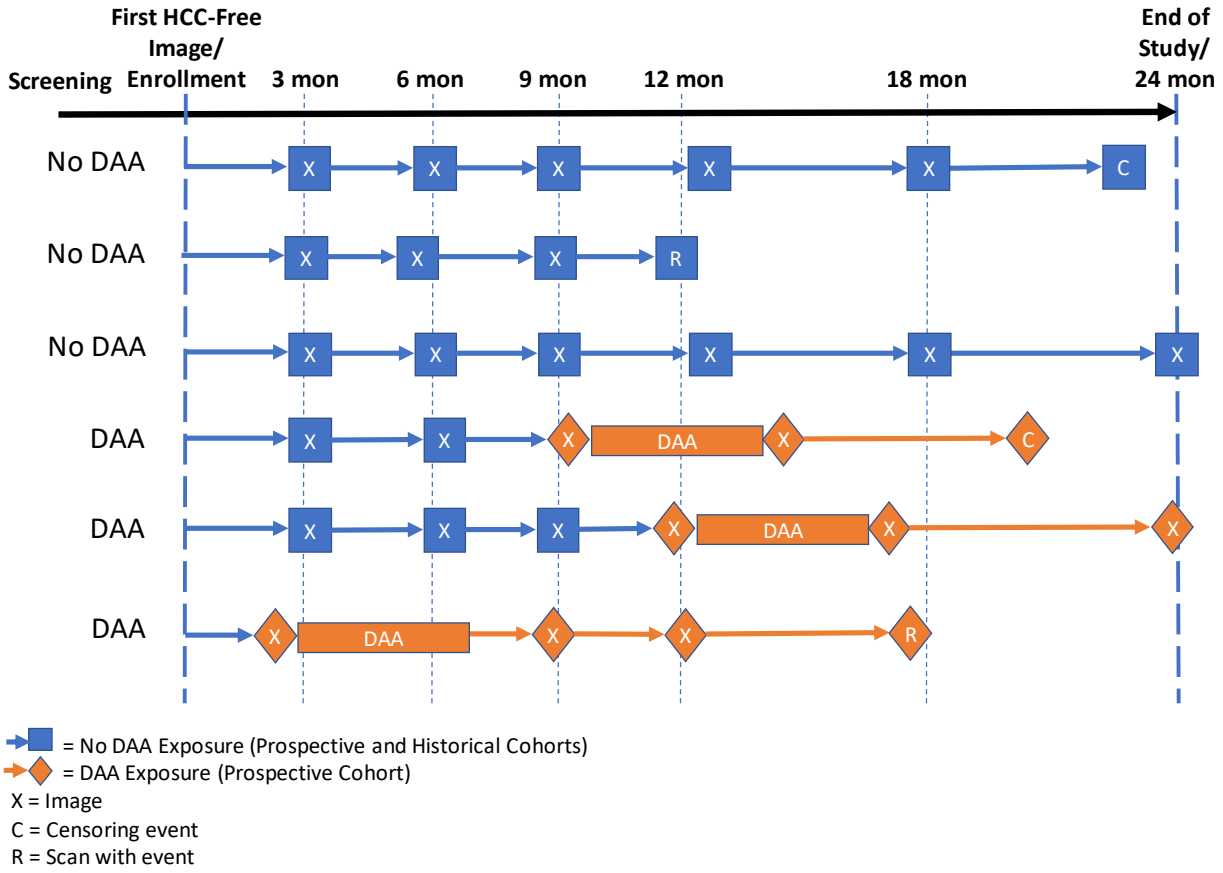
Historical Cohort Design

For Secondary Objectives B and C, data from the prospective DAA-PASS cohort will be integrated with data from a historical cohort of patients with active HCV infection who were successfully treated for previous HCC to provide an additional investigation into potential bias associated with the decision to treat with DAAs in the prospective cohort and to increase the untreated exposure time. Data from the prospective and historical cohorts will be integrated into the same dataset to permit adjustment for covariates that may differ in their distribution between DAA exposure versus non-exposure, and prospective versus historical participants. The ITA.LI.CA study cohort has been identified as a source of historical data for this analysis.

Prospective Cohort Analysis Design

The analysis for the Primary Objective and Secondary Objective A will compare DAA therapy exposure to no DAA therapy exposure in the prospective cohort. All participants will have no DAA therapy exposure at Enrollment. During the follow-up period, any participant may start DAA therapy, at the physician's discretion, and would then contribute to the DAA therapy exposure in the analysis. The analysis will consider DAA exposure as a time-varying variable. Individual participants in the prospective DAA-PASS cohort can contribute person-time at risk to both the DAA-exposed condition and the unexposed condition (see Figure 2).

Figure 2. Analysis Schema



Historical Cohort Analysis Design

Secondary Objectives B and C will repeat the analyses of the Primary Objective and Secondary Objective A after integrating data from the prospective cohort with data from the historical cohort, and comparing risk between DAA exposure vs no DAA exposure. Participants in the prospective cohort with DAA exposure will contribute person-time at risk to both the DAA-exposed condition and the unexposed condition (i.e., the time prior to DAA exposure). Participants in the prospective cohort who never receive DAA therapy during follow-up and all participants in the historical cohort will contribute person-time at risk to the unexposed condition only (see Figure 2).

Additional information related to the analysis including the historical cohort data is described in Section 9.7.9.

Furthermore, an additional descriptive analysis for the Exploratory Objective will be performed to characterize the cumulative risk of HCC recurrence in the historical cohort only (see Section 9.7.10). The ITA.LI.CA study cohort has been identified as a source of historical data for this analysis.

9.2. Setting

The information in Section 9.2 addresses the prospective DAA-PASS cohort only. Information related to the historical cohort is described in Section 9.7.9.

9.2.1. Study Population

The prospective DAA-PASS cohort will include a subset of HCV RNA positive participants in TARGET-HCC who meet screening criteria including HCV (with no prior history of DAA therapy) and newly diagnosed BCLC Stage A HCC (see Section 9.2.2). Participants will be enrolled if they fulfil the enrollment criteria (see Section 9.2.3).

Participants will be enrolled in the countries participating in TARGET-HCC which will include US, France, Germany, Italy, and Spain.

9.2.2. Screening

Participants in the prospective cohort will be screened during or before a regularly scheduled clinic visit. The following will be completed:

- Obtain signed informed consent
- Review and confirm screening inclusion/exclusion criteria

Participants who consent will enter the Screening Phase of DAA-PASS and will be identified by their unique Participant ID number from TARGET-HCC.

9.2.2.1. Screening Inclusion Criteria

Participants must meet all of the following to be eligible for participation in DAA-PASS:

Current participant in TARGET-HCC

Adults, age ≥18 years

First diagnosis of HCC (mixed HCC/cholangiocarcinoma may be included). Diagnosis may be histological/cytological and/or radiological.

BCLC Stage A

Underwent, undergoing, or planned to undergo therapy for HCC, with exception that transplant as prior or planned treatment for HCC is excluded.

HCV RNA positive

9.2.2.2. Screening Exclusion Criteria

Participants who meet any of the following exclusion criteria will not be eligible for participation in DAA-PASS:

- Inability to provide informed consent
- HCC-free imaging (as defined in Section 9.1.1) after treatment of initial HCC that is greater than 4 weeks prior to Screening (see Section 9.2.9 for imaging details)

- Prior liver transplantation
- Hepatitis B Virus (HBV) surface antigen positive (HBsAg)
- Previously treated with direct-acting antiviral agents (not DAA-naïve); Note that prior (peg)IFN and/or ribavirin therapy is allowed

9.2.3. Enrollment/Baseline

Successful treatment of HCC must be confirmed by imaging for enrollment (see Section 9.2.9). Additionally, it must be confirmed that the participant meets the Enrollment criteria. Once confirmed, the participant will be enrolled and the date of the first HCC-free image will be considered Enrollment/Baseline for DAA-PASS.

9.2.3.1. Enrollment Inclusion Criteria

Participants must meet all of the following to be enrolled in DAA-PASS:

Continued participation in TARGET-HCC

No recurrence or progression of initial HCC beyond BCLC Stage A prior to Enrollment/Baseline

HCC-free imaging (as defined in Section 9.1.1) at Enrollment/Baseline (see Section 9.2.9 for imaging details; participants may remain in Screening until an HCC -free image is obtained)

Remains DAA-naïve (prior therapy with (peg)IFN and/or ribavirin is allowed)

9.2.3.2. Enrollment Exclusion Criteria

Participants who meet the following exclusion criterion will not be enrolled in DAA-PASS:

- Liver transplantation since Screening

9.2.4. Follow-up

The Follow-up period will continue for up to 24 months from Enrollment/Baseline for all participants. Imaging will be performed per standard of care[10,11], as follows (see Table 2):

- Every 3 months for the first 12 months after Enrollment/Baseline
- At 18 and 24 months after Enrollment/Baseline

9.2.4.1. DAA Therapy

Once enrolled in the study, the decision to treat participants with DAA therapy for HCV will be made per standard of care and at the discretion of the treating physician. For all participants who receive DAA therapy after enrollment in DAA-PASS, details regarding the DAA therapy and virologic response will be recorded.

9.2.5. Screen Failures

Participants will be considered Screen Failures if they do not meet the Screening or Enrollment Inclusion criteria and/or if they meet the Screening or Enrollment Exclusion criteria (see

Section 9.2.2 and Section 9.2.3). Details regarding reasons for Screen Failure will be collected in the DAA-PASS database. Participants who are Screen Failures will remain enrolled in TARGET-HCC.

9.2.6. Completion and Discontinuation of Participants

A participant will be considered as complete in the DAA-PASS, if they meet any of the following:

- Complete up to 24 months of Follow-up after Enrollment/Baseline
- Death (due to any cause) during Follow-up while still enrolled in DAA-PASS

Participants will be discontinued from DAA-PASS for the following reasons:

- Participant choice, withdrawal of consent
- Lost to follow-up
- Administrative (e.g., site closure, Sponsor termination of the study, study completion as defined in Section 9.2.7)

Although participation in DAA-PASS for each participant will end after Screen Failure (at Screening or Enrollment/Baseline), Completion, or Premature Discontinuation, living participants will remain enrolled in TARGET-HCC. For clarity, any subsequent data collected after participation in DAA-PASS will only be available as part of TARGET-HCC.

If a participant chooses to withdraw from TARGET-HCC, they will consequently also be choosing to withdraw from DAA-PASS.

If a participant chooses to withdraw from DAA-PASS, all data collected up to the point of withdrawal will remain for use in the study database, unless otherwise prohibited by local regulations, but no further data may be collected. A request to withdraw must be documented in the participant's medical record by the study site personnel to be consistent with privacy guidelines and regulations.

For participants who die during their participation in DAA-PASS, it will be the responsibility of the Investigator to assign a cause of death based upon available clinical information, hospital records, and/or death certificate; the relevant death information will be included in the database. Site staff may also search publicly available sources for any information regarding death of a participant and may submit that information for entry into the database after the discontinuation date.

9.2.7. Completion or Discontinuation of DAA-PASS

DAA-PASS will be considered complete after the last enrolled participant completes or discontinues from the DAA-PASS (as described in Section 9.2.6).

Additionally, the Sponsor may terminate DAA-PASS after consultation with the PRAC.

9.2.8. DAA-PASS Schedule of Events

The schedule of events is summarized in Table 2.

Table 2. Prospective DAA-PASS Cohort Events Schedule

Assessment	Screening	Enrollment / Baseline	Follow-up: Imaging Months 3, 6, 9, 12, 18, and 24[1]	End of DAA-PASS
Informed consent[2,3]	X			
Review of Screening inclusion/exclusion criteria	X[4, 7]			
Review of Enrollment inclusion/exclusion criteria		X[4]		
Imaging[1]		X	X	
Confirm successful treatment of HCC (HCC-free image; see Section 9.1.1 and Section 9.2.9)		X[5]		
Confirm no HCC recurrence			X	
DAA therapy exposure[6]		X	X	
Final disposition				X

1 Per standard of care (See Section 9.2.9).
2 Study procedures will be completed during or before regularly scheduled clinic visits.
3 Participant can withdraw her/his consent at any time after she/he is enrolled in the study.
4 Participants who do not meet criteria are Screen Failures.
5 Participants who do not have an HCC-free image may remain in Screening for additional initial HCC-treatment intervention(s) and subsequent imaging until HCC-free on imaging as appropriate per standard of care.
6 DAA therapy can be initiated anytime from Enrollment/Baseline through Follow-up.
7 Participants are allowed to enroll using an HCC-free image obtained up to 4 weeks prior to signing DAA-PASS consent.

NOTE: As all participants enrolled in DAA-PASS remain enrolled in TARGET-HCC, the data collected as part of TARGET-HCC up to completion or discontinuation of DAA-PASS will also be available and therefore are not specified in 2:

- All data available in the medical record up to 3 years prior to enrollment in TARGET-HCC (e.g., clinic notes/encounters and telephone contact notes/reports, laboratory reports, medical history [including HCV and other comorbid diseases] medication lists, hospitalization records, radiographic/imaging reports/results, biopsy reports/results, diagnostic procedures such as liver biopsy reports and endoscopic examinations, all prior clinical details specific to screening methods, diagnostic evaluation, and HCC treatment intervention).
- Any/all details regarding prior and current HCV and HBV including: treatments, assessment results, and responses.
- Any/all investigator-assessed HCC disease staging/scoring and responses to HCC treatment interventions.

- Any/all investigator-assessed liver disease staging/scoring.
- All prospective data available in the medical record from enrollment in TARGET-HCC. Data are collected every 3 months for the first year and every 6 months for subsequent years, unless requested more frequently for planned analyses.
- Any adverse events (AEs; see Section 11.1.1), including serious adverse events (SAEs; see Section 11.3).

9.2.9. Clinical Activity Assessments

All clinical activity assessments and imaging in the prospective cohort will follow the standard of care (AASLD[10] and/or EASL[11] HCC Guidelines) and imaging will be performed as described in Table 2. These guidelines recommend dynamic computed tomography (CT) or magnetic resonance imaging (MRI) to assess response approximately one month after HCC treatment interventions (resection, loco-regional, or systemic therapies), every 3 months for the first year after HCC treatment intervention(s), and every 6 months thereafter to complete up to 24 months.

All clinical data and imaging records, including raw images, will be collected and analyzed, as appropriate, during the study.

9.3. Variables

The prospective DAA-PASS cohort will include information on participant demographics, laboratory values, medical history events, concomitant medication use (including hepatotoxic medications), alcohol use, staging of liver disease and HCC (including but not limited to Child-Pugh score, Model for End Stage Liver Disease [MELD] score, performance status, and BCLC stage), HCC treatment intervention(s) and response, tumor assessments, additional liver imaging information, prior and subsequent HCV treatment (including IFN), DAA therapy, and virologic response data.

The data for the prospective DAA-PASS cohort include imaging collection and details of DAA therapy from the TARGET-HCC database. The database includes information on participant demographics, laboratory values, comorbid liver conditions (including but not limited to HCV status), medical history events (including adverse events), concomitant medication use, HCV treatment history, HCC staging information, tumor assessment and response, HCC treatment history, and additional liver imaging information.

The model will include the following baseline covariates as available: alpha-fetoprotein (AFP) level, albumin level, platelet count, MELD score, age in years, gender, diabetes status, alcohol use/AUDIT score ≥ 7, HCC treatment modality, and study centre (see Section 9.7.6.2).

The historical cohort will include similar data extracted from the ITA.LI.CA database (where available). Information related to the variables collected in the historical cohort is described in Section 9.7.9.

Definition of HCC Recurrence

The objectives are based on the analysis of early HCC recurrence (see Section 9.1.1) as indicated on imaging following Enrollment/Baseline (date of first HCC-free image; see Section 9.1.1). Periodic screening for HCC recurrence will rely on conventional imaging-based evaluations. HCC recurrence is defined (see Section 9.1.1) as having evidence of enhancing lesions suggestive of new HCC on imaging after successful treatment of HCC. The onset of HCC recurrence will be assumed to occur during the time interval between a previous negative imaging evaluation and the subsequent positive imaging evaluation. The time of onset will thus be interval-censored instead of being known precisely. Participants will be considered to have an event if they have an HCC recurrence in an interval as demonstrated by imaging.

DAA exposure

The analyses for the Primary Objective and Secondary Objective B estimate the risk of HCC recurrence associated with exposure to DAA therapy for HCV versus no DAA therapy using a proportional hazards model with DAA therapy included as a time-varying exposure variable. DAA therapy can be initiated at any time after Enrollment/Baseline when absence of detectable HCC is documented (i.e., successful treatment of HCC). For purposes of fitting the statistical model, the time-dependent risk associated with DAA therapy will be assumed to start at the time of the image preceding the start of DAA therapy and is a positive risk in all subsequent intervals. For purposes of these analyses, it will be assumed that the risk of HCC recurrence is a function of DAA exposure only and does not require participants to complete the prescribed HCV regimen or achieve sustained virologic response (SVR). Sensitivity analyses will be used to explore the impact on the estimate of the HR associated with DAA exposure relative to no DAA therapy related to the date of DAA therapy initiation.

9.4. Data Sources

Data for the prospective DAA-PASS cohort will be obtained through abstraction of the participant medical record into the TARGET-HCC database. For selected sites outside of the US, the abstraction will be performed by study site personnel (or designee) while for sites in the US, electronic copies of the participant information will be uploaded for abstraction or imported electronically. Imaging data will be abstracted from local radiological reports. Imaging information will be collected from initial HCC diagnosis through study Follow-up (up to 24 months after the first HCC-free image; the definition of first HCC-free image is defined in Section 9.1.1.).

TPS performed a review of the current participants in TARGET-HCC and it is expected that 15% to 20% of enrolled participants would meet the DAA-PASS inclusion/exclusion criteria.

The abstraction process provides a masking number that is applied to all participant data and used for linking the participant data for analysis purposes. Data are subject to cleaning processes used for TARGET-HCC that evaluate data integrity through a query and review process.

Information regarding the historical cohort data source is described in Section 9.7.9.

9.5. Study Size

9.5.1. Sample Size Justification

Prospective Cohort

A sample size of 600 enrolled participants was planned for the prospective DAA-PASS cohort to capture an expected 122 HCC recurrence events through the 24 months of follow-up based on a 15% annual recurrence rate and 195 expected HCC recurrence events based on a 25% annual recurrence rate. This range of rates is consistent, ± approximately 5%, with a recently published meta-analysis of HCC recurrence rates by Cabibbo et al8 where the 1-year HCC recurrence rate was reported as 20% with 95% CI of 13% to 27%. The sample size was selected based on the expected precision of the estimated HR when the true HR is equal to 1.0 and allows for a conservative rate of censoring from liver transplant or other reasons. The expected precision follows below.

While there are no standards for the timing of DAA therapy following the treatment of HCC, TPS performed a feasibility assessment at HCC study sites on the use of DAAs. The DAA therapy pattern assumed for the sample size evaluation was consistent with what was reported and allowed for 90% (42% by 6 months, an additional 44% by 12 months, and 4% between 12 and 24 months) of participants without recurrence of HCC to be treated through 24 months.

The ability to meaningfully interpret the HR is predicated on the level of precision, quantified by the 95% CI around the effect estimate. As mentioned earlier (see Section 7.2), among other limitations, prior studies had insufficient sample sizes to allow for meaningfully precise estimates (i.e., that could exclude rates greater than two times the rate expected from historical data). Therefore, a key criterion for consideration is that the study should be able to exclude a HR value of 2.0 given a “true” HR of 1.0 (no effect).

Assuming the DAA HR is equal to 1.0, a sample size of 600 participants with an HCC recurrence rate of 15% per 12 months will provide two-sided 95% confidence bounds of 0.66 to 1.61. For a 12-month recurrence rate of approximately 25%, the expected CI bounds of 0.72 to 1.39 would be obtained based on this sample size. Hence, the planned sample size was sufficient to clearly distinguish from a HR of 2.0 if there were no additional HCC recurrence risk related to DAA exposure.

After 2 years of screening and enrollment in DAA-PASS, 30 participants have been enrolled. The primary reason for the low enrollment is that there are very few eligible patients. Most HCC patients are treated for HCV before they are treated for HCC. Assuming the DAA HR is equal to 1.0, a sample size of 70 participants with an HCC recurrence rate of 35% per 12 months will provide two-sided 95% confidence bounds of 0.46 to 2.82. Hence, a sample size of 70can distinguish from a HR of 3.0 if there is no additional HCC recurrence risk related to DAA exposure. A sample size of 60 participants with an HCC recurrence rate of 35% per 12 months

will provide two-sided 95% confidence bounds of 0.43 to 3.10, and a sample size of 50 participants will yield two-sided 95% confidence bounds of 0.39 and infinity.

Historical Cohort

Information related to the analysis including historical cohort data is described in Section 9.7.9.

9.6. Data Management

Data management activities for the prospective cohort will be performed in accordance with TPS procedures. A separate Data Management Plan (DMP) and other design documents describing study-specific information will be generated and finalized prior to initiating data management activities for DAA-PASS.

All data for the prospective DAA-PASS cohort will be collected, processed, and stored centrally via an electronic data capture system by Sponsor personnel or their designee. Data management activities will be performed by TPS or their designee. Coding of data will be performed as appropriate using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization (WHO) Drug dictionaries.

In addition, copies of the raw images used for HCC assessment in the prospective cohort will be obtained and stored centrally.

Information related to the historical cohort is described in Section 9.7.10.

9.7. Data Analysis

The analyses below will be generated under ideal circumstances, though in practice, they may be contingent according to the final sample size, its distribution among subpopulations determined by important covariates, and the final number of recurrence events observed. A separate Statistical Analysis Plan (SAP) will also be generated that will include further details of the planned analyses.

The analysis for the Primary Objective provides an estimate of the HR associated with recurrence of HCC associated with DAA therapy relative to no DAA therapy. The planned analyses use a proportional hazards model with DAA exposure included in the model as a time-dependent variable. Details of the analysis methods are provided below, including the approach to adjust for potential bias and sensitivity analyses.

The analysis for Secondary Objective A will evaluate the adjusted incidence of HCC recurrence using data from the DAA-PASS, as described in Section 9.7.8.

Analyses for Secondary Objectives B and C will repeat those of the Primary Objective and Secondary Objective A, incorporating data from the historical cohort as part of the non-DAA exposure condition. A description of this cohort is provided in Section 9.7.9 and the analyses are described in Section 9.7.8 and Section 9.7.9.

Furthermore, an additional descriptive analysis for the Exploratory Objective will be performed to characterize the cumulative risk of HCC recurrence in the historical cohort only (see Section 9.7.10).

9.7.1. General Conventions

Descriptive statistical methods for interval-scale measures will include tabulation of count, mean, standard deviation, median, and range. For categorical measures with fixed levels the number of participants will be displayed along with percentages based on participants with available results.

Time to HCC recurrence will be summarized with a life table displaying the numbers of participants at risk entering the time interval, cumulative censored participants, and cumulative proportion with events at the end of the interval. HCC recurrence status will only be evaluated when imaging for HCC is completed. Methods designed to handle interval censoring will be utilized. In addition, if applicable, the cumulative number of participants ongoing or censored by time will be provided.

Descriptive summaries of baseline information, such as demographics, disease characteristics and HCC treatment interventions, will be tabulated. Populations of interest to be displayed in the descriptive summaries are outlined in Section 9.7.2.

All statistical estimates will be reported along with corresponding 95% two-sided CIs. P-values for model parameters will be provided based on Wald statistics.

Unless otherwise specified, all statistical computations will be performed using R software or SAS software (Version 9.4. Copyright © 2012, SAS Institute Inc., Cary, NC).

9.7.2. Study Populations

The analysis for the Primary Objective will include all enrolled DAA-PASS participants in the prospective cohort. Participants eligible for enrollment are those with their first HCC-free image (see in Section 9.1.1) following HCC treatment intervention(s), HCV RNA positive, DAA-naïve, and BCLC Stage A at the time of initial HCC diagnosis (see Section 9.2.2 and Section 9.2.3). Inclusion of only those who are BCLC Stage A will decrease heterogeneity of the prospective cohort and will provide consistency with the historical cohort.

Subgroups of interest include: (1) participants initiating DAA therapy in the first 6 (≤6) months following Enrollment/Baseline, (2) participants initiating DAA therapy > 6 months following Enrollment/Baseline, (3) participants that received DAA therapy at any time following Enrollment/Baseline, (4) participants who achieve SVR following Enrollment/Baseline, and (5) participants who never receive DAA therapy within the follow up period from Enrollment/Baseline.

Information related to the historical cohort and analysis is described in Section 9.7.9.

9.7.3. DAA Exposure as Time-Varying Exposure

Individual participants in the prospective DAA-PASS cohort can contribute person-time to both DAA exposure and no DAA exposure. DAA exposure is a function of time. The no DAA exposure starts at the enrollment/baseline image (Index Date; i.e., successful treatment of HCC) and continues until the participant has an event (i.e., HCC recurrence), initiates DAA therapy, completes the study without initiating DAA therapy, or is otherwise censored. The DAA exposure starts at the first date a DAA is initiated and continues until the participant has an event, completes the study, or is otherwise censored. Participants are censored in whichever exposure type they are in (no DAA exposure or DAA exposure) if they receive IFN treatment, a liver transplant, die, withdraw from the study, or are otherwise removed or lost to follow-up while enrolled in DAA-PASS. Participants that receive DAA therapy starting on the date of Enrollment/Baseline only contribute person-time-to DAA exposure and participants that never receive DAA therapy only contribute person-time to the no DAA therapy exposure person-time. The completion of the study is defined by obtaining imaging corresponding to the 24-month follow-up assessment. Note that participants who received a liver transplant while enrolled in DAA-PASS will continue to be followed up to 24 months from Enrollment/Baseline.

Additional information on DAA therapy will be collected including, as available, the DAA prescribed, duration of dosing and planned duration, and SVR response. These will be summarized descriptively.

9.7.4. Coding Convention for HCC Recurrence and DAA as Time-Varying Exposure for the Primary Analysis

This section provides additional details on the coding of the HCC recurrence endpoint for analysis. The primary model of time of onset is based on interval-censoring as outlined in Section 9.7.6.1. The intervals between imaging evaluations are not required to have a fixed length and a participant with a missed visit would simply experience an extended interval -- assuming they have a later follow-up assessment. For the analysis, individuals will have a record of an event or not corresponding to each available interval of no DAA exposure or DAA exposure. The table below provides some examples of participant data where t_{i0} is baseline and t_{ij} for $j = 1$ to n_i represent sequential imaging assessment times for the i^{th} participant:

Table 3. Handling of HCC Recurrence and DAA as Time-Varying Exposure

Situation	Handling in Model
Participant completes study without DAA therapy and without detection of a recurrence event	Participant has *n* imaging evaluations that define *n* intervals $(t_{i0}, t_{i1}]$, , $(t_{i\,(ni-1)}, t_{i\,ni}]$ which are labeled to indicate no events and no exposures have occurred.
Participant receives DAA in an interval and has no events	Participant does not experience recurrence during the study and first receives DAA during $(t_{i\,(m-1)}, t_{i\,m}]$ with $m \leq n_i$. This and subsequent intervals are labeled as being exposed to DAA initiation. If a participant receives DAA in the first interval, they are included as having DAA therapy from the beginning of follow-up.
Participant has an HCC recurrence detected at time $t_{i\,k}$.	Participant experiences a recurrence during $(t_{i\,(k-1)}, t_{i\,k})$. For this participant $n_i = k$. Some of the k intervals may be labeled as having no DAA therapy, and some as having DAA exposure.
Participant discontinues prematurely or is censored	Participant has multiple intervals up to the last imaging evaluation at time $t_{i\,k}$ with $n_i = k$.

9.7.5. Conventions for Missing Data and Post-Baseline Data Collection

DAA-PASS collects select covariates at the time of screening. Additional data will be collected as it is available within the participant's record. DAA-PASS has no data collection requirements that are not considered standard of care. Outside of imaging for the assessment of HCC recurrence, data will be available when they appear in the participant's medical record and are not otherwise considered missing. Details will be provided in the SAP as appropriate.

The analysis of the interval-censored data accommodates missed or unavailable HCC assessments for a given time interval if a later HCC assessment is completed. However, the statistical analyses will include a participant's data only up to the time of their last completed HCC assessment and will be censored after that time.

9.7.6. Analysis of Early Risk of HCC Recurrence Associated with DAA Therapy (Primary Objectives and Secondary Objective B)

9.7.6.1. Modeling Approach

A Cox proportional hazards model will be used to estimate the relative risk associated with DAA exposure for the time from baseline to HCC recurrence as determined by an absence of detectable HCC on imaging using the HR for the time-dependent DAA exposure variable. The proposed analysis approach is based on a model that uses a time-dependent risk strategy for interval-censored data. The rationale for this approach was based on the following points:

- DAA therapy administration has a natural variation in practice that introduces an accumulation of DAA exposures over time that relates to patient access to medication, considerations of access to transplant that vary with HCV status, and physician practices
- Accommodates the expectation that most HCV positive participants will likely receive DAA therapy at some point in the first 24 months following HCC treatment intervention (i.e., there

will not be a large pool of participants that remain DAA-free to use as a comparison group after this time)

- The use of this approach creates the ability to recruit a larger number of patients under current medical treatment practices from a known cohort where the possible risk associated with DAA therapy is important
- The plan accommodates use of baseline factors that might be associated with outcomes and/or DAA therapy to address potential biases and confounding by indication
- Allows the ability to set a sample size based on desired precision of the risk estimate

Use of the time-dependent risk model for interval-censored data has been utilized successfully for evaluating the impact on risk of an event in many other settings. The time-dependent risk model for interval censored data is discussed in Zeng, Mao, and Ling (2016)[12]. Good et al (2015)[13] demonstrated the use of time-dependent proportional hazards for a colon cancer model of surveillance data. Additional references are Sparling et al. (2006)[14] and Seaman and Bird (2001)[15].

9.7.6.2. Model Parameters

To address the potential for bias in the estimation of the HR of DAA therapy associated with HCC recurrence, baseline factors are included in the risk model based on possible associations of each covariate with time-to-HCC recurrence or possible associations with time-to-DAA therapy. In addition to the time-varying DAA exposure, the model will include the following baseline covariates as available: alpha-fetoprotein (AFP) level, albumin level, platelet count, MELD score, age in years, gender, diabetes status, alcohol use/AUDIT score ≥ 7, HCC treatment modality, and study centre. In the model, AFP level, albumin level, platelet count, MELD score, and age are interval-scale variables, whereas gender, diabetes status, alcohol use/AUDIT score ≥ 7, HCC treatment modality, and study centre are categorical variables. Study centre will be included in the model as a random effect.

9.7.6.3. Supporting Summaries (Primary Objective)

The following activities are planned to evaluate the robustness of the analysis results to perturbations of the methods and assumptions used, and to fully explore and describe the data.

- Evaluate time to HCC recurrence by treatment of initial HCC.
- Utilize goodness-of-fit measures to explore the appropriateness of the model.
- Evaluate homogeneity of the DAA response across study sites. This may involve only larger sites, pooling, or considering regional differences.
- Descriptive statistics will be used to explore the impact of the period of time the DAA therapy was initiated. A proportional hazards model will also be used to separately code the DAA treatment effect based on those who initiate therapy up to 6 months and after 6 months from the baseline in order to explore the impact of the timing of the initiation of DAA therapy.

- Sensitivity analyses may include: analyses to understand the impact of the proposed handling of DAA therapy that initiates in the interval where a HCC recurrence occurs, an analysis that adds back in the participant follow-up time for those censored due to IFN use, an analysis using time-dependent values of AFP and the MELD score, and an exploration of additional covariates in the model.

9.7.7. Additional Summaries of Study Data

Descriptive summaries will be provided to assist in the study reporting and may include:

- Information on patient participation, participant study completion status, total duration of follow-up
- Information associated with the participant HCC status including the participant MELD score, Child-Pugh Score, performance status, HCV genotype, and all other factors in the primary model
- Timing of DAA therapy
- Extent of HCC (severity) at initial diagnosis,
- Extent (stage and severity [e.g., number and size of tumors, extrahepatic spread, macrovascular involvement]) and aggressiveness of HCC at time of HCC recurrence, and during follow up after DAA exposure versus no exposure
- Information relating to the overall survival and timing of any deaths

The study may also summarize laboratory values before and after the initiation of DAA therapy or following achievement of SVR (when applicable).

9.7.8. Evaluation of Incidence of HCC Recurrence (Secondary Objectives A and C)

Secondary Objectives A and C are to evaluate the adjusted incidence of recurrence of HCC using the endpoint of the number of events.

An analysis approach based on inverse-probability of censoring weighted averages (IPCW) as outlined in Satten and Datta[16] will be used to obtain an adjusted estimate of the cumulative risk and expected total events for the prospective cohort under the assumption that none of the participants had received DAA. For this analysis, a proportional hazards model of the time-to-censoring event of the non-DAA HCC exposure caused by the start of DAA exposure using the primary analysis covariates will be performed. The model parameters will give individual participants IPC weights in order get an adjusted estimate of the cumulative risk and total events had participants not gotten DAA exposure.

This estimate of risk will be compared to the actual observed risk in the cohort (estimated by the complement of the Kaplan-Meier estimator) to assess the impact of DAA use on HCC recurrence in the prospective cohort. The results will be presented at follow-up time points of 3, 6, 9, 12, 18, and 24 months.

In order to obtain CIs for the estimated risk difference and differences in number of HCC recurrence events at each of the time points, bootstrapping will be used to resample participants from the entire prospective population.

The estimated and actual cumulative event counts will be displayed at the indicated time points. Survival and cumulative event curves will be displayed in figures. Information on significance of the modeling parameters used in the IPCW model will be provided.

9.7.9. Secondary Analyses Using the Historical Cohort

The analyses to address Secondary Objectives B and C will (1) estimate the risk of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC, and (2) estimate the incidence of early HCC recurrence among DAA exposed vs. DAA non-exposed patients, by integrating data from the prospective DAA-PASS cohort with data from a historical cohort of HCV patients with no DAA exposure, to permit adjustment for covariates that may differ between patients in the prospective and historical cohorts.

The ITA.LI.CA study cohort has been identified as a source of historical data for this analysis. The ITA.LI.CA database collects data on all consecutive consenting adult patients with HCC who were diagnosed after 2007 (when the database began to capture follow-up clinical and imaging data) and who were managed at ITA.LI.CA participating centers in Italy. Patients were diagnosed with HCC and followed up in each center according to diagnostic and clinical management guidelines at that time. Approximately 40% of patients in ITA.LI.CA are BCLC Stage A at initial HCC diagnosis, and the median follow-up of patients is 24 months. Patient-level data were abstracted from medical records at the time of initial HCC diagnosis and treatment; subsequent data abstractions were performed at the time of any HCC recurrence event. The last verified database update was in December 2016.

The ITA.LI.CA database will be used to assemble data for a historical cohort of HCV-infected patients who were successfully treated for BCLC Stage A HCC with curative therapy, and not treated with DAAs for their HCV infection after HCC diagnosis. Per the ITA.LI.CA investigators, practice among the ITA.LI.CA participating hospitals was such that patients who had HCV (either treatment-naïve or previously treated with IFN-based therapy) were not treated with IFN after successful HCC treatment. A small number of recently-enrolled patients were treated with DAAs; these patients will be excluded from the historical cohort. Therefore, the patients for the historical cohort will include patients who have active HCV infection who were not treated for HCV (IFN-based or DAA-based regimens) during the follow-up period. Prior HCV treatment with IFN-based non-DAA regimens prior to HCC will be allowed. After considering the aforementioned inclusion/exclusion criteria for the prospective DAA-PASS, an initial examination of the ITA.LI.CA database indicates that there will be approximately 400 eligible patients for inclusion in the historical cohort.

The historical cohort will include similar data extracted from the ITA.LI.CA database (where available) as that collected in the prospective DAA-PASS cohort (see Section 9.3). The ITA.LI.CA database includes patient-level data on demographics (sex, age, birth province),

laboratory values, comorbid liver conditions (including but not limited to HCV status), medical history events, concomitant medication use (including hepatotoxic medications), alcohol use, staging of liver disease, HCC diagnosis and tumor characteristics, HCC treatment intervention(s), and prior interferon-based HCV treatment.

Based on a convenience sample size of 50 participants in the prospective cohort and the inclusion of approximately 400 historical cohort participants the expected 95% CI of the HR (assumed to be equal to 1.0) based on a 15% annual recurrence rate is 0.51 to 2.13, and based on a 25% annual recurrence rate is 0.57 to 1.82, and based on a 35% annual recurrence rate is 0.62 to 1.69.
Descriptive summaries for the historical cohort will be provided in similar formats provided for the prospective cohort. Statistical tests will be used to test the null hypothesis that the historical and prospective cohorts are homogeneous with respect to available demographics and baseline disease characteristics.

The analysis for Secondary Objective B will mirror that of the Primary Objective by integrating data from the prospective and historical cohorts. Participants in the prospective cohort with DAA exposure will contribute person-time at risk to both the DAA-exposed condition and the unexposed condition (i.e., the time prior to DAA exposure). Participants in the prospective cohort who never receive DAA therapy during follow-up and all participants in the historical cohort will contribute person-time at risk to the unexposed condition only.

For Secondary Objective C, the assessment of adjusted incidence of HCC recurrence analysis based on the IPCW approach (described in Section 9.7.8) will be performed by integrating data from the prospective and historical cohorts. Similar to the analysis for the Primary Objective, this will be used to provide an estimate of the cumulative incidence rate and number of events in participants receiving DAA therapy when compared to the estimated rates of those participants if they had not received DAA therapy.

9.7.10. Exploratory Objective Analysis Using the Historical Cohort

A non-comparative descriptive summary of the cumulative risk of HCC recurrence over time will be provided for the historical cohort alone. Estimates of cumulative incidence will be provided for 3, 6, 9, 12, 18, and 24 months.

9.8. Quality Control

The DAA-PASS database will be maintained by TPS. Data will be collected as detailed in Section 9.4. The database will be validated in accordance with the procedures of TPS. Data quality will be further ensured through electronic checks, source data verification activities, and clinical monitoring (see Section 10.4). The process will include ongoing assessment of the database to evaluate trends, site performance, and performance of staff (including those abstracting, processing, and monitoring data).

Statistical analyses will be documented in a formal SAP (see Section 9.7). For any data analyses completed, the data used in the analysis will be archived. Analyses will be validated through independent programming.

9.9. Limitations of the Research Methods

Considerations in the choice of study design

A prospective, non-randomized cohort study was chosen and within this cohort the optimal study design to address the research question is being justified hereafter. Considerable effort was given to determining the best methodological approach with which to compare rates of HCC recurrence in the presence and absence of DAA treatment. The conceptual goal of the observational study design is similar to that of a randomized clinical trial: to ensure that patients with DAA exposure are as similar as possible to patients with no DAA exposure with regard to factors related to the outcome (HCC recurrence).

An important challenge of observational studies of drug effects is the identification and mitigation of sources of bias, including confounding (e.g., by indication/channeling bias, etc.), which results from the absence of randomized treatment assignment. Therefore, a major component of developing such a prospective study is careful consideration of potential sources of bias and development of an optimal study design with appropriate inclusion and exclusion criteria and analytical plans using pharmacoepidemiologic methods to address likely bias that may jeopardize the validity of the effect estimate observed.

Two sources of bias were considered in determining the appropriate study design for comparative evaluation: 1) selection bias (bias arising from selection of patients with DAA exposure and patients with no DAA exposure from different source populations) and 2) confounding by indication (i.e., channeling bias or bias arising from differences between patients with DAA exposure and patients with no DAA exposure that impact the underlying risk of recurrence but is not due to DAA treatment).

To minimize selection bias, the use of data from a single prospective cohort of patients is preferable to the use of an externally derived comparator because the former approach increases the comparability of DAA exposure and no DAA exposure, even for factors for which identification or measurement are challenging or infeasible[17]. It has been shown that there is substantial heterogeneity in HCC recurrence rates between studies, due to patient level and study level factors. This further supports the use of an internal comparator to reduce selection bias affecting the estimated DAA effect. Additionally, the heterogeneity of recurrence rates and the various identified and potentially unmeasurable predictors of recurrence risk further illustrates

the need to utilize a design with internal comparator in order to estimate the effect of DAA therapy on HCC recurrence risk.

To mitigate confounding by indication to treat HCV with DAAs, several points were considered. The bias to treat HCV with DAAs exists, regardless of whether an internal contemporary or external historical comparator is used (i.e., it is independent from consideration of selection bias). It is, however, easier to control for confounding with an internal comparator as data on patients and confounders will be collected in a similar manner between the 2 groups. Lastly, as sufficient variability exists in clinical practice regarding timing of DAA use, this allows for an internal HCV no DAA exposure comparator.

For the reasons outlined above, the primary analysis in this study is based on the prospectively collected data in DAA-PASS, comparing DAA-exposure vs. contemporary no DAA exposure time and adjusting for baseline covariates. However, although an internal contemporary comparator is preferable, secondary analyses will be conducted to estimate the risk of HCC recurrence associated with DAA therapy relative to no DAA therapy in a pooled dataset that includes data for patients from the prospective study as well as from patients from a historical cohort. This pooled data approach will expand the amount of HCV no DAA exposure person-time, providing a clearer picture of the risk of early HCC recurrence associated with DAA exposure, and also provide an opportunity to characterize the risk of HCC recurrence in HCV-infected patients prior to the introduction of DAAs.

9.9.1. Limitations of Prospective Model and Study Design

The proposed study design was selected based on the expectations of DAA therapy, how HCC recurrence is assessed, and the expected HCC recurrence rate. This study does have limitations because the DAA therapy is not pre-specified and may vary in a manner that affects the precision of estimators. Further, time-dependent covariates may not be completely captured if they are not part of standard of care. Underlying non-ignorable censoring mechanisms, particularly due to potentially high rates of liver transplantation, could potentially bias study results or could reduce precision.

These biases may exist regardless of whether an internal contemporary (i.e., independent from consideration of selection bias) or external historical comparator is used. The use of an internal comparator allows for easier control since data on participants and confounders will be collected in a similar manner between the 2 groups. Factors that differ between patients treated with DAAs and those untreated or not yet treated, may be static (baseline) factors such as demographics and HCC treatment modality or time dependent confounders such as those that occur or change after baseline and which predict DAA treatment and HCC recurrence.

To address the limitations in the study design, especially given that this is a safety study, sensitivity analyses will be used to evaluate the robustness of the primary results to reasonable perturbations of the methods and assumptions used, measures of goodness of fit will be examined, and auxiliary supportive analyses will be used to aid interpretation of the study.

9.9.2. Limitations of the Historical Cohort Comparison

The historical cohort comparison provides additional non-DAA follow-up time (particularly 12-24 months post HCC treatment), and addresses the potential for unmeasured confounders relating to timing of DAA treatment. The inclusion of the historical cohort data may be difficult to interpret if the treatment of HCC has changed from the pre-DAA to post-DAA era. While the historical comparators provide additional information on the recurrence of HCC among HCV patients, systematic differences in the characteristics of these patients from patients in the DAA-exposure cohort may exist; therefore, the addition of the historical cohort to the analysis may not address possible confounding factors related to the decision to initiate DAA therapy. Statistical adjustment for observed patient characteristics will be carried out but residual confounding may exist.

Analyses involving the historical cohort data may be further complicated by attempting to obtain complete information from older participant records, changes in imaging technology affecting the ability to assess disease progression in a similar fashion, and differences in the timing of assessments. The use of external cohort data decreases the comparability of treated and untreated patients, especially with factors the various identified and potentially unmeasurable predictors of recurrence risk. As mentioned above, bias may exist whether an internal or external comparator is used.

Homogeneity tests are proposed in order to assess the overall homogeneity of the prospective and historical cohorts. Results of these investigations can be used to assist in properly weighting the results of the secondary analyses involving data from the historical cohort against those of the primary analysis based only on the prospective DAA-PASS cohort.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Regulatory Compliance

DAA-PASS will be conducted in accordance with Good Pharmacovigilance Practice (GVP), as applicable, as well as all applicable local and regional regulations. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. DAA-PASS will also be carried out in accordance with local legal requirements.

10.2. Institutional Review Board/Ethics Committee

The DAA-PASS protocol, informed consent form (ICF), and any advertising will be reviewed and approved by an Institutional Review Board (IRB)/ Ethics Committee (EC) before participants are screened for entry. The IRB/EC will comply with applicable ICH and as required locally. A central IRB/EC will be used for sites that allow this option.

Amendments to the DAA-PASS protocol will be subject to the same requirements as the original protocol. The Investigator will submit all periodic reports and updates as required by the

IRB/EC. The Investigator will inform the IRB/EC of any reportable adverse events or reportable protocol violations.

10.3. Informed Consent

Each participant and/or their legal representative will be provided with oral and written information describing the nature and duration of DAA-PASS, in language they can understand, and must document consent in writing to participate before completing any study-related procedures. The signed consent form will be retained with the study site's records. Each participant will also be given a copy of his or her signed and dated consent form.

10.4. Study Monitoring

Sponsor personnel (or designees) will monitor DAA-PASS as outlined in the Clinical Monitoring Plan to ensure compliance with the protocol, and to verify data abstraction/data entry, as appropriate, by direct comparison of source records and the data. This will be handled via centralized monitoring where the source records are available remotely; traditional on-site monitoring will be utilized where source records are not available remotely. Additional on-site monitoring may be necessary during DAA-PASS. The Investigator agrees to permit such monitoring, as well as audits or reviews by regulatory authorities and the IRB/EC.

10.5. Records Retention

The Investigator will maintain adequate records for DAA-PASS including participants' signed consent forms, safety reports, information regarding discontinued participants, and any other pertinent data as required by local and regional regulations and legal contract with the Sponsor.

10.6. Data Privacy

All data used in the study will be anonymized (see Section 9.4). Sponsor policies and local data privacy regulations of each country participating in the study will be followed during data collection, storage, processing, and analyses.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events (AEs) and adverse drug reactions (ADRs) that **occur concomitantly with a specific DAA therapy** will be collected for the prospective DAA-PASS cohort and reported as required by local and regional regulations (e.g., GVP Module VI).

11.1. Adverse Events and Adverse Reactions Definitions

11.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in humans, whether or not considered related to a treatment intervention. It can be any unfavorable and unintended sign (including

laboratory values), symptom or disease. HCC and HCC recurrence will not be reported as AEs in DAA-PASS.

All clinic notes, nursing/staff telephone notes, evaluations and lab results, and other relevant medical records will be used as sources of data for AEs and SAEs. All AEs noted in the medical record will be captured in the DAA-PASS database along with the associated details as abstracted from the medical records and/or reported by the study site staff.

11.1.2. Adverse Events of Special Interest

Some adverse events may be recognized to be uniquely specific to a disease process, treatment intervention, or combination regimen. It is recognized that regulatory authorities or other interested parties may have needs for special classification and data collection around these types of AEs of special interest (AESI).

11.1.3. Adverse Drug Reactions

An ADR is an AE that is a response to a medicinal product and is noxious and unintended.

11.2. Adverse Event and Adverse Drug Reaction Timing

AEs and ADRs will be captured in the DAA-PASS database from enrollment in DAA-PASS until premature discontinuation or study completion.

