KCE REPORT 276

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ECONOMIC EVALUATION OF NOVEL DIRECT ACTING ANTIVIRAL (DAA) TREATMENT STRATEGIES FOR CHRONIC HEPATITIS C

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HEALTH TECHNOLOGY ASSESSMENT

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COLOPHON

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
BOC	Boceprevir
CBA	Cost-benefit analysis
CC	Compensated cirrhosis
CEA	Cost-effectiveness analysis
CHC	Chronic hepatitis C
CMA	Cost-minimization analysis
CUA	Cost-utility analysis
DAA	Direct acting antiviral
DC	Decompensated cirrhosis
DCV	Daclatasvir
EQ-5D	EuroQoL 5 dimensions
F0-F4	METAVIR fibrosis stages F0 to F4
HCC	Hepatocellular carcinoma
HCP	Health care payer
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
INAMI – RIZIV	Institut national d'assurance maladie-invalidité – RijksInstituut voor Ziekte en Invaliditeits Verzekering (Belgium)

INAHTA	International Network of Agencies for Health Technology Assessment
LDV	Ledipasvir
LT	Liver transplant
LY	Life year
NHS EED	National Health Service Economic Evaluation Database
OSoC	Old standard of care
PEG	Pegylated-interferon
QALY	Quality adjusted life-year
QoL	Quality of life
RBV	Ribavirin
RCT	Randomised controlled trial
SA	Sensitivity analysis
SF-6D	Short Form-6 dimension
SF-36	Medical Outcome Study Short Form 36-Item Health Survey
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained viral response
TEL	Telaprevir
WTP	Willingness to pay

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

1.1.1 Transmission

The hepatitis C virus (HCV), a ribonucleic acid (RNA) virus that caused the so-called non-A, non-B hepatitis infections, was discovered in 1989.[1]

HCV is mainly transmitted using blood. Before the screening of blood for HCV was introduced in 1990, blood transfusions and organ transplants formed a main source of infection (often HCV genotype 1b). This has been reduced by nearly 100%. Nowadays, in the Western world, about 80 to 90% of new infections with HCV (often subtypes 1a and 3a) are seen in injection/intravenous drug users (IDU).[2, 3] Transmission occurs mostly via shared needles and other drug injection paraphernalia. Overall at least 50% of the IDU population in Western Europe is chronically infected with HCV.[4] Another less frequent route of infection is intranasal transmission using contaminated drug sniffing implements such as straws, used to snort cocaine, heroin, and other powdered drugs.[5]

Sexual transmission occurs most frequently in immunodeficiency virus (HIV) positive gay and bisexual men, especially after contracted clinical syphilis and/or lymphogranuloma venereum rectitis.[6-8] No significant overlap with the IDU population seems to exist. Other routes of transmission include tattooing, nosocomial transmission and childbirth.[3, 9-11]

Migration is another source of infected persons in Belgium, although statistics allowing to assess the extent of the problem are scarce.

1.1.2 Hepatitis C in Belgium

In Belgium, forty percent (40%) of end-stage cirrhosis is due to hepatitis C. In southern Belgium, 44% of 57 HCC cases were associated with HCV infection.[12] Among 131 new diagnoses of HCC in 14 Belgian centres in 2003 (HepCar Registry database), cirrhosis was present in 120 (92%). The aetiology of the underlying liver disease was: HCV (n=54), HBV (17%, n=22), alcoholic liver disease (miscellaneous (12%, n=16)).[13]

1.1.2.1 General population

Seroprevalence data suggest a growing concentration of HCV infection in risk groups.

Screening for HCV of the blood products in Belgium was introduced in July 1, 1990.[14] The seroprevalence of HCV (positive EIA test result) in Belgium has been estimated at **0.87%-1%** of the population (or extrapolated to Belgium, about 93 000-107 000 individuals).[15, 16] These data are all based on a single seroprevalence study dating back to 1993-94 and performed on hospital residual blood samples of the Flemish population.[15]

A more recent study in the Flanders region reports a lower HCV prevalence rate of 0.12% (or extrapolated to Belgium, about 12 500 individuals, range 9000 to 40 000), based on saliva testing.[17] Study participation in the latter survey was about a third and was based on the reply to a regular mail. It is clear that homeless, institutionalized or incarcerated individuals may not be reached using this approach. Consequently, only a subset of IDUs may thus have been reached, leading to an underestimation of the overall seroprevalence of hepatitis C. The data suggest however that hepatitis C prevalence is quite low in the mainstream population in Flanders, and consequently population wide screening may not be very effective.

Since 2005, a surveillance of the hepatitis C virus has been implemented by the Scientific Institute of Public Health (ISP – WIV) through a network of microbiology laboratories. Based on the number of cases reported from this network and on the number of HCV genotyping performed, the number of new Belgian HCV cases per year has been estimated at 1500 (incidence of 13.6 per 100 000 inhabitants per year).[18]

1.1.2.2 High risk groups

Intravenous drug users

In 2004-2005, blood samples were collected from injecting drug users at treatment centres all over Belgium. A seroprevalence rate (anti-HCV antibody positive) of 50% (286 / 569) was reported for ever injecting drug users and 61% (205 / 335) for those sharing their injecting equipment. Sharing of sniffing equipment could not be determined as transmission route. Only 17% of the HCV positive drug users had ever received medical treatment for it.[19] The mean age was 33 in a random subsample of 147 testing positive for anti-HCV antibodies that was analysed for HCV-RNA.[20]

The 2011 systematic review published in the Lancet[4] reports for Belgium a hepatitis C seroprevalence in people who inject drugs of 55%. This is the unweighted mean of two percentages (27% and 82.7%) reported for the year 2008 (http://www.emcdda.europa.eu/publications/country-overviews/be) and needs to be interpreted with caution. The 27% seropositivity (17 out of 63) was seen in a subset of the 166 IDUs being treated in 2008 in a residential care setting (De Sleutel) where the physician judged HCV testing to be appropriate after discussion with the individual. It is important to note that the De Sleutel setting provides residential care to IDUs and therefore serves a somewhat different IDU population compared with low threshold services (e.g. Free Clinic Antwerp) where the aim is harm reduction. The 82.7% was the proportion of IDUs tested positive for anti-HCV antibodies at The Free Clinic Antwerp in 2008.

Based on the limited data available there seems to be no clear trend in seroprevalence rates over the last 10 years for HCV in IDUs in Belgium. The proportion of IDUs tested positive for anti-HCV antibodies at the De Sleutel setting remained around a third of the IDUs tested per year in the period 1994 to 2010. However, in the small subgroup of IDUs aged over 34 years tested at the De Sleutel setting, the seroprevalence remained at around 66% for the same period (data kindly provided by G Lombaert, De Sleutel). At the Free Clinic Antwerp, about 79% of the IDUs were tested positive from 2001 to 2004 (on average 264 IDUs were tested per year), which is similar to the 82.7% reported for 2008.

For the French speaking community, a 67% seroprevalence rate was reported for IDUs willing to be tested and treated.[19] Data for 2010 from project Lama, Brussels, show that among 494 IDUs under follow-up, 281 individuals had been tested for anti-HCV antibodies, and 150 were tested positive (53%). HCV-RNA testing had been performed in 72, often in the context of possible treatment. Most recent data show a negative HCV-RNA test in 36 individuals, consisting of 18 subjects with a spontaneous clearance (25%), 10 with SVR and 8 with EVR (personal communication Jerry Wérenne).

In Luxemburg (not the Belgian province), a recent multicentre study found a seroprevalence in IDU of 81% for HCV (218/268, 95%CI=[77; 86]), 29% for HBV, 2.5% for HIV and 57% for HAV and in non-injecting drug users, 19% for HCV, 9% for HBV, 5% for HIV-1 and 66% for HAV. Prisoners showed the highest rates for all infections. Age, imprisonment and setting of recruitment were statistically associated with HCV seropositivity.[21]

Prisons

The prevalence of hepatitis C antibodies in Belgian prisons has been estimated at 7.5 % in 2006.[22] About 76% of imprisoned drug injectors seeking healthcare were tested positive for anti-HCV antibodies according to a 2005 Belgian report.[19]

Men having sex with men

Situation of MSM is not well documented, but Bottieau et al.[8] reviewed all cases of newly acquired HCV infection in HIV-positive MSM, followed from 2001 to 2009 at the HIV/sexually transmitted infection (STI) reference clinic of the Institute of Tropical Medicine in Antwerp. Newly acquired HCV infection was considered as certain or probable according to local definitions. During the study period, 69 episodes of newly acquired HCV infection (40 certain and 29 probable) were diagnosed in 67 HIV-infected MSM. In only 10 episodes (14%) the patients were symptomatic. The annual incidence of HCV infection in our population of HIV-infected MSM rose steadily from 0.2% in 2001 to 1.51% in 2008, and then peaked to 2.9% in 2009. For 60 episodes (87%), another STI (mainly syphilis and lymphogranuloma venereum) had been diagnosed within the six months before the diagnosis of HCV infection.[8]

Others

Migration is another source of infected persons in Belgium, although statistics allowing to assess the extent of the problem are scarce.

People borned during 1945-1965 are also cited by experts of this report.

1.1.3 Treatments

There is no preventive vaccine available against hepatitis C.

The first treatments for hepatitis C developed were based on interferon-alpha (IFN-α) injections, which have a broad antiviral effect. Longer-acting formulations, such as pegylated IFN [Peg-IFN]) and the addition of oral ribavirin improved efficacy. These treatments however have important setbacks.[23]

Fatigue and depression, which may already occur in treatment-naive patients with chronic hepatitis C, often worsen with Peg-IFN plus ribavirin treatment. These side-effects, together with the complex psychosocial state of the individual may hamper treatment uptake. Moreover, the numerous contra-indications limited the number of patient eligible for treatment.[23]

According to the recommendations of the EASL Guidelines:

- “HCV treatment should be delivered within a multidisciplinary team, with experience in HCV assessment and therapy;
- HCV-infected patients should be counselled on the importance of adherence for attaining a sustained virological response (SVR);
- In patients with socioeconomic disadvantages and in migrants, social support services should be a component of HCV clinical management;
- In persons who actively inject drugs, access to harm reduction programs is mandatory;

- Peer-based support should be evaluated as a means to improve HCV clinical management;
- Patients should be counselled to abstain from alcohol during antiviral therapy. Patients with ongoing alcohol consumption during treatment should receive additional support during antiviral therapy;
- HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. Also, the potential for drug–-drug interactions involving prescribed and non-prescribed drugs need to be considered".[24]

The new-generation DAAs offer treatment options that are IFN-free, and sometimes even ribavirin-free. Combinations of the new-generation DAAs show very high SVR rates of 95% and more, are well tolerated, have reduced the duration of treatment even further (often to 12 weeks or even less), and have less contra-indications which allow more patients to be treated.[25]

Nevertheless, the high price of these pharmaceuticals threat the accessibility to these products and an economic evaluation that take into account the budget impact of the new HCV therapies is essential.[25]

1.2 Objective of this report and research questions

This report follows two previous studies in which the KCE was the principal investigator:

- a KCE report on screening and prevention of hepatitis C, addressing Belgian epidemiologic data as well as the effectiveness and cost-effectiveness of screening and prevention programs for hepatitis C in the general population and in injection drug users (IDUs).23
- a rapid relative effectiveness assessment of new DAA therapies for the treatment of chronic Hepatitis C performed by the KCE in collaboration with other institutions[a] of the EunetHTA network, addressing the clinical effectiveness of the new HCV therapies.[25]

Because the EunetHTA report only covers the effectiveness assessment of new DAA therapies, the first research question was to assess their cost-effectiveness, i.e.:

- Based on the literature, what is the cost-effectiveness of the novel direct acting antiviral (DAA) therapies for the treatment of chronic hepatitis C (CHC) in adult patients.

The aim of this first part of the report is to document, in addition to the two previous reports, available data around these therapies to help us in the selection of parameters for the model performed in the second part.

The aim of the second part is to help Belgian public authorities in the reimbursement decision process. Indeed, in Belgium, treatments with the second generation DAA therapies are currently only reimbursed for patients with advanced disease (i.e. METAVIR fibrosis stage F3 and F4) who are at risk of developing decompensated cirrhosis and pre- and post-transplanted patients. Extension of the reimbursement is under discussion but the cost-effectiveness and budget-impact of treating new patient groups still needs to be assessed.

[a] Authors: KCE, Belgium; AAZ, Croatia; Agostino Gemelli Teaching Hospital, Italy; Co-Author: HVB, Austria; Reviewer(s): SNHTA, Switzerland SAGEM HTA, Turkey ZIN, Netherlands AETSA, Spain AIFA, Italy MoH, Slovakia NOKC, Norway HAS, France MoH Malta, Malta NHS Latvia, Latvia FIMEA, Finland SMC, Scotland IQWiG, Germany INFARMED, Portugal

The following research questions are thus addressed in this second part:

- What is the cost-effectiveness of different strategies in terms of patient eligibility criteria for the treatment of chronic hepatitis C (CHC) with IFN-free therapies in adult patients from the Belgian setting?
- What is the budget impact of a phased strategy that enlarges the target population progressively?

As specified in the research question, only interferon free therapies are considered in this report. This choice has been strongly advocated by representatives from the Belgian National Institute of Health and Disability Insurance (INAMI-RIZIV: CRM-CTG) as well as Belgian hepatologists. The question asked by Belgian public authorities is therefore not to determine which therapies are cost-effective but to only consider new DAA therapies and to assess from an economic point of view which patients should be eligible.

It should also be noted that in Belgium, conventions for temporary reimbursement (with confidential conditions) can be concluded between the pharmaceutical companies and the Belgian National Institute for Health and Disability Insurance since 2010 and that all of these new therapies are under convention. A lot of important information (such as the price after rebates) are therefore confidential and could not be used in this report. Moreover, because re-negotiation of these conventions were foreseen for mid- 2016, this report had to be finished in September/October to be used during the negotiations. As a consequence, it was not possible to collect raw data (e.g. on costs or utilities) from Belgian CHC patients within the timeframe of this study and we had to limit us to already published studies.

2 REVIEW OF THE PUBLISHED ECONOMIC EVALUATIONS

2.1 Introduction

This section aims at reviewing the published full economic evaluations of the novel direct acting antiviral (DAA) therapies for the treatment of chronic hepatitis C (CHC) in adult patients.

2.2 Methods

2.2.1 Inclusion and exclusion criteria

The following criteria were developed:

- Population: adults aged 18 years and over with genotype 1, 2, 3, 4, 5 or 6 chronic hepatitis C. Treatment-naïve or treatment-experienced patients. No limitations in terms of fibrosis and/or compensated/decompensated cirrhosis and/or hepatocellular carcinoma and/or other concomitant clinical condition(s).
- Intervention: any regimen incorporating at least a novel DAA such as sofosbuvir, sofosbuvir+ledipasvir, ombitasvir+paritaprevir+ritonavir, dasabuvir, simeprevir, daclatasvir. HCV screening programmes or HCV vaccination are not considered relevant.
- Comparator: depending on the genotype and other patients characteristics, the comparators of interest are:
  - no treatment,
  - the combination peginterferon-ribavirin with or without one of the first generation protease inhibitors (telaprevir or boceprevir),
  - any novel DAA defined under Intervention.
- Design: only published full economic evaluations are considered, i.e. published studies comparing at least two alternative treatments in terms of both costs and outcomes. Cost-minimization analyses (CMA), cost-utility analyses (CUA, with results expressed as incremental cost per

quality-adjusted life year (QALY) gained), cost-effectiveness analyses (CEA, with results expressed as cost per life-year (LY) gained) and cost-benefit analyses (CBA, with a monetary valuation of health outcomes) are eligible. Cost comparisons (not considering health outcomes), cost-outcome descriptions (not considering an alternative treatment) and cost-consequence analyses[b] are not relevant for inclusion. Both published primary studies and reviews of full economic evaluations are relevant for inclusion; letters, news, conference proceedings and editorials were removed.

- Timing: as for the clinical efficacy and safety reviews, the current search is limited to recent studies published from 2010 up to September 2015.

2.2.2 Search strategy

Both electronic and manual searches were performed.

- Electronic search: the following databases were searched in September 2015: Medline(Ovid), Medline(Ovid) in-process and other non-indexed citations, Embase, CRD (Centre for Review and Dissemination) HTA and CRD NHS EED (National Health Service Economic Evaluation Database). A combination of MeSH, EMTREE and text word terms related to chronic hepatitis C and the novel DAA were combined with those related to full economic evaluations (see appendix). The websites of the HTA institutes listed on the International Network of Agencies for Health Technology Assessment (INAHTA) were also consulted (see appendix).
- Manual search: the reference list of relevant review papers and full economic evaluations were scrutinized for additional relevant articles.

2.2.3 Selection procedure

The selection was performed in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment if the title or the abstract or the keywords suggested relevant information, or if no abstract was available. The flow chart of the selection processes can be found in appendix.

The search strategy yielded 605 unique, potentially relevant citations. After title and abstract review, 535 articles were excluded, the majority of which were not economic studies. Other reason for exclusion was that most relevant abstracts were very recent conference proceedings for which no full text publication was available yet. Of the 70 full-text articles reviewed, 46 were further excluded. Main reasons for exclusion were studies did not report any economic results (safety/efficacy studies); were no full economic evaluations (but cost description, cost comparison or cost consequence analyses instead[26, 27]);[26-33] or did not assess the novel DAAs listed above (their study intervention was limited to peginterferon-ribavirin dual therapy, with or without telaprevir/boceprevir).[34-41] A final study was excluded as it assessed a novel DAA (asunaprevir) that is not approved in Europe and that was used in a very narrow and specific Japanese population.[42]

A total of 24 articles were identified: 20 full economic evaluations,[43-62] 3 literature reviews[63-65] and 1 HTA report[66] that contained both a literature review and a full economic evaluation. The list of the 21 economic evaluations identified is presented in Table 1.

[b] In cost-consequence analyses, both costs and outcomes of different alternatives are described. In such studies however, an incremental cost-effectiveness ratio (ICER) is not calculated or the results are expressed in disease-specific outcome (e.g. incremental cost per additional sustained virological response percentage point gained). Such studies are discarded as their results cannot be compared with those of other types of economic evaluations, mainly CEA and CUA.

Table 1 – List of identified economic evaluations

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Gimeno-Ballester V, Mar J, San Miguel R. Cost–effectiveness analysis of simeprevir with daclatasvir for non-cirrhotic genotype-1b-naïve patients plus chronic hepatitis C. Expert Review of Pharmacoeconomics and Outcomes Research. 2015.47
Kuwabara H, Westerhout K, Treur M, Cerri K, Mahlich J, Yatsuhashi H. Cost-effectiveness analysis of simeprevir in combination with peginterferon and ribavirin for treatment-naive chronic hepatitis C genotype 1 patients in Japan. J Med Econ. 2015;18(7):502-11.50
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2014
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Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol. 2014;60(3):530-7.61

2013
Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. J Viral Hepat. 2013;20(12):847-57.49

2.2.4 Coverage of the reviews

The review by Bickerstaff et al.[63] is the most comprehensive as it covers the literature up to 2015. It is limited to economic evaluations of novel DAAs performed in the USA and includes 7 publications. Six of those publications were also identified in our literature review.[43, 48, 52, 54, 58, 60] The last publication[67] identified in Bickerstaff was not retained in our review as it relates to HCV screening.

The review by Mark et al.[65] is limited to sofosbuvir and simeprevir hepatitis C treatments and covers the literature up to November 2014. It includes 4 publications, of which 3 were also identified in our review.[51, 56, 58] The fourth study[2] reviewed by Mark was discarded in our review as it was appraised as being a cost consequence analysis, not a full economic evaluation.

The 2015 review by Tice et al.[66] covers the literature up to September 2014 and includes 9 full economic evaluations, all of them also identified in our review.[46, 48, 49, 51, 53, 56, 58, 59, 61] However their review was limited to a very brief narrative description of each study included.

The 2014 CADTH review[64] covers the literature up to May 2014 and is limited to 2 economic evaluations; one[48] also identified in our review and the other[2] excluded as being appraised a cost consequence analysis.

Therefore, after critical and qualitative analysis, we did not retain any of these reviews. Our analysis is based on the 21 primary full economic evaluations listed above.

2.3 Classification of the economic evaluations

The economic evaluations were grouped in four categories, each being handled separately in this literature review.

2.3.1 Early publications based on emerging and weak evidence

Four of the oldest publications modelled a hypothetic interferon-free DAA regimen (either as base-case[46, 49, 61, 64] or as sensitivity analysis[53]) without specifying a particular molecule. Interferon-free regimens were still unapproved at the time of writing those studies and as evidence on efficacy, safety and tolerability was only emerging and sourced from abstract publications, their model was mainly based on assumptions.

Now that recent economic evaluations have been published using more robust evidence on all-oral interferon-free therapies, these oldest publications were not further considered in our review.

2.3.2 Pegylated interferon as an intervention

Considering the substantial higher antiviral effect of new therapies and the side effects and contra-indications of peginterferon that can now be avoided by the new therapies, treating patients with peginterferon-associated regimens is not anymore accepted by Belgian and internalionnal hepatologists. This position has been strongly advocated by representatives from the Belgian National Institute of Health and Disability Insurance (INAMI-RIZIV: CRM-CTG).

Therefore, the 6 economic evaluations limited to the assessment of peginterferon-associated new DAA treatment regimens were discarded.[46, 50, 53, 55, 56, 58] Only the economic evaluations assessing at least one interferon-free novel DAA regimen were kept.

2.3.3 Disease progression after sustained viral response

In models in which it is assumed that all patients (any fibrosis stage) with sustained viral response (SVR) are cured and have no longer liver-related disease progression (or experience the same rate of progression as individuals in the general population), the long-term costs associated with SVR are likely to be underestimated and the quality of life is likely to be overestimated. Recent evidence suggests indeed that CHC patients (even non-cirrhotic) have many co-morbidities (e.g. alcoholism) and are much more likely than the general population to experience liver-related morbidity; and have therefore a residual rate of disease progression post-SVR.

As a consequence, the 10 studies assuming that all SVR patients are cured and incur no further risk of progression to any liver-related disease have been discarded.[44, 45, 50-54, 57, 58, 62]

2.3.4 Selected economic evaluations

The assignment of the 21 economic evaluations according to the categories defined above is presented in the table 2. The studies not belonging to any of those three categories were considered relevant for inclusion in the literature review.

Table 2 – Classification of the identified economic evaluations

References	Early publication based on assumptions	Treatment limited to PEG-based direct-acting antivirals	Model assuming no disease progression after SVR
Chhatwal, 2015			
Cure, 2015 (Italy)			x
Cure, 2015 (UK)			x
Gimeno-Ballester, 2015			
Kuwabara, 2015		x	x
Leleu, 2015			x
Linas, 2015			x
Najafzadeh, 2015			x
Pfeil, 2015			x
San Miguel, 2015			
Tice, 2015			
Younossi, 2015			
Zhang, 2015			x
Deuffic-Burban, 2014	x	x	
Hagan, 2014			
Liu, 2014	x	x	x
Obach, 2014		x	
Petta, 2014		x	
Saab, 2014		x	x
Younossi, 2014	x		
Hagan, 2013	x		

*Note: Studies belonging to any of those categories (marked with an "**x**") are discarded from the literature review (grey shaded). Studies without any "**x**" (not shaded) are included in the literature review.*
SVR: sustained viral response, PEG: pegylated interferon.

2.4 Overview of the selected economic evaluations

Table 3 gives an overview of the characteristics of the 6 studies selected that assess the cost-effectiveness of interferon-free novel DAAs against CHC.

2.4.1 Country and study design

Four studies were performed in the USA[43, 48, 60, 66] and two in Spain.[47, 59] All were cost-utility analyses, with outcomes expressed as quality-adjusted life years (QALYs). This design seems appropriate because, CHC being a potentially severe long-term disease that can result in liver-related death, novel DAA treatments against CHC aim both at improving the quality of life of the patients and at extending their lives.

2.4.2 Perspective

All studies adopted a health care payer perspective in their base-case, including direct medical and intervention costs only. Indirect productivity costs due to work absenteeism from the patients and direct non-health care costs (such as travel costs or informal care costs due to relatives caring for a sick patient) were not accounted for in any of the studies.

2.4.3 Time horizon and discount rate

All studies used a lifelong time horizon where patients are followed up to the end of their life. Given that complications from HCV infection may not occur until many years in the future, economic evaluations of HCV therapy typically require such lifelong time horizons. Future costs and outcomes were discounted at a rate of 3% in all studies.

In three studies scenario analyses were conducted using different discount rates.[47, 59, 60] Scenario analyses for shorter time horizons (10, 20 and 30 years) were conducted in Chhatwal et al.[43]

2.4.4 Targeted patient group

Genotype 1 is the most common HCV genotype in the USA and in Europe. As such, all studies assessed the cost-effectiveness of DAA-based therapeutic options in HCV genotype 1 infected patients. Only two studies assessed the cost-effectiveness of DAA treatments for HCV patients with other genotypes: 2 and 3 in San Miguel et al.[59] and 2, 3 and 4 in Chhatwal et al.[43]

Four studies specified that only HCV mono-infected patients were modelled, thereby excluding e.g. patients co-infected with the human immunodeficiency virus (HIV).[47, 59, 43, 48, 60, 66] The other studies did not specify whether they modelled mono- or co-infected HCV patients.

In the base-case of the economic evaluations, either all patients were assumed to be treated irrespective of their fibrosis stage[43, 48, 60, 66] or they were stratified according to the absence (treatment of the F0-F3 patients) or presence (treatment of the F4 patients) of cirrhosis.[43, 48, 60, 66] Stratification per other fibrosis stage was performed in the scenario analyses of four studies: treating each stage separately;[18] treating F0-F1 versus F2-F3 patients;[34] treating F0-F1 versus F2 versus F3-F4 patients[35] or treating F3-F4 patients only[41].

2.4.5 Intervention and comparators

Depending on the respective national clinical guidelines and on the proposed indications of the new drugs for each HCV genotype, four interferon-free DAA-based treatment strategies were investigated: sofosbuvir+ribavirin[43, 59, 66] (SOF+RBV), sofosbuvir+ledipasvir[43, 60, 66] (SOF+LDV), simeprevir+daclatasvir[47] (SMV+DCV) and sofosbuvir+simeprevir[48, 66] (SOF+SMV).

In five studies,[43, 47, 59, 60, 66] the comparator of interest was the old standard of care (OSoC), with peginterferon/ribavirin-based therapies with or without boceprevir/telaprevir (BOC/TEL). In three studies, the comparator of interest is another interferon-free DAA combination: SOF+RBV and/or SOF+SMV.[48, 60, 66] Only three studies modelled a “no treatment” option as a comparator;[43, 60, 66] in Chhatwal et al.[18] this option being only valid for the treatment-naïve pegylated interferon intolerant patients.

A precise description of the treatment regimens and durations considered in each study, per genotype and per treatment history can be found in Table 4, together with the list of the source RCTs used to document the SVR rates of the new DAAs.

We could not identify a unique economic evaluation where the recently approved interferon-free DAAs are all compared with each other's, and considering all HCV genotypes.

2.4.6 Assumptions used in modelling the HCV natural history

A synthetic presentation of those assumptions is provided in Table 5.

2.4.6.1 Treatment effect on disease progression

All but one studies[66] assumed that non-cirrhotic patients with liver fibrosis stages F0, F1 or F2 do not experience any further HCV disease progression when they achieve SVR. In Tice et al.,[66] based on undocumented computations and source, such patients were assumed to keep a residual risk of progression to worse stages of disease.

In patients with cirrhosis (F4), the studies assumed that disease could still progress after achievement of SVR, although at a slower rate. Using the adjusted hazard ratios (HR) derived in the retrospective study by Cardoso et al.[68] (non-SVR HR for decompensated cirrhosis: 4.73; non-SVR HR for hepatocellular carcinoma: 3.06; median follow-up time of 2.5 (1-18) years), three economic evaluations consistently report annual rates of 0.8-1% for the post-SVR transition from F4 to decompensated cirrhosis (instead of 4% without SVR) and of 0.5% from F4 to hepatocellular carcinoma (instead of 1.4% without SVR).[43, 47, 59] Though referring to various sources, the three other economic evaluations[48, 60, 66] report similar post-SVR transition rates of 0.3% for F4 to decompensated cirrhosis and 4% without SVR (this corresponds to the ratio reported in the prospective study by Bruno et al.,[69] HR SVR 0.0857). The 0.58% post-SVR transition rate from F4 to hepatocellular carcinoma (2.4% without SVR) reported in Younossi et al.[60] was based on a meta-analysis[70] of 12 observational studies that computed an SVR HR of 0.24. In Hagan et al.,[48] based on the prospective study by Bruno et al.[69] the transition from F4 to hepatocellular carcinoma was 1.9% post-SVR versus 3% without SVR. Tice et al.[66] refer to Hagan et al.[49] for the 1.24% transition rate from F4 to hepatocellular carcinoma. However no such value was found in the cited reference and no reference to another source is provided.

The transition from post-SVR F3 fibrosis stage to more advanced health states is less clear. In three studies treated F3 patients who achieve SVR were assumed to maintain SVR and to experience no further disease progressions.[43, 47, 59] In Tice et al.,[66] Younossi et al.[60] and Hagan et al.[48] however patients who achieved SVR at fibrosis score F3 could still progress to hepatocellular carcinoma (0.26-0.7% post-SVR versus 0.73-1.1% without SVR), or to decompensated cirrhosis (0.1% post-SVR versus 1.2% without SVR in Hagan et al.[48] and in Tice et al.[66]). In Younossi et al.[60] it was assumed (expert opinion) that there was no progression from F3 to decompensated cirrhosis post-SVR.

2.4.6.2 Post-SVR fibrosis regression

In three studies[48, 60, 66] patients who achieved SVR could experience fibrosis regression over the course of their life to account for liver regeneration after viral eradication. In Younossi et al.,[60] SVR patients with METAVIR fibrosis scores F4 and F3 could regress to, respectively, F3 and F2 scores at an annual rate of 0.076 and 0.264. In Hagan et al.,[48] post-SVR fibrosis regression rates were much higher at 0.34 (0.19-0.49) for F4 to F3, 0.08 (0.06-0.10) for F4 to F2 and 0.50 (0.25-0.82) for F3 to F2. In Tice et al.,[66] rates reported for similar transitions were in between.

No post-SVR fibrosis regression was allowed in the other economic evaluations.

2.4.6.3 Reinfection/relapse after viral clearance

Although unusual, virologic relapse (defined as an HCV RNA rebound) or a *de novo* HCV infection can occur in successfully treated patients with undetectable serum HCV RNA at the end of treatment.

None of the studies reviewed here modelled such a risk of reinfection / relapse after viral clearance, thereby slightly overestimating the benefits of the HCV therapies.

2.4.7 Non-liver mortality

Three studies[47, 59, 60] assumed that the risk of death from non-liver causes in patients infected with HCV is the same as the background mortality of the general population (Table 5).

