IQWiG Reports – Commission No. A18-05

Sofosbuvir/velpatasvir/ voxilaprevir (chronic hepatitis C) –

Addendum to Commission A17-35[1]

Addendum

Commission: A18-05
Version: 1.0
Status: 25 January 2018

[1] Translation of addendum A18-05 *Sofosbuvir/Velpatasvir/Voxilaprevir (Chronische Hepatitis C) – Addendum zum Auftrag A17-35* (Version 1.0; Status: 25 January 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Sofosbuvir/velpatasvir/voxilaprevir (chronic hepatitis C) – Addendum to Commission A17-35

Commissioning agency:
Federal Joint Committee

Commission awarded on:
9 January 2018

Internal Commission No.:
A18-05

Address of publisher:
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Keywords: sofosbuvir, velpatasvir, voxilaprevir, hepatitis C – chronic, benefit assessment, NCT02607800, NCT02639338, NCT02639247

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct acting antiviral agent
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
NS5A	non-structural protein 5A
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SOC	System Organ Class
SOF	Sofosbuvir
VEL	velpatasvir
VOX	voxilaprevir

1 Background

On 9 January 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-35 (Sofosbuvir/velpatasvir/voxilaprevir – Benefit assessment according to §35a Social Code Book V [1]).

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had used the results of a subpopulation of a randomized controlled trial (RCT) (POLARIS-2) for the assessment of the added benefit of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for adults with chronic hepatitis C (CHC) genotype 2 and without cirrhosis (research question 2.1) and for adults with CHC genotype 3 and without cirrhosis (research question 3.1). These results were also used for the benefit assessment.

The company included a subpopulation of the RCT POLARIS-4 for adults with CHC genotype 2 and 3 who were pretreated with direct acting antiviral agents (DAAs), but not with a non-structural protein 5A (NS5A) inhibitor (subpopulation within research question 7). This study was not used for the assessment of the added benefit because it did not implement the appropriate comparator therapy (ACT) (individual treatment specified by the physician). The results of this study were presented as additional information in the appendix to the assessment [1].

Based on the data provided by the company in the dossier, complete identification of specific adverse events (AEs) was not ensured for the subpopulations of the POLARIS-2 study and of the POLARIS-4 study presented as additional information. With its comments, the company submitted supplementary information on AEs, which went beyond the information provided in the dossier [3,4]. The G-BA commissioned IQWiG with the assessment of the analyses presented by the company on AEs for the studies POLARIS-2 and POLARIS-4 under consideration of the information in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Data availability on specific AEs of the studies POLARIS-2 and POLARIS-4

In its dossier [2], the company had presented the results of a subpopulation of the RCT POLARIS-2 for the assessment of the added benefit of SOF/VEL/VOX for adults with CHC genotype 2 and without cirrhosis (research question 2.1) and for adults with CHC genotype 3 and without cirrhosis (research question 3.1). These results were used for the benefit assessment.

The company included a subpopulation of the RCT POLARIS-4 for DAA-experienced and NS5A-naive adults with CHC genotype 2 and 3 (subpopulation within research question 7). This study was not used for the assessment of the added benefit because it did not implement the ACT (individual treatment specified by the physician). The results of the subpopulations of this study were presented as additional information in the appendix to the assessment, separated by CHC virus genotype [1].

Specific AEs were included neither for the POLARIS-2 study nor for the POLARIS-4 study presented as additional information. The reason was that the company had not presented the analyses of all AEs by System Organ Class (SOC) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA) for the corresponding subpopulations.

With its comments, the company subsequently submitted corresponding analyses at SOC and PT level for AEs and serious AEs (SAEs). Concurring with the methods described in the dossier assessment [1], specific AEs are chosen using the events that occurred in the relevant study on the basis of frequency and differences between the treatment arms and under consideration of the patient relevance.

Appendix A.1 and Appendix A.2 of the present addendum show common AEs of the respective subpopulation of the studies for research question 2.1 and 3.1, and Appendix A.3 shows those of the POLARIS-4 study presented as additional information.

Study POLARIS-2, research question 2.1

On the basis of the methods described, no specific AEs were chosen for research question 2.1. The result of the assessment A17-35 (added benefit not proven) therefore remains unchanged for research question 2.1.

Study POLARIS-2, research question 3.1

The outcome “psychiatric disorders (SOC)” was identified as specific AE for research question 3.1. Psychiatric disorders did not occur as SAE. Correspondingly, the results on this outcome were allocated to the outcome category “non-serious/non-severe side effects”.

A statistically significant difference in favour of the SOF/VEL/VOX combination for psychiatric disorders was shown between SOF/VEL/VOX (8 weeks) and SOF/VEL (12 weeks)

(relative risk [RR]: 0.40; 95% confidence interval [CI]: [0.20; 0.82]; p = 0.009). Due to the open-label study design and the 4-week difference in observation periods between the study arms (12 weeks for SOF/VEL/VOX, 16 weeks for SOF/VEL), there was a high risk of bias for this outcome. A hint of lesser harm from SOF/VEL/VOX was therefore derived.

Only frequencies of events with RR used as effect estimate were available for the data on specific AEs. The interpretation of the result must take into account that this effect measure is highly biased in the present data situation and that the observed difference between the study arms could be caused by differences in the observation periods. The extent of lesser harm for psychiatric disorders was therefore rated as "non-quantifiable", at most "minor". Under consideration of the bias due to the differences in observation periods, the effect could be no more than marginal.

Table 1 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 1: Positive and negative effects from the assessment of SOF/VEL/VOX in comparison with SOF/VEL (DAA-naive adults with CHC genotype 3, without cirrhosis) (research question 3.1)

Positive effects	**Negative effects**
Hint of lesser harm – extent: "non-quantifiable", at most "minor" (outcome category: non-serious/non-severe side effects)	–
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir	

In summary, there is a hint of a non-quantifiable, at most minor added benefit of SOF/VEL/VOX versus SOF/VEL for DAA-naive patients with CHC genotype 3 and without cirrhosis.

Study POLARIS-4 presented as additional information, research question 7

For the POLARIS-4 study, the outcome "diarrhoea (PT)" was identified, on the basis of the methods described, as specific AE for patients with CHC genotype 1 and 2 virus. A disadvantage of SOF/VEL/VOX in comparison with SOF/VEL was shown for both subpopulations. No specific AEs were identified for patients with CHC genotype 3 virus.

As described in assessment A17-35, the POLARIS-4 study was unsuitable for the assessment of the added benefit. The result of the assessment A17-35 (added benefit not proven) therefore remains unchanged for research question 7.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of SOF/VEL/VOX from dossier assessment A17-35 for research question 3.1 as follows: There is a hint of a non-quantifiable, at most minor added benefit of SOF/VEL/VOX versus SOF/VEL for DAA-naive patients with CHC genotype 3 and without cirrhosis. Under consideration of the bias due to the differences in observation periods, the effect could be no more than marginal. For the other research questions, there was no change in comparison with dossier assessment A17-35.

The following Table 2 shows the result of the benefit assessment of SOF/VEL/VOX under consideration of dossier assessment A17-35 and the present addendum.

Table 2: Sofosbuvir/velpatasvir/voxilaprevir – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
DAA-naive adult patients with CHC genotype 1, without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)	Added benefit not proven
DAA-naive adult patients with CHC genotype 1, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 2, without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 2, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 3, without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Hint of non-quantifiable, at most minor added benefit[b, c]
DAA-naive adult patients with CHC genotype 3, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Hint of lesser benefit[b, d]
DAA-naive adult patients with CHC genotype 4, without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus ribavirin	Added benefit not proven
DAA-naive adult patients with CHC genotype 4, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 5, without cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 5, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 6, without cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 6, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-experienced adult patients with CHC	Individual treatment specified by the physician under consideration of the pretreatment(s), the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, particularly in the case of protease inhibitors.[e]	Added benefit not proven

(continued)

Table 2: Sofosbuvir/velpatasvir/voxilaprevir – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Patients with HBV or HIV coinfection were not included in the study.
c: Under consideration of the bias due to the differences in observation periods, the effect could be no more than marginal.
d: In the POLARIS-3 study included, sofosbuvir/velpatasvir/voxilaprevir was used for 8 weeks. Conclusions on the added benefit in 12-week treatment with sofosbuvir/velpatasvir/voxilaprevir, which is also in compliance with the approval, are not possible on the basis of the study.
e: In accordance with the G-BA's specification it is assumed that interferon-based regimens are not an option for the patients.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HIV: human immunodeficiency virus

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sofosbuvir/Velpatasvir/ Voxilaprevir (chronische Hepatitis C): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-35 [online]. 13.11.2017 [Accessed: 17.11.2017]. (IQWiG-Berichte; Volume 559). URL: https://www.iqwig.de/download/A17-35_Sofosbuvir-Velpatasvir-Voxilaprevir_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Gilead Sciences. Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 03.08.2017 [Accessed: 12.12.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/306/#tab/dossier.

3. Gilead. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks compared to sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-naïve subjects with chronic HCV infection: study GS-US-367-1172 (POLARIS-2); Zusatzanalysen [unpublished]. 2017.

4. Gilead. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 12 weeks and sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-experienced subjects with chronic HCV infection who have not received an NS5A inhibitor: study GS-US-367-1170 (POLARIS-4); Zusatzanalysen [unpublished]. 2017.

Appendix A – Results on side effects

A.1 – DAA-naive adults with CHC genotype 2, without cirrhosis (research question 2.1)

Table 3: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (8 W)** **N = 49**	**SOF/VEL (12 W)** **N = 40**
POLARIS-2		
Overall rate of AEs	26 (53.1)	24 (60.0)
Eye disorders	0 (0)	2 (5.0)
Gastrointestinal disorders	15 (30.6)	11 (27.5)
Nausea	4 (8.2)	4 (10.0)
Diarrhoea	7 (14.3)	3 (7.5)
Abdominal pain	1 (2.0)	2 (5.0)
Abdominal pain upper	2 (4.1)	1 (2.5)
Abdominal distension	2 (4.1)	0 (0)
General disorders and administration site conditions	8 (16.3)	13 (32.5)
Fatigue	5 (10.2)	10 (25.0)
Asthenia	1 (2.0)	2 (5.0)
Infections and infestations	7 (14.3)	6 (15.0)
Injury, poisoning and procedural complications	4 (8.2)	2 (5.0)
Musculoskeletal and connective tissue disorders	6 (12.2)	4 (10.0)
Arthralgia	2 (4.1)	0 (0)
Myalgia	3 (6.1)	1 (2.5)
Muscle spasms	1 (2.0)	2 (5.0)
Nervous system disorders	9 (18.4)	9 (22.5)
Headache	9 (18.4)	5 (12.5)
Psychiatric disorders	2 (4.1)	3 (7.5)
Respiratory, thoracic and mediastinal disorders	3 (6.1)	1 (2.5)
Cough	2 (4.1)	0 (0)
Vascular disorders	2 (4.1)	0 (0)

a: MedDRA version 19.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus; W: weeks

Table 4: All SAEs (SOC/PT) – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (8 W)** **N = 49**	**SOF/VEL (12 W)** **N = 40**
POLARIS-2		
Overall rate of SAEs	3 (6.1)	2 (5.0)
Hepatobiliary disorders	1 (2.0)	0 (0)
Cholelithiasis	1 (2.0)	0 (0)
Infections and infestations	1 (2.0)	0 (0)
Perineal abscess	1 (2.0)	0 (0)
Injury, poisoning and procedural complications	0 (0)	1 (2.5)
Multiple fractures	0 (0)	1 (2.5)
Road traffic accident	0 (0)	1 (2.5)
Musculoskeletal and connective tissue disorders	0 (0)	1 (2.5)
Myositis	0 (0)	1 (2.5)
Psychiatric disorders	0 (0)	1 (2.5)
Suicide attempt	0 (0)	1 (2.5)
Respiratory, thoracic and mediastinal disorders	1 (2.0)	0 (0)
Asthma	1 (2.0)	0 (0)

a: MedDRA version 19.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks

A.2 – DAA-naive adults with CHC genotype 3, without cirrhosis (research question 3.1)

Table 5: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (8 W)** **N = 91**	**SOF/VEL (12 W)** **N = 89**
POLARIS-2		
Overall rate of AEs	72 (79.1)	73 (82.0)
Gastrointestinal disorders	34 (37.4)	26 (29.2)
Nausea	12 (13.2)	12 (13.5)
Diarrhoea	12 (13.2)	10 (11.2)
Abdominal pain	3 (3.3)	2 (2.2)
Abdominal pain upper	4 (4.4)	0 (0)
Vomiting	6 (6.6)	3 (3.4)
Constipation	4 (4.4)	1 (1.1)
Gastrooesophageal reflux disease	3 (3.3)	2 (2.2)
General disorders and administration site conditions	38 (41.8)	35 (39.3)
Fatigue	27 (29.7)	20 (22.5)
Asthenia	8 (8.8)	10 (11.2)
Pyrexia	4 (4.4)	1 (1.1)
Infections and infestations	8 (8.8)	15 (16.9)
Nasopharyngitis	1 (1.1)	3 (3.4)
Upper respiratory tract infection	0 (0)	5 (5.6)
Injury, poisoning and procedural complications	6 (6.6)	3 (3.4)
Metabolism and nutrition disorders	6 (6.6)	6 (6.7)
Decreased appetite	5 (5.5)	4 (4.5)
Musculoskeletal and connective tissue disorders	18 (19.8)	21 (23.6)
Arthralgia	6 (6.6)	7 (7.9)
Myalgia	3 (3.3)	3 (3.4)
Back pain	3 (3.3)	3 (3.4)
Muscle spasms	1 (1.1)	5 (5.6)
Nervous system disorders	29 (31.9)	33 (37.1)
Headache	23 (25.3)	27 (30.3)
Dizziness	3 (3.3)	2 (2.2)

(continued)

Table 5: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1) (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (8 W)** **N = 91**	**SOF/VEL (12 W)** **N = 89**
Psychiatric disorders	9 (9.9)	22 (24.7)
Insomnia	3 (3.3)	9 (10.1)
Anxiety	3 (3.3)	5 (5.6)
Irritability	2 (2.2)	5 (5.6)
Depression	0 (0)	3 (3.4)
Sleep disorder	0 (0)	3 (3.4)
Respiratory, thoracic and mediastinal disorders	7 (7.7)	10 (11.2)
Oropharyngeal pain	5 (5.5)	2 (2.2)
Skin and subcutaneous tissue disorders	7 (7.7)	8 (9.0)
Rash	3 (3.3)	1 (1.1)
Vascular disorders	4 (4.4)	2 (2.2)

a: MedDRA version 19.0.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus; W: weeks

Table 6: All SAEs (SOC/PT) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (8 W)** **N = 91**	**SOF/VEL (12 W)** **N = 89**
POLARIS-2		
Overall rate of SAEs	2 (2.2)	0 (0)
Gastrointestinal disorders	1 (1.1)	0 (0)
Small intestinal obstruction	1 (1.1)	0 (0)
Musculoskeletal and connective tissue disorders	1 (1.1)	0 (0)
Back pain	1 (1.1)	0 (0)

a: MedDRA version 19.0.
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks

A.3 – Additional presentation for DAA-experienced, NS5A-naive adults (research question 7)

DAA-experienced, NS5A-naive adults with CHC genotype 1, with and without cirrhosis

Table 7: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 1, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 78[b]**	**SOF/VEL (12 W)** **N = 66[b]**
POLARIS-4		
Overall rate of AEs	63 (80.8)[b]	50 (75.8)[b]
Cardiac disorders	1 (1.3)[b]	3 (4.5)[b]
Eye disorders	2 (2.6)[b]	3 (4.5)[b]
Gastrointestinal disorders	35 (44.9)[b]	22 (33.3)[b]
Diarrhoea	19 (24.4)[b]	5 (7.6)[b]
Nausea	12 (15.4)[b]	4 (6.1)[b]
Abdominal pain upper	5 (6.4)[b]	4 (6.1)[b]
Constipation	2 (2.6)[b]	3 (4.5)[b]
Dry mouth	1 (1.3)[b]	2 (3.0)[b]
Abdominal pain	2 (2.6)[b]	5 (7.6)[b]
Vomiting	3 (3.8)[b]	2 (3.0)[b]
Flatulence	3 (3.8)[b]	1 (1.5)[b]
Dyspepsia	2 (2.6)[b]	2 (3.0)[b]
Toothache	3 (3.8)[b]	0 (0)
Abdominal discomfort	3 (3.8)[b]	0 (0)
General disorders and administration site conditions	23 (29.5)[b]	24 (36.4)[b]
Fatigue	17 (21.8)[b]	13 (19.7)[b]
Asthenia	4 (5.1)[b]	4 (6.1)[b]
Energy increased	2 (2.6)[b]	2 (3.0)[b]
Feeling abnormal	0 (0)	2 (3.0)[b]
Infections and infestations	15 (19.2)[b]	13 (19.7)[b]
Upper respiratory tract infection	5 (6.4)[b]	2 (3.0)[b]
Nasopharyngitis	3 (3.8)[b]	4 (6.1)[b]
Injury, poisoning and procedural complications	4 (5.1)[b]	4 (6.1)[b]
Metabolism and nutrition disorders	3 (3.8)[b]	5 (7.6)[b]
Decreased appetite	2 (2.6)[b]	3 (4.5)[b]

(continued)

Table 7: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 1, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 78[b]**	**SOF/VEL (12 W)** **N = 66[b]**
Musculoskeletal and connective tissue disorders	11 (14.1)[b]	14 (21.2)[b]
Back pain	6 (7.7)[b]	4 (6.1)[b]
Arthralgia	3 (3.8)[b]	2 (3.0)[b]
Pain in extremity	0 (0)	2 (3.0)[b]
Nervous system disorders	32 (41.0)[b]	23 (34.8)[b]
Headache	25 (32.1)[b]	22 (33.3)[b]
Dizziness	5 (6.4)[b]	0 (0)
Lethargy	3 (3.8)[b]	1 (1.5)[b]
Psychiatric disorders	10 (12.8)[b]	8 (12.1)[b]
Insomnia	5 (6.4)[b]	0 (0)
Irritability	0 (0)	2 (3.0)[b]
Anxiety	1 (1.3)[b]	2 (3.0)[b]
Abnormal dreams	0 (0)	2 (3.0)[b]
Respiratory, thoracic and mediastinal disorders	9 (11.5)[b]	9 (13.6)[b]
Cough	3 (3.8)[b]	3 (4.5)[b]
Oropharyngeal pain	1 (1.3)[b]	3 (4.5)[b]
Skin and subcutaneous tissue disorders	8 (10.3)[b]	7 (10.6)[b]
Rash	3 (3.8)[b]	1 (1.5)[b]
Surgical and medical procedures	0 (0)	2 (3.0)[b]
Vascular disorders	4 (5.1)[b]	2 (3.0)[b]
Hypertension	2 (2.6)[b]	2 (3.0)[b]

a: MedDRA version 19.0.
b: Institute's calculation.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus; W: weeks

Table 8: All SAEs (SOC/PT) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 1, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 78[b]**	**SOF/VEL (12 W)** **N = 66[b]**
POLARIS-4		
Overall rate of SAEs	3 (3.8)[b]	3 (4.5)[b]
Cardiac disorders	1 (1.3)[b]	1 (1.5)[b]
Angina unstable	0 (0)	1 (1.5)[b]
Cardiac failure congestive	1 (1.3)[b]	0 (0)
Gastrointestinal disorders	1 (1.3)[b]	0 (0)
Abdominal hernia	1 (1.3)[b]	0 (0)
Injury, poisoning and procedural complications	1 (1.3)[b]	1 (1.5)[b]
Road traffic accident	0 (0)	1 (1.5)[b]
Toxicity to various agents	1 (1.3)[b]	0 (0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (1.5)[b]
Lumbar spinal stenosis	0 (0)	1 (1.5)[b]

a: MedDRA version 19.0.
b: Institute's calculation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks

DAA-experienced, NS5A-naive adults with CHC genotype 2, with and without cirrhosis

Table 9: Common AEs (in the SOC and in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 2, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 31**	**SOF/VEL (12 W)** **N = 33**
POLARIS-4		
Overall rate of AEs	21 (67.7)	20 (60.6)
Gastrointestinal disorders	12 (38.7)	6 (18.2)
Diarrhoea	8 (25.8)	0 (0)
Nausea	3 (9.7)	1 (3.0)
Constipation	1 (3.2)	2 (6.1)
Dry mouth	3 (9.7)	0 (0)
Gastrooesophageal reflux disease	2 (6.5)	0 (0)
Frequent bowel movements	2 (6.5)	0 (0)
General disorders and administration site conditions	11 (35.5)	14 (42.4)
Fatigue	9 (29.0)	11 (33.3)
Asthenia	1 (3.2)	2 (6.1)
Infections and infestations	5 (16.1)	2 (6.1)
Injury, poisoning and procedural complications	0 (0)	3 (9.1)
Metabolism and nutrition disorders	2 (6.5)	1 (3.0)
Musculoskeletal and connective tissue disorders	8 (25.8)	7 (21.2)
Back pain	1 (3.2)	2 (6.1)
Arthralgia	3 (9.7)	1 (3.0)
Myalgia	2 (6.5)	3 (9.1)
Muscle spasms	2 (6.5)	0 (0)
Nervous system disorders	13 (41.9)	8 (24.2)
Headache	10 (32.3)	6 (18.2)
Psychiatric disorders	3 (9.7)	2 (6.1)
Insomnia	3 (9.7)	1 (3.0)
Renal and urinary disorders	1 (3.2)	2 (6.1)
Haematuria	0 (0)	2 (6.1)
Respiratory, thoracic and mediastinal disorders	3 (9.7)	1 (3.0)
Cough	2 (6.5)	0 (0)
Skin and subcutaneous tissue disorders	4 (12.9)	3 (9.1)
Night sweats	2 (6.5)	0 (0)

a: MedDRA version 19.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus; W: weeks

Table 10: All SAEs (SOC/PT) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 2, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 31**	**SOF/VEL (12 W)** **N = 33**
POLARIS-4		
Overall rate of SAEs	0 (0)	1 (3.0)
Nervous system disorders	0 (0)	1 (3.0)
Cerebrovascular accident	0 (0)	1 (3.0)

a: MedDRA version 19.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks

DAA-experienced, NS5A-naive adults with CHC genotype 3, with and without cirrhosis

Table 11: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 3, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 54**	**SOF/VEL (12 W)** **N = 52**
POLARIS-4		
Overall rate of AEs	41 (75.9)	41 (78.8)
Ear and labyrinth disorders	0 (0)	2 (3.8)
Eye disorders	2 (3.7)	1 (1.9)
Gastrointestinal disorders	22 (40.7)	16 (30.8)
Diarrhoea	7 (13.0)	2 (3.8)
Nausea	7 (13.0)	7 (13.5)
Abdominal pain upper	2 (3.7)	1 (1.9)
Constipation	5 (9.3)	0 (0)
Abdominal pain	0 (0)	3 (5.8)
Vomiting	0 (0)	2 (3.8)
Flatulence	1 (1.9)	2 (3.8)
Dyspepsia	2 (3.7)	0 (0)
Toothache	1 (1.9)	2 (3.8)
General disorders and administration site conditions	17 (31.5)	24 (46.2)
Fatigue	13 (24.1)	19 (36.5)
Asthenia	2 (3.7)	3 (5.8)
Oedema peripheral	1 (1.9)	2 (3.8)
Infections and infestations	12 (22.2)	7 (13.5)
Upper respiratory tract infection	2 (3.7)	1 (1.9)
Influenza	2 (3.7)	0 (0)
Ear infection	0 (0)	2 (3.8)
Injury, poisoning and procedural complications	4 (7.4)	3 (5.8)
Musculoskeletal and connective tissue disorders	9 (16.7)	9 (17.3)
Back pain	2 (3.7)	2 (3.8)
Arthralgia	3 (5.6)	1 (1.9)
Myalgia	2 (3.7)	0 (0)
Muscle spasms	1 (1.9)	2 (3.8)
Pain in extremity	1 (1.9)	2 (3.8)

(continued)

Table 11: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 3, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 54**	**SOF/VEL (12 W)** **N = 52**
Nervous system disorders	15 (27.8)	19 (36.5)
Headache	9 (16.7)	15 (28.8)
Dizziness	2 (3.7)	2 (3.8)
Disturbance in attention	0 (0)	2 (3.8)
Lethargy	2 (3.7)	1 (1.9)
Syncope	0 (0)	2 (3.8)
Psychiatric disorders	9 (16.7)	9 (17.3)
Insomnia	1 (1.9)	2 (3.8)
Irritability	2 (3.7)	5 (9.6)
Sleep disorder	3 (5.6)	0 (0)
Nervousness	0 (0)	2 (3.8)
Respiratory, thoracic and mediastinal disorders	6 (11.1)	7 (13.5)
Cough	0 (0)	3 (5.8)
Oropharyngeal pain	3 (5.6)	1 (1.9)
Nasal congestion	2 (3.7)	1 (1.9)
Skin and subcutaneous tissue disorders	2 (3.7)	7 (13.5)
Rash	1 (1.9)	2 (3.8)
Pruritus	0 (0)	4 (7.7)
Vascular disorders	3 (5.6)	0 (0)
Hypertension	2 (3.7)	0 (0)

a: MedDRA version 19.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus; W: weeks

Table 12: All SAEs (SOC/PT) – RCT, direct comparison: DAA-experienced, NS5A-naive adults with CHC genotype 3, with and without cirrhosis, SOF/VEL/VOX vs. SOF/VEL

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**SOF/VEL/VOX (12 W)** **N = 54**	**SOF/VEL (12 W)** **N = 52**
POLARIS-4		
Overall rate of SAEs	1 (1.9)	0 (0)
Musculoskeletal and connective tissue disorders	1 (1.9)	0 (0)
Intervertebral disc protrusion	1 (1.9)	0 (0)

a: MedDRA version 19.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks