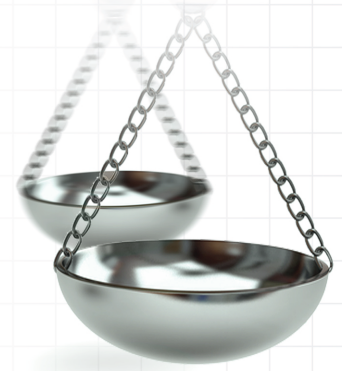




A comparison of healthcare resource utilization and costs between patients with chronic lymphocytic leukemia treated with first-line ibrutinib or acalabrutinib using two large US real-world databases

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Aim: Real-world evidence comparing healthcare resource utilization (HRU) and costs between ibrutinib and acalabrutinib, two Bruton's tyrosine kinase inhibitors for the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) is limited. **Materials & methods:** Commercial claims from IQVIA PharMetrics Plus and electronic medical records from Acentrus were used to separately evaluate HRU and costs in CLL/SLL patients initiating first-line (1L) single-agent ibrutinib or acalabrutinib on or after 21 November 2019 (index date). Imputed costs were used for Acentrus using previously published assumptions. Regression analyses adjusted for baseline characteristics were used to compare HRU and costs between ibrutinib and acalabrutinib during 1L therapy. **Results:** In IQVIA, 537 and 355 patients initiated 1L ibrutinib and acalabrutinib, respectively; in Acentrus, 710 and 373 patients initiated 1L ibrutinib and acalabrutinib, respectively. The mean duration of 1L (in years) was longer for ibrutinib (IQVIA: 1.2; Acentrus: 1.3) than acalabrutinib (IQVIA: 0.8; Acentrus: 0.9). The number of CLL/SLL-related outpatient visits were significantly lower for ibrutinib versus acalabrutinib (IQVIA: 0.86 vs 1.09 per-patient-per-month, rate ratio: 0.85, $p = 0.018$; Acentrus: 0.57 vs 0.74 per-patient-per-month, rate ratio: 0.80, $p = 0.036$). Using claims data for IQVIA and imputed costs for Acentrus, total all-cause costs (IQVIA: mean monthly cost difference [MMCD]: -\$764, $p = 0.279$; Acentrus: MMCD: -\$1355, $p = 0.004$) and CLL/SLL related costs (IQVIA: MMCD: -\$649, $p = 0.133$; Acentrus: MMCD: -\$1215, $p = 0.004$) were lower for ibrutinib versus acalabrutinib. **Conclusion:** In this large real-world study using a mix of claims data and imputed cost estimates, CLL/SLL patients treated with ibrutinib had longer duration of 1L, fewer days with CLL/SLL-related outpatient services and numerically lower all-cause and CLL/SLL-related costs versus acalabrutinib, showing that ibrutinib can be an optimal cost-effective option in 1L.

Plain language summary

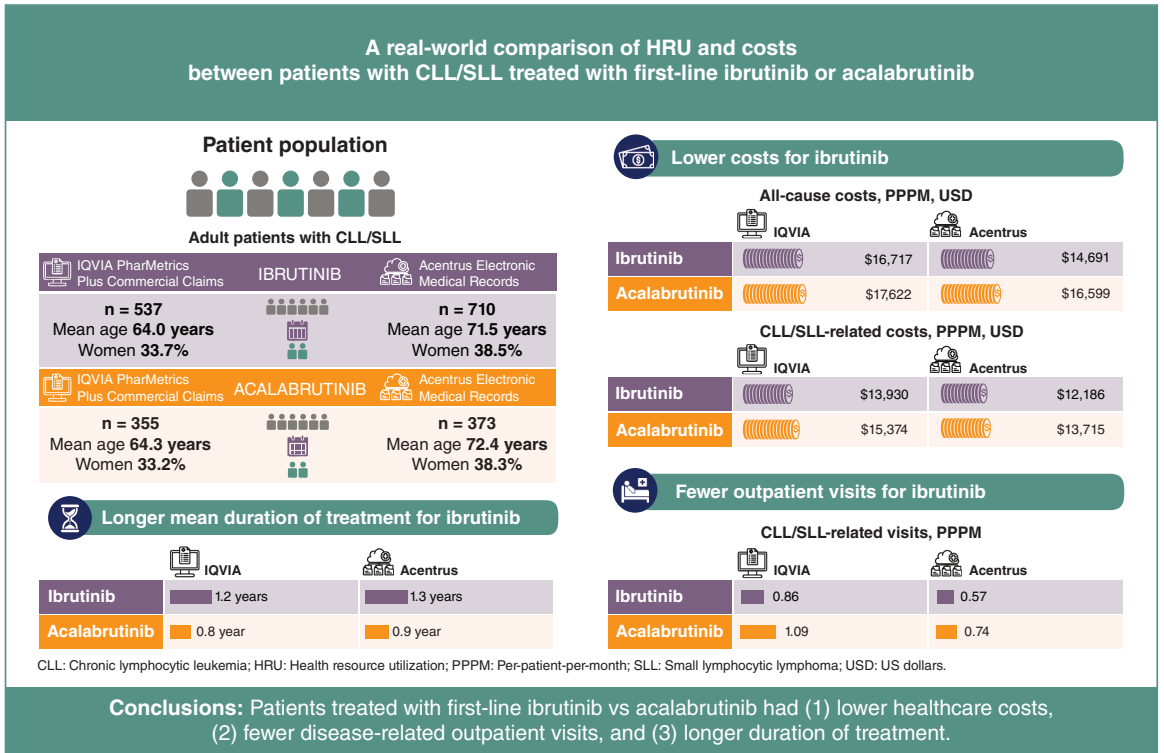
What is this article about? Ibrutinib and acalabrutinib are recommended for first-line (1L) treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). This study compared the number of hospital admissions and outpatient visits, as well as healthcare costs between patients with CLL/SLL treated with either ibrutinib or acalabrutinib using two large databases representative of the US population.

What were the results? Findings were similar for the two databases. Patients treated with ibrutinib had longer duration of 1L, fewer disease-related outpatient visits and consistently similar or lower healthcare costs compared with patients treated with acalabrutinib.

What do the results mean? The use of two large databases allows for improved generalizability of study findings, and suggests that ibrutinib is a cost-effective option for 1L CLL/SLL therapy compared with acalabrutinib.

Tweetable abstract: A study found that patients with CLL/SLL treated with ibrutinib had fewer disease-related outpatient visits and similar or lower healthcare costs compared with patients treated with acalabrutinib. Results suggest ibrutinib can be a more cost-effective option for first-line CLL/SLL therapy.

Graphical abstract:



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Keywords: acalabrutinib • chronic lymphocytic leukemia • claims data • cost comparison • costs • EMR • healthcare resource use • ibrutinib • real-world study • small lymphocytic lymphoma

Background

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is a type of hematologic cancer characterized by the clonal expansion of mature B lymphocytes [1]. It is the most common form of leukemia in adults in the US, with a 5-year survival rate of 88.5% [1]. The American Cancer Society estimates that there will be approximately 23,690 new cases of CLL and 4460 deaths from CLL in the US in 2025 [2].

With the advent of oral targeted therapies, Bruton tyrosine kinase inhibitors (BTKis) such as ibrutinib (once-daily) and acalabrutinib (twice-daily) have become standard-of-care first-line (1L) treatments for CLL/SLL [3]. Since the approval of ibrutinib in February 2014 for relapsed/refractory CLL, followed by its approval in 1L in March 2016 [3], insurance claims data on file from the IQVIA database have reported that over 250,000 patients with CLL/SLL have been treated with ibrutinib in the US. In addition, several phase III clinical trials and real-world studies with long-term follow-up have demonstrated improved progression-free survival and overall survival in CLL/SLL patients initiating 1L ibrutinib versus comparator cohorts [4–12]. In November 2019, acalabrutinib was also approved for the treatment of CLL/SLL, either as a monotherapy or in combination with obinutuzumab [13]. While there is currently no clinical trial comparing ibrutinib and acalabrutinib in the 1L setting, real-world evidence comparing these two treatments in 1L is emerging, including some real-world studies reporting higher adherence and longer time to next treatment (TTNT; overall and among a subgroup with high-risk characteristics) for ibrutinib relative to acalabrutinib [14–17]. Dose adjustment with ibrutinib, which allows patients to maintain

ibrutinib efficacy while preventing recurrence or worsening of adverse events [18–22], was also associated with numerically longer duration of treatment and TTNT compared with acalabrutinib [23].

In addition to clinical outcomes, ibrutinib has been shown to result in net healthcare cost savings relative to other therapy classes such as anti-CD20 based chemoimmunotherapy (CIT) regimens [24,25]. However, except for an early analysis with short follow-up [26], there are limited real-world studies comparing healthcare resource utilization (HRU) and costs between different BTKis in 1L. As emerging real-world data suggests improved clinical outcomes for patients initiated on ibrutinib versus acalabrutinib [14–17], there is a need to evaluate the corresponding HRU and costs for these treatments in the real-world setting and over longer follow-up time. Therefore, the current study was conducted to compare HRU and costs between patients with CLL/SLL treated with 1L single-agent ibrutinib and acalabrutinib using two large real-world databases covering a diversified population.

Materials & methods

Data sources

Claims data from IQVIA PharMetrics Plus (IQVIA) from 21 November 2018 to most recent at the time the study was conducted (30 September 2022) and electronic medical records (EMR) from Acentrus from 21 November 2018 to most recent at the time the study was conducted (30 April 2022) for patients initiating ibrutinib or acalabrutinib in 1L on or after 21 November 2019 were used to maximize generalizability and robustness of results. Claims data from 21 November 2018 were accessed for both databases to ensure at least 1 year of data prior to initiation of treatment.

The IQVIA database is an adjudicated health plan claims database. It is made up of fully adjudicated health plan claims data and enrollment information for more than 215 million unique individuals with commercial health insurance. IQVIA comprises information from over 70 contributing health plans and self-insured employer groups throughout the US with more than 140 million unique enrollees. The database includes medical and pharmacy claims data, patient-level enrollment records and patient demographics and is representative of the commercially insured US population.

Acentrus is a health system solution used by 128,000 prescribers, containing inpatient and outpatient data from 27 sites. This includes six National Comprehensive Cancer Network members and ten National Cancer Institute designated sites, all contributing data from both medication orders and refills. Acentrus includes patient records from 15 academic and 12 nonteaching hospital systems across 15 US states.

Data from both the IQVIA and Acentrus databases are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA).

Study design

A retrospective cohort study design was used. Analyses were conducted separately for IQVIA and Acentrus. In both databases, adult patients initiating 1L single-agent ibrutinib or acalabrutinib on or after 21 November 2019 (acalabrutinib approval) were analyzed, with the index date defined as the date of initiation of ibrutinib or acalabrutinib. A window of 28 days post-index was used to ascertain that no other antineoplastic agents were used in combination with ibrutinib or acalabrutinib (Figure 1). In IQVIA analyses, a washout period of at least 6 months of continuous eligibility prior to the index date was used to confirm 1L therapy and assess baseline characteristics (6 months was required instead of 12 months, to account for plan member turnover associated with commercial plans, with or without changing the medical providers), while in Acentrus, a washout period of at least 12 months of data availability (insurance eligibility not available in Acentrus) prior to the index date was used. The follow-up period was defined as the period from the index date to the earliest of initiation of second-line (2L) therapy, death (only available in Acentrus), end of continuous enrollment (only available in IQVIA), or end of data availability. As add-on of certain anticancer therapies may indicate late initiation of agents as part of a combination regimen in 1L rather than disease progression, patients were censored on the date of add-on if they had an anti-CD20 antibody (i.e., obinutuzumab or rituximab) or venetoclax add-on to the index BTKi within 180 days post-index, as done in a previous study [17] based on prescribing guidelines recommending initiation of the second agent within 6 months of therapy initiation [13,27–30]. Furthermore, patients switching to another BTKi were censored at the date of switch, as this may indicate a switch due to tolerability rather than disease progression [31–34]. These censoring rules were implemented to make sure HRU and costs are evaluated during 1L single-agent therapy use and prior to a potential indicator of disease progression.

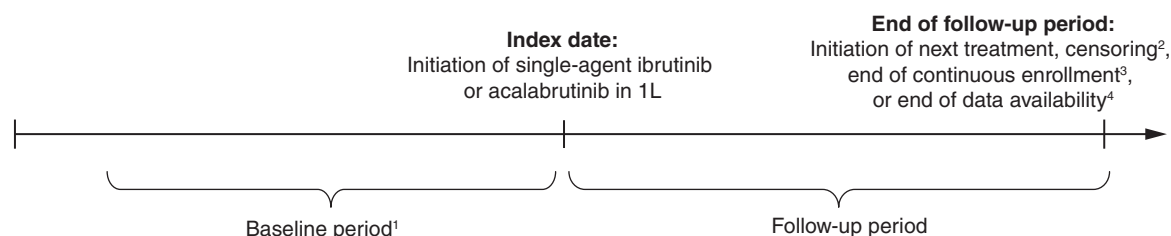


Figure 1. Study design for IQVIA and Acentrus analyses.

¹A 6-month baseline period was used in IQVIA. A 12-month baseline period was used in Acentrus.

²Patients were censored on the date of switch or add-on if they had one of the following: a within-class BTKi switch (i.e., the next treatment is also a BTKi) or an anti-CD20 antibody (i.e., obinutuzumab or rituximab) or venetoclax add-on to the index BTKi within 180 days post-index.

³End of continuous enrollment was used as an indicator of end of follow-up in IQVIA analyses only.

⁴End of data availability in IQVIA was 30 September 2022. End of data availability in Acentrus was 30 April 2022.

1L: First-line; BTKi: Bruton's tyrosine kinase inhibitor.

Study population

In both IQVIA and Acentrus analyses, patients were required to meet the following criteria: at least 18 years of age, initiation of ibrutinib or acalabrutinib in 1L on or after 21 November 2019 (index date), at least 6 months of continuous enrollment (IQVIA) or at least 12 months of data availability (Acentrus) prior to the index date, and at least one diagnosis for CLL/SLL prior to the index date (International Classification of Disease, 9th Revision, Clinical Modification [ICD-9 CM]: 204.1; International Classification of Disease, 10th Revision, Clinical Modification [ICD-10-CM]: C91.1, C83.0). Patients with other malignancies or end-stage renal disease prior to the index date were excluded. Additional details regarding inclusion and exclusion criteria are presented in [Figure 2](#).

Study measures

Patient demographics and clinical characteristics (i.e., Quan-Charlson Comorbidity Index [Quan-CCI], comorbidities, cardiovascular risk and medication use) were evaluated during the baseline period (i.e., 6 months pre-index for IQVIA and 12 months pre-index for Acentrus).

HRU and cost outcomes were evaluated during the follow-up period (i.e., during 1L therapy). All-cause and CLL/SLL-related HRU outcomes included inpatient admissions and outpatient visits (including emergency department visits). All-cause and CLL/SLL-related healthcare costs included pharmacy (broken down into BTKi costs and other pharmacy costs for IQVIA) and medical costs, with medical costs further broken down into inpatient and outpatient costs. CLL/SLL-related HRU and medical costs were defined as services with a diagnosis code for CLL/SLL. CLL/SLL-related pharmacy costs were defined as costs related to BTKi treatment.

In IQVIA, costs were based on paid claims while in Acentrus, costs were not available and were thus imputed based on available literature, to estimate costs from a mixed commercial and Medicare population. More specifically, guided by prior literature using cost imputation methods [35–38], costs were calculated based on HRU results observed in Acentrus and relevant available literature on healthcare costs for CLL/SLL patients treated with BTKis. In particular, published data from Fradley *et al.* [26] evaluating costs for 1L ibrutinib and acalabrutinib were used. As Fradley *et al.* did not present costs for each medical service separately, data from Huang *et al.* [24] was used to estimate the proportion of costs attributable to each category under medical costs, which were then summed to report total medical costs. All-cause and CLL/SLL-related pharmacy costs were also imputed based on Fradley *et al.* [26], using per-patient-per-month [PPPM] pharmacy costs and medication adherence information. Details of the calculations and assumptions are presented in [Supplementary Table 1](#) for medical costs and [Supplementary Table 2](#) for pharmacy costs.

In both IQVIA and Acentrus analyses, HRU and costs were reported PPPM, to account for varying durations of follow-up between patients. All cost estimates were inflated to 2022 US dollars using the medical care component of the Consumer Price Index.

Statistical analyses

All analyses were performed using SAS (SAS Institute, NC, USA). Baseline characteristics were described using means, standard deviations, and medians for continuous variables and frequencies and proportions for categorical

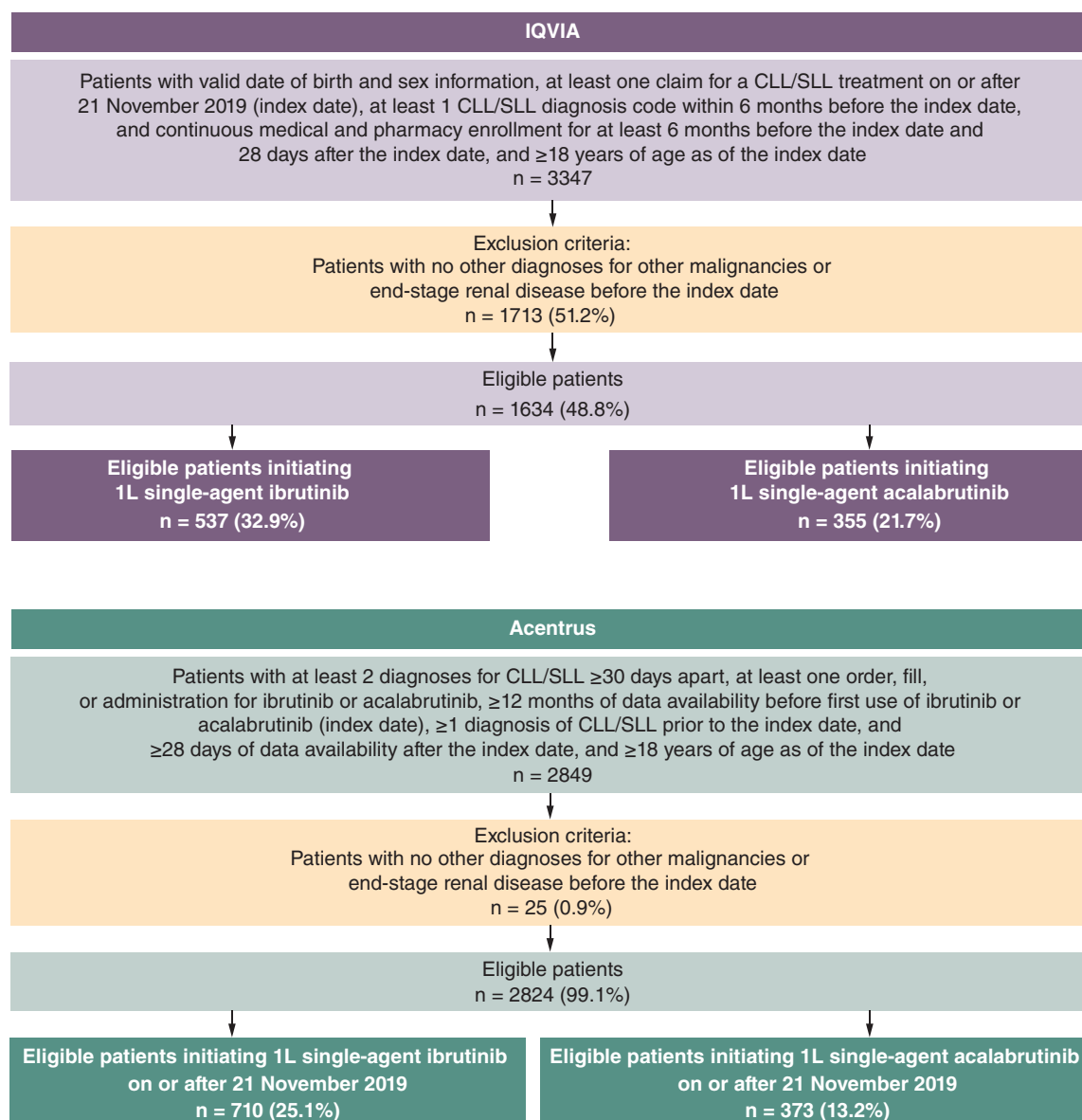


Figure 2. Study population selection.

1L: First line; CLL: Chronic lymphocytic leukemia; SLL: Small lymphocytic lymphoma.

variables. Standardized differences (std diff.) were calculated in both analyses to compare baseline characteristics (characteristics with differences $<10\%$ were considered similar [39]). To account for differences in baseline characteristics between cohorts, baseline demographics, comorbidities, CLL/SLL-related symptoms, medications, HRU and costs were adjusted for. Additional details regarding the characteristics adjusted for in each analysis are provided in [Supplementary Table 3](#). All-cause and CLL/SLL-related HRU were compared between the two cohorts using Poisson regression models, with results reported as rate ratios (RRs). Healthcare costs were compared between the two cohorts using ordinary least squares regression models, with results reported as adjusted mean monthly cost differences (MMCDs).

Results

Study population & baseline characteristics

In IQVIA, a total of 537 and 355 patients with CLL/SLL initiating 1L single-agent ibrutinib or acalabrutinib were included, respectively ([Figure 2](#)). Mean observed duration of 1L treatment was 1.2 years and 0.8 years for ibrutinib

and acalabrutinib. Mean age (ibrutinib vs acalabrutinib: 64.0 vs 64.3 years, std diff.: 3.1%), proportion of women (33.7 vs 33.2%, std diff.: 1.0%), mean Quan-CCI score (2.7 vs 2.7, std diff.: 3.0%), and mean CHA₂DS₂-VASc risk score (as an indicator of cardiovascular risk; 1.7 vs 1.7, std diff.: 3.4%) were similar between cohorts (Table 1).

In Acentrus, a total of 710 and 373 patients with CLL/SLL initiating 1L single-agent ibrutinib or acalabrutinib were included, respectively (Figure 2). Mean observed duration of 1L treatment was 1.3 and 0.9 years for ibrutinib and acalabrutinib, respectively. Mean age (ibrutinib vs acalabrutinib: 71.5 vs 72.4 years, std diff.: 9.1%), proportion of women (38.5% vs 38.3%, std diff.: 0.2%), mean Quan-CCI (3.1 vs 3.0, std diff.: 3.4%) and mean CHA₂DS₂-VASc risk score (2.3 vs 2.3, std diff.: 5.6%) were similar between the two cohorts (Table 1).

Comparison of HRU & costs

In both databases, the number of all-cause inpatient admissions was comparable for ibrutinib versus acalabrutinib (IQVIA: 0.08 vs 0.07 PPPM, RR: 0.96, $p = 0.614$; Acentrus: 0.06 PPPM for both cohorts, RR: 1.08, $p = 0.730$) (Figure 3). A similar trend was observed for CLL/SLL-related inpatient admissions (IQVIA: 0.03 PPPM for both cohorts, RR: 0.90, $p = 0.763$; Acentrus: 0.03 vs 0.04 PPPM, RR: 0.78, $p = 0.381$). CLL/SLL-related outpatient visits were significantly lower in both databases for ibrutinib versus acalabrutinib (IQVIA: 0.86 vs 1.09 PPPM, RR: 0.85, $p = 0.018$; Acentrus: 0.57 vs 0.74 PPPM, RR: 0.80, $p = 0.036$).

Healthcare costs were numerically lower for ibrutinib versus acalabrutinib (Figure 4). In IQVIA, total all-cause costs (including medical and pharmacy costs) were \$16,717 and \$17,622 for the ibrutinib and acalabrutinib cohorts, respectively (MMCD: -\$764, $p = 0.279$), with the majority of costs being CLL/SLL-related (\$13,930 and \$15,374 for the ibrutinib and acalabrutinib cohorts, respectively; MMCD: -\$649, $p = 0.133$). While statistically nonsignificant, BTKi drug costs were a driver of lower all-cause and CLL/SLL-related costs for ibrutinib versus acalabrutinib (MMCD: -\$467, $p = 0.248$), along with inpatient costs (MMCD: -\$379, $p = 0.479$).

In Acentrus, total imputed (estimated) all-cause and CLL/SLL-related costs (including medical and pharmacy costs) were significantly lower in the ibrutinib versus acalabrutinib cohort. More specifically, total all-cause imputed (estimated) costs were \$14,691 and \$16,599 for the ibrutinib and acalabrutinib cohorts, respectively (MMCD: -\$1355, $p = 0.004$), while total CLL/SLL-related imputed (estimated) costs were \$12,186 and \$13,715 for the ibrutinib and acalabrutinib cohorts, respectively (MMCD: -\$1215, $p = 0.004$). Imputed (estimated) pharmacy costs were significantly lower for both all-cause and CLL/SLL-related costs (MMCD: -\$940, $p = 0.008$), and were a driver of lower costs for the ibrutinib versus acalabrutinib cohort.

Discussion

To our knowledge, the current study is one of the largest to report on HRU and costs of patients with CLL/SLL treated with 1L ibrutinib or acalabrutinib. Two separate real-world databases were analyzed in this study, covering patients with various characteristics and insurance types, increasing the generalizability of study findings. The results showed longer duration of 1L, lower CLL/SLL-related outpatient visits, as well as numerically lower all-cause and CLL/SLL-related healthcare costs based on a mix of cost data from claims (IQVIA) and imputed cost data (Acentrus) for patients treated with ibrutinib compared with acalabrutinib.

There is limited literature comparing the economic outcomes associated with ibrutinib and acalabrutinib treatment in patients with CLL/SLL. In a previous real-world analysis of patients initiated on 1L ibrutinib or acalabrutinib by Fradley *et al.* CLL/SLL-related HRU and costs were similar in both cohorts (number of outpatient visits: 1.44 vs 1.47 PPPM, $p = 0.624$; total costs: \$15,451 vs \$15,169, $p = 0.220$) [26]. These costs are generally consistent with those observed in the current study, but this early analysis was conducted with data up to December 2021. The current study builds on the previously observed trends in HRU and costs [26] by using two distinct real-world databases and shows that over longer follow-up (September and April 2022, for IQVIA and Acentrus analyses, respectively), lower HRU and costs are observed for patients treated with ibrutinib compared with acalabrutinib.

While the reason for the difference in CLL/SLL-related outpatient visits could not be assessed and warrants additional research, it is possible that the lower number of visits for patients treated with ibrutinib was due to less monitoring compared with acalabrutinib, given that ibrutinib has been a well-established 1L treatment for CLL/SLL for a longer period of time. Indeed, based on further explorations of the data, it was found that the lower number of CLL/SLL-related outpatient visits for ibrutinib may have been due to a lower number of visits for management of CLL/SLL and associated laboratory testing (e.g., complete blood count or metabolic panel). Other potential reasons for the lower HRU and costs observed for ibrutinib may be related to the clinical outcomes observed for the two BTKis in prior real-world studies [14–17]. For instance, ibrutinib has been associated with

Table 1. Baseline characteristics.

	IQVIA			Acentrus		
	Ibrutinib (n = 537)	Acalabrutinib (n = 355)	Standardized difference, %	Ibrutinib (n = 710)	Acalabrutinib (n = 373)	Standardized difference, %
Demographics[‡]						
Age at index date, years, mean (SD)	64.0 (10.4)	64.3 (10.2)	3.1	71.5 (10.4)	72.4 (9.8)	9.1
Women, n (%)	181 (33.7)	118 (33.2)	1.0	273 (38.5)	143 (38.3)	0.2
Year of index date, n (%)						
2019	–	–	–	45 (6.3)	7 (1.9)	22.6 [†]
2020	287 (53.4)	73 (20.6)	72.4 [†]	408 (57.5)	119 (31.9)	53.2 [†]
2021	178 (33.1)	141 (39.7)	13.7 [†]	217 (30.6)	200 (53.6)	48.0 [†]
2022	72 (13.4)	141 (39.7)	62.4 [†]	40 (5.6)	47 (12.6)	24.4 [†]
Payer type[§], n (%)						
Medicare [¶]	138 (25.7)	85 (23.9)	4.1	196 (27.6)	104 (27.9)	0.6
Managed care	–	–	–	61 (8.6)	34 (9.1)	1.8
Medicaid	–	–	–	15 (2.1)	0 (0.0)	20.8 [†]
Commercial	280 (52.1)	192 (54.1)	3.9	–	–	–
Self-insured	119 (22.2)	78 (22.0)	0.5	–	–	–
Other	–	–	–	252 (35.5)	137 (36.7)	2.6
Unknown	–	–	–	186 (26.2)	98 (26.3)	0.2
US region, n (%)						
South	210 (39.1)	144 (40.6)	3.0	213 (30.0)	138 (37.0)	14.9 [†]
West	86 (16.0)	61 (17.2)	3.1	212 (29.9)	118 (31.6)	3.9
Midwest	173 (32.2)	104 (29.3)	6.3	188 (26.5)	86 (23.1)	7.9
Northeast	–	–	–	21 (3.0)	9 (2.4)	3.4
East	68 (12.7)	46 (13.0)	0.9	–	–	–
Unknown	–	–	–	76 (10.7)	22 (5.9)	17.5 [†]
Race, n (%)						
White	–	–	–	320 (45.1)	150 (40.2)	9.8
Black	–	–	–	25 (3.5)	19 (5.1)	7.8
Asian	–	–	–	13 (1.8)	7 (1.9)	0.3
Other	–	–	–	352 (49.6)	197 (52.8)	6.5
Clinical characteristics[#]						
Quan-CCI ^{††} , mean ± SD [median]	2.7 (1.2)	2.7 (1.3)	3.0	3.1 (1.7)	3.0 (1.7)	3.4
Baseline comorbidities, n (%)						
Hypertension	–	–	–	294 (41.4)	120 (32.2)	19.2 [†]
Atrial fibrillation	30 (5.6)	22 (6.2)	2.6	50 (7.0)	37 (9.9)	10.3 [†]
Atrial flutter	6 (1.1)	3 (0.8)	2.8	8 (1.1)	0 (0.0)	15.1 [†]
Bleeding/hemorrhage	20 (3.7)	16 (4.5)	3.9	14 (2.0)	8 (2.1)	1.2
Gastrointestinal symptoms	92 (17.1)	62 (17.5)	0.9	120 (16.9)	47 (12.6)	12.2 [†]
Metastatic cancer	–	–	–	17 (2.4)	17 (4.6)	11.8 [†]
CHA ₂ DS ₂ -VASc, mean (SD) ^{‡‡}	1.7 (1.5)	1.7 (1.5)	3.4	2.3 (1.5)	2.3 (1.4)	5.6

†Standardized difference ≥10%.

‡Demographic characteristics were evaluated on the date of treatment initiation.

§Insurance coverage type is identified by selecting the payer record closest to index date.

¶For IQVIA, the Medicare category includes Medicare Advantage and Medicare Supplemental.

#Clinical characteristics evaluated during the 6-month (IQVIA) or 12-month (Acentrus) baseline period, excluding the date of treatment initiation.

††Reference: [40].

‡‡The CHA₂DS₂-VASc risk score is calculated based on age, sex and presence of congestive heart failure, hypertension, diabetes, stroke/transient ischemic attack/thromboembolism and vascular disease. Reference: [41,42].

ACE: Angiotensin-converting enzyme; Quan-CCI: Quan-Charlson Comorbidity Index; SD: standard deviation US: United States.

Table 1. Baseline characteristics (cont.).

Clinical characteristics [#]						
Baseline medication, n (%)						
Use of corticosteroids	–	–	–	103 (14.5)	75 (20.1)	14.8 [†]
Use of antiplatelets	–	–	–	50 (7.0)	13 (3.5)	16.0 [†]
H2-receptor antagonists	15 (2.8)	7 (2.0)	5.4	36 (5.1)	16 (4.3)	3.7
Anticoagulants	40 (7.4)	28 (7.9)	1.6	87 (12.3)	42 (11.3)	3.1
ACE inhibitors	181 (33.7)	127 (35.8)	4.3	–	–	–
Diuretics	83 (15.5)	52 (14.6)	2.3	–	–	–
Beta blockers	98 (18.3)	80 (22.5)	10.7 [†]	99 (13.9)	53 (14.2)	0.8
Antihyperlipidemics	198 (36.9)	142 (4.0)	6.4	140 (19.7)	68 (18.2)	3.8

[†]Standardized difference $\geq 10\%$.

[‡]Demographic characteristics were evaluated on the date of treatment initiation.

[§]Insurance coverage type is identified by selecting the payer record closest to index date.

[¶]For IQVIA, the Medicare category includes Medicare Advantage and Medicare Supplemental.

[#]Clinical characteristics evaluated during the 6-month (IQVIA) or 12-month (Acentrus) baseline period, excluding the date of treatment initiation.

^{††}Reference: [40].

^{‡‡}The CHA₂DS₂-VASC risk score is calculated based on age, sex and presence of congestive heart failure, hypertension, diabetes, stroke/transient ischemic attack/thromboembolism and vascular disease. Reference: [41,42].

ACE: Angiotensin-converting enzyme; Quan-CCI: Quan-Charlson Comorbidity Index; SD: standard deviation US: United States.

higher treatment adherence [14,15] and longer TTNT compared with acalabrutinib for 1L CLL/SLL patients [16,17]. As treatment non-adherence has been associated with higher healthcare costs in previous studies [43,44], potentially due to increased rates of adverse events [45,46], the generally lower costs found for ibrutinib therapy in the current study may potentially be explained by higher adherence. Similarly, longer TTNT, as a proxy for progression-free disease [47,48], may indicate improved tolerability and a reduced need for patient follow-up and management. Finally, the possibility of dose reduction with ibrutinib may have contributed to lower pharmacy costs compared with acalabrutinib by extending the duration of ibrutinib prescriptions. Recent real-world analyses reported that 14.4–19.6% [49,50] of patients initiating ibrutinib in 1L for the treatment of CLL/SLL have a dose reduction, which may reduce the risk of adverse events and improve treatment adherence [51], while maintaining efficacy compared with those without a dose reduction [49,50]. Therefore, dose reduction may further improve TTNT and overall survival for the overall population of patients treated with ibrutinib compared with acalabrutinib [17,52], and contribute to the extended follow-up time and reduced pharmacy costs observed for ibrutinib.

Overall, with the current emerging real-world evidence for ibrutinib and acalabrutinib, the current study provides another perspective, contrasting with other economic evaluations including cost effectiveness analyses (CEAs), by capturing current clinical practice and implications on actual costs incurred in the management of CLL/SLL with BTKis. A recent publication on CEA comparing BTKis found higher costs per quality-adjusted life-year for ibrutinib compared with acalabrutinib, based on disease progression and extrapolated survival data, and with estimation of treatment duration, adverse event frequency, and all-cause death probability [53]. The CEA model also used the wholesale acquisition cost to estimate BTKis costs, which is different from actual paid amounts based on plan-negotiated contracts with providers. Finally, TTNT and real-world clinical practice involving dose reductions were not accounted for, despite their impact on real-world costs. In contrast, this real-world study captured all-cause medical services reimbursed by the payer for each patient, including costs related to BTKis and other treatments received for comorbidities. Given that patients with CLL/SLL with diverse characteristics initiating BTKis live longer and require a variety of medical services, this comprehensive approach with adjustment of covariates addresses the need for a real-world perspective on the cost burden to payers managing patients with CLL/SLL. Our study found lower per-patient all-cause costs for patients with CLL/SLL treated with ibrutinib versus acalabrutinib (IQVIA MMCD: -\$764, Acentrus MMCD: -\$1355) after accounting for age, comorbidity burden, and other differences in patient characteristics. Therefore, by leveraging real-world data, the economic evaluation of BTKi treatment in this study addresses key limitations associated with CEAs in the current literature. As the current results show, along with previous real-world evidence on improved clinical outcomes in patients treated with 1L ibrutinib compared with acalabrutinib, ibrutinib can be a cost-effective option for the 1L treatment of CLL/SLL.

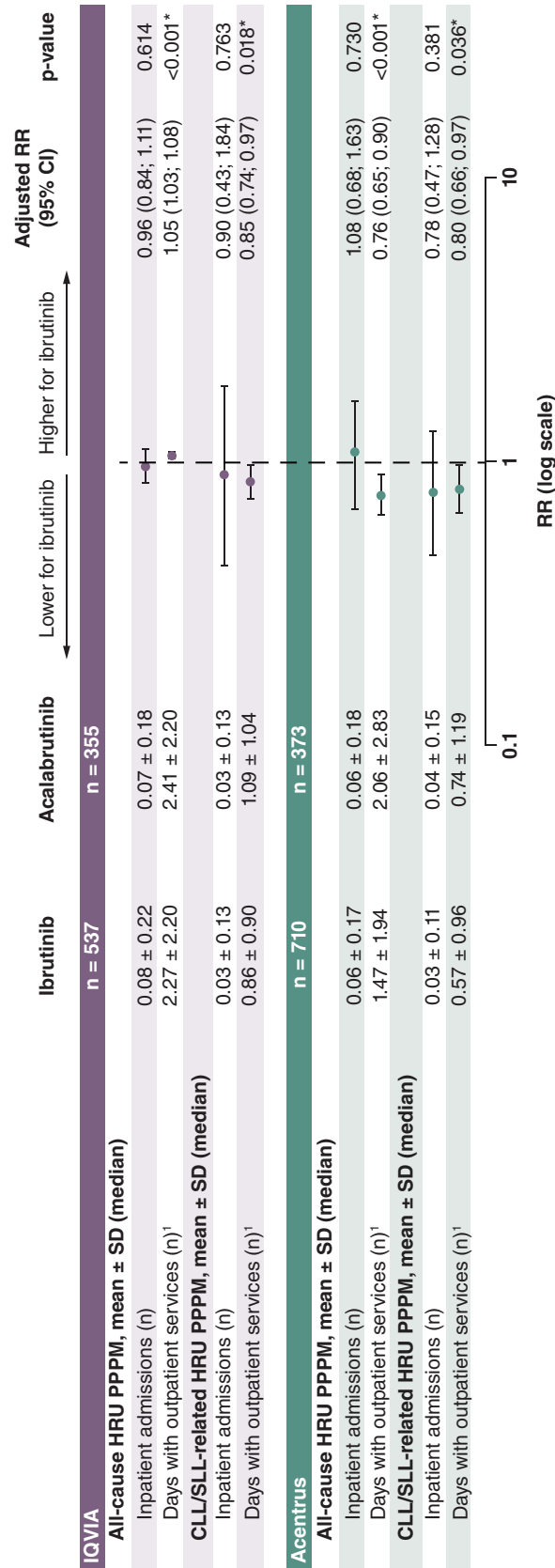


Figure 3. Comparison of healthcare resource use in chronic lymphocytic leukemia/small lymphocytic lymphoma patients initiating first-line ibrutinib or acalabrutinib.
¹Outpatient services included outpatient and emergency department visits.
*p-value ≤ 0.05.
1L: First-line; CI: Confidence interval; CLL: Chronic lymphocytic leukemia; HRU: Healthcare resource use; PPPM: Per-patient-per-month; RR: Rate ratio; SD: Standard deviation; SLL: Small lymphocytic lymphoma.

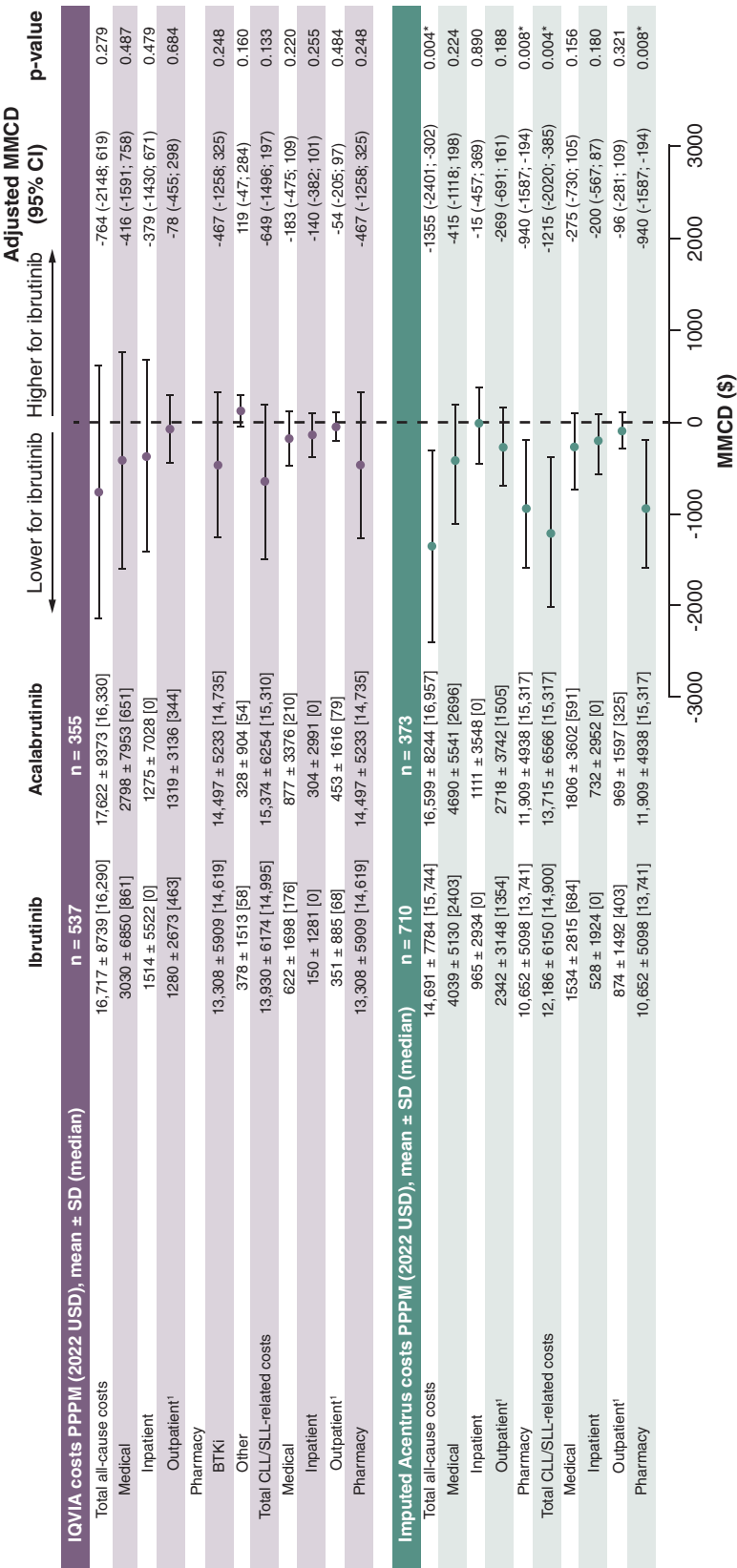


Figure 4. Comparison of costs in chronic lymphocytic leukemia/small lymphocytic lymphoma patients initiating first-line ibrutinib or acalabrutinib.

¹Outpatient service costs included outpatient and emergency department visit-related costs.

*p-value ≤ 0.05.

1L: First-line; CI: Confidence interval; CLL: Chronic lymphocytic leukemia; MMCD: Mean monthly cost difference; PPPM: Per-patient-per-month; SD: Standard deviation; SLL: Small lymphocytic lymphoma; USD: United States dollar.

The analyses presented in the current study are subject to some limitations. First, analyses were based on real-world claims and EMR data, which may contain omissions or inaccuracies. However, these should equally impact all patients and thus should not affect the overarching results. In addition, Acentrus is a provider-based data source, where records are only available for patient visits that occur in the network of academic and nonteaching hospital systems that are included in the database, which may explain the slightly lower number of visits observed in this database compared with IQVIA. Furthermore, both analyses used washout periods to define 1L use of ibrutinib and acalabrutinib (IQVIA: 6 months; Acentrus: 12 months). While these definitions have been extensively used in real-world studies [24,54–57], they may have allowed for patients with longer remission periods after a previous anticancer therapy to be included in the study populations. In the Acentrus analyses, claims data were unavailable; therefore, costs were imputed using literature-based estimates from a mix of commercial and Medicare patients, with the assumption that the mean cost was the same for all units of a given HRU. As such, the intensity of a unit of HRU did not vary between patients and costs may not be representative of the Acentrus patient population receiving 1L ibrutinib or acalabrutinib treatment for CLL/SLL. Lastly, while all analyses accounted for differences in baseline characteristics, it is possible that residual or unmeasured confounding (e.g., mutation status) remains.

Conclusion

In this real-world study of two large databases covering various populations, CLL/SLL patients initiating 1L single-agent ibrutinib had longer duration of 1L, significantly lower CLL/SLL-related outpatient visits and numerically lower costs compared with patients initiating 1L single-agent acalabrutinib. These findings, along with previous real-world studies showing higher treatment adherence [14,15] and longer TTNT [16,17] for 1L ibrutinib as compared with acalabrutinib, suggest that ibrutinib can be a cost-effective 1L therapy for CLL/SLL.

Summary points

- This study evaluated healthcare resource use (HRU) and costs between first-line (1L) single-agent ibrutinib and acalabrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) using real-world data from claims and electronic medical records.
- IQVIA PharMetrics Plus claims data and Acentrus electronic medical records data were used. Previously published cost assumptions were used to impute costs in Acentrus.
- Patients initiating 1L ibrutinib or acalabrutinib treatment after 21 November 2019 were included. Sample sizes were 537 and 355 for IQVIA, and 710 and 373 for Acentrus, for ibrutinib and acalabrutinib, respectively.
- Regression analyses adjusted for baseline differences were used to compare HRU and costs.
- Patients initiating ibrutinib had longer duration of 1L than those on acalabrutinib.
- Patients initiating ibrutinib had significantly fewer outpatient visits than those on acalabrutinib, indicating reduced need for outpatient services with ibrutinib in both datasets.
- Total all-cause and CLL/SLL related costs were numerically lower for ibrutinib versus acalabrutinib in both datasets.
- These findings suggest that ibrutinib can be a cost-effective 1L therapy for CLL/SLL.
- The use of two large real-world databases bolstered the generalizability of study findings.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0210>

Author contributions

ZP Qureshi, J He, A Bokun, Z Ding contributed to study conception and design, and drafting and revision of the manuscript; MH Lafeuille, B Emond and P Gogna contributed to study conception and design, acquisition of data, data analysis and drafting and revision of the manuscript; KA Rogers, B Muluneh and M Fradley contributed to study conception and design and drafting and revision of the manuscript. All authors have provided final approval of this version to be published and agree to be accountable for all aspects of the work.

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Competing interests disclosure

MH Lafeuille, B Emond and P Gogna are employees of Analysis Group, Inc., which has received research funding from Janssen Scientific Affairs, LLC, a Johnson & Johnson company. ZP Qureshi, J He and A Bokun are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company and stockholders of Johnson & Johnson. Z Ding was an employee of Janssen Scientific Affairs, LLC, a Johnson & Johnson company at the time the study was conducted. KA Rogers received research funding from Genentech, AbbVie, AstraZeneca and LOXO@lilly and consults for Genentech, AbbVie, Janssen, Pharmacyclics, BeiGene, LOXO@Lilly, Alpine Immune Sciences. M Fradley received research funding from AstraZeneca and Medtronic, and consults for AstraZeneca, Pfizer, Johnson and Johnson, AbbVie, Janssen and Zoll. B Muluneh's spouse is an employee and stockholder in Novartis Pharmaceuticals. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed

Writing disclosure

No funded writing assistance was utilized in the production of this manuscript.

Data sharing statement

The data that support the findings of this study are available from IQVIA and Acentrus, but restrictions apply to the availability of these data, which were used pursuant to a data use agreement. The data are available through requests made directly to IQVIA and Acentrus, subject to their respective requirements for access.

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