Research Article
Viral Hepatitis

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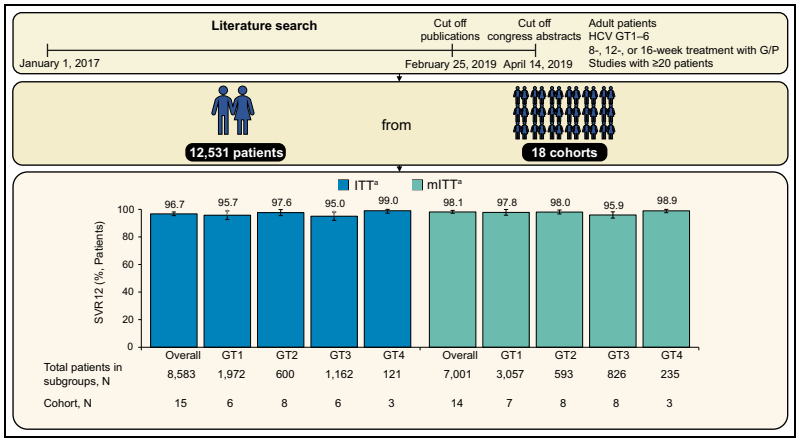
Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: A meta-analysis

Graphical abstract



Highlights

- Meta-analysis of real-world data from 12,583 patients taking glecaprevir/pibrentasvir.
- Glecaprevir/pibrentasvir achieved 96.7% virologic cure overall.
- Virologic cure was ≥95% across subgroups of interest.
- Serious adverse events were reported in 1.0% of patients.
- Effectiveness and safety results were consistent with those from clinical trials.

Authors

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Lay summary

It is important to assess treatments for hepatitis C virus (HCV) in the real world, as patient populations tend to be more diverse and potentially less adherent to treatment compared to those in clinical trials. Results from 18 studies performed in real-world clinics were pooled and analyzed to investigate the effectiveness and safety of a direct-acting antiviral combination (glecaprevir/pibrentasvir) in routine clinical practice. This analysis showed that glecaprevir/pibrentasvir is highly effective and well tolerated across all HCV genotypes and patient groups studied. It also showed that results seen in the real world are similar to the results seen in clinical trials, even in patients historically considered more challenging to treat.

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Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: A meta-analysis

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Background & Aims: Glecaprevir/pibrentasvir is approved for treating adults infected with HCV genotypes 1–6. In clinical trials, glecaprevir/pibrentasvir was associated with high rates of sustained virologic response at post-treatment week 12 (SVR12) and was well tolerated. A systematic review and meta-analysis of the real-world effectiveness and safety of glecaprevir/pibrentasvir were undertaken.

Methods: Real-world studies reporting SVR12 in adults with HCV infection (n ≥20) treated with glecaprevir/pibrentasvir were identified in journal publications from January 1, 2017, to February 25, 2019, and congress presentations through April 14, 2019. Random-effects meta-analysis was used to determine SVR12 rates using data from ≥2 cohorts; intention-to-treat (ITT) analyses included patients treated with glecaprevir/pibrentasvir who had SVR12 data available, discontinued early, or were lost to follow-up; modified ITT (mITT) analyses excluded those with non-virologic failure. Naïve pooling was used to calculate adverse event (AE) rates.

Results: Overall, 12,531 adults were treated with glecaprevir/pibrentasvir (18 cohorts). Of patients with post-treatment week 12 data, SVR12 rates were 96.7% (95% CI 95.4–98.1) in the ITT population (n = 8,583, 15 cohorts) and 98.1% (95% CI 97.1–99.2) in the mITT population (n = 7,001, 14 cohorts). SVR12 rates were ≥95% across subgroups (HCV genotype, cirrhosis status, treatment history, treatment duration, on-label treatment, and subgroups of interest). AEs were reported in 17.7% (1,271/7,199) of patients (8 cohorts). Serious AEs were reported in 1.0% (55/5,522) of patients (6 cohorts). The most frequent AEs were pruritus, fatigue, and headache. AE-related treatment discontinuations were reported in 0.6% (33/5,595) of patients (6 cohorts).

Conclusions: Consistent with clinical trials, real-world evidence indicates that glecaprevir/pibrentasvir is a well-tolerated and highly effective pangenotypic treatment for a broad range of HCV-infected patients.

Lay summary: It is important to assess treatments for hepatitis C virus (HCV) in the real world, as patient populations tend to be more diverse and potentially less adherent to treatment compared to those in clinical trials. Results from 18 studies performed in real-world clinics were pooled and analyzed to investigate the effectiveness and safety of a direct-acting antiviral combination (glecaprevir/pibrentasvir) in routine clinical practice. This analysis showed that glecaprevir/pibrentasvir is highly effective and well tolerated across all HCV genotypes and patient groups studied. It also showed that results seen in the real world are similar to the results seen in clinical trials, even in patients historically considered more challenging to treat.

Introduction

Glecaprevir/pibrentasvir is a pangenotypic, direct-acting antiviral (DAA) drug regimen, given as a once-daily, all-oral, interferon (IFN)-free, ribavirin (RBV)-free, fixed-dose combination. It was approved for the treatment of patients with chronic HCV genotypes (GT) 1–6 infection in the European Union in July 2017,[1] in the United States in August 2017,[2] and in Japan in September 2017.[3] The duration of glecaprevir/pibrentasvir therapy depends on prior HCV treatment, cirrhosis status, and HCV GT.[1,2] In HCV treatment-naïve patients, treatment for 8 weeks is recommended for patients without cirrhosis or with compensated cirrhosis for all GTs.[1,2] In HCV treatment-experienced

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patients (who failed prior treatment with pegylated IFNα + RBV ± sofosbuvir, or sofosbuvir + RBV) with GT1, 2, 4–6 infection, treatment for 8 weeks is recommended for those without cirrhosis, while 12 weeks is recommended for those with compensated cirrhosis.[1,2] In HCV treatment-experienced patients with GT3 infection, treatment for 16 weeks is recommended, irrespective of cirrhosis status,[1,2] although European Association for the Study of the Liver guidelines recommend treatment for 12 weeks in treatment-experienced, non-cirrhotic, GT3-infected patients.[4] In the United States, treatment for 16 weeks is also recommended for patients with GT1 infection who were previously treated with an NS5A inhibitor (but not an NS3/4A protease inhibitor) and 12 weeks in patients previously treated with an NS3/4A protease (but not an NS5A inhibitor), irrespective of cirrhosis status.[2] In Japan, DAA-naïve, non-cirrhotic patients with HCV GT1 or 2 infection are treated for 8 weeks with glecaprevir/pibrentasvir. Patients with HCV GT3–6 infection, those with compensated cirrhosis, and DAA-experienced patients are treated for 12 weeks.[3]

