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Impact of eradicating hepatitis C virus on the work productivity of chronic hepatitis C (CH-C) patients: an economic model from five European countries

Z. Younossi,[1] A. Brown,[2] M. Buti,[3] S. Fagiuoli,[4] S. Mauss,[5] W. Rosenberg,[6] L. Serfaty,[7] A. Srivastava,[6] N. Smith,[8] M. Stepanova[9] and R. Beckerman[8] [1]*Inova Fairfax Medical Campus, Falls Church, VA, USA;* [2]*Imperial College Healthcare NHS Trust, London, UK;* [3]*Vall d'Hebron University Hospital in Barcelona, Barcelona, Spain;* [4]*Ospedale Papa Giovanni XXIII, Bergamo, Italy;* [5]*Center for HIV and Hepatogastroenterology, Dusseldorf, Germany;* [6]*Division of Medicine, Institute for Liver and Digestive Health, University College London, London, UK;* [7]*Hepatology Service, Saint-Antoine Hospital, APHP, INSERM U_936, Pierre&Marie Curie University, Paris, France;* [8]*CBPartners, New York City, NY, USA; and* [9]*Center for Outcomes Research in Liver Diseases, Washington DC, DC, USA*

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SUMMARY. CH-C negatively affects work productivity (WP), creating a large economic burden. The aim of this study was to model the impact of sustained virologic response (SVR) on WP in CHC genotype 1 (GT1) patients in five European countries (EU5). Work Productivity and Activity Index-Specific Health Problem questionnaire was administered to patients across the ION clinical trials (n = 629 European patients). The analysis modelled a population of GT1 CHC patients over one year, who had been either not treated or treated with LDV/SOF. Sensitivity analyses assessed the possibility that CHC patients' labour costs were lower than the general population's and presented results by fibrosis stage. Before initiation of treatment, EU patients with CHC GT1 exhibited absenteeism and presenteeism impairments of 3.54% and 9.12%, respectively. About 91.8% of EU patients in the ION trials achieved SVR and improved absenteeism and presenteeism impairments by 16.3% and 19.5%, respectively. Monetizing these data, treatment with LDV/SOF resulted in an annual productivity gain of €435 million and a weighted average per-employed patient (PEP) gain of €900 in the EU5. PEP gains from treatment are projected to be higher in cirrhotic than in noncirrhotic patients. If CHC patients are assumed to earn 20% less than the general population, gains of €348 million (€720 PEP) annually are projected. CHC results in a significant economic burden to European society. Due to improvements in WP, SVR with treatment could provide substantial economic gains, partly offsetting the direct costs related to its widespread use.

Keywords: absenteeism, all-oral regimen, economic burden, hepatitis C treatment, presenteeism, societal impact.

INTRODUCTION

Chronic hepatitis C (CHC) is a global health challenge, affecting an estimated 130–170 million people globally, with 3–4 million people newly infected each year [1,2]. Hepatitis C virus (HCV) has an incidence of 7.8 per 100 000 in the European Union (EU); approximately 9 million patients have HCV infection in Europe, with greater prevalence in the southern and eastern regions [1]. CHC genotype 1 (GT1) is the most common CHC genotype in Europe [3–8]. While the incidence of new cases of HCV infection is low, only approximately 15% of patients exposed to the virus spontaneously clear the infection, and so exposure typically results in chronic infection that will continue indefinitely [1,2,9].

Abbreviations: CHC, chronic hepatitis C; DAA, direct-acting antiviral; EMA, European medicines agency; EU5, France, United Kingdom, Spain, Germany, Italy; EU, European Union; EUR, Euro; FR, France; GBP, pound sterling; GER, Germany; GT, genotype; HCV, hepatitis C virus; IT, Italy; LDV/SOF, ledipasvir/sofosbuvir; PegIFN, peginterferon; PEP, per employed patient; PP, per patient; PRO, patient-reported outcome; RBV, ribavirin; SOF, sofosbuvir; SP, Spain; SVR12, sustained viral response at 12 weeks post-treatment completion; SVR, sustained viral response; UK, United Kingdom; USA, United States of America; USD, US dollar; WPAI-SHP, work productivity and activity index – specific health problem; WP, work productivity.

