A Cost-Effectiveness Analysis of Glecaprevir/Pibrentasvir Versus Existing Direct-Acting Antivirals to Treat Chronic Hepatitis C in Japan

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ABSTRACT

Introduction: The objective of the study was to evaluate the cost-effectiveness of glecaprevir/pibrentasvir versus other direct-acting antivirals (DAAs) for treating chronic hepatitis C virus (HCV) infections in Japan.

Methods: We developed a health state transition model to capture the natural history of HCV. A cost-effectiveness analysis of DAAs from the perspective of a public healthcare payer in Japan with a lifetime horizon over annual cycles was performed. Treatment attributes, baseline

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demographics, transition probabilities, health-state utilities, and costs data were extracted from publications. Costs and outcomes were discounted at 2% per annum. In the base case we focused on genotype 1 (GT1) treatment-naïve patients without cirrhosis. The scenario analysis examined a pan-genotype treatment in GT1–3 (i.e., portfolio), treatment-naïve, and treatment-experienced patients. The portfolio cost-effectiveness of DAAs was derived by calculating a weighted average of patient segments defined by treatment history, cirrhosis status, and genotype.

Results: The base case results indicated that glecaprevir/pibrentasvir was dominant (i.e., generating higher quality-adjusted life years [QALYs] and lower lifetime costs) compared to all other DAAs. The predicted lifetime risk of hepatocellular carcinoma was 3.66% for glecaprevir/pibrentasvir and sofosbuvir/ledipasvir, 4.99% for elbasvir/grazoprevir, and 5.27% for daclatasvir/asunaprevir/beclabuvir. In scenario analysis the glecaprevir/pibrentasvir (GLE/PIB) portfolio dominated the sofosbuvir (SOF)-based portfolio (namely sofosbuvir/ledipasvir in GT1–2 and sofosbuvir + ribavirin in GT3). The base case probabilistic sensitivity analysis (PSA) showed that glecaprevir/pibrentasvir was cost-effective in 93.4% of the simulations for a willingness-to-pay/QALY range of Japanese yen (JPY) 1.6–20 million. The PSA for the portfolio scenario indicated that the GLE/PIB portfolio was cost-effective in 100% of simulations until

the willingness-to-pay/QALY reached JPY 5.2 million; this proportion decreased to 69.4% at a willingness-to-pay/QALY of JPY 20 million. Results were also robust in deterministic sensitivity analyses.

Conclusion: In GT1 treatment-naïve non-cirrhotic patients GLE/PIB was a cost-effective strategy compared to other DAAs. When a pan-genotypic framework was used, the GLE/PIB portfolio dominated the SOF-based portfolio.

Keywords: Cost-effectiveness; Direct-acting antiviral; Genotype 1–6; Hepatitis C virus; Infectious disease; Japan; Pan-genotype

Key Summary Points

Why carry out this study?

Glecaprevir/pibrentasvir (GLE/PIB) is the first and only ribavirin-free pan-genotypic (i.e., genotype [GT] 1–6) approved to treat chronic hepatitis C virus (HCV) infections with or without compensated cirrhosis in Japan. However, no study comparing GLE/PIB to other approved direct-acting antivirals (DAAs) comparators in Japan has been published to date.

This study examined the cost-effectiveness of GLE/PIB versus approved DAAs for treating GT1–3, HCV infections in Japan.

What was learned from the study?

GLE/PIB was cost-saving and had better outcomes, making GLE/PIB a dominant treatment option compared to other DAAs and no treatment in GT1 treatment-naïve patients without cirrhosis.

When a pan-genotypic framework was used, the GLE/PIB portfolio dominated (i.e., better outcomes at a lower cost) a sofosbuvir-based portfolio.

INTRODUCTION

Japan has one of the highest rates of hepatitis C virus (HCV) infection in the industrialized world, with approximately 2 million people living with the disease [1]. The prevalence of HCV in the general population is estimated to be between 0.6% and 0.9% [2]. Genotype 1b (GT1b) has been reported as the most prevalent subtype (65%), followed by GT2 (34%) [3].¹ As liver disease progresses, some patients may develop cirrhosis and eventually progress from compensated cirrhosis to decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver failure. Japan also has the highest prevalence of HCC amongst the industrialized countries with HCV and its complications being the leading causes [4]. In fact, HCV-related HCC accounts for 70% of HCC cases in Japan [5]. Moreover, HCC is the fifth leading cause of death in Japan, and the societal costs associated with HCC morbidity and mortality are high [6]. In response, Japan introduced liver cancer screening programs in the 1980s, as well as awareness programs targeted at the public and healthcare providers in the 1990s [7]. Between 2000 and 2005, there was an estimated 55% decrease in undiagnosed HCV carriers [8]. In addition, the estimated societal burden of HCC fell from Japanese yen (JPY) 863.1 billion in 1996 to JPY 607.2 billion in 2014 [6].

Sustained virologic response (SVR) is a marker for viral eradication in HCV infection. The introduction of all-oral, direct-acting antivirals (DAAs) has drastically improved SVR rates and management of chronic HCV [7, 9, 10]. In addition, SVR achieved with DAA treatment has been demonstrated to persist long-term [11, 12]. In a cohort of 10,000 GT1b Japanese patients, the total economic savings of treatment with approved DAAs versus no treatment (calculated as: [savings due to treatment from avoiding projected health state costs] + [quality-adjusted life years (QALYs) gained by treatment] × [value of QALY] – weighted DAA costs) was estimated to be JPY 7.5 million and JPY

¹ We refer to a specific genotype (GT) in the document as GT + the genotype. Thus, for genotype 1b we use the abbreviation GT1b.

12.8 million per patient, at willingness-to-pay (WTP) thresholds of JPY 4 million and JPY 6 million per QALY, respectively. The considerable direct and indirect savings may be attributed to avoidance of HCC and DCC [13].

The HCV treatment landscape in Japan has some differentiating features compared to other countries. For one, regulatory approval in Japan requires specific clinical trials performed in Japan amongst Japanese patients. Secondly, approved HCV treatments in Japan include some treatment options that are not commonly used in other countries. In September 2017, glecaprevir/pibrentasvir (GLE/PIB) became the first and only 8-week treatment option in Japan for GT1 and GT2 HCV-infected patients without cirrhosis, and who are naïve to DAA treatment. These patients represent the majority of people living with HCV in Japan. The GLE/PIB regimen can also be prescribed as a 12-week course for patients infected with GT3–6, those with compensated cirrhosis, and those not cured with previous DAA treatment [14, 15]. However, to our knowledge, no study comparing GLE/PIB to other approved all-oral, interferon- and ribavirin-free DAA comparators in Japan has been published to date. Because of the unique HCV treatment landscape, a cost-effectiveness analysis of HCV therapies in Japan would broaden the scope of information on HCV and may offer insight into less common treatment options.

We based our model on previously published models of the natural history of chronic HCV infection, including Virabhak et al. [16], Ishida and Yotsuyanagi [17], and Hartwell et al. [18]. Most notably, we extended the same natural history model structure to capture lifetime disease progression of patients with HCV regardless of treatment history (i.e., treatment-naïve or treatment-experienced) and genotype (i.e., GT1–3).

METHODS

Natural History Model

The natural history model structure is presented in Fig. 1. The model was made up of eight health states including five disease progression

states (i.e., no cirrhosis [F0–F3], compensated cirrhosis [F4]²; DCC; HCC; and liver transplant), two SVR states (i.e., SVR, history of no cirrhosis; and SVR, history of compensated cirrhosis), and an absorbing mortality state (i.e., liver-related and non-liver-related death) which could be reached from any state. DCC was modeled as one health state [18, 20, 21]. Our model allowed variation in disease progression across genotypes [22, 23]. Firstly, the risks of cirrhosis and HCC have been shown to be higher in patients with GT3 compared to GT1 infected patients [24]. Secondly, GT2 patients are at significantly lower risk and GT3 patients are at higher risk for long-term morbidity and mortality relative to GT1 patients [25, 26].

Patients entering the model initiated treatment through one of two initial fibrosis states (i.e., F0–F3 or F4). With successful treatment patients achieved SVR and transitioned to SVR states [18]. In the absence of successful treatment patients either remained in their current health state or progressed to more severe stages of liver disease following natural disease progression.

In the model, patients could develop HCC from any SVR state, albeit at lower rates than patients who did not achieve SVR. In turn, patients who achieved SVR from compensated cirrhosis were assumed to face a higher risk of HCC than those who achieved SVR from no cirrhosis [27, 28]. A proportion of patients with compensated cirrhosis progressed to DCC [29, 30]. Some patients with DCC progressed to HCC, while a proportion received liver transplants. Patients with HCC could also receive liver transplants [21, 31, 32]. In addition, DCC, HCC, and liver transplant are commonly accepted as advanced stages of liver disease and thus we applied excess liver-related mortality risks [17, 18, 33]. Finally we assumed that spontaneous remission was not possible for patients with chronic HCV.

Table 1 shows model inputs such as patient characteristics, transition probabilities associated with fibrosis and non-fibrosis disease

² The model health states are based on METAVIR liver fibrosis stage which classifies chronic HCV from fibrosis 0 (F0), no fibrosis to F4 cirrhosis [19].

Fig. 1 Natural history model schematic. *DCC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *SVR* sustained virologic response. Health states are depicted by ellipses, arrows represent permissible transitions between health states, while loops represent no transition.

Dashed arrows depict the possibility of recovering (i.e., SVR). The dotted arrow depicts transition from “SVR, history of F0–F3” and “No cirrhosis (F0–F3)” to HCC. Death is possible from any health state. Liver-related death is possible from DCC, HCC, and liver transplant

progression, genotype-specific fibrosis and non-fibrosis progression hazard ratios, and background age- and gender-adjusted probability of death.

Study Population and Treatment Comparators

In the base case we focused on GT1, treatment-naïve non-cirrhotic patients, who comprise the largest patient segment in Japan [3]. In a PMOS of GLE/PIB, treatment-naïve patients accounted for 67.8% and non-cirrhotic patients accounted for 84.4% [34] of all patients with HCV. Fifty percent of patients with HCV had GT1 (of whom GT1b patients formed the vast majority), and 50.6% were male. The average age of the HCV population was 66.5 years. Using a segmented approach (i.e., the comparison of one intervention versus one comparator within a pre-specified patient segment, defined by patients’ treatment history, cirrhosis status, and/or genotype), we compared GLE/PIB versus other comparators approved for HCV treatment in Japan: sofosbuvir/ledipasvir (SOF/LDV) elbasvir/grazoprevir (EBR + GZR), daclatasvir/asunaprevir/beclabuvir (DCV/ASV/BCV), and no treatment. Since the combination of sofosbuvir and velpatasvir is only approved for patients who have failed on DAA or those with

DCC in Japan, it is not a relevant comparator in the current segmented analysis which is restricted to treatment-naïve patients without cirrhosis.

Given that GLE/PIB is a pan-genotypic treatment, we also analyzed cost-effectiveness from a broader perspective to inform decision-making in the entire patient population with a portfolio approach. The portfolio approach involved the comparison of treatment strategies in combinations of patient segments (i.e., treatment history–cirrhosis status–genotype combination), which in turn enabled flexible computation of a pan-genotypic incremental cost-effectiveness ratio (ICER) for the overall HCV population of interest. Computationally, the model calculated outcomes for each segment, and aggregated costs, QALYs, and clinical outcomes by weighting each segment on the basis of the patients’ treatment history, cirrhosis status, and genotype distribution to obtain a consolidated, weighted portfolio ICER and clinical outcomes. In portfolio analysis, we compared the GLE/PIB portfolio to a portfolio comprising treatment with SOF/LDV in GT1–2 and SOF + ribavirin in GT3 patients. Although GT3–6 patients were eligible to enroll in the GLE/PIB trial in Japan, only GT3 patients ended up being recruited. Subsequently, approval of GLE/PIB in the GT3–6 segment was based on clinical trial data comprising GT3 patients only.

Table 1 Model inputs for the base case, DSA, and PSA

Variable	Base case value	Sensitivity low	Sensitivity high	PSA, second statistical moment	Distribution in PSA	Source
Demographics						
Genotype distribution						GLE/PIB PMOS [34]
GT1	50.0%	NA	NA	NA	NA	
GT2	43.8%	NA	NA	NA	NA	
GT3	6.2%	NA	NA	NA	NA	
Treatment-naïve (%)	67.8%	NA	NA	NA	NA	GLE/PIB PMOS [34]
Age (in years)	66.5	NA	NA	NA	NA	GLE/PIB PMOS [34]
Male	50.6%	NA	NA	NA	NA	GLE/PIB PMOS [34]
Transitional probabilities (annual)						
GT1 fibrosis progression						
F0–F3 to F4	0.019	0.015	0.023	0.002	Beta	Ishida and Yotsuyanagi [17]
GT-specific fibrosis progression HR						
GT2	0.680	0.640	0.730	0.026	Normal	Kanwal et al. [24]
GT3 ^a	1.300	1.220	1.390	0.046	Normal	Kanwal et al. [24]
Non-fibrosis disease progression						
SVR, history of F4 to HCC (first year)	0.018	0.009	0.027	0.005	Beta	McEwan et al. [28]
F0–F3 to HCC (first year)	0.029	0.015	0.044	0.007	Beta	Suka et al. [71]
F4 to DCC	0.056	0.028	0.084	0.014	Beta	Suka et al. [71]
F4 to HCC (first year)	0.056	0.028	0.084	0.014	Beta	Suka et al. [71]
DCC to HCC (first year)	0.056	0.028	0.084	0.014	Beta	Suka et al. [71]
SVR, history of F0–F3 to HCC (first year)	0.002	0.001	0.003	0.001	Beta	Maruoka et al. [27]
Liver transplant						
DCC to liver transplant (first year)	0.004	0.002	0.005	0.001	Beta	Ishida and Yotsuyanagi [17]
HCC to liver transplant (first year)	0.003	0.002	0.005	0.001	Beta	Ishida and Yotsuyanagi [17]

Table 1 continued

Variable	Base case value	Sensitivity low	Sensitivity high	PSA, second statistical moment	Distribution in PSA	Source
Liver-related mortality						
DCC to liver death	0.151	0.076	0.227	0.038	Beta	Suka et al. [71]
Liver transplant to liver death	0.209	0.105	0.314	0.052	Beta	Ishida and Yotsuyanagi [17]
After liver transplant to liver death	0.018	0.009	0.027	0.005	Beta	Ishida and Yotsuyanagi [17]
HCC first year to liver death	0.118	0.059	0.177	0.030	Beta	Ishida and Yotsuyanagi [17]
HCC subsequent year to Liver death	0.222	0.111	0.333	0.056	Beta	Ishida and Yotsuyanagi [17]
Background age- and gender-adjusted probability of death	Variable	NA	NA	NA	NA	Abridged life tables [72]
GT-specific non-fibrosis transition rate HR						
F4 to HCC HR						
GT2	0.620	0.500	0.770	0.077	Normal	Kanwal et al. [24]
GT3	1.440	1.230	1.680	0.122	Normal	Kanwal et al. [24]
DCC to HCC HR						Assume same as F4 to HCC HR for each genotype
Health state utilities ^c						
F0–F3	0.854	0.684	0.940	0.064	Beta	Ishida and Yotsuyanagi [17]
F4	0.737	– 0.004	– 0.150	0.037	Log-normal	Ishida and Yotsuyanagi [17]
No HCV	0.930	0.720	1.000	NA	NA	Assumed equal to SVR, history of F0–F3
SVR, history F0–F3	0.930	0.720	1.000	NA	NA	Ishida and Yotsuyanagi [17]
SVR, history of F4	0.930	0.720	1.000	NA	NA	Ishida and Yotsuyanagi [17]
DCC	0.671	0.500	0.700	0.050	Beta	Ishida and Yotsuyanagi [17]

Table 1 continued

Variable	Base case value	Sensitivity low	Sensitivity high	PSA, second statistical moment	Distribution in PSA	Source
HCC (first year)	0.675	0.500	0.700	0.050	Beta	Ishida and Yotsuyanagi [17]
HCC (subsequent year)	0.428	0.300	0.500	0.050	Beta	Ishida and Yotsuyanagi [17]
Liver transplant (first year)	0.600	0.450	0.860	0.103	Beta	Ishida and Yotsuyanagi [17]
Liver transplant (subsequent year)	0.750	0.620	0.900	0.070	Beta	Ishida and Yotsuyanagi [17]
Health state costs (2019 JPY [¥]) ^b						
F0–F3	345,300	172,700	518,000	345,300	Gamma	Ishida and Yotsuyanagi [17]
F4	478,600	239,300	717,900	478,600	Gamma	Ishida and Yotsuyanagi [17]
No HCV	0	0	345,300			Assumption
SVR, history of F0–F3	57,186	0	345,300	57,186	Gamma	McEwan et al. [28]
SVR, history of F4	124,439	0	478,600	124,439	Gamma	McEwan et al. [28]
DCC	706,600	353,300	1,059,900	706,600	Gamma	Ishida and Yotsuyanagi [17]
HCC (first year)	1,148,500	574,300	1,722,800	1,148,500	Gamma	Ishida and Yotsuyanagi [17]
HCC (subsequent year)	1,992,800	996,400	2,989,300	1,992,800	Gamma	Ishida and Yotsuyanagi [17]
Liver transplant (first year)	14,995,200	7,497,600	22,492,800	14,995,200	Gamma	Ishida and Yotsuyanagi [17]
Liver transplant (subsequent year)	2,019,000	1,009,500	3,028,500	2,019,000	Gamma	Ishida and Yotsuyanagi [17]
Regimen costs (per day, Apr 2019 JPY [¥])						Japanese National Health Insurance [52]
GLE/PIB	54,406	NA	NA	NA	NA	
EBR + GZR	44,546	NA	NA	NA	NA	
SOF/LDV	54,686	NA	NA	NA	NA	
DCV/ASV/BCV	45,062	NA	NA	NA	NA	

Table 1 continued

Variable	Base case value	Sensitivity low	Sensitivity high	PSA, second statistical moment	Distribution in PSA	Source
SOF	42,238	NA	NA	NA	NA	
R	1573	NA	NA	NA	NA	

DCC decompensated cirrhosis, *DCV/ASV/BCV* daclatasvir/asunaprevir/beclabuvir, *DSA* deterministic sensitivity analysis, *EBR + GZR* elbasvir/grazoprevir, *F0–F3* no cirrhosis, *F4* compensated cirrhosis, *GLE/PIB* glecaprevir/pibrentasvir, *GT* genotype, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *JPY* Japanese yen [¥], *NA* not applicable, *PMOS* post-marketing observational study, *PSA* probabilistic sensitivity analysis, *R* ribavirin, *SOF* sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SVR* sustained virologic response

^a The inputs are based on Table 2 from Kanwal et al. [24]. Note that there is a discrepancy in the Kanwal publication for GT3 fibrosis progression hazard ratio. In the introduction and the results section, the text mentions 1.31 but the results in Table 2 show 1.30

^b As a result of negligible inflation in Japan, costs data are not inflated between 2006 (for liver transplant health state costs) and 2014 (for all other health state costs) to present year

^c F4 is not sampled from a beta distribution. Rather the relative difference (delta or ratio) between F4 and F0–F3 was sampled from the log-normal distribution which was applied to obtain health utilities in F4 at each simulation. The SVR states are not sampled from a beta distribution. Rather a fixed + 0.05 increase (base case value) from the initial fibrosis stage is assumed. No HCV state is not sampled from a beta distribution. Rather the drawn value for SVR, history F0–F3 is used (base case assumption)

Clinical Inputs

We extracted efficacy and duration data directly from Japanese phase III clinical trials [35–43], on the basis of the approved label for each regimen [14, 44–47]. Adverse event (AE) rates with DAA treatment were low; thus, AE costs had a negligible impact on overall cost and were excluded from the analysis. In the case of regimens with no Japanese trials, we used data from international trials [48]. For regimens with multiple phase III trials for a given patient segment, we consolidated data across relevant trials [48]. We used an intention-to-treat (ITT) perspective.

The expected treatment duration for each regimen was computed on the basis of labeled duration and trial-based discontinuation rates [35–43]. Table 2 shows the treatment efficacy for all patient segments included in the analysis for both the segmented and portfolio approach. For transparency, we reported SVR rate by patient segment.

Health Utilities

Health state utilities were drawn from Ishida and Yotsuyanagi [17] (Table 1). Treatment-related health utility reflects the effect of treatment on quality of life over the treatment duration. Treatment-related health utility data were derived from published literature, when available [49, 50]. When no relevant published data existed, we made the simplifying assumption that treatment-related utility matched that observed in the AbbVie clinical trials of GLE/PIB [35, 36].

Costs

We included only direct medical costs in this study (Table 1) [51]. Direct cost estimates for health states were taken from published Japanese studies [17, 28]. As a result of negligible inflation in Japan, cost data were not inflated from 2006 (for liver transplant-related health state costs) and 2014 (for all other health state

Table 2 Inputs for treatment efficacy in HCV GT1–3 patients using clinical trial data

Patient segment	Regimen	SVR F0–F3 (<i>n/N</i>)	Reference	SVR F4 (<i>n/N</i>)	Reference
TN GT1	GLE/PIB ^a	100.0% (94/94)	CERTAIN-1 [35], Chayama et al. [37]	100.0% (38/38)	Chayama et al. [37]
	DCV/ASV/BCV	95.9% (118/123)	Toyota et al. [38]	N/A	
	EBR + GZR ^b	96.6% (144/149)	Kumada et al. [39]	N/A	
	SOF/LDV ^c	100.0% (70/70)	Mizokami et al. [40]	100.0% (13/13)	Mizokami et al. [40]
TN GT2	GLE/PIB ^a	97.3% (73/75)	CERTAIN-2 [36], Toyoda et al. [41]	100.0% (18/18)	Toyoda et al. [41]
	SOF/LDV ^c	97.7%	Asahina et al. [43]	93.9%	Asahina et al. [43]
TN GT3	GLE/PIB ^a	83.3% (10/12)	Kumada et al. [42]	83.3% (10/12)	Kumada et al. [42]
	SOF + ribavirin ^d	91.5% (227/248)	Foster et al. [73], Zeuzem et al. [48]	77.6% (45/58)	Foster et al. [73], Zeuzem et al. [48]
TE GT1	GLE/PIB ^a	97.1% (34/35)	CERTAIN-1 [35], Chayama et al. [37]	100.0% (38/38)	Chayama et al. [37]
	SOF/LDV ^c	100.0% (60/60)	Mizokami et al. [40]	100.0% (28/28)	Mizokami et al. [40]
TE GT2	GLE/PIB ^a	100.0% (15/15)	CERTAIN-2 [36], Toyoda et al. [41]	100.0% (18/18)	Toyoda et al. [41]
	SOF/LDV ^c	94.6%	Asahina et al. [43]	90.7%	Asahina et al. [43]
TE GT3	GLE/PIB ^a	83.3% (10/12)	Kumada et al. [42]	83.3% (10/12)	Kumada et al. [42]
	SOF + ribavirin ^d	81.7% (107/131)	Foster et al. [73], Zeuzem et al. [48]	59.0% (49/83)	Foster et al. [73], Zeuzem et al. [48]

DCV/ASV/BCV daclatasvir/asunaprevir/beclabuvir, EBR + GZR elbasvir/grazoprevir, F0–F3 no cirrhosis, F4 compensated cirrhosis, GLE/PIB glecaprevir/pibrentasvir, GT genotype, N/A not applicable, SOF/LDV sofosbuvir/ledipasvir, SVR sustained virologic response, TE interferon-treatment-experienced, TN treatment-naïve

^a GLE/PIB: GT1 and GT2 F0–F3 patients are treated with GLE/PIB for 8 weeks. GLE/PIB for 12 weeks used to treat: (1) GT1 and GT2 F4 patients, (2) GT3 F0–F4 patients. For GT1 and GT2, we consolidate SVR for all F4 patients combining TN and TE patients. For GT3, we consolidate SVR in F0–F3 and F4 patients because of small sample sizes

^b EBR + GZR: GT1 patients are treated for 12 weeks

^c SOF/LDV: GT1 patients are treated with 12 weeks. We have consolidated SVR data for all GT2 patients by cirrhosis status or prior treatment history, but not both. Thus SVRs for TN and TE needs to be imputed; this is done using (1) the number of patients with TN and TE, respectively, (2) the cirrhosis distribution of the overall population, and (3) the difference between the SVRs of F0–F3 and F4 of the overall population

^d SOF + ribavirin: GT3 patients are treated for 24 weeks

costs) to the present year. Japanese guidelines support not inflating cost estimates [51]. The cost per course of a therapy was calculated by multiplying daily cost of the regimen [52] and

the mean (trial-based) duration of treatment. The DAA treatment options generally require little monitoring. Furthermore, these costs would be similar across the treatment options

considered in this evaluation. Therefore, we also assumed that there were no on-treatment monitoring costs. All data were deidentified when used for this analysis. This article does not contain any studies with human participants or animals performed by any of the authors and did not require institutional review.

Analysis

The model was developed following good modeling practices [53, 54]. We estimated the direct medical costs, liver outcomes, QALYs, and ICERs. Discount rates (costs, utilities and life years) in the base case were set to 2% as per Japanese guidelines [51, 55]. We assumed a payer WTP of JPY 5 million/QALY (USD 46,015/QALY) [56] as a threshold for assessing the cost-effectiveness of GLE/PIB with the net monetary benefit (NMB) approach [57]. The NMB is a summary statistic that represents the net value of an intervention compared to an alternative health technology, considering the WTP threshold per QALY. A positive NMB indicates that the intervention is cost-effective compared to the alternative at the given WTP threshold. The NMB approach was chosen in favor of ICERs to report results as the NMB was easier to interpret in a situation where a treatment option is dominant.

Base Case

In the base case analysis, we compared GLE/PIB to four DAAs and no treatment in treatment-naïve non-cirrhotic GT1 patients. We performed a sequential analysis to derive the cost-effectiveness frontier by eliminating sequentially dominated and extendedly dominated strategies.

In the context of multiple comparisons, pairwise comparisons of ICERs may be misleading [58]. To establish a complete comparison of treatment options, we performed a fully incremental analysis which involved calculating the incremental QALY gains and costs for treatment options and ranking them by ascending costs. Options that were dominated (i.e., more expensive and less effective than one

or more alternatives) or extendedly dominated (i.e., more expensive and less effective than a combination of two alternatives) were removed. The ICERs of each of the remaining options were then calculated as the additional costs divided by the additional QALYs by comparing one option with the next least costly [59]. If one treatment dominates all the others, either by dominance or extended dominance then only that treatment option is considered cost-effective. The sets of remaining treatment options form the cost-effectiveness frontier, which represented the set of points corresponding to treatment alternatives that were considered to be cost-effective at different values of the cost-effectiveness threshold [60]. Any option above, or to the left of the frontier, represented an inefficient option (i.e., suboptimal) as more QALYs were achievable at equal or lower costs (i.e., dominated or extendedly dominated) [59].

Scenario Analyses

In scenario analyses, we assessed the cost-effectiveness of GLE/PIB by varying the method of comparison or key model parameters. In scenario 1, we adopted a portfolio approach whereby a pan-genotypic ICER for the overall GT1–3 HCV population was derived. This overall ICER was calculated as a weighted average of patient segments defined by genotype, treatment history, and cirrhosis status, with weights based on the Japanese HCV population. In this scenario analysis, we reported findings of a GLE/PIB portfolio in GT1–3 versus a sofosbuvir (SOF)-based portfolio (namely SOF/LDV in GT1–2 and SOF + ribavirin in GT3). In scenarios 2 and 3, we varied the baseline age by ± 5 years, namely a “low” age of 61.5 years and a “high” age of 71.5 years. The impact of discount rates was explored in scenario 4 (0%) and scenario 5 (4%).

Sensitivity Analyses

Baseline demographics, background death rate, discount rates, regimen duration, and costs were not varied in deterministic sensitivity analyses (DSA) and probabilistic sensitivity

analyses (PSA). The non-treatment-specific variables tested in DSA included transition probabilities related to disease progression, health state costs, and health utilities. For the PSA, 500 simulations were drawn from the variables' distributions. For SVR rates, values of 100% were varied in the DSA and PSA using a method proposed by Briggs et al. [61]. Several parameters were tested in multi-way sensitivity analysis including SVR rates in patients without cirrhosis and the GT-specific fibrosis and non-fibrosis progression hazard ratios. As a result of the lack of data, PSA variation on treatment-related utility change was only possible for GLE/PIB where a normal distribution was assumed. The results of the PSAs are summarized graphically using cost-effectiveness acceptability curves (CEAC). Each point on a CEAC indicates the percentage of simulations where a treatment option is cost-effective compared to the other treatment option for a specific WTP per QALY. Each CEAC line is obtained by varying the payer WTP/QALY from JPY 0 to 20 million. For each treatment option the CEAC is the line indicating the percentage of simulations where that strategy yields the highest NMB compared to the other treatment options. When comparing multiple treatment options for each WTP/QALY, the sum of all lines add up to 100%. Table 1 provides details of DSA and PSA inputs.

RESULTS

Base Case

In the base case segmented analysis, we compared GLE/PIB to DAAs such as SOF/LDV, EBR + GZR, DCV/ASV/BCV as well as no treatment in GT1 treatment-naïve non-cirrhotic patients. Table 3 presents the clinical outcomes for the different treatment regimens using baseline parameter input values. In the base case the percentage of patients ever reaching more advanced liver disease (such as DCC, HCC, or liver transplant) or dying from a liver-related cause was lowest with GLE/PIB and SOF/LDV compared with the remaining DAA treatment regimens and no treatment. For instance the lifetime risks of DCC and HCC were 0.00%

and 3.66% for GLE/PIB and SOF/LDV, respectively. These lifetime risks were 0.25% and 4.99% for EBR + GZR, 0.30% and 5.27% for DCV/ASV/BCV, and 7.41% and 43.17% for no treatment.

Table 3 also presents results of a pairwise ICER analysis and a fully incremental analysis. In GT1 treatment-naïve non-cirrhotic patients, GLE/PIB was a dominant strategy compared to EBR + GZR, DCV/ASV/BCV, SOF/LDV, and no treatment: it conferred better outcomes at a lower cost.

Scenario Analysis

In scenario analysis, we ran an analysis using the portfolio approach where we compared a GLE/PIB portfolio versus a portfolio containing SOF/LDV in GT1–2 and SOF + ribavirin in GT3 patients (i.e., SOF portfolio). The long-term clinical outcomes of the GLE/PIB portfolio were close to those of the SOF portfolio (Table 4): GLE/PIB had a lower risk of DCC, HCC, liver transplant, and liver-related death. Table 4 also shows incremental results: with better outcomes (i.e., QALYs) at a lower cost, GLE/PIB dominated the SOF portfolio. Our base case conclusions were robust to scenarios in which we varied age insofar as GLE/PIB continued to dominate EBR + GZR, DCV/ASV/BCV, SOF/LDV, and no treatment. When we assumed a lower average age of patients with HCV, successfully treated patients gained more life years and QALYs. On the other hand, the older the average age of patients with HCV, the fewer QALYs accrued over a lifetime from successful treatment. Our scenario analyses suggested that there were higher benefits of treatment in a younger population. To further explore the impact of age, we derived the net NMB assuming a WTP threshold of JPY 5 million/QALY (USD 46,015/QALY) [56]. The NMB of GLE/PIB versus no treatment decreased by about 45% as mean patient age increased from 61.5 years (NMB = JPY 29,755,761 [USD 273,843]) to 71.5 years (NMB = JPY 16,256,617 [USD 149,610]). This analysis indicated that, although a younger population experienced greater benefits from treatment due to the

Table 3 Lifetime discounted costs and health benefits of treatment strategies: treatment-naïve GT1 patients without cirrhosis

Regimen	Percentage ever reaching (%)				Total costs, JPY ['000s ¥]	Total QALY ^a	Pairwise ICER ^b , JPY/QALY ['000s ¥]	ICER incremental ^c , JPY/QALY ['000s ¥]
	DCC	HCC	LrT	LrD				
GLE/PIB	0.00	3.66	0.05	2.74	4131	14.20	NA	NA
EBR + GZR	0.25	4.99	0.07	3.91	4996	14.07	– 6301	Dominated
DCV/ASV/BCV	0.30	5.27	0.07	4.15	5509	14.04	– 8200	Dominated
SOF/LDV	0.00	3.66	0.05	2.74	5678	14.20	– 542,502	Dominated
No treatment	7.41	43.17	0.67	37.56	6800	10.19	– 665	Dominated

DCC decompensated cirrhosis, DCV/ASV/BCV daclatasvir/asunaprevir/beclabuvir, *Dominated* more costly and less effective, EBR + GZR elbasvir/grazoprevir, GLE/PIB glecaprevir/pibrentasvir, GT genotype, HCC hepatocellular carcinoma, ICER incremental cost-effectiveness ratio, JPY Japanese yen [¥], LrD liver-related death, LrT liver transplant, QALY quality-adjusted life year, SOF/LDV sofosbuvir/ledipasvir

^a Total QALY for GLE/PIB = 14.204 (to 3 decimal places) and for SOF/LDV = 14.202 (3 decimal places)

^b Pairwise ICER = incremental cost divided by incremental QALY for all regimens compared with GLE/PIB

^c ICER incremental = fully incremental cost-effectiveness analysis. In the table above, GLE/PIB is the least costly of all treatment options and, aside from SOF/LDV, it generates higher QALYs. Thus GLE/PIB dominates all alternatives including SOF/LDV as GLE/PIB is less costly

Table 4 Lifetime discounted costs and health benefits of treatment strategies in the portfolio approach

Outcome	Percentage ever reaching (%)				Total costs, JPY ['000s ¥]	Total QALYs	ICER, JPY/QALY
	DCC	HCC	LrT	LrD			
GLE/PIB portfolio	0.20	8.29	0.11	6.42	4901	13.86	NA
SOF-based portfolio ^a	0.45	8.30	0.12	6.61	6312	13.83	SOF-based portfolio dominated

Even though the total QALYs were comparable, the GLE/PIB portfolio was significantly less costly than the SOF-based portfolio. Therefore the SOF-based portfolio was dominated by the GLE/PIB portfolio

DCC decompensated cirrhosis, *Dominated* more costly and less effective, GLE/PIB glecaprevir/pibrentasvir, GT genotype, HCC hepatocellular carcinoma, ICER incremental cost-effectiveness ratio, JPY Japanese yen [¥], LrD liver-related death, LrT liver transplant, QALY quality-adjusted life year, SOF sofosbuvir

^a In the portfolio approach SOF portfolio is made up of SOF/LDV in GT1–2 and SOF + ribavirin in GT3 patients

expected life duration after the treatment, the benefits were still cost-effective with an older population as the NMB remained positive.

Increasing the discount rate lowered the present value of future costs and outcomes

leading to lower total lifetime costs and QALYs. In the scenarios where discount rates were set to zero and 4%, the conclusions of the incremental analysis were unchanged from the base case. Quantitatively the NMB of GLE/PIB versus the

second least costly option, EBR + GZR, decreased as the discount rate increased from 0% (NMB = JPY 1,820,109 [USD 16,750]) to 4% (NMB = JPY 1,365,476 [USD 12,566], assuming a WTP threshold of JPY 5 million/QALY (USD 46,015/QALY) [56].

Results of Uncertainty Analysis

Deterministic Sensitivity Analyses: Key Results

A DSA was conducted using the NMB approach for the cost-effectiveness analysis of GLE/PIB compared with SOF/LDV in GT1 treatment-naïve non-cirrhotic patients by varying the base case parameter values across their assumed ranges and assuming a payer WTP of JPY 5 million/QALY. Efficacy of both the intervention and comparator was equal and at their maximum value of 100%; thus the outcomes of both regimens were identical, i.e., only varying SVR rates affected model outcomes.

For completeness we presented results of the DSA for the portfolio approach (the cost-effectiveness analysis of the GLE/PIB portfolio compared to the SOF portfolio) (Fig. 2). Results were most sensitive to SVR rates and to a smaller extent health utility of SVR for patients (history of F4).

Fig. 2 DSA results showing the 10 most influential disease model parameters in the portfolio approach comparing the GLE/PIB portfolio to the SOF portfolio. DCC decompensated cirrhosis, DSA deterministic sensitivity analysis, F0–F3 no cirrhosis, F4 compensated cirrhosis, GLE/PIB

Probabilistic Sensitivity Analyses: Key Results

Figure 3 presents the cost-effectiveness acceptability curves for all DAAs included in the analysis in the GT1 treatment-naïve non-cirrhotic population. At a WTP threshold of JPY 5 million/QALY, GLE/PIB was the optimal treatment in 99.4% of simulations. This remained at 99.0% of simulations when we increased the WTP threshold to JPY 7 million/QALY. Furthermore GLE/PIB was the only treatment option on the cost-effectiveness acceptability frontier. At a WTP threshold of JPY 5 million/QALY, EBR + GZR was cost-effective in 0.6% of simulations. At a WTP threshold of JPY 9 million/QALY, SOF/LDV was cost-effective in 0.2% of simulations; these probabilities rose to 1.6% and 4.6% for EBR + GZR and SOF/LDV, respectively, at JPY 20 million/QALY.

Figure 4 presents the PSA in the portfolio analysis where the GLE/PIB portfolio was compared to the SOF portfolio. At a WTP threshold of JPY 5 million/QALY, GLE/PIB was the optimal treatment strategy in 100.0% of simulations. At a WTP threshold of JPY 20 million/QALY or below, GLE/PIB was the optimal treatment strategy in at least 69.4% of simulations.

glecaprevir/pibrentasvir, HCC hepatocellular carcinoma, JPY Japanese yen [¥], NMB net monetary benefit (in JPY), SOF sofosbuvir, SVR sustained virologic response, TP transition probability. The NMB assumes a payer willingness-to-pay of JPY 5 million per quality-adjusted life year

Fig. 3 Cost-effectiveness acceptability curves in genotype 1 treatment-naïve non-cirrhotic patients

DISCUSSION

To our knowledge this is the first analysis of the cost-effectiveness of GLE/PIB against other DAAs in Japan. We found that GLE/PIB was associated with higher QALY gains due to improved SVR and long-term health outcomes. Our study suggested that in a population of Japanese patients with HCV, GLE/PIB was a dominant strategy compared to EBR + GZR, SOF/LDV, DCV/ASV/BCV, and no treatment as it conferred better outcomes at a lower cost. The QALYs for GLE/PIB and SOF/LDV were close—14,204 versus 14,202, respectively. Thus assuming QALYs were similar, GLE/PIB would be cost-minimizing compared to SOF/LDV, which is a more conservative interpretation of the results than characterizing GLE/PIB as dominant to SOF/LDV. The base case results persisted across different scenarios as well as DSA and PSA.

The model had several strengths. It was developed in line with previously published models [58], which improved consistency with previous health technology assessments [62, 63], facilitated comparisons with other technologies, and supported the validity of the model results. Secondly, the model used Japanese-based input parameters to model disease progression and health state utilities; where

available, SVR data were also extracted directly from published clinical trials conducted in Japan. To the extent that some treatment options approved in Japan are not commonly used elsewhere, our study broadens our knowledge of available treatment options to treat HCV. Third, we assessed model validity in terms of technical validation, internal validation, and external validation. To assess external validity of the model, the model's estimates of compensated cirrhosis in untreated GT1 patients with F0 were generated. The base case model predicted that 20.9% of patients would have a history of compensated cirrhosis 20 years post-infection, which was concordant with rates from other HCV studies [16, 64–67]. Fourth, we included two modeling approaches: the portfolio approach and the segmented approach; this facilitated the assessment of GLE/PIB from the perspective of both broadly and narrowly defined markets. Finally, we included probabilistic and deterministic sensitivity analyses to assess the robustness of the results.

The model also had several limitations. Most phase III HCV clinical trials had single arms and indirect evidence obtained through a common comparator was unavailable. We could not conduct a robust network meta-analysis because of the paucity of data [49, 50]. Aligned with previous cost-effectiveness analyses in HCV, we

Fig. 4 Cost-effectiveness acceptability curves using the portfolio approach comparing the GLE/PIB portfolio to the SOF portfolio. *GLE/PIB* glecaprevir/pibrentasvir, *SOF* sofosbuvir

extracted and compared data directly from clinical trials [16, 18, 33]. Even though GLE/PIB is indicated in GT1–6, we only conducted the analyses in GT1–3. As reported by Mochida et al., there were no GT4–6 patients recruited in the GLE/PIB Japan PMOS [34]. Although GT3–6 patients were eligible to enroll, only GT3 patients ended up being recruited. Thus the approval of GLE/PIB in GT3–6 patients in Japan was based on clinical trial data in GT3 patients. Therefore we excluded GT4–6 because of the lack of data. The model did not include monitoring costs and treatment-related AE costs primarily because of the lack of reliable costs data. However given that DAAs generally require little monitoring and have low AE rates, we did not believe that the overall monitoring and AE cost would be influential to the analysis. Secondly, as a result of the absence of robust data, the model included the conservative assumption that there was no spontaneous remission from F0 and no viral reinfection. Future research to inform these parameters would be beneficial. There was limited information on the demographics of patients with chronic HCV in Japan. As a result, baseline data for patient distribution across genotypes, treatment history, and fibrosis distribution were estimated using the PMOS of GLE/PIB [34].

To determine how these and other limitations affected our findings, we conducted DSA

and PSA where inputs were varied across a range of plausible values. For these analyses, treatment history, background mortality rate, and the duration and costs of the regimen were not varied. The DSA and PSA confirmed the robustness of our findings in our base case and scenario analyses. In DSA, SVR rates were the most influential parameters: SVR differences between the intervention and comparator were not large (or even zero); QALY differences, which are affected by SVR and treatment-related disutility, were in turn small. Thus the denominator of the cost-effectiveness ratio was small, and changes in SVR had a relatively large impact on the upper and lower bounds of the ICERs. We relied on Japanese trials which had relatively small sample sizes within each patient segment. This led to wide confidence intervals around SVR as illustrated in the tornado diagram. We also introduced the method suggested by Briggs et al. [61] to add variation to the SVR rates that were 100%, thus allowing for parameter uncertainty. In fact the method by Briggs penalized trials with smaller samples such as the GLE/PIB trials. Though analytically robust our results may not be broadly generalizable to the Japanese population because of the small sample sizes of the clinical trials and the lack of published data on the demographic characteristics of Japanese patients with chronic HCV. Better characterizations of these parameters will

be beneficial for future assessments of the economic implications of various therapeutic options for HCV infection. Nevertheless real-world evidence studies of GLE/PIB are emerging from multiple cohorts with close to 10,000 patients across various countries, supporting the safety and efficacy in real-world settings [68] including Asian populations: Ogawa et al. [69] in Japan and Hsu et al. in Taiwanese patients [70]. Ogawa et al. [69] studied a cohort of 314 Japanese patients: 122 GT1 and 192 GT2. They reported 12-week SVR rates in GT1 and GT2 patients of 99.2% and 98.9%, respectively. In addition they found that serious adverse events were rare with discontinuation due to an adverse event observed in only 1.6% of patients.

CONCLUSION

In GT1 treatment-naïve non-cirrhotic patients compared with SOF/LDV, EBR + GZR, DCV/ASV/BCV, and no treatment, GLE/PIB demonstrated superior efficacy, lower probabilities of progressing to advanced stages of liver disease or dying from liver-related causes, and higher QALY gains. GLE/PIB was a dominant strategy compared to EBR + GZR, DCV/ASV/BCV, SOF/LDV, and no treatment: it conferred better outcomes at a lower cost. In portfolio analysis, we compared the GLE/PIB portfolio versus a SOF-based portfolio comprising SOF/LDV in GT1–2 and SOF + ribavirin in GT3. The GLE/PIB portfolio dominated the SOF-based portfolio. Our results remained consistent during sensitivity analyses. Our analysis offers important preliminary insight into the cost-effectiveness of novel DAA treatments for patients with HCV for the public healthcare payers in Japan.

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