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ORIGINAL RESEARCH

Characteristics, Treatment Patterns, and Clinical Outcomes of Chronic Hepatitis B Across 3 Continents: Retrospective Database Study

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ABSTRACT

Introduction: The prevalence of chronic hepatitis B virus (HBV) infection is high in many countries; however, robust, real-world epidemiological data are lacking. This study describes the prevalence, characteristics, treatment patterns, and long-term clinical outcomes of patients with chronic HBV infection in the US, Germany, and Taiwan.

Methods: This was a retrospective cohort analysis of three healthcare/insurance claims databases. Individuals were identified as patients with chronic HBV infection if their records contained HBV diagnostic codes from 1 January 2010 to 31 December 2012 (Germany and Taiwan) or 1 January 2013 (USA). Included patients

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were indexed on 1 January 2013. Patients' demographics, clinical characteristics, and healthcare utilisation were described. Treatment patterns and long-term clinical outcomes over follow-up (to 31 December 2016 or loss to follow-up) were estimated.

Results: The prevalence of chronic HBV infection was 0.10%, 0.17%, and 2.39% in the US, Germany, and Taiwan respectively. Prevalence was very low in children, increased rapidly in adulthood, and peaked in 50– < 65 year olds before declining in the elderly. More US (16.6%) and German (15.4%) patients were HIV ± HCV coinfected than in Taiwan (4.1%). Baseline clinical characteristics and healthcare utilisation were broadly similar between countries. In total, 19.2%, 11.1%, and 5.9% of non-coinfected adult patients received treatment at index in the US, Germany, and Taiwan, respectively; most frequently with nucleos(t)ide analogue monotherapy (94.4%, 97.2%, 99.8% of treated patients, respectively) and rarely with interferons (0.27%, 1.63%, and 0.06%, respectively). Untreated Taiwanese patients were more likely to remain untreated than elsewhere, and treated Taiwanese patients were less likely to persist with therapy. Generally, the cumulative incidence of long-term clinical outcomes was lowest in Germany.

Conclusion: This study provides a contemporary, real-world, intercontinental snapshot of chronic HBV infection. Long-term sequelae occurred in all populations, and treatment levels were low, suggesting an unmet need for (or access to) effective treatments.

Keywords: Epidemiology; Hepatitis B virus; Prevalence; Sequelae; Therapeutics

Key Summary Points

Why carry out this study?

Approximately 257 million people were living with chronic hepatitis B virus (HBV) infection globally (in 2015), and nearly 1 million deaths are caused by the infection each year; however, there is a lack of real-world epidemiological data on these patients

This study used patient medical claims data to determine the prevalence, characteristics, treatment patterns, and clinical outcomes of patients infected with chronic HBV in the US, Germany, and Taiwan

What was learned from the study?

Chronic HBV infection prevalence was highest in Taiwan versus Germany and the US, with the lowest proportion of patients coinfected with HCV and/or HIV in Taiwan

Nucleos(t)ide monotherapy was the most commonly used treatment in each country; however, the proportions of patients receiving treatment was low and long-term sequelae occurred in all populations, suggesting a potential unmet need for (or access to) effective treatments

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a global public health concern caused by failure to clear HBV following acute infection. It is classically defined by the presence of hepatitis B surface antigen (HBsAg) in serum for 6 months or more [1, 2]. Chronic HBV infection is associated with life-threatening sequelae, including cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC) [3, 4]. In 2015, the World Health Organization (WHO) estimated

that 257 million people (3.5% of the global population) were living with chronic HBV infection and 887,000 HBV-attributable deaths occur annually [2, 4]. In the same year, the WHO estimated that 27 million people (10.5% of those living with hepatitis B) were aware of their HBV infection, 4.5 million of whom (16.7%) were receiving treatment [2].

The introduction of HBV vaccination programmes has seen the global prevalence of chronic HBV infection in young children (< 5 years) drop from ~ 5% in the 1980s to ~ 1% as of 2019 [2]. The success of vaccination is evident in Taiwan, where seroprevalence of HBsAg in children aged < 15 years dropped from 9.8% in 1984 to 0.5% in 2004, when 97% of this population had been vaccinated [5].

The goal of chronic HBV treatment is to improve patients' quality of life and survival by reducing or reversing the progression of liver disease, preventing cirrhosis, liver decompensation, and HCC [6–8]. Sustained viral suppression is associated with reduced disease progression and improved long-term outcomes [7, 9]. The two classes of anti-HBV drug currently available are interferon (IFN) therapy and nucleos(t)ide analogues (NAs) [6]. IFN therapy offers a finite treatment duration (typically 48 weeks), but the regimens are inconvenient and poorly tolerated, carry safety concerns, and are not available to all patients [6, 10]. Of the NAs, tenofovir and entecavir are recommended [2]. They rarely lead to drug resistance, have few adverse effects, and, as oral therapies, are easy to self-administer [2]; however, treatment duration is prolonged or indefinite [8]. In Taiwan, discontinuation of NA treatment is recommended after 3 years [11, 12].

This paper reports three separate but comparable retrospective analyses of administrative healthcare claims data, conducted during similar periods, in the USA, Germany, and Taiwan. The study aimed to quantify the prevalence of chronic HBV infection, describe patient characteristics and treatment patterns, and assess, by treatment status, long-term clinical outcomes. These data will contribute to current understanding of patient characteristics, treatment, and associated outcomes.

METHODS

All three retrospective cohort studies sought to adopt similar approaches to generate comparable data. The over-arching methodology is described here, with details from each country-specific study included in the supplementary materials.

Healthcare in Study Countries and Respective Data Sources

The USA does not have a uniform health system and most healthcare coverage is provided through private health insurance and public health coverage. In 2020 91.4% of the US population had health insurance coverage for all or part of the year, with private and public coverage accounting for 66.5% and 34.8% respectively [13]. The US data in this study were collected from Optum Clinformatics Data Mart (CDM) [14], a longitudinal Health Insurance Portability and Accountability Act (HIPAA)-compliant administrative claims database from the largest healthcare insurance provider in the US. Claims data included those for commercial and Medicare Advantage patients. The CDM data are broadly representative of the US population (southern states are marginally over-represented) and findings may not be generalisable to patients covered by Medicaid (a comparable analysis, conducted using Medicaid claims data, is available upon request).

German citizens enjoy near-universal healthcare through mandated health insurance, most of which (88%) is publicly funded statutory health insurance (SHI), paid for through employer and employees contributions [15]. Care is often received through General Practitioners and specialists in the ambulatory (office-based) care setting. German data in this study were sourced from the WIG2 database, an anonymised healthcare claims database that collects longitudinal data from German SHI providers (mainly company or guild health insurances) [16] and hence may be less generalisable to patients covered by private health insurance (PHI). This database has been shown

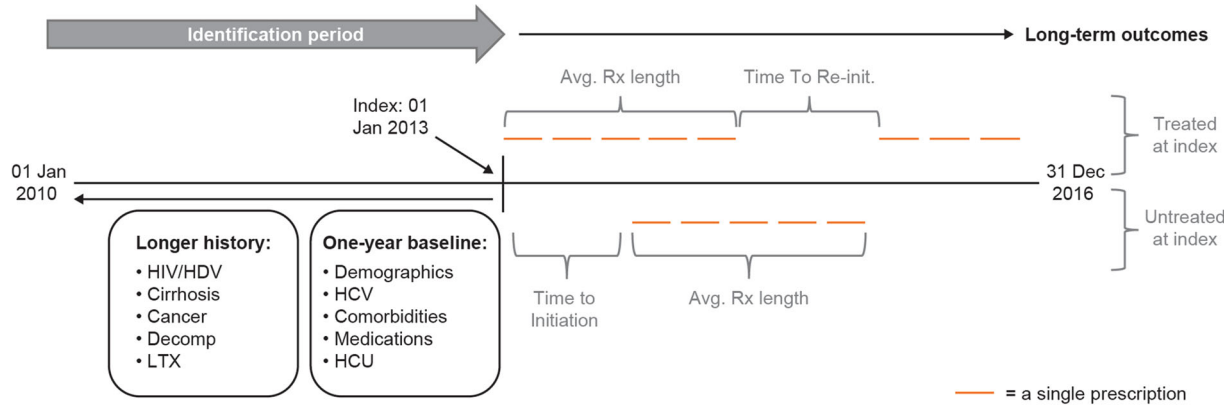

Fig. 1 Study design schematic. *Avg* average, *Decomp* decompensated liver disease, *HCU* healthcare utilisation, *HIV* human immunodeficiency virus, *HDV* hepatitis delta virus, *LTX* liver transplant, *Rx* treatment, *Re-Init* re-initiation

to be representative of the German SHI population, especially in terms of morbidity [17].

Taiwan's national health insurance (NHI) was introduced in 1995 and provides universal, mandatory coverage primarily through payroll-based premiums [18]. Almost all (99%) of the Taiwanese population (approximately 23 million residents) are covered [19]. The nationwide Taiwanese database used in this study were provided by the Health and Welfare Data Science Unit of the Department of Statistics, Ministry of Health and Welfare [20], and are fully representative of the NHI population.

Study Periods

The study period was from 1 January 2010 to 31 December 2016 (Fig. 1). For annual period prevalence calculations, all patients identified from 1 January 2010 up to 31 December in each calendar year were included (only data for 2013 are included here). For other analyses (baseline characteristics, treatment patterns, and long-term clinical outcomes), patients identified up to and including 31 December 2012 were included; patients were indexed on 1 January 2013. The baseline period was defined as the 12 months before index date, although for some clinical conditions, all available history was used. For longitudinal analyses (treatment patterns and clinical outcomes), patients were followed up to 31 December 2016 where data allowed, or until loss to follow-up, death, or data cutoff.

Study Populations

To determine prevalence, patients with chronic HBV infection were identified using HBV-specific diagnostic codes. Patients with chronic HBV infection were required to have at least one medical claim with a diagnostic code for chronic HBV, or two or more claims for acute HBV infection separated by at least 6 months, the second of which had to be within the study period (Table S1). Feasibility analyses, conducted in the subset of patients within the Optum CDM database with laboratory data, demonstrated that this definition, as described by Han et al. [21], was more discriminate for identifying HBsAg-positive or HBV medication-treated patients than an internal code-based definition or an alternative definition described by Chen et al. [22] (Table S2).

Analysis cohorts for each objective were created by applying exclusion criteria to the study population. For the prevalence calculations, no exclusion criteria were applied. For the remaining analyses, patients aged $\geq$ 2 years were required to have 12 months of pre-index registration. For treatment pattern analyses, patients with evidence of treatment within 12 months before the treatment index date were excluded. For the long-term clinical outcomes analyses, patients reporting any history

of a specific outcome were excluded from analyses involving that outcome.

Specific periods of follow-up were generated for patients included in longitudinal analyses. For the treatment patterns analyses, patients untreated at index date were followed from index until earliest treatment initiation, loss to follow-up, death, or data cutoff date. Treated patients were followed from index until treatment discontinuation, loss to follow-up, death, or data cutoff date. Patients untreated at index date who subsequently initiated treatment were followed from date of initiation until discontinuation, loss to follow-up, death, or data cutoff date. For the long-term clinical outcomes analyses, patients were followed until the earliest of event of interest, loss to follow-up, death, or data cutoff.

Data Generation

Patients were classed by coinfection status, age, and sex. Age was determined by subtracting the birth year from 2013; adults were those > 18 years. Coinfection status was defined as baseline history of chronic hepatitis C (HCV) infection or any history of human immunodeficiency virus (HIV); history of hepatitis delta virus (HDV) infection was also captured. Patients were defined as clinically managed in the US and Germany based on at least one HBV-related office-based physician visit during baseline and for Taiwan, an insurance claim for chronic HBV or two claims for acute HBV more than 6 months apart, or the use of chronic HBV medications.

History of liver-related comorbidities (liver fibrosis, cirrhosis, decompensated liver disease, liver transplantation) was ascertained through diagnostic codes; however, the prevalence of liver fibrosis was measured only during baseline. For comparability across studies, patients with a history of decompensated liver disease were considered to have a history of decompensated cirrhosis. History of cancer (including HCC), osteodystrophy, and chronic kidney disease was also captured. German outpatient diagnostic data were captured quarterly, but all other data were date-specific.

Treatment status was defined based on active prescriptions at index; alternative treatment definitions (baseline or any history) were explored in Taiwan. For the US and Taiwanese populations, healthcare utilisation included outpatient presentations (outpatient clinic visits or emergency room visits) and inpatient admissions during baseline, and for the German population, office-based physician or acute day-ward visits and inpatient admissions during baseline were included.

For treatment pattern analyses, discontinuation was defined by a gap of > 30 days between the end of a prescription and the next. Treatment patterns and long-term clinical outcomes data presented in this manuscript largely focus on non-coinfected adult (NCIA) patients.

Statistical Analysis

The prevalence of chronic HBV infection in 2013 was calculated by using the number of patients with chronic HBV infection from 1 January 2010 until 31 December 2013 (US and Taiwan cohorts) or 31 December 2012 (German cohort) as the numerator and covered individuals in each respective database or age group as the denominator.

For baseline characteristics, relative frequencies and percentages were calculated for categorical data, means and standard deviations (SDs) for continuous data. Confidence intervals (CIs) of 95% around proportions were calculated using standard formulae and presented in squared parentheses. If p^*N or $(1 - p)^*N$ was < 10, where p was the proportion and N was the denominator, exact CIs were calculated in Stata 14.

Treatment patterns were described using Kaplan-Meier (KM) methodology, with the cumulative proportion of patients remaining on/off treatment, with 95% CIs reported at set periods. 91, 182, 365, 730, and 1095 days were used to represent 3, 6, 12, 24, and 36 months, respectively, in the US and Germany; in Taiwan, 90, 180, 360, 720, and 1080 days were used.

Treatment data were further visualised through the production of Sankey plots. Patients' quarterly treatment exposure was

recorded sequentially as a string variable, producing lines of therapy, and these data were summarised at population level by age group and coinfection status. The resulting graphic shows the movement of patients from one treatment status to the next; the width of the bars depicts the proportion of patients moving from one state to another. Sequences that accounted for < 1% of all patients were removed to aid visualisation.

The cumulative incidence of specified long-term clinical outcomes was estimated for the same periods as described above using KM analyses. Patients retained their index treatment exposure status (untreated; NA-treated; IFN-treated) and continued to contribute person-time even after discontinuing treatment (for those treated at index). A sensitivity analysis, whereby patients were censored if their index treatment status changed during follow-up, was also conducted.

Ethics

No formal ethical approval was required as no primary collection of individual human data occurred; data were anonymised or pseudonymised at source (researchers had no access to identifiable data). In Taiwan, the study was approved by the National Taiwan University Hospital Research Ethics Committee (approval document 201805146 W); informed consent was waived.

RESULTS

The flow of patients included in each analysis, presented by study country, is shown in Fig. 2.

Prevalence

In total, 12,553 (US), 8182 (Germany), and 565,615 (Taiwan) individuals were identified as having chronic HBV infection in 2013, corresponding to a prevalence of 0.095% [0.093–0.096%] in the US, 0.23% [0.22–0.23%] in Germany, and 2.39% [2.38–2.40%] in Taiwan. Similar age-specific prevalence patterns were observed. Prevalence was very low in children (< 18 years), rose in younger adults (18 to < 50 years), peaked in adults aged 50 to < 65 years, and declined in older adults (> 65 years) (Fig. 3; Tables S3 and S4).

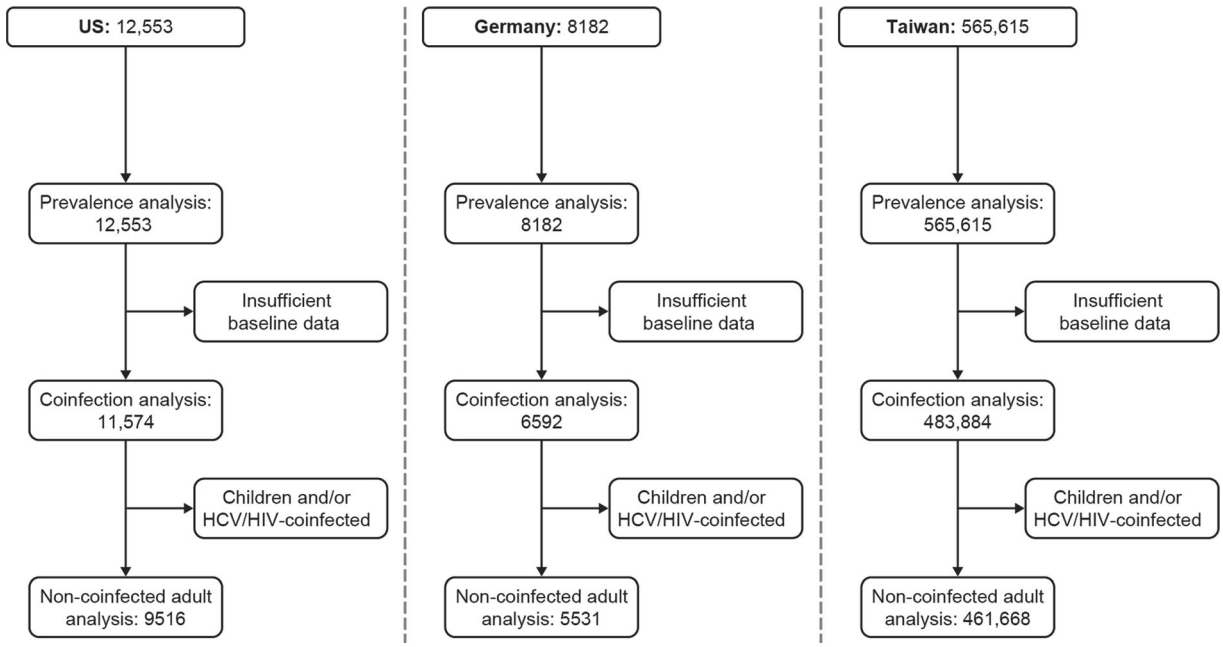

Fig. 2 Patient data flow in each country

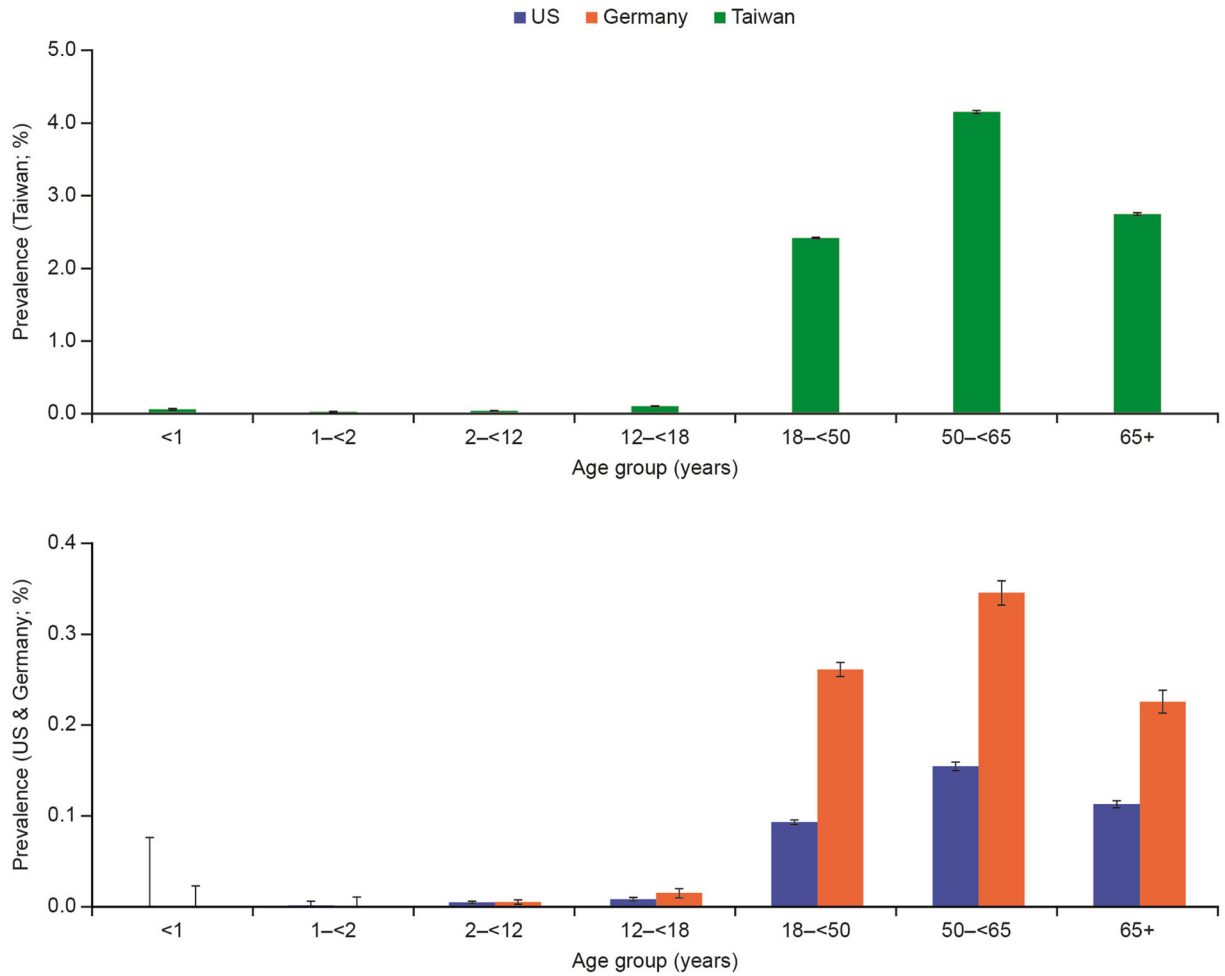

Fig. 3 Age-specific point prevalence of chronic HBV infection in 2013 (all patients). *HBV* hepatitis B virus

Subsequent analyses were restricted to patients with sufficient baseline data: 11,574 patients in the US, 6592 in Germany, and 483,884 in Taiwan; applying this exclusion criterion had little impact on the age distribution of patients with chronic HBV (Table S3).

Patient Characteristics

HCV/HIV Coinfection Status

In total, 16.6% [16.0–17.3%] of patients in the US, 15.4% [14.5–16.3%] in Germany, and 4.1% [4.1–4.2%] in Taiwan were coinfected with HCV and/or HIV. Proportions of patients coinfected (with either HCV or HIV) differed by age; 2.9% [0.8–7.4%] of patients age < 18 years were coinfected in the US compared with 16.8% [16.1–17.5%] of patients aged ≥ 18 years. In Taiwan, these proportions were 1.2% [0.8–1.8%] and 4.2% [4.1–4.2%] respectively. In Germany, all coinfected patients were aged ≥ 18 years. Levels of HCV coinfection were similar in the US (12.1% [11.5–12.7%]) and Germany (13.5% [12.7–14.4%]), but lower in Taiwan (3.9% [3.8–4.0%]); HIV-coinfection was highest in the US (5.7% [5.3–6.1%]), followed by Germany (2.7% [2.3–3.1%]) and Taiwan (0.32% [0.31–0.34%]) (Table S5). Children and HCV/HIV-coinfected patients were excluded from subsequent analyses; however, patients coinfected with HDV were included. In total, there were 9516 NCIA patients in the US, 5531 in Germany, and 461,668 in Taiwan.

Table 1 Baseline characteristics (NCIA patients)

Parameter	United States Patients (%; 95% CI)	Germany Patients (%; 95% CI)	Taiwan Patients (%; 95% CI)
Sex			
Male	5073 (53.3%; 52.3–54.3)	2918 (52.8%; 51.4–54.1)	267,504 (57.9%; 57.8–58.1)
Female	4440 (46.7%; 45.7–47.7)	2613 (47.2%; 45.9–48.6)	191,555 (41.5%; 41.3–41.6)
Unknown	3 (0.03%)	0 (0%)	2609 (0.6%; 0.5–0.6)
Clinically managed			
Yes	5557 (58.4%; 57.4–59.4)	4224 (76.4%; 75.3–77.5)	207,011 (44.8%; 44.7–45.0)
No	3959 (41.6%; 40.6–42.6)	1307 (23.6%; 22.5–24.8)	254,657 (55.2%; 55.0–55.3)
Coinfection[a]			
Hepatitis delta	303 (3.2%; 2.8–3.5)	193 (3.5%; 3.0–4.0)	11,661 (2.5%; 2.5–2.6)
Cancer[a]			
Haematological	174 (1.8%; 1.6–2.1)	103 (1.9%; 1.5–2.2)	2539 (0.5%; 0.5–0.6)
HCC	298 (3.1%; 2.8–3.5)	26 (0.5%; 0.3–0.7)	12,384 (2.7%; 2.6–2.7)
Non-HCC solid state	637 (6.7%; 6.2–7.2)	303 (5.5%; 4.9–6.1)	25,341 (5.5%; 5.4–5.6)
Cancer NOS	139 (1.5%; 1.2–1.7)	98 (1.8%; 1.4–2.1)	784 (0.17%; 0.16–0.18)
None	8499 (89.3%; 88.7–89.9)	5113 (92.5%; 91.7–93.1)	420,620 (91.1%; 91.0–91.2)
Liver fibrosis			
Any evidence	74 (0.8%; 0.6–1.0)	44 (0.8%; 0.6–1.0)	5220 (1.1%; 1.1–1.2)
No evidence	9442 (99.2%; 99.0–99.4)	5487 (99.2%; 99.0–99.4)	456,448 (98.9%; 98.8–98.9)
Cirrhosis[a]			
Decompensated	308 (3.2%; 2.9–3.6)	262 (4.7%; 4.2–5.3)	14,670 (3.2%; 3.1–3.2)
Compensated	483 (5.1%; 4.6–5.5)	235 (4.3%; 3.7–4.8)	25,734 (5.6%; 5.5–5.6)
None	8725 (91.7%; 91.1–92.2)	5034 (91%; 90.3–91.8)	421,264 (91.2%; 91.2–91.3)
Liver transplant[a]			
Any history	135 (1.4%; 1.2–1.7)	47 (0.9%; 0.6–1.1)	1076 (0.2%; 0.2–0.2)
No history	9381 (98.6%; 98.3–98.8)	5484 (99.2%; 98.9–99.4)	460,592 (99.8%; 99.8–99.8)
Osteodystrophy			
Any evidence	977 (10.3%; 9.7–10.9)	279 (5%; 4.5–5.6)	7765 (1.7%; 1.6–1.7)
No evidence	8539 (89.7%; 89.1–90.3)	5252 (95%; 94.4–95.5)	453,903 (98.3%; 98.3–98.4)
Hyperlipidaemia			
Any evidence	3820 (40.1%; 39.2–41.1)	1245 (22.5%; 21.4–23.6)	90,012 (19.5%; 19.4–19.6)
No evidence	5696 (59.9%; 58.9–60.8)	4286 (77.5%; 76.4–78.6)	371,656 (80.5%; 80.4–80.6)

Table 1 continued

Parameter	United States Patients (%; 95% CI)	Germany Patients (%; 95% CI)	Taiwan Patients (%; 95% CI)
Chronic kidney disease			
CKD	845 (8.9%; 8.3–9.5)	274 (4%; 4.4–5.5)	15,877 (3.4%; 3.4–3.5)
None	8671 (91.1%; 90.5–91.7)	5257 (95%; 94.5–95.6)	445,791 (96.6%; 96.5–96.6)
Outpatient presentation			
N (%)	9205 (96.7%; 96.4–97.1)	–	455,709 (98.7%; 98.7–98.7)
Mean (SD)	15.58 (22.24; 15.1–16.0)	–	18.08 (14.32; 18.0–18.1)
Office-based physician			
N (%)	–	5401 (97.6%; 97.3–98.0)	–
Mean (SD)	–	14.04 (14.45; 13.7–14.4)	–
Acute day ward			
N (%)	–	769 (13.9%; 13–14.8)	–
Mean (SD)	–	2.05 (1.27; 2.0–2.1)	–
Hospital admission			
N (%)	1050 (11%; 10.4–11.7)	1443 (26.1%; 24.9–27.3)	58,331 (12.6%; 12.5–12.7)
Mean (SD)	0.21 (0.86; 0.2–0.3)	2.11 (2.03; 15.0–16.2)	1.76 (1.79; 1.7–1.8)
Total	9516	5531	461,668

CI confidence interval, *CKD* chronic kidney disease, *HCC* hepatocellular carcinoma, *NCIA* non-coinfected adults, *NOS* not otherwise stated, *SD* standard deviation

[a]Characteristics were assessed throughout patients' available historical records

NCIA Patients' Baseline Characteristics

Males predominated in each country, particularly Taiwan (57.9% [57.8–58.1%]), compared with the US (53.3% [52.3–54.3%]) and Germany (52.8% [51.4–54.1%]) (Table 1). A greater proportion of German patients (76.4% [75.3–77.5%]) were clinically managed compared with those in the US (58.4% [57.4–59.4%]) and Taiwan (44.8% [44.7–45.0%]); the low level observed in Taiwan was despite the less conservative definition applied there. The number of patients coinfected with HDV was generally low across all countries but lower in Taiwan (2.5% [2.5–2.6%]) than in the US (3.2% [2.8–3.5%]) and Germany (3.5% [3.0–4.0%]). Levels of fibrosis in the US (0.8% [0.60–1.0%]), Germany (0.8% [0.6–1.0%]), and Taiwan (1.1% [1.1–1.2%]) were comparable. History of cirrhosis (compensated or decompensated) was similar among the US (8.3% [7.8–8.9%]), Germany (9.0% [8.2–9.7%]), and Taiwan (8.8% [8.7–8.8%]). Within the cirrhotic population, less than two-thirds of US (61.1% [57.7–64.5%]) and Taiwanese (63.7% [63.2–64.2%]) patients had a history of compensated cirrhosis only, whilst these patients accounted for just under half of cirrhotic patients in Germany (47.3% [42.9–51.7%]). History of HCC was similar in the US (3.1% [2.8–3.5%]) and Taiwan (2.7% [2.6–2.7%]); few German patients had a history of HCC (0.5% [0.3–0.7%]). History of liver transplantation was more prevalent in US patients (1.4% [1.2–1.7%]) than in Germany (0.9% [0.6–1.1%]) or Taiwan (0.2% [0.2–0.2%]).

Almost all patients were seen at least once during baseline. The mean number of outpatient visits (SD) per patient during baseline was 15.6 (22.2) in the US, 14.0 (14.5) in Germany, and 18.1 (14.3) in Taiwan. However, hospitalisations were highest in Germany, with 26.1% [24.9–27.3%] of patients requiring at least one inpatient admission compared with 11.0% [10.4–11.7%] in the US and 12.6% [12.5–12.7%] in Taiwan (Table 1).

Baseline characteristics of non-coinfected children and both coinfected adults and children are shown in Table S5.

Treatment Patterns

At Index

Most NCIA patients from each country were untreated at index (Table S6); a greater proportion of US patients received treatment (19.2% [18.4–20.0%] compared with German (11.1% [10.3–11.9%]) and Taiwanese patients (5.9% [5.8–6.0%]. In Taiwan, 8.6% of patients [8.5–8.6%; *n*/*N*: 39,505/461,668] received treatment during baseline and 9.7% [9.7–9.8%; 44,935/461,668] had any history of treatment. Amongst those treated at index, NA monotherapy was the most prevalent treatment in each cohort (US, 94.4% [93.3–95.4%]; Germany, 97.2% [95.9–98.5%]; Taiwan, 99.8% [99.8–99.9%]); however, the distribution of NAs differed (Fig. 4A, Table S6). Combination therapy was observed more frequently in the US (5.4% [4.3–6.4%]) than in Germany (1.3% [0.6–2.5%]) or Taiwan (0.1% [0.1–0.1%]). Tenofovir was the most common treatment in the US and Germany, whilst entecavir was most common in Taiwan. IFNs were rarely used alone or in combination (US, 0.27% [0.09–0.64%]; Germany, 1.63% [0.63–2.63%]; Taiwan, 0.06% [0.03–0.09%]; Table S6).

During Follow-up

Most patients untreated at index remained so throughout follow-up (Fig. 5A). Within 12 months of follow-up, the highest proportion of untreated patients was in Taiwan (98.2% [98.2–98.3%]), followed by Germany (96.8% [96.3–97.3%]) and the US (94.6% [94.1–95.1%]). At 36 months, the proportions of patients who remained untreated were highest in Taiwan (95.5% [95.4–95.5%]) and Germany (95.3% [94.7–95.9%]) and lowest in the US (91.1% [90.4–91.8%]).

Differences were observed between countries in the distribution of patients' treatment at index and among those untreated at index who initiated treatment during follow-up (Fig. 4B; Table S7). A greater proportion of US patients initiated NA monotherapy during follow-up (98.8% [76.1–83.2%]) than received it at index (94.4% [93.3–95.4%]). In Germany and Taiwan, a greater proportion initiated IFN monotherapy during follow-up (Germany, 8.0% [4.8–11.2%]; Taiwan, 2.6% [2.4–2.9%]) than received it at index (Germany, 1.5% [0.7–2.8%]; Taiwan, 0.1% [0.0–0.1%]). Additionally, the distribution of NA monotherapy differed between countries. In the US and Taiwan, more patients initiated tenofovir treatment during follow-up (US, 63.9% [59.3–68.6%]; Taiwan, 26.7% [26.2–27.3%]) than at index (US, 49.6% [47.3–51.9%]; Taiwan, 11.0% [10.6–11.3%]). In Germany, more patients were prescribed lamivudine during follow-up (23.6% [18.6–28.7%]) than at index (9.3% [7.0–11.6%]).

Persistence to NAs differed between countries among patients treated at index and those untreated at index who initiated treatment during follow-up (Fig. 5B–E; Table S8). For those prescribed NAs at index, divergence between countries was observed after 3 months of follow-up, with lower cumulative persistence in Germany (74.0% [70.5–77.5%]) and Taiwan (71.9% [71.3–72.4%]) compared with the US (86.2% [84.7–87.8%]) (Fig. 5B). Further divergence was observed throughout follow-up to 36 months, when the lowest cumulative probability of persistence was observed in Taiwan (3.7% [3.4–3.9%]) compared with the US (44.3% [41.6–47.0%]) and Germany (29.7% [26.0–33.4%]) (Fig. 5B). In the US, persistence to NAs was lower in those who initiated therapy during follow-up compared with those at index from 3 months throughout follow-up (Fig. 5C). A similar pattern was observed in Germany, but persistence eventually converged after 3 years of follow-up (Fig. 5D). In Taiwan, however, lower persistence was observed in patients treated at

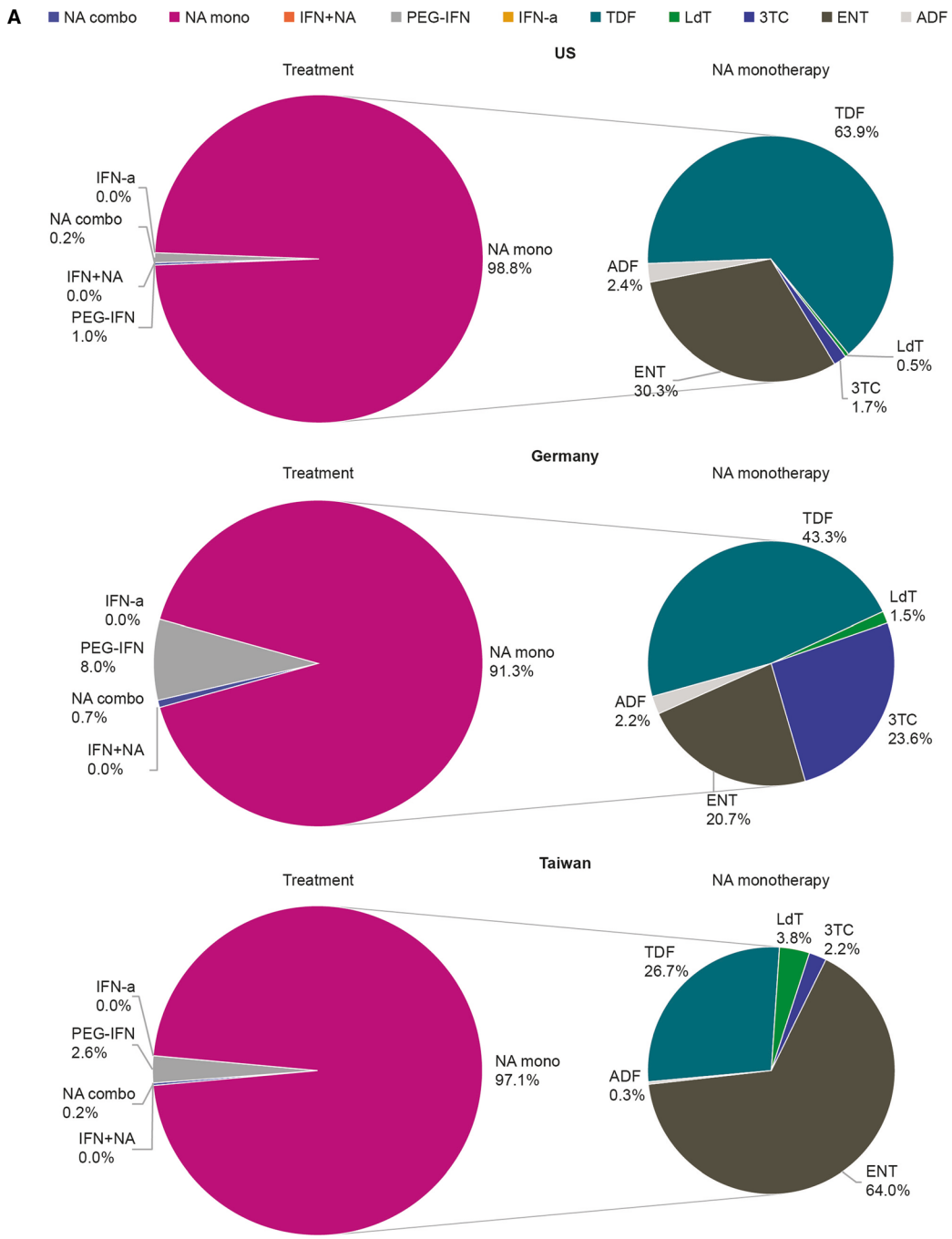

Fig. 4 Treatment patterns of NCIA patients. **A** At index; **B** amongst those initiating treatment during follow-up. Note: The proportions in 'Treatment' charts from panel **A** (US and Taiwan) and panel **B** (Taiwan) do not equal 100.0%, and the proportions in 'NA monotherapy' charts from panel **A** (US and Germany) and panel **B** (Taiwan) do not equal exactly the corresponding proportion in the 'Treatment' charts due to rounding to one decimal place. *3TC* lamivudine, *ADF* adefovir, *ENT* entecavir, *IFN* interferon, *IFN-a* interferon alpha, *LdT* telbivudine, *NA* nucleos(t)ide analogue, *NCIA* non-coinfected adults, *PEG-IFN* pegylated interferon, *TDF* tenofovir disoproxil fumarate

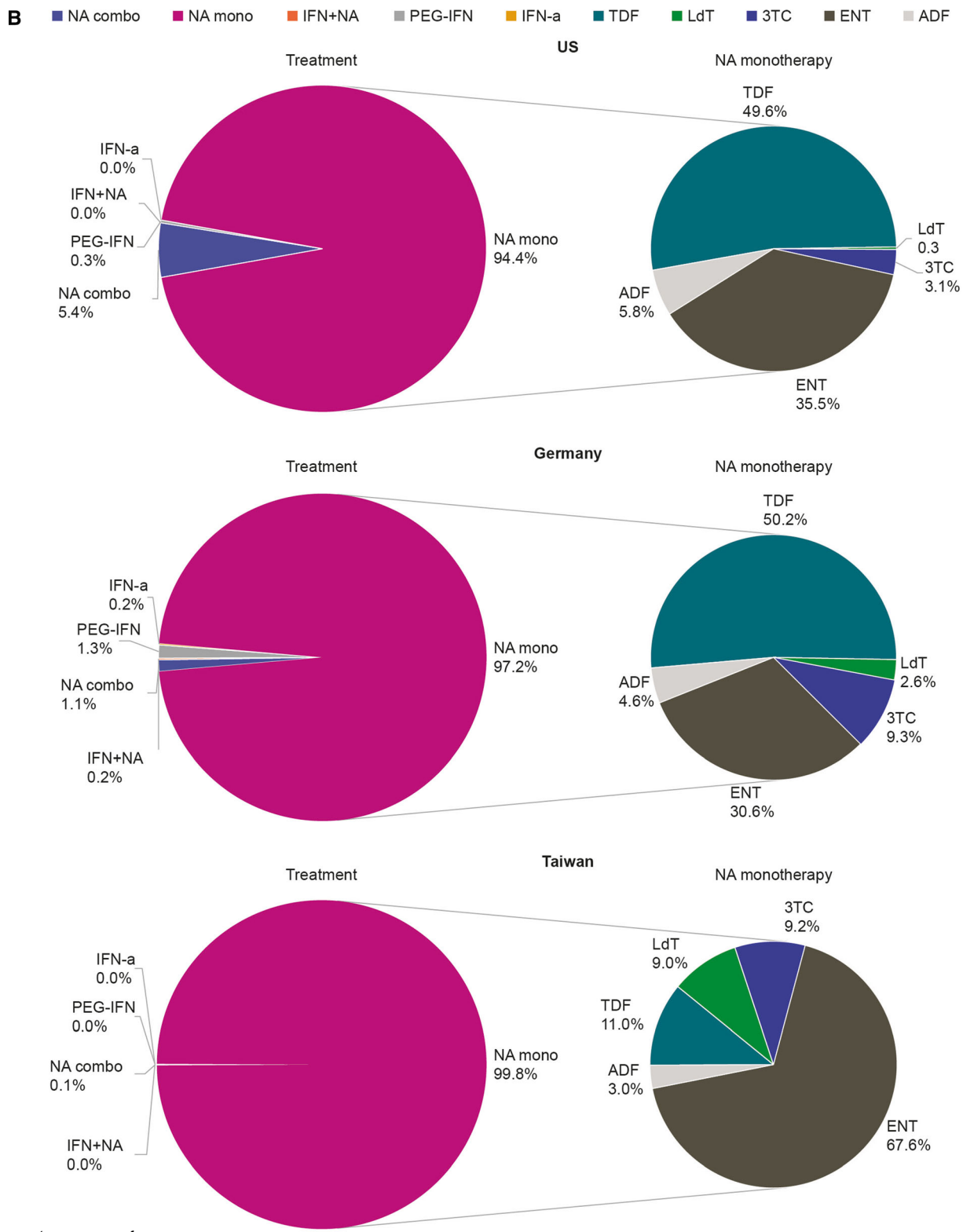

Fig. 4 continued

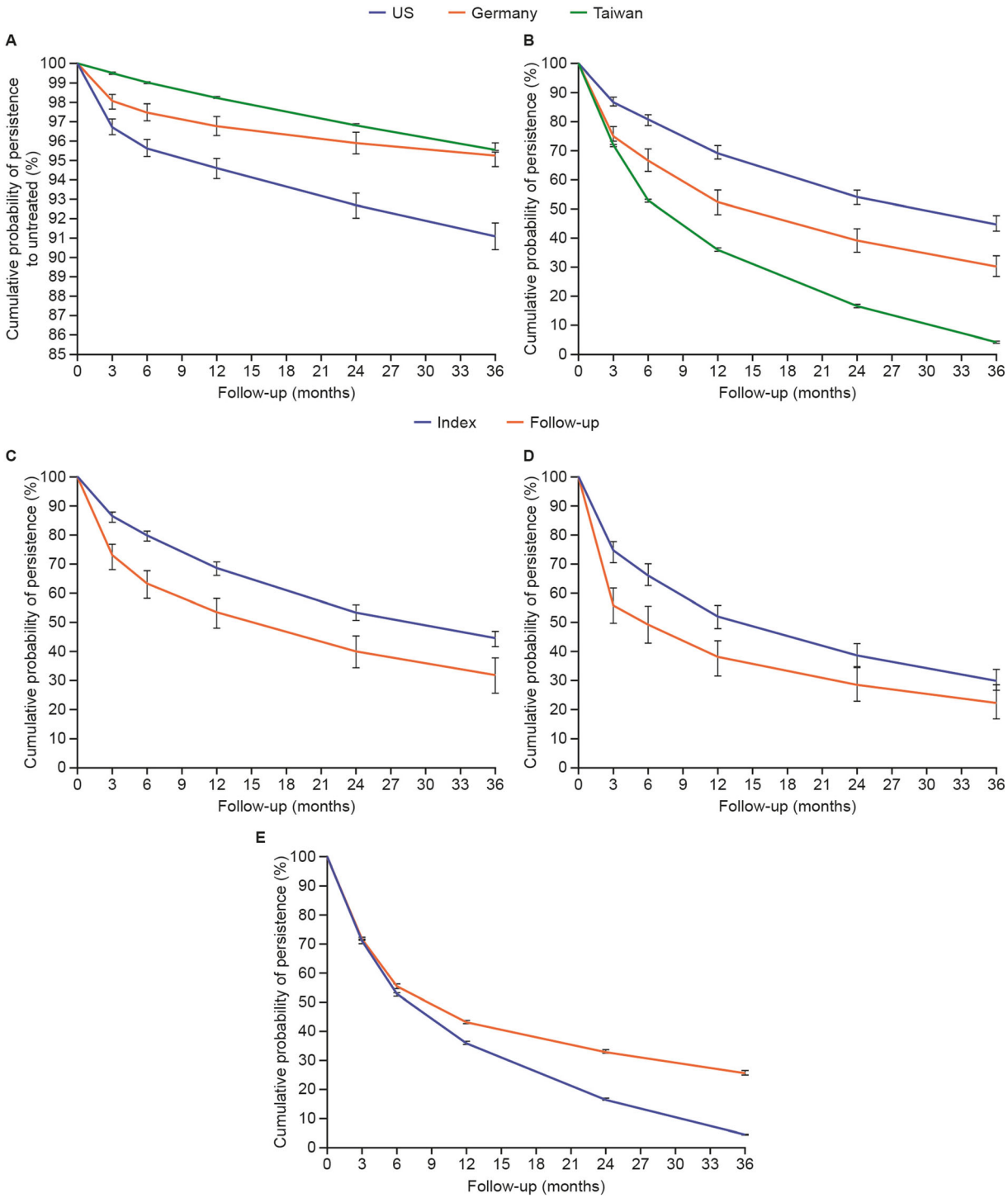

Fig. 5 Persistence to treatment status among NCIA patients. **A** Untreated at index; **B** treated with NAs at index; **C**–**E** untreated at index who initiated during follow-up in the US (**C**), Germany (**D**) and Taiwan (**E**). *NCIA* non-coinfected adults

index from 6 months; divergence continued to increase throughout follow-up (Fig. 5E). Generally, most patients who contributed ≥ 2 years of observation time retained their index treatment status; however, some cycling on and off different treatments was observed (Fig. 6). Persistence to NAs amongst coinfected adult patients is shown in Table S9.

Long-term Clinical Outcomes

Estimates of the cumulative incidence of cirrhosis, decompensated liver disease, and HCC are shown in Fig. 7 and Tables S10 and S11 (too few observations were identified for liver transplantations; data are available on request). For both untreated and NA-treated patients at index, the cumulative incidence of the outcomes in the US was either higher than, or comparable with, that observed in Taiwan, and both were higher than in Germany. The cumulative incidence of each outcome was higher among NA-treated patients than for patients who were untreated at index.

Sensitivity analyses tested the effect of persistence to patients' index treatment status by censoring on-treatment status change (Figure S1; Table S12); findings varied when subsequent treatment changes were considered. In the US, the cumulative incidence was comparable among untreated patients (95% CIs overlapped) but lower among NA-treated patients. Conversely, in Taiwan, the incidence was lower in untreated patients but comparable in NA-treated patients. In Germany, the cumulative incidence among untreated patients was consistently lower. For NA-treated patients, however, the cumulative incidence of cirrhosis and decompensated liver disease was higher whilst HCC incidence was lower.

DISCUSSION

This study describes the prevalence, characteristics, treatment patterns, and long-term clinical outcomes of patients with chronic HBV infection in the US, Germany, and Taiwan. Uniquely, the same study objectives and analyses were applied to three geographically disparate cohorts to generate current contemporaneous data. Each cohort comprised patients under distinct medical care systems, and study findings must be interpreted accordingly. Nevertheless, the study provides real-world generalisability from large study populations, providing a one-time snapshot of patients with chronic HBV infection.

The prevalence of chronic HBV infection was higher in Taiwan than in the US or Germany. This accords with a recent global seroprevalence study where reported diagnosed cases equate to a prevalence of approximately 0.3%, 0.3%, and 9.4% in the US, Germany, and Taiwan respectively [23]. Whilst the direction of the estimates is similar, the relative difference for Taiwan is greater in the Polaris Study [23]. This might reflect different case definitions (cases of HBsAg-positive infection versus patients with chronic HBV infection in our study) and different methodological approaches (modelling versus real-world data). Eligibility in the current study may also explain the difference, as the requirement for an active chronic HBV claim from 2010 would exclude patients with clinically mild infections not actively seeking care. The consistent prevalence pattern with age reflects the natural history of disease, diagnosis, and (potentially, for the elderly) mortality or the competing risk of other co-morbidities. Consistent with previous findings, most patients were male [24].

This study stratified by HCV/HIV coinfection status to delineate the confounding effect of coinfection status on patient characteristics, treatment, and associated outcomes. Whilst the focus was on non-coinfected patients, the coinfected population warrants comment. Whilst the direction of HIV coinfection rate (US > Germany > Taiwan) follows the same pattern for global HIV prevalence, the pattern seen for HCV (US ≈ Germany > Taiwan) differs from global HCV prevalence (Taiwan > USA > Germany) [25]. This suggests different predominating routes of infection for these viruses in different countries, although differential testing strategies may also play a role.

Acknowledging the stringent treatment definition in the current study, requiring patients to have a prescription covering their index date,

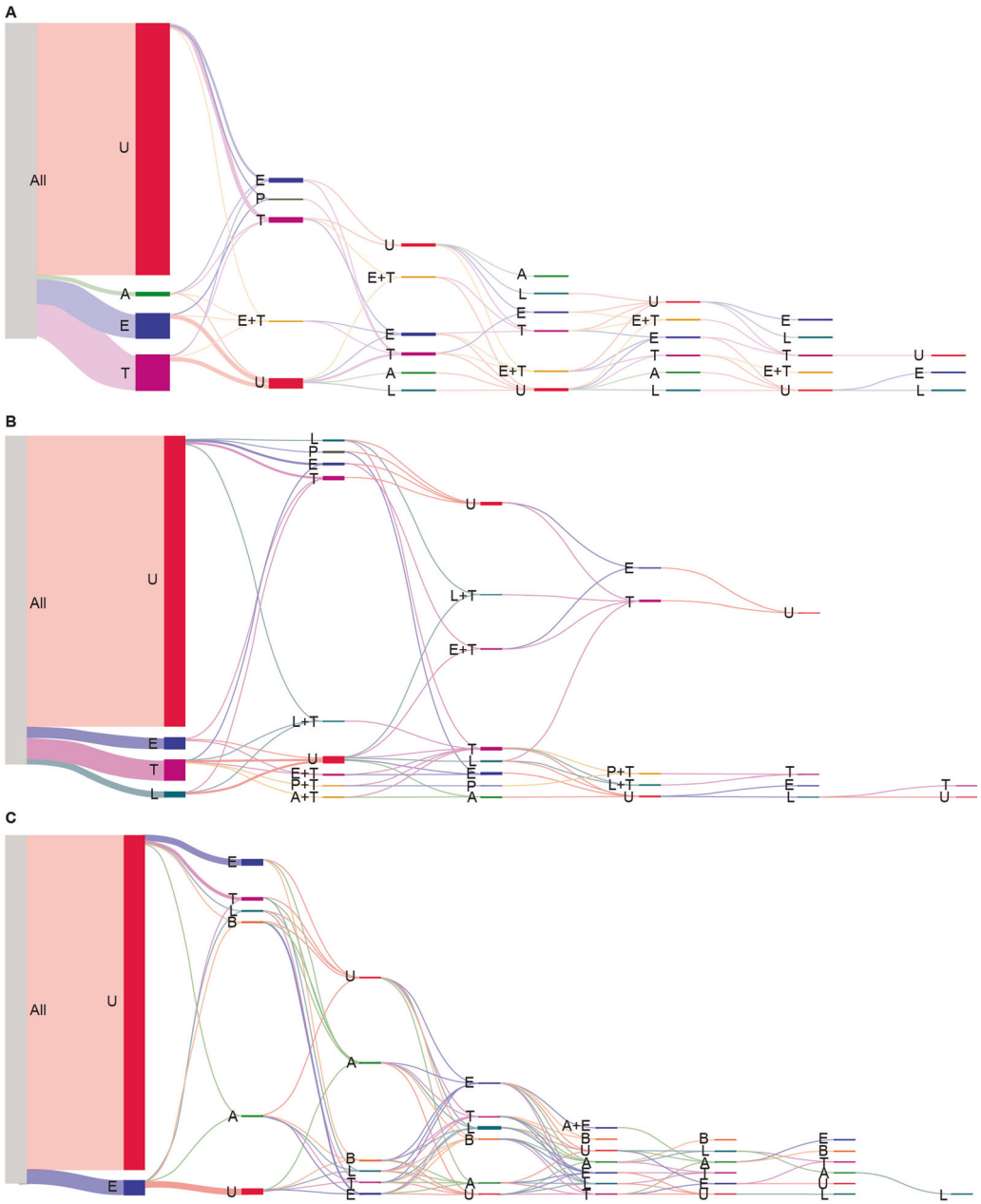

Fig. 6 Longitudinal treatment patterns in NCIA patients who remained in the study for 2 years. **A** US; **B** Germany; **C** Taiwan. The nodes (vertical bars) represent the order of treatments prescribed in the year, and the width of the links (horizontal connectors) represents the proportion of patients moving from one treatment state to another. Lines of therapy prescribed ≥ 1% are presented here. *A* adefovir, *B* telbivudine, *E* entecavir, *I* interferon, *L* lamivudine, *NCIA* non-coinfected adults, *P* pegylated interferon, *T* tenofovir, *U* untreated

treatment levels were low. Lower treatment levels in Taiwan may be due to their stringent treatment eligibility: The National Health Insurance programme determines that patients must meet four criteria to receive antiviral therapy. Furthermore, not all eligible patients receive treatment; it was estimated that just 15–25% of eligible Taiwanese patients were

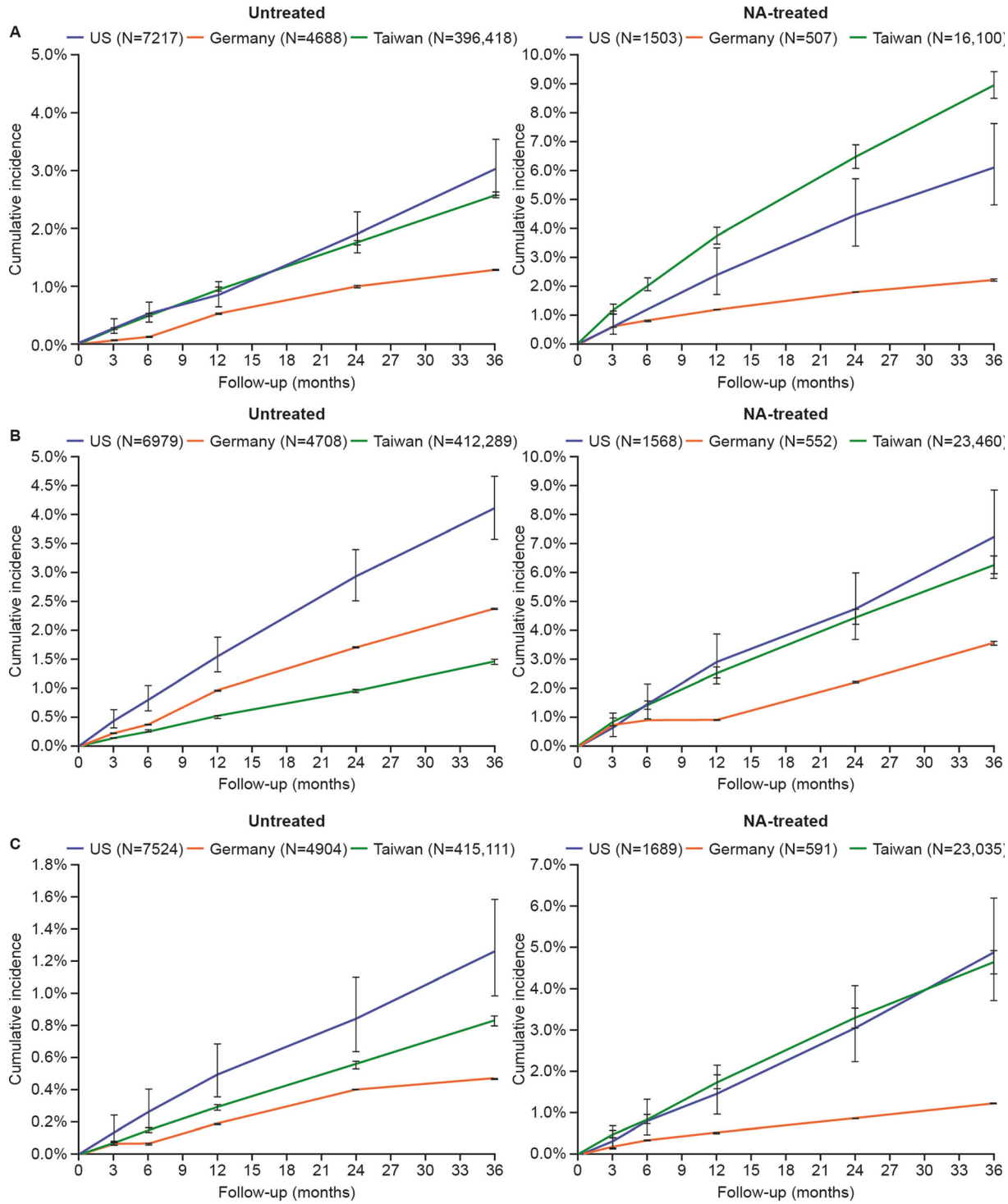

Fig. 7 Long-term clinical outcomes in NCIA patients by index treatment status. **A** Cirrhosis; **B** decompensated liver disease; **C** hepatocellular carcinoma. *NA* nucleos(t)ide analogues, *NCIA* non-coinfected adult

treated between 2004 and 2011 [26]. Most patients untreated at index in the current study remained so throughout follow-up, suggesting a possible unmet need for effective treatments, or that access to current treatments could be improved.

Consistent with existing clinical practice guideline recommendations, NAs were the most common treatment option in all three countries [2]; IFN treatment was comparatively rare. NAs are recommended for long-term use, whilst IFNs are a finite treatment [7]; hence the cross-sectional nature of ascertaining treatment via 'active' prescriptions at timepoints in this study may favour long-term therapies. Persistence to NA treatment appeared to be low among patients receiving NAs at index; 44%, 30%, and 4% in the US, Germany, and Taiwan respectively. The lower relative persistence in Taiwan is in line with Taiwanese guidelines, which recommend that patients discontinue therapy after 3 years [11, 12]. This contrasts with broader Asian guidelines which recommend treatment cessation in patients without liver cirrhosis largely following specific clinical events (HBeAg seroconversion in HBeAg-positive patients; HBsAg loss/anti-HBs seroconversion in HBeAg-negative patients) and often after a period of treatment consolidation [12]; guidelines in the US and Europe [6] offer similar advice. The difference in the within-country data for patients treated at index versus those untreated at index who initiated treatment during follow-up reinforces this difference. In both the US and Germany, persistence was lower in patients initiating treatment during follow-up, as those treated at index would not include those with poor persistence soon after initiation. In Taiwan, however, the opposite was observed as those treated at index were closer to the 3-year threshold for discontinuation. The Sankey plots substantiate the finding that most patients remain untreated or on the same treatment. The cycling on and off therapy, observed for a proportion of patients, suggests, however, that the a priori grace period of 30 days for defining discontinuation was potentially too short; 60 or even 90 days is recommended for future studies. A surprising number of patients in Germany initiated lamivudine treatment during follow-up. Whilst German clinical practice guidelines (2011; as-yet not updated) make no clear statement about initiating treatment with lamivudine, they could be interpreted as favouring it, particularly in patients with a low viral load and no evidence of advanced liver fibrosis [27]. Furthermore, and anecdotally, uptake of newer drugs can be relatively slow in Germany. Combined, these facts suggest that despite the availability of newer NAs in 2013, some reluctance in initiating treatment differently existed.

In all three countries, patients who received NA treatment had higher cumulative incidence rates of cirrhosis and HCC during follow-up than patients who were untreated. This finding reflects confounding by indication, as those with more severe disease, thus at greatest risk of sequelae, are more likely to receive treatment. The sensitivity analyses attenuated but did not eliminate this. Additional studies are required to adjust for prognostic patient characteristics to determine the effect of treatment on long-term chronic HBV infection outcomes.

The study had several limitations common to claims database studies [28]. Findings may reflect health-care providers' reimbursement claims rather than the patients' diagnosis, and there is potential for missing/inaccurate coding. Claims for laboratory testing exist but the accompanying results are rarely available routinely, limiting diagnostic accuracy; the universally low levels of fibrosis observed in each patient population alludes to this and suggests that this condition is not well captured by claims databases. It was assumed that prescribed medications were dispensed and taken which may not be the case. Additionally, the cross-sectional nature of the prevalence and baseline data may mask natural variation over time. Finally, causal relationships cannot be inferred about the effect of treatment on long-term clinical outcomes. The US analysis, conducted on commercially insured individuals, their dependents, or those with Medicare coverage, may be less representative of the broader population if certain subsets are at increased risk of chronic HBV infection but are less likely to be commercially insured. Asian Americans, for example, account for almost 60% of the HBV-

related HCC burden despite representing only 6% of the US population, but 14.6% of Asian Americans are uninsured [29]. For German data, the quarterly availability of outpatient diagnoses may result in differential misclassification of exposure and outcomes in this setting.

In conclusion, this study described the prevalence, patient characteristics, real-world treatment patterns, and long-term clinical outcomes of patients with chronic HBV infection. The proportions of patients with chronic HBV receiving treatment appeared to be low among all three populations, suggesting a potential unmet need for (or access to) effective treatments. Further investigations to identify and explore patient populations who would benefit most from chronic HBV treatment are warranted.

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Disclosures. Iain Andrew Gillespie, Yunhao Liu, Eleonora Morais, Stuart Kendrick, and Dickens Theodore are employees of GSK and hold stocks/shares in the company. Elisabeth Kap, Naomi Boxall, and Sarah Jenner are employees of IQVIA, which received funding from GSK to conduct the research. Wendy Cheng, Rose Chang, Mei Sheng Duh, and Suna Park are employees of Analysis Group, Inc., which received funding from GSK to conduct the research study. Miriam Ketz and Christian Schindler had no conflicts. K. Arnold Chan is an employee at the National Taiwan University, which received funding support from GSK to conduct the research. Shu-Feng Hsieh has no perceived conflicts to disclose.

Compliance with Ethics Guidelines. No formal ethical approval was required as no primary collection of individual human data occurred; data were anonymised or pseudonymised at source (researchers had no access to identifiable data). In Taiwan, the study was approved by the National Taiwan University Hospital Research Ethics Committee (approval document 201805146 W); informed consent was waived.

Data Availability. GSK makes available anonymised individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data,

and for clinical studies not listed, please submit an enquiry via the website.

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