11.3. Serious Adverse Events

An SAE is any untoward event that:

- results in death (other than from HCC), or
- is life-threatening (HCC is excluded), or
- requires inpatient hospitalization or prolongs an existing hospitalization (NOTE: hospitalization for HCC-treatment or clinical deterioration due to HCC is not considered an SAE), or
- results in a persistent or significant incapacity or significant disruption of the ability to conduct normal life functions (other than from HCC), or
- is a congenital anomaly or birth defect in an infant born by a study participant

Medical and scientific judgment should be used in evaluating other AEs for seriousness, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or require intervention to prevent one of the outcomes defining SAEs. These events may also be considered serious. Examples of such events are intensive treatment for bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

For DAA-PASS, the Investigator or designee will be asked to assign relationship of any SAE to DAA therapy, as applicable.

11.3.1. Adverse Event Reporting

All AEs, including SAEs, collected throughout DAA-PASS will be summarized in aggregate during all reporting efforts referenced in Section 6. Details regarding the reporting methods will be detailed in a separate safety plan and/or in the relevant SAP.

11.3.1.1. Adverse Drug Reaction Reporting Requirements

Any ADR **related to a specific DAA therapy** will be reported by the Sponsor, as appropriate, via relevant reporting systems (e.g., individual case safety reports [ICSRs]), to the local and regional regulatory agencies, and to the MAH of the specific DAA therapy.

Details regarding transmission of any ADR to the MAH of the specific DAA therapy will be detailed in a separate safety plan. Each MAH will follow their company policies with regard to the reporting of any relevant ICSRs

11.3.1.2. Expedited Serious Adverse Event Reporting Requirements

Any SAE that **occurs concomitantly with a specific DAA therapy** will be reported by the Sponsor, as appropriate, via relevant reporting systems (e.g., Form FDA 3500 [MedWatch], ICSR, CIOMS), to the local and regional regulatory agencies, and to the MAH of the specific DAA therapy.

Details regarding transmission of any SAE to the MAH of the specific DAA therapy will be detailed in a separate safety plan. Each MAH will follow their company policies with regard to the reporting of any relevant ICSRs.

Any relevant safety information will be summarized by the MAH of the specific DAA therapy in the appropriate Periodic Safety Update Report and/or development of Development Safety Update Report, if required.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study status, and report(s) will be included in regulatory communications in line with the DAA MAH EU risk management plans and other regulatory milestones and requirements.

Study status and results will be considered for publication, in line with the TARGET-HCC Publication Manual and Publication Plan. In addition, communication(s) at appropriate scientific meetings will be considered, where relevant.

13. REFERENCES

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TABLE 1 References: Additional references that correspond to the updated literature review table in Table 1 follow:

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14. ANNEXES

Annex 1. List of Stand-Alone Documents

The following documents are available upon request.

Number	Document reference number	Date	Title
1	Version 2.0	19 December 2017	Listing of Investigators and details for Study Sites participating in TARGET HCC

Annex 2. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy

EU PAS Register® number: EUPAS22896
Study reference number (if applicable): Version 6.0; 22 November 2021

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

1.1.3 Interim and final reports planned.

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.5
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4 The purpose of the study is to assess risk and provides estimates with associated confidence limits.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2.2.1
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	9.2.2.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

4.2.3: Country of origin is not planned for use in analysis but country of the study sites would be available for analysis

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.7.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7.7
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.7.10

Comments:

5.4, 5.5: The study is an observational study

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8, 9.7.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.5.1 9.7.10
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

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Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

7.1: All subjects are treated for the same indication.

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.7
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.2.2

Comments:

9.3.3: None of the planned covariates require coding.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8, 10.4
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.3 The study is an observational study.

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	4.2, 9.5

Comments:

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Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.4, 10.6

Comments:

13.2 The protocol has yet to be submitted for Ethics Committee/Institutional Review Board review.

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Andrea Mospan

Date: 23/Nov/2021

Signature: Andrea Mospan

Annex 3. MAH Details and Direct-Acting Antiviral Information

MAH Details

Marketing Authorisation Holder	Address and Regulatory Contact
AbbVie Deutschland GmbH & Co. KG	Paul Sugden Associate Director Western Europe Regulatory Affairs – Global Regulatory Strategy Abbvie House Vanwall Road Maidenhead Berkshire SL6 4UB Phone: +44 7584 140100 E-mail: paul.sugden@abbvie.com
Gilead Sciences Ireland UC	Emi Aydin, MSci Director, International Regulatory Affairs Gilead Science International Granta Park, Abington, Cambridge CB21 6GT Phone: +44 (0)1223 897522 Fax: +44 (0)1223 897284 E-mail: emi.aydin@gilead.com
Merck Sharp & Dohme B.V.	Claudia Silva Associate Director, Regulatory Affairs Europe Merck Sharp & Dohme (Europe), Inc. 5, Clos du Lynx 1200 Bruxelles, Belgium Phone: +31 (0) 6 2166 4258 E-mail: claudia.silva@merck.com

Direct-acting Antiviral Information

Active substance(s)*	ATC Code	Medicinal product(s)	Product Reference	MAH(s)
Daclatasvir**	J05AP07	Daklinza	EMEA/H/C/003768	Bristol-Myers Squibb Pharma EEIG
dasabuvir	J05AP09	Exviera	EMEA/H/C/003837	AbbVie Deutschland GmbH & Co. KG
elbasvir/grazoprevir	J05AP54	Zepatier	EMEA/H/C/004126	Merck Sharp & Dohme B.V.
glecaprevir/pibrentasvir	J05AP57	Maviret	EMEA/H/C/004430	AbbVie Deutschland GmbH & Co. KG
ombitasvir/paritaprevir/ritonavir	J05AP53	Viekirax	EMEA/H/C/003839	AbbVie Deutschland GmbH & Co. KG
simeprevir*	J05AP05	Olysio	EMEA/H/C/002777	Janssen-Cilag International NV
sofosbuvir	J05AP08	Sovaldi	EMEA/H/C/002798	Gilead Sciences Ireland UC
sofosbuvir/ledipasvir	J05AP51	Harvoni	EMEA/H/C/003850	Gilead Sciences Ireland UC
sofosbuvir/velpatasvir	J05AP55	Epclusa	EMEA/H/C/004210	Gilead Sciences Ireland UC
sofosbuvir/velpatasvir/voxilaprevir	J05AP56	Vosevi	EMEA/H/C/004350	Gilead Sciences Ireland UC

* Olysio (simeprevir) European Union Marketing Authorisation was withdrawn on 01 May 2018 and is no longer effective within Europe
** Daklinza (daclatasvir) European Union Marketing Authorisation was withdrawn on 26 August 2019 and is no longer effective within Europe

Abbreviations: ATC = Anatomical Therapeutic Chemical classification system; EEIG = European Economic Interest Grouping; EMA = European Medicines Agency; MAH = Marketing Authorization Holder