ORIGINAL RESEARCH

Real-World Comparison of First-Line Treatment Adherence Between Single-Agent Ibrutinib and Acalabrutinib in Patients with Chronic Lymphocytic Leukemia

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Purpose: Increased dosing frequency adversely affects treatment adherence and outcomes in chronic diseases; however, such data related to treatment adherence is lacking in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). This study compared adherence between patients treated with ibrutinib (once-daily) versus acalabrutinib (twice-daily) as first-line (1L) therapy for CLL/SLL.

Patients and Methods: Specialty pharmacy electronic medical records were used to identify adults with CLL/SLL initiating 1L ibrutinib or acalabrutinib between 01/01/2018 and 11/30/2020. Adherence was measured by the proportion of days covered (PDC) and medication possession ratio (MPR) and was compared between cohorts using odds ratios (ORs) obtained from logistic regression models adjusted for baseline characteristics.

Results: Between 01/01/2018 and 11/30/2020, 1374 and 140 patients initiated ibrutinib and acalabrutinib, respectively. Based on PDC/MPR ≥80%, patients treated with once-daily ibrutinib were more likely to be adherent than those treated with twice-daily acalabrutinib (OR ranges: PDC: 1.04–1.76; MPR: 1.03–1.58). At 6 months, patients on ibrutinib had a 58–76% higher likelihood of staying adherent compared to patients on acalabrutinib (PDC: 75.9% for ibrutinib vs 63.6% for acalabrutinib, OR: 1.76, *P*=0.008; MPR: 76.8% vs 66.9%, OR: 1.58, *P*=0.036) with a similar trend noted for the entire line of treatment (LOT) (PDC: 53.0% vs 41.4%, OR: 1.53, *P*=0.021; MPR: 58.7% vs 47.1%, OR: 1.50, *P*=0.027).

Conclusion: In this real-world analysis, CLL/SLL patients initiating 1L once-daily ibrutinib had >50% higher treatment adherence than those initiating twice-daily acalabrutinib during their LOT. Given the importance of sustained adherence for disease control in CLL/SLL, dosing frequency may be an important consideration for patients and physicians.

Keywords: CLL/SLL, Bruton's tyrosine kinase inhibitor, treatment compliance, proportion of days covered, medication possession ratio

Introduction

The need to manage multiple chronic conditions is common in older populations,[1] as more than 60% of Americans over the age of 65 have two or more chronic conditions.[2] Therefore, polypharmacy (ie, simultaneous treatment with multiple medications) is an important consideration in this population, and consequences of such a phenomenon include increased health-care costs, adverse drug events, increased potential for drug interactions, and treatment nonadherence.[3] Simplifying dosing regimens and the frequency of uptake can help avoid subsequent adverse clinical and health-care consequences.

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Graphical Abstract
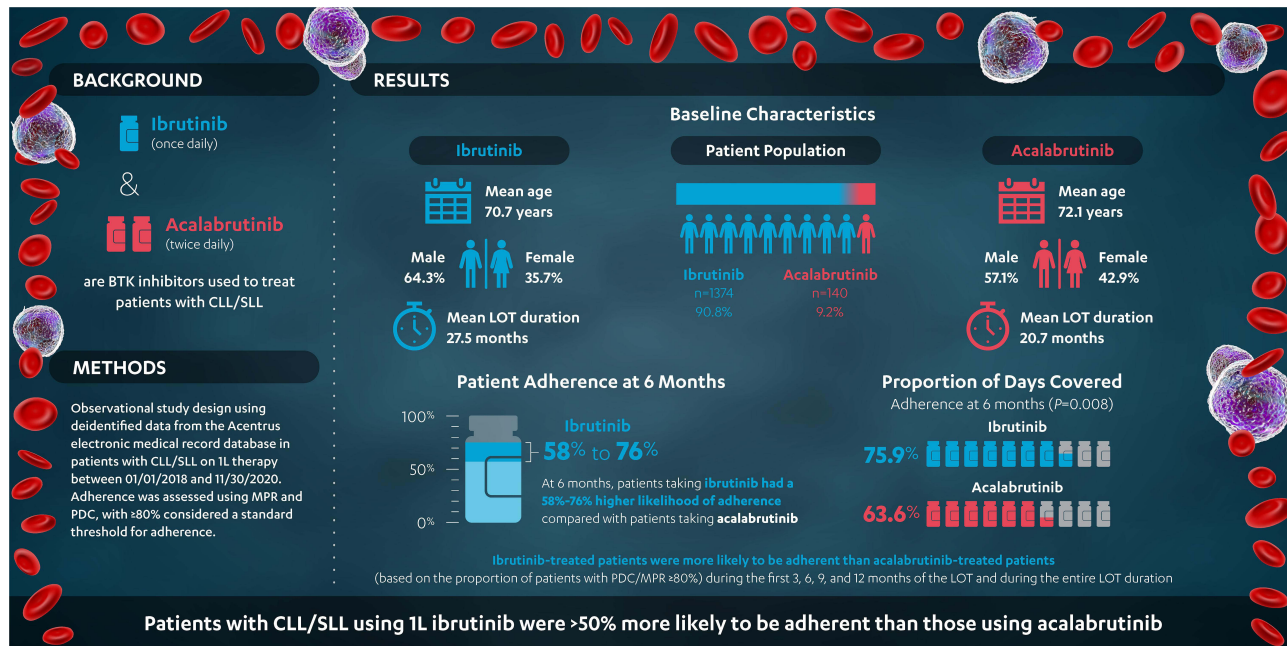
Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is a lymphoid malignancy affecting B cells and is the most common leukemia in adults above 65 years old; in the United States (US), the estimated number of new cases of CLL/SLL in the adult population for 2022 was 20,160.[4,5] Among available treatment options, once-daily ibrutinib[6] and twice-daily acalabrutinib[7] are Bruton's tyrosine kinase inhibitors (BTKis) approved by the US Food and Drug Administration as oral targeted therapies for CLL/SLL, with ibrutinib currently being a standard of care for first-line (1L) treatment in patients with CLL/SLL.[8]

To date, based on insurance claims data on file from the IQVIA database, more than 250,000 CLL/SLL patients have been treated with ibrutinib, with demonstrable efficacy in patients with high-risk cytogenetics.[9,10] Ibrutinib is also the only targeted therapy to demonstrate improved overall survival (OS) compared to chemo and/or immunotherapy in multiple Phase 3 clinical trials in 1L or relapsed/refractory CLL/SLL.[11–16] In November 2019, acalabrutinib, a newer BTKi administered twice daily, was approved for 1L or relapsed/refractory CLL/SLL.[17–19] While data on progression-free survival (PFS) and response for acalabrutinib has previously been reported in 1L,[20] OS data is still accumulating.

The proportion of days covered (PDC) and medication possession ratio (MPR) are both commonly used and validated measures to evaluate adherence using electronic medical records (EMR).[21,22] Additionally, PDC is recommended by the Pharmacy Quality Alliance as a measure of treatment adherence, particularly for treatments used over a long period of time (eg, for chronic conditions).[21] While clinical outcomes (including safety and efficacy) associated with ibrutinib and acalabrutinib have been evaluated in clinical trials, there is limited data comparing the real-world treatment adherence of these two agents. Considering disease chronicity, assessing adherence becomes important as sustained adherence to medication is essential to achieve and maintain optimal clinical outcomes for patients with CLL/SLL.[23,24] Therefore, the current real-world study was conducted to describe and compare treatment adherence between patients with CLL/SLL treated with 1L once-daily ibrutinib or twice-daily acalabrutinib in the US.

Materials and Methods

Data Source

This study used EMR data from the Acentrus database between January 1, 2017, to November 30, 2020, to select patients diagnosed with CLL/SLL who started treatment with 1L ibrutinib or acalabrutinib between January 1, 2018, and November 30, 2020. Acentrus is a health system solution used by specialty pharmacies (including 128,000 prescribers), where BTKis are typically dispensed.[25,26] It includes inpatient and outpatient data from 27 sites, including 10 National Cancer Institute designated sites, and 6 National Comprehensive Cancer Network members. Records of patients from 15 academic and 12 non-teaching hospital systems across 15 US states are available (ie, Arizona, California, Florida, Kansas, Massachusetts, Missouri, North Carolina, North Dakota, New York, Ohio, Tennessee, Texas, Virginia, Washington, and West Virginia), thus providing data on the experience of a large number of patients treated in a diverse set of hospital systems across the US. The database provides rich information on medication orders/fills/administrations, which are key to evaluate the main outcome of the study, ie, adherence. It also includes information on patients' demographic characteristics, insurance plan, medications, visits, date of death, diagnoses, and clinical characteristics including laboratory test results, and vitals. Acentrus is a provider-based data source, in which records are available to the extent that visits are part of the network of academic and non-teaching hospital systems included in the Acentrus data, ie, the database does not capture services that patients receive from a provider outside of the network. Data in the Acentrus database is de-identified and complies with patients' requirements of the Health Insurance Portability and Accountability Act (HIPAA).

Study Design

A retrospective cohort design was used. The index date was defined as the date of initiation of ibrutinib or acalabrutinib in 1L between January 1, 2018, and November 30, 2020. A washout period of ≥12 months of data availability without use of any antineoplastic agents prior to the index date was required to confirm use as 1L therapy. The same period was used to establish the baseline period for the evaluation of patient characteristics. Patients were required to have received no other antineoplastic agents in the 28 days on or after the index date. This time period was selected to ensure that the entire regimen used in the first cycle was observed, since treatment cycles with ibrutinib and acalabrutinib typically last for 28 days.[6,7] The follow-up period spanned from the index date to the earliest initiation of second-line (2L) treatment, censoring (based on the rules discussed in the paragraph below), death, or end of study period (November 30, 2020).

Line of Therapy Definition

The 1L therapy period used to evaluate adherence was defined as the period from the initiation of 1L treatment until the earliest of initiation of 2L treatment, death, or end of the study period (November 30, 2022). To allow for a comparison of adherence during a period when patients only received ibrutinib or acalabrutinib, patients with a within-class BTKi switch (ie, 2L treatment is also a BTKi) were censored at the time of switch, as this may have indicated a switch due to tolerability rather than disease progression. Patients who added an anti-CD20 antibody (ie, obinutuzumab or rituximab) or venetoclax to the index BTKi within 180 days post-index were censored at the time of add-on, as these may not have indicated overt disease progression but rather late initiation of a second anti-cancer agent as part of a 1L combination treatment strategy. The 180-day timeframe was selected based on prescribing guidelines, all recommending initiation of the additional agent within the first 6 months (cycles 1–2 for the anti-CD20 agent or cycles 3–4 for venetoclax, allowing for some delay in initiation until 6 months post-index).[6,7,27–29] Beyond the first 180 days post-index, anti-CD20 or venetoclax add-ons triggered the start of 2L treatment.

Study Population

Patients were required to meet the following inclusion criteria: ≥2 diagnoses for CLL/SLL ≥30 days apart, including one diagnosis prior to the index date; ≥1 order, fill, or administration for ibrutinib or acalabrutinib; ≥12 months of data availability before the index date (to confirm use of ibrutinib or acalabrutinib in 1L); ≥28 days of data availability after the index date; initiation of ibrutinib or acalabrutinib in 1L between January 1, 2018, and November 30, 2020; and ≥18 years of age as of the index date. Patients were excluded if they had ≥1 diagnosis of end-stage renal disease prior to the

index date or ≥2 diagnoses of other blood cancers ≥30 days apart, evaluated from 24 months prior to the index date to 6 months prior to their first CLL/SLL diagnosis.

Study Measures

Patient demographics (ie, age, sex at birth, race, year of the index date, US region and type of insurance) and clinical characteristics (ie, Quan-Charlson Comorbidity Index [Quan-CCI], comorbidities, and use of other medications) were evaluated during the baseline period (up to 12 months prior to the index date). PDC and MPR were used as measures of adherence during the first 3, 6, 9, and 12 months of the ibrutinib or acalabrutinib line of therapy (LOT), as well as over the duration of the entire LOT. PDC was defined as the sum of non-overlapping days of supply over the period of interest (ie, first 3, 6, 9, and 12 months of the LOT, as well as the entire LOT duration), where prescriptions with overlapping days of supply are shifted forward, divided by the duration of the period of interest. MPR was defined as the number of days of medication supplied during the period of interest (ie, first 3, 6, 9, and 12 months of the LOT, as well as the entire LOT duration) divided by the duration of the period of interest and was capped at 100% to account for potential stockpiling of medication. Supplementary Figure 1 provides a summary of the calculation for PDC and MPR.

Statistical Analysis

All analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC). Characteristics reported during the baseline period were described using means, standard deviations (SDs), and medians for continuous variables, and frequencies and proportions for categorical variables. *P*-values for the comparison of baseline characteristics between cohorts were obtained using *t*-tests for continuous variables and chi-squared tests for categorical variables.

Mean, SD, and median PDC and MPR were reported, in addition to the proportion of patients with PDC or MPR above specific thresholds (ie, ≥50%, ≥60%, ≥70%, ≥80%, and ≥90%; with ≥80% considered a standard threshold to consider patients as adherent).[30,31] Mean differences (MDs) with 95% confidence intervals (CIs) and *P*-values obtained from ordinary least-squares regression models were used to compare mean PDC and MPR between cohorts. Odds ratios (ORs) with 95% CIs and *P*-values obtained from logistic regression models were used to compare the proportion of patients with PDC or MPR above specific thresholds. Models were adjusