HARVONI
(LEDIPASVIR/SOFOSBUVIR 90 MG/400 MG FILM-COATED TABLETS)
EU/1/14/958/002

POST-AUTHORISATION SAFETY STUDY GS-EU-337-1820
ANNUAL PROGRESS REPORT

SOF5885-17-527

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ATR	Atripla
BMI	body mass index
COBI	cobicistat
CRA	Clinical Research Associate
CRF, eCRF	Case Report Form, electronic Case Report Form
DSPH	Drug Safety & Public Health
DUS	Drug Utilization Study
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
eGFR	estimated Glomerular Filtration Rate
EU	European Union
EVG	elvitegravir
FAS	Full Analysis Set
FTC	emtricitabine
GPP	Good Pharmacoepidemiology Practices (guidelines for)
HIV (HIV-1)	human immunodeficiency virus (type 1)
HCV	Hepatitis C Virus
ICH	International Conference on Harmonization
LDV	ledipasvir
MedDRA	Medical Dictionary for Regulatory Activities
PASS	post-authorization safety study
PK	pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SAE	serious adverse event
SADR	Serious Adverse Drug Reaction
SmPC	Summary of Product Characteristics
SOF	sofosbuvir
SSR	Special Situation Report
SQQ	Site Qualification Questionnaire
TDF	tenofovir disoproxil fumarate
TVD	Truvada® (FTC/TDF)
VIR	Viread

1. INTRODUCTION

The purpose of this annual progress report is to provide the Pharmacovigilance Risk Assessment Committee (PRAC) with an update on the progress of the post authorization measure (EMEA/H/C/003850/MEA013.2) study GS-EU-337-1820 assessing adults co-infected with chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV-1) infection, who will be prescribed Harvoni whilst receiving HIV treatment containing tenofovir disoproxil fumarate (TDF) and a pharmacokinetic (PK) enhancer.

Following a review of the draft protocol for the study submitted by Gilead Sciences International Ltd. (Gilead), PRAC recommended a number of changes to the protocol that were implemented in the final approved protocol (original, dated 16 March 2016) entitled "An Observational Drug Utilization Study of Ledipasvir/Sofosbuvir and Tenofovir Disoproxil Fumarate + Pharmacokinetic Enhancer Co-Administration in Adults Co-Infected with Chronic Hepatitis C and HIV-1 Infections". The study was subsequently named as the HAVEN (Harvoni and Viread + Pharmacokinetic Enhancer) co-infection study.

The primary study objective is to characterize the frequency of co-administration of Harvoni with TDF + PK enhancers in the post-marketing setting.

The study has a commitment to provide annual study progress reports until the end of data collection. This is the second progress report Gilead has provided PRAC, which provides updates from the ad-hoc interim report that was submitted 21 July 2017.

The conclusions from the July 2017 ad-hoc interim report were as follows:

- Since the study started in December 2016, Gilead observed a noticeable reduction in access to Harvoni as a treatment and its frequency of use. This was attributed to an increase in EMA-approved treatments for HCV, a declining patient pool, and reimbursement / access changes by national health authorities.

- All available data at the time of the July report, including information from the study sites and Gilead's local country affiliate, medical and commercial intelligence, projected a continuing significant reduction of patient starts on Harvoni throughout the study duration.

- The future plan stated was that Gilead would continue to increase the number of participating sites in attempt to enroll as many patients as possible.

- If the continued downward trend in Harvoni usage and patient enrollment was observed at the time of the December 2017 annual report, the main objective of the study to assess the extent of co-prescribing and consequently possible size of the population exposed may have been reached.

  The purpose of this annual progress report is to specifically address PRAC comments as to the recommendations for the study, provide a study status update, as well as detail Gilead's future plans for the study as detailed in Section 4.

2. STUDY STATUS UPDATE

2.1. Site feasibility and qualification

2.1.1. Site feasibility and qualification process

The initial country list in the approved protocol was determined by data collected from literature review and Gilead's local country affiliate, medical and commercial intelligence on the prevalence of HCV/HIV co-infected patients in combination with treatment access to Harvoni. The countries identified were Austria, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the United Kingdom (UK).

Gilead appointed a contract research organization partner (CRO), Mapi Group (Mapi), to manage the study, commencing with the site feasibility and qualification process. This process was performed in four steps:

1) Identification of potential study sites.

Careful consideration was taken to identify the appropriate investigators and sites that would routinely treat specific patient populations, covering both disease areas, and the unique treatment pathway.

Gilead provided Mapi with a list of potential investigators and sites known to (1) have the relevant HCV/HIV co-infected patient population, and (2) be using or soon commencing use of Harvoni during the protocol-defined data collection period. The list was derived from a combination of Gilead's local country affiliate, medical and commercial intelligence, and a database of investigators who have participated in previous HCV and/or HIV clinical trials. Mapi supplemented the list with additional potential investigators and sites from internal and external databases, and subsequently a final consolidated investigator and site list was approved by Gilead to contact for interest in the GS-EU-337-1820 study.

2) Gilead contacted potential investigators/ sites via email and/or through direct contact by the Gilead local affiliate and provided information about the study. All interested investigators/sites completed a feasibility questionnaire requesting information on the treatment utilized, patient population, and general site logistics. Multiple attempts, where applicable, were made to reach all potential investigators/sites to confirm interest and complete the questionnaire.

3) At the end of this process, all questionnaires received were reviewed and the most suitable sites, based on an analysis of feedback provided, were chosen for a selection visit.

4) The site selection visits were completed remotely by a Mapi Clinical Research Associate (CRA). Information/outputs from the selection visits added greater detail on the patient population and treatment management options available at sites, and confirmed the investigators'/sites' willingness and ability to conduct the study. All suitable sites at this stage were to be included in the GS-EU-337-1820 study.

Table 1. Site feasibility and qualification milestones

Activity	Dates
Invitation letter and questionnaire to potential /investigators/sites	May 2016 – Sep 2016
First site identified for site selection visit	July 2016
First site confirmed participation	July 2016

2.1.2. Site qualification progress – December 2016

The qualification progress of sites that were contacted and selected by the end of 2016 is shown in Table 2. The aim was to identify approximately 50 sites who collectively could achieve the targeted sample size of 2000 patients.

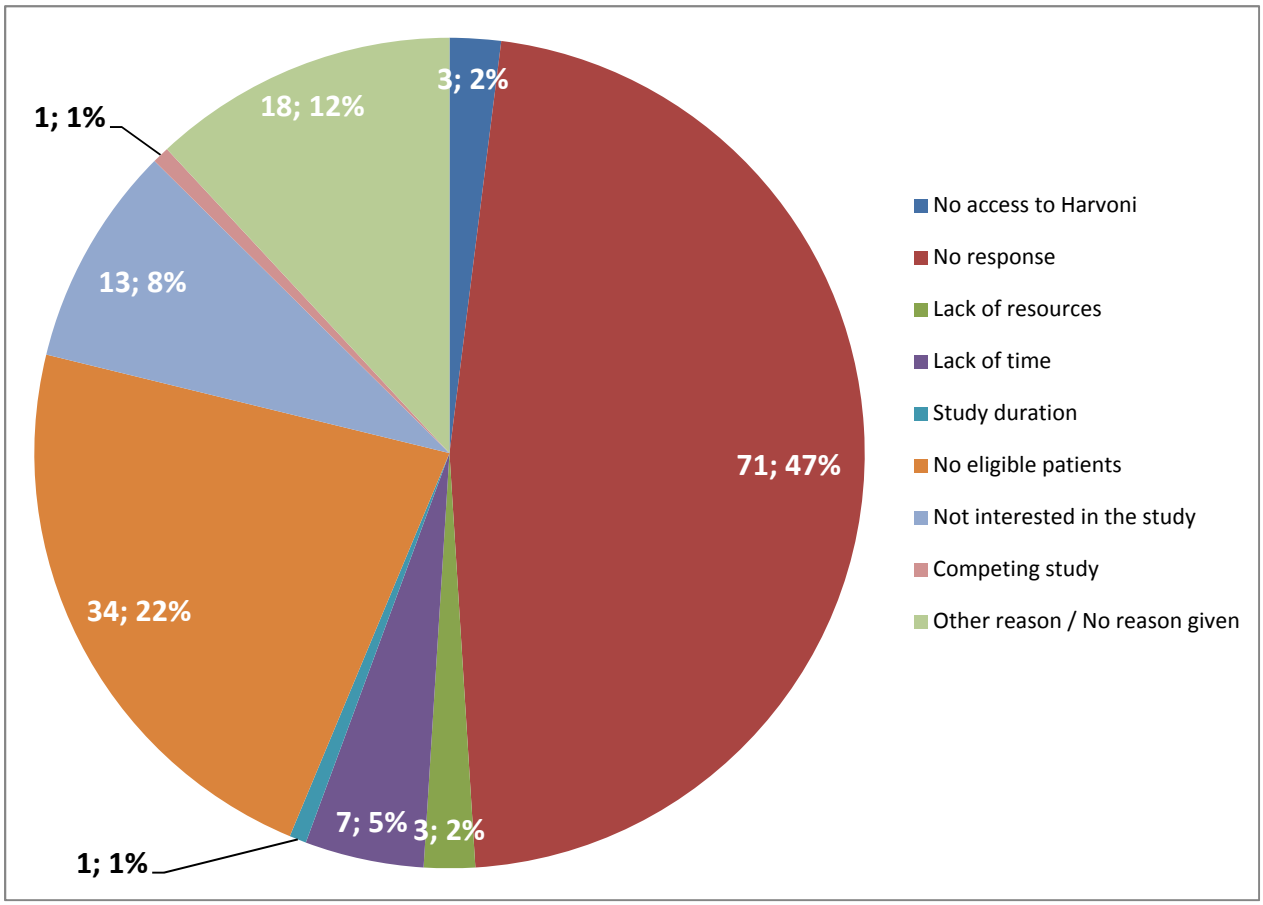
Table 2. Summary of site qualification status - December 2016

Country	Number of sites invited to participate in the study	Number of responders - completed questionnaires by site	Number of sites chosen for selection visit	Sites approved for participation in study
Austria	5	1	1	0
France	36	10	8	7
Germany	40	12	9	9
Italy	20	13	11	9
Netherlands	20	0	0	0
Poland	9	2	2	1
Portugal	12	5	4	3
Spain	18	13	11	10
Sweden	9	2	2	1
Switzerland	8	0	0	0
UK	47	15	9	7
TOTAL	**224**	**73**	**57**	**47**

Out of the 224 sites that were initially invited to participate in the study, 73 (33%) completed the questionnaire, and 57 (25%) of those were suitable for the next step of a selection visit.

There were 151 sites that did not complete the questionnaire – the reasons for non-participation were requested from each site and are summarized in Figure 1 below.

Figure 1. Reasons for site non participation (N=151)



2.1.3. Site qualification evaluation

After evaluating the feedback responses received during the site feasibility and qualification process, Gilead chose the most suitable countries and sites that could adequately contribute to the study. The rationale for the omission of countries identified in the original anticipated country list or inclusion of new countries is detailed below:

<u>Austria</u>

Five suitable investigators were identified initially and only one site confirmed interested. The main reasons cited for the low interest were a restricted eligible patient population and Harvoni not being reimbursed at the time. Unfortunately, despite multiple attempts to organize a selection visit, the one interested site became unresponsive and the country was closed.

Netherlands

Table 2 shows a high level of engagement from sites in the Netherlands initially. However, due to a national program that gave immediate access to Harvoni and treated HCV patients including those HIV co-infected, regardless of cirrhotic state, only a minimal number of relevant patients were left available. Therefore the country was closed.

Switzerland

No sites confirmed interest in participating in the study and response of any kind was very low with no clear reason obtained. Therefore the country was closed.

Ireland

The Gilead local country affiliate highlighted initial interest from investigators/sites in Ireland to participate. Two sites were identified with a suitable patient population and access to Harvoni after the feasibility and qualification process. Therefore Ireland was added as a new country.

Additional sites changes

Upon reviewing the high levels of interested and suitable sites during the feasibility and qualification process, Gilead increased the number of participating sites in Spain, Italy and Portugal. Conversely, an adjustment to the sites in France and the UK was seen due to smaller number of committed sites than anticipated.

2.1.4. Summary of sites selected

The main challenges experienced during the initial site qualification process were identifying countries and sites with the following: (1) a relevant and eligible patient population still requiring HCV treatment, and (2) access to prescribe Harvoni where either reimbursement models at national, regional and/or site level were not in place, or had been in place a long time prior to study start and consequently exhausted the patient pool. The number of participating countries reduced from 11 to 9 (although Ireland was added), and the number of sites approved to participate increased from 47 at the end of 2016, to 52 at the end of the site selection process. Additional sites were identified in Ireland, Italy, Poland and Portugal.

Since the end of the initial site selection process, there has been an observed decline in the number of originally selected sites taking part in the study. This is mainly due to the continuing change in the Harvoni prescription landscape across the target study countries, as noted below. In an attempt to mitigate this, and maintain initiation of the initial target number of sites, Site Qualification Questionnaires (SQQ) were distributed to new potential sites. These additional sites were identified from a combination of Gilead's local country affiliate, medical and commercial intelligence.

Belgium was also considered as a potential new study country due to the expected efficiency in its start-up timelines. As a result, 2 sites in Belgium were invited to complete the SQQ. To further increase the number of participating sites, an additional 3 sites were approached in France, 2 sites in Portugal and 1 site in the UK. However, the vast majority of potential new sites were identified in Spain, where 14 sites were provided the SQQ for completion.

In total 22 additional sites were invited to participate. An updated number of total approved sites for participation after the second wave of SQQs are listed in Table 3.

Table 3. Summary of total approved sites for participation – November 2017

Country	Updated Number of sites invited to participate in the study	Number of responders – completed questionnaires by site	Number of sites chosen for selection visit	Initial Total Sites approved for participation	Updated Total Sites approved for participation after second SQQ wave
Belgium	2	0	0	0	0
France	39	11	9	7	8
Germany	40	12	9	9	9
Ireland	3	2	2	2	2
Italy	20	13	11	10	10
Poland	9	2	2	2	2
Portugal	14	7	4	4	4
Spain	32	24	22	10	21
Sweden	9	2	2	1	1
UK	48	15	9	7	7
TOTAL	**216**	**88**	**70**	**52**	**64**

The results of the second distribution of SQQs identified an additional 12 sites which were ultimately approved for participation in the study. Eleven of the identified sites were in Spain, and the other site was located in France. The potential patient pool from all newly selected sites was positive, particularly in Spain. Gilead is targeting site initiations for the additional 12 sites to take place late 2017/early 2018. As country approvals are already in place, it is expected start-up efficiencies can be gained to open the sites for enrollment as soon as possible.

Both Belgian sites declined to participate prior to completion of the qualification questionnaire. Their decision was based on the expected low number of co-infected patients to be treated at these sites, as well as the fact other competing HCV therapies are first line.

The two additional sites in Portugal were not chosen for a site selection visit. This was based on the low number of expected patients, as well as an anticipated reduction in Harvoni prescriptions beginning early 2018. In addition, the 2 sites already activated in Portugal have yet to enroll a patient. This further reinforced the decision not to open any extra sites in the country. The 1 additional site in the UK also declined to participate. The rationale from the site was attributed to the expected low usage of Harvoni in 2017/2018.

In summary, the addition of the new sites from the second wave of site qualifications should enable Gilead to meet the original target of opening 52 sites. The updated expected number of sites in each country is shown in Table 4 and Table 5 below.

2.2. Planned site activations and target activation dates

At the time of the ad-hoc progress report submitted in July 2017, the planned number of site activations was reduced. The reduction to 41 planned sites, with 2 potential back-up sites, occurred after the original 52 sites were approved for participation. Lower than expected site numbers were observed in Poland, Portugal, Italy and the United Kingdom. Gilead attributed the initial reduction in sites to the following:

1) The competitive treatment environment for HCV patients. Due to the increased choice of approved HCV therapy from other companies and availability of Gilead's Epclusa, Harvoni may no longer remain the first-line treatment across many European countries. For example, as of June 2017, the National Health Service in the UK repositioned Harvoni as the second-line treatment for patients with genotypes 1 and 4, and the fourth-line treatment for other patient populations. As a result, a site in the UK withdrew participation, and indicated that they will use the new first-line treatment over Harvoni in most instances and the anticipated diminished pool of relevant eligible patients did not warrant participation in the study.

2) Harvoni is not/will not be accessible as it is no longer reimbursed nationally. For example, as of June 2017, national legislation in Italy has stopped reimbursement of Harvoni. This impact on patient access to Harvoni will greatly reduce the patient population size of Harvoni. Although there are currently 2 sites activated in Italy, Gilead no longer plans to initiate the remaining 8 sites, unless the investigators/sites can demonstrate that local use is still possible.

3) The majority of HCV/HIV co-infected patients prescribed Harvoni have already been treated by the site prior to the site initiation, and therefore the initial patient population is not eligible for the GS-EU-337-1820 study. As of June 2017, this was evident with a Portuguese site that withdrew participation due to this factor.

4) The facilities to treat patients were no longer viable due to unforeseen logistical issues with the Investigator and site as of June 2017; this was evident in a Polish site that withdrew participation.

These factors were provided by sites as rationale for withdrawing interest in taking part in the study. This was further supported by, and in line with the latest information received from Gilead's local country affiliate and medical colleagues.

Based on latest estimates, the remaining planned site activations and corresponding target activation dates have been updated and are shown in Table 4. The target number of sites has been updated to include the additional sites identified from the second wave of qualification questionnaires and subsequent site approvals.

Table 4. Planned sites activations

Country	Updated number of total planned sites	Number of sites to be activated	Planned/Actual Activation Dates
France	8	1	Dec 2017 / Jan 2018
Germany	9	0	All sites activated
Ireland	2	2	Nov/Dec 2017
Italy	1	0	All sites activated
Poland	1	0	All sites activated
Portugal	3	0	All sites activated
Spain	21	11	Dec 2017 / Jan 2018
Sweden	1	0	All sites activated
UK	6	2	Nov/Dec 2017
TOTAL	**52**	**16**	

Ultimately, the reduction in the total expected site number noted in the July 2017 ad-hoc progress report, stimulated the activity to identify new study sites, and led to the inclusion of additional sites in Spain and France, 11 and 1 respectively. With the newly added sites, Gilead will be able to initiate the target number of 52 sites as originally planned, in an attempt to identify and enroll as many patients as possible.

2.3. Site and recruitment status as of November 2017

Data collection started at the end of Q4 2016. The first site was activated in Germany on 31 October 2016 and the first subject was entered into the database on 13 December 2016.

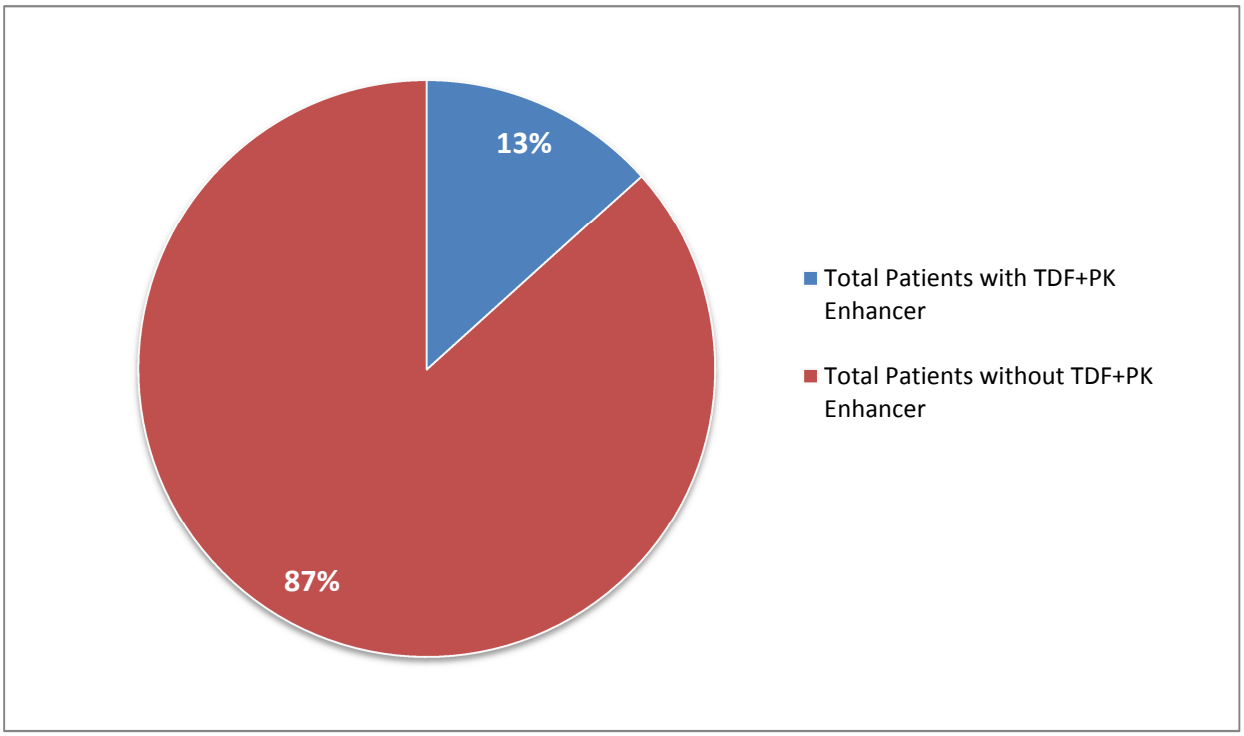
The recruitment status by country as of 30 November 2017 is shown in Table 5. There has been a total of 143 subjects enrolled. This is an increase of 94 patients since the interim progress report submitted in July 2017.

Table 5. Sites activation and subject recruitment status as of November 2017

Country	Initial Target number of activated sites	Updated Target number of activated sites	Number of activated sites	Total enrolled patients	Total non-TDF+PK Enhancer	Total TDF+PK Enhancer
France	7	8	7	21	16	5
Germany	9	9	9	38	32	6
Ireland	2	2	0	0	0	0
Italy	10	1	1	0	0	0
Poland	2	1	1	3	3	0
Portugal	4	3	3	0	0	0
Spain	10	21	10	66	58	8
Sweden	1	1	1	8	8	0
UK	7	6	4	7	7	0
TOTAL	**52**	**52**	**36**	**143**	**124**	**19**

Figure 2 below identifies the breakdown of enrolled patients to date, whether they fall within the TDF+PK enhancer group, or are patients that are receiving HIV treatment without TDF+PK enhancer. From the total of 143 patients enrolled, only 19 (13%) are currently receiving an antiretroviral (ARV) therapy containing TDF+PK enhancer and commencing Harvoni therapy. At the time of the ad-hoc July progress report7 patients from the 49 enrolled were within the TDF+PK enhancer group.

Figure 2. Breakdown of enrolled patients by treatment group



2.4. Projected subject enrollment

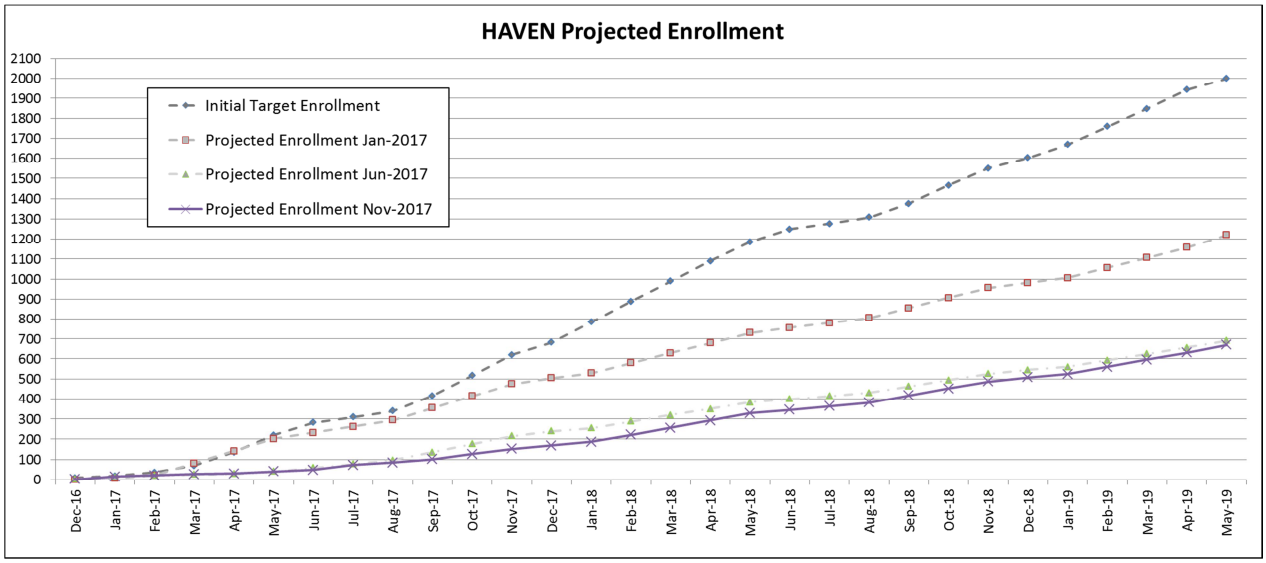
Based on the latest estimate from November 2017, there has been a substantial change in projected subject enrollment versus the initial target enrollment for each country, with a continuing downwards trend from July to November 2017. This is shown below in both Table 6 and Figure 3.

Table 6. Previous and current enrollment projections

Country	Initial country enrollment target – July 2016	Projected enrollment – January 2017	Projected enrollment – June 2017	Projected enrollment – November 2017
France	280	173	117	101
Germany	360	201	148	88
Ireland	70	10	6	4
Italy	400	361	6	0
Poland	70	25	21	17
Portugal	140	117	43	10
Spain	400	323	307	417

Country	Initial country enrollment target – July 2016	Projected enrollment – January 2017	Projected enrollment – June 2017	Projected enrollment – November 2017
Sweden	35	11	15	13
UK	280	0	33	21
TOTAL	**2000**	**1221**	**697**	**670**

Figure 3. Updated total enrollment projections – November 2017



Taking into account both actual and anticipated enrollment figures based on the current information, the total number of enrolled patients for this study by the end of May 2019 is expected to be:

- 600-800 HIV/HCV co-infected patients receiving Harvoni for their treatment of HCV and an ARV regimen for their treatment of HIV

The November enrollment projections are within the same range as stated in the ad-hoc July 2017 progress report. The projections are based on feedback from sites, incorporating projected Harvoni use in the HCV/HIV co-infected population, as well as utilizing Gilead's local country affiliate, medical and commercial intelligence regarding expected Harvoni usage per country over the course of the GS-EU-337-1820 enrollment period.

The latest projection of 670 patients is marginally lower than the June 2017 projections, and is inclusive of the newly identified sites in France and Spain expected to commence enrollment early 2018. The additional variations in expected enrollment are explained below.

The reduction in projected total enrollment remains attributed to the factors listed in the ad-hoc July 2017 progress report. These factors also coincided with the reasons that a lower than expected site number was initially observed prior to the addition of new sites in France and Spain, as mentioned above. Further detail has been included since the July progress report to more accurately reflect contributing factors observed at the time of this annual report.

1) Country and site start-up delays

Due to the extended review cycle during the finalization of the study protocol with the PRAC (initial full protocol submission on 30 October 2015 and final CHMP opinion on agreed protocol 23 June 2016), the start of the study was later than anticipated during the original study conception. This resulted in the first subject enrollment commencing in December 2016 as opposed to the planned date of October 2016.

Subsequent challenges with several country and site approvals, in conjunction with site contract negotiation timelines, were greater than originally expected. This was evident in France, where a change in legislation for non-interventional studies in Q4 2016 delayed regulatory submission and approvals to early 2017, and Spain, where the AEMPS extended the approval timelines due to administrative error in the submitted package. At site level, Italy in particular, was shown to have a protracted contract approval cycle.

As a result, fewer sites have been activated to enroll patients than originally planned. Further start-up delays were observed in Ireland and Poland due to complexities at the site level with regards to contracting and local approvals. However, since the July report, the one site in Poland has been initiated and enrolled its first patient soon after.

2) Relevant patients already treated at sites at time of site initiation visit (SIV)

Based on feedback received from sites during SIVs, previously eligible patients had already commenced HCV treatment prior to the SIV, and as per the protocol, are no longer eligible for the study. Due to the increased treatment choice and access (described in Section 2.2), the pool of HCV/HIV co-infected patients has continued to decrease since study start in 2016. This has been evident in Portugal where a site declined to participate in the study as the previously identified patient pool had been treated, thus reducing the expected enrollment numbers from Portugal. This was the case in the ad-hoc July report, and remains a factor at the time of this annual report, where the initiated sites in Portugal are yet to enroll any patients.

3) Changes in predicted site enrollment totals from study start to Q4 2017

In conjunction with the abovementioned point, the predicted enrollment total at the majority of target sites has been greatly reduced. During the feasibility and qualification process, the targeted number of patients per site was discussed and estimates given in 2016. By Q2 2017, where the majority of SIVs were completed, at least one site in all countries had requested this number be reduced in the final executed contract. This factor has continued to impact the predicted enrollment as additional sites have been initiated in Q3 and Q4. This factor has had a substantial impact on the enrollment projections. This has been particularly evident in the UK, where an

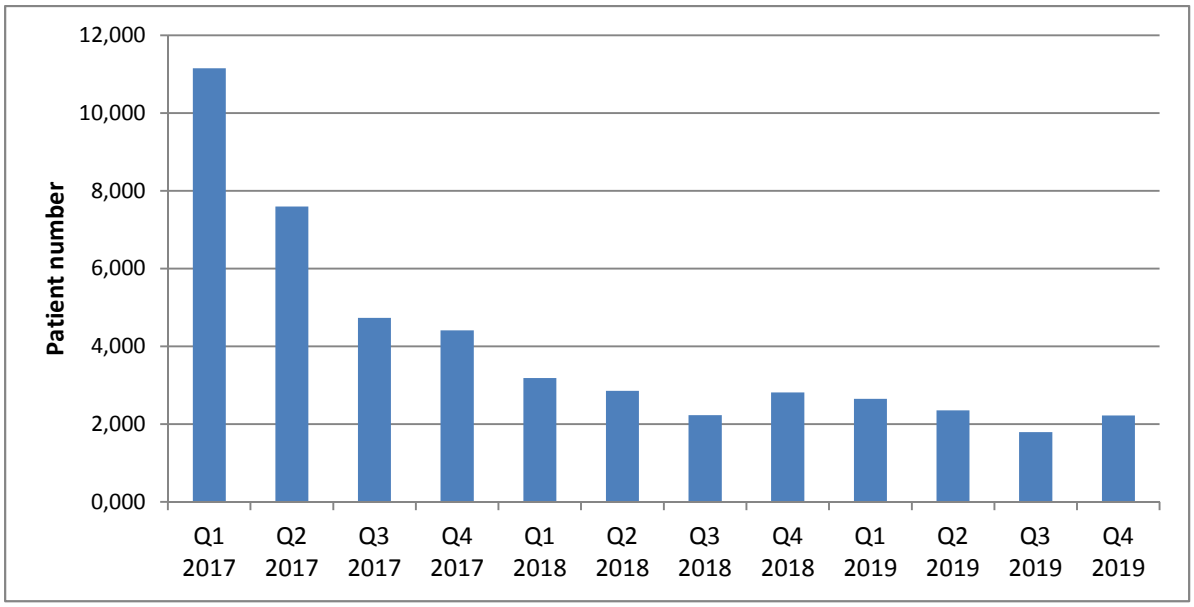
estimated target of approximately 40 patients per site has been replaced with an average of 5 patients per site.

4) Changes in the Harvoni prescription environment in target countries

As previously stated in the ad-hoc July progress report, Harvoni use continues to be impacted by the competitive HCV treatment environment in certain countries. Gilead has seen access completely halted in Italy, whilst other countries such as the UK, Germany, Sweden, and Portugal have seen Harvoni re-positioned and no longer available as first-line treatment for any genotype. This has impacted the number of patients utilizing Harvoni in the real world setting.

This factor has continued to significantly impact enrollment on the study, and is the main contributing reason why projected enrollment in all study countries, apart from Spain, has been further reduced since the ad-hoc July report. The largest impact is expected within Germany and UK. Feedback from sites in Germany indicates Harvoni prescriptions will continue to decline as other approved treatments are preferred. This has substantially reduced the expected enrollment potential of the sites in Germany, which Gilead will continue to monitor into 2018. Within the UK, in Q3 2017 Harvoni was further re-positioned as a new tender was approved. As a result, no new patients are likely to be enrolled in the UK for a minimum period of six months; however, this is expected to be longer. Figure 4 below shows the expected decline in Harvoni usage based on actual sales to date and quarterly market projections in all the participating study countries and throughout the study enrollment period. From Q1 2017 to Q4 2019, there is a dramatic 80.0% decline anticipated for new patient starts.

Figure 4. Actual and projected Harvoni uptake in HAVEN study countries (Q1 2017 – Q4 2019)



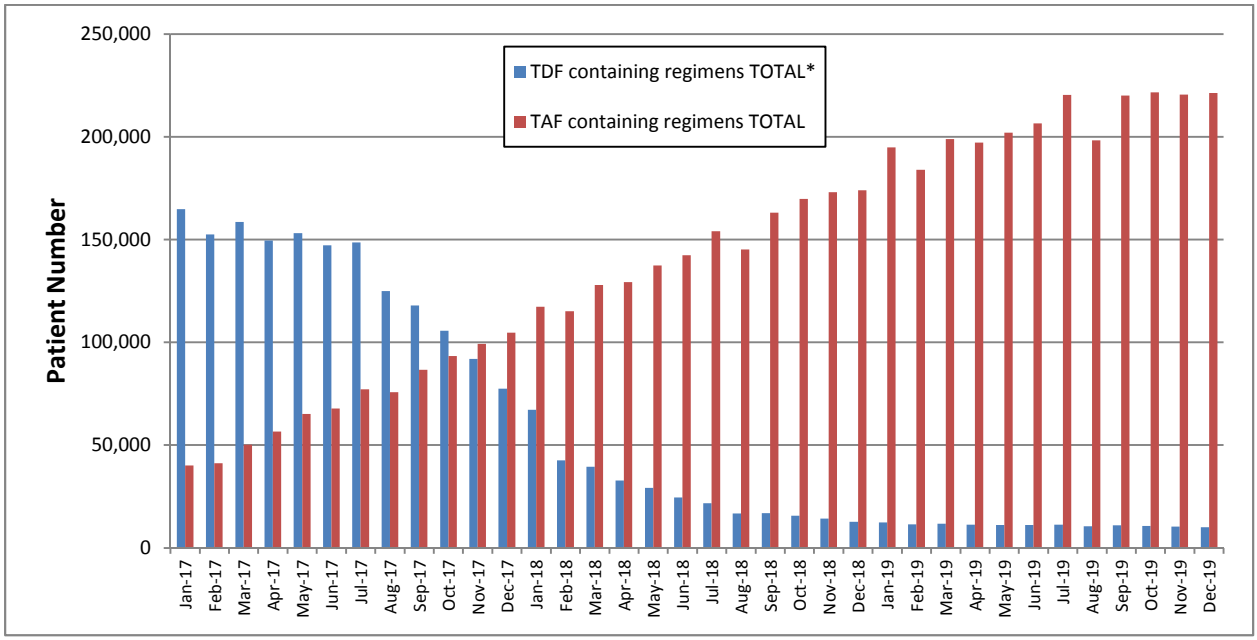
Source: IMS/GERs databases, registries and primary market research

As mentioned above, in an attempt to mitigate the expected continuing decline in Harvoni uptake across the study countries, additional sites will be initiated in Spain and France. At this point, the feedback from sites indicates the patient pool within Spain will remain high in the short term, and is the reason an additional 11 sites will be added within the country. However, even though additional study sites with good enrollment potential are being included, Gilead still expects patient uptake to decline in Spain and the enrollment projections to decrease as a result.

5) Changes in the TDF prescription environment in target countries

In addition, it is anticipated there will continue to be further variations in both the HCV and HIV prescription landscapes with the continuing reduction in Harvoni utilization, and the expectation that the majority of patients currently receiving TDF for treatment of HIV will be switched to TAF-based regimens by the end of 2018. Figure 5 below indicates the expected reduction in TDF vs TAF based HIV therapies in HIV-infected patients overall, across all of the participating HAVEN study countries through to the end of 2019. The figure includes TDF based treatments that either are included as part of a single tablet regimen (i.e., Stribild® [EVG/COBI/FTC/TDF]) or could be used concomitantly with a PK enhancer (i.e. Truvada® [FTC/TDF] and Viread® [TDF]).

Figure 5. Actual and projected TDF vs. TAF containing regimen uptake in HAVEN study countries (Q1 2017 – Q4 2019)



*Includes TDF containing regimens that contain a PK enhancer (Stribild), or could be used in combination with a PK enhancer. The data excludes Atripla and Eviplera which are highly unlikely to be used in combination with a PK enhancer; however this may be the case for a small number of patients

The estimates do not take into account generic versions of TDF that are expected to become available in 2018, or the smaller subset comprised of the HCV/HIV co-infected population. However, the significant expected increase for the use of TAF-containing regimens suggests that the number of patients prescribed generic versions of TDF may not be substantial. Data from a chart audit review from Therapy Watch EU completed by 253 HCV prescribers within the EU5 countries identified that only 7% of the total 674 patients who were prescribed Harvoni throughout the first 3 quarters of 2017, were also co-infected with HIV. Of the 47 co-infected patients prescribed Harvoni, a quarter received Stribild, Truvada, and Viread as their HIV treatment.

As outlined above and for the multiple contributing factors that make it impossible to reach the targeted overall study enrollment numbers, Gilead concludes that it is already clear that the co-prescribing of Harvoni with TDF+PK enhancers is already minimal and due to decrease further in the future. Therefore, Gilead concludes that by a different route than initially expected, the primary objective of the study has actually been met.

3. SUBJECT DATA SUMMARY

3.1. Baseline Characteristics

As of the cut-off date, 19 subjects have been enrolled receiving Harvoni and TDF + PK enhancer treatment. Table 7 presents a summary of subject baseline characteristics at the initiation of Harvoni treatment.

Table 7. Baseline characteristics for subjects with Harvoni and TDF+PK Enhancer treatment

	N (%)
Total	**19**
Age (years)	
< 30	0
31 – 44	8 (42.1)
45 – 54	9 (42.1)
55 – 64	2 (10.5)
≥ 65	0
Sex	
Male	17 (89.5)
Female	2 (11.5)
Race	
White	14 (73.7)
Other	2 (11.5)
Data entry not permitted	3 (15.8)
Country	
France	5 (26.3)
Germany	6 (31.6)
Spain	8 (42.1)
HCV Genotype*	
1*	16 (84.2)
1a	13 (68.4)
1b	2 (10.5)
4	3 (15.8)
HCV Treatment History	
Treatment Naïve	15 (78.9)
Treatment Experienced*	4 (21.1)
Peg-IFN + Ribavirin	3

	N (%)
Total	**19**
HIV Concomitant Treatment*	
Stribild (EVG/COBI/FTC/TDF)	5 (26.3)
Truvada (FTC/TDF)	12 (63.2)
+ Atazanavir and Ritonavir	2 (10.5)
+ Darunavir and COBI	5 (26.3)
+ Darunavir and Ritonavir	4 (21.1)
+ Lopinavir and Ritonavir	1 (5.3)
Viread (TDF) + Darunavir, Ritonavir, and Etravirine	1 (5.3)

*Data up to 30 November 2017. Total may not sum to 100% due to missing/unknown data.

3.2. Reported Safety Events

Table 8 below shows the adverse events that have been reported to date amongst the 19 enrolled subjects treated with Harvoni and an ARV therapy containing TDF+PK enhancer.

At the time of this report, there have been six adverse events reported in four subjects, none of which were renal related events. There was one reported death due to multi visceral failure from suspected myeloproliferative syndrome that was not attributed to either Harvoni or TDF utilization.

Table 8. Listing of reported adverse events

Subject ID	System Organ Class*	Preferred Term*	Reported Term	Seriousness (Y/N)	Onset Date	End Date	Related to Harvoni By Investigator (Y/N)	Related to TDF Containing Product By Investigator (Y/N)
0001	General disorders and administration site conditions	Fatigue	FATIGUE	No	06Jan2017	23Jan2017	Related	Not Related
0076	Psychiatric disorders	Nightmare	NIGHTMARE	No	10Aug2017	14Sep2017	Related	Related
0076	Musculoskeletal and connective tissue disorders	Myalgia	MYALGIA LOWER EXTREMITY	No	10Aug2017	14Sep2017	Related	Related
0078	General disorders and administration site conditions	Multiple organ dysfunction syndrome	MULTI VISCERAL FAILURE	Yes	12Sep2017	01Oct2017	Not Related	Not Related
0081	Psychiatric disorders	Irritability	MOOD CHANGES (SHORT TEMPEREDLY)	No	.	.	Related	Not Related
0081	Psychiatric disorders	Sleep disorder	SLEEP DISORDER	No	.	.	Related	Not Related

*Adverse events were mapped according to MedDRA Version 20.0.

4. STUDY MILESTONES & FUTURE PLANS

The current status of the GS-EU-337-1820 post authorization measure compared to the originally defined milestones is presented in Table 9.

Table 9. Study milestones and status

Milestone	Planned Date	Actual Date / Status
Start of subject enrollment / data collection	N/A	December 2016
Annual Interim study progress report 1	December 2017	December 2017
Annual Interim study progress report 2	December 2018	pending
End of enrollment	May 2019	pending
End of data collection	October 2019	pending
Final report of study results	May 2020	pending

The annual interim study progress report submissions were rescheduled to December of each year, as indicated in Table 9, to coincide with the actual start of subject enrollment / data collection. The end of data collection is still scheduled to occur in October 2019, however as mentioned in Section 2.4, a substantially lower sample size is expected, despite the inclusion of additional sites since the ad-hoc July report.

4.1. Plans for the future

Although Harvoni is still utilized throughout Europe to treat HCV/HIV co-infected patients, Gilead has continued to see a noticeable reduction in access to treatment and frequency of use since the study started in December 2016. This decline was observed at the time of the July progress report, and is expected to continue into 2018 and throughout the remaining enrollment period. The reduction has been driven by an increase in EMA-approved treatments for HCV, declines in utilization of TDF-based regimens for HIV, a declining patient pool, and reimbursement / access changes by national health authorities. In addition, all available data at the time of this report, including information from the study sites and Gilead's local country affiliate, medical and commercial intelligence have projected a continuing significant reduction in patients prescribed Harvoni throughout the anticipated study duration. Since the ad-hoc report submitted in July, a decline in patient enrollment has continued in all activated study countries, with the largest impact being witnessed in Germany, due to patients being prescribed alternative HCV therapies.

Gilead has remained dedicated to activating the newly identified sites in Spain and France, in an attempt to enroll as many patients as possible. It is expected that by end of Q1 2018 all study sites will be initiated, inclusive of the newly identified sites. Based on current enrollment projections, it is expected that approximately 60% of the total patients will be enrolled in Spain. Despite the efforts to include additional sites, if the prescribing position of Harvoni changes within Spain in the same way it has in other EU markets, there will be a significant impact on the total study enrollment, which has already shown declines across other EU countries in both Harvoni and TDF prescription environments overall.

The increasing downward trend in Harvoni usage and patient enrollment is expected to be observed throughout 2018. Given that the main objective of this study was to assess the extent of co-prescribing and consequently possible size of the population exposed, current data indicates that the study objective has been addressed. Such data suggesting the low usage would thus indicate a low public health concern for HIV/HCV co-infected patients. Therefore, Gilead proposes to PRAC to terminate the study early. Gilead will continue with the initiation of new sites as planned until a response is received from PRAC regarding the proposal to terminate the study early.

4.2. Gilead's response to PRAC's assessment report received October 2017

In response to the member state's suggestion included in the PRAC assessment report (EMEA/H/C/003850/MEA/013.3 dated 19 October 2017) to consider the inclusion of Epclusa (SOF/VEL) patients into the study to boost enrollment, Gilead does not feel this addition to the GS-EU-337-1820 study would appropriately address the safety objective of the study.

The study was designed to specifically investigate the drug utilization of Harvoni and TDF+PK enhancer in a HCV/HIV co-infected population. The current Epclusa RMP does not contain a similar concern as was raised for Harvoni, due to the fact that this matter was identified prior to Epclusa approval and the dataset for Epclusa MAA already contained substantial data that directly addressed the concern for co-infected patients.

The potential DDI risk has been evaluated in a number of clinical studies with SOF/VEL and concomitant drugs, including antiretroviral HIV treatments. Based on short-term safety and PK data from the Phase 1 Study GS-US-342-1326, SOF/VEL may be co-administered with Stribild, darunavir (DRV)+ritonavir (RTV)+FTC/TDF, atazanavir (ATV)+RTV+FTC/TDF, and lopinavir (LPV)/RTV+FTC/TDF. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to premature study drug discontinuation were reported in the study. Also, in the Phase 3 Study GS-US-342-1202 (ASTRAL-5), treatment with SOF/VEL was safe and well tolerated in 106 adults with HCV/HIV co-infection. At enrollment, subjects were on the following ARV regimens: boosted TDF-containing regimens (52.8%; 56 subjects), non-boosted TDF-containing regimens (33.0%; 35 subjects), and non-TDF-containing regimens (14.2%; 15 subjects). The boosted regimens were those containing TDF and RTV or COBI boosted protease inhibitors (PIs) or other agents (e.g., EVG/COBI). With respect to renal safety, there were no Grade 3 or above AEs under the MedDRA Renal and Urinary Disorders system organ class (SOC) reported in any group. Overall, 3 subjects (2.8%) had an AE under the Renal and Urinary Disorders SOC, including pollakiuria, glycosuria, and proteinuria. Of these, two subjects were on boosted TDF-containing regimens

(COBI+EVG+FTC+TDF and ATV+FTC+RTV+TDF), and 1 subject was on a non-boosted TDF-containing regimen (FTC+RPV+TDF). All events were Grade 1 in severity, with no events of concern. A total of 5 subjects (4 on boosted TDF-containing regimens) developed laboratory abnormalities consistent with changes in renal function during treatment; however, no changes were made to any ARV regimens. In the majority of these cases (80%; 4 subjects), these abnormalities were transient and asymptomatic. One subject with persistent abnormalities had chronic kidney disease under the care of a nephrologist predating study treatment. This subject completed study treatment without modifications to his ARV regimen. Additionally, tenofovir exposures following administration of boosted or unboosted TDF-containing regimens with SOF/VEL were within the range of exposure observed in HIV mono-infected subjects using boosted ARV regimens in the absence of SOF/VEL.

With regards to HCV therapies, based on recent feedback from study sites, Gilead is also expecting a further increase in the prescription of competitor products throughout Europe in 2018 among the present declining HCV-infected population. This is expected to continue to have an impact on the HAVEN GS-EU-337-1820 study enrollment as it stands; therefore, the effect observed for Harvoni declining use would be the same for Epclusa.

Additionally, Epclusa data from the same chart audit review from Therapy Watch EU (section 2.4) identified that only 6% of the total 336 patients who were prescribed Epclusa throughout the first 3 quarters of 2017, were also co-infected with HIV. Of the 21 co-infected patients prescribed Epclusa, a third received Stribild, Truvada, and Viread as their HIV treatment, further highlighting the risk of TDF+PK enhancer and Epclusa co-prescription is low.

Furthermore, the set-up time to include Epclusa patients would be substantial and no benefits for enrollment numbers are achievable.

It is for these reasons that Gilead believes including Epclusa patients on the study would not be a suitable approach. As noted in Section 4.1 regarding the continued decline in Harvoni usage, the public health risk for the use of Harvoni with a TDF+PK enhancer is considered low and thus, Gilead proposes to PRAC to terminate the HAVEN study early as the public health concern of the primary objective for this study has been fully addressed.