Correspondence: Zobair M. Younossi, MD, MPH, Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042, USA.
E-mail: zobair.younossi@inova.org

CHC pathology ranges from mild to severe, with hepatic as well as extra-hepatic manifestations. CHC patients are at greater risk for development of cirrhosis, liver failure and hepatocellular carcinoma, all of which are associated with high morbidity and mortality [1,2]. An estimated 12.5% of CHC patients in the EU have cirrhosis [10]; these patients experience significant cirrhosis-related morbidity and mortality. In the systematic assessment performed by Mühlberger *et al.*, [5] HCV was estimated to have caused more than 86 000 deaths in the World Health Organization European region in 2002. A recent study projects that in the context of 2013 (previous to direct-acting antivirals) treatment paradigm HCV-related morbidity and mortality will continue to increase as the infected patient population continues to progress to advanced liver disease complications [10]. Extrahepatic symptoms, such as depression, certain types of lymphoma and type 2 diabetes, have also been shown to contribute significantly to HCV patient morbidity and impact upon quality of life [11].

CHC infection imposes tremendous economic burden, on patients, their employers and society [12,13], although few studies have assessed the economic burden of the condition from the European patient perspective. Direct medical costs of CHC are elevated among patients in five European countries (EU5: United Kingdom, France, Germany, Spain and Italy), with annual costs over 75% greater than matched controls [14]. Indirect costs of CHC are also a contributing factor to the disease's overall economic burden, as employment rates are lower in CHC patients than in the general population [15]; of those patients that are employed, recent studies are in agreement that work productivity impairment is estimated to range from 26% to 30% [14,15]. Recent work has monetized this HCV patient impairment into an average of €1914 worth of productivity lost to absenteeism (missed hours of work) per year, 60% more than matched controls [14]; presenteeism (decreased productivity while working) due to HCV resulted in annual productivity losses averaging €5268 per patient, versus €3176 for the matched controls [14]. This translates to an overall indirect cost of €7182 per year, €2810 more per employed patient per year than controls [14]. A similar burden has also been shown in the United States of America (USA) [16]. Therefore, there is a clear need for HCV treatments that can positively impact upon the economic burden of disease from both a direct and indirect perspective.

Until recently, most European Medicines Agency (EMA)-approved treatment regimens for CHC GT1 patients were administered with pegylated interferon 2-alpha (PegIFN) and ribavirin (RBV). PegIFN and RBV are associated with many adverse effects, further exacerbating the patient's already-compromised productivity and economic burden [17]. Sofosbuvir and ledipasvir (LDV/SOF) have been developed as a Peg-IFN- and RBV-free (in most patients) single oral tablet regimen with excellent clinical efficacy and tolerability in CHC GT1, GT3 and GT4 patients; the efficacy and safety of LDV/SOF with or without RBV, administered for 8–24 weeks, were studied in the phase 3 ION clinical trial programme [18–20]. Patient-reported outcomes (PROs) for this regimen have been captured across the ION clinical trial programme [21]. The benefits on quality of life of treating patients with LDV/SOF are evident even during the course of therapy – the first time an on-treatment benefit has been shown [21–24]. Although the impact of achieving sustained viral response (SVR) on decreasing work productivity impairment has been quantified from the USA perspective [16], this impact has not been assessed from the EU patient perspective. In fact, achieving SVR-12 with LDV/SOF in the United States could lead to a saving of $2.7 billion per year [16]. Given that the introduction of these all-oral regimens can lead to short-term costs for the EU budget holders, there is a need to understand the holistic set of cost-offsets – both direct and indirect – to patients and the society.

As CHC GT1 patients comprise both the majority of infections in the EU [7] and the majority of patients enrolled in the LDV/SOF trials, the aim of this study was therefore to develop an economic model to estimate the work productivity-related gains costs for CHC GT1 patients treated with LDV/SOF-based regimens versus no treatment in France (FR), Germany (GER), Italy (IT), Spain (SP) and the United Kingdom (UK).

METHODS

Model structure

The anticipated impact of LDV/SOF on productivity loss in each of the EU5 was calculated over a one-year period. Patients entered the model post-treatment, after having achieved or not achieved sustained viral response 12 weeks post-treatment completion (SVR12). For patients not achieving SVR, no productivity gain is assumed, and thus, absenteeism and presenteeism rates were estimated based on Work Productivity and Activity Index – Specific Health Problem (WPAI-SHP) data collected from the ION trials at baseline prior to treatment; for patients achieving SVR, productivity gains are estimated based on the difference between baseline WPAI-SHP data and absenteeism and presenteeism rates at SVR12.

