IQWiG — Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Daclatasvir – Benefit assessment according to §35a Social Code Book V[1]

Extract

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Daclatasvir – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

2 September 2014

Internal Commission No.:

A14-31

Address of publisher:

Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Christoph F. Dietrich, Caritas Hospital Bad Mergentheim, Bad Mergentheim, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Sebastian Werner

- Andreas Gerber-Grote

- Wolfram Groß

- Elke Hausner

- Thomas Kaiser

- Corinna Kiefer

- Stefanie Reken

- Guido Skipka

- Min Zhou

---

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

---

[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BBA	Bayesian Benchmarking Analysis
BOC	boceprevir
CHC	chronic hepatitis C
DCV	daclatasvir
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
PEG	peginterferon alfa
PEG-2a	peginterferon alfa-2a
PI	protease inhibitor
PLC	placebo
RBV	ribavirin
RGT	response-guided therapy
RNA	ribonucleic acid
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SVR	sustained virologic response
TVR	telaprevir

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daclatasvir. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 September 2014.

Research question

The aim of this report was to assess the added benefit of daclatasvir (DCV) compared with the appropriate comparator therapy (ACT) in the treatment of adult patients with chronic hepatitis C (CHC).

The G-BA specified different ACTs for different subindications. Table 2 shows the research questions of the benefit assessment.

Table 2: Research questions of the benefit assessment of daclatasvir

Research question	Therapeutic indication CHC	ACT specified by the G-BA
1	Genotype 1	
1a	Treatment-naive patients without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1c	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)[b]
1d	Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)[c]
2	Genotype 3 (with compensated cirrhosis and/or treatment-experienced)	Dual therapy (combination of peginterferon and ribavirin)
3	Genotype 4	Dual therapy (combination of peginterferon and ribavirin)
a: The information in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present. b: Data currently available prove no superiority of triple therapy for treatment-naive patients with cirrhosis. Dual therapy is therefore to be regarded as ACT in these situations. c: Only very few data for triple therapy are currently available for patients with HIV coinfection. Dual therapy is therefore to be regarded as ACT in these situations. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; SPC: Summary of Product Characteristics		

The assessment was based on patient-relevant outcomes.

Results

Research question 1: CHC genotype 1

Regarding CHC genotype 1 patients, the company only presented data on one of the subquestions (treatment-naive CHC genotype 1 patients without cirrhosis). Regarding treatment-experienced patients, treatment-naive patients with cirrhosis and patients with human immunodeficiency virus (HIV) coinfection, the company presented no data (Table 3).

Table 3: Data presented on the subquestions on CHC genotype 1 patients (research question 1)

Research question	Therapeutic indication CHC genotype 1	Data presented by the company
1a	Treatment-naive patients without cirrhosis	▪ matching-adjusted indirect comparison (MAIC) ▪ Bayesian Benchmarking Analysis (BBA)
1b	Treatment-experienced patients	No data
1c	Treatment-naive patients with cirrhosis	No data
1d	Patients with HIV coinfection	No data
CHC: chronic hepatitis C; HIV: human immunodeficiency virus		

No direct comparative studies were available for subquestion 1a. The information retrieval conducted for the further investigations presented by the company for subquestion 1a was incomplete in each case.

Matching-adjusted indirect comparison

The company presented the results of a "matching-adjusted indirect comparison" (MAIC) versus the ACT for treatment-naive CHC genotype 1 patients without cirrhosis.

This investigation was a comparison of individual study arms with the aim to present conclusions on the superiority of daclatasvir over the ACT (triple therapy of telaprevir [TVR] or boceprevir [BOC] in combination with peginterferon alfa [PEG] and ribavirin [RBV]). Individual patient data on the outcomes under consideration of individual patient characteristics were incorporated for daclatasvir, and aggregate data were incorporated for the comparator therapy. An adjustment of possible differences in (fixed) patient characteristics between the arms with daclatasvir and the comparator therapy is performed in MAIC by means of individual weighting of the patients in the arm with daclatasvir for calculating weighted means.

The MAIC investigations presented were unsuitable for conclusions on the added benefit of daclatasvir because the underlying information retrieval and the resulting study pool with the ACT were incomplete. On the one hand, the company conducted no search in trial registries

on the ACT as required by the dossier templates. Hence the requirements specified in the dossier templates were not fulfilled. On the other hand, unsuitable inclusion and exclusion criteria were used for the selection of the studies (inclusion criterion "phase 3 study", exclusion criterion "all study centres outside EU or USA"), which resulted in the exclusion of at least one additional relevant study with the ACT (triple therapy with telaprevir).

No further check of the MAIC methodology was conducted because of the incompleteness detected.

Bayesian Benchmarking Analysis

In addition to the MAIC investigation, the company presented results of a Bayesian Benchmarking Analysis (BBA) for the outcome "sustained virologic response [SVR] 24" for treatment-naive CHC genotype 1 patients without cirrhosis.

The aim of this BBA was to calculate a threshold for estimated responder rates that a hypothetical study with a new treatment would have to reach at least so that a statistically significant superiority versus the ACT (triple therapy of TVR or BOC in combination with PEG and RBV) can be derived.

The analysis was not evaluable for the benefit assessment because, on the one hand, it was conducted selectively for a single outcome (SVR). On the other, the underlying information retrieval was incomplete because of the lack of search in trial registries and the limitation of the literature search to a search period until 2012. Hence the requirements specified in the dossier templates were also not fulfilled.

No further check of the BBA methodology was conducted because of the incompleteness detected.

Summary

In summary, the data presented by the company for treatment-naive CHC genotype 1 patients without cirrhosis (research question 1a) are unsuitable for the assessment of the added benefit of daclatasvir.

The company presented no data on the subquestions 1b, 1c and 1d (treatment-experienced CHC genotype 1 patients, treatment-naive CHC genotype 1 patients with cirrhosis, and CHC genotype 1 patients with HIV coinfection).

Research question 2: CHC genotype 3 (with compensated cirrhosis and/or treatment-experienced)

No data were presented in the dossier for CHC genotype 3 patients (with compensated cirrhosis and/or treatment-experienced).

Research question 3: CHC genotype 4

For treatment-naive CHC genotype 4 patients, the company presented 2 studies on the direct comparison of DCV + PEG + RBV versus placebo (PLC) + PEG + RBV (AI444010, AI444042), but did not use the AI444010 study for the derivation of an added benefit.

Due to the study design and the resulting relevant proportion of patients who were not treated in compliance with the approval, the AI444010 study is unsuitable for conclusions on the added benefit of daclatasvir.

Criteria for treatment discontinuation because of treatment futility were applied in both treatment arms in the AI444042 study. Whereas the criteria applied in the treatment arm with daclatasvir only deviated from the specifications in the Summary of Product Characteristics (SPC) to a comparably small degree, no criteria for treatment discontinuation due to treatment futility are described in the SPC of the ACT (peginterferon alfa-2a [PEG-2a] + RBV) and are also not reasonable. Due to these criteria for treatment discontinuation, the study design of the AI444042 study did not ensure the optimum treatment duration with the ACT for a relevant proportion of patients (28.6%). In these patients, the treatment duration was substantially shortened by 24 or 36 weeks. The study put the ACT at a disadvantage regarding the outcome "SVR" because of this. In addition, these patients constituted the main part of the missing values in the SVR analysis in the treatment arm with the ACT. This resulted in different proportions of missing values in the 2 treatment arms of the study and to a particularly high proportion of missing values in the treatment arm with the ACT. The imputation strategy for missing values chosen by the company (missing value = non-responder) resulted in a bias to the disadvantage of the ACT in the present situation and is unsuitable. Sensitivity analyses showed that the effect for the SVR 24 was not robust.

Overall, the AI444042 study is unsuitable for conclusions on the added benefit of daclatasvir because of the unsuitable criteria for treatment discontinuation in the study arm with the ACT and the resulting differences in the proportions of missing values in the treatment arms of the study on the outcome "SVR".

It should also be noted that due to the problems described above, the results on adverse events were biased in favour of the ACT, but are generally only interpretable to a limited extent because of the different observation periods.

In summary, there were no suitable data for the assessment of the added benefit of daclatasvir for CHC genotype 4 patients.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Table 4 presents a summary of the extent and probability of the added benefit of daclatasvir.

Table 4: Daclatasvir – extent and probability of added benefit

Research question	Therapeutic indication CHC	ACT specified by the G-BA[a]	Extent and probability of added benefit
1	Genotype 1		
1a	Treatment-naive patients without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Added benefit not proven
1b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Added benefit not proven
1c	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
1d	Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
2	Genotype 3 (with compensated cirrhosis and/or treatment-experienced)	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
3	Genotype 4	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
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**.			
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus			

The G-BA decides on the added benefit.

---

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research questions

The aim of this report was to assess the added benefit of daclatasvir compared with the ACT in the treatment of adult patients with CHC.

The G-BA specified different ACTs for different subindications. Table 5 shows the research questions of the benefit assessment and the corresponding ACTs specified by the G-BA.

Table 5: Research questions of the benefit assessment of daclatasvir and corresponding ACTs by the G-BA

Research question	Therapeutic indication CHC	ACT specified by the G-BA
1	Genotype 1	
1a	Treatment-naive patients without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1c	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)[b]
1d	Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)[c]
2	Genotype 3 (with compensated cirrhosis and/or treatment-experienced)	Dual therapy (combination of peginterferon and ribavirin)
3	Genotype 4	Dual therapy (combination of peginterferon and ribavirin)
a: The information provided in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present. b: Data currently available prove no superiority of triple therapy for treatment-naive patients with cirrhosis. Dual therapy is therefore to be regarded as ACT in these situations. c: Only very few data for triple therapy are currently available for patients with HIV coinfection. Dual therapy is therefore to be regarded as ACT in these situations. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; SPC: Summary of Product Characteristics		

The ACT specified by the G-BA was used for the present benefit assessment.

This deviates partly from the company's approach, which, within research question 1 (CHC genotype 1), on the one hand separated the patient group after failure of protease inhibitor (PI)-based triple therapy and specified a separate comparator therapy for this group ("watchful waiting"). On the other hand, it made no specific statement on treatment-naive patients with cirrhosis and on patients with HIV coinfection. The deviation from the ACT in CHC genotype 1 patients after failure of PI-based triple therapy was not followed (see Section

2.3.1 and Section 2.7.1 of the full dossier assessment). The deviation concerning treatment-naive patients with cirrhosis and patients with HIV coinfection had no consequences because the company claimed no added benefit due to a lack of data.

Furthermore, the company specified further research questions on CHC genotype 2 patients and on treatment-naive CHC genotype 3 patients without cirrhosis. However, these are not specified in the approved treatment situations for daclatasvir [3].

The assessment was based on patient-relevant outcomes.

2.3 Research question 1: CHC genotype 1

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on daclatasvir (studies completed up to 3 July 2014)

- bibliographical literature search on daclatasvir (last search on 2 July 2014)

- search in trial registries for studies on daclatasvir (last search on 3 July 2014)

- bibliographical literature search on the ACT for the MAIC (last search on 10 June 2014)

- bibliographical literature search on the ACT for the BBA (last search in March 2013)

To check the completeness of the study pool:

- bibliographical literature search on daclatasvir (last search on 12 September 2014)

- search in trial registries for studies on daclatasvir (last search on 12 September 2014)

Regarding CHC genotype 1 patients, the company only presented data on one of the subquestions (treatment-naive CHC genotype 1 patients without cirrhosis). An overview of the data presented by the company is shown in Table 6.

Table 6: Data presented on the subquestions on CHC genotype 1 patients (research question 1)

Research question	Therapeutic indication CHC genotype 1	Data presented by the company
1a	Treatment-naive patients without cirrhosis	- matching-adjusted indirect comparison (MAIC) - Bayesian Benchmarking Analysis (BBA)
1b	Treatment-experienced patients	No data
1c	Treatment-naive patients with cirrhosis	No data
1d	Patients with HIV coinfection	No data
CHC: chronic hepatitis C; HIV: human immunodeficiency virus		

The company identified no direct comparative studies for any of the subquestions. No direct comparative studies were identified from the check of the completeness of the study pool either. The information retrieval conducted for the further investigations conducted by the company for subquestion 1a was incomplete in each case. Below the analyses are briefly described separately and the incompleteness of the information retrieval is explained.

Matching-adjusted indirect comparison

The company presented the results of a MAIC versus the ACT (triple therapy of TVR or BOC in combination with PEG and RBV) for treatment-naive CHC genotype 1 patients without cirrhosis who were treated with the combination of DCV + sofosbuvir (SOF) for 12 weeks.

This investigation was a comparison of individual study arms with the aim to present conclusions on the superiority of daclatasvir over the ACT (triple therapy of TVR or BOC in combination with PEG and RBV). Individual patient data on the outcomes under consideration of individual patient characteristics were incorporated for daclatasvir, and aggregate data were incorporated for the comparator therapy. An adjustment of possible differences in (fixed) patient characteristics between the arms with daclatasvir and the comparator therapy is performed in MAIC by means of individual weighting of the patients in the arm with daclatasvir for calculating weighted means (see Section 2.7.2.7 of the full dossier assessment).

The MAIC investigations presented were unsuitable for conclusions on the added benefit of daclatasvir because the underlying information retrieval and the resulting study pool with the ACT were incomplete. On the one hand, the company conducted no search in trial registries on the ACT as required by the dossier templates. Hence the requirements specified in the dossier templates were not fulfilled (see Sections 2.7.2.3.1 und 2.7.2.3.2.1 of the full dossier assessment). On the other hand, unsuitable inclusion and exclusion criteria were used for the selection of the studies (inclusion criterion "phase 3 study", exclusion criterion "all centres outside the EU or the USA"), which resulted in the exclusion of at least one additional relevant study with the ACT (triple therapy with telaprevir) [4] (see Section 2.7.2.3.1 of the full dossier assessment).

No further check of the MAIC methodology was conducted because of the incompleteness detected.

Bayesian Benchmarking Analysis

The company presented results from a BBA for the outcome "SVR 24" for treatment-naive CHC genotype 1 patients without cirrhosis who were treated with the combination of DCV + SOF for 12 weeks.

The aim of this BBA was to calculate a threshold for estimated responder rates that a hypothetical study with a new treatment would have to reach at least so that a statistically significant superiority versus the ACT (triple therapy of TVR or BOC in combination with PEG and RBV) can be derived.

The analysis was not evaluable for the benefit assessment because, on the one hand, it was conducted selectively for a single outcome (SVR). On the other, the underlying information retrieval was incomplete because of the lack of search in trial registries and the limitation of the literature search to a search period until 2012. Hence the requirements specified in the

dossier templates were also not fulfilled (see Sections 2.7.2.3.1 und 2.7.2.3.2.1 of the full dossier assessment).

No further check of the BBA methodology was conducted because of the incompleteness detected.

2.3.2   Results on added benefit

No suitable data were available for assessing the added benefit of daclatasvir for treatment-naive CHC genotype 1 patients without cirrhosis (research question 1a).

The company presented no data on the subquestions 1b, 1c and 1d (treatment-naive CHC genotype 1 patients with cirrhosis, treatment-experienced CHC genotype 1 patients, and CHC genotype 1 patients with HIV coinfection).

Overall, the added benefit of daclatasvir versus the ACT is therefore not proven for CHC genotype 1 patients.

This result partly deviates from the company's assessment, which, within the research question on CHC genotype 1, derived an added benefit for treatment-naive patients without cirrhosis and for pretreated patients without cirrhosis.

2.3.3   Extent and probability of added benefit

The added benefit of daclatasvir versus the ACT is not proven for CHC genotype 1 patients.

This result partly deviates from the company's assessment, which derived an indication of major added benefit for the subpopulations of treatment-naive CHC genotype 1 patients without cirrhosis, and a hint of a major added benefit for the subpopulation of pretreated CHC genotype 1 patients without cirrhosis.

2.4 Research question 2: CHC genotype 3 (with compensated cirrhosis and/or treatment-experienced)

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on daclatasvir (studies completed up to 3 July 2014)
- bibliographical literature search on daclatasvir (last search on 2 July 2014)
- search in trial registries for studies on daclatasvir (last search on 3 July 2014)
- bibliographical literature search on the ACT for the BBA (last search in March 2013)

To check the completeness of the study pool:

- bibliographical literature search on daclatasvir (last search on 12 September 2014)
- search in trial registries for studies on daclatasvir (last search on 12 September 2014)

The company identified neither direct comparative studies nor studies for an indirect comparison for research question 2. No relevant direct comparative studies were identified from the check of the completeness either.

2.4.2 Results on added benefit

No data were available for assessing the added benefit of daclatasvir for CHC genotype 3 patients (with compensated cirrhosis and/or treatment-experienced). The added benefit of daclatasvir versus the ACT is therefore not proven for these patients.

This result concurs with the company's assessment.

2.4.3 Extent and probability of added benefit

The added benefit of daclatasvir versus the ACT is not proven for CHC genotype 3 patients (with compensated cirrhosis and/or treatment-experienced).

This result concurs with the company's assessment.

2.5 Research question 3: CHC genotype 4

2.5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on daclatasvir (studies completed up to 3 July 2014)

- bibliographical literature search on daclatasvir (last search on 2 July 2014)

- search in trial registries for studies on daclatasvir (last search on 3 July 2014)

To check the completeness of the study pool:

- bibliographical literature search on daclatasvir (last search on 12 September 2014)

- search in trial registries for studies on daclatasvir (last search on 12 September 2014)

No additional relevant studies were identified from the check.

For treatment-naive CHC genotype 4 patients, the company presented 2 studies on the direct comparison of DCV + PEG + RBV versus PLC + PEG + RBV (AI444010 [5], AI444042 [6]).

Study AI444010

The company did not use the results of the AI444010 study for the derivation of an added benefit because the company itself considered them to be highly biased, but nonetheless presented the results as additional information. The company's approach not to use this study for conclusions on the added benefit was followed because, due to the study design and the resulting relevant proportion of patients who were not treated in compliance with the approval, the study is unsuitable for conclusions on the added benefit of daclatasvir (for reasons see Section 2.7.2.3.2.3 of the full dossier assessment).

Study AI444042

The AI444042 study is unsuitable for conclusions on the added benefit of daclatasvir. This is justified below.

The AI444042 study was a randomized, double-blind, placebo-controlled, multicentre approval study, in which treatment-naive CHC genotype 4 patients were included. These were randomly assigned in a ratio of 2:1 to the treatment arms with DCV + PEG-2a + RBV (response-guided therapy [RGT]) or PLC + PEG-2a + RBV). Table 7 shows the characteristics of the study. Table 8 shows the interventions.

Table 7: Characteristics of the AI444042 study – RCT, direct comparison: DCV + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 4 patients)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AI444042	RCT, double-blind[b], parallel	Adult patients with CHC genotype 4; treatment-naive (without pretreatment with IFN preparations, RBV or DAA); no cirrhosis or compensated cirrhosis; HCV RNA viral load $\geq$ 10 000 IU/mL; seronegative for HIV and HBsAg; no HCC	Group 1: DCV + PEG-2a + RBV (RGT) (N = 83) Group 2: PLC + PEG-2a + RBV (N = 42)	72 weeks Treatment: 24 or 48 weeks Follow-up: 48 or 24 weeks	26 study centres in France (11), Greece (1), Great Britain (3), Italy (2), Puerto Rico (1), Spain (4), United States (4) 12/2011–10/2013	Primary: SVR 12[c] Secondary: SVR 24, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Partial unblinding was conducted during the study at week 24 for patients in the study arm with DCV + PEG-2a + RBV (RGT) who had discontinued treatment after 24 weeks.
c: HCV RNA < LLOQ (TD or TND) at week 12 after the end of treatment, measured with Roche HCV COBAS® TaqMan® Test v. 2.0 with (L)LOQ = 25 IU/mL and LOD ~ 10 IU/mL for HCV genotype 1.

CHC: chronic hepatitis C; DAA: direct acting antiviral agent; DCV: daclatasvir; HBsAg: hepatitis B surface antigen; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IFN: interferon; IU: international unit; LLOQ: lower limit of quantification; LOD: limit of detection; N: number of randomized patients; PEG: peginterferon alfa; PEG-2a: peginterferon alfa-2a; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RGT: response-guided therapy; RNA: ribonucleic acid; SVR: sustained virologic response; TD: target detected; TND: target not detected; vs.: versus

Table 8: Characteristics of the interventions (AI444042) – RCT, direct comparison: DCV + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 4 patients)

Study	Intervention	Comparison	Prohibited or limited concomitant medication
AI444042	Patients **with** virologic response[a,b,c]: DCV + PEG-2a + RBV (24 W) Patients **without** virologic response[a,b,c]: DCV + PEG-2a + RBV (24 W), then PEG-2a + RBV (24 W) *each with* DCV 60 mg orally once daily + PEG-2a 180 µg subcutaneously once weekly + RBV 1000 mg or 1200 mg daily (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg; orally, in 2 daily doses [morning and evening with food]) dose adjustments for PEG-2a or RBV were allowed to control intolerances	PLC + PEG-2a + RBV (24 W), then PEG-2a + RBV (24 W) **with** PLC orally once daily + PEG-2a 180 µg subcutaneously once weekly + RBV 1000 mg or 1200 mg daily (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg; orally, in 2 daily doses [morning and evening with food]) dose adjustments for PEG-2a or RBV were allowed to control intolerances	Prohibited: ■ strong and moderate CYP3A4 inhibitors ■ CYP3A4 inducers ■ strong P-gp inhibitors Limited: ■ P-gp substrates with narrow therapeutic index (e.g. digoxin) ■ OATP1B1 and/or OATP1B3 substrates ■ BCRP substrates

a: Virologic response: undetectable HCV RNA (< LLOQ, TND) at week 4 and 12.
b: Results of the HCV RNA analyses were blinded for study centres and patients, and treatment decisions (i.e. response-guided treatment duration, discontinuation due to treatment futility) were determined by an IVRS.
c: Measured with Roche HCV COBAS® TaqMan® Test v. 2.0 with (L)LOQ = 25 IU/mL and LOD ~ 10 IU/mL for HCV genotype 1 at the time point of the production of the protocol.
BCRP: breast cancer resistance protein; CHC: chronic hepatitis C; CYP3A4: cytochrome P450 3A4; DCV: daclatasvir; HCV: hepatitis C virus; IU: international unit; IVRS: interactive voice response system; LLOQ: lower limit of quantification; LOD: limit of detection; OATP: organic anion transporting polypeptide; PEG: peginterferon alfa; PEG-2a: peginterferon alfa-2a; P-gp: P-glycoprotein 1; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; TND: target not detected; vs.: versus; W: weeks

Study used unsuitable criteria for treatment discontinuation

Criteria for treatment discontinuation because of treatment futility were applied in both treatment arms in the AI444042 study. Whereas the criteria applied in the treatment arm with daclatasvir only deviated from the specifications in the SPC to a comparably small degree [3], no criteria for treatment discontinuation due to treatment futility are described in the SPC of the ACT (PEG-2a + RBV) and are also not reasonable [7,8]. In the corresponding treatment arm with PEG-2a + RBV, treatment discontinuation due to treatment futility was envisaged when early virologic response (< 2 $\log_{10}$ reduction of HCV ribonucleic acid [RNA] compared with baseline) was not achieved at week 12 or when the HCV RNA was ≥ 25 IU/mL at week 24 [6].

Table 9 shows the criteria for treatment discontinuation due to treatment futility in both treatment arms of the AI444042 study in comparison with the information provided in the SPC.

Table 9: Criteria for treatment discontinuation with all drugs due to insufficient virologic response (treatment futility) in the AI444042 study with information in the SPC for the study arms with DCV or PEG-2a + RBV

Information in the SPC	Study AI444042
DCV [3]	*Study arm DCV + PEG-2a + RBV [6]*
<u>Week 4</u>: ▪ HCV RNA > 1000 IU/mL	<u>Week 4</u>: ▪ breakthrough (confirmed increase > 1 $\log_{10}$ from nadir) or ▪ HCV RNA ≥ LLOQ after confirmed undetectable HCV RNA during treatment starting from week 2
<u>Week 12</u>: ▪ HCV RNA ≥ 25 IU/mL	<u>Week 12</u>: ▪ HCV RNA > 1000 IU/mL
<u>Week 24</u>: ▪ HCV RNA ≥ 25 IU/mL	<u>Week 24</u>: ▪ HCV RNA ≥ 25 IU/mL
PEG-2a + RBV [7,8]	▪ *Study arm PLC + PEG-2a + RBV [6]*
<u>Week 12</u>: ▪ No information[a]	<u>Week 12</u>: ▪ early virologic response (< 2 $\log_{10}$ reduction of HCV RNA at week 12 compared with baseline) not achieved
<u>Week 24</u>: ▪ No information[a]	<u>Week 24</u>: ▪ HCV RNA ≥ 25 IU/mL
a: The SPC contains no criteria for treatment-naive genotype 4 patients for which discontinuation of treatment with PEG-2a and RBV due to treatment futility is recommended. DCV: daclatasvir; HCV: hepatitis C virus; IU: international unit; LLOQ: 25 IU/mL = lower limit of quantification; PEG-2a: peginterferon alfa-2a; PLC: placebo; RBV: ribavirin; RNA: ribonucleic acid; SPC: Summary of Product Characteristics	

Due to the criteria provided for treatment discontinuation due to treatment futility, the study design did not ensure the optimum treatment duration with the ACT (PEG-2a + RBV for 48 weeks). A large proportion of patients discontinued all study medications early in the control arm because of treatment futility (28.6%). In these patients, the treatment duration was substantially shortened by 24 or 36 weeks. Because of this design and because of the high proportion of patients who actually discontinued treatment due to treatment futility, the study put the ACT at a disadvantage regarding the outcome "SVR 24". Moreover, these patients constituted the main part of the missing values in the SVR analysis in the treatment arm with the ACT.

Different proportions of missing values in both study arms regarding SVR 24
Besides the missing values for patients who discontinued treatment because of inadequate criteria for treatment futility, there were further missing values in the SVR analysis due to

other causes (e.g. lost to follow-up). Overall, the proportions of missing values differed between the 2 study arms. The proportion of missing values (n [%)]) was particularly high in the treatment arm with the ACT (DCV + PEG-2a + RBV: 9 [10.8%]; PLC + PEG-2a + RBV: 14 [33.3%]). The imputation strategy for missing values chosen by the company (missing value = non-responder) resulted in a bias to the disadvantage of the ACT in the present situation and is unsuitable.

The effect for the outcome SVR 24 was investigated in sensitivity analyses with several imputation strategies to estimate the influence the different proportions of missing values have in the 2 treatment arms (see Section 2.7.2.3.2.3 of the full dossier assessment). This revealed that the statistically significant effect observed by the company for SVR 24 in favour of daclatasvir is not robust and that no certain advantage of DCV + PEG-2a + RBV versus PLC + PEG-2a + RBV could be derived for the SVR 24.

Due to the different proportions of missing values in the 2 treatment arms and the particularly high proportion of missing values in the treatment arm with the ACT, the study results were therefore not interpretable with regard to the SVR 24.

It should also be noted that due to the problems described above, the results on adverse events were biased in favour of the ACT, but are generally only interpretable to a limited extent because of the different observation periods.

Conclusions

The AI444042 study is unsuitable for conclusions on the added benefit of daclatasvir because of the unsuitable criteria for treatment discontinuation in the study arm with the ACT and the resulting differences in the proportions of missing values in the treatment arms of the study on the outcome "SVR".

2.5.2 Results on added benefit

No suitable data were available for assessing the added benefit of daclatasvir for CHC genotype 4 patients. The added benefit of daclatasvir versus the ACT is therefore not proven for CHC genotype 4 patients.

This result deviates from the company's assessment, which derived an added benefit for treatment-naive CHC genotype 4 patients without cirrhosis.

2.5.3 Extent and probability of added benefit

The added benefit of daclatasvir versus the ACT is not proven for CHC genotype 4 patients.

This result deviates from the company's assessment, which derived an indication of a major added benefit for treatment-naive CHC genotype 4 patients without cirrhosis.

2.6 Extent and probability of added benefit – summary

Table 10 summarizes the extent and probability of the added benefit of daclatasvir.

Table 10: Daclatasvir – extent and probability of added benefit

Research question	Therapeutic indication CHC	ACT specified by the G-BA[a]	Extent and probability of added benefit
1	Genotype 1		
1a	Treatment-naive patients without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Added benefit not proven
1b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Added benefit not proven
1c	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
1d	Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
2	Genotype 3 with compensated cirrhosis and/or treatment-experienced	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
3	Genotype 4	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
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**.			
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus			

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Bristol-Myers Squibb. Daklinza Filmtabletten: Fachinformation [online]. August 2014 [accessed: 3 September 2014]. URL: http://www.fachinfo.de.

4. Marcellin P, Forns X, Goeser T, Ferenci P, Nevens F, Carosi G et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterology 2011; 140(2): 459-468.

5. Bristol-Myers Squibb. A phase 2b study of BMS-790052 in combination with peg-interferon alfa-2a and ribavirin in treatment naive subjects with chronic hepatitis C genotype 1 and 4 infection: study AI444010; final clinical study report [unpublished]. 2013.

6. Bristol-Myers Squibb. A phase 3 evaluation of daclatasvir (BMS-790052) in combination with peg-interferon alfa-2a and ribavirin in treatment-naive subjects with chronic hepatitis C genotype 4: study AI444042; addendum 01 to the final clinical study report [unpublished]. 2014.

7. Roche. Copegus: Fachinformation [online]. April 2014 [accessed: 10 November 2014]. URL: http://www.fachinfo.de.

8. Roche. Pegasys 90/135/180 Mikrogramm: Fachinformation [online]. April 2014 [accessed: 10 November 2014]. URL: http://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-31-daclatasvir-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6348.html.