In phase II and III multinational clinical studies, glecaprevir/pibrentasvir treatment resulted in high rates of sustained virologic response at post-treatment week 12 (SVR12) and a favorable safety profile in a broad range of patients with chronic HCV infection.[1,2] In the overall intention-to-treat (ITT) population, SVR12 was achieved in 97.5% of patients with chronic HCV infection who were treated for the recommended duration, irrespective of prior HCV treatment experience or the presence of cirrhosis.[1] Data from clinical trials and additional subgroup analyses have also shown that glecaprevir/pibrentasvir is efficacious in some ITT patient populations historically considered more challenging to treat, including patients aged ≥65 years (SVR12: 97.9%),[5] those with recent or former drug use (SVR12: 96.3%),[6] those receiving opioid substitution therapy (OST; SVR12: 96.2%),[7] patients with severe chronic kidney disease (CKD) including those requiring dialysis (SVR12: 98.4%),[8] liver or kidney transplant recipients (≥3 months post-transplant; SVR12: 98.0%),[9] and patients coinfected with human immunodeficiency virus (SVR12: 98.0%).[10]

In routine clinical practice, DAA effectiveness may be lower than that seen in clinical trials because patient populations tend to be more diverse and potentially less adherent to treatment.[11,12] For many DAA regimens, a similar efficacy in real-world settings to that observed in clinical trials has already been confirmed.[13,14] However, as glecaprevir/pibrentasvir was approved for the treatment of patients with chronic HCV in the latter part of 2017, published data regarding its use in clinical practice are currently limited to a small number of real-world cohorts.[15,16] Furthermore, analyses of distinct settings and a broader analysis combining different settings and countries are currently lacking. To address this, we undertook a systematic review and meta-analysis of available real-world data reporting the effectiveness and/or safety of glecaprevir/pibrentasvir for the treatment of adults with chronic HCV infection.

Materials and methods

Systematic review and screening

A literature search was undertaken to identify any real-world studies published in English from January 1, 2017, to February 25, 2019, using the search terms: (hepatitis C OR hepacivirus OR HCV) AND ([glecaprevir AND pibrentasvir]) OR Maviret OR Mavyret) AND (real world). The following databases were searched: BIOSIS (EBSCO, Ipswich, MA), Derwent Drug File (Ovid, New York, NY), Embase® (Elsevier, Amsterdam, Netherlands), International Pharmaceutical Abstracts (EBSCO, Ipswich, MA), MEDLINE® (National Network of Libraries of Medicine, Bethesda, MD), and SciSearch (Clarivate Analytics, London, UK). Embase was also used to search local/regional and international conference abstracts, posters, and oral presentations using the same search terms. In addition, conference-specific websites were queried up to April 14, 2019.

Abstracts and their titles were manually screened to identify eligible prospective or retrospective real-world cohort studies (comparative and non-comparative) in which glecaprevir/pibrentasvir was used to treat chronic HCV infection in adults (≥20 patients) and in which SVR12 and/or safety parameters were reported. Clinical trials, case reports, and studies that did not distinguish glecaprevir/pibrentasvir-treated patients from other patients were excluded.

Efficacy

Efficacy outcomes were the overall SVR12 rate in the ITT population (*i.e.*, all patients treated with at least one dose of glecaprevir/pibrentasvir who had SVR12 data available, discontinued early, or were lost to follow-up). SVR12 rates in the following subgroups of interest (ITT populations) were evaluated: HCV GT (GT1, 2, 3, 4, 5, or 6), cirrhosis status (no cirrhosis or compensated cirrhosis), HCV treatment history (treatment naïve or treatment experienced [prior HCV treatment with IFN, pegylated-IFN, RBV, and DAAs according to local labels]), and glecaprevir/pibrentasvir treatment duration (8, 12, or 16 weeks). These analyses were also undertaken in the modified ITT (mITT) population (*i.e.*, the ITT population excluding patients who did not achieve SVR12 for reasons other than virologic failure). Of note, in the Veterans Affairs (VA) cohort, the mITT population was defined as all patients who received the label-recommended duration of glecaprevir/pibrentasvir; thus, it excluded patients who prematurely discontinued drug but did not exclude patients who did not have SVR12 data. As a result, sensitivity analyses of efficacy of the mITT population excluding data from the VA cohort were also undertaken.

Other efficacy outcomes were SVR12 rates in treatment-naïve patients who received on-label glecaprevir/pibrentasvir treatment (mITT and ITT populations) and treatment-naïve and treatment-experienced patients in the following subgroups of interest (mITT populations): severe fibrosis (F3; data included only where F3 was specified), alcohol abuse/dependency, CKD stage 4–5, OST, psychiatric disorder, and proton-pump inhibitor (PPI) use. Treatment-experienced patients who received on-label glecaprevir/pibrentasvir were not analyzed as insufficient data were reported.

Safety

Safety outcomes were the percentages of patients with adverse events (AEs; any grade), common AEs, serious AEs (SAEs), AE of special interest (hepatic decompensation or liver failure), and discontinuation due to AEs. Patients from cohorts reporting any of these data categories were included in the safety population. Analyses of each AE category included only those cohorts reporting those data.

Data extraction and meta-analysis

Data extraction was performed manually by one reviewer and validated by a second independent reviewer. The following rules

for data abstraction were applied: if the number of patients in the total study population was not available, the number of patients used for the estimation of SVR12 in the ITT population was applied instead; the number of patients used for the estimation of SVR12 in the ITT population was applied to the mITT population if SVR12 in the ITT population was 100%. Patient numbers were summed across the different GTs if the number of patients in the total study population was not available. If additional patients were excluded beyond virologic failures, these patients were not used in the mITT population analyses. If data for patients infected with GT4–6 were reported in combination, these values were not used to determine SVR12 by GT. The VA does not collect information on the prescribed treatment regimen; therefore, the VA cohort was excluded from the on-label treatment analyses.