These data were converted into work hours lost via standard assumptions as described below. The total number of work hours lost was then multiplied by the average hourly wage, to calculate the total productivity loss in monetary terms.

In the model's base case, the impact of treating all employed CHC GT1 patients with LDV/SOF-based regimens compared to no treatment was evaluated, and the difference between the two was taken as the estimate of productivity gains due to treatment.

Model inputs

Model inputs are described in Table 1. The WPAI-SHP assesses patient productivity in terms of absenteeism and presenteeism [25]. This questionnaire was administered to patients in the ION clinical trial programme at baseline (prior to treatment) and every four weeks until SVR12 [21]. Patients not achieving SVR after week 4 post-treatment were not followed up further and the full questionnaire was only assessed in patients who reported being employed at the time of the questionnaire.

SVR rates for patients receiving treatment with LDV/SOF-based regimens were sourced from an analysis of EU5 patients enrolled in the ION clinical trials (data on file). In our model, it was assumed that no untreated patient achieved an SVR. Work productivity scores upon achievement of SVR12 were assumed to remain constant through the one-year time horizon of the model. Work productivity among those not achieving SVR was assumed to remain at baseline values.

The total number of patients with CHC in the EU5 workforce was estimated from real-world sources: the country-specific National Health and Wellness Surveys [26–30] and the prevalence of GT1 CHC infection in Europe [7,8,31]. The age range of patients in the model was assumed to match the age range of the population studied in country-specific prevalence data sources to avoid extrapolation of published prevalence to other age groups, as CHC prevalence varies significantly with age [8,32]. Age ranges considered were 15 years or older in Great Britain and Italy, 18–80 years in France, 20–80 years in Germany and 25 years or older in Spain. Retired patients were not considered in this study.

The human capital method [33], using standard assumptions sourced from the literature, was used to translate these findings into the estimated annual economic burden in the EU5. Hourly wages and other labour costs, estimated by official government sources, ranged from €20.90 to €34.30 [34–38]; hours per working day, from 6.46 to 7.70; and number of work days per year, from 220 to 227.2 [34,35,39].

Sensitivity and subset analyses

Given that cirrhotic patients have been shown to be more impaired from a work productivity perspective than noncirrhotic patients [22], a specific subset analysis of the impact of LDV/SOF-based regimens on work productivity in cirrhotic versus noncirrhotic patients was performed. For this sensitivity analysis, in the absence of real-world data on employment rates among CHC patients by fibrosis stage, the rate of labour force participation was sourced directly from the ION trials.

A sensitivity analysis assuming that labour costs were 20% lower than those of the general population was performed, to account for the possibility that CHC patients'

Table 1 Country-specific model inputs

	GER	FR	SP	IT	UK	Sources
Country population*	61 787 109	46 536 113	34 926 363	51 764 532	52 798 300	[46–50]
HCV Prevalence	0.30%	0.40%	1.00%	1.50%	0.40%	[7,8,31]
GT1 Prevalence	62.50%	59.90%	69.30%	64.70%	45.00%	[7,8,51]
% Noncirrhotic Patients	87.5%	83.21%	89.34%	72.01%	92.81%	[10,30,40]
% HCV Patients Employed	41.60%	58.60%	53.60%	40.00%	43.10%	[26–30]
Hourly Wage	€31.30	€34.30	€21.10	€28.10	€20.90	[34–38]
# Hours Worked/Day	7.54	7.12	7.70	7.20	6.46	[34,35,39]
# Days Worked/Year	220	220	222.8	223	227.2	[39]

GER, Germany; FR, France; SP, Spain; IT, Italy; UK, United Kingdom; HCV, hepatitis C virus; GT1, genotype 1.
*Age ranges considered were 15 years or older in Great Britain and Italy, 18–80 years in France, 20–80 years in Germany and 25 years or older in Spain.

labour costs may be lower than those of the general population.

RESULTS

Productivity loss due to CHC

At baseline, based on data collected from the ION trials, among GT1 CHC patients not receiving treatment, overall work impairment was 12.6% (presenteeism, 9.1%; absenteeism, 3.5%) (Table 2).

The proportion of patients employed varied between 40% in IT and 58.6% in FR. Annualized, per patient and per-employed patient work productivity losses by country are summarized in Table 3. Across the EU5, annual work productivity losses among untreated patients were monetized as costing €2.6 billion annually (Fig. 1) (weighted average by number of HCV patients/number of employed HCV patients: €2442 per patient; €5366 per employed patient).

Impact of LDV/SOF-based regimen treatment on productivity

Treatment with LDV/SOF-based regimens resulted in 91.82% of European patients in ION trials achieving an SVR12 (Table 2). This was associated with a relative improvement in work productivity from baseline of 17.9% (12.5% at baseline to 10.3% post-SVR12). The overall improvement in work productivity was based on a relative presenteeism improvement of 19.53% and a relative absenteeism improvement of 16.28% from baseline. Across the EU5, work productivity improvements due to treatment with LDV/SOF were therefore monetized as saving €435 million annually (Fig. 1) (weighted average savings by number of HCV patients/number of employed HCV patients: €409 per patient; €900 per employed patient). Annualized, per patient and per-employed patient work productivity savings by country are summarized in Table 3.

Subset analysis: results in cirrhotic vs noncirrhotic EU patients

In the ION studies, noncirrhotic patients (n = 527) were significantly less impaired than cirrhotic patients (n = 102) across a range of metrics (Table 4): employment (65% *vs* 41%); rate of absenteeism at baseline (2.8% *vs* 7.8%); and rate of presenteeism at baseline (8.5% *vs* 13.1%). SVR rates among noncirrhotic patients were also significantly higher than those in cirrhotic patients (94.1% *vs* 81.6%).

Upon treatment with LDV/SOF, absenteeism significantly improved in cirrhotic patients (to 4.4%, a relative

Table 2 WPAI model inputs - aggregate population

	No treatment	Treatment with LDV/SOF	Source
% patients achieving SVR	0%	91.82%	Data on file
SVR achieved			
Absenteeism	N/A	2.97%	Data on file
Presenteeism	N/A	7.34%	
Baseline (and SVR not achieved)			
Absenteeism	3.54%	3.54%	Data on file
Presenteeism	9.12%	9.12%	

SVR, sustained viral response; LDV/SOF, ledipasvir/sofosbuvir.

Table 3 Base case model results

	GER	FR	SP	IT	UK
Baseline loss					
Annual aggregate (in million €)	€308.9	€433.3	€579.7	€1119.1	€155.1
Per patient	€2666	€3886	€2395	€2228	€1632
Per employed patient	€6409	€6632	€4468	€5569	€3786
Savings due to LDV/SOF treatment					
Annual aggregate (in million €)	€51.8	€72.6	€97.2	€187.6	€26.0
Per patient	€447	€651	€401	€373	€274
Per employed patient	€1074	€1112	€749	€934	€635

GER, Germany; FR, France; SP, Spain; IT, Italy; UK, United Kingdom; LDV/SOF, ledipasvir/sofosbuvir.

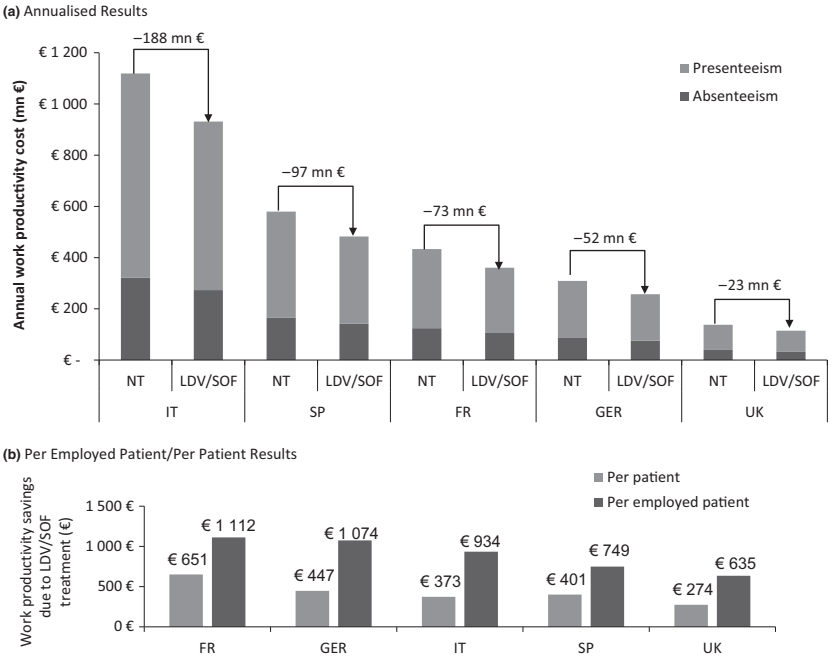

Fig. 1 Base case model results. (a) Costs due to work productivity impairment reported in terms of annual budget impact for patients treated or not treated with LDV/SOF, by country. (b) Costs due to work productivity impairment reported per employed patient (dark grey) or per patient (light grey) for patients treated or not treated with LDV/SOF, by country. LDV/SOF, ledipasvir/sofosbuvir; mn, million; NT, not treated; IT, Italy; SP, Spain; FR, France; GER, Germany; UK, United Kingdom.

Table 4 WPAI model inputs – noncirrhotic and cirrhotic patients

	Noncirrhotic		Cirrhotic		Source
% HCV patients employed	65.22%		41.13%		Data on file
	No treatment	LDV/SOF	No treatment	LDV/SOF	
% patients achieving SVR	0%	94.1%	0%	81.6%	Data on file
SVR achieved					
Absenteeism	N/A	2.8%	N/A	4.4%	Data on file
Presenteeism	N/A	6.8%	N/A	11.7%	Data on file
Baseline (and SVR Not achieved)					
Absenteeism	2.8%	2.8%	7.8%	7.8%	Data on file
Presenteeism	8.5%	8.5%	13.1%	13.1%	Data on file

SVR, sustained viral response; LDV/SOF, ledipasvir/sofosbuvir.

improvement of 43.5%), but not in noncirrhotic patients (remaining constant at 2.8%) (Table 4). Presenteeism improved to a larger degree in noncirrhotic patients (to 6.8%, a relative improvement of 20.1%) than in cirrhotic patients (to 11.7%, a relative improvement of 11.3%) (Table 4). Monetizing these improvements into cost savings (Fig. 2, Table 5), the per patient per year and per employed patient per year savings among cirrhotic patients treated with LDV/SOF are projected to be higher compared with noncirrhotic patients across all countries (weighted average savings by number of HCV patients/number of employed HCV patients: €454 per noncirrhotic patient; €696 per employed noncirrhotic patient; €657 per cirrhotic patient; €1597 per employed cirrhotic patient).

However, because only 8% to 28% of CHC patients in the EU are projected to have cirrhosis [10,30,40], the absolute savings per year are higher for the noncirrhotic population (€28.4 million - €171.3 million) versus the cirrhotic population (€3.1 million - €92.9 million) across all examined countries. Annualized, per patient and per-employed patient work productivity savings by country are summarized in Table 5.

Sensitivity analysis: labour costs

Assuming that labour costs for HCV patients were 20% lower than for the general population, work productivity losses among untreated patients were monetized as costing

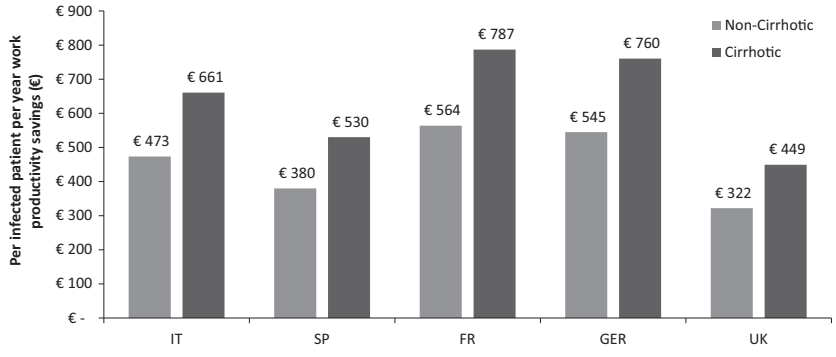

Fig. 2 Subgroup analysis: cirrhotic *vs* noncirrhotic patients. Costs due to work productivity impairment stratified by cirrhosis status, reported per patient, for patients treated or not treated with LDV/SOF, by country. LDV/SOF, ledipasvir/sofosbuvir; NT, not treated; IT, Italy; SP, Spain; FR, France; GER, Germany; UK, United Kingdom.

Table 5 Fibrosis stage sensitivity analysis results

	GER	FR	SP	IT	UK
Baseline loss: noncirrhotic patients					
Annual aggregate (in million €)	€380.8	€359.9	€565.2	€1178.5	€195.4
Per patient	€3749	€3879	€2614	€3258	€2215
Per employed patient	€5748	€5948	€4008	€4.995	€3396
Savings due to LDV/SOF treatment: noncirrhotic patients					
Annual aggregate (in million €)	€55.2	€52.3	€82.1	€171.2	€28.4
Per patient	€545	€564	€380	€473	€322
Per employed patient	€835	€864	€582	€726	€494
Baseline loss: cirrhotic patients					
Annual aggregate (in million €)	€61.6	€82.4	€76.5	€519.9	€17.2
Per patient	€4255	€4403	€2966	€3697	€2514
Per employed patient	€10 345	€10 705	€7213	€8990	€6112
Savings due to LDV/SOF treatment: cirrhotic patients					
Annual aggregate (in million €)	€11.0	€14.7	€13.7	€92.9	€3.1
Per patient	€760	€787	€530	€661	€449
Per employed patient	€1849	€1913	€1289	€1607	€1092

GER, Germany; FR, France; SP, Spain; IT, Italy; UK, United Kingdom; LDV/SOF, ledipasvir/sofosbuvir.

€2.1 billion annually (Fig. 3, Table 6) (weighted average by number of HCV patients/number of employed HCV patients: €1953 per patient, €4293 per employed patient). Annualized, per patient and per-employed patient work productivity savings by country are summarized in Table 6.

Using this assumption, across the EU5, work productivity improvements due to treatment with LDV/SOF were monetized as saving €348 million annually (Fig. 3, Table 6) (weighted average savings by number of HCV patients/number of employed HCV patients: €327 per patient, €720 per employed patient). Annualized, per patient and per-employed patient work productivity savings by country are summarized in Table 6.

DISCUSSION

The aim of this analysis was to evaluate the productivity loss due to CHC in GT1 patients, and estimate the potential savings due to improved work productivity resulting from achieving SVR-12 with treatment in the EU5.

First, we show here that the indirect costs of HCV infection as related to reduced work productivity contribute significantly to the economic burden of disease. In our model, the work productivity impairment of untreated HCV patients is projected to be substantial: approximately €2.6 bn across the EU5 annually. These results are lower than a recent study from the RAND group, which projected an annual cost in the UK of £192 million due to lost work productivity attributable to HCV in 2015 (versus €138 million in our model) [41]; however, this study assessed the productivity burden associated with CHC patients of all genotypes, rather than just CHC GT1 patients as in our study. Using the authors' assumption of 45% of CHC patients infected with GT1, their estimate of an annual productivity loss of £86.4 million is in line with the results of our model.

Further, on a per employed patient basis, our analysis is also slightly lower (€6414 *vs* €5366 in our study) than work productivity losses reported in a recent retrospective study assessing the economic burden of HCV in Europe

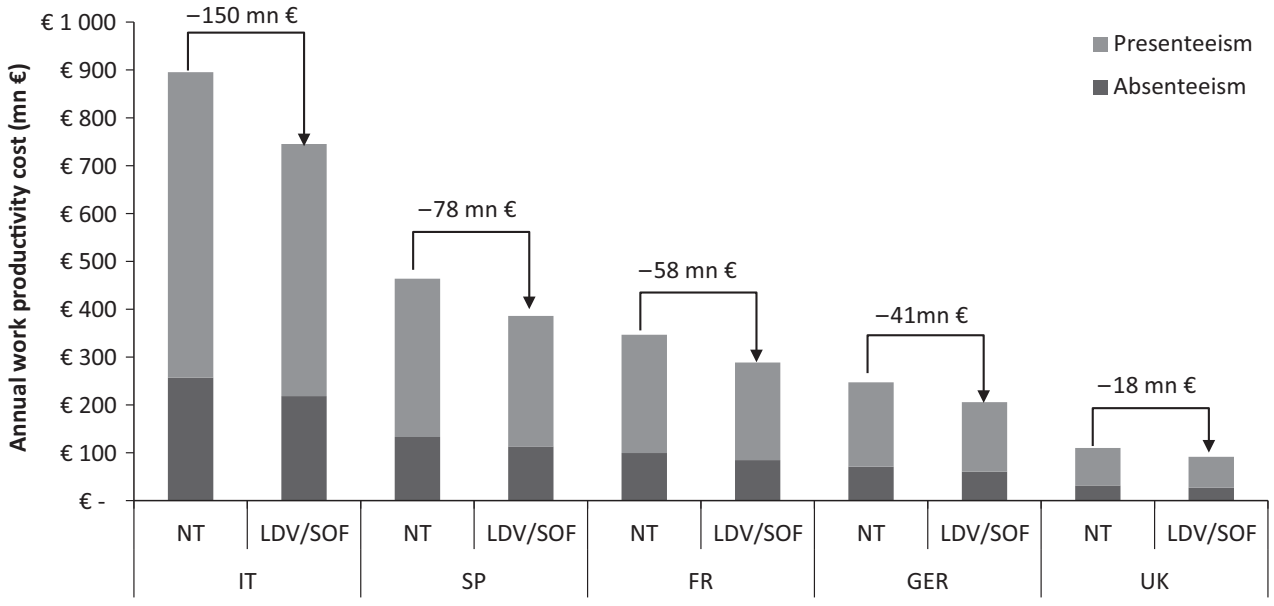

Fig. 3 Sensitivity analysis: −20% labour costs. Costs due to work productivity impairment reported in terms of annual budget impact for patients treated or not treated with LDV/SOF, by country, assuming a 20% reduction in labour costs. LDV/SOF, ledipasvir/sofosbuvir; NT, not treated; IT, Italy; SP, Spain; FR, France; GER, Germany; UK, United Kingdom.

Table 6 Labour cost sensitivity analysis results

	GER	FR	SP	IT	UK
Baseline loss					
Annual aggregate (in million €)	€247.1	€346.7	€463.7	€895.2	€124.1
Per patient	€2133	€3109	€1916	€1782	€1306
Per employed patient	€5127	€5305	€3574	€4455	€3029
Savings due to LDV/SOF treatment					
Annual aggregate (in million €)	€41.4	€58.1	€77.7	€150.1	€20.8
Per patient	€358	€521	€321	€299	€219
Per employed patient	€860	€889	€599	€747	€508

GER, Germany; FR, France; SP, Spain; IT, Italy; UK, United Kingdom; LDV/SOF, ledipasvir/sofosbuvir.

from the patient perspective [14]. The difference may be due to the fact that this study only evaluated treatment-naïve patients whose assessed presenteeism rates were threefold higher than in the ION trials, potentially due to differences in the demographics of patients who enrol in clinical trials versus those who are surveyed in real-world retrospective analyses.

In our model, costs due to lost productivity of HCV-infected patients at baseline were more driven by presenteeism than by absenteeism. This could be because of a higher barrier for patients to call out from work and forego wages entirely versus going into work impaired and being less productive, but collecting a wage. Presenteeism was the stronger driver of impairment across cirrhotic and non-cirrhotic patients alike, although as reported previously [22], at baseline patients with cirrhosis were projected to experience a greater magnitude of work productivity impairment in general and absenteeism in particular, than in noncirrhotic patients.

We show that in the overall EU population from the ION trials, LDV/SOF treatment results in substantial improvements in both presenteeism and absenteeism rates. Cirrhotic patients showed a significant improvement in both absenteeism and presenteeism, while noncirrhotic patients only showed an improvement in presenteeism; despite the lower baseline work productivity scores of cirrhotic patients, the percentage increase in productivity is similar in patient subpopulations.

Further, we show that as a result of reducing impaired work productivity, the LDV/SOF regimen has the potential to significantly reduce societal economic costs. Anticipated savings due to treatment with LDV/SOF differed significantly across examined countries, with the greatest annual savings projected in Italy and the smallest in the United

Kingdom. This was driven primarily by the estimated size of the employed CHC patient population, which was highest in Italy (502 375 patients) and lowest in the UK (95 037 patients). The differences in size of the employed CHC patient population among EU5, in turn, were based on country-specific CHC and GT1 prevalence rates (lowest in UK; high in IT) and employment rates (which ranged from a low of 40% in IT to a high of 58.6% in FR).

The employment rates used in our model were sourced from a real-world analysis of HCV patients; few other real-world studies have examined labour force participation among European HCV patients, but those who do [42,43] report employment rates (30% to 60%) that are in line to what was sourced for the present analysis. Nonetheless, these studies [42,43] and the real-world analyses used to feed our own model inputs estimate a lower participation than have been reported in clinical trials [21].

From both a per patient and per employed patient perspective, the greatest savings due to LDV/SOF treatment were projected to be realized in FR, and the smallest in the UK. This was driven by both the hourly labour cost inputs, which were highest in France (€34.30) and lowest in the UK (€20.90), and the higher labour force participation rate sourced for French patients relative to other countries [29].

In line with the reported differences in presenteeism and absenteeism improvements in cirrhotic *vs* noncirrhotic patients, our model projects differences in savings due to LDV/SOF treatment in these patient populations. The per patient per year savings for cirrhotic patients treated with LDV/SOF are projected to be higher compared with noncirrhotic patients. However, because only 8 to 28% of CHC patients in the EU are projected to have cirrhosis, the absolute savings per year are much higher for the noncirrhotic population.

These results differ from our previously published USA analysis in several respects. Expected annual cost savings due to treatment with LDV/SOF were projected to be lower in the EU5 than in the USA (€ 435 million in the EU5 in this analysis *vs* $2.7 bn in the USA [16]). Labour cost assumptions were of similar magnitude in both models, but the projected size of the employed GT1 population in absolute terms in the USA was 200% larger than in the EU5 (estimated as approximately 1.44 million patients in our USA model [16] *vs* 0.48 million patients in this EU5 analysis); differences were also likely driven by the percentage of HCV patients employed (64% in the USA as sourced from the ION trials *vs* 40–59% in the EU as sourced from real-world data), and the magnitude of work productivity improvements (+41.3% in the USA analysis *vs* +17.9% in the EU analysis). However, on a per employed patient basis, per patient savings were more similar but depending on the exchange rate assumed, still larger in the USA ($1874 [16] *vs* € 900), likely due to the greater magnitude of presenteeism improvements assessed in these patients. Further, in terms of the magnitude and nature of work productivity improvements, in the USA analysis, absenteeism was not significantly impacted by LDV/SOF treatment, while presenteeism was; in the EU, both metrics improved (with the absenteeism improvement driven by improvements in cirrhotic patients only). This may be due to more generous vacation/sick leave policy in the EU markets, where patients may feel greater security in taking time off for health-related reasons as compared to USA patients.

Although we used a one-year time horizon in our model, it is more realistic that the work productivity gains are spread over a longer period of time. This is due to the limitation of screening programmes to identify all HCV patients in a short period of time and to link them to care. Unlike the United States where the majority of HCV-infected patients remain undiagnosed, a larger proportion of HCV patients in EU are identified (1-10). Nevertheless, health access to healthcare capacity and treating physicians remain a challenge and an important constraint [44].

It is important to note that our model did have some limitations which may lead to an underestimation of the actual economic benefit of work productivity improvement due to HCV cure. The baseline presenteeism and absenteeism rates of 9.12% and 3.54%, respectively, in the ION trial EU patients, are lower than the rates assessed by other studies [14,45]. This difference could be due to the inclusion of healthier patients in the ION studies with different baseline demographics or disease progression than those included in the real-world analyses; additional real-world studies are needed to further validate this hypothesis. Further, because our study only models a one-year horizon, indirect costs related to longer term complications of CHC infection are not explicitly accounted for, nor has the possibility that the unemployment rate of HCV patients will decrease once the patient is free of virus. Importantly also, data within this model aggregated ribavirin-containing and ribavirin-free LDV/SOF regimens; due to its AE profile, ribavirin significantly affects patient-reported outcomes [17,21], and the use of LDV/SOF without ribavirin may therefore potentially result in further work productivity gains than modelled herein. It is also possible that the productivity gains after SVR-12 continue to increase. In fact, longer term follow-up may show a positive impact of SVR-12 on absenteeism which can in turn increase the long-term economic benefit of HCV cure. Therefore, longer term work productivity data must be collected. Finally, although real-world employment rates were sourced from a representative sample of each country's population, our modelled patient population employment rates did not specifically take into account the fact that CHC is highly prevalent in the incarcerated population and high-risk groups such IV drug users – groups that are likely to have lower rates of employment in general, but also higher rates of absenteeism and presenteeism when employed.

Because no head-to-head studies of LDV/SOF-based regimens versus other newer treatment regimens are available, our model evaluated the impact of treatment with LDV/SOF versus no treatment rather than other treatment regimens. Given that work productivity scores have been shown to worsen with the use of IFN-based regimens [20–23], the advantage of IFN-free and RBV-free (LDV/SOF) over these other regimens will be even more substantial.

In conclusion, based on our model, there is clear evidence that SVR-12 achieved with LDV/SOF-based regimens leads to a substantial indirect cost benefit to society by reducing work productivity impairment in CHC GT1 patients. Given that the economic losses due to work productivity are expected to recur annually in untreated HCV patients, further work is needed to place our results in context with direct cost of only a finite course of treatment for these patients with these highly effective and safe regimens.

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