In Tice et al.[66] and in Hagan et al.[48] non-liver mortality in CHC patients before SVR was set at 2.37 times the mortality for individuals without CHC. After SVR, subjects were assigned lower background mortality rates, set at 1.4 times non-CHC rates, based on the evidence that viral clearance improves overall health outcomes.[71] In Chhatwal et al.,[43] the general population background mortality was adjusted with sex-specific hazard ratios (2.58 for men and 1.97 for women) to account for the higher risk of non-liver related death in CHC patients. These adjusted mortality rates were used both in non-SVR as in SVR patients.

2.4.8 Quality of life

2.4.8.1 Quality of life weights for CHC health states

Prior to initiation of any treatment, CHC patients experience health-related quality of life (HRQoL) impairments which worsen with the severity of liver disease, such as the presence of cirrhosis or liver cancer.

This is reflected in the QoL weights used in the economic evaluations with much lower values reported for more advanced (0.45[47, 59] to 0.80[43] for decompensated cirrhosis and 0.45[47, 59] to 0.79[43] for hepatocellular carcinoma) than for early stages of liver disease (0.77[47, 59] to 0.98[66] for F0-F1 fibrosis scores), Table 6.

There was a great diversity in the values reported for a single health state across the studies. For example, QoL weights reported for the F4 fibrosis score (cirrhosis) ranged from as low as 0.55[47, 59] up to 0.90.[43] This may have a potentially strong impact on the cost-effectiveness results as studies with lower QoL weights for a health state have more room for improvement with treatments that favour SVR.

In order to understand the discrepancies in the QoL weights reported between the studies, the source references (and references of the references to go back to the primary QoL studies) listed in the economic evaluations were analysed. A summary of the methods used by each study source is presented in Table 6. QoL weights reported in Chhatwal et al.[43] for the different CHC health states were highly consistent as they all originated from a unique EQ-5D primary QoL study performed in Canadian CHC patients.[72] Though no detail on the computations are reported, Chhatwal et al.[43] adjusted those weights to the US population norms. The QoL weights reported in Gimeno-Ballester et al.[47] and in San Miguel et al.[59] were also fairly consistent as, although the weights were derived from 3 different primary QoL studies thereby limiting their comparability,[73-75] they were all measured with the same EQ-5D instrument and in similar CHC patient populations in the UK. In Younossi et al.,[60] QoL weights were obtained from two studies, using different measurement instruments (SF-6D[76] versus a metaregression of 6 EQ-5D studies[77]) and performed in different patient populations (Canada[77] versus Canada, USA, Germany and the UK[76]). This lack of consistency in the methodology used for valuing the utilities of different health states implies that the QoL values may not be comparable. It is not clear further which adjustments were performed to the QoL weights for the F0-F3 fibrosis stages, as they are different from the original value reported in the source reference, i.e. 0.747 in McLernon et al.[77] versus 0.79 in Younossi et al.[60] QoL weights used in Tice et al.[66] also suffer from methodological non-consistency as they originate from 2 studies using different methods (translated SF-36 scores[78] versus standard gamble/time trade-off[79]) and respondent populations (CHC patients[78] versus hepatologists[79]). Further though a reference[78] is provided for the health state liver transplant (1rst year), no such value could be found there. In Hagan et al.[48] most QoL weights were obtained from the study by Thein et al.[78] that translated the SF-36 scores reported in published studies into utilities. Other QoL weights were taken from a past economic evaluation for HCV screening[80] where either no clear reference is reported or where assumptions have been used.

2.4.8.2 Quality of life adjustments during antiviral treatment

In addition to the baseline impairment in QoL for patients with CHC, treatment regimens can have additional QoL burden. The standard PEG- and RBV-based treatments have substantial side effects (such as anaemia and depression) that further amplify the already impaired QoL of CHC patients. This is reflected in all the economic evaluations reviewed here, where patients treated with PEG+RBV-based regimens were assigned further QoL decrements (-10% to -16.5%) or QALYs reduction (-0.02 to -0.21) applied to their F0-F4 weights for the duration of the treatment. It should be noted however that, except in Chhatwal et al.,[43] none of the decrement/reduction values reported could exactly be found in the cited source references.

Newer PEG-free regimens seem to minimally impact the health utility scores. In all studies, patients undergoing RBV-only treatment (i.e. SOF+RBV) experienced minimal decreases in their QoL during treatment: -5% to -5.7% QoL decrements or -0.05 to -0.09 QALYs reductions, usually based on assumptions.

In studies where patients are treated with both PEG- and RBV-free regimens, either an improvement in QoL during treatment is modelled (+4.5%),[60] or no change in QoL is assumed (i.e. QoL weights during treatment remain those of F0-F4 scores),[47, 48] or a very small QALY reduction is applied (-0.075 to -0.087).[66] Note that the QoL improvement reported by Younossi et al.[60] could not be found in the cited source reference.[61]

2.4.8.3 Quality of life adjustments post-SVR

After treatment completion, usually the QoL of the patients slowly improves for those who achieve SVR. This was accounted for in all the economic evaluations reviewed here.

In Younossi et al.[60] and in Hagan et al.[48] patients who achieved SVR were assumed to receive a utility increment of 0.05 and 0.07 QALY, respectively. In Gimeno-Ballester et al.,[47] San Miguel et al.[59] and Tice et al.[66] improvements in the QoL of SVR patients were stratified according to the health state the patient came from: +0.02-0.05 QALYs in fibrosis stages F0-F1, +0.01-0.11 fibrosis stage F2, +0.07-0.11 QALYs in fibrosis stages F3 and +0.06-0.07 QALYs in fibrosis stages F4. Note that although reference to the studies by Cure[81, 82] and Liu[38] are provided, we were not able to identify the primary QoL studies on which those values originate, not even in the sources cited in those references.

In Chhatwal et al.[43] patients achieving SVR were assigned the age-specific QoL weights of the US general population. However CHC patients suffer from many comorbidities that will certainly persist post-SVR and it is thus likely that their QoL is lower than that of the general population.

Table 3 – General characteristics of the selected economic evaluations

	Chhatwal et al., 2015[43]	Gimeno-Ballester et al., 2015[47]	San Miguel et al., 2015[59]	Tice et al., 2015[66]	Younossi et al., 2015[60]	Hagan et al., 2014[48]
Country	USA	Spain	Spain	USA	USA	USA
Funding source§	No industry support	No industry support	Unknown	No industry support	Industry sponsored (Gilead)	No industry sponsored
Study design	CUA	CUA	CUA	CUA	CUA	CUA
Perspective	HCP	HCP	HCP	HCP	HCP	HCP‡
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Discount rate†	3%	3%	3%	3%	3%	3%
Costing year	2014	2015	2013	2014	2014	2013
Analytic technique	Individual-based state transition model	Markov model	Markov model	Markov model	Markov model	Markov model
Target patient group	CHC patients with genotypes 1, 2, 3, 4	Genotype 1b treatment-naïve CHC patients with moderate fibrosis (F2-F3)	CHC patients aged 50 years with genotypes 1, 2, 3	CHC patients aged 60 years with genotype 1	CHC patients aged 52 years with genotype 1	CHC interferon-intolerant patients aged 50 years with genotype 1
Coinfection	Not specified	No coinfection	No coinfection	No coinfection	No coinfection	Not specified
Intervention	SOF+RBV SOF+LDV	SMV+DCV	SOF+RBV	Incremental analysis: SOF+LDV SOF+SMV SOF+RBV OSoC No treatment	SOF+LDV	SOF+SMV
Comparator	OSoC No treatment*	OSoC	OSoC		OSoC No treatment SOF+RBV SOF+SMV	SOF+RBV
Adverse event costs considered?	Comparator: yes Intervention: yes	Comparator: yes Intervention: no	Comparator: no Intervention: no	Comparator: yes Intervention: yes	Comparator: yes Intervention: yes	Comparator: yes Intervention: yes
Uncertainty analyses	One-way SA Probabilistic SA Scenario analyses	One-way SA Probabilistic SA Scenario analyses	One-way SA Probabilistic SA Scenario analyses	One-way SA Probabilistic SA Scenario analyses	One-way SA** Probabilistic SA** Scenario analyses	No***
Subgroup analyses	Presence of cirrhosis, fibrosis stage, gender, age	Age	Fibrosis stage, age	Fibrosis stage, age	Presence of cirrhosis, fibrosis stage	No***

CUA: cost-utility analysis, HCP: health care payer, SA: sensitivity analysis, DCV: daclatasvir, LDV: ledipasvir, RBV: ribavirin, SMV: simeprevir, SOF: sofosbuvir, OSoC: old standard of care, defined as peginterferon/ribavirin-based therapies with or without boceprevir/telaprevir (BOC/TEL). § Funding source was classified using three categories. Industry support: any explicit acknowledgment of support from private industry (generally manufacturers of medical devices). Unknown: no information about support provided.

*No industry support: explicit acknowledgment of support that did not include private industry (generally from either public sources or private foundations). An explicit statement of "funding source: none" was also included in this last category. † For both costs and effects. ‡ The base-case perspective reported in this study is societal. However only direct medical costs are included (drug, adverse event and treatment costs) which corresponds to a health care payers perspective. * No treatment option modelled only for the treatment-naïve peginterferon-intolerant patients. ** Sensitivity analyses performed on treatment-naïve patients only. *** One-way sensitivity analysis is performed but is not reported as standard way (not as ICER, Tornado graph…). The results are thus non-exploitable.*

Table 4 – Treatment-related variables used in the economic evaluations

	Chhatwal et al., 2015[43]	Gimeno-Ballester et al., 2015[47]	San Miguel et al., 2015[59]	Tice et al., 2015[66]	Younossi et al., 2015[60]	Hagan et al., 2014[48]
Treatment regimens and durations, per genotype and per treatment history						
Genotype 1	*Treatment-naïve* SOF+LDV (8-12 w*) BOC+PEG+RBV (28-48 w) TEL+PEG+RBV (24-48 w) No treatment§	*Treatment-naïve* SMV+DCV (12 w) BOC+PEG+RBV† TEL+PEG+RBV†	*Treatment-naïve* SOF+RBV (24 w) PEG+RBV (48 w) BOC+PEG+RBV† TEL+PEG+RBV†	*Treatment-naïve* SOF+LDV (8-12 w*) SOF+SMV (12 w) SOF+RBV (24 w) SOF+PEG+RBV (12 w) PEG+RBV (48 w) No treatment	*Treatment-naïve* SOF+LDV (8-12 w*) SOF+RBV (24 w) SOF+SMV (12-24 w**) BOC+PEG+RBV† No treatment	*Treatment-naïve*‡ SOF+SMV (12 w) SOF+RBV (24 w)
	Treatment-experienced SOF+LDV (12-24 w**) BOC+PEG+RBV (36-48 w) TEL+PEG+RBV (48 w)			*Treatment-experienced* SOF+LDV (12-24 w**) SOF+SMV (12 w) SOF+PEG+RBV (12 w) PEG+RBV (48 w) No treatment	*PEG+RBV-experienced* SOF+LDV (12-24 w**) SOF+RBV (24 w) SOF+SMV (12-24 w**) BOC+PEG+RBV† No treatment *BOC/TEL+PEG+RBV-experienced* SOF+LDV (12-24 w**) SOF+RBV (24 w) No treatment	*PEG+RBV-experienced*‡ SOF+SMV (12 w) SOF+RBV (24 w) ***
Genotype 2	*Treatment-naive* SOF+RBV (12 w) PEG+RBV (24 w) No treatment§		*Treatment-naive* SOF+RBV (12 w) PEG+RBV (24 w)			
	Treatment-experienced SOF+RBV (12 w) PEG+RBV (24 w)		*Treatment-experienced* SOF+RBV (12 w) PEG+RBV (48 w)			

Genotype 3	Treatment-naive SOF+RBV (24 w) PEG+RBV (24 w) No treatment§		Treatment-naive SOF+RBV (24 w) PEG+RBV (24 w)			
	Treatment-experienced SOF+RBV (24 w) PEG+RBV (24 w)		*Treatment-experienced* SOF+RBV (24 w) PEG+RBV (48 w)			
Genotype 4	*Treatment-naive* SOF+PEG+RBV (12 w) PEG+RBV (48 w) SOF+RBV (24 w)§ No treatment§					
	Treatment-experienced SOF+PEG+RBV (12 w) PEG+RBV (48 w)					
Sustained virological response						
Treatment effect stratification	SVR split by presence/absence of cirrhosis	No stratification	No stratification	SVR split by presence/absence of cirrhosis	SVR split by METAVIR stage and by sub-genotype	SVR split by METAVIR stage in Q80K+ subjects
Source for SVR rate of novel DAAs	ION-1, ION-2, ION-3, NEUTRINO, FISSION, VALENCE, POSITRON, FUSION, the Egyptian Ancestry study	LEAGUE-1	NEUTRINO, QUANTUM, 11-I-0258, FISSION, ELECTRON, PROTON, VALENCE, FUSION, LONESTAR-2	QUANTUM, NIH SPARE, NIH SPARE-2, ELECTRON, ELECTRON-2, COSMOS, LONESTAR, SYNERGY, ION-1, ION-2, ION-3 (meta-analyses)	ION-1, ION-2, ION-3, NEUTRINO	COSMOS, PHOTON-1, SPARE

*BOC: boceprevir, DCV: daclatasvir, LDV: ledipasvir, PEG: pegylated-interferon, RBV: ribavirin, SMV: simeprevir, SOF: sofosbuvir, TEL: telaprevir, SVR: sustained viral response. * 8 weeks treatment duration in non-cirrhotic patients with HCV RNA less than 6 million IU/mL, 12 weeks treatment duration in non-cirrhotic patients with HCV RNA over than 6 million IU/mL and in cirrhotic patients. ** 12 weeks treatment duration in non-cirrhotic patients, 24 weeks treatment in cirrhotic patients. *** Failed prior BOC/TEL-experienced patients are not modelled as they may harbour HCV variants resistant to SMV. † Response-guided therapy. ‡ Subjects not reaching SVR are re-treated with SOF+LDV (24 weeks) rescue therapy. § Option modelled for the treatment-naïve peginterferon-intolerant patients only.*

Table 5 – Modelling assumptions of the economic evaluations

	Chhatwal et al., 2015[43]	Gimeno-Ballester et al., 2015[47]	San Miguel et al., 2015[59]	Tice et al., 2015[66]	Younossi et al., 2015[60]	Hagan et al., 2014[48]
Disease progression with no sustained virological response (% per year)						
- **F0 to F1**	11.7 (10.4-13)	3.7 †	3.7 †	7.7 (6.7-8.8)	11.7	12 (9-14)
- **F1 to F2**	8.5 (7.5-9.6)			7.4 (6.4-8.6)	8.5	9 (7-10)
- **F2 to F3**	12 (10.9-13.3)	5.1 ‡	5.1 ‡	8.9 (7.7-10.3)	12.1	12 (10-14)
- **F3 to F4**	11.6 (10.4-12.9)			8.8 (7.5-10.4)	11.5	12 (9-14)
- **F3 to DC**	Not relevant	Not relevant	Not relevant	1.2 (1-1.4)	1.2	1.2 (1-1.4)
- **F3 to HCC**	Not relevant	Not relevant	Not relevant	0.73 (0-2.7)	1.1	1.1 (0.9-1.3)
- **F4 to DC**	3.9 (1-7.9)	4.0	4.0	3.9 (3-4.8)	3.9	4 (3-5)
- **F4 to HCC**	1.4 (1-7.9)	1.4	1.4	1.9 (1.7-5.5)	2.4	3 (2-4)
Disease progression post sustained virological response (% per year)						
- **F0 to F1**	0	0 †	0 †	1 (0.50-1.5)	0	0
- **F1 to F2**	0			0.72 (0.36-1.09)	0	0
- **F2 to F3**	0	0 ‡	0 ‡	1.02 (0.51-1.54)	0	0
- **F3 to F4**	0			0.99 (0.49-1.49)	?	?
- **F3 to DC**	Not relevant	Not relevant	Not relevant	0.1 (0.05-0.15)	0	0.1 (0.08-0.12)
- **F3 to HCC**	Not relevant	Not relevant	Not relevant	0.48 (0.1-0.7)	0.26	0.7 (0.6-0.8)
- **F4 to DC**	0.8 (0.2-3.6)	1.0	1.0	0.33 (0.2-0.5)	0.33	0.3 (0.2-0.4)
- **F4 to HCC**	0.5 (0.2-1.3)	0.5	0.5	1.24 (0.6-1.9)	0.58	1.9 (1.5-2.3)
- **Source**	Cardoso, 2010[68]	Cardoso, 2010[68] Veldt, 2007[83]	Cardoso, 2010[68] Veldt, 2007[83]	Author computation Hagan, 2013* [49]	Expert opinion Morgan, 2013[70]	Bruno, 2009[69]
Non CHC-related mortality						
- **In CHC non-SVR patients**	General population mortality adjusted with hazard ratios 2.58 (men) and 1.97 (women)	Mortality of the general population	Mortality of the general population	2.37 (1.28-4.38) times the general population mortality	Mortality of the general population	2.37 times the general population mortality
- **In SVR-patients**				1.4 (1-2.5) times the general population mortality		1.4 times the general population mortality

- **Source**	Armstrong, 2006[84] Liu, 2013[85]	-	-	El-Kamary, 2011[86] Veldt, 2004[71]	-	El-Kamary, 2011[86] Veldt, 2004[71]
Post-SVR fibrosis regression rate	No	No	No	F4 to F3: 0.22 F4 to F2: 0.14 F4 to F1: 0.09 F3 to F2: 0.46 F3 to F1: 0.24 F2 to F1: 0.58 F2 to F0: 0.12 F1 to F0: 0.35	F4 to F3: 0.076 - - F3 to F2: 0.267 - - - -	F4 to F3: 0.34 F4 to F2: 0.08 - F3 to F2: 0.50 - - - -
- **Source**	-	-	-	Razavi, 2013[87] Veldt, 2004[71]	D'Ambrosio, 2012[88] Maylin, 2008[89]	Mallet 2008[90] Maylin 2008[89] Pol 2004[91] Poynard 2002[92]
Reinfection / relapse after viral clearance	No	No	No	No	No	No

F0 to F4: METAVIR fibrosis stages, CC: compensated cirrhosis, DC: decompensated cirrhosis, HCC: hepatocellular carcinoma, LT: liver transplant, CHC: chronic hepatitis C, SVR: sustained viral response. † Mild hepatitis (F0-F1) to moderate hepatitis (F2-F3). ‡ Moderate hepatitis (F2-F3) to compensated cirrhosis (F4). Reference to Hagan et al.,[49] 2013 is provided as the source for the post-SVR transitions from F3 to DC and HCC or F4 to DC and HCC. However no such values were found in the cited reference, and no reference to another source is provided.*

Table 6 – Quality of life weights used in the economic evaluations

	Chhatwal et al., 2015[43]	Gimeno-Ballester et al., 2015[47]	San Miguel et al., 2015[59]	Tice et al., 2015[66]	Younossi et al., 2015[60]	Hagan et al., 2014[48]
Chronic hepatitis C health states						
Weights used in the economic evaluations						
- **F0**	0.93	0.77	0.77	0.98	0.79	0.85
- **F1**	0.93	0.77	0.77	0.98	0.79	0.85
- **F2**	0.93	0.66	0.66	0.92	0.79	0.85
- **F3**	0.93	0.66	0.66	0.79	0.79	0.79
- **F4 / CC**	0.90	0.55	0.55	0.76	0.748	0.76
- **DC**	0.80	0.45	0.45	0.69	0.672	0.69
- **HCC**	0.79	0.45	0.45	0.67	0.61	0.67
- **LT**	0.84	0.45	0.45	0.50	0.65	0.50
- **Post-LT**	0.84	0.45	0.45	0.77	0.709	0.77
Reference source	Chong, 2003[72]	Grieve, 2006 (F0-F1),[73] Wright, 2006 (F2-F4),[74] Longworth, 2003 (DC, HCC, LT)[75]	Grieve, 2006 (F0-F1),[73] Wright, 2006 (F2-F4),[74] Longworth, 2003 (DC, HCC, LT)[75]	Wong, 1998 (F0-F2),[79] Thein, 2005 (F3-F4, DC, HCC, post-LT),[78] no reference (LT)	McLernon, 2008 (F0-F4, DC and post-LT)[77] Hsu, 2012 (HCC, LT)[76]	Coffin, 2012 (F0-F2, LT),[80]Thein, 2005 (F3-F4, DC, HCC, post-LT)[78]
• **Instrument**	EQ-5D	EQ-5D	EQ-5D	TTO/SG (F0-F2), SF-36 translated to utilities (F3-F4, DC, HCC, post-LT), assumption (LT)	EQ-5D (F0-F4, DC and post-LT), SF-6D (HCC, LT)	SF-36 translated to utilities (F3-F4, DC, HCC, post-LT), assumption (F0-F2, LT)
• **Respondents**	CHC patients	CHC patients	CHC patients	Hepatologists (F0-F2), CHC patients (F3-F4, DC, HCC, post-LT)	CHC patients	CHC patients
• **Sample size**	n=44 (F0-F3), 24 (F4), 9 (DCC), 15 (HCC), 30 (LT)	n=185 (F0-F1), 71 (F2-F3), 40 (F4), 64 (DC, HCC, LT)	n=185 (F0-F1), 71 (F2-F3), 40 (F4), 64 (DC, HCC, LT)	N=6 (F0-F2), 44 (F3), 64 (F4), 49 (DC), 15 (HCC), 30 (post-LT)	n=7-77 (F0-F4, DC and post-LT), 20 (HCC), 50 (LT)	n=44 (F3), 64 (F4), 49 (DC), 15 (HCC), 30 (post-LT)
• **Population norm**	Canada	UK	UK	USA (F3, F4, DC, HCC, post-LT)	Canada, USA, Germany, UK (F0-F4, DC and post-LT); Canada (HCC, LT)	USA (F3, F4, DC, HCC, post-LT)

Adjustments for use in the economic evaluation	Population norms adjusted to the US	Combination of the weights form 3 UK EQ-5D studies	Combination of the weights form 3 UK EQ-5D studies	Combination of the weights from 1 SF-36 study and 1 TTO/SG study, and assumption	Combination of the weights from a metaregression of 6 EQ-5D studies and of 1 Canadian SF-6D study	Combination of the weights from a review of 2 SF-36 studies and assumptions
Treatment-related adverse event						
PEG+RBV-based	-10% (-16% to -4%)	TEL: -0.080 BOC: -0.019	PEG+RBV: -0.21* SOF+PEG+RBV: -0.15*	PEG+RBV: -0.19 SOF+PEG+RBV: -0.17	BOC: -16.5% Other: -14.6%	-
• **Source**	• Siebert, 2003[93]	• Grieve, 2006[73]	• Grieve, 2006[73]	• Gao, 2012[94] McHutchison, 2012[95]	• Younossi, 2014[61] Liu, 2012[96]	• -
RBV-only	-5% (-10% to 0%)	-	-0.06*	-0.09	-5.7%	-0.05
• **Source**	• Not reported	• -	• Assumption	• Lawitz, 2013[97] Lawitz, 2014[98]	• Younossi, 2014[61]	• Assumption
PEG+RBV-free	SOF+LDV: Not reported	SMV+DCV: No change	-	SOF+LDV: -0.075 SOF+SMV: -0.087	SOF+LDV: +4.5%	SOF+SMV: No change
• **Source**	• Not reported	• Assumption	• -	• Lawitz, 2013[97] Lawitz, 2014[98]	• Younossi, 2014[61]	• Assumption
Post-sustained virological response						
Treatment effect	QoL of the general population	+0.05 in F0-F1 +0.11 in F2-F3 +0.06 in F4	+0.05 in F0-F1 +0.11 in F2-F3 +0.06 in F4	+0.02 in F0-F1 +0.01 in F2 +0.07 in F3-F4	+0.05 in F0-F4	+0.07 in F0-F4
- **Source**	Not reported	Cure, 2014[81] Cure, 2014[82]	Cure, 2014[81] Cure, 2014[82]	Liu, 2012[38]	Wright, 2006[74]	Coffin, 2012[80] Thein, 2005[78]

*F0 to F4: METAVIR fibrosis stages, CC: compensated cirrhosis, DC: decompensated cirrhosis, HCC: hepatocellular carcinoma, LT: liver transplant. EQ-5D: Euroqol 5-dimensions, TTO: time trade-off, SG: standard gamble, QoL: quality of life. PEG: pegylated-interferon, RBV: ribavirin, TEL: telaprevir, BOC: boceprevir, SOF: sofosbuvir, SMV: simeprevir, LDV: ledipasvir, DCV: daclatasvir * Original values, reported for the duration of the treatment, were transformed into yearly values (QALYs) assuming 52.14 weeks per year.*

2.5 Main results of the economic evaluations

Table 7 and Table 8 give an overview of the results of the economic evaluations.

2.5.1 Genotype 1

All but one studies performed predetermined pairwise comparisons of the interventions of interest (e.g. SOF+LDV versus OSoC, SOF+LDV versus no treatment, SOF+SMV versus SOF+RBV…). In Tice et al.[66] the treatment regimens investigated are all compared with each other's according to the efficiency frontier approach, where the appropriate comparator to an intervention is identified by ordering the interventions sequentially from the least to the most costly and by excluding the (extendedly) dominated interventions. As both approaches are different, we present the results of the pairwise comparisons and of the incremental analyses separately.

2.5.1.1 Pairwise comparisons

Two studies compared the combination **SOF+LDV** to the old standard of care (BOC/TEL+PEG+RBV) for genotype 1 patients.[43, 60] In both studies, the number of QALYs gained from SOF+LDV differed substantially by treatment history and presence of cirrhosis. The gain in QALYs was greater in patients with cirrhosis (F4) compared to those without cirrhosis (F0-F3); and in treatment-naïve patients compared to treatment experienced patients. In treatment-naïve patients, SOF+LDV was either found to be dominant[60] (i.e. both more clinically effective and less costly than its comparator) or cost-effective,[43] with an incremental cost of $9700 and $31 450 per QALY gained in cirrhotic and non-cirrhotic patients, respectively. In Younossi et al.[60] SOF+LDV remained the dominant option for treatment-experienced patients. By contrast, in Chhatwal et al.[43] ICERs were less favourable than for treatment-naïve patients, i.e. $79 200 and $35 800 per QALY gained in cirrhotic and non-cirrhotic patients, respectively, mainly due to the longer duration of treatment required for such difficult-to-treat population (SOF-LDV for 8-12 weeks in treatment-naïve versus 12-24 weeks in treatment-experienced patients).

In both studies[43, 60] a no treatment option was also included as a comparator to SOF+LDV. In both treatment-naïve and treatment experienced patients, SOF+LDV resulted in higher QALYs gained when compared to no treatment, and remained the preferred treatment option.

In Younossi et al.[60] the cost-effectiveness of SOF+LDV was also assessed against other SOF-based combinations: either SOF+SMV or SOF+RBV. Compared to SOF+RBV, SOF+LDV remained the dominant option in either treatment-naïve or treatment-experienced patients. Compared to SOF+SMV, SOF+LDV was also found to be less costly but slightly less effective (-0.16 QALYs gained in cirrhotic treatment-naïve patients, -0.02 in treatment-experienced patients), still resulting in largely favourable ICERs for SOF+LDV.

The cost-effectiveness of **SMV+DCV** versus old standard of care (BOC/TEL+PEG+RBV) was investigated in one study, in genotype 1b treatment-naïve non-cirrhotic patients, where it is reported that this therapeutic combination was cost-effective.[47]

With an incremental cost of €138 070 per QALY gained, the combination **SOF+RBV** was not found to be cost-effective compared to PEG+RBV in treatment-naïve patients.[59] In the same study, SOF+RBV was further found to be dominated by triple therapy with a protease inhibitor (BOC/TEL+PEG+RBV), as it was both less clinically effective and more costly.

The cost-effectiveness of **SOF+SMV** in genotype 1 interferon intolerant/ineligible CHC patients was investigated in Hagan et al.[48] The combination SOF+SMV was found to dominate (i.e. be more clinically effective and less costly) SOF+RBV.

2.5.1.2 *Comparison of the interventions according to the efficiency frontier approach*

In the incremental analysis by Tice et al.,[66] among all the (PEG-free) treatment regimens compared, the combination **SOF+LDV** was found to be the most cost-effective, with favourable ICERs of about $20 000 and $25 000 per QALY gained in genotype 1 treatment-naïve and treatment experienced patients, respectively. ICERs were slightly higher for the treatment-experienced patients due to the longer treatment duration required for those patients (SOF+LDV for 12-24 weeks) compared to treatment-naïve patients (SOF+LDV for 8-12 weeks) and due to the slightly lower effectiveness.

2.5.2 *Genotype 2*

The cost-effectiveness of SOF+RBV for CHC genotype 2 patients was assessed in Chhatwal et al.[43] and in San Miguel et al.[59] Both studies failed to demonstrate the cost-effectiveness of this therapy versus OSoC (PEG+RBV) in treatment-naïve and in treatment experienced patients.

In interferon-ineligible patients, SOF+RBV was found to be cost-effective for cirrhotic patients but not for non-cirrhotic patients in which no treatment was the preferred option.[43]

2.5.3 *Genotype 3*

The cost-effectiveness of SOF+RBV for CHC genotype 3 patients was assessed in Chhatwal et al.[43] and in San Miguel et al.[59] Both studies failed to demonstrate the cost-effectiveness of this therapy versus OSoC[43, 59] (PEG+RBV) in treatment-naïve and in treatment experienced patients or versus no treatment[43] in interferon-ineligible patients.

2.5.4 *Genotype 4*

Chhatwal et al.[43] report favourable ICERs (about $30 000 per QALY gained) for SOF+PEG+RBV versus OSoC (PEG+RBV) in cirrhotic genotype 4 patients, irrespective of their past treatment experience. In genotype 4 non-cirrhotic patients ICERs for SOF+PEG+RBV were not found to be favourable. In interferon-intolerant patients SOF+RBV was not cost-effective compared to “no treatment”.

2.6 Sensitivity and subgroup analyses

2.6.1 *Sensitivity analyses*

In Chhatwal et al.,[43] Gimeno-Ballester et al.,[47] San Miguel et al.,[59] Younossi et al.[60] and Tice et al.,[66] the results were most sensitive to the price (and discount obtained on the price) of the new DAAs, with lower prices considerably improving the cost-effectiveness of the treatment.

Variations in the assumed utilities of the CHC health states also had an impact (though more limited) on the results in Younossi et al.[60] and in Tice et al.[66] Other inputs had much smaller effects on the results.

In Chhatwal et al.[43] results were highly sensitive to the quality of life after SVR. They assumed however that QoL after achievement of SVR was equivalent to that of a healthy person, which could have overestimated the benefits of the new therapies.

2.6.2 *Subgroup analyses*

2.6.2.1 *Fibrosis stage*

Stratification of the results per stage of fibrosis (other than the cirrhotic/non-cirrhotic stratification) was performed in four studies.[43, 59, 60, 66]

In Chhatwal et al.[43] results per fibrosis stage (F0 to F4 separately) are presented graphically (no figure reported) and clearly illustrate the relationship between lower ICER and higher fibrosis stage in treatment-naïve patients, irrespective of their genotype. Likewise, in San Miguel et al.[59] moderate hepatitis patients (F2-F3) had more favourable (lower) ICERs than mild hepatitis patients (F0-F1), irrespective of the genotype and the treatment status of the patient. A similar trend was found by Tice et al.[66] who reported better ICERs when treating at F3-F4 stages instead of treating all patients (Table 8).

By contrast, in Younossi et al.[60] no clear pattern emerged as treating with the novel DAAs was the dominant option for each fibrosis stage investigated in treatment-naïve patients (F0-F1, F2 or F3-F4), such that no priority could be set among the fibrosis stages. Note that this is not in line with Younossi et al.[60] conclusion to treat less advanced fibrosis stages first, but this seems rather based on budget-impact than on cost-effectiveness considerations.

2.6.2.2 Age at start of treatment

Age at start of treatment had a substantial effect on the results of the economic evaluations. In Chhatwal et al.[43] results were more favourable in younger (40-year old) versus older (70-year-old) patients, irrespective of the genotype and treatment status of the patient. In Gimeno-Ballester et al.[47] and San Miguel et al.[59] an increased age at treatment initiation (over the range 30 to 70 years) strongly affected the ICER upwards. In Tice et al.[66] decreasing the age of the cohort to 50 years (instead of 60 in the base-case) resulted in more favourable (lower) ICERs.

2.6.2.3 Gender

In Chhatwal et al.[43] the results were more favourable in men than in women, irrespective of the genotype and treatment status of the patient.

Table 7 – Results of the economic evaluations – Pairwise comparisons

Author	Patient group	Intervention	Incremental outcome (QALYs gained)	Incremental cost-effectiveness ratio	Cost-effective therapy at local WTP threshold ‡
PEG-FREE DIRECT ACTING ANTIVIRAL VERSUS OLD STANDARD OF CARE					
Genotype 1 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+LDV	0.45	$31 452	SOF+LDV
	F4	SOF+LDV	1.17	$9703	SOF+LDV
Younossi et al.[60]	F0-F3	SOF+LDV	1.27	Dominant	SOF+LDV
	F4	SOF+LDV	2.45	Dominant	SOF+LDV
Gimeno-Ballester et al.[47]	F2-F3	SMV+DCV	0.87 – 0.94	€23 774 – €28 524	SMV+DCV
San Miguel et al.[59]	All patients	SOF+RBV	-0.19 – 0.67	Dominated – €138 070	OSoC (BOC/TEL+PEG+RBV, PEG+RBV)
Genotype 1 – Treatment-experienced patients					
Chhatwal et al.[43]	F0-F3	SOF+LDV	0.37	$35 853	SOF+LDV
	F4	SOF+LDV	1.01	$79 238	OSoC (BOC/TEL+PEG+RBV)
Younossi et al.[60]	All patients	SOF+LDV	1.76	Dominant	SOF+LDV
Genotype 2 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	0.37	$149 463	OSoC (PEG+RBV)
	F4	SOF+RBV	0.78	$62 428	OSoC (PEG+RBV)
San Miguel et al.[59]	All patients	SOF+RBV	0.63	€71 865	OSoC (PEG+RBV)
Genotype 2 – Treatment-experienced patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	0.40	$128 770	OSoC (PEG+RBV)
	F4	SOF+RBV	0.20	$281 317	OSoC (PEG+RBV)
San Miguel et al.[59]	All patients	SOF+RBV	0.88	€46 636	OSoC (PEG+RBV)
Genotype 3 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	0.46	$284 327	OSoC (PEG+RBV)
	F4	SOF+RBV	1.24	$95 083	OSoC (PEG+RBV)
San Miguel et al.[59]	All patients	SOF+RBV	1.14	€83 679	OSoC (PEG+RBV)
Genotype 3 – Treatment-experienced patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	0.31	$410 548	OSoC (PEG+RBV)

	F4	SOF+RBV	0.34	$382 819	OSoC (PEG+RBV)
San Miguel et al.[59]	All patients	SOF+RBV	0.86	€108 258	OSoC (PEG+RBV)
Genotype 4 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+PEG+RBV	0.66	$81 802	OSoC (PEG+RBV)
	F4	SOF+PEG+RBV	1.39	$30 986	SOF+PEG+RBV
Genotype 4 – Treatment-experienced patients					
Chhatwal et al.[43]	F0-F3	SOF+PEG+RBV	0.52	$80 793	OSoC (PEG+RBV)
	F4	SOF+PEG+RBV	0.99	$34 349	SOF+PEG+RBV
PEG-FREE DIRECT ACTING ANTIVIRAL VERSUS NO TREATMENT					
Genotype 1 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+LDV	1.16	$39 635	SOF+LDV
	F4	SOF+LDV	2.37	$17 977	SOF+LDV
Younossi et al.[60]	F0-F3	SOF+LDV	2.98	Dominant	SOF+LDV
	F4	SOF+LDV	5.25	Dominant	SOF+LDV
Genotype 1 – Treatment-experienced patients					
Younossi et al.[60]	All patients	SOF+LDV	3.35 – 3.39	Dominant	SOF+LDV
Genotype 2 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	1.22	$44 805	No treatment
	F4	SOF+RBV	2.28	$16 455	SOF+RBV
Genotype 3 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	1.25	$104 628	No treatment
	F4	SOF+RBV	2.28	$49 959	No treatment
Genotype 4 – Treatment-naïve patients					
Chhatwal et al.[43]	F0-F3	SOF+RBV	1.25	$105 227	No treatment
	F4	SOF+RBV	2.30	$49 592	No treatment
PEG-FREE DIRECT ACTING ANTIVIRAL VERSUS ANOTHER PEG-FREE DIRECT ACTING ANTIVIRAL					
Genotype 1 – Treatment-naïve patients					
Younossi et al.[60]	F0-F3	SOF+LDV	Comparator: SOF+SMV	0.02	Dominant	SOF+LDV
	F4	SOF+LDV		-0.16	$1 238 263†	SOF+LDV
	F0-F3	SOF+LDV		1.15	Dominant	SOF+LDV

	F4	SOF+LDV	Comparator: SOF+RBV	2.77	Dominant	SOF+LDV
Genotype 1 – Treatment-experienced patients						
Younossi et al.[60]	All patients	SOF+LDV	Comparator: SOF+SMV	-0.02	$3 180 450†	SOF+LDV
	All patients	SOF+LDV	Comparator: SOF+RBV	0.80 – 0.84	Dominant	SOF+LDV
Genotype 1 – Treatment-naïve and treatment-experienced patients						
Hagan et al.[48]	All patients	SOF+SMV	Comparator: SOF+RBV	0.24	Dominant	SOF+SMV

QALY: quality-adjusted life year, WTP: willingness to pay, ICER: incremental cost-effectiveness ratio. PEG: pegylated-interferon, RBV: ribavirin, SOF: sofosbuvir, SMV: simeprevir, LDV: ledipasvir, OSoC: old standard of care, BOC: boceprevir, TEL: telaprevir.

† In the south-west quadrant of the cost-effectiveness plane, an intervention of interest is less expensive but also less clinically effective than its comparator. Thus lower costs are possible, but at the expense of lower benefits. An ICER can be calculated, although its interpretation will be the opposite of the "more frequent" ICER falling in the north-east quadrant where an intervention is more costly and more clinically effective than its comparator. ICERs in the south-west quadrant refer to a cost saving per unit of effect lost, instead of an incremental cost per QALY gained for ICERs in the north-east quadrant. In the south-west quadrant, ICERs greater than a cost-effectiveness threshold are considered acceptable. ‡ A treatment is selected if, based on the results of the probabilistic sensitivity analysis, its probability to be cost-effective is >50% at the local WTP threshold. If no probabilistic sensitivity analysis is performed, the treatment selected is based on the authors' conclusions. Local thresholds considered: $50 000/QALY in Chhatwal et al.[43] and in Younossi et al.,[60] €40 000/QALY in Gimeno-Ballester et al.[47] and in San Miguel et al.[59]

Table 8 – Results of the economic evaluations – Efficiency frontier approach†

Author	Patient group	Intervention	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER	Cost-effective therapy at local WTP threshold‡
Genotype 1 – Treatment-naïve patients								
Tice et al.[66]	All patients	No treatment	$45 313	11.82	-	-	-	-
		PEG+RBV	$62 540	13.34	$17 227	1.51	$11 385	PEG+RBV
		SOF+LDV (8-12w*)	$90 991	14.75	$28 451	1.41	$20 132	SOF+LDV (8-12 w*)
		SOF+PEG+RBV	$107 942	14.52	$16 951	-0.23	Dominated	-
		SOF+LDV (12w)	$108 619	14.81	$17 628	0.06	$283 927	-
		SOF+SMV	$163 336	14.74	$54 717	-0.08	Dominated	-
		SOF+RBV	$186 513	13.99	$77 894	-0.82	Dominated	-
	F3-F4	No treatment	$45 313	11.82	-	-	-	-
		PEG+RBV	$48 435	12.97	$3121	1.14	$2727	PEG+RBV
		SOF+LDV (8-12w*)	$65 287	14.02	$16 853	1.06	$15 940	SOF+LDV (8-12 w*)
		SOF+PEG+RBV	$70 701	13.85	$5414	-0.17	Dominated	-
		SOF+LDV (12w)	$80 653	14.07	$15 365	0.04	$349 851	-
		SOF+SMV	$99 733	13.98	$19 080	-0.09	Dominated	-
		SOF+RBV	$115 070	13.42	$34 417	-0.65	Dominated	-
Genotype 1 – Treatment-experienced patients								
Tice et al.[66]	All patients	No treatment	$45 313	11.82	-	-	-	-
		PEG+RBV	$72 305	12.13	$26 992	0.31	Ext. dominated	-
		SOF+PEG+RBV	$112 226	14.11	$39 922	1.98	Ext. dominated	-
		SOF+LDV (12-24w**)	$119 603	14.84	$7376	0.72	$24 599***	SOF+LDV (12-24 w**)
		SOF+SMV	$165 800	14.70	$46 197	-0.14	Dominated	-
	F3-F4	No treatment	$45 313	11.82	-	-	-	-
		PEG+RBV	$59 873	11.90	$14 560	0.08	Ext. dominated	-
		SOF+PEG+RBV	$75 121	13.47	$15 248	1.57	Ext. dominated	-
		SOF+LDV (12-24w**)	$80 382	14.08	$5261	0.61	$15 517*	SOF-LDV (12-24**)
		SOF+SMV	$101 840	14.00	$21 458	-0.08	Dominated	-

QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, WTP: willingness to pay, Ext dominated: dominated by extended dominance, PEG: pegylated-interferon, RBV: ribavirin, SOF: sofosbuvir, SMV: simeprevir, LDV: ledipasvir. † Calculations of the ICERs follow the efficiency frontier approach. In this approach, interventions

*are ranked from the least to the most expensive one. Each intervention that is (extendedly) dominated by another intervention is then removed. An intervention is dominated when its effectiveness is lower and its cost higher than another intervention. An intervention is extendedly dominated when its incremental cost-effectiveness ratio is greater than that of a more effective intervention. ICER are only computed for the remaining interventions, by comparing each intervention with the previous less costly and less effective intervention. ‡ A treatment is selected if, based on the results of the probabilistic sensitivity analysis, its probability to be cost-effective is >50% at the local WTP threshold. If no probabilistic sensitivity analysis is performed, the treatment selected is based on the authors' conclusions. Local thresholds considered: $50 000/QALY in Tice et al.66 * 8 weeks treatment duration in non-cirrhotic patients with HCV RNA less than 6 million IU/mL, 12 weeks treatment duration in non-cirrhotic patients with HCV RNA over than 6 million IU/mL and in cirrhotic patients. ** 12 weeks treatment duration in non-cirrhotic patients, 24 weeks treatment in cirrhotic patients. *** Own computation: ICER of the intervention versus no treatment according to the efficiency frontier approach.*

2.7 Discussion

2.7.1 Summary of the results

This review of the literature aimed at evaluating whether the novel DAAs against CHC are cost-effective, and more specifically whether patient subgroups could be identified that would benefit most from those therapies from a cost-effectiveness point of view, and that could be prioritized to receive those treatments first.

In the last years, many economic evaluations have been published on this topic. However not all of them were estimated to be adequate to answer our research question such that our literature review was limited to the studies 1) whose input data are based on robust recent published evidence, 2) that modelled at least one PEG-free treatment regimen, and 3) in which a residual risk of disease progression after reaching SVR was modelled.

The cost-effectiveness analyses reviewed showed different results according to the patient population targeted. The differences were mainly due to the patient clinical profile such as genotype, treatment history and fibrosis stage.

Genotype 1

In genotype 1 CHC patients, there was a consensus between the studies' results that **SOF+LDV** is the most cost-effective treatment option compared to the old standard of care (i.e. PEG+RBV, BOC/TEL+PEG+RBV), compared to no treatment and compared to other PEG-free interventions (SOF+SMV, SOF+RBV).[43, 60, 66] Within genotype 1 patients, the SOF+LDV combination was most cost-effective in treatment-naïve (versus treatment-experienced) patients with a more advanced stage of disease (F3-F4 and cirrhotic versus non-cirrhotic).

Compared to the old standard of care (BOC/TEL+PEG+RBV), the combination **SMV+DCV** was found to be cost-effective in genotype 1b treatment-naïve non-cirrhotic patients. This conclusion is however based on the results of a single study with no other DAA as comparator.[47]

The **SOF+RBV** combination was not found to be cost-effective mainly due to the long treatment duration required (24 weeks) and the resulting high cost.[48, 59, 60, 66]

Genotypes 2 and 3

The combination SOF+RBV (12 weeks) was the only PEG-free treatment evaluated in the economic evaluations reviewed here for genotype 2 and 3 CHC patients. Compared to the old standard of care (PEG+RBV) or to no treatment in interferon-intolerant patients, SOF+RBV was generally not found to be cost-effective (except in cirrhotic interferon-intolerant patients).[43, 59] However, as another more effective PEG-free treatment regimen is now available and recommended by the EASL guidelines for those genotypes (SOF + DCV), the cost-effectiveness of this treatment regimen should also be considered in future studies.

Genotype 4

In genotype 4 interferon-tolerant patients, SOF+PEG+RBV was the only DAA-based regimen investigated. It was cost-effective in cirrhotic patients, but not cost-effective in non-cirrhotic patients where the old standard of care (PEG+RBV) was preferred. In interferon-intolerant patients, no treatment was preferred to a SOF+RBV regimen. This is however based on the results of a single cost-effectiveness study.[43] Future cost-effectiveness analyses should also consider at least the new treatments recommended by the EASL guidelines for this genotype (e.g. SOF+LDV, 3DAA, SOF+SMV, daclatasvir).

2.7.2 General conclusion

Based on this review, SOF+LDV appears thus to be a cost-effective treatment option for genotype 1 patients, while the cost-effectiveness of this and other regimens in other genotypes still needs to be demonstrated/confirmed. This conclusion is based on the results of various studies with fragmented results as each study typically targeted only one specific patient genotype and only assessed a limited number of interventions. We could not identify a single economic evaluation that considered all currently approved novel PEG-free DAA therapies (such as sofosbuvir, sofosbuvir+ledipasvir, ombitasvir+paritaprevir+ritonavir, dasabuvir, simeprevir, daclatasvir) for all relevant genotypes. Nevertheless, the development of an economic evaluation comparing all PEG-free DAA therapies is hampered by the fact that there exists no direct comparisons between those combinations. Moreover, the newer combinations all have similarly high SVR and relatively few side effects, such that current evidence is not even able to demonstrate a difference in indirect comparisons. Studies able to demonstrate such a difference would require large sample sizes.

Unsurprisingly the cost of the new antivirals was identified as the variable having the highest impact on the results of the studies, such that lower costs would improve the cost-effectiveness of the new therapies.

Given the huge cost of the second-generation DAA therapies, treating all patients would dramatically affect the public health care budgets. As such, subgroups analyses in the economic evaluations are useful tools to identify patients that could benefit most from the new treatments and to which these should be prioritized and reimbursed first. This review highlighted that the new PEG-free HCV therapies would benefit most (from a cost-effectiveness point of view) to younger,[43, 47, 59, 66] male[43] patients with more advanced stages of liver disease.[43, 59, 66] It can be debated however whether age and gender are acceptable prioritizing criteria. Other relevant patient characteristics, such as the presence/absence of alcoholism, could have been used to differentiate the impact on the economic evaluations results but this was not found in any of the studies reviewed here, probably also because of a lack of data (e.g. on disease progression) to stratify the model accordingly.

It should be added that the majority of the economic evaluations reviewed here pertained to the USA, where different epidemiology, health care system and pricing methods prevail. It is hard therefore to apply any of this review's conclusions to Belgium. Further the studies had to rely on the available published effectiveness data to perform their simulations. Given the high price of the new DAAs, such studies are most probably exclusively sponsorded by pharmaceutical companies such that a publication biais towards positive results cannot be excluded.

In Belgium, currently, reimbursed treatments with the second generation DAA therapies are targeted to patients with advanced disease (i.e. METAVIR fibrosis stage F3 and F4) who are at risk of developing decompensated cirrhosis and hepatocellular carcinoma in the short term. Extension of the reimbursement to F2 patients has been proposed by the hepatitis C working group, based on the combined results of an elastography (Fibroscan ≥ 7.2 kPa or ShearWave ≥ 7.1 kPa or ARFI ≥ 1.32 m/s) and a biological test (FIB4 > 1.45 or Fibrotest ≥ 0.49). However the cost-effectiveness and budget-impact of treating this new patient group in Belgium still needs to be assessed. This is the objective of the next chapter.

3 THE COST-EFFECTIVENESS AND BUDGET IMPACT OF TREATMENT STRATEGIES FOR HEPATITIS C IN BELGIUM

3.1 Introduction

This chapter aims at modelling the cost-effectiveness and budget impact of different strategies of IFN-free initiation in terms of patient eligibility criteria for the treatment of chronic hepatitis C (CHC) in adult patients from the Belgian setting. It should nevertheless be noted that there is important non random uncertainty, both on key parameters and on the appropriate model structure. Although we did an effort to capture this uncertainty and to discuss about it in details, results should be interpreted with a lot of caution.

3.2 Methods

The following aspects of the model are described in this section: design and analytic technique, perspective, time window and discounting, target population, intervention and comparator, model structure, and the values (and uncertainty) for input parameters. Details on scenario analyses are also provided. In a subsequent section, results are presented.

3.2.1 Design and analytic technique

CHC being a potentially severe long-term disease that can result in liver-related death, novel DAA treatments against CHC aim both at improving the quality of life of the patients and at extending their lives. Therefore, both cost-effectiveness (with outcomes expressed in life-years gained) and cost-utility analyses (with life-years gained adjusted for quality of life) were performed.

For this purpose, a Markov simulation model was developed in Excel. This technique allowed us modelling the evolution of a cohort of patients over time and assumed that individuals were always in one of a finite number of health states, called "Markov states". For each Markov state, a fixed

transition probability towards the following state (see section 1.1.1), a cost (see section 3.2.10) and a utility (see section 3.2.11) were referred.

3.2.2 Perspective

According to the Belgian guidelines for economic evaluations:[99]

- only direct health care costs from the perspective of the health care payers were considered for the cost-effectiveness analysis, i.e. payments of the national health and disability insurance (RIZIV – INAMI) and patients official co-payments, and
- only payments of the national health and disability insurance (RIZIV – INAMI) were considered for the budget impact analysis, and not patients official co-payments.

3.2.3 Time window and discounting

For patients with CHC, the evolution of the disease is low but consequences in the long term are severe. In order to capture these long term consequences, a lifetime horizon was applied. In the base-case, future costs were discounted at a rate of 3.0% and future outcomes were discounted at a rate of 1.5%, as recommended in the Belgian guidelines for economic evaluations.[99] Other scenarios were also tested in the appendix (0%-3%-5%).

3.2.4 Target population

The target population is adult patients with chronic HCV. Only treatment-naïve patients were considered. The analysis was based on the cohorts described in Table 9 reflecting the heterogeneity of the CHC patients in Belgium.[100] The model starts with both non-cirrhotic and cirrhotic patients, with a distinction according to their fibrosis score. A cohort of patients aged of 45 years old were modelled at baseline, which is assumed to roughly correspond to the average age of patients detected has having CHC. Because this parameter is uncertain, other scenarios were tested in the scenario analysis (35-55).

Children were not considered because the new DAA regimens are not registered for children (i.e. it is an off-label use). Moreover, most of the parameters used in the model are unknown for this specific population.

Specific analyses for co-infected patients (e.g. with HIV) or specific populations such as IDUS were also not performed (see the KCE report 173 for specific analyses on IDUs).[23]

For the assumed metavir distribution in the initial cohort we took data on 1902 patients from a multicentre - multicountry cohort were fibrosis stage was measured in all consecutive patients.[100] The percentages obtained were very similar to a Belgian study on 190 patients as reported by De Maeght et al.[101] However, we do not know what the current stage distribution of the patients in Belgium is, as treatment of more advanced has shifted the distribution of the pool of patients.

Table 9 – Population modelled100

Population at start of treatment	N (%)	Gender	Mean age
Mixed cohort of non-cirrhotic and cirrhotic patients		70% men 30% women	45 years old
Patients with mild CHC (Fibrosis score F0)	13 300 (13.3%)		
Patients with mild CHC (Fibrosis score F1)	38 300 (38.3%)		
Patients with moderate CHC (Fibrosis score F2)	25 900 (25.9%)		
Patients with severe CHC (Fibrosis score F3)	12 450 (12.45%)		
Patients with compensated cirrhosis (Fibrosis score F4)	10 050 (10.05%)		

3.2.5 Intervention and comparator

The overall aim of this analysis was to assess the incremental cost-effectiveness of different "test-treatment" strategies. As already mentioned in section 1.2, only INF-free therapies are considered. The model differs from most previously published models in the fact that strategies for an hypothetical "gold standard interferon-free novel DAA regimen" (see also section 3.2.9) were compared instead of comparing one treatment to other treatments (as done in chapter 2). Based on the proposal of the working group on hepatitis C of the RIZIV – INAMI, the following strategies were compared:

- **Strategy 0 "No treatment":** Patients are neither tested nor treated. They follow the natural history of the disease.This strategy is only considered to be able to highlight medical care costs saved by the treatment of patients in the budget impact analysis.
- **Strategy 1 "Treating from F3" (=past practice in Belgium):** All patients identified as having CHC undergoing a biopsy (as described in section 3.2.8) and patients identified as having a fibrosis score ≥F3 are treated. Patients with a fibrosis score below F3 are followed and re-tested each year until they become eligible for a treatment.
- **Strategy 2 "Treating from F2", based on patients positive to both an elastography (e.g. fibroscan) and a blood non-invasive test of fibrosis (e.g. Fib-4, fibro test):** All patients identified as having CHC undergo a combination of two non-invasive liver tests (as described in section 3.2.8) and patients identified in both tests as having a fibrosis score ≥F2 (see section 3.2.8 for the cut-offs) are treated. Other patients are followed and re-tested each year until they become eligible for a treatment.
- **Strategy 3 "Treating patients with blood non invasive test +", based on patients positive to a blood non-invasive test of fibrosis:** All patients identified as having CHC undergo one non-invasive liver test and patients identified as positive with this test are treated (see section 3.2.8 for the cut-offs). Other patients are followed and re-tested each year until they become eligible for a treatment.
- **Strategy 4 "Treating every patients":** All patients identified as having CHC are treated (F0-F4) without undergoing non-invasive liver tests.

It is important to highlight here that in all of these "staging strategies", all patients are finally treated (except in the strategy 0). Patients that were not eligible one year could become eligible the following year.
At the beginning of the model, patients were distributed among the different stages F0-F4 according to available Belgian epidemiologic data (in which stages were assessed according to biopsy results) (see section 3.2.4). For the strategies of treating from F2 or patients with a blood test positive, sensitivity and specificity values of these tests were used to determine patients eligibility, with as consequences that false positive were considered as eligible for the treatment and false negative not (see section 3.2.8).

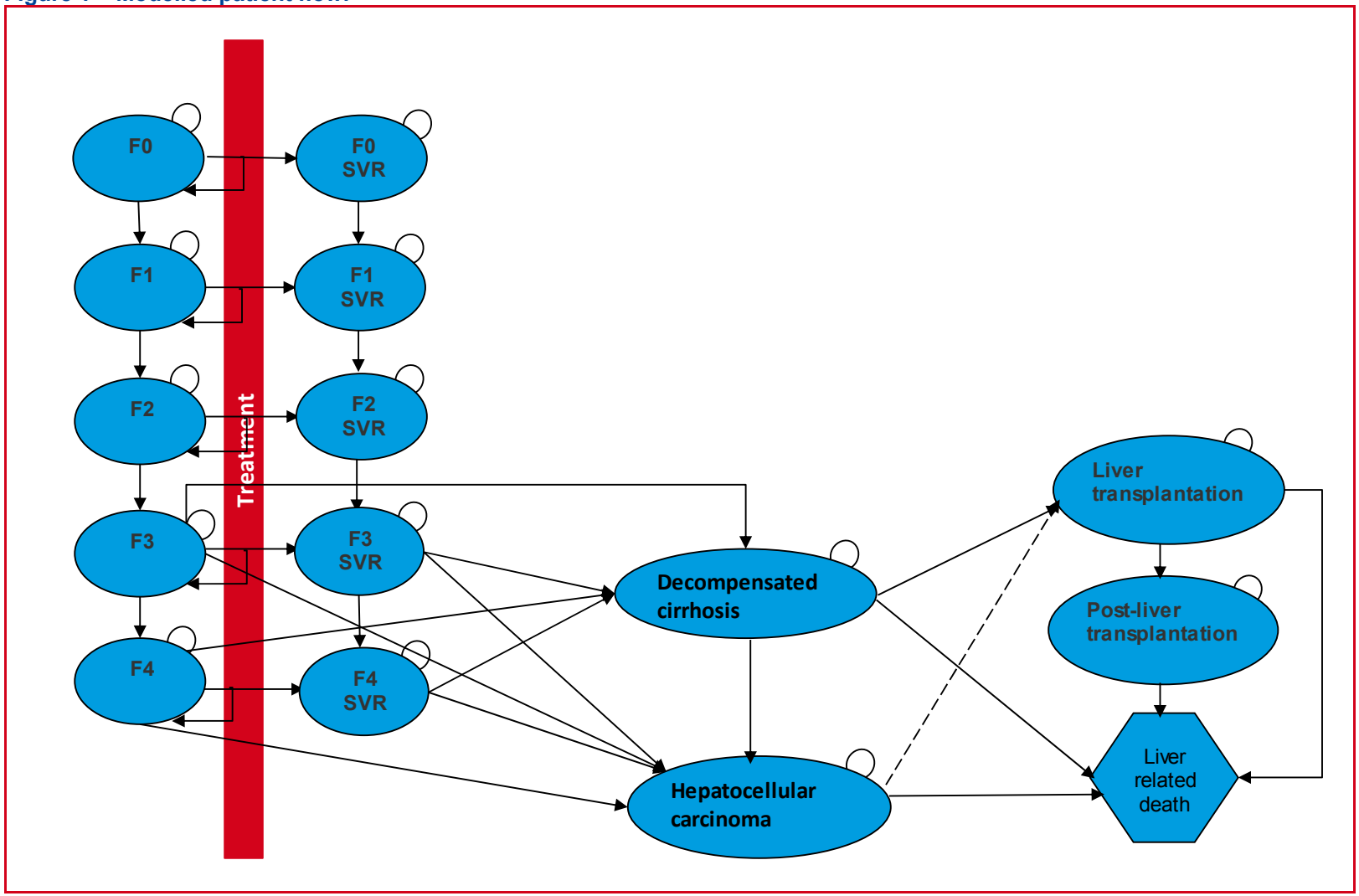
3.2.6 Model structure and basic assumptions

Patients progressed in a fixed unit of time, referred to as "Markov cycle". A 1-year cycle length was chosen, meaning that evolution or not to the following state of the disease was evaluated on a yearly basis. Patients' progression between the disease states is described in Figure 1. Patients could remain in the same state with a certain probability for more than one year except in the liver transplant state, from where they move either to the post-liver transplant state or to death. For the states of decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant (LT) and post-liver transplant (post-LT), liver related death rates were applied and all-cause mortality was added; for all other states only all-cause mortality was applied. A broad definition was used for DC, including all non-HCC complications associated with liver related mortality, e.g. bleeding esophagal varices. It should also be noted that we only had an overall HCC-related death rate, without distinction on the fact that the patient was transplanted or not. The state "liver transplantation" in our model therefore only corresponds to "liver transplantation" following decompensated cirrhosis, with the corresponding transition probabilities and costs. For HCC patients, the overall HCC-related death rate was applied, and a specific liver transplantation cost was added for the percentage of patients with HCC that were transplanted.

Assumptions specific to sections 3.2.1 to 3.2.6

- **Model outcomes: both life-years (LY) and quality-adjusted life-years (QALYs).**
- **Time window: Lifelong period.**
- **Discounting: For the base-case, a discount rate of 3.0% for costs and 1.5% for outcomes was used according to the Belgian guidelines.[99]**
- **Perspective: Health care payers according to the Belgian guidelines.[99]**

Figure 1 – Modelled patient flow.



**As specified in section 0, an overall HCC-related death probability was applied, and the progression probability to liver transplantation was only used for the cost calculations.*

3.2.7 Transition probabilities

3.2.7.1 Natural history of the disease

As reported in the study of Westbrook et al.,[102] the definition of the natural history of hepatitis C remains incomplete. Heterogeneous population have been included in the patient cohort studies, often with many co-founders impacting the progression of hepatic fibrosis. Because of the difficulty of identifying patients cohort and because a long length of follow-up was required to reach meaningful endpoints, few studies were prospective and the majority were retrospective, with several limitations. These retrospective studies were likely skewed towards patients with hepatic complications and hence sought medical input. Moreover, the timing of the initial infection can often be inaccurate when it is based on patient's recall of first contact with blood products or intravenous drug abuse.[102]

Because fibrosis progression rates are not directly measured, they need to be derived from modelling. We do not have Belgian data that are suited for this exercise. Therefore we had to use rates derived in other modelling exercises.

In the base-case, transition probabilities between the different fibrosis scores F0-F4 of a disease progression model as reported by Razavi et al.[103] were used. These transition probabilities were age- and gender- dependent and are summarized in the appendix to this chapter. They derived fibrosis progression rates from US data. The reported number of new annual liver cancers (by gender) and liver cancer deaths in 1999–2009 from the US Surveillance, Epidemiology and End Results (SEER) programme was used to back-calculate the fibrosis progression rates required in the model to match published data.

In a second scenario, we used the progression rates as derived and reported by Thein et al.[104], who did a systematic review of published prognostic studies and derived annual stage-specific transition probabilities using the Markov maximum likelihood estimation method. They also performed a meta-analysis and evaluated the impact of potential covariates using meta-regression. A total of 111 studies of individuals with chronic HCV infection (n = 33 121) were included.

Other transition probabilities were derived from the EunetHTA report[25] (as described in the introduction of this report) and results of the literature review on economic evaluations presented in the chapter 2, completed with data from a preliminary analysis of a large cohort of untreated CHB patients followed at Leuven University Hospital that is described in a previous KCE report on the treatment of patients with HBV[105] and data from the Belgian cancer registry (BCR).