Data were analyzed only if reported in at least 2 cohorts. Random-effects meta-analysis was used to determine SVR12 rates in R with the metafor package.[17] The I^2 statistic was used to measure statistical heterogeneity between studies. The I^2 statistic estimates the percentage of variability across studies due to heterogeneity rather than chance. Heterogeneity was considered substantial if I^2 ≥50%.[18] The safety population included all the patients for whom AE rates were reported. Naïve pooling was used to calculate the following AE rates: overall AE rate, rates of most frequently reported AEs, and the rate of AEs leading to discontinuations.

Results

Data sources and patient population

Fig. 1 shows the results of the systematic publication review and screening process. The database and congress search identified 119 publications, of which 101 were deemed ineligible after screening (see Fig. 1 for reasons). The final 18 publications included data from 18 unique patient cohorts eligible for analysis, including 3 cohorts from published journal articles (all published in 2019)[16,19,20] and 15 cohorts from conference abstracts (4 published in 2019 and 11 in 2018).[21–35] Seven studies were undertaken in Europe,[16,21–26] 6 in Japan,[19,20,27–29,35] and 3 in the United States;[30–32] there were 2 multi-country studies.[33,34] In total, data from 12,531 adults with chronic HCV infection treated with glecaprevir/pibrentasvir were analyzed. Brief details of the studies included and the baseline demographics and disease characteristics of the patients enrolled in these studies are shown in Table S1.

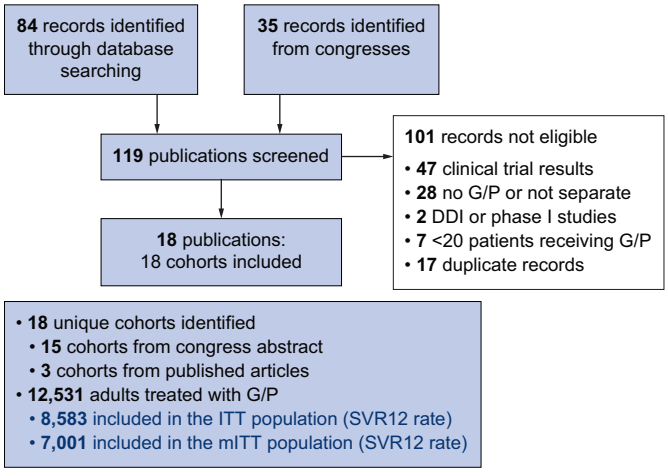

Fig. 1. Screening of publications and congress abstracts. DDI, drug–drug interaction; G/P, glecaprevir/pibrentasvir; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

Efficacy analyses: SVR12 rates, overall and by subgroups

Of the 12,531 patients included in the 18 studies, SVR12 data from 8,583 patients were included in the meta-analysis of the ITT population (reported in 15 of the 18 studies). This included all patients who had SVR12 data available, discontinued early, or were lost to follow-up. SVR12 rates in the individual cohorts of the ITT population ranged from 92.1% to 100% (Fig. 2). Results from the 7,001 patients who had SVR12 data available were included in the meta-analysis of the mITT population (reported in 14 of 18 studies; 11 [n = 6,091] that also reported SVR12 in the ITT population and 3 [n = 910] that only reported SVR12 in the mITT population). SVR12 rates in the individual cohorts of the mITT population ranged from 92.2% to 100% (Fig. 2).

The results from the meta-analysis showed that overall SVR12 rates with glecaprevir/pibrentasvir were 96.7% (95% CI 95.4–98.1, I^2 = 93.1%) in the ITT population (n = 8,583) and 98.1% (95% CI 97.1–99.2, I^2 = 92.3%) in the mITT population (n = 7,001), both with considerable heterogeneity between studies (Fig. 3). The significant heterogeneity was further examined by excluding the VA study in ITT and mITT populations. The values of I^2 after excluding the VA study (I^2 = 90.1% in ITT; I^2 = 25.1% in mITT) showed that the significant heterogeneity in the mITT population was caused by the VA study, and SVR12 rates in the mITT population had much greater consistency between studies than in the ITT population when the VA study was excluded. The SVR12 rate for GT1 (n = 1,972; 6 cohorts) was 95.7% (95% CI 92.6–98.8), for GT2 (n = 600; 8 cohorts) was 97.6% (95% CI 95.4–99.8), for GT3 (n = 1,162; 6 cohorts) was 95.0% (95% CI 92.0–98.0), and for GT4 (n = 121; 3 cohorts) was 99.0% (95% CI 97.2–100) (Fig. 3). There were insufficient published cohort data to evaluate SVR12 rates for patients infected with HCV GT5 or GT6.

The estimate for SVR12 rate in the ITT population without cirrhosis (n = 4,123; 5 cohorts) was 97.0% (95% CI 94.3–99.7) and in those with compensated cirrhosis (n = 676; 6 cohorts) was 97.8% (95% CI 96.4–99.2) (Fig. 4A). ITT data were reported in <2 cohorts of HCV treatment-naïve patients and, therefore, only data in the subgroup of patients who were treatment experienced were analyzed. In HCV treatment-experienced patients (ITT population; n = 262; 6 cohorts), the SVR12 rate was 97.4% (95% CI 95.5–99.3) (Fig. 4B). The estimates for SVR12 rates in the ITT population prescribed glecaprevir/pibrentasvir for either 8 weeks (n = 1,781; 4 cohorts) or 12 weeks (n = 624; 5 cohorts) were 96.5% (95% CI 93.0–100) and 96.0% (95% CI 93.0–99.1), respectively (Fig. 4C). There were insufficient published cohort data available to evaluate SVR12 rates for patients prescribed 16 weeks of glecaprevir/pibrentasvir treatment (GT3-infected, treatment-experienced patients).

SVR12 rates for the mITT populations were similar to those in the ITT populations for all subgroups (Fig. 3 and 4A–C). In a sensitivity analysis that excluded the VA cohort, SVR12 rates for the mITT populations were 98.9% overall and 99.6%, 98.9%, 97.2% and 98.9% for GT1, GT2, GT3, and GT4 subgroups, respectively (Fig. S1). SVR12 rates were also improved in subgroups by cirrhosis status, treatment experience, and treatment duration when the VA cohort was excluded (Fig. S2A–C).

Short title/data source	Primary author	Country	Patients, N	ITT SVR12, % (n/N)	mITT SVR12, % (n/N)
VA Registry (US)[28,a]	Belperio	US	1,940	92.1 (1,496/1,625)	92.2 (1,076/1,167)
Spanish HepaC Cohort[24]	Puigvehi	Spain	1,581	97.7 (1,190/1,218)	98.9 (1,190/1,203)
Global G/P PMOS[31]	NA	Global	1,276	98.6 (712/722)	98.9 (712/720)
German Hepatitis-C Registry[19]	Wiegand	Germany	1,242	97.2 (592/609)	99.5 (592/595)
Italian MISTRAL[20]	Aglitti	Italy	1,177	99.4 (974/980)	
Trio (US)[29]	Flamm	US	1,131	92.7 (1,049/1,131)	98.4 (1,049/1,066)
Japan Registry[25]	Higuchi	Japan	798	99.0 (300/303)	99.0 (300/303)
England NHS Registry[22,b]	Drysdale	UK	773	97.9[c] (757/773)	
Target HCV[32]	Sterling	Global	726		97.3 (467/489)
Italian NAVIGATORE-Lombardia[16]	D'Ambrosio	Italy	723	94.1 (680/723)	99.3 (680/685)
Japan Tamori[26]	Tamori	Japan	434		97.5 (357/366)
Scottish HCV Registry[21]	Boyle	Scotland	354	97.0 (288/297)	99.0 (285/288)
Japan Uemura[27]	Uemura	Japan	131	95.6 (87/91)	
Austrian Real-life Cohort[23]	Gschwantler	Austria	116	100 (40/40)	100 (40/40)
Kaiser Permanente (US)[30]	Saxena	US	50		100 (47/47)
Japan DAA-experienced[17]	Osawa	Japan	30	93.3 (28/30)	
Japanese GT2 retreatment[33]	Kusakabe	Japan	29	100 (21/21)	100 (21/21)
Japan DAA-experienced[18]	Akuta	Japan	20	100 (20/20)	100 (20/20)

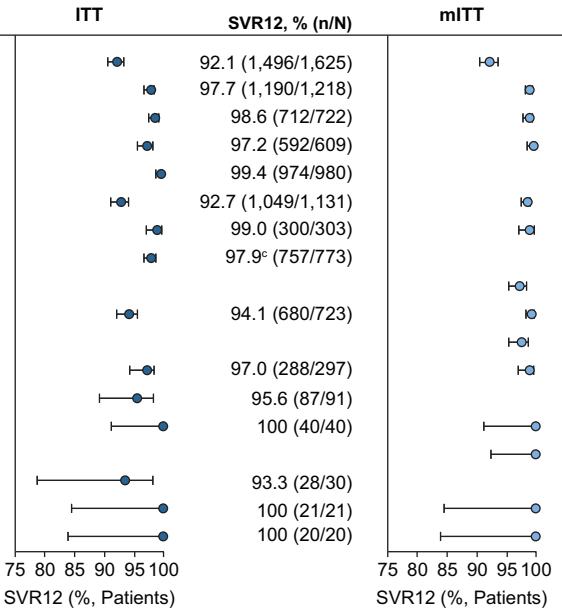

Fig. 2. SVR12 rates in the ITT and mITT populations in each study included in the meta-analysis. [a]ITT population excluded patients treated for less than 8 weeks; mITT population included patients who received US on-label treatment duration but did not exclude those with missing SVR12 data. [b]Number of patients in the study was imputed using number of patients in the ITT population. [c]SVR12 rate deduced from graphs using total N provided in the oral presentation. Error bars represent 95% confidence intervals. DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; ITT, intention-to-treat; mITT, modified intention-to-treat; NA, not applicable; NHS, National Health Service; PMOS, post-marketing observational study; SVR12, sustained virologic response at post-treatment week 12; VA, Veterans Affairs.

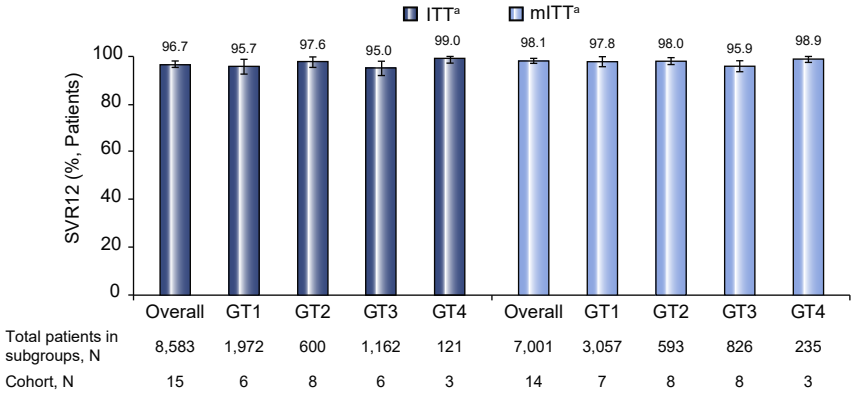

Fig. 3. SVR12 rates overall and by HCV genotype. [a]ITT population included patients treated with ≥1 dose of glecaprevir/pibrentasvir and with SVR12 data available, discontinued early, or who were lost to follow-up; mITT population excluded patients who did not achieve SVR12 for reasons other than virologic failure. ITT and mITT analyses included patients from different cohorts. 11 cohorts included both ITT and mITT SVR12 results. Error bars represent 95% confidence intervals. GT, genotype; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

The virologic failure rate in the mITT population was 2.4% (n/N = 165/7,001). Of the 165 virologic failures, 91 patients from the VA cohort were considered virologic failures as they did not have SVR12 data in the mITT population.[30] When data from the VA cohort were excluded (sensitivity analysis), the virologic failure rate in the mITT population was 1.2% (74/5,834). No information was available on resistance-associated substitutions.

SVR12 rates in treatment-naïve patients who received on-label treatment and by subgroup of interest

The SVR12 rate in the ITT population for treatment-naïve patients without cirrhosis who received on-label treatment (glecaprevir/pibrentasvir for 8 weeks; n = 697; 2 cohorts) was 98.2% (95% CI 96.7–99.6). The mITT SVR12 rate for treatment-naïve patients without cirrhosis who received on-label treatment for 8 weeks (n = 3,657; 9 cohorts) was 99.3% (95% CI 98.8–99.7); SVR12 rates for GT1–4 ranged from 98.3% to 99.6% (Fig. 5A). There were insufficient ITT data available (<2 cohorts) for treatment-naïve patients with compensated cirrhosis who received on-label treatment (glecaprevir/pibrentasvir for 12 weeks). The mITT SVR12 rate in patients with compensated cirrhosis who received on-label treatment for 12 weeks (n = 362; 7 cohorts) was 99.0% (95% CI 97.9–100) (Fig. 5B).

There were insufficient data available (<2 cohorts) for an analysis of SVR12 rates in the ITT population for subgroups of interest. SVR12 rates in the mITT population, in subgroups of interest, were as follows: F3 fibrosis (n = 181; 4 cohorts): 98.5% (95% CI 96.8–100); OST (n = 301; 4 cohorts): 98.9% (95% CI

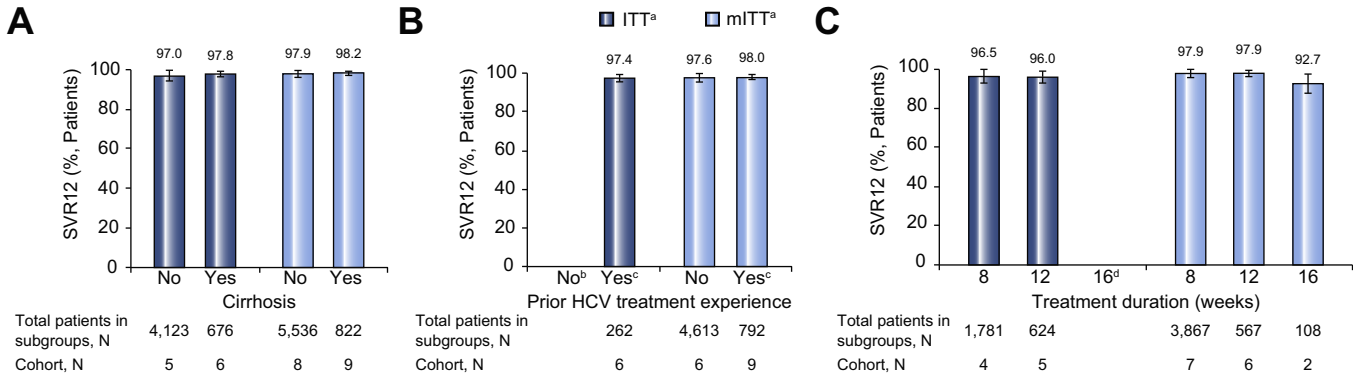

Fig. 4. SVR12 rates by subgroups. (A) Cirrhosis status; (B) Prior HCV treatment experience; (C) Prescribed treatment duration. [a]ITT population included patients treated with ≥1 dose of glecaprevir/pibrentasvir and with SVR12 data available, discontinued early, or who were lost to follow-up; mITT population excluded patients who did not achieve SVR12 for reasons other than virologic failure. ITT and mITT analyses included patients from different cohorts. [b]Data in treatment-naïve ITT populations reported in <2 cohorts. [c]Treatment experience included prior HCV treatment with (pegylated) interferon, ribavirin, and/or DAAs according to local labels. [d]Data for 16 weeks' treatment duration in ITT populations reported in <2 cohorts. Error bars represent 95% confidence intervals. DAA, direct-acting antiviral; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

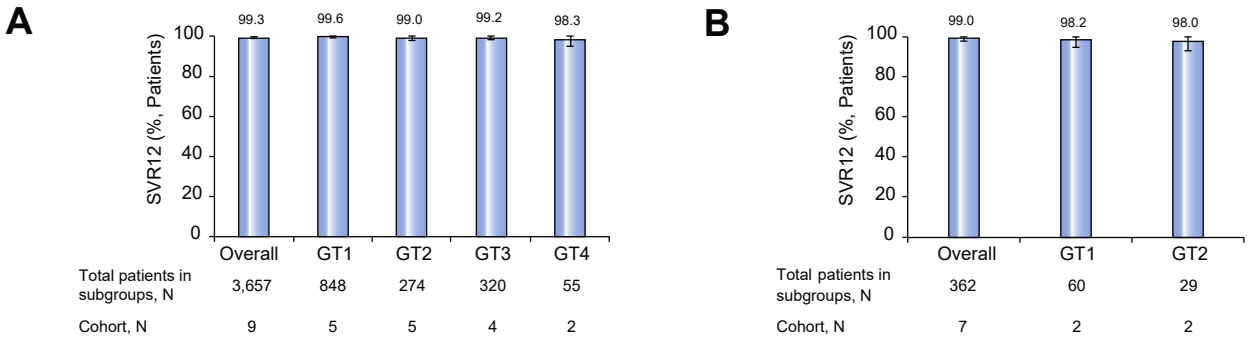

Fig. 5. SVR12 rates in patients receiving on-label treatment (mITT population[a]). (A) Treatment-naïve patients without cirrhosis who received treatment for 8 weeks; (B) Treatment-naïve patients with cirrhosis who received treatment for 12 weeks.[b] [a]mITT population excluded patients from the ITT population who did not achieve SVR12 for reasons other than virologic failure. [b]GT3 and GT4 reported in 1 cohort. Error bars represent 95% confidence intervals. GT, genotype; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

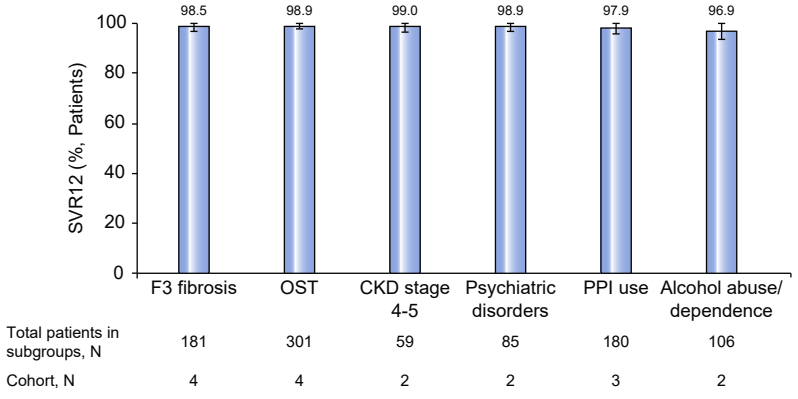

Fig. 6. SVR12 rates in patient subgroups of interest (mITT population[a]). [a]mITT population excluded patients from the ITT population who did not achieve SVR12 for reasons other than virologic failure. Error bars represent 95% confidence intervals. CKD, chronic kidney disease; ITT, intention-to-treat; mITT, modified intention-to-treat; OST, opioid substitution therapy; PPI, proton pump inhibitor; SVR12, sustained virologic response at post-treatment week 12.

97.8–100); CKD stage 4–5 (n = 59; 2 cohorts): 99.0% (95% CI 96.5–100); psychiatric disorder (n = 85; 2 cohorts): 98.9 (95% CI 96.8–100); PPI use (n = 180; 3 cohorts): 97.9% (95% CI 95.8–100); alcohol abuse/dependency (n = 106; 2 cohorts): 96.9% (95% CI 93.6–100) (Fig. 6).

Safety analysis

Safety data were summarized for 7,199 patients (safety population; 8 cohorts), and AEs were reported in 1,271 patients (17.7%, Table 1). No single AE was reported with a frequency above 5%; the most frequently reported AEs were pruritus (4.7%), fatigue

Table 1. Patients with AEs (safety population).

AEs	% (n/N)	Cohorts, N[a]
Any AE	17.7 (1,271/7,199)	8
Any SAE	1.0 (55/5,522)[b]	6
Any AE leading to discontinuation	0.6 (33/5,595)	6
AE of hepatic decompensation or liver failure	0.2 (4/2,233)[c]	4
Common AEs		
Pruritus	4.7 (126/2,698)	3
Fatigue	4.2 (158/3,766)	4
Headache	2.7 (115/4,220)	4

AE, adverse event; n, number of patients with AE; N, total number of patients included in cohorts reporting AE data.
[a]Safety data may have been pooled from different cohorts for different AE categories; cohorts included are all those reporting data for the specified AE category.
[b]Includes 1 severe AE.
[c]Percentage could be lower as cohorts that did not report any AEs of hepatic decompensation or liver failure are not included, as it is unknown whether such events did not occur or occurred but were not reported.

(4.2%), and headache (2.7%). Six cohorts included data on SAEs: these were reported in 55 of 5,522 patients (1.0%; including 1 severe AE). In total, 33 of 5,595 patients (0.6%) discontinued study treatment because of an AE across the 6 cohorts in which these data were reported. Four patients (4/2,233, 0.2%) who received glecaprevir/pibrentasvir had documented hepatic decompensation events (ascites, n = 1; esophageal varices rupture, n = 1; jaundice, n = 2; Table 2).

Discussion

Real-world studies enable evaluation of treatment effectiveness, safety, and prescribing patterns in routine clinical practice. They provide valuable information for clinicians, patients, policy-makers, and payers and are an important complement to the results obtained from clinical trials. The results of this meta-analysis indicate that glecaprevir/pibrentasvir is an effective and well-tolerated pangenotypic treatment option for patients with chronic HCV infection in real-world clinical practice.

Of the 12,531 patients included in the studies in this meta-analysis, 8,583 patients had SVR12 results, were lost to follow-up, or prematurely discontinued and thus, were included in the ITT population. This decrease in patient number is because several of the studies were ongoing at the time of presentation or publication so SVR12 data were not available on all patients, and because 3 studies did not report on the ITT population at all.

Table 2. Patients with SAEs and AEs of special interest in each study.

Short title/data source	Patients, N	SAEs	Hepatic decompensation or liver failure
VA Registry (US)[28]	1,940	Not reported	Not reported
Spanish HepaC Cohort[24]	1,581	1 “severe” AE (not specified) was reported	Not reported
Global G/P PMOS[31]	755	14 SAEs (not specified) were reported	1 patient experienced ascites; this patient had evidence of synthetic dysfunction and risk factors for passive congestion of the liver at baseline
German Hepatitis-C Registry[19]	1,242	10 SAEs were reported[a]	Not reported
Italian MISTRAL[20]	1,177	6 SAEs were reported, including 2 deaths[b]	2 patients experienced jaundice
Trio (US)[29]	1,131	Not reported	Not reported
Japan Registry[25]	798	13 patients discontinued treatment because of AEs	Not reported
England NHS Registry[22]	773	Not reported	Not reported
Target HCV[32]	487	17 SAEs were reported[c]	Not reported
Italian NAVIGATORE-Lombardia[16]	723	4 patients discontinued treatment because of AEs; 3 deaths were reported	Not reported
Japan Tamori[26]	280	7 SAEs were reported, including 1 death[d]	1 patient experienced esophageal varices rupture
Scottish HCV Registry[21]	354	Not reported	Not reported
Japan Uemura[27]	131	Not reported	Not reported
Austrian Real-life Cohort[23]	116	Not reported	Not reported
Kaiser Permanente (US)[30]	50	32/277 patients who received G/P or SOF/VEL experienced AEs requiring hospitalization[e]	7/32 patients who experienced AEs requiring hospitalization had hepatic decompensation; regimen received was indeterminable
Japan DAA-experienced (Osawa)[17]	30	Not reported	Not reported
Japanese GT2 retreatment[33]	915	Not reported[f]	Not reported
Japan DAA-experienced (Akuta)[18]	20	Not reported	Not reported

AE, adverse event; G/P, glecaprevir/pibrentasvir; n, number of patients with AE; N, total number of patients included in cohorts reporting AE data; PMOS, post-marketing observational study; SAE, serious adverse event; SOF/VEL, sofosbuvir/velpatasvir.
[a]Limb abscess (n = 1), atrial flutter (n = 1), circulatory collapse (n = 1), colitis (n = 1), detoxification (n = 1), humerus fracture (n = 1), injection-site abscess (n = 1), Ménière’s disease (n = 1), pleural effusion (n = 1), and vomiting (n = 1). In the effectiveness population: limb abscess (n = 1), atrial flutter (n = 1), circulatory collapse (n = 1), colitis (n = 1), detoxification (n = 1), humerus fracture (n = 1), injection-site abscess (n = 1), Ménière’s disease (n = 1), and pleural effusion (n = 1).
[b]Death (n = 2; myocardial infarction and car accident), jaundice (n = 2), anemia (n = 1), and pruritus (n = 1).
[c]Cellulitus (n = 2), chronic obstructive pulmonary disease (n = 2), dyspnea (n = 2), acute myocardial infarction (n = 1), aortic dissection (n = 1), cardiac arrest (n = 1), hemarthrosis (n = 1), hypertensive crisis (n = 1), kidney transplant rejection (n = 1), mental status changes (n = 1), myasthenia gravis (n = 1), respiratory failure (n = 1), rhinovirus infection (n = 1), and tibia fracture (n = 1).
[d]Esophageal varices rupture (n = 1), cerebral bleeding (n = 1), cardiac dysfunction (n = 1), burn (n = 2), fracture of femoral bone (n = 1), and death (n = 1).
[e]Reasons for hospitalization were: infection (n = 11), hepatic decompensation (n = 7), cardiovascular event (n = 4), elective procedure (n = 4), new cancer diagnosis (n = 3), and other (n = 3). Of note, 20 patients with a history of decompensated cirrhosis were included in the study. The data source did not specify which, if any, of the patients who reported hepatic decompensation had a history of decompensated cirrhosis at screening and which, if any, of the patients hospitalized due to AE received G/P.
[f]1 patient experienced renal dysfunction but this was not specified as an SAE.

The effectiveness and safety of a treatment in clinical practice may differ from those observed in clinical trials, because of a more heterogeneous real-world population that often includes patients who were excluded from clinical trials during drug development, such as those with multiple comorbidities including, psychiatric disorders, diabetes, and substance abuse, which have been shown to decrease the likelihood of achieving SVR.[36] Although the SVR12 rates in the individual cohorts of the ITT population were all >92%, rates from 92.1% to 100% combined with cohort sizes from 20 to 1,625 resulted in a high measurement of heterogeneity (I^2 >90). There was similar heterogeneity in the SVR12 rates and cohort sizes in the mITT population; however, excluding the VA cohort in sensitivity analyses of the mITT population greatly decreased the heterogeneity (I^2 = 25.1%) because the VA cohort was both the largest cohort and had the lowest SVR12 rate. Despite high heterogeneity between the cohorts included, the overall ITT SVR12 rate in this meta-analysis of real-world data (96.7%) is consistent with the ITT SVR12 rate achieved across the glecaprevir/pibrentasvir clinical development program (97.5%).[1] Indeed, the ITT SVR12 rates with glecaprevir/pibrentasvir in this meta-analysis were uniformly high (≥95.0%) irrespective of GT and in populations often considered more challenging to treat, such as HCV treatment-experienced patients, patients with cirrhosis, those who use illicit drugs/OST, those with psychiatric disorders, and those taking PPIs.[36–39]

The overall mITT SVR12 rate was also high in this meta-analysis (98.1%) and comparable with that observed in clinical trials (99.1%).[40] The virologic failure rate was 2.4%. Because the mITT population for the VA cohort included patients without an SVR12 rate as well as those with virologic failure, sensitivity analyses of the SVR12 rates for the mITT population were conducted excluding the VA cohort. In these sensitivity analyses, the overall SVR12 rate was 98.9% and the virologic failure rate was 1.2%, similar to the rates seen in registrational trials.[40]

It is important to report mITT SVR12 rates in subpopulations in which there is suspicion of lower efficacy; thus, mITT SVR12 rates were presented for most cohorts by labeled regimen or comorbidities. Looking at subpopulations of interest, the mITT SVR12 rate in patients who used OST in this meta-analysis (98.9%) was similar to the mITT rate reported in patients receiving OST in clinical trials (99.3%) in which adherence to treatment was high (98%).[7] This is particularly important given the evolving epidemiology of HCV in some countries. The number of younger people with milder disease (fibrosis stage F0–F1) who are infected with HCV is increasing,[41] and the majority of new cases in these younger patients occur in those who use illicit injectable drugs.[41,42] The mITT SVR12 rate in patients with CKD stage 4–5 in this meta-analysis (99.0%) was also similar to that reported in a clinical study (100%).[8]

The introduction of highly effective DAA therapies with short durations of treatment that can cure HCV infection has transformed the treatment landscape in recent years. In this meta-analysis, the SVR12 rates were high in patients who received glecaprevir/pibrentasvir treatment for 8 weeks (96.5% in the ITT population and 97.9% in the mITT population). In treatment-naïve patients without cirrhosis who received on-label treatment for 8 weeks, the mITT SVR12 rate was 99.3%, similar to that seen in the glecaprevir/pibrentasvir clinical development program (99.2%).[1] One group of particular interest is patients infected with HCV GT3 as they are considered a more difficult-to-treat population. The SVR12 rate for treatment-naïve patients with GT3 treated for 8 weeks with glecaprevir/pibrentasvir in this meta-analysis of real-world data was 99.2% (mITT population), which is higher than the rates seen in the registrational trials (ITT SVR12, 95.2%; mITT SVR12, 97.5%).[43] For HCV-infected patients with compensated cirrhosis, current international guidelines for HCV management recommend treatment for at least 12 weeks.[4,44] In this meta-analysis, the mITT SVR12 rate was 99.0% in treatment-naïve patients with compensated cirrhosis who received on-label treatment for 12 weeks. Data suggest that an 8-week treatment course with glecaprevir/pibrentasvir may be as effective as a 12-week treatment course in HCV treatment-naïve patients with compensated cirrhosis.[45,46] A clinical trial using an 8-week treatment regimen for treatment-naïve patients infected with HCV GT1–6 infection who have compensated cirrhosis has been completed.[46] At the time of this meta-analysis, there were no pangenotypic regimens approved for 8 weeks in all treatment-naïve patients with compensated cirrhosis. Based on the results of EXPEDITION-8 study, the European Medicines Agency has granted marketing authorization and the US Food and Drug Administration has approved the use of glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with compensated cirrhosis and HCV genotypes 1–6.[1,2]

In May 2016, the World Health Assembly adopted the World Health Organization (WHO) Global Health Sector Strategy on Viral Hepatitis, 2016–2021. The aim is to eliminate HCV as a major public health threat by 2030, by reducing new infections by 80% and HCV-related deaths by 65%, which requires 90% of individuals with chronic HCV infection to be diagnosed and 80% of those diagnosed to be treated.[47,48] In 2015, only 20% (14 million) of the estimated 71 million individuals living with chronic HCV worldwide were aware that they were infected,[47] and in 2016, only 13% of those aware of having chronic HCV were being treated.[47] To help eradicate HCV, the WHO recommends treating all adults with chronic HCV infection and advocates using pangenotypic DAA regimens, which they state are highly effective and well tolerated with only minor adverse effects, based on data from clinical studies.[48] The tolerability profile of glecaprevir/pibrentasvir in this meta-analysis was similar to that reported in ~2,300 patients participating in the clinical development program, with headache and fatigue among the most commonly reported AEs and <1% of patients discontinuing treatment because of AEs.[1] Pruritus was the most common AE reported in this meta-analysis, possibly mediated at least in part by DAA-driven alterations to bile acid metabolism or protease regulation.[49,50] Additionally, pruritus is commonly observed in specific HCV-infected populations, such as patients with renal impairment[51,52] or cirrhosis.[53,54] These populations are represented in the cohorts included in this meta-analysis. Hepatic decompensation events were rare (reported in <0.2% of patients). Information regarding these events and the patients who developed these events are not available, precluding further analysis. Taken together, these real-world data support the use of pangenotypic glecaprevir/pibrentasvir in all patients with HCV, irrespective of whether they were historically considered more challenging to treat, to help achieve the WHO goal of HCV elimination.

Although data from meta-analyses are considered to be among the most robust, this meta-analysis has a number of limitations. The level of detail reported across the individual studies was inconsistent; indeed, because of the relatively recent

approval of glecaprevir/pibrentasvir for the treatment of chronic HCV infection, most real-world data were only available in congress presentations. This lack of consistency was also illustrated by SVR12 rates in the mITT population being reported in 3 studies that did not report SVR12 rates in the ITT population. There were insufficient data available to analyze SVR12 rates in patients with HCV GT5 or GT6 infection and those who received 16 weeks' treatment with glecaprevir/pibrentasvir, and data from only a small number of patients were available for some subgroups of interest. Furthermore, no data were available for the 165 patients who experienced virologic failure. Finally, manual data extraction may have been subject to error (although this was a relatively small dataset).

In conclusion, the results of this meta-analysis demonstrate that the real-world effectiveness and safety of glecaprevir/pibrentasvir in more than 12,000 patients were consistent with those observed in clinical trials. Furthermore, real-world evidence indicates that glecaprevir/pibrentasvir is a highly effective and well-tolerated pangenotypic treatment option for a broad range of patients with chronic HCV infection, regardless of patient characteristics, supporting its use in HCV eradication programs and its inclusion in the WHO clinical recommendations to adopt a pangenotypic DAA regimen and to treat all patients.[48]

Abbreviations

AE, adverse event; CKD, chronic kidney disease; DAA, direct-acting antiviral; DDI, drug–drug interaction; G/P, glecaprevir/pibrentasvir; GT, genotype; ITT, intention-to-treat; mITT, modified intention-to-treat; NHS, National Health Service; OST, opioid substitution therapy; PMOS, post-marketing observational study; PPI, proton-pump inhibitor; SAE, serious adverse event; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virologic response at post-treatment week 12; VA, Veterans Affairs; WHO, World Health Organization.

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Conflict of interest

Pietro Lampertico: Speaker/advisor for Bristol-Myers Squibb, Roche, Gilead Sciences, GSK, AbbVie, MSD, Arrowhead, Alnylam, Janssen, MYR Pharma, Eiger BioPharmaceuticals. Jose A Carrión: Speaker for AbbVie, Gilead, and MSD; advisor for AbbVie. Michael P Curry: Consultant for Trio Health; advisor for Gilead Sciences, AbbVie, and Bristol-Myers Squibb; research support from Gilead. Juan Turnes: Speaker/consultant for AbbVie, Gilead, and MSD; research support from Gilead. Markus Cornberg: Speaker/advisor for AbbVie, Gilead, and Merck (MSD) related to this project; personal fees from AbbVie, Bristol-Myers Squibb, Gilead, Janssen-Cilag, Roche, MSD, Biogen, Falk Foundation, Boehringer Ingelheim, Siemens, Spring Bank outside submitted work. Francesco Negro: Advisor for AbbVie, Merck, and Gilead; research support from Gilead Sciences. Ashley Brown: Investigator, advisor and speaker for AbbVie, Gilead, and Merck; received financial support for attending academic meetings. Marcello Persico: Consultant for Gilead, MSD, and AbbVie. Nicole Wick: Trio Health employee; research support from AbbVie, Gilead, and Merck. Heiner Wedemeyer: Grants from Abbott, AbbVie, Bristol-Myers Squibb, Eiger, Falk and Falk Foundation, Gilead, Novartis, Merck/MSD, Roche, Roche Diagnostics; investigator in clinical trials for Transgene; advisor, committee chair, and investigator for MyrmbH. Ariel Porcalla, Andreas Pangerl, Eric Crown, Lois Larsen, and Yao Yu: Employees (or former employees) of AbbVie and may hold stock or share options.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors had access to relevant data, and participated in the writing, review, and approval of the final manuscript. Pietro Lampertico: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Jose A Carrión: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Michael P Curry: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Juan Turnes: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Markus Cornberg: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Francesco Negro: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Ashley Brown: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Marcello Persico: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; critical insights to support the oral presentation of the data used in drafting this manuscript. Nicole Wick: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Heiner Wedemeyer: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Ariel Porcalla: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Andreas Pangerl: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Eric Crown: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Lois Larsen: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis. Yao Yu: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis.

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Supplementary data

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