Moreover, based on a study done by Boursier et al. 2014[106], who found that a low value for blood tests for fibrosis was an indicator of slow progression if patient had F0 at diagnosis, we modelled a slow progression for this group of patients in the 4th strategy, where treatment decision was taken only on blood test (i.e. an annual transition probability of 1%; range 0.5 – 1.5).

Table 10 – Transition probabilities based on the natural history of the disease

Markov states From	To	Transition probabilities (Base case)	Other scenarios**	Sources
F0-F1; F1-F2; F3-F4; F3-HCC; F4-HCC		Age-dependent[103]	No range tested because the estimates come from a modelled estimation obtained on a large dataset, where no meaningful estimate of the second order uncertainty can be derived. An alternative scenario's based on the review of Thein et al.[104] is presented in the sensitivity analyses.	Razavi et al.[103] Thein et al.[104]
F3	DC	1.2%	0.6-1.8%	Dienstag et al.[107]
F4	DC	3.9%	1.95-5.85%	Dienstag et al.[107]
DC	HCC	1.4%	0.7-2.1%	Fattovich at al. [108]
	LT 1st year, following DC	50%	25-75%	Schwierz et al. [105]
	Death (DC specific)	20 % per year	10-30 %	D'amico [109]
HCC 1st year*	LT 1st year, following (HCC)	15%	7.5-22.5%	Schwierz et al. [105]
	Death (HCC specific)	53.7%	No range actual data for Belgium based on a large dataset.	Data from the Belgian Cancer Registry
HCC 2th year*	Death (HCC specific)	20.09%	No range actual data for Belgium based on a large dataset.	Data from the Belgian Cancer Registry
HCC 3st year*	Death (HCC specific)	25.14%	No range actual data for Belgium based on a large dataset.	Data from the Belgian Cancer Registry
HCC 4th year*	Death (HCC specific)	12.64%	No range actual data for Belgium based on a large dataset.	Data from the Belgian Cancer Registry
HCC 5st year*	Death (HCC specific)	14.46%	No range actual data for Belgium based on a large dataset.	Data from the Belgian Cancer Registry
HCC 6th year*	Death (All-cause mortality)	Age dependent	No range actual data for Belgium based on a large dataset.	Data from the Belgian Cancer Registry
LT, first year, following DC*	Death (LT specific)	9%	4.5-13.5%	Data from the Leuven University Hospital as reported by Schwierz et al. [105]
Post-LT, following DC*	Death (LT specific)	2%	1-3%	Data from the Leuven University Hospital as reported by Schwierz et al. [105]
All states	Death (All-cause mortality)	Age dependent (see appendix)	No range, actual data for Belgium based on a large dataset.	Statistics Belgium[110]

As specified above, the annual transition probabilities from LT to LT-specific death only concern LT related to DC and the annual transition probabilities from HCC to HCC-specific death include transplanted patients (following HCC), meaning that the annual transition probabilities from HCC to LT is only used for cost calculations. 95% confidence interval were not available, a variation of +/- 50% was therefore applied. Original yearly transition rates have been converted to yearly transition probabilities for inclusion in the model using the following formula: transition probability = 1 – exp(-rate).*

3.2.7.2 Progression after SVR

Some models assume that after SVR, progression is the same as in the general population, but this is not likely, patients may have other risk factors and the damage inflicted in the more advanced stages will lead to a higher risk of HCC and complications. Therefore we modelled a relative reduction, based on a systematic review of Smith-Palmer et al.[111] They found that patients who achieve SVR frequently demonstrate some regression of fibrosis/cirrhosis and have a substantially reduced risk for hepatocellular carcinoma. The magnitude of this effect varied, with reported RRs for HCC in patients with SVR versus non-responders or untreated patients ranging from 0.09–0.35. The 2010 meta-analysis by Singal et al.[112] showed that patients who had SVR (following treatment with IFN alone or IFN plus ribavirin) had a RR (95% CI) for HCC of 0.35 (0.26–0.46) in comparison with non-responders in patients with cirrhosis. A meta-analysis by Kimer et al.[113] reported a RR (95% CI) for HCC of 0.15 (0.05–0.45); the comparator group was untreated patients, rather than non-responders to therapy, this in a mix of patients with cirrhosis and non-cirrhosis. However, these two latest meta-analyses are problematic because both designs and results of the primary studies are very heterogeneous, moreover, it is debatable if the results are valid. Singal et al.[112] meta-analysed cohort studies, a procedure not recommended by the Cochrane collaboration. Kimer et al.[113] based their result on 3 small RCT comparing treated and not treated, but based their estimation on the comparison responder-not treated, this is a rather unusual procedure of doubtful validity at best. Deriving transition rates from these data is therefore not straightforward and surrounded by considerable structural uncertainty.

Therefore, for F1-F2, F2-F3 F3-F4 we assume that the risk of progression falls with 95 %, ranging from 85 to 100% (conservative assumption done by the author, no data available). We did not model the possibility of regression. For F3-F4 to HCC, a reduction of 80 % in base case was applied based on the study of Smith-Palmer et al,[111] with a range of 65 to 91 %. We assumed the same reduction for F3-F4 to DC (no data available). After DC or HCC we assume that transition probabilities were the same between SVR and non SVR patients.

The large variability is largely due to the fact that co-factors such as alcohol and cannabis use play a role in the residual progression after SVR and it is unclear to which degree our cohort is affected by those.

Table 11 – Transition probabilities after SVR

Markov States	RR (Base case)	Other scenarios	Sources
F0-F1; F1-F2; F2-F3; F3-F4	0.05	0-0.15	Assumption
F3-HCC; F4-HCC	0.2	0.09-0.35	Smith-Palmer et al[111]
F3-DC; F4-DC	0.2	0.09-0.35	Assumption

Assumption specific to this section

F0-F4 patients with SVR continue to progress to the following states, but at a reduced probability (see Table 11). From the following states (DC, HCC, LT), the progression rate was the same for all patients (SVR-non SVR).

3.2.8 Performance of non-invasive liver tests

There are no long term follow up studies measuring the progression of patients depending on the results of the newer non invasive liver tests (most the studies that exist have a too short follow up and the longest has 9.5 years but is relatively small). There are mainly transversal studies measuring sensitivity and specificity with liver biopsy as a gold standard. Liver biopsy has limitations as a gold standard, reproducibility is limited, but the evolution and longer term morbidity of different categories as determined by liver biopsy results, such as METAVIR categories, is much better documented. Therefore we choose to apply the results of these validation studies in the model, i.e. using reported sensitivities and specificities to estimate the proportion of patients with F0, F1, F2, F3 and F4 that would be considered eligible for treatment and treated depending on the test results.

We limited the tests selected to the tests commonly used in Belgium. We based ourselfes for this on expert opinion and the minutes of the working group hepatitis C of the commission of the reimboursment of drugs of the RIZIV – INAMI.[114]

They proposed following criteria for reimbursement, i.e. a combination of one elastography test and one blood test. Both would need to be positive:

- **elastography (Fibroscan ≥ 7.2 kPa or ShearWave ≥ 7.1 kPa or ARFI ≥ 1,32 m/s)**
- **+ FIB4 > 1.45 or Fibrotest equal or > 0.49**

When preparing the EunetHTA report, we found a comprehensive systematic review on the sensitivity and specificity of those tests.[115]

The meta-analysis provided estimations for the sensitivity and specificity of different tests at different cut-off points. The selection relevant to us is given in Table 12.

Table 12 – Treatment eligibility: Performance of the tests with histology as reference test (Source: NIHR[115])

Test	Sensitivity	Specificity
FIB-4(high cut-off)(1–3.25)	0.68(0.6 - 0.75)	0.73(0.67 - 0.79)
FIB-4(low cut-off) (0.6–1.45)	0.89(0.79 - 0.95)	0.42(0.25 - 0.61)
Fibrotest(high cut-off) (0.6–0.7)	0.57(0.46 - 0.67)	0.85(0.74 - 0.92)
Fibrotest (low cut-off) (7 0.1–0.3)	0.91 (0.86 to 0.94)	0.41 (0.37 to 0.46)
APRI(low cut-off)	0.77(0.73 - 0.81)	0.78(0.74 - 0.81)
APRI(high cut-off)	0.48(0.41 - 0.56)	0.94(0.91 - 0.95)
ARFI(1.21–1.34)	0.79(0.75 - 0.83)	0.89(0.84 - 0.93)
Fibroscan(9.2–17.3)	0.89(0.84 - 0.92)	0.91(0.89 - 0.93)

However, there is considerable uncertainty that is difficult to quantify:

- We do not have information on the sensitivity and specificity of a combination of tests. We scanned the primary studies for information on this but we did not find useful information. Some studies reported a measure of association between two tests, but this does not provide information on their conditional dependence, this is the chance that a false positive or false negative by one test is also a false positive or false negative by the second test. We assume a more sensitive but less specific scenario of conditional dependence, all false negatives and false positives in one test will also be false negatives and false positives in the second test (i.e. a sensitivity of 85 % and a specificity of 90 %) and a less sensitive but more specific scenario where there is conditional independence, with a drop in sensitivity but an increase in specificity (i.e. a sensitivity of 80 % and a specificity of 95 %). For the base case, we choose the scenario with a sensitivity of 85 % and a specificity of 90 %.
- We do not have information on the conditional dependence of repeated tests, this is, if one year a patient is false negative, what is the chance that he will be identified the following year. On the other hand, we do not know what the chance is that a true negative will become a false positive the next year. We assumed here conditional independence in the model, but this is not sure.

Sensitivity and specificity values used in the model are described in Table 13. According to sensitivity and specificity values described in this table, patients in strategy 2 and 4 could be correctly or falsely identified as being eligible for a treatment. As consequences, some patients were only detected as eligible for treatment once they reached the state of decompensated cirrhosis or hepatocellular carcinoma and were only treated at these stages. Conversely, F0-F1 patients faslelly identified as having a fibrosis score ≥F2 in strategy 2-4 or ≥F3 in strategy 1 were also treated.

Table 13 – Treatment eligibility: sensitivity and specificity used in the model

Test	Sensitivity		Specificity		Sources
	Base case	Range	Base case	Range	
Biopsy (gold standard) in strategy 1	1	-	1	-	
Blood test* + Elastography (Fibroscan) in strategies 3	0.85	0.7-0.95	0.9	0.8-0.95	Assumption
Blood test* in strategy 3	0.90	0.79-0.95	0.40	0.25-0.60	Assumption and NIHR[115]

**Based on the Fib-4 as proxy*

Assumptions in this model

- **Patients that are not eligible for a treatment are re-tested each year. Once patients have been treated, they are not anymore tested.**
- **Patients with DC and HCC are automatically identified (no false negative results).**
- **All tests are independents. Results of a new test are not influenced by results of the previous tests. See Table 12 for assumed sensitivity and specificity.**

3.2.9 Effectiveness of antiviral treatment

To follow the position strongly advocated by representatives from the Belgian National Institute of Health and Disability Insurance (INAMI – RIZIV), only interferon-free novel DAA regimens were considered in this study (see also section 2.3.2).

We reviewed the effectiveness of the new generation antiviral treatment in the framework of a EUneTHA project, results were reported elsewhere.[25]

In summary, the results show that for IFN-free combinations containing at least 2 of the newer combinations for treatment-naive non-cirrhotic patients with HCV genotype 1 infection, all treatment arms have SVR12 rates above 95% and lower CIs above 90%. Some differences exist in point estimates but the studies do not have the power to prove evidence that these differences are statistically different. Furthermore there are no direct comparisons between them. Date show a tendency towards somewhat lower SVR in cirrhotic and treatment experienced patients but this is not proven.

Therefore we assumed hypothetical "gold standard interferon-free novel DAA regimen", with SVR rates of 95 % in base case, ranging from 90 to 99.9 in the scenario analysis. An overall SVR combining two treatment schemes was then used in the model, assuming that non-responder patients were retreated only one time within the same year, with a SVR rate for these retreated patients of 80%, ranging from 50 to 90 (based on expert opinion).

Table 14 – Effectiveness of antiviral treatment: SVR used in the model

Test	Base case	Range	Source
Naïve patients	0.95	0.90-0.9990	EunetHTA report[25]
Retreated patients	0.80	0.50-0.95	Assumption
Overall SVR	0.99 0.95+(0.5*0.8)	0.95-0.9999	Own calculation

Assumptions in this model

- **An hypothetical "gold standard interferon-free novel DAA regimen" was assumed, with a global SVR of 99% for two treatment schemes, ranging from 95% to 99.99%.**
- **Treated patients without SVR were re-treated a second time within the same year. Patients in a "non SVR" state therefore correspond to patients that have not responded to two treatments schemes. We assumed they were not anymore re-treated (maximum two treatment schemes per patient). Given the high SVR for the new therapies, this corresponds to a limited number of patients, which limits the impact of such an assumption on the results (also limited by the fact that this assumption was done in all strategies, except the no treatment strategy).**

3.2.10 Disease management, diagnostic tests and treatment costs

3.2.10.1 Disease management costs

In a previous KCE study on the treatment of patients with chronic hepatitis B (CHB), disease management costs were assessed for CC, DC, HCC and LT from Belgian patients (see section 2.4 of this KCE report and the related appendix for more details). These costs calculations were based on actual billing records from patients collected in 18 Belgian hepatology centres for the year 2006. Since these patients could also undergo treatments related to other diseases, billing records were – in a major effort – thoroughly sorted according to their probability to be due to CHB or not. Cost not related to CHB (i.e. treatments for other non-related diseases) were excluded. Costs of CHB therapies were also excluded. Finally, these costs were inflated to year 2015 Euros using the Belgian Health Index. The resulting disease management costs are depicted in Table 15 (first column).

One drawback of these data is the low number of patients in decompensated cirrhosis, HCC and liver transplant. Nevertheless, the costs are in the range of disease management costs as identified in chapter 2 (seeTable 15).

Another drawback was the fact that this study did not provided cost estimates for CHC patients with fibrosis score F0-F3. From the literature review performed in chapter 2, we identified other studies having reported Belgian costs for patients with hepatitis C.[116-118] In these studies costs data were either based on our KCE study or on the study of Nevens et al.[116] The study of Nevens et al.[116] was performed from the Belgian health care payer perspective during the period January 2005–July 2007. All hospital and outpatient records of genotype 1 Belgian patients with CHC were reviewed for liver-related medical resource use. Results of this study for CHC patients in stage F0-F4 are nevertheless higher than in other studies (see Table 15). Moreover, follow-up costs for patients with mild CHC (F0-F2) were higher than costs for patients with moderate CHC (F3 of F4 without varices) and for F4 patients with varices. Because such differences would impact the choice between treatments strategies while there are no rational to justify these differences, results of this study could not be used. We therefore decided to assume no difference in costs between F0-F1-F2-F3 patients and we used the average percentage reduction between patients with compensated cirrhosis and F3 patients observed in the seven studies described in Table 15 (i.e. -37.42%, deduced from the cost for patients with compensated cirrhosis obtained in the KCE study).

Based on a pooled analysis of mild and moderate patients (n=85), the study of Nevens et al.[116] also provided a mean cost of care (excluding the cost of CHC drug treatment) for SVR and no SVR patients, with a percentage reduction of -35.76%. This percentage was therefore also used in our base case to deduce differences in costs between SVR and non SVR patients.

In the scenario analysis, 95% confidence intervals of the studies were used, or where not available, a variation of +/- 50%. For the stages F0-F3, the lower range tested in the scenario analysis was based on the cost of two consultations with a specialist in internal medicine (with a repartition between accredited and non-accredited physician based on 2015 RIZIV – INAMI data), i.e. €78.67.

Table 15 – Disease management costs from the literature (converted in 2015 Belgian prices, in Euro)*

Adapted from:	Previous KCE study[105] average / (sd; n) (95%CI)	Nevens et al. 2012[116]*	Chhatwal et al., 2015[43]**	Gimeno-Ballester et al., 2015[47]**	San Miguel et al., 2015[59]**	Tice et al., 2015[66]**	Younossi et al., 2015[60]**	Hagan et al., 2014[48]**
F0	_	€2305.75	€595.17	€334.43	€340.80	€662.21	€128.05	€155.46
F1	_	€2305.75 F0-F1-F2	€595.17	€334.43	€340.80	€662.21	€128.05	€155.46
F2	_	€2305.75 F0-F1-F2	€602.53	€334.43	€340.80	€662.21	€128.05	€155.46
F3	_	€1929.89 F3 - F4 without varices	€1223.04	€334.43	€340.80	€1757.71	€128.05	€155.46
CC	€1284.78 (sd: €1696.29; n=47) (95% CI: €799.83 - €1769.73)	€2064.40 F4 with varices	€1426.61	€489.36	€498.37	€2056.93	€590.79	€1034.99
DC	€7663.69 (sd: €6201.98; n=5) (95% CI: €2227.51 - €13099.87)		€15 851.29	-	-	€24 358.61	€23 477.82	€13 266.19
HCC	€12 465.96 (sd: €13 310.39; n=4) (95%CI: -€577.98 – €25 509.9)		€29 149.39	€5820.62	€5924.31	€38 853.59	€36 821.68	€41 527.70
LT	€111 363.49 (sd: €18 828.51; n=5) (95%CI: €94 859.88 - €127 867.1)		€84 290.02	€6080.05	€6189.38	€154 246.11	€142 193.20	€253 665.32
Post-LT	€ 8519.86 (sd: €7573.88; n=40) (95%CI: €6172.73 - €10 866.99)		€22 120.18	€5122.25	€5213.39	€33 592.72	€32 052.77	€38 444.34

**Only follow-up costs were taken into account (therapy costs and costs for the diagnosis were excluded) and were converted in 2015 annual cost using the health index for Belgium. **All these foreign costs were inflated to year 2015 using the consumer price index of the country and converted in Belgian price using the OECD purchasing power parity (PPP).*

Table 16 – Disease management costs used in the model (2015 Belgian prices, in Euro)

Disease state	Base case	Range		Sources
F0	€804.06	€78.67*	€1206.09**	Studies of Table 15 + RIZIV – INAMI data for the lower range.
F1	€804.06	€78.67*	€1206.09**	Studies of Table 15 + RIZIV – INAMI data for the lower range.
F2	€804.06	€78.67*	€1206.09**	Studies of Table 15 + RIZIV – INAMI data for the lower range.
F3	€804.06	€78.67*	€1206.09**	Studies of Table 15 + RIZIV – INAMI data for the lower range.
CC	€1284.78	€799.83	€1769.73	Schwierz et al[105]
DC	€7663.69	€2227.51	€13 099.87	Schwierz et al[105]
HCC	€12 465.96	€6232.98**	€18 698.94**	Schwierz et al[105]
LT	€111 363.49	€94 859.88	€127 867.10	Schwierz et al[105]
Post-LT	€ 8519.86	€6172.73	€10 866.99	Schwierz et al[105]
With SVR	- 35.76%	33.94%	36.48%	Nevens et al[116]

**Based on the assumption of 2 consultations with a specialists in internal medicine.*
***A variation of +/-50% was assumed.*

3.2.10.2 Costs for the diagnosis

For strategies 2, 3, and 4, the cost of the tests to determine the fibrosis score were taken into account. Not all of these tests are currently reimbursed by the RIZIV-INAMI and we had to use proxy. For the blood tests, we decided to use the cost of the Fib-4 as a proxy for all possible blood tests of fibrosis. For this, we calculated the cost of measuring blood platelets, ALAT and ASAT according to 2015 RIZIV – INAMI fees, i.e. €21.66 (25% per act + lump sum for ambulant patients). For elastography, we had to use the 2015 RIZIV – INAMI fee for an echography as proxy. For the cost of a biopsy, 2015 RIZIV – INAMI fees for material, the biopsy itself, and a lump sum for ambulant patient was taken into account.

Fees for the medical specialist in internal medicine are considered in the section before and are not anymore considered here.

Table 17 – Costs of "diagnostic" tests used in the model (2015 Belgian prices, in Euro)

Disease state	Base case	Sources
Strategy 1 (Biopsy)	€281.67	2015 RIZIV – INAMI fees
Strategy 2 (elastography +blood test)	€125.89	2015 RIZIV – INAMI fees
Strategy 3 (blood test)	€21.66	2015 RIZIV – INAMI fees

3.2.10.3 Treatment costs

Recommendations from the Belgian Association for the Study of the Liver (BASL) on treatment of hepatitis were followed to determine the diverse treatments possibilities according to the patient genotype.[119] Any regimen incorporating at least a novel DAA were considered but treatment incorporating pegylated interferon were not taken into account (as already mentioned in section 3.2.9). Treatment costs for each possible combination are described from Table 18 to Table 21. Official prices listed on the RIZIV – INAMI database for pharmaceuticals were used.[120]

Because these costs were based on the official list prices without taking into account the negotiated rebates (that are confidentials as stated in section 1.2) and because the repartition between the different DAA combinations is uncertain, different scenario were considered. In the base case scenario, a median cost for each genotype was calculated[c]. The genotype repartition described in Van Damme et al.[121] was then used and the cost obtained was reduced according to the percentage reduction of the turnover obtained in 2015 for products under conventions, published by the RIZIV – INAMI (i.e. -26.3%).[122] This gave a treatment cost of €40 000 (rounded) for non cirrhotic patients and € 63 000 (rounded) for cirrhotic patients.

In the worst case scenario, we assumed that patients combined two expensive DAA regimens and used facial prices, which gave a cost around €70 000 for patients without cirrhosis (rounded) and around €84 000 for patients with cirrhosis (rounded). It should nevertheless be noted that these costs does not include rebates and therefore have few chance to happen in practice. We also tested two other scenarios, in which the treatment cost assumed as "worst case" was decreased by 50% and 75% (best case).

[c] An equal repartition was assumed for each treatment possibilities, except for patients with cirrhosis, for which it was assumed that 15% of patients were intolerant to Ribavirin (according to Belgian experts). The genetype repartition described in Van Damme et al. 2014 was used: genotype 1: 61%, genotype 2: 6%, genotype 3: 19%, genotype 4: 14%.

Table 18 – Treatment cost for genotype 1 patients

	Treatment combination	Duration	Cost
Without cirrhosis	Sofosbuvir + Ledipasvir (if naïve and HCVRNA > 6.10 UI/mL)	8 weeks	€ 36 584.22
	Sofosbuvir + Ledipasvir	12 weeks	€ 54 876.33
	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir + Ribavirin (genotype 1a)	12 weeks	€ 42 143.90
	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir (genotype 1b)	12 weeks	€ 41 382.67
	Sofosbuvir + Simeprevir	12 weeks	€ 70 003.74
	Sofosbuvir + Daclatasvir	12 weeks	€ 72 785.16
With compensated cirrhosis	Sofosbuvir + Ledipasvir + Ribavirin	12 weeks	€ 55 637.56
	Sofosbuvir + Ledipasvir (in case of poor Ribavirin tolerance)	24 weeks	€ 109 752.65
	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir + Ribavirin (genotype 1a)	24 weeks	€ 84 287.81
	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir + Ribavirin (genotype 1b)	12 weeks	€ 42 143.90
	Sofosbuvir + Simeprevir + Ribavirin	12 weeks	€ 70 764.98
	Sofosbuvir + Simeprevir (in case of poor Ribavirin tolerance)	24 weeks	€ 140 007.49
	Sofosbuvir + Daclatasvir + Ribavirin	12 weeks	€ 73 546.40
	Sofosbuvir + Daclatasvir (in case of poor Ribavirin tolerance)	24 weeks	€ 145 570.32

Table 19 – Treatment cost for genotype 2 patients

	Treatment combination	Duration	Cost
Without cirrhosis	Sofosbuvir + Ribavirin	12 weeks	€ 44 243 .63
	Sofosbuvir + Daclatasvir + Ribavirin (only post-LT with F3-F4)	12 weeks	€ 72 785 .16 +/- € 761
With compensated cirrhosis	Sofosbuvir + Ribavirin	12 weeks	€ 58 991.50
	Sofosbuvir + Daclatasvir + Ribavirin (only post-LT with F3-F4)	12 weeks	€ 72 785.16 +/- € 761

Table 20 – Treatment cost for genotype 3 patients

	Treatment combination	Duration	Cost
Without cirrhosis	Sofosbuvir + Daclatasvir	12 weeks	€ 72 785.16
With compensated cirrhosis	Sofosbuvir + Daclatasvir + Ribavirin	24 weeks	€ 147 092.79

Table 21 – Treatment cost for genotype 4 patients

	Treatment combination	Duration	Cost
Without cirrhosis	Sofosbuvir + Ledipasvir	12 weeks	€ 54 876.33
	Ombitasvir + Paritaprevir + Ritonavir + Ribavirin	12 weeks	€ 38 815.37
	Sofosbuvir + Simeprevir	12 weeks	€ 70 003.74
	Sofosbuvir + Daclatasvir	12 weeks	€ 72 785.16
With compensated cirrhosis	Sofosbuvir + Ledipasvir + Ribavirin	12 weeks	€ 55 637.56
	Sofosbuvir + Ledipasvir (in case of poor Ribavirin tolerance)	24 weeks	€ 109 752.65
	Ombitasvir + Paritaprevir + Ritonavir + Ribavirin	24 weeks	€ 77 630.74
	Sofosbuvir + Simeprevir + Ribavirin	12 weeks	€ 70 764.98
	Sofosbuvir + Simeprevir (in case of poor Ribavirin tolerance)	24 weeks	€ 140 007.49
	Sofosbuvir + Daclatasvir + Ribavirin	12 weeks	€ 73 546.40
	Sofosbuvir + Daclatasvir (in case of poor Ribavirin tolerance)	24 weeks	€ 145 570.32

Table 22 – Treatment costs used in the model

	Base case*	Scenario 2* (worst case)	Scenario 3*	Scenario 4* (best case)
For patients without cirrhosis (<F4)	€ 40 000	€ 70 000	€ 35 000	€ 17 500
Patients from F4	€ 63 000	€ 84 000	€ 42 000	€ 21 000

**In the worst case scenario (i.e. scenario 2), we assumed that patients combined two expensive DAA regimens (e.g. Sofosbuvir + Simeprevir) and we used facial prices. We then decreased this cost by 50% and by 75% in the scenario 3 and 4.*

Assumptions specific to this section

- **Perspective: According to the Belgian guidelines, only direct health care costs from the perspective of the health care payers were considered, i.e. payments of the national health and disability insurance (RIZIV – INAMI) and patients official co-payments. For the budget impact analysis, patients official co-payments were not considered.**
- **Costs were inflated to year 2015 Belgian Euros.**
- **Discounting: For the base-case, a discount rate of 3.0% for costs was used according to the Belgian guidelines (0% for the budget impact).99**
- **Disease management costs were assumed similar between F0-F3 patients.**
- **For the more advanced stages of the diseases (CC, DC, HCC, LT), disease management costs were expected to be similar between CHC and CHB patients.**

3.2.11 Utilities

We have not identified Belgian studies having reported utilities in patients with CHC. Nevertheless, in a previous KCE report, an EQ-5D survey has been performed on the Belgian population with CHB (n= 527 patients), providing utility scores calculated based on the EQ-5D scores of these patients and processed based on social preference data collected in Flanders. Results of this Belgian study were therefore used as basis. By doing this, we assume that the quality of life between CHC patients and CHB patients does not differ for the more advanced stages of the diseases, i.e. CC, DC, HCC and post-LT. A drawback of these data is nevertheless the low number of patients in decompensated cirrhosis, HCC and liver transplant but these utilities are in the range of values as identified in chapter 2 (see Table 23). To estimate utilities for the states F0-F3, we returned to the original sources identified in the literature review performed in the chapter 2 and in the EunetHTA report. For the consistency of results, we only selected studies having used the same instrument than the KCE study, i.e. the EQ-5d instrument (see Table 24). From all studies having assessed utilities for the states F3 and F4, we calculated the average percentage changes from F4 to F3, i.e. (+7.52%) that we then applied to the F4 score in the KCE study. We assume no differences between the states F0-F3. It should be noted that if the three UK studies73, 74, 123 had been combined, as done by Gimeno-Ballester et al., 201547, we would obtain different scores between F0-F1 and F2-F3. Nevertheless, we have not identified any single studies having highlighted such differences (here different sources). It should also be noted that, because the strategies of treating from F2 or treating from F3 were assessed, differences in utilities between F2 and F3 is expected to impact results. As shown in Table 23, two studies have reported such differences.48, 66 Nevertheless, different sources were again used and it can easily be expected that these differences were due to the use of different instruments. This show the importance of at least combining studies having used the same instrument for the consistency of results.

Concerning liver transplantation, one study had assessed the quality of life of patients using the EQ-5D instrument at different time interval.123 To estimate the utility of the year of the transplant, we therefore used the percentage difference between post-LT and LT calculated from this study123, i.e. -14.10% (see Table 24).

For patients with SVR, an increase in utilities was considered in the stages F0-F4, based on the average percentage increase in the three studies having assessed post SVR utilities with the EQ-5d instrument,72-74 i.e. +8.26% (range: +4.97% - + 13.89%).

In the scenario analysis, two scenarios were considered, i.e. one based on the studies having on average reported the lowest and highest utilities identified in the review of the literature, i.e. the studies of Chhatwal et al.,43 Gimeno-Ballester et al.47 and San Miguel et al.59

Table 23 – Utilities from the literature

	KCE[105]	Chhatwal et al., 2015[43]	Gimeno-Ballester et al., 2015[47]	San Miguel et al., 2015[59]	Tice et al., 2015[66]	Younossi et al., 2015[60]	Hagan et al., 2014[48]
F0		0.93	0.77	0.77	0.98	0.79	0.85
F1		0.93	0.77	0.77	0.98	0.79	0.85
F2		0.93	0.66	0.66	0.92	0.79	0.85
F3		0.93	0.66	0.66	0.79	0.79	0.79
F4 / CC	0.78	0.90	0.55	0.55	0.76	0.748	0.76
DC	0.70	0.80	0.45	0.45	0.69	0.672	0.69
HCC	0.67	0.79	0.45	0.45	0.67	0.61	0.67
LT	-	0.84	0.45	0.45	0.50	0.65	0.50
Post-LT	0.82	0.84	0.45	0.45	0.77	0.709	0.77
Treatment related adverse events (PEG/RBV-free)		SOF+LDV: Not reported	SMV+DCV: No change	-	SOF+LDV: -0.075 SOF+SMV: -0.087	SOF+LDV: +4.5%	SOF+SMV: No change
With SVR		QoL of the general population	+0.05 in F0-F1 +0.11 in F2-F3 +0.06 in F4	+0.05 in F0-F1 +0.11 in F2-F3 +0.06 in F4	+0.02 in F0-F1 +0.01 in F2 +0.07 in F3-F4	+0.05 in F0-F4	+0.07 in F0-F4
Instrument	EQ-5D	EQ-5D	EQ-5D	EQ-5D	TTO/SG, SF-36 translated to utilities assumption	EQ-5D	Assumption; SF-36 translated to utilities
Respondents	CHB patients	CHC patients	CHC patients	CHC patients	Hepatologists (F0-F2), CHC patients (F3-F4, DC, HCC, post-LT)	CHC patients	CHC patients
Sample size	n=69 (F4), 2 (DC), 10 (HCC), 0.82 (post-LT)	n=44 (F0-F3), 24 (F4), 9 (DCC), 15 (HCC), 30 (LT)	n=185 (F0-F1), 71 (F2-F3), 40 (F4), 64 (DC, HCC, LT)	n=185 (F0-F1), 71 (F2-F3), 40 (F4), 64 (DC, HCC, LT)	N=6 (F0-F2), 44 (F3), 64 (F4), 49 (DC), 15 (HCC), 30 (post-LT)	n=7-77 (F0-F4, DC and post-LT), 20 (HCC), 50 (LT)	n=44 (F3), 64 (F4), 49 (DC), 15 (HCC), 30 (post-LT)

Table 24 – Utilities from original studies having used the EQ-5D instrument

	Chong, 2003[72]	Grieve, 2006 [73]	Wright, 2006 [74]	Ratcliffe, 2002[123]	McLernon, 2008 (F0-F4, DC and post-LT)[77]
F0	0.76	0.77			0.747
F1	0.76	0.77			0.747
F2	0.76		0.66		0.747
F3	0.76		0.66		0.747
F4 / CC	0.74		0.55		0.748
DC	0.66			0.53	0.672
HCC	0.65			0.53	
LT	0.69			0.67*	
Post-LT	0.69			0.78**	0.709
If SVR	0.83	0.82	0.72		
Instrument	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D
Respondents	CHC patients	CHC patients	CHC patients	CHC patients	CHC patients
n	n=44 (F0-F3), 24 (F4), 9 (DCC), 15 (HCC), 30 (LT)	n=185	n=71 (F2-F3), 40 (F4)	n=164 at listing; 147 at 3 – 6 – 12 – 24 months	n=7-77

**Average values for the measurements at the point of listing (0.53), 3 months (0.67), 6 months (0.71), and 12 months (0.77). **Measured at 24 months (0.78).*

Table 25 – Utilities used in the model

Disease state	Base case	95% CI	Worst case tested (Chhatwal et al., 2015[43])	Best case tested (Gimeno-Ballester et al.[47] and San Miguel et al.[59])
F0	0.84	0.77-0.90	0.93	0.77
F1	0.84	0.77-0.90	0.93	0.77
F2	0.84	0.77-0.90	0.93	0.66
F3	0.84	0.77-0.90	0.93	0.66
CC	0.78	0.73-0.84	0.90	0.55
DC	0.70	0.66-0.75	0.80	0.45
HCC	0.67	0.44-0.90	0.79	0.45
LT	0.70	0.64-0.76	0.84	0.45
Post-LT	0.82	0.75-0.88	0.84	0.45
Treatment related adverse events (PEG -free)	No effect		No effect	No effect
F0-F1-F2-F3-F4 With SVR	+8%		+5%	+14%

Assumptions specific to this section

- **Perspective: Health outcomes were measured in patients and health state values come from the general public, according to Belgian guidelines. [99]**
- **Discounting: For the base-case, a discount rate of 1.5% for outcomes was used according to the Belgian guidelines.[99]**

3.2.12 Uncertainty

Uncertainty around the model parameters was explored by running the model under a number of different scenarios (univariate and multivariate scenario analyses). The base case model was run by considering higher and/or lower values for a large range of uncertain parameters, separately (see also the appendix).

3.2.12.1 Why we did not do a probabilistic sensitivity analysis.

Probabilistic sensitivity analysis (PSA) is usually recommended in guidelines for economic evaluations. It requires however meaningful estimates of the second order uncertainty of most of the parameters. Although we have estimates of the second order uncertainty for some parameters, we do not have them for the majority of the clinical epidemiological parameters, especially for the parameters related to the natural history of the disease, the effect of the treatment after sustained viral response and the accuracy of test used to identify fibrosis stage. Doing PSA only using the parameters for which we have distributions on the base case is misleading and the alternative, doing PSA on all possible combinations of scenarios does not lead to interpretable results.

3.2.12.2 Scenario analyses

Instead of a PSA, a multivariate scenario analysis was performed by simultaneously varying several clinical parameters to their worst and best estimate. Table 26 lists the analyses performed. The best case scenario include parameters that were positive to the increasing of the number of patients treated (e.g. in favour of strategy 4 compared to no treatment) and the worst case scenario include parameters that were positive to no treatment.

It should be noted that another worst case scenario could be to assume a low impact of the treatment for patients with mild HCV (e.g. high evolution even after SVR) and an high impact from F3 (e.g. low evolution after SVR), which would lead to the conclusion to limit the treatment from F3 patients. Nevertheless, such a scenario is unrealistic and was therefore not presented.

Table 26 – Ranges tested in the scenario analysis

	Base Case	"Worst case"	"Best case"
Age	45	55	35
Transition probabilities[d]			
• **F4-DC**	1.2%	0.6%	1.8%
• **DC-HCC**	3.9%	1.95%	5.85%
• **DC-LT**	1.4%	0.7%	2.1%
• **DC- Death DC specific**	50%	25%	75%
• **HCC-LT**	20 % per year	10%	30%
• **LT - Death LT from DC specific**	9%	4.5%	13.5%
• **Post-LT - Death LT from DC specific**	2%	1%	3%
Transition probabilities – RR after SVR			
F0-F1; F1-F2; F2-F3; F3-F4	0.05	0.15	0.00
F3-HCC; F4-HCC; F3-DC; F4-DC	0.2	0.35	0.09
Sensitivity			
• **Blood test for fibrosis + Elastography (strategy 2)**	0.85	0.70	0.95
• **Blood test for fibrosis (strategy4)**	0.90	0.80	0.95
Specificity			
• **Blood test for fibrosis + Elastography (strategy 2)**	0.90	0.80	0.95
• **Blood test for fibrosis (strategy4)**	0.40	0.25	0.60
SVR			
• **For naïve patients**	0.95	0.90	0.99.9
• **For re-treated patients**	0.80	0.50	0.90
• **Overall**	0.99	0.95	0.9999

[d] For transition probabilities between F0-F4, the scenario tested is presented in Table 10 and results can be found in the appendix. Different scenarios on the discount rate are also presented in the appendix but are not taken into account in the worst-best case analysis. This is why they are not presented in this table.

Disease management costs			
• **F0**	€804.06	€78.67*	€1206.09**
• **F1**	€804.06	€78.67*	€1206.09**
• **F2**	€804.06	€78.67*	€1206.09**
• **F3**	€804.06	€78.67*	€1206.09**
• **CC**	€1284.78	€799.83	€1769.73
• **DC**	€7663.69	€2227.51	€13099.87
• **HCC**	€12 465.96	€6232.98**	€18 698.94**
• **LT**	€111 363.49	€94 859.88	€127 867.10
• **Post-LT**	€ 8519.86	€6172.73	€10 866.99
• **With SVR**	- 35.76%	-33.94%	-36.48%
Treatment costs			
• **For patients without cirrhosis (<F4)**	€ 40 000	€ 70 000	€ 17 500
• **Patients from F4**	€ 63 000	€ 84 000	€ 21 000
Utilities			
• **F0**	0.84	0.93	0.77
• **F1**	0.84	0.93	0.77
• **F2**	0.84	0.93	0.66
• **F3**	0.84	0.93	0.66
• **CC**	0.78	0.90	0.55
• **DC**	0.70	0.80	0.45
• **HCC**	0.67	0.79	0.45
• **LT**	0.70	0.84	0.45
• **Post-LT**	0.82	0.84	0.45
• **F0-F1-F2-F3-F4 With SVR**	+8%	+5%	+14%

3.2.13 Validation of the model

We tested the descriptive validity, the technical validity and the convergent validity of the model. To test the descriptive or face validity, i.e. determine if the structure of the model is acceptable and is a simplified but adequate representation of reality, the model and results were submitted to Belgian hepatologists.

The technical validity was also checked by testing the impact of extreme hypotheses on results, as for example SVR rate of 0 and 100%, sensitivity-specificity parameters of 1 and 0, or utility scores of 1.

The convergent validity was tested by checking if our model gave similar results compared to other models constructed independently (which was the case, see the discussion for details).

Nevertheless, the validation of these results in daily practice is needed and the current conventions should be linked with data collection.

3.3 Results

3.3.1 Cost-effectiveness analysis

3.3.1.1 Base case

Table 27 shows the results from the base case analysis. Without treatment, the model predicts that 24% of patients will develop an HCC, and 31% of patients will be transplanted over the lifetime of a cohort of 1 000 patients, with a total medical costs of € 54 823 613 (discounted) and a total number of life years of 24 250 (discounted). If patients are treated, an important number of HCC and LT cases could be prevented in all treatment strategies.

If we rank the different strategies,

Table 28 and Table 29 show that the “no treatment strategy” was the less expensive strategy but also the strategy with the lowest outcomes (in life years and QALYs). Then, more the patients can be treated at an early stage, more we gained in LY and QALYs at an acceptable additional cost, expect for the strategy of treating everybody if we do not take into account the impact on the quality of life (with an ICER >€100 000/LY).Therefore, if we consider that the impact on the quality of life is an important parameter that must be taken into account in the decision, the choice between these strategies will mostly be based on the available budget (see section 3.3.2).

Table 27 – Results from the base case analysis (per cohort of 1 000 patients for a lifelong period)

	Strategy 0: No treatment	Strategy 1: Treating from F3	Strategy 2: Treating from F2	Strategy 3: Treating if Blood test +	Strategy 4: Treating everybody
• **Health outcomes**					
% HCC cases	23.96%	3.48%	2.17%	2.07%	2.05%
% LT cases	31.22%	6.26%	3.42%	3.22%	3.15%
% Liver related deaths	39.89%	6.89%	4.07%	3.86%	3.78%
• **Cost**					
Drug cost	€ 0.00	€ 32 681 667.25	€ 39 953 852.54	€ 40 918 332.41	€ 43 059 690.46
Non-invasive liver tests - Biopsy	€ 0.00	€ 2 060 750.24	€ 295 015.00	€ 161 215.79	€ 0.00
Medical care costs	€ 54 823 613.18	€ 20 819 364.73	€ 16 644 215.30	€ 16 127 275.93	€ 15 640 063.28
Total costs (Discounted)	€ 54 823 613.18	€ 55 561 782.21	€ 56 893 082.83	€ 57 206 824.13	€ 58 699 753.74
• **Efficacy**					
Life Years (Discounted)	23 749.60	26 942.94	27 159.82	27 177.64	27 189.32
QALYs (Discounted)	19 369.99	23 616.35	24 290.64	24 379.14	24 499.91

Table 28 – Base case cost-effectiveness analysis (cost/LY)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 893 082.83	€ 1 331 300.62	€ 6 138.47
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 206 824.13	€ 313 741.29	€ 17 606.97
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 699 753.74	€ 1 492 929.61	€ 127 845.66

Table 29 – Base case cost-utility analysis (cost/QALY)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 893 082.83	€ 1 331 300.62	€ 1 974.38
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 206 824.13	€ 313 741.29	€ 3 545.05
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 699 753.74	€ 1 492 929.61	€ 12 362.23

3.3.1.2 Scenario analyses

As shown from Table 39 to Table 150 in the appendix, the interpretation of results remain the same under most scenarios explored. Major exceptions concerned the performance of the tests assumed or if it is assumed that the impact of the treatment will differ between patients with mild (F0-F1), moderate (F2) or severe patients (F3-F4).

The choices between the treatment strategies 2, 3, 4, i.e. treating (i) from F3 (based on a biopsy), (ii) from F2 (based on an elastography and a blood test) or (iii) patients with a positive blood test is highly conditioned by the performance of the combined test, which is currently uncertain.

The impact of the treatment also has a role and the ranking of strategies can be modified if we consider that such an impact differ according to the fibrosis stage. Indeed, if we assume that the impact of the treatment for patients with mild or moderate CHC (F0-F1-F2) is better than for other patients (i.e. higher SVR rates), limiting the treatment to F3 patients will be dominated by an earlier treatment from F2. The same observation can be done if we assume that the impact of the treatment for patients with severe CHC (from F3) is lower (i.e. lower SVR rates or faster evolution after SVR). In this case, limiting the treatment to F3 patients is also dominated by an earlier treatment from F2. The same reasoning can also be apply to a limitation to F2 patients, i.e. if the impact of the treatment is better for F0-F1 patients and/or lower from F2 patients, it would be more interesting to treat patients earlier. Differences according to the fibrosis scores are nevertheless not well documented.

The treatment cost, the disease management costs or the evolution at the later stage of the disease also impacted results.

For more details, the scenario analyses reported in the appendix showed that the strategy 1 (treating from F3) was dominated by the strategy 2 (treating from F2) in the following cases:

- If the response to the treatment (SVR) increase for F0-F1-F2 or decrease from F3 (for the higher/lower value of the range tested).
- If patients evolve more quickly after SVR from F3 (for the higher value of the range tested).
- If disease management costs are higher (for the higher value of the range tested).
- If the treatment cost is less expensive (for the lowest value of the range tested).
- With no discount rate.

The strategy 2 (treating from F2 based on an elastography and a blood test) was dominated by the strategy 3 (treating patients with positive blood test) in the following cases:

- If the performance of the combined tests decrease (lower sensitivity or lower specificity, for the lower value of the range tested).
- If the specificity of the blood test alone increase (for the higher value of the range tested).
- If patients evolve more quickly after SVR from F2 (for the higher value of the range tested).
- If the response to the treatment (SVR) increase for F0-F1 patients or decrease from F2 patients (for the higher/lower value of the range tested).
- If the utilities after SVR are lower from F2 (for the lowest value of the range tested).
- If the treatment cost is less expensive (for the lowest value of the range tested).
- With no discount rate.

The strategy 3 (treating patients positive at the blood test) is dominated by the strategy of treating everybody if the sensitivity of the blood test is lower (for the lower value of the range tested).

It should also be noted that the "no treatment strategy" was dominated by the strategy 1 in the following cases:

- If patients have 35 years old at the start of the model (instead of 45 years old).
- If patients evolve more quickly (for the higher values of the range tested).
- If the response to the treatment (SVR) is higher (for the higher values of the range tested).
- If patients evolve more slowly after SVR from F3 (for the lower values of the range tested).
- If the disease management costs are higher (for the higher value of the range tested).
- If the treatment cost is less expensive (from €38 874), which is an amount very close to the base case.
- With no discount rate.

3.3.1.3 Worst and best case scenarios

In the assumed best case scenario, the strategy of treating everybody dominate all other strategies.

In the worst case scenario, the ICER for all strategies remains inferior to €50 000/QALY (therefore if we take into account the impact on the quality of life). Moreover, this worst case scenario is based on a price that is not expected in practice.

An extended dominance is nevertheless observed for the strategy 2 (i.e. treating from F2 based on an elastography and a blood test), meaning that in the worst case, it would be better to directly treat patients with positive blood test only. This is nevertheless highly conditioned by the assumed performance of the combined tests which is totally uncertain. This should therefore be assessed in practice.

It should also be noted that if we do not take into account the impact on the quality of life, ICER of all treatment strategies are superior to €25 000/LYG and only the strategy 1 has an ICER inferior to €50 000 /LYG.

Table 30 – ICER in life-year gained from the "best case" scenario analysis

	LY	Cost	ICER (/LY)
Strategy 0: No treatment	26 587.67	€ 83 130 203.11	Dominated
Strategy 1: Treating from F3 (Biopsy)	32 098.97	€ 44 905 583.33	Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	32 301.68	€ 41 301 076.33	Dominated
Strategy 3: Treating if blood test +	32 302.30	€ 41 035 814.07	Dominated
Strategy 4: Treating everybody	32 310.54	€ 41 009 482.38	-

Table 31 – ICER in QAILY gained from the "best case" scenario analysis

	QALY	Cost	ICER (QALY)
Strategy 0: No treatment	16 731.67	€ 83 130 203.11	Dominated
Strategy 1: Treating from F3 (Biopsy)	23 378.20	€ 44 905 583.33	Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 777.62	€ 41 301 076.33	Dominated
Strategy 3: Treating if blood test +	25 653.43	€ 41 035 814.07	Dominated
Strategy 4: Treating everybody	26 018.92	€ 41 009 482.38	-

Table 32 – ICER in life-year gained from the "worst case" scenario analysis

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	19 849.42	-	€ 21 709 119.21	-	-
Strategy 1: Treating from F3 (Biopsy)	21 418.44	1 569.01	€ 72 332 958.37	€ 50 623 839.16	€ 32 264.78
Strategy 2: Treating from F2 (Blood test + Elastography)	21 569.19		€ 83 941 978.39		Extended dominance
Strategy 3: Treating if blood test +	21 592.48	174.04	€ 84 841 101.03	€ 12 508 142.67	€ 71 868.65
Strategy 4: Treating everybody	21 603.79	11.31	€ 87 453 065.57	€ 2 611 964.54	€ 230 939.34

Table 33 – ICER in QAILY gained from the "worst case" scenario analysis

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	18 062.95	-	€ 21 709 119.21	-	-
Strategy 1: Treating from F3 (Biopsy)	20 335.45	2 272.50	€ 72 332 958.37	€ 50 623 839.16	€ 22 276.71
Strategy 2: Treating from F2 (Blood test + Elastography)	20 783.68		€ 83 941 978.39		Extended dominance
Strategy 3: Treating if blood test +	20 845.14	509.69	€ 84 841 101.03	€ 12 508 142.67	€ 24 540.62
Strategy 4: Treating everybody	20 899.80	54.66	€ 87 453 065.57	€ 2 611 964.54	€ 47 786.16

3.3.2 Budget impact analysis

3.3.2.1 Base case

To avoid an explosion of the budget, beginning with the strategy of only treating patients from F2 and then progressively enlarge to more patients could be considered. In this section, we assessed the budget impact of the phases described in Table 34, with results described inTable 35.

To highlight the medical care costs saved by the treatment of these patients, this scheme was then compared to a "no treatment" strategy (see Table 36).

It should also be noted that, as explained in the method section, the same parameters are used for the budget impact analysis, except for the costs parameters: patient co-payments were not taken into account and no discount rate was applied. Moreover, the number of patients that will be tested according to the new criteria is a crucial parameter in the budget impact analysis, unfortunately this is absolutely not possible to predict. For the moment we know that, based on the estimation of the Belgian public health institute, yearly 1500 new cases are diagnosed.[18] This however does not include the existing pool of patients that were not eligible for treatment until now. We therefore assumed a higher number of patients considered for treatment eligibility (see Table 34). These numbers are therefore based on assumptions and must be monitored in the future.

Table 34 – Description of the "treatment strategies" phases tested in the budget impact

Year	Treatment strategy	Number of new patients considered for treatment eligibility	Range
Year 1	Strategy 2: Treating from F2 (Blood test + Elastography)	3000	2000-3500
Year 2	Strategy 2: Treating from F2 (Blood test + Elastography)	3000	2000-3500
Year 3	Strategy 3: Treating if blood test +	3000	2000-3500
Year 4	Strategy 3: Treating if blood test +	3000	2000-3500
Year 5	Strategy 4: Treating everybody	3000	2000-3500
Year 6	Strategy 4: Treating everybody	2500	2000-3000
Year 7	Strategy 4: Treating everybody	2000	1500-2500
From Year 8	Strategy 4: Treating everybody	1500	1000-2000

Table 35 – Budget impact for the treatment strategies phases described in Table 34 (Base case)
Zoom for 8 years

Year	Costs	2 017	2 018	2 019	2 020	2 021	2 022	2 023	2 024
2017	Medical care costs	€ 2 026 811	€ 2 071 929	€ 2 124 695	€ 2 069 955	€ 2 007 502	€ 2 060 501	€ 2 069 832	€ 2 079 410
	Treatment costs	€ 64 417 247	€ 17 755 595	€ 32 190 774	€ 9 277 886	€ 9 267 701	€ 0	€ 0	€ 0
	Diagnostic costs	€ 198 468	€ 44	€ 5	€ 1	€ 0	€ 0	€ 0	€ 0
	Total cost	**€ 66 642 525**	**€ 19 827 568**	**€ 34 315 473**	**€ 11 347 842**	**€ 11 275 203**	**€ 2 060 501**	**€ 2 069 832**	**€ 2 079 410**
2018	Medical care costs		€ 2 026 811	€ 1 891 355	€ 2 074 921	€ 2 002 876	€ 2 004 061	€ 2 058 217	€ 2 067 975
	Treatment costs		€ 64 417 247	€ 45 549 197	€ 11 616 801	€ 11 416 770	€ 0	€ 0	€ 0
	Diagnostic costs		€ 198 468	€ 29	€ 3	€ 0	€ 0	€ 0	€ 0
	Total cost		**€ 66 642 525**	**€ 47 440 582**	**€ 13 691 725**	**€ 13 419 646**	**€ 2 004 061**	**€ 2 058 217**	**€ 2 067 975**
2019	Medical care costs			€ 1 793 754	€ 1 815 469	€ 1 959 634	€ 1 982 959	€ 1 992 753	€ 2 050 141
	Treatment costs			€ 100 383 369	€ 18 212 856	€ 14 462 613	€ 0	€ 0	€ 0
	Diagnostic costs			€ 94 170	€ 20	€ 0	€ 0	€ 0	€ 0
	Total cost			**€ 102 271 293**	**€ 20 028 344**	**€ 16 422 247**	**€ 1 982 959**	**€ 1 992 753**	**€ 2 050 141**
2020	Medical care costs				€ 1 793 754	€ 1 721 273	€ 1 955 330	€ 1 974 470	€ 1 989 411
	Treatment costs				€ 100 383 369	€ 32 697 899	€ 0	€ 0	€ 0
	Diagnostic costs				€ 94 170	€ 0	€ 0	€ 0	€ 0
	Total cost				**€ 102 271 293**	**€ 34 419 172**	**€ 1 955 330**	**€ 1 974 470**	**€ 1 989 411**
2021	Medical care costs					€ 1 580 632	€ 1 681 208	€ 1 877 694	€ 1 944 602
	Treatment costs					€ 133 054 444	€ 0	€ 0	€ 0
	Total cost					**€ 134 635 075**	**€ 1 681 208**	**€ 1 877 694**	**€ 1 944 602**
2022	Medical care costs						€ 1 317 193	€ 1 401 007	€ 1 564 745
	Treatment costs						€ 110 878 703	€ 0	€ 0
	Total cost						**€ 112 195 896**	**€ 1 401 007**	**€ 1 564 745**
2023	Medical care costs							€ 1 053 755	€ 1 120 805
	Treatment costs							€ 88 702 962	€ 0
	Total cost							**€ 89 756 717**	**€ 1 120 805**
2024	Medical care costs								€ 790 316
	Treatment costs								€ 66 527 222
	Total cost								**€ 67 317 538**
Total	**Treatment cost**	**€ 64 417 247**	**€ 82 172 842**	**€ 178 123 340**	**€ 139 490 911**	**€ 200 899 427**	**€ 110 878 703**	**€ 88 702 962**	**€ 66 527 222**
	Total Cost	**€ 66 642 525**	**€ 86 470 094**	**€ 184 027 348**	**€ 147 339 204**	**€ 210 171 342**	**€ 121 879 955**	**€ 101 130 689**	**€ 80 134 626**

Year	Costs	2 017	2 018	2 019	2 020	2 021	2 022	2 023	2 024	2 025	2 026	2 027	2 028	2 029	2 030
2017	Medical care costs	€ 2 026 811	€ 2 071 929	€ 2 124 695	€ 2 069 955	€ 2 007 502	€ 2 060 501	€ 2 069 832	€ 2 079 410	€ 2 088 042	€ 2 095 062	€ 2 100 233	€ 2 103 686	€ 2 106 273	€ 2 107 693
	Treatment costs	€ 64 417 247	€ 17 755 595	€ 32 190 774	€ 9 277 886	€ 9 267 701	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs	€ 198 468	€ 44	€ 5	€ 1	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost	**€ 66 642 525**	**€ 19 827 568**	**€ 34 315 473**	**€ 11 347 842**	**€ 11 275 203**	**€ 2 060 501**	**€ 2 069 832**	**€ 2 079 410**	**€ 2 088 042**	**€ 2 095 062**	**€ 2 100 233**	**€ 2 103 686**	**€ 2 106 273**	**€ 2 107 693**
2018	Medical care costs		€ 2 026 811	€ 1 891 355	€ 2 074 921	€ 2 002 876	€ 2 004 061	€ 2 058 217	€ 2 067 975	€ 2 077 578	€ 2 086 091	€ 2 092 951	€ 2 097 949	€ 2 101 226	€ 2 103 635
	Treatment costs		€ 64 417 247	€ 45 549 197	€ 11 616 801	€ 11 416 770	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs		€ 198 468	€ 29	€ 3	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost		**€ 66 642 525**	**€ 47 440 582**	**€ 13 691 725**	**€ 13 419 646**	**€ 2 004 061**	**€ 2 058 217**	**€ 2 067 975**	**€ 2 077 578**	**€ 2 086 091**	**€ 2 092 951**	**€ 2 097 949**	**€ 2 101 226**	**€ 2 103 635**
2019	Medical care costs			€ 1 793 754	€ 1 815 469	€ 1 959 634	€ 1 982 959	€ 1 992 753	€ 2 050 141	€ 2 060 925	€ 2 070 680	€ 2 079 113	€ 2 085 827	€ 2 090 663	€ 2 093 774
	Treatment costs			€ 100 383 369	€ 18 212 856	€ 14 462 613	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs			€ 94 170	€ 20	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost			**€ 102 271 293**	**€ 20 028 344**	**€ 16 422 247**	**€ 1 982 959**	**€ 1 992 753**	**€ 2 050 141**	**€ 2 060 925**	**€ 2 070 680**	**€ 2 079 113**	**€ 2 085 827**	**€ 2 090 663**	**€ 2 093 774**
2020	Medical care costs				€ 1 793 754	€ 1 721 273	€ 1 955 330	€ 1 974 470	€ 1 989 411	€ 2 048 228	€ 2 059 418	€ 2 069 306	€ 2 077 756	€ 2 084 462	€ 2 089 284
	Treatment costs				€ 100 383 369	€ 32 697 899	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs				€ 94 170	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost				**€ 102 271 293**	**€ 34 419 172**	**€ 1 955 330**	**€ 1 974 470**	**€ 1 989 411**	**€ 2 048 228**	**€ 2 059 418**	**€ 2 069 306**	**€ 2 077 756**	**€ 2 084 462**	**€ 2 089 284**
2021	Medical care costs					€ 1 580 632	€ 1 681 208	€ 1 877 694	€ 1 944 602	€ 1 973 332	€ 2 035 795	€ 2 048 398	€ 2 058 602	€ 2 067 128	€ 2 073 847
	Treatment costs					€ 133 054 444	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost					**€ 134 635 075**	**€ 1 681 208**	**€ 1 877 694**	**€ 1 944 602**	**€ 1 973 332**	**€ 2 035 795**	**€ 2 048 398**	**€ 2 058 602**	**€ 2 067 128**	**€ 2 073 847**
2022	Medical care costs						€ 1 317 193	€ 1 401 007	€ 1 564 745	€ 1 620 502	€ 1 644 444	€ 1 696 496	€ 1 706 999	€ 1 715 502	€ 1 722 607
	Treatment costs						€ 110 878 703	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost						**€ 112 195 896**	**€ 1 401 007**	**€ 1 564 745**	**€ 1 620 502**	**€ 1 644 444**	**€ 1 696 496**	**€ 1 706 999**	**€ 1 715 502**	**€ 1 722 607**
2023	Medical care costs							€ 1 053 755	€ 1 120 805	€ 1 251 796	€ 1 296 401	€ 1 315 555	€ 1 357 197	€ 1 365 599	€ 1 372 401
	Treatment costs							€ 88 702 962	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost							**€ 89 756 717**	**€ 1 120 805**	**€ 1 251 796**	**€ 1 296 401**	**€ 1 315 555**	**€ 1 357 197**	**€ 1 365 599**	**€ 1 372 401**
2024	Medical care costs								€ 790 316	€ 840 604	€ 938 847	€ 972 301	€ 986 666	€ 1 017 897	€ 1 024 199
	Treatment costs								€ 66 527 222	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost								**€ 67 317 538**	**€ 840 604**	**€ 938 847**	**€ 972 301**	**€ 986 666**	**€ 1 017 897**	**€ 1 024 199**
2025	Medical care costs									€ 790 316	€ 840 604	€ 938 847	€ 972 301	€ 986 666	€ 1 017 897
	Treatment costs									€ 66 527 222	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost									**€ 67 317 538**	**€ 840 604**	**€ 938 847**	**€ 972 301**	**€ 986 666**	**€ 1 017 897**
2026	Medical care costs										€ 790 316	€ 840 604	€ 938 847	€ 972 301	€ 986 666
	Treatment costs										€ 66 527 222	€ 0	€ 0	€ 0	€ 0
	Total cost										**€ 67 317 538**	**€ 840 604**	**€ 938 847**	**€ 972 301**	**€ 986 666**
2027	Medical care costs											€ 790 316	€ 840 604	€ 938 847	€ 972 301
	Treatment costs											€ 66 527 222	€ 0	€ 0	€ 0
	Total cost											**€ 67 317 538**	**€ 840 604**	**€ 938 847**	**€ 972 301**
2028	Medical care costs												€ 790 316	€ 840 604	€ 938 847
	Treatment costs												€ 66 527 222	€ 0	€ 0
	Total cost												**€ 67 317 538**	**€ 840 604**	**€ 938 847**
2029	Medical care costs													€ 790 316	€ 840 604
	Treatment costs													€ 66 527 222	€ 0
	Total cost													**€ 67 317 538**	**€ 840 604**
2030	Medical care costs														€ 790 316
	Treatment costs														€ 66 527 222
	Total cost														**€ 67 317 538**
Total	**Treatment cost**	**€ 64 417 247**	**€ 82 172 842**	**€ 178 123 340**	**€ 139 490 911**	**€ 200 899 427**	**€ 110 878 703**	**€ 88 702 962**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**
	Total Cost	**€ 66 642 525**	**€ 86 470 094**	**€ 184 027 348**	**€ 147 339 204**	**€ 210 171 342**	**€ 121 879 955**	**€ 101 130 689**	**€ 80 134 626**	**€ 81 278 545**	**€ 82 384 879**	**€ 83 471 341**	**€ 84 543 970**	**€ 85 604 705**	**€ 86 661 293**

Table 36 – Budget impact for the treatment strategies phases described in Table 34 compared to no treatment (Base case)

Zoom for 8 years

Year	Costs	2 017	2 018	2 019	2 020	2 021	2 022	2 023	2 024
2017	Medical care costs	-€ 420 079	-€ 610 732	-€ 1 517 988	-€ 2 010 901	-€ 2 371 838	-€ 2 668 402	-€ 2 911 350	-€ 3 133 467
	Treatment costs	€ 64 417 247	€ 17 755 595	€ 32 190 774	€ 9 277 886	€ 9 267 701	€ 0	€ 0	€ 0
	Diagnostic costs	€ 198 468	€ 44	€ 5	€ 1	€ 0	€ 0	€ 0	€ 0
	Total cost	**€ 64 195 636**	**€ 17 144 907**	**€ 30 672 791**	**€ 7 266 985**	**€ 6 895 863**	**-€ 2 668 402**	**-€ 2 911 350**	**-€ 3 133 467**
2018	Medical care costs		-€ 420 079	-€ 791 307	-€ 1 567 762	-€ 2 077 981	-€ 2 375 279	-€ 2 670 686	-€ 2 913 207
	Treatment costs		€ 64 417 247	€ 45 549 197	€ 11 616 801	€ 11 416 770	€ 0	€ 0	€ 0
	Diagnostic costs		€ 198 468	€ 29	€ 3	€ 0	€ 0	€ 0	€ 0
	Total cost		**€ 64 195 636**	**€ 44 757 920**	**€ 10 049 042**	**€ 9 338 789**	**-€ 2 375 279**	**-€ 2 670 686**	**-€ 2 913 207**
2019	Medical care costs			-€ 653 136	-€ 867 193	-€ 1 683 049	-€ 2 097 898	-€ 2 386 587	-€ 2 678 762
	Treatment costs			€ 100 383 369	€ 18 212 856	€ 14 462 613	€ 0	€ 0	€ 0
	Diagnostic costs			€ 94 170	€ 20	€ 0	€ 0	€ 0	€ 0
	Total cost			**€ 99 824 403**	**€ 17 345 683**	**€ 12 779 564**	**-€ 2 097 898**	**-€ 2 386 587**	**-€ 2 678 762**
2020	Medical care costs				-€ 653 136	-€ 961 389	-€ 1 687 352	-€ 2 106 386	-€ 2 389 929
	Treatment costs				€ 100 383 369	€ 32 697 899	€ 0	€ 0	€ 0
	Diagnostic costs				€ 94 170	€ 0	€ 0	€ 0	€ 0
	Total cost				**€ 99 824 403**	**€ 31 736 510**	**-€ 1 687 352**	**-€ 2 106 386**	**-€ 2 389 929**
2021	Medical care costs					-€ 866 258	-€ 1 001 453	-€ 1 764 989	-€ 2 136 255
	Treatment costs					€ 133 054 444	€ 0	€ 0	€ 0
	Total cost					**€ 132 188 186**	**-€ 1 001 453**	**-€ 1 764 989**	**-€ 2 136 255**
2022	Medical care costs						-€ 721 881	-€ 842 234	-€ 1 479 647
	Treatment costs						€ 110 878 703	€ 0	€ 0
	Total cost						**€ 110 156 822**	**-€ 842 234**	**-€ 1 479 647**
2023	Medical care costs							-€ 577 505	-€ 683 015
	Treatment costs							€ 88 702 962	€ 0
	Total cost							**€ 88 125 457**	**-€ 683 015**
2024	Medical care costs								-€ 433 129
	Treatment costs								€ 66 527 222
	Total cost								**€ 66 094 093**
	Medical care costs	**-€ 420 079**	**-€ 1 030 811**	**-€ 2 962 430**	**-€ 5 098 991**	**-€ 7 960 514**	**-€ 10 552 265**	**-€ 13 259 738**	**-€ 15 847 411**
	Treatment costs	**€ 64 417 247**	**€ 82 172 842**	**€ 178 123 340**	**€ 139 490 911**	**€ 200 899 427**	**€ 110 878 703**	**€ 88 702 962**	**€ 66 527 222**
	Total Cost	**€ 64 195 636**	**€ 81 340 543**	**€ 175 255 114**	**€ 134 486 114**	**€ 192 938 913**	**€ 100 326 438**	**€ 75 443 225**	**€ 50 679 811**

Year	Costs	2 017	2 018	2 019	2 020	2 021	2 022	2 023	2 024	2 025	2 026	2 027	2 028	2 029	2 030
2017	Medical care costs	-€ 420 079	-€ 610 732	-€ 1 517 988	-€ 2 010 901	-€ 2 371 838	-€ 2 668 402	-€ 2 911 350	-€ 3 133 467	-€ 3 353 587	-€ 3 575 276	-€ 3 795 716	-€ 4 014 846	-€ 4 231 849	-€ 4 443 951
	Treatment costs	€ 64 417 247	€ 17 755 595	€ 32 190 774	€ 9 277 886	€ 9 267 701	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs	€ 198 468	€ 44	€ 5	€ 1	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost	**€ 64 195 636**	**€ 17 144 907**	**€ 30 672 791**	**€ 7 266 985**	**€ 6 895 863**	**-€ 2 668 402**	**-€ 2 911 350**	**-€ 3 133 467**	**-€ 3 353 587**	**-€ 3 575 276**	**-€ 3 795 716**	**-€ 4 014 846**	**-€ 4 231 849**	**-€ 4 443 951**
2018	Medical care costs		-€ 420 079	-€ 791 307	-€ 1 567 762	-€ 2 077 981	-€ 2 375 279	-€ 2 670 686	-€ 2 913 207	-€ 3 135 299	-€ 3 355 539	-€ 3 577 387	-€ 3 798 000	-€ 4 017 306	-€ 4 234 488
	Treatment costs		€ 64 417 247	€ 45 549 197	€ 11 616 801	€ 11 416 770	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs		€ 198 468	€ 29	€ 3	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost		**€ 64 195 636**	**€ 44 757 920**	**€ 10 049 042**	**€ 9 338 789**	**-€ 2 375 279**	**-€ 2 670 686**	**-€ 2 913 207**	**-€ 3 135 299**	**-€ 3 355 539**	**-€ 3 577 387**	**-€ 3 798 000**	**-€ 4 017 306**	**-€ 4 234 488**
2019	Medical care costs			-€ 653 136	-€ 867 193	-€ 1 683 049	-€ 2 097 898	-€ 2 386 587	-€ 2 678 762	-€ 2 920 257	-€ 3 142 197	-€ 3 362 517	-€ 3 584 511	-€ 3 805 286	-€ 4 024 757
	Treatment costs			€ 100 383 369	€ 18 212 856	€ 14 462 613	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs			€ 94 170	€ 20	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost			**€ 99 824 403**	**€ 17 345 683**	**€ 12 779 564**	**-€ 2 097 898**	**-€ 2 386 587**	**-€ 2 678 762**	**-€ 2 920 257**	**-€ 3 142 197**	**-€ 3 362 517**	**-€ 3 584 511**	**-€ 3 805 286**	**-€ 4 024 757**
2020	Medical care costs				-€ 653 136	-€ 961 389	-€ 1 687 352	-€ 2 106 386	-€ 2 389 929	-€ 2 680 675	-€ 2 921 764	-€ 3 143 571	-€ 3 363 874	-€ 3 585 877	-€ 3 806 665
	Treatment costs				€ 100 383 369	€ 32 697 899	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Diagnostic costs				€ 94 170	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost				**€ 99 824 403**	**€ 31 736 510**	**-€ 1 687 352**	**-€ 2 106 386**	**-€ 2 389 929**	**-€ 2 680 675**	**-€ 2 921 764**	**-€ 3 143 571**	**-€ 3 363 874**	**-€ 3 585 877**	**-€ 3 806 665**
2021	Medical care costs					-€ 866 258	-€ 1 001 453	-€ 1 764 989	-€ 2 136 255	-€ 2 406 007	-€ 2 693 108	-€ 2 932 783	-€ 3 154 275	-€ 3 374 502	-€ 3 596 492
	Treatment costs					€ 133 054 444	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost					**€ 132 188 186**	**-€ 1 001 453**	**-€ 1 764 989**	**-€ 2 136 255**	**-€ 2 406 007**	**-€ 2 693 108**	**-€ 2 932 783**	**-€ 3 154 275**	**-€ 3 374 502**	**-€ 3 596 492**
2022	Medical care costs						-€ 721 881	-€ 842 234	-€ 1 479 647	-€ 1 789 880	-€ 2 015 493	-€ 2 261 504	-€ 2 461 786	-€ 2 647 004	-€ 2 831 246
	Treatment costs						€ 110 878 703	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost						**€ 110 156 822**	**-€ 842 234**	**-€ 1 479 647**	**-€ 1 789 880**	**-€ 2 015 493**	**-€ 2 261 504**	**-€ 2 461 786**	**-€ 2 647 004**	**-€ 2 831 246**
2023	Medical care costs							-€ 577 505	-€ 683 015	-€ 1 194 305	-€ 1 443 506	-€ 1 624 979	-€ 1 829 899	-€ 1 990 788	-€ 2 139 734
	Treatment costs							€ 88 702 962	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost							**€ 88 125 457**	**-€ 683 015**	**-€ 1 194 305**	**-€ 1 443 506**	**-€ 1 624 979**	**-€ 1 829 899**	**-€ 1 990 788**	**-€ 2 139 734**
2024	Medical care costs								-€ 433 129	-€ 523 797	-€ 908 963	-€ 1 097 132	-€ 1 234 466	-€ 1 398 295	-€ 1 519 791
	Treatment costs								€ 66 527 222	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost								**€ 66 094 093**	**-€ 523 797**	**-€ 908 963**	**-€ 1 097 132**	**-€ 1 234 466**	**-€ 1 398 295**	**-€ 1 519 791**
2025	Medical care costs									-€ 433 129	-€ 523 797	-€ 908 963	-€ 1 097 132	-€ 1 234 466	-€ 1 398 295
	Treatment costs									€ 66 527 222	€ 0	€ 0	€ 0	€ 0	€ 0
	Total cost									**€ 66 094 093**	**-€ 523 797**	**-€ 908 963**	**-€ 1 097 132**	**-€ 1 234 466**	**-€ 1 398 295**
2026	Medical care costs										-€ 433 129	-€ 523 797	-€ 908 963	-€ 1 097 132	-€ 1 234 466
	Treatment costs										€ 66 527 222	€ 0	€ 0	€ 0	€ 0
	Total cost										**€ 66 094 093**	**-€ 523 797**	**-€ 908 963**	**-€ 1 097 132**	**-€ 1 234 466**
2027	Medical care costs											-€ 433 129	-€ 523 797	-€ 908 963	-€ 1 097 132
	Treatment costs											€ 66 527 222	€ 0	€ 0	€ 0
	Total cost											**€ 66 094 093**	**-€ 523 797**	**-€ 908 963**	**-€ 1 097 132**
2028	Medical care costs												-€ 433 129	-€ 523 797	-€ 908 963
	Treatment costs												€ 66 527 222	€ 0	€ 0
	Total cost												**€ 66 094 093**	**-€ 523 797**	**-€ 908 963**
2029	Medical care costs													-€ 433 129	-€ 523 797
	Treatment costs													€ 66 527 222	€ 0
	Total cost													**€ 66 094 093**	**-€ 523 797**
2030	Medical care costs														-€ 433 129
	Treatment costs														€ 66 527 222
	Total cost														**€ 66 094 093**
	Treatment cost	**€ 64 417 247**	**€ 82 172 842**	**€ 178 123 340**	**€ 139 490 911**	**€ 200 899 427**	**€ 110 878 703**	**€ 88 702 962**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**	**€ 66 527 222**
	Total Cost	**€ 64 195 636**	**€ 81 340 543**	**€ 175 255 114**	**€ 134 486 114**	**€ 192 938 913**	**€ 100 326 438**	**€ 75 443 225**	**€ 50 679 811**	**€ 48 090 286**	**€ 45 514 450**	**€ 42 865 743**	**€ 40 122 545**	**€ 37 278 829**	**€ 34 334 317**

3.3.2.2 *Impact of the treatment cost*

We tested here what should be the treatment costs to maintain a total budget at different level each year in the base case. Results are showed in Table 37.

Table 37 – Changes in treatment cost to maintain different budget limits each year (base case)

Budget limit	Maximum treatment cost for years 1-2 « Treating from F2 »	Maximum treatment cost for years 3-4 « Treating if blood test +»	Maximum treatment cost from year 5 « Treating everybody »
€ 20 000 000	€ 9 736	€ 4 491	€ 3 982
€ 40 000 000	€ 19 471	€ 8 983	€ 7 964
€ 60 000 000	€ 29 207	€ 13 474	€ 11 946
€ 80 000 000	€38 942	€ 17 965	€ 15 928
€ 100 000 000	€48 678	€ 22 456.35	€ 19 910

3.3.2.3 *Scenario analyses on budget impact*

Table 38 summarizes how the budget impact evolves according to certain parameters. The worst case / best case analysis combines inputs from the worst / best case analysis performed above (see Table 26), with a higher / lower number of people (see Table 34). The variations of results in this table show the important uncertainty around what would be the budget impact in the future and the important risk of an explosion of the budget if prices are not reduced. The number of patients that will be tested and treated is crucial and is totally impossible to predict. This should therefore be monitored in the future and decision on the enlargement of the population need to be reassessed according to results.

Table 38 – Budget impact: Scenarios on treatment cost, number of patients, and worst-best cases

Scenarios	Costs	2 017	2 018	2 019	2 020	2 021	2 022	2 023
On the treatment cost								
€17 500 (€21 000 from F4)	Treatment costs	€ 26 419 655	€ 33 889 283	€ 75 686 048	€ 58 910 432	€ 85 570 420	€ 46 781 109	€ 37 424 887
	Total cost	**€ 28 644 934**	**€ 38 186 506**	**€ 81 590 034**	**€ 66 758 709**	**€ 94 842 336**	**€ 57 782 361**	**€ 49 852 614**
€35 000 (€42 000 from F4)	Treatment costs	€ 52 839 311	€ 67 778 567	€ 151 372 097	€ 117 820 864	€ 171 140 840	€ 93 562 218	€ 74 849 774
	Total cost	**€ 55 064 589**	**€ 72 075 804**	**€ 157 276 093**	**€ 125 669 149**	**€ 180 412 756**	**€ 104 563 470**	**€ 87 277 501**
€40 000 (€63 000 from F4)	Treatment costs	€ 64 417 247	€ 82 172 842	€ 178 123 340	€ 139 490 911	€ 200 899 427	€ 110 878 703	€ 88 702 962
	Total cost	**€ 66 642 525**	**€ 86 470 094**	**€ 184 027 348**	**€ 147 339 204**	**€ 210 171 342**	**€ 121 879 955**	**€ 101 130 689**
€70 000 (€84 000 from F4)	Treatment costs	€ 105 678 621	€ 135 557 133	€ 302 744 194	€ 235 641 728	€ 342 281 681	€ 187 124 435	€ 149 699 548
	Total cost	**€ 107 903 900**	**€ 139 854 400**	**€ 308 648 213**	**€ 243 490 029**	**€ 351 553 597**	**€ 198 125 688**	**€ 162 127 275**
On the number of patients		**2 017**	**2 018**	**2 019**	**2 020**	**2 021**	**2 022**	**2 023**
year 1-6: 2000; year 7: 1500; from year 8: 1000	Treatment costs	€ 42 944 831	€ 54 781 895	€ 118 748 893	€ 92 993 941	€ 133 932 951	€ 88 702 962	€ 66 527 222
	Total cost	**€ 44 428 350**	**€ 57 646 729**	**€ 122 684 898**	**€ 98 226 136**	**€ 140 114 228**	**€ 96 212 756**	**€ 75 086 987**
year 1-5: 3000; year 6: 2500; year 7: 2000; from year 8: 1500	Treatment costs	€ 64 417 247	€ 82 172 842	€ 178 123 340	€ 139 490 911	€ 200 899 427	€ 110 878 703	€ 88 702 962
	Total cost	**€ 66 642 525**	**€ 86 470 094**	**€ 184 027 348**	**€ 147 339 204**	**€ 210 171 342**	**€ 121 879 955**	**€ 101 130 689**
year 1-5: 3500; year 6: 3000; year 7: 2500; from year 8: 2000	Treatment costs	€ 75 153 455	€ 95 868 315	€ 207 810 563	€ 162 739 396	€ 234 382 664	€ 133 054 444	€ 110 878 703
	Total cost	**€ 77 749 613**	**€ 100 881 776**	**€ 214 698 572**	**€ 171 895 738**	**€ 245 199 900**	**€ 145 933 144**	**€ 125 512 230**
Best-worst case (see appendix)		**2 017**	**2 018**	**2 019**	**2 020**	**2 021**	**2 022**	**2 023**
Best case	Treatment costs	€ 20 344 479	€ 22 485 191	€ 41 343 832	€ 37 106 735	€ 71 340 687	€ 38 530 481	€ 28 897 861
	Total cost	**€ 22 462 916**	**€ 26 572 455**	**€ 47 092 896**	**€ 44 598 944**	**€ 79 666 871**	**€ 48 575 059**	**€ 40 223 198**
Worst case	Treatment costs	€ 137 427 804	€ 197 591 137	€ 424 510 099	€ 311 976 589	€ 403 159 910	€ 253 017 829	€ 210 848 190
	Total cost	**€ 138 023 984**	**€ 198 859 115**	**€ 426 305 317**	**€ 314 470 462**	**€ 406 269 637**	**€ 256 952 317**	**€ 215 629 278**

Scenarios	Costs	2 024	2 025	2 026	2 027	2 028	2 029	2 030
On the treatment cost								
€17 500 (€21 000 from F4)	Treatment costs	€ 28 068 665	€ 28 068 665	€ 28 068 665	€ 28 068 665	€ 28 068 665	€ 28 068 665	€ 28 068 665
	Total cost	**€ 42 819 988**	**€ 43 926 322**	**€ 45 012 785**	**€ 46 085 414**	**€ 47 146 149**	**€ 48 202 736**	**€ 42 819 988**
€35 000 (€42 000 from F4)	Treatment costs	€ 56 137 331	€ 56 137 331	€ 56 137 331	€ 56 137 331	€ 56 137 331	€ 56 137 331	€ 56 137 331
	Total cost	**€ 70 888 654**	**€ 71 994 988**	**€ 73 081 450**	**€ 74 154 079**	**€ 75 214 814**	**€ 76 271 401**	**€ 70 888 654**
€40 000 (€63 000 from F4)	Treatment costs	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222
	Total cost	**€ 81 278 545**	**€ 82 384 879**	**€ 83 471 341**	**€ 84 543 970**	**€ 85 604 705**	**€ 86 661 293**	**€ 81 278 545**
€70 000 (€84 000 from F4)	Treatment costs	€ 112 274 661	€ 112 274 661	€ 112 274 661	€ 112 274 661	€ 112 274 661	€ 112 274 661	€ 112 274 661
	Total cost	**€ 127 025 984**	**€ 128 132 318**	**€ 129 218 780**	**€ 130 291 410**	**€ 131 352 145**	**€ 132 408 732**	**€ 127 025 984**
On the number of patients		**2 024**	**2 025**	**2 026**	**2 027**	**2 028**	**2 029**	**2 030**
year 1-6: 2000; year 7: 1500; from year 8: 1000	Treatment costs	€ 44 351 481	€ 44 351 481	€ 44 351 481	€ 44 351 481	€ 44 351 481	€ 44 351 481	€ 44 351 481
	Total cost	**€ 54 506 080**	**€ 55 250 545**	**€ 55 983 390**	**€ 56 703 346**	**€ 57 412 337**	**€ 58 118 243**	**€ 54 506 080**
year 1-5: 3000; year 6: 2500; year 7: 2000; from year 8: 1500	Treatment costs	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222	€ 66 527 222
	Total cost	**€ 81 278 545**	**€ 82 384 879**	**€ 83 471 341**	**€ 84 543 970**	**€ 85 604 705**	**€ 86 661 293**	**€ 81 278 545**
year 1-5: 3500; year 6: 3000; year 7: 2500; from year 8: 2000	Treatment costs	€ 88 702 962	€ 88 702 962	€ 88 702 962	€ 88 702 962	€ 88 702 962	€ 88 702 962	€ 88 702 962
	Total cost	**€ 106 342 992**	**€ 107 794 705**	**€ 109 227 626**	**€ 110 647 291**	**€ 112 055 448**	**€ 113 459 637**	**€ 106 342 992**
Best-worst case		**2 024**	**2 025**	**2 026**	**2 027**	**2 028**	**2 029**	**2 030**
Best case	Treatment costs	€ 28 897 861	€ 28 897 861	€ 28 897 861	€ 28 897 861	€ 28 897 861	€ 28 897 861	€ 28 897 861
	Total cost	**€ 41 577 256**	**€ 42 895 228**	**€ 44 218 031**	**€ 45 542 315**	**€ 46 864 682**	**€ 48 187 246**	**€ 49 510 118**
Worst case	Treatment costs	€ 168 678 552	€ 168 678 552	€ 168 678 552	€ 168 678 552	€ 168 678 552	€ 168 678 552	€ 168 678 552
	Total cost	**€ 175 064 316**	**€ 175 868 979**	**€ 176 663 159**	**€ 177 445 569**	**€ 178 215 721**	**€ 178 993 457**	**€ 179 776 514**

4 DISCUSSION AND CONCLUSION

The first part of this study aims at reviewing the published full economic evaluations of the novel direct acting antiviral (DAA) therapies for the treatment of chronic hepatitis C (CHC) in adult patients. Based on this review, the combination of Sofosbuvir and Ledipasvir appears to be a cost-effective treatment option for genotype 1 patients. The cost-effectiveness for other genotypes / interferon-free therapies still needs to be confirmed because of a lack of economic evaluations at the moment of the research.

Given the huge cost of DAA therapies, treating all patients would dramatically affect the public health care budgets. As such, subgroups analyses in the economic evaluations are useful tools to identify patients that could benefit most from the new treatments and to which these should be prioritized and reimbursed first. This review highlighted that the new interferon-free HCV therapies would benefit most (from a cost-effectiveness point of view) to younger (e.g. 40-year old versus older 70-year-old patients),[43, 47, 59, 66] male[43] patients with more advanced stages of liver disease.[43, 59, 66] Other relevant patient characteristics, such as the presence/absence of alcoholism, could have been used to differentiate the impact on the economic evaluations results but this was not found in any of the studies reviewed here, probably also because of a lack of data (e.g. on disease progression) to stratify the model accordingly.

In Belgium, currently, reimbursed treatments with the second generation DAA therapies are targeted to patients with advanced disease (i.e. METAVIR fibrosis stage F3 and F4) who are at risk of developing decompensated cirrhosis and pre- and post-transplanted patients. Extension of the reimbursement to F2 patients has been proposed based on the combined results of an elastography and a blood test. However the cost-effectiveness and budget-impact of treating this new patient group still needs to be assessed. This is the objective of the next part of this report. Results showed that more the patients are treated at an early stage, more we gained in LY and QALYs at an acceptable ICER, expect for the strategy of treating everybody without taking into account the impact on the quality of life (with an ICER >€100 000/LY). The choice between these strategies will therefore mostly be conditioned by the available budget.

This analysis differs from most previously published models in the fact that various treatment strategies in terms of patient eligibility for a hypothetical "gold standard interferon-free novel DAA regimen" were compared instead of comparing one treatment to other treatments. We choose to only take interferon-free regimens into account, as strongly advocated by members of our National Institute for Health and Disability Insurance. A similar study having assessed treatment strategies has been identified, also showing the interest of early treatment and concluding that treating all patients regardless of stage of liver disease was a cost-effective approach. This other study was nevertheless based on older therapies (e.g. Peg-interferon + telaprevir+ ribavirin) and the budget impact was not taken into account.

Compared to other published studies, this analysis has the following advantages:

- Data were as much as possible based on the Belgian situation, such as life expectancy, quality of life and HCV related costs by clinical disease stage.
- Some studies based disease progression between the different fibrosis stages on a single parameter. In our base case, disease progression between the different fibrosis stages were function of patient age and gender, and were based on a large American study (no Belgian data available).
- Our model took into account the fact that if patients were not eligible one year, they could become eligible the second year because of an evolution of the disease or a false positive result of the test. This also explain why total cost differs between year 1 and 2 in the budget impact even if the strategy tested and the number of patients considered for testing are the same.
- Some studies assumed a QoL equal to the general population and no progression after SVR, which is not a conservative approach (i.e. this goes in favor of HCV treatments). We decided to only assume an improvement in QoL and a reduction of the progression, based on available studies or on expert opinion if no study was found.

We were however confronted with important limitations related to the high uncertainty around the critical parameters and structure of the model, related to the fact that a number of crucial questions on the epidemiology and treatment of HCV remain unresolved. We summarize here the main limitations that make that the results should be interpreted with a lot of caution:

- Studies are single arm trials with SVR as main endpoint, there are no long term randomized controlled trials available for HCV treatment showing an effect on disease progression and hard clinical endpoints. Results in this study are therefore based on an extrapolation of long terms effects with a lot of assumptions and must interpreted with caution.
- There is considerable uncertainty around the natural history of HCV, both globaly and what the natural history is in the Belgian population. The natural history has important regional variation due to the role of (mainly lifestyle related) co-factors,. This is made worse by the fact that active screening, identifying more asymptomatic patients, may have as consequence that more 'slow or non evolvers' will be treated in the future.
- We do not know what the long term relapse rates may be and what the re-infection rate is, this may be an increasing problem if more patients with high risk behavour are included. This may thoroughly affect cost effectiveness, but can go in two directions: in one hand treatment may diminish transmission but on the other hand impact of treatment will be limited by re-infections in patients who continue the share needles or have other high risk behaviours. Data on reinfection rates are conflicting, and may depend on the quality of measures that go with treatment. Moreover, data from the past are probably a poor guide as the interferferon based treatments used at the time require much more commitment from the patients and this may induce considerable selection bias.
- Injecting drug users form an increasing proportion of especially the newly acquired infections. In Belgium very little is known about the behaviour and transmission patterns in this group. Mathei et al[124] showed that networks of IDU's are on top of that fragmented even within a small country as Belgium, with large differences between regions and subpopulations. This makes the effect of treatment in this group very unpredictable[124].
- Because of the market entry agreements performed in the different countries, including Belgium, the real treatment cost of new DAA regimens is unkown. The fact that studies are often based on a list price that does not take into account the discounts obtained makes that results published are unreliable. In this study, we therefore tested a large range of scenarios.
- Children were not considered in our study because most of the parameters of our model are unknown for this specific population. Analysis for specific populations such as drug users or HIV co-infected person were also not done for the same reasons.
- No probabilistic analysis was performed because there were a lot of uncertainties on the distributions around parameters, distributions that were totally unknown for most crucial parameters. Presenting a probabilistic analysis would confuse the readers by giving the impression that results are strong and based on well-documented data which is totally not the case. Nevertheless, the "worst" and "best" case scenarios performed does not contradict the results obtained in the base case for the treatment of all patients, i.e. the ICER remains acceptable if the quality of life is taken into account.
- The performance of the non-invasive liver tests, and especially of the combination of a blood test and an electrography impacted the choice between which patients should be targeted, i.e. (i) from F3 (based on a biopsy), (ii) from F2 (based on an elastography and a blood test), (iii) patients with a positive blood test, or (iv) all patients. Not much is known on the conditional dependence of different tests. Also the effect of repeating the same test on the accuracy of the test (the conditional dependence of repeated tests) is a major source of uncertainty. Differences in the treatment impact according to the stage of liver disease also modified the choice on which patients to target and is not enough documented.

- Especially for the strategy 4, the differences between the ICERs in life-year and in QALY are important. This can be explained by the fact that hepatitis C is a chronic diseases. Nevertheless another parameters had an important impact on these results, i.e. the increase in the quality of life after SVR for F0 to F4 patients. Current estimates are based on the “limited” literature available on this topic but it should be interesting to assess such an impact on Belgian patients to validate our results. Moreover, available studies have not assessed what would be the impact in assymptomatic patients that are not aware of their disease. It can be expected that for these patients, the increase after SVR would be more limited. Results presented here are therefore not valid in case of mass screening of the (also asymptomatic) population.
- The budget impact is highly influenced by the number of patients that will be tested and treated. Such a parameter is nevertheless impossible to predict and is related to a lot of variables such as the importance of screening programs and of informantion of the population, the capacity of the system to respond to the demand (e.g. availability of physicians), or the policies related to specific populations such as prisoners or IDUs.

An important issue that remain is the number of patients that will be eligible for a treatment in real practice (also depending of the sensitivity and specificity of the tests). This should therefore be monitored and decisions should be re-assessed at regular intervals.

APPPENDICES

APPENDIX 1. SCENARIO ANALYSES

Appendix 1.1. KCE reports 157 Antiviral Treatment - Annual transition probabilities between fibrosis stages[103]

	Men						Women					
Age	F0 to F1	F1 to F2	F2 to F3	F3 to Cirrhosis	F3 to HCC	Cirrhosis to HCC	F0 to F1	F1 to F2	F2 to F3	F3 to Cirrhosis	F3 to HCC	Cirrhosis to HCC
0	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
1	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
2	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
3	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
4	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
5	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
6	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
7	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
8	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
9	0.053	0.038	0.054	0	0	0.003	0.044	0.032	0.045	0	0	0.003
10	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
11	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
12	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
13	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
14	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
15	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
16	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
17	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
18	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
19	0.064	0.047	0.066	0.008	0	0.003	0.054	0.039	0.055	0.006	0	0.003
20	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
21	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
22	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
23	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
24	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
25	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
26	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
27	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003

28	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
29	0.052	0.038	0.053	0.025	0	0.003	0.043	0.031	0.044	0.021	0	0.003
30	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
31	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
32	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
33	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
34	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
35	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
36	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
37	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
38	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
39	0.038	0.027	0.039	0.057	0	0.005	0.031	0.023	0.032	0.047	0	0.004
40	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
41	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
42	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
43	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
44	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
45	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
46	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
47	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
48	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
49	0.139	0.101	0.143	0.088	0.001	0.009	0.116	0.084	0.119	0.074	0	0.007
50	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
51	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
52	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
53	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
54	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
55	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
56	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
57	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
58	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
59	0.171	0.124	0.175	0.048	0.001	0.014	0.143	0.104	0.146	0.04	0.001	0.012
60	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
61	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
62	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
63	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
64	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02

65	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
66	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
67	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
68	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
69	0.194	0.141	0.199	0.099	0.002	0.024	0.162	0.117	0.166	0.083	0.001	0.02
70	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
71	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
72	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
73	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
74	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
75	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
76	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
77	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
78	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
79	0.218	0.158	0.224	0.191	0.003	0.039	0.182	0.132	0.186	0.159	0.002	0.033
80	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
81	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
82	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
83	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
84	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
85	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
86	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
87	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
88	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
89	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
90	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
91	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
92	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
93	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
94	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
95	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
96	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
97	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
98	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
99	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
100	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
101	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033

102	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
103	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
104	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
105	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
106	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
107	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
108	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033
109	0.179	0.13	0.183	0.191	0.003	0.039	0.149	0.108	0.153	0.159	0.002	0.033

Appendix 1.2. Tables of the scenario analyses for the cost-effectiveness analyses

Impact of age (35 years – 55 years old)

This analysis shows that results are better for young people aged 35 years old than people aged 55 years old.

Table 39 – ICER in life-year gained from the sensitivity analysis on age – lower values (35 years)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	27 893.74		€ 59 206 907.65		Dominated
Strategy 1: Treating from F3 (Biopsy)	31 791.52	-	€ 57 069 667.61	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	32 076.24	284.72	€ 58 704 210.18	€ 1 634 542.57	€ 5 740.87
Strategy 3: Treating if blood test +	32 093.35	17.11	€ 59 375 253.05	€ 671 042.87	€ 39 226.13
Strategy 4: Treating everybody	32 103.02	9.67	€ 60 822 029.10	€ 1 446 776.05	€ 149 538.78

Table 40 – ICER in QALY gained from the sensitivity analysis on age – lower values (35 years)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	22 811.63		€ 59 206 907.65		Dominated
Strategy 1: Treating from F3 (Biopsy)	27 849.51	-	€ 57 069 667.61	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	28 744.04	894.54	€ 58 704 210.18	€ 1 634 542.57	€ 1 827.25
Strategy 3: Treating if blood test +	28 852.28	108.24	€ 59 375 253.05	€ 671 042.87	€ 6 199.63
Strategy 4: Treating everybody	28 983.54	131.25	€ 60 822 029.10	€ 1 446 776.05	€ 11 022.66

Table 41 – ICER in life-year gained from the sensitivity analysis on age – higher values (55 years)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	19 318.93	-	€ 46 785 454.72	-	-
Strategy 1: Treating from F3 (Biopsy)	21 616.87	2 297.94	€ 51 486 737.86	€ 4 701 283.14	€ 2 045.86
Strategy 2: Treating from F2 (Blood test + Elastography)	21 747.46	130.59	€ 53 881 795.12	€ 2 395 057.26	€ 18 339.91
Strategy 3: Treating if blood test +	21 759.40	11.93	€ 54 309 578.86	€ 427 783.74	€ 35 846.92
Strategy 4: Treating everybody	21 768.26	8.86	€ 55 976 401.27	€ 1 666 822.41	€ 188 140.14

Table 42 – ICER in QAILY gained from the sensitivity analysis on age – higher values (55 years)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	15 731.80	-	€ 46 785 454.72	-	-
Strategy 1: Treating from F3 (Biopsy)	18 916.89	3 185.09	€ 51 486 737.86	€ 4 701 283.14	€ 1 476.03
Strategy 2: Treating from F2 (Blood test + Elastography)	19 429.60	512.71	€ 53 881 795.12	€ 2 395 057.26	€ 4 671.38
Strategy 3: Treating if blood test +	19 512.79	83.19	€ 54 309 578.86	€ 427 783.74	€ 5 142.19
Strategy 4: Treating everybody	19 614.45	101.66	€ 55 976 401.27	€ 1 666 822.41	€ 16 395.58

Impact of transition probabilities between F0-F4

In a second scenario, we used the progression rates as derived and reported by Thein et al.[104]. Conclusions remain the same.

Table 43 – ICER in life-year gained from the sensitivity analysis on transition probabilities between F0-F4, as reported by Thein et al.[104]

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 748.86		€ 53 665 240.01		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 957.95	-	€ 53 340 778.43	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	27 153.37	195.41	€ 56 693 600.49	€ 3 352 822.06	€ 17 157.50
Strategy 3: Treating if blood test +	27 167.87	14.50	€ 57 229 165.85	€ 535 565.36	€ 36 927.27
Strategy 4: Treating everybody	27 180.27	12.40	€ 58 709 389.21	€ 1 480 223.36	€ 119 361.47

Table 44 – ICER in QAILY gained from the sensitivity analysis on transition probabilities between F0-F4, as reported by Thein et al.[104]

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 373.40		€ 53 665 240.01		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 502.58	-	€ 53 340 778.43	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 268.50	765.92	€ 56 693 600.49	€ 3 352 822.06	€ 4 377.48
Strategy 3: Treating if blood test +	24 366.49	97.99	€ 57 229 165.85	€ 535 565.36	€ 5 465.47
Strategy 4: Treating everybody	24 488.57	122.07	€ 58 709 389.21	€ 1 480 223.36	€ 12 125.56

Impact of transition probabilities after SVR

In this section, we tested the impact of changing the transition probabilities after SVR, with a distinction for people with mild (F0-F1), moderate (F2) and severe (F3-F4) CHC. Results showed that if patients with mild chronic hepatitis C does not evolve anymore after SVR, results are better than in the base case but if we used the lower range for all stages, results are slightly worst. Moreover, if patients evolves more rapidly after SVR from F2, the strategies of treating from F2 or F3 are dominated and the ICER of treating everybody is improved, showing that in this case, it is better to treat all patients earlier rather than to wait for the stage F2-F3. It is when we combined no evolution after SVR for F0-F1 and a higher evolution from F2 that the strategy of treating everybody has the lower ICER.

F0-F1 (lower range)

Table 45 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the lower ranges described in Table 11 for F0-F1

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.83	216.89	€ 56 892 888.07	€ 1 331 105.86	€ 6 137.24
Strategy 3: Treating if blood test +	27 177.66	17.83	€ 57 206 483.67	€ 313 595.60	€ 17 589.68
Strategy 4: Treating everybody	27 189.35	11.69	€ 58 699 186.31	€ 1 492 702.64	€ 127 673.25

Table 46 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the lower range described in Table 11 for F0-F1

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.66	674.30	€ 56 892 888.07	€ 1 331 105.86	€ 1 974.05
Strategy 3: Treating if blood test +	24 379.17	88.51	€ 57 206 483.67	€ 313 595.60	€ 3 542.87
Strategy 4: Treating everybody	24 499.96	120.79	€ 58 699 186.31	€ 1 492 702.64	€ 12 358.28

F0-F1; F1-F2 (lower range)

Table 47 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the lower ranges described in Table 11 for F0-F1; F1-F2

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 160.49	217.55	€ 56 882 844.34	€ 1 321 062.13	€ 6 072.36
Strategy 3: Treating if blood test +	27 179.03	18.54	€ 57 186 215.05	€ 303 370.72	€ 16 366.66
Strategy 4: Treating everybody	27 190.85	11.83	€ 58 677 052.20	€ 1 490 837.15	€ 126 072.47

Table 48 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the lower range described in Table 11 for F0-F1; F1-F2

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 291.58	675.23	€ 56 882 844.34	€ 1 321 062.13	€ 1 956.45
Strategy 3: Treating if blood test +	24 381.06	89.48	€ 57 186 215.05	€ 303 370.72	€ 3 390.39
Strategy 4: Treating everybody	24 502.03	120.96	€ 58 677 052.20	€ 1 490 837.15	€ 12 324.60

F0-F1; F1-F2; F2-F3 (lower range)

Table 49 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the lower ranges described in Table 11 for F0-F1; F1-F2; F2-F3

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 186.97	244.03	€ 56 528 109.97	€ 966 327.76	€ 3 959.84
Strategy 3: Treating if blood test +	27 197.23	10.25	€ 56 945 817.11	€ 417 707.14	€ 40 738.28
Strategy 4: Treating everybody	27 207.99	10.76	€ 58 451 113.51	€ 1 505 296.40	€ 139 861.89

Table 50 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the lower range described in Table 11 for F0-F1; F1-F2; F2-F3

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 326.13	709.78	€ 56 528 109.97	€ 966 327.76	€ 1 361.44
Strategy 3: Treating if blood test +	24 404.59	78.46	€ 56 945 817.11	€ 417 707.14	€ 5 324.04
Strategy 4: Treating everybody	24 524.15	119.56	€ 58 451 113.51	€ 1 505 296.40	€ 12 589.83

F0-F1; F1-F2; F2-F3; F3-F4 (lower range)

Table 51 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the lower ranges described in Table 11 for F0-F1; F1-F2; F2-F3: F3-F4

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 999.41	3 249.82	€ 54 842 304.47	€ 18 691.29	€ 5.75
Strategy 2: Treating from F2 (Blood test + Elastography)	27 200.84	201.43	€ 56 360 612.34	€ 1 518 307.87	€ 7 537.70
Strategy 3: Treating if blood test +	27 210.64	9.80	€ 56 784 135.89	€ 423 523.55	€ 43 227.32
Strategy 4: Treating everybody	27 221.23	10.59	€ 58 291 682.10	€ 1 507 546.21	€ 142 381.77

Table 52 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the lower range described in Table 11 for F0-F1; F1-F2; F2-F3; F3-F4

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 742.29	4 372.30	€ 54 842 304.47	€ 18 691.29	€ 4.27
Strategy 2: Treating from F2 (Blood test + Elastography)	24 355.09	612.80	€ 56 360 612.34	€ 1 518 307.87	€ 2 477.67
Strategy 3: Treating if blood test +	24 432.52	77.43	€ 56 784 135.89	€ 423 523.55	€ 5 469.60
Strategy 4: Treating everybody	24 551.68	119.16	€ 58 291 682.10	€ 1 507 546.21	€ 12 651.05

F0-F1; F1-F2; F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC (lower range)

Table 53 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the lower ranges described in Table 11 for F0-F1; F1-F2; F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	27 291.40	-	€ 51 734 019.13	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	27 374.64	83.24	€ 54 735 808.17	€ 3 001 789.04	€ 36 061.26
Strategy 3: Treating if blood test +	27 382.90	8.26	€ 55 177 653.63	€ 441 845.47	€ 53 507.30
Strategy 4: Treating everybody	27 392.72	9.82	€ 56 693 907.31	€ 1 516 253.68	€ 154 333.13

Table 54 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the lower range described in Table 11 for F0-F1; F1-F2; F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	24 028.73	-	€ 51 734 019.13	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 516.27	487.53	€ 54 735 808.17	€ 3 001 789.04	€ 6 157.10
Strategy 3: Treating if blood test +	24 592.09	75.83	€ 55 177 653.63	€ 441 845.47	€ 5 827.08
Strategy 4: Treating everybody	24 710.47	118.37	€ 56 693 907.31	€ 1 516 253.68	€ 12 808.96

F3-HCC; F4-HCC; F3-DC; F4-DC (higher range)

Table 55 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F3-HCC; F4-HCC; F3-DC; F4-DC

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 550.98		€ 59 683 024.13		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	26 929.12	3 179.53	€ 59 101 303.08	€ 4 277 689.90	€ 1 345.39
Strategy 3: Treating if blood test +	26 954.51	25.39	€ 59 320 552.25	€ 219 249.17	€ 8 636.11
Strategy 4: Treating everybody	26 967.94	13.43	€ 60 793 155.87	€ 1 472 603.61	€ 109 666.41

Table 56 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F3-HCC; F4-HCC; F3-DC; F4-DC

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 235.95		€ 59 683 024.13		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 075.30	4 705.31	€ 59 101 303.08	€ 4 277 689.90	€ 909.12
Strategy 3: Treating if blood test +	24 171.61	96.31	€ 59 320 552.25	€ 219 249.17	€ 2 276.47
Strategy 4: Treating everybody	24 294.16	122.55	€ 60 793 155.87	€ 1 472 603.61	€ 12 016.45

F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC (higher range).

Table 57 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 397.15		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	26 878.97	3 129.37	€ 59 638 164.46	€ 4 814 551.28	€ 1 538.50
Strategy 3: Treating if blood test +	26 909.34	30.37	€ 59 799 162.47	€ 160 998.01	€ 5 300.83
Strategy 4: Treating everybody	26 923.69	14.35	€ 61 261 336.06	€ 1 462 173.58	€ 101 900.22

Table 58 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	22 978.31		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	23 992.74	4 622.75	€ 59 638 164.46	€ 4 814 551.28	€ 1 041.49
Strategy 3: Treating if blood test +	24 097.97	105.23	€ 59 799 162.47	€ 160 998.01	€ 1 529.91
Strategy 4: Treating everybody	24 222.13	124.16	€ 61 261 336.06	€ 1 462 173.58	€ 11 776.32

F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC (higher range)

Table 59 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 397.15		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	26 786.23		€ 60 797 368.66		Dominated
Strategy 3: Treating if blood test +	26 842.96	3 093.36	€ 60 622 382.23	€ 5 798 769.05	€ 1 874.58
Strategy 4: Treating everybody	26 860.45	17.49	€ 62 045 195.08	€ 1 422 812.85	€ 81 367.84

Table 60 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	22 978.31		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	23 871.61		€ 60 797 368.66		Dominated
Strategy 3: Treating if blood test +	24 011.81	4 641.82	€ 60 622 382.23	€ 5 798 769.05	€ 1 249.24
Strategy 4: Treating everybody	24 140.08	128.27	€ 62 045 195.08	€ 1 422 812.85	€ 11 092.11

F0-F1; F1-F2; F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC (higher range)

Table 61 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11for F0-F1; F1-F2; F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 397.15		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	26 778.99		€ 60 899 224.73		Dominated
Strategy 3: Treating if blood test +	26 828.38	3 078.78	€ 60 822 653.36	€ 5 999 040.18	€ 1 948.51
Strategy 4: Treating everybody	26 844.04	15.66	€ 62 270 061.13	€ 1 447 407.77	€ 92 417.19

Table 62 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the higher range described in Table 11 for F0-F1; F1-F2; F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	22 978.31		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	23 861.40		€ 60 899 224.73		Dominated
Strategy 3: Treating if blood test +	23 991.56	4 621.57	€ 60 822 653.36	€ 5 999 040.18	€ 1 298.05
Strategy 4: Treating everybody	24 117.33	125.77	€ 62 270 061.13	€ 1 447 407.77	€ 11 508.08

F0-F1 and F1-F2 (lower range) and F2-F3; F3-F4; F3-HCC; F4-HCC; F3-DC; F4-DC (higher range)

Table 63 – ICER in life-year gained from the scenario analysis on transition probabilities after SVR based on the lower ranges described in Table 11 for F0-F1 and F1-F2 and the higher range from F2

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 397.15		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	26 790.21		€ 60 740 716.04		Dominated
Strategy 3: Treating if blood test +	26 851.09	3 101.49	€ 60 509 390.09	€ 5 685 776.91	€ 1 833.24
Strategy 4: Treating everybody	26 869.42	18.33	€ 61 920 948.39	€ 1 411 558.30	€ 77 005.06

Table 64 – ICER in QAILY gained from the scenario analysis on transition probabilities after SVR based on the lower range described in Table 11 for F0-F1 and F1-F2 and the higher range from F2

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	22 978.31		€ 61 355 065.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	23 877.26		€ 60 740 716.04		Dominated
Strategy 3: Treating if blood test +	24 023.18	4 653.19	€ 60 509 390.09	€ 5 685 776.91	€ 1 221.91
Strategy 4: Treating everybody	24 152.60	129.42	€ 61 920 948.39	€ 1 411 558.30	€ 10 906.69

Impact of other transition probabilities

If patients evolve more slowly in the latest stages of the disease, the ICER of all treatment strategies are worsen. Conversely, if patients evolve more quickly in the latest stages of the disease, the no treatment strategy is dominated while the ICER of other strategies is improved.

Table 65 – ICER in life-year gained from the scenario analysis on other transition probabilities based on the lower range described in Table 10

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	24 623.96	-	€ 45 610 572.21	-	-
Strategy 1: Treating from F3 (Biopsy)	27 185.18	2 561.21	€ 52 986 906.92	€ 7 376 334.71	€ 2 880.02
Strategy 2: Treating from F2 (Blood test + Elastography)	27 308.05	122.87	€ 55 411 369.93	€ 2 424 463.01	€ 19 731.60
Strategy 3: Treating if blood test +	27 318.71	10.66	€ 55 661 562.09	€ 250 192.16	€ 23 462.95
Strategy 4: Treating everybody	27 325.20	6.49	€ 57 346 088.54	€ 1 684 526.45	€ 259 511.75

Table 66 – ICER in QAILY gained from the scenario analysis on other transition probabilities based on the lower range described in Table 10

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	20 023.31	-	€ 45 610 572.21	-	-
Strategy 1: Treating from F3 (Biopsy)	23 842.79	3 819.48	€ 52 986 906.92	€ 7 376 334.71	€ 1 931.24
Strategy 2: Treating from F2 (Blood test + Elastography)	24 423.68		€ 55 411 369.93		Extended dominance
Strategy 3: Treating if blood test +	24 498.64	655.84	€ 55 661 562.09	€ 2 674 655.17	€ 4 078.18
Strategy 4: Treating everybody	24 621.40	122.77	€ 57 346 088.54	€ 1 684 526.45	€ 13 721.34

Table 67 – ICER in life-year gained from the scenario analysis on other transition probabilities based on the higher range described in Table 10

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	22 778.12		€ 60 167 667.72		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 653.68	-	€ 57 656 660.90	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	26 984.91	331.23	€ 58 043 437.34	€ 386 776.44	€ 1 167.70
Strategy 3: Treating if blood test +	27 011.22	26.32	€ 58 415 614.36	€ 372 177.02	€ 14 141.86
Strategy 4: Treating everybody	27 029.01	17.78	€ 59 746 489.00	€ 1 330 874.64	€ 74 833.51

Table 68 – ICER in QAILY gained from the scenario analysis on other transition probabilities based on the higher range described in Table 10

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	18 621.47		€ 60 167 667.72		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 352.56	-	€ 57 656 660.90	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 136.33	783.77	€ 58 043 437.34	€ 386 776.44	€ 493.48
Strategy 3: Treating if blood test +	24 238.69	102.36	€ 58 415 614.36	€ 372 177.02	€ 3 636.09
Strategy 4: Treating everybody	24 358.92	120.23	€ 59 746 489.00	€ 1 330 874.64	€ 11 069.14

Impact of the performance of the combined tests (performance of other tests maintained)

If we test the performance of the combined test separately, the analysis shows that if you decrease the sensitivity or the specificity of the combined test, this strategy is dominated (or extended dominance) by treating patients positive at the blood test alone (performance maintained).

Specific scenario

For the combination of tests (elastography + blood test), we test here the impact of a less sensitive but more specific scenario where there is conditional independence, with a drop in sensitivity but an increase in specificity (i.e. a sensitivity of 80 % and a specificity of 95 %).

Table 69 – ICER in life-year gained from the scenario analysis on the performance of combined tests (specific scenario)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 147.19	204.25	€ 56 267 981.04	€ 706 198.83	€ 3 457.54
Strategy 3: Treating if blood test +	27 177.64	30.45	€ 57 206 824.13	€ 938 843.09	€ 30 833.66
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 699 753.74	€ 1 492 929.61	€ 127 845.66

Table 70 – ICER in QAILY gained from the scenario analysis on the performance of combined tests (specific scenario)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 213.46	597.11	€ 56 267 981.04	€ 706 198.83	€ 1 182.70
Strategy 3: Treating if blood test +	24 379.14	165.68	€ 57 206 824.13	€ 938 843.09	€ 5 666.51
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 699 753.74	€ 1 492 929.61	€ 12 362.23

Lower sensitivity (0.7) – Base case specificity

Table 71 – ICER in life-year gained from the scenario analysis on the performance of combined tests: Lower sensitivity (0.7) – Base case specificity

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 130.66		€ 57 112 830.54		Extended dominance
Strategy 3: Treating if blood test +	27 177.64	234.70	€ 57 206 824.13	€ 1 645 041.92	€ 7 009.21
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 699 753.74	€ 1 492 929.61	€ 127 845.66

Table 72 – ICER in QAILY gained from the scenario analysis on the performance of combined tests: Lower sensitivity (0.7) – Base case specificity

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 245.81		€ 57 112 830.54		Extended dominance
Strategy 3: Treating if blood test +	24 379.14	762.79	€ 57 206 824.13	€ 1 645 041.92	€ 2 156.62
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 699 753.74	€ 1 492 929.61	€ 12 362.23

Higher sensitivity (0.95) – Base case specificity

Table 73 – ICER in life-year gained from the scenario analysis on the performance of combined tests: Higher sensitivity (0.95) – Base case specificity

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 173.95	231.01	€ 56 790 580.91	€ 1 228 798.70	€ 5 319.21
Strategy 3: Treating if blood test +	27 177.64	3.69	€ 57 206 824.13	€ 416 243.22	€ 112 934.47
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 699 753.74	€ 1 492 929.61	€ 127 845.66

Table 74 – ICER in QAILY gained from the scenario analysis on the performance of combined tests: Higher sensitivity (0.95) – Base case specificity

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 312.44	696.09	€ 56 790 580.91	€ 1 228 798.70	€ 1 765.29
Strategy 3: Treating if blood test +	24 379.14	66.70	€ 57 206 824.13	€ 416 243.22	€ 6 240.62
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 699 753.74	€ 1 492 929.61	€ 12 362.23

Base case sensitivity – Lower specificity (0.8)

Table 75 – ICER in life-year gained from the scenario analysis on the performance of combined tests: Base case sensitivity – Lower specificity (0.8)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 136.74		€ 57 865 260.95		Dominated
Strategy 3: Treating if blood test +	27 177.64	234.70	€ 57 206 824.13	€ 1 645 041.92	€ 7 009.21
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 699 753.74	€ 1 492 929.61	€ 127 845.66

Table 76 – ICER in QAILY gained from the scenario analysis on the performance of combined tests: Base case sensitivity – Lower specificity (0.8)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 320.28		€ 57 865 260.95		Dominated
Strategy 3: Treating if blood test +	24 379.14	762.79	€ 57 206 824.13	€ 1 645 041.92	€ 2 156.62
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 699 753.74	€ 1 492 929.61	€ 12 362.23

Base case sensitivity – Higher specificity (0.95)

Table 77 – ICER in life-year gained from the scenario analysis on the performance of combined tests: Base case sensitivity – Higher specificity (0.95)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 156.04	213.10	€ 56 204 990.27	€ 643 208.06	€ 3 018.37
Strategy 3: Treating if blood test +	27 177.64	21.60	€ 57 206 824.13	€ 1 001 833.85	€ 46 382.45
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 699 753.74	€ 1 492 929.61	€ 127 845.66

Table 78 – ICER in QAILY gained from the scenario analysis on the performance of combined tests: Base case sensitivity – Higher specificity (0.95)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 227.39	611.04	€ 56 204 990.27	€ 643 208.06	€ 1 052.64
Strategy 3: Treating if blood test +	24 379.14	151.75	€ 57 206 824.13	€ 1 001 833.85	€ 6 601.98
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 699 753.74	€ 1 492 929.61	€ 12 362.23

Impact of the performance of the blood test alone (performance of other tests maintained)

Not surprisingly, if you decrease the performance of the blood test alone, results get worst for strategy 3 while if you increase it, results are improved.

Lower sensitivity (0.8) – Base case specificity

Table 79 – ICER in life-year gained from the scenario analysis on the performance of the blood test: Lower sensitivity (0.8) – Base case specificity

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 893 082.83	€ 1 331 300.62	€ 6 138.47
Strategy 3: Treating if blood test +	27 163.51		€ 57 321 521.33		Extended dominance
Strategy 4: Treating everybody	27 189.32	29.50	€ 58 699 753.74	€ 1 806 670.90	€ 61 249.84

Table 80 – ICER in QAILY gained from the scenario analysis on the performance of the blood test: Lower sensitivity (0.8) – Base case specificity

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 893 082.83	€ 1 331 300.62	€ 1 974.38
Strategy 3: Treating if blood test +	24 358.51	67.87	€ 57 321 521.33	€ 428 438.49	€ 6 312.90
Strategy 4: Treating everybody	24 499.91	141.40	€ 58 699 753.74	€ 1 378 232.41	€ 9 747.08

Higher sensitivity (0.95) – Base case specificity

Table 81 – ICER in life-year gained from the scenario analysis on the performance of the blood test: Higher sensitivity (0.95) – Base case specificity

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 893 082.83	€ 1 331 300.62	€ 6 138.47
Strategy 3: Treating if blood test +	27 183.57	23.75	€ 57 159 299.41	€ 266 216.57	€ 11 209.74
Strategy 4: Treating everybody	27 189.32	5.75	€ 58 699 753.74	€ 1 540 454.33	€ 267 995.99

Table 82 – ICER in QAILY gained from the scenario analysis on the performance of the blood test: Higher sensitivity (0.95) – Base case specificity

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 893 082.83	€ 1 331 300.62	€ 1 974.38
Strategy 3: Treating if blood test +	24 387.81	97.17	€ 57 159 299.41	€ 266 216.57	€ 2 739.75
Strategy 4: Treating everybody	24 499.91	112.10	€ 58 699 753.74	€ 1 540 454.33	€ 13 741.95

Base case sensitivity – Lower specificity (0.25)

Table 83 – ICER in life-year gained from the scenario analysis on the performance of the blood test: Base case sensitivity – Lower specificity (0.25)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 893 082.83	€ 1 331 300.62	€ 6 138.47
Strategy 3: Treating if blood test +	27 178.02	18.20	€ 57 822 425.08	€ 929 342.24	€ 51 053.42
Strategy 4: Treating everybody	27 189.32	11.29	€ 58 699 753.74	€ 877 328.66	€ 77 684.99

Table 84 – ICER in QAILY gained from the scenario analysis on the performance of the blood test: Base case sensitivity – Lower specificity (0.25)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 893 082.83	€ 1 331 300.62	€ 1 974.38
Strategy 3: Treating if blood test +	24 420.49	129.86	€ 57 822 425.08	€ 929 342.24	€ 7 156.71
Strategy 4: Treating everybody	24 499.91	79.41	€ 58 699 753.74	€ 877 328.66	€ 11 047.99

Base case sensitivity – Higher specificity (0.6)

Table 85 – ICER in life-year gained from the scenario analysis on the performance of the blood test: Base case sensitivity – Higher specificity (0.6)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82		€ 56 893 082.83		Dominated
Strategy 3: Treating if blood test +	27 176.52	233.58	€ 56 299 413.77	€ 737 631.56	€ 3 157.90
Strategy 4: Treating everybody	27 189.32	12.79	€ 58 699 753.74	€ 2 400 339.96	€ 187 646.47

Table 86 – ICER in QAILY gained from the scenario analysis on the performance of the blood test : Base case sensitivity – Higher specificity (0.6)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64		€ 56 893 082.83		Dominated
Strategy 3: Treating if blood test +	24 315.78	699.43	€ 56 299 413.77	€ 737 631.56	€ 1 054.62
Strategy 4: Treating everybody	24 499.91	184.12	€ 58 699 753.74	€ 2 400 339.96	€ 13 036.57

Impact of the performance of all tests

Table 87 – ICER in life-year gained from the scenario analysis on the performance of all tests (lower range for sensitivity)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 130.66		€ 57 112 830.54		Extended dominance
Strategy 3: Treating if blood test +	27 163.51	220.57	€ 57 321 521.33	€ 1 759 739.12	€ 7 978.20
Strategy 4: Treating everybody	27 189.32	25.81	€ 58 699 753.74	€ 1 378 232.41	€ 53 406.22

Table 88 – ICER in QAILY gained from the scenario analysis on the performance of all tests (lower range for sensitivity)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 245.81		€ 57 112 830.54		Extended dominance
Strategy 3: Treating if blood test +	24 358.51	742.15	€ 57 321 521.33	€ 1 759 739.12	€ 2 371.13
Strategy 4: Treating everybody	24 499.91	141.40	€ 58 699 753.74	€ 1 378 232.41	€ 9 747.08

Table 89 – ICER in life-year gained from the scenario analysis on the performance of all tests (higher range for sensitivity)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 173.95	231.01	€ 56 790 580.91	€ 1 228 798.70	€ 5 319.21
Strategy 3: Treating if blood test +	27 183.57	9.62	€ 57 159 299.41	€ 368 718.50	€ 38 347.26
Strategy 4: Treating everybody	27 189.32	5.75	€ 58 699 753.74	€ 1 540 454.33	€ 267 995.99

Table 90 – ICER in QAILY gained from the scenario analysis on the performance of all tests (higher range for sensitivity)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 312.44	696.09	€ 56 790 580.91	€ 1 228 798.70	€ 1 765.29
Strategy 3: Treating if blood test +	24 387.81	75.37	€ 57 159 299.41	€ 368 718.50	€ 4 892.39
Strategy 4: Treating everybody	24 499.91	112.10	€ 58 699 753.74	€ 1 540 454.33	€ 13 741.95

Table 91 – ICER in life-year gained from the scenario analysis on the performance of all tests (lower range for specificity)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 164.31	221.37	€ 57 648 862.11	€ 2 087 079.90	€ 9 427.87
Strategy 3: Treating if blood test +	27 178.02	13.71	€ 57 822 425.08	€ 173 562.97	€ 12 661.44
Strategy 4: Treating everybody	27 189.32	11.29	€ 58 699 753.74	€ 877 328.66	€ 77 684.99

Table 92 – ICER in QAILY gained from the scenario analysis on the performance of all tests (lower range for specificity)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 361.66	745.30	€ 57 648 862.11	€ 2 087 079.90	€ 2 800.31
Strategy 3: Treating if blood test +	24 420.49	58.84	€ 57 822 425.08	€ 173 562.97	€ 2 949.85
Strategy 4: Treating everybody	24 499.91	79.41	€ 58 699 753.74	€ 877 328.66	€ 11 047.99

Table 93 – ICER in life-year gained from the scenario analysis on the performance of all tests (higher range for specificity)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 156.04	213.10	€ 56 204 990.27	€ 643 208.06	€ 3 018.37
Strategy 3: Treating if blood test +	27 176.52	20.49	€ 56 299 413.77	€ 94 423.50	€ 4 609.35
Strategy 4: Treating everybody	27 189.32	12.79	€ 58 699 753.74	€ 2 400 339.96	€ 187 646.47

Table 94 – ICER in QAILY gained from the scenario analysis on the performance of all tests (higher range for specificity)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 227.39	611.04	€ 56 204 990.27	€ 643 208.06	€ 1 052.64
Strategy 3: Treating if blood test +	24 315.78	88.39	€ 56 299 413.77	€ 94 423.50	€ 1 068.27
Strategy 4: Treating everybody	24 499.91	184.12	€ 58 699 753.74	€ 2 400 339.96	€ 13 036.57

Table 95 – ICER in life-year gained from the scenario analysis on the performance of all tests (lower range for sensitivity and specificity)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 136.74		€ 57 865 260.95		Extended dominace
Strategy 3: Treating if blood test +	27 164.02	221.08	€ 57 936 956.84	€ 2 375 174.63	€ 10 743.64
Strategy 4: Treating everybody	27 189.32	25.30	€ 58 699 753.74	€ 762 796.89	€ 30 152.99

Table 96 – ICER in QAILY gained from the scenario analysis on the performance of all tests (lower range for sensitivity and specificity)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 320.28		€ 57 865 260.95		Extended dominance
Strategy 3: Treating if blood test +	24 400.13	783.77	€ 57 936 956.84	€ 2 375 174.63	€ 3 030.43
Strategy 4: Treating everybody	24 499.91	99.78	€ 58 699 753.74	€ 762 796.89	€ 7 644.91

Table 97 – ICER in life-year gained from the scenario analysis on the performance of all tests (higher range for sensitivity and specificity)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 170.81	227.87	€ 56 102 791.23	€ 541 009.02	€ 2 374.23
Strategy 3: Treating if blood test +	27 182.57	11.76	€ 56 251 861.02	€ 149 069.79	€ 12 678.03
Strategy 4: Treating everybody	27 189.32	6.75	€ 58 699 753.74	€ 2 447 892.72	€ 362 663.58

Table 98 – ICER in QAILY gained from the scenario analysis on the performance of all tests (higher range for sensitivity and specificity)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 250.69	634.34	€ 56 102 791.23	€ 541 009.02	€ 852.87
Strategy 3: Treating if blood test +	24 324.69	74.00	€ 56 251 861.02	€ 149 069.79	€ 2 014.38
Strategy 4: Treating everybody	24 499.91	175.21	€ 58 699 753.74	€ 2 447 892.72	€ 13 971.05

Impact of SVR rates

If we have higher SVR for patients with mild CHC (F0-F1) or lower SVR rates from F3, the strategy of treating from F3 becomes dominated

For F0-F1

Table 99 – ICER in life-year gained from the scenario analysis on SVR rates for F0-F1 (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 165.79		€ 56 330 296.14		Dominated
Strategy 3: Treating if blood test +	27 188.64	245.70	€ 56 229 700.40	€ 667 918.19	€ 2 718.38
Strategy 4: Treating everybody	27 202.08	13.44	€ 57 557 060.05	€ 1 327 359.65	€ 98 793.62

Table 100 – ICER in QAILY gained from the scenario analysis on SVR rates for F0-F1 (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 301.50		€ 56 330 296.14		Dominated
Strategy 3: Treating if blood test +	24 398.66	782.30	€ 56 229 700.40	€ 667 918.19	€ 853.78
Strategy 4: Treating everybody	24 522.67	124.01	€ 57 557 060.05	€ 1 327 359.65	€ 10 703.40

Table 101 – ICER in life-year gained from the scenario analysis on SVR rates for F0-F1 (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 3: Treating if blood test +	27 133.16		€ 58 625 730.28		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	27 135.71	192.77	€ 57 700 583.37	€ 2 138 801.16	€ 11 095.06
Strategy 4: Treating everybody	27 137.74	2.03	€ 60 356 400.79	€ 2 655 817.42	€ 1 310 434.60

Table 102 – ICER in QAILY gained from the scenario analysis on SVR rates for F0-F1 (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 246.74	630.39	€ 57 700 583.37	€ 2 138 801.16	€ 3 392.81
Strategy 3: Treating if blood test +	24 300.29		€ 58 625 730.28		Extended dominance
Strategy 4: Treating everybody	24 407.93	161.19	€ 60 356 400.79	€ 2 655 817.42	€ 16 476.30

For F0-F1-F2

Table 103 – ICER in life-year gained from the scenario analysis on SVR rates for F0-F1-F2 (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94		€ 55 561 782.21		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	27 182.09	3 432.49	€ 55 321 749.54	€ 498 136.36	€ 145.12
Strategy 3: Treating if blood test +	27 199.45	17.35	€ 55 579 673.00	€ 257 923.46	€ 14 862.30
Strategy 4: Treating everybody	27 212.21	12.77	€ 56 950 263.26	€ 1 370 590.26	€ 107 347.19

Table 104 – ICER in QAILY gained from the scenario analysis on SVR rates for F0-F1-F2 (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35		€ 55 561 782.21		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 325.73	4 955.74	€ 55 321 749.54	€ 498 136.36	€ 100.52
Strategy 3: Treating if blood test +	24 414.55	88.81	€ 55 579 673.00	€ 257 923.46	€ 2 904.05
Strategy 4: Treating everybody	24 537.55	123.00	€ 56 950 263.26	€ 1 370 590.26	€ 11 142.59

Table 105 – ICER in life-year gained from the scenario analysis on SVR rates for F0-F1-F2 (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 3: Treating if blood test +	27 069.82		€ 59 292 711.21		Extended dominance
Strategy 2: Treating from F2 (Blood test + Elastography)	27 089.52	146.58	€ 59 659 007.35	€ 4 097 225.14	€ 27 952.17
Strategy 4: Treating everybody	27 096.79	7.27	€ 61 322 219.39	€ 1 663 212.04	€ 228 695.26

Table 106 – ICER in QAILY gained from the scenario analysis on SVR rates for F0-F1-F2 (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 148.84		€ 59 292 711.21		Extended dominance
Strategy 3: Treating if blood test +	24 236.08	619.72	€ 59 659 007.35	€ 4 097 225.14	€ 6 611.38
Strategy 4: Treating everybody	24 347.79	111.72	€ 61 322 219.39	€ 1 663 212.04	€ 14 887.62

For F3-F4-DC-HCC

Table 107 – ICER in life-year gained from the scenario analysis on SVR rates for F3-F4-DC-HCC (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 813.92		€ 58 491 961.11		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	27 112.03	3 362.43	€ 57 938 544.64	€ 3 114 931.46	€ 926.39
Strategy 3: Treating if blood test +	27 130.77	18.75	€ 58 229 795.98	€ 291 251.34	€ 15 537.50
Strategy 4: Treating everybody	27 142.86	12.09	€ 59 710 923.26	€ 1 481 127.29	€ 122 545.69

Table 108 – ICER in QAILY gained from the scenario analysis on SVR rates for F3-F4-DC-HCC (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 444.78		€ 58 491 961.11		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 233.62	4 863.63	€ 57 938 544.64	€ 3 114 931.46	€ 640.45
Strategy 3: Treating if blood test +	24 323.41	89.79	€ 58 229 795.98	€ 291 251.34	€ 3 243.66
Strategy 4: Treating everybody	24 444.75	121.34	€ 59 710 923.26	€ 1 481 127.29	€ 12 206.89

Table 109 – ICER in life-year gained from the scenario analysis on SVR rates for F3-F4-DC-HCC (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 974.87	-	€ 53 696 595.25	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	27 171.65	196.77	€ 56 218 126.19	€ 2 521 530.93	€ 12 814.42
Strategy 3: Treating if blood test +	27 189.24	17.59	€ 56 546 602.91	€ 328 476.73	€ 18 674.07
Strategy 4: Treating everybody	27 200.81	11.58	€ 58 047 956.49	€ 1 501 353.57	€ 129 690.53

Table 110 – ICER in QAILY gained from the scenario analysis on SVR rates for F3-F4-DC-HCC (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 658.82	-	€ 53 696 595.25	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 304.75	645.93	€ 56 218 126.19	€ 2 521 530.93	€ 3 903.69
Strategy 3: Treating if blood test +	24 392.93	88.18	€ 56 546 602.91	€ 328 476.73	€ 3 724.98
Strategy 4: Treating everybody	24 513.56	120.62	€ 58 047 956.49	€ 1 501 353.57	€ 12 446.53

For F2-F3-F4-DC-HCC

Table 111 – ICER in life-year gained from the scenario analysis on SVR rates for F2-F3-F4-DC-HCC (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 813.92	3 064.32	€ 58 491 961.11	€ 3 668 347.92	€ 1 197.12
Strategy 2: Treating from F2 (Blood test + Elastography)	27 046.14		€ 59 530 672.47		Dominated
Strategy 3: Treating if blood test +	27 087.13	273.21	€ 59 263 073.04	€ 771 111.94	€ 2 822.38
Strategy 4: Treating everybody	27 101.91	14.78	€ 60 676 741.87	€ 1 413 668.82	€ 95 616.79

Table 112 – ICER in QAILY gained from the scenario analysis on SVR rates for F2-F3-F4-DC-HCC (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 444.78	4 074.79	€ 58 491 961.11	€ 3 668 347.92	€ 900.25
Strategy 2: Treating from F2 (Blood test + Elastography)	24 135.72		€ 59 530 672.47		Dominated
Strategy 3: Treating if blood test +	24 259.20	814.42	€ 59 263 073.04	€ 771 111.94	€ 946.83
Strategy 4: Treating everybody	24 384.61	125.41	€ 60 676 741.87	€ 1 413 668.82	€ 11 272.43

Table 113 – ICER in life-year gained from the scenario analysis on SVR rates for F2-F3-F4-DC-HCC (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 974.87	-	€ 53 696 595.25	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	27 187.95	213.08	€ 55 209 579.59	€ 1 512 984.33	€ 7 100.54
Strategy 3: Treating if blood test +	27 200.04	12.08	€ 55 896 575.52	€ 686 995.93	€ 56 850.32
Strategy 4: Treating everybody	27 210.95	10.91	€ 57 441 159.70	€ 1 544 584.19	€ 141 593.57

Table 114 – ICER in QAILY gained from the scenario analysis on SVR rates for F2-F3-F4-DC-HCC (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 658.82	-	€ 53 696 595.25	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 328.98	670.17	€ 55 209 579.59	€ 1 512 984.33	€ 2 257.63
Strategy 3: Treating if blood test +	24 408.83	79.84	€ 55 896 575.52	€ 686 995.93	€ 8 604.18
Strategy 4: Treating everybody	24 528.44	119.62	€ 57 441 159.70	€ 1 544 584.19	€ 12 912.86

For F0-F1 (higher SVR) and F2-F3-F4-DC-HCC (lower SVR)

Table 115 – ICER in life-year gained from the scenario analysis on SVR rates for F0-F1 (higher range) and F2-F3-F4-DC-HCC (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 813.92		€ 58 491 961.11		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	27 052.11		€ 58 967 885.78		Dominated
Strategy 3: Treating if blood test +	27 098.14	3 348.54	€ 58 285 949.31	€ 3 462 336.13	€ 1 033.98
Strategy 4: Treating everybody	27 114.68	16.54	€ 59 534 048.18	€ 1 248 098.86	€ 75 446.54

Table 116 – ICER in QAILY gained from the scenario analysis on SVR rates for F0-1 (higher range) and F2-F3-F4-DC-HCC (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 444.78		€ 58 491 961.11		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 146.58		€ 58 967 885.78		Dominated
Strategy 3: Treating if blood test +	24 278.71	4 908.72	€ 58 285 949.31	€ 3 462 336.13	€ 705.34
Strategy 4: Treating everybody	24 407.37	128.66	€ 59 534 048.18	€ 1 248 098.86	€ 9 700.98

Impact of all SVR rates

Table 117 – ICER in life-year gained from the scenario analysis on SVR rates (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 813.92	3 064.32	€ 58 491 961.11	€ 3 668 347.92	€ 1 197.12
Strategy 2: Treating from F2 (Blood test + Elastography)	27 022.03	208.12	€ 60 338 173.01	€ 1 846 211.90	€ 8 871.10
Strategy 3: Treating if blood test +	27 042.66	20.62	€ 60 681 979.20	€ 343 806.19	€ 16 670.51
Strategy 4: Treating everybody	27 050.34	7.68	€ 62 333 388.92	€ 1 651 409.72	€ 214 989.62

Table 118 – ICER in QAILY gained from the scenario analysis on SVR rates (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 444.78	4 074.79	€ 58 491 961.11	€ 3 668 347.92	€ 900.25
Strategy 2: Treating from F2 (Blood test + Elastography)	24 091.82	647.04	€ 60 338 173.01	€ 1 846 211.90	€ 2 853.31
Strategy 3: Treating if blood test +	24 180.35	88.52	€ 60 681 979.20	€ 343 806.19	€ 3 883.78
Strategy 4: Treating everybody	24 292.64	112.29	€ 62 333 388.92	€ 1 651 409.72	€ 14 706.93

Table 119 – ICER in life-year gained from the scenario analysis on SVR rates (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 974.87	-	€ 53 696 595.25	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	27 193.92	219.05	€ 54 646 792.89	€ 950 197.64	€ 4 337.87
Strategy 3: Treating if blood test +	27 211.05	17.13	€ 54 919 451.79	€ 272 658.90	€ 15 921.64
Strategy 4: Treating everybody	27 223.71	12.67	€ 56 298 466.02	€ 1 379 014.23	€ 108 869.56

Table 120 – ICER in QAILY gained from the scenario analysis on SVR rates (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 658.82	-	€ 53 696 595.25	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 339.85	681.03	€ 54 646 792.89	€ 950 197.64	€ 1 395.24
Strategy 3: Treating if blood test +	24 428.34	88.50	€ 54 919 451.79	€ 272 658.90	€ 3 081.04
Strategy 4: Treating everybody	24 551.20	122.86	€ 56 298 466.02	€ 1 379 014.23	€ 11 223.95

Impact of disease management costs

Table 121 – ICER in life-year gained from the scenario analysis on disease management costs (lower range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 33 510 917.06	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 42 567 841.68	€ 9 056 924.62	€ 2 836.19
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 45 685 048.78	€ 3 117 207.10	€ 14 373.08
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 46 309 839.47	€ 624 790.69	€ 35 062.88
Strategy 4: Treating everybody	27 189.32	11.68	€ 48 152 812.86	€ 1 842 973.39	€ 157 821.34

Table 122 – ICER in QAILY gained from the scenario analysis on disease management costs (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 33 510 917.06	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 42 567 841.68	€ 9 056 924.62	€ 2 132.87
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 45 685 048.78	€ 3 117 207.10	€ 4 622.97
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 46 309 839.47	€ 624 790.69	€ 7 059.68
Strategy 4: Treating everybody	24 499.91	120.77	€ 48 152 812.86	€ 1 842 973.39	€ 15 260.78

Table 123 – ICER in life-year gained from the scenario analysis on disease management costs (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 72 176 549.32		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 942.94		€ 63 943 085.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	-	€ 63 918 399.98	-	-
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 64 030 428.27	€ 112 028.29	€ 6 286.96
Strategy 4: Treating everybody	27 189.32	11.68	€ 65 312 262.19	€ 1 281 833.92	€ 109 768.67

Table 124 – ICER in QAILY gained from the scenario analysis on disease management costs (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 72 176 549.32		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 616.35		€ 63 943 085.99		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	-	€ 63 918 399.98	-	-
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 64 030 428.27	€ 112 028.29	€ 1 265.84
Strategy 4: Treating everybody	24 499.91	120.77	€ 65 312 262.19	€ 1 281 833.92	€ 10 614.25

Impact of disease management costs after SVR

As with the transition probabilities after SVR, when we combined lower costs after SVR for F0-F1 and higher costs from F2 that the strategy of treating everybody has the lower ICER.

For F0-F1

Table 125 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F0-F1 (lower range: -36.48%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 865 537.65	€ 1 303 755.44	€ 6 011.47
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 157 128.23	€ 291 590.58	€ 16 363.89
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 640 597.17	€ 1 483 468.94	€ 127 035.50

Table 126 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F0-F1 (lower range: -36.48%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 865 537.65	€ 1 303 755.44	€ 1 933.53
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 157 128.23	€ 291 590.58	€ 3 294.76
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 640 597.17	€ 1 483 468.94	€ 12 283.89

Table 127 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F0-F1 (higher range: -33.94%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 962 814.28	€ 1 401 032.07	€ 6 460.00
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 332 630.77	€ 369 816.49	€ 20 753.88
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 849 510.36	€ 1 516 879.59	€ 129 896.59

Table 128 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F0-F1 (higher range: -33.94%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 962 814.28	€ 1 401 032.07	€ 2 077.80
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 332 630.77	€ 369 816.49	€ 4 178.65
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 849 510.36	€ 1 516 879.59	€ 12 560.55

For F0-F1-F2

Table 129 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F0-F1-F2 (lower range: -36.48%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 818 516.37	€ 1 256 734.16	€ 5 794.66
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 123 776.85	€ 305 260.49	€ 17 131.03
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 608 815.89	€ 1 485 039.04	€ 127 169.96

Table 130 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F0-F1-F2 (lower range: -36.48%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 818 516.37	€ 1 256 734.16	€ 1 863.80
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 123 776.85	€ 305 260.49	€ 3 449.22
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 608 815.89	€ 1 485 039.04	€ 12 296.89

Table 131 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F0-F1-F2 (higher range: -33.94%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 561 782.21	€ 738 169.03	€ 231.16
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 57 081 850.09	€ 1 520 067.88	€ 7 008.86
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 417 060.79	€ 335 210.70	€ 18 811.82
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 929 965.62	€ 1 512 904.83	€ 129 556.22

Table 132 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F0-F1-F2 (higher range:-33.94%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 561 782.21	€ 738 169.03	€ 173.84
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 57 081 850.09	€ 1 520 067.88	€ 2 254.34
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 417 060.79	€ 335 210.70	€ 3 787.63
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 929 965.62	€ 1 512 904.83	€ 12 527.64

For F3-F4

Table 133 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F3-F4 (lower range: -36.48%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 477 301.29	€ 653 688.11	€ 204.70
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 854 403.40	€ 1 377 102.11	€ 6 349.66
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 170 484.52	€ 316 081.12	€ 17 738.28
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 663 888.49	€ 1 493 403.97	€ 127 886.28

Table 134 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F3-F4 (lower range: -36.48%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 477 301.29	€ 653 688.11	€ 153.94
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 854 403.40	€ 1 377 102.11	€ 2 042.31
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 170 484.52	€ 316 081.12	€ 3 571.48
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 663 888.49	€ 1 493 403.97	€ 12 366.16

Table 135 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F3-F4 (higher range: -33.94%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 775 648.19	€ 952 035.01	€ 298.13
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 991 000.99	€ 1 215 352.80	€ 5 603.85
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 298 818.93	€ 307 817.94	€ 17 274.56
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 790 547.69	€ 1 491 728.75	€ 127 742.83

Table 136 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F3-F4 (higher range:-33.94%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 775 648.19	€ 952 035.01	€ 224.20
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 991 000.99	€ 1 215 352.80	€ 1 802.43
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 298 818.93	€ 307 817.94	€ 3 478.12
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 790 547.69	€ 1 491 728.75	€ 12 352.29

For F2-F3-F4

Table 137 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F2-F3-F4 (lower range: -36.48%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 477 301.29	€ 653 688.11	€ 204.70
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 56 807 382.11	€ 1 330 080.82	€ 6 132.85
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 137 133.14	€ 329 751.03	€ 18 505.43
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 632 107.21	€ 1 494 974.07	€ 128 020.74

Table 138 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F2-F3-F4 (lower range: -36.48%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 477 301.29	€ 653 688.11	€ 153.94
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 56 807 382.11	€ 1 330 080.82	€ 1 972.58
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 137 133.14	€ 329 751.03	€ 3 725.94
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 632 107.21	€ 1 494 974.07	€ 12 379.16

Table 139 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F2-F3-F4 (higher range: -33.94%)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 775 648.19	€ 952 035.01	€ 298.13
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 57 110 036.79	€ 1 334 388.60	€ 6 152.71
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 383 248.95	€ 273 212.16	€ 15 332.50
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 871 002.95	€ 1 487 754.00	€ 127 402.45

Table 140 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F2-F3-F4 (higher range:-33.94%)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 775 648.19	€ 952 035.01	€ 224.20
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 57 110 036.79	€ 1 334 388.60	€ 1 978.96
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 383 248.95	€ 273 212.16	€ 3 087.10
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 871 002.95	€ 1 487 754.00	€ 12 319.38

For F0-F1 (lower range) and F2-F3-F4 (higher range)

Table 141 – ICER in life-year gained from the scenario analysis on disease management costs after SVR for F0-F1 (lower range) and F2-F3-F4 (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 55 775 648.19	€ 952 035.01	€ 298.13
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 57 082 491.61	€ 1 306 843.42	€ 6 025.70
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 57 333 553.05	€ 251 061.44	€ 14 089.42
Strategy 4: Treating everybody	27 189.32	11.68	€ 58 811 846.38	€ 1 478 293.33	€ 126 592.30

Table 142 – ICER in QAILY gained from the scenario analysis on disease management costs after SVR for F0-F1 (lower range) and F2-F3-F4 (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 55 775 648.19	€ 952 035.01	€ 224.20
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 57 082 491.61	€ 1 306 843.42	€ 1 938.11
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 57 333 553.05	€ 251 061.44	€ 2 836.81
Strategy 4: Treating everybody	24 499.91	120.77	€ 58 811 846.38	€ 1 478 293.33	€ 12 241.04

Impact of treatment costs

Table 143 – ICER in life-year gained from the scenario analysis on treatment costs (lower range: €17 500 - €21 000)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 942.94		€ 36 507 150.70		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82		€ 33 736 902.70		Dominated
Strategy 3: Treating if blood test +	27 177.64	-	€ 33 512 467.52	-	-
Strategy 4: Treating everybody	27 189.32	11.68	€ 33 807 484.17	€ 295 016.65	€ 25 263.48

Table 144 – ICER in QAILY gained from the scenario analysis on treatment costs (lower range: €17 500 - €21 000)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 616.35		€ 36 507 150.70		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64		€ 33 736 902.70		Dominated
Strategy 3: Treating if blood test +	24 379.14	-	€ 33 512 467.52	-	-
Strategy 4: Treating everybody	24 499.91	120.77	€ 33 807 484.17	€ 295 016.65	€ 2 442.89

Table 145 – ICER in life-year gained from the scenario analysis on treatment costs (lower range: €35 000 - €42 000)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	26 942.94	-	€ 50 134 186.44	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 50 534 575.10	€ 400 388.66	€ 1 846.15
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 50 736 443.32	€ 201 868.22	€ 11 328.72
Strategy 4: Treating everybody	27 189.32	11.68	€ 51 974 905.06	€ 1 238 461.75	€ 106 054.54

Table 146 – ICER in QAILY gained from the scenario analysis on treatment costs (lower range: €17 500 - €21 000)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99		€ 54 823 613.18		Dominated
Strategy 1: Treating from F3 (Biopsy)	23 616.35	-	€ 50 134 186.44	-	-
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 50 534 575.10	€ 400 388.66	€ 593.80
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 50 736 443.32	€ 201 868.22	€ 2 280.96
Strategy 4: Treating everybody	24 499.91	120.77	€ 51 974 905.06	€ 1 238 461.75	€ 10 255.11

Table 147 – ICER in life-year gained from the scenario analysis on treatment costs (higher range)

	LY	Incremental LY	Cost	Incremental cost	ICER (/LY)
Strategy 0: No treatment	23 749.60	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	26 942.94	3 193.34	€ 77 388 257.92	€ 22 564 644.73	€ 7 066.15
Strategy 2: Treating from F2 (Blood test + Elastography)	27 159.82	216.88	€ 84 129 919.90	€ 6 741 661.98	€ 31 085.02
Strategy 3: Treating if blood test +	27 177.64	17.82	€ 85 184 394.91	€ 1 054 475.01	€ 59 176.50
Strategy 4: Treating everybody	27 189.32	11.68	€ 88 309 746.85	€ 3 125 351.94	€ 267 636.65

Table 148 – ICER in QAILY gained from the scenario analysis on treatment costs (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 616.35	4 246.36	€ 77 388 257.92	€ 22 564 644.73	€ 5 313.88
Strategy 2: Treating from F2 (Blood test + Elastography)	24 290.64	674.29	€ 84 129 919.90	€ 6 741 661.98	€ 9 998.22
Strategy 3: Treating if blood test +	24 379.14	88.50	€ 85 184 394.91	€ 1 054 475.01	€ 11 914.79
Strategy 4: Treating everybody	24 499.91	120.77	€ 88 309 746.85	€ 3 125 351.94	€ 25 879.54

Impact of utilities

Table 149 – ICER in QAILY gained from the scenario analysis on utilities (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	14 807.92	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	19 754.67	4 946.75	€ 55 561 782.21	€ 738 169.03	€ 149.22
Strategy 2: Treating from F2 (Blood test + Elastography)	20 763.13		€ 56 893 082.83		Extended dominance
Strategy 3: Treating if blood test +	21 266.59	1 511.92	€ 57 206 824.13	€ 1 645 041.92	€ 1 088.05
Strategy 4: Treating everybody	21 444.90	178.31	€ 58 699 753.74	€ 1 492 929.61	€ 8 372.69

Table 150 – ICER in QAILY gained from the scenario analysis on utilities (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	21 559.39	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	25 726.43	4 167.04	€ 55 561 782.21	€ 738 169.03	€ 177.14
Strategy 2: Treating from F2 (Blood test + Elastography)	26 488.94	762.51	€ 56 893 082.83	€ 1 331 300.62	€ 1 745.94
Strategy 3: Treating if blood test +	26 583.12	94.18	€ 57 206 824.13	€ 313 741.29	€ 3 331.16
Strategy 4: Treating everybody	26 706.23	123.11	€ 58 699 753.74	€ 1 492 929.61	€ 12 126.59

Impact of utilities after SVR

Again, it is when we combined higher utilities after SVR for F0-F1 and lower utilities from F2 that the strategy of treating everybody has the lower ICER.

For F0-F1

Table 151 – ICER in QAILY gained from the scenario analysis on utilities after SVR for F0-F1 (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 622.37	4 252.38	€ 55 561 782.21	€ 738 169.03	€ 173.59
Strategy 2: Treating from F2 (Blood test + Elastography)	24 587.08	5 217.09	€ 56 893 082.83	€ 2 069 469.65	€ 396.67
Strategy 3: Treating if blood test +	24 897.83	1 275.46	€ 57 206 824.13	€ 1 645 041.92	€ 1 289.76
Strategy 4: Treating everybody	25 113.42	215.59	€ 58 699 753.74	€ 1 492 929.61	€ 6 924.76

For F2-F3-F4

Table 152 – ICER in QAILY gained from the scenario analysis on utilities after SVR for F2-F3-F4 (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 132.98	3 762.99	€ 55 561 782.21	€ 738 169.03	€ 196.17
Strategy 2: Treating from F2 (Blood test + Elastography)	23 805.81		€ 56 893 082.83		Extended dominance
Strategy 3: Treating if blood test +	23 999.59	866.60	€ 57 206 824.13	€ 1 645 041.92	€ 1 898.26
Strategy 4: Treating everybody	24 133.55	133.97	€ 58 699 753.74	€ 1 492 929.61	€ 11 144.05

For F0-F1-F2-F3-F4

Table 153 – ICER in QAILY gained from the scenario analysis on utilities after SVR for F0-F1-F2-F3-F4 (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 132.98	3 762.99	€ 55 561 782.21	€ 738 169.03	€ 196.17
Strategy 2: Treating from F2 (Blood test + Elastography)	23 627.91	494.93	€ 56 893 082.83	€ 1 331 300.62	€ 2 689.90
Strategy 3: Treating if blood test +	23 688.21	60.30	€ 57 206 824.13	€ 313 741.29	€ 5 203.17
Strategy 4: Treating everybody	23 764.85	76.64	€ 58 699 753.74	€ 1 492 929.61	€ 19 479.94

Table 154 – ICER in QAILY gained from the scenario analysis on utilities after SVR for F0-F1-F2-F3-F4 (higher range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	24 456.98	5 086.99	€ 55 561 782.21	€ 738 169.03	€ 145.11
Strategy 2: Treating from F2 (Blood test + Elastography)	25 418.72	6 048.73	€ 56 893 082.83	€ 2 069 469.65	€ 342.13
Strategy 3: Treating if blood test +	25 553.25	1 096.27	€ 57 206 824.13	€ 1 645 041.92	€ 1 500.59
Strategy 4: Treating everybody	25 746.69	193.44	€ 58 699 753.74	€ 1 492 929.61	€ 7 717.89

For F0-F1 (higher range) and F2-F3-F4 (lower range)

Table 155 – ICER in QAILY gained from the scenario analysis on utilities for F0-F1 (higher range) and F2-F3-F4 (lower range)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	19 369.99	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	23 132.98	3 762.99	€ 55 561 782.21	€ 738 169.03	€ 196.17
Strategy 2: Treating from F2 (Blood test + Elastography)	24 099.44	4 729.45	€ 56 893 082.83	€ 2 069 469.65	€ 437.57
Strategy 3: Treating if blood test +	24 513.52	1 380.53	€ 57 206 824.13	€ 1 645 041.92	€ 1 191.60
Strategy 4: Treating everybody	24 742.10	228.58	€ 58 699 753.74	€ 1 492 929.61	€ 6 531.20

Impact of the discount rate

0% for both costs and outcomes

Table 156 – ICER in LY gained from the scenario analysis on the discount rate (0% for both costs and outcomes)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	30 690.78		€ 107 843 932.23		Dominated
Strategy 1: Treating from F3 (Biopsy)	35 863.31		€ 82 663 214.47		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	36 228.34		€ 73 873 741.54		Dominated
Strategy 3: Treating if blood test +	36 257.23	-	€ 71 802 852.79	-	-
Strategy 4: Treating everybody	36 274.35	17.13	€ 72 387 920.34	€ 585 067.54	€ 34 163.19

Table 157 – ICER in QAILY gained from the scenario analysis on the discount rate (0% for both costs and outcomes)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	24 948.90		€ 107 843 932.23		Dominated
Strategy 1: Treating from F3 (Biopsy)	31 510.83		€ 82 663 214.47		Dominated
Strategy 2: Treating from F2 (Blood test + Elastography)	32 439.33		€ 73 873 741.54		Dominated
Strategy 3: Treating if blood test +	32 527.28	-	€ 71 802 852.79	-	-
Strategy 4: Treating everybody	32 681.43	154.15	€ 72 387 920.34	€ 585 067.54	€ 3 795.48

3% for both costs and outcomes

Table 158 – ICER in LY gained from the scenario analysis on the discount rate (3% for both costs and outcomes)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	18 962.94	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	20 993.48	2 030.54	€ 55 561 782.21	€ 738 169.03	€ 363.53
Strategy 2: Treating from F2 (Blood test + Elastography)	21 125.69	132.21	€ 56 893 082.83	€ 1 331 300.62	€ 10 069.96
Strategy 3: Treating if blood test +	21 137.10	11.41	€ 57 206 824.13	€ 313 741.29	€ 27 507.79
Strategy 4: Treating everybody	21 145.37	8.27	€ 58 699 753.74	€ 1 492 929.61	€ 180 510.07

Table 159 – ICER in QAILY gained from the scenario analysis on the discount rate (3% for both costs and outcomes)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	15 511.07	-	€ 54 823 613.18	-	-
Strategy 1: Treating from F3 (Biopsy)	18 356.95	2 845.88	€ 55 561 782.21	€ 738 169.03	€ 259.38
Strategy 2: Treating from F2 (Blood test + Elastography)	18 870.26	513.31	€ 56 893 082.83	€ 1 331 300.62	€ 2 593.56
Strategy 3: Treating if blood test +	18 957.95	87.69	€ 57 206 824.13	€ 313 741.29	€ 3 577.69
Strategy 4: Treating everybody	19 056.29	98.34	€ 58 699 753.74	€ 1 492 929.61	€ 15 181.46

5% for both costs and outcomes

Table 160 – ICER in LY gained from the scenario analysis on the discount rate (5% for both costs and outcomes)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	14 639.35	-	€ 37 599 600.09	-	-
Strategy 1: Treating from F3 (Biopsy)	15 800.78	1 161.42	€ 45 450 704.55	€ 7 851 104.46	€ 6 759.90
Strategy 2: Treating from F2 (Blood test + Elastography)	15 871.77	70.99	€ 50 293 400.46	€ 4 842 695.91	€ 68 215.71
Strategy 3: Treating if blood test +	15 878.43	6.66	€ 51 806 446.10	€ 1 513 045.63	€ 227 094.38
Strategy 4: Treating everybody	15 883.94	5.51	€ 53 687 964.76	€ 1 881 518.67	€ 341 446.18

Table 161 – ICER in QAILY gained from the scenario analysis on the discount rate (5% for both costs and outcomes)

	QALY	Incremental QALY	Cost	Incremental cost	ICER (/QALY)
Strategy 0: No treatment	12 013.65	-	€ 37 599 600.09	-	-
Strategy 1: Treating from F3 (Biopsy)	13 773.46	1 759.81	€ 45 450 704.55	€ 7 851 104.46	€ 4 461.34
Strategy 2: Treating from F2 (Blood test + Elastography)	14 152.96	379.50	€ 50 293 400.46	€ 4 842 695.91	€ 12 760.63
Strategy 3: Treating if blood test +	14 238.23	85.26	€ 51 806 446.10	€ 1 513 045.63	€ 17 745.48
Strategy 4: Treating everybody	14 316.78	78.55	€ 53 687 964.76	€ 1 881 518.67	€ 23 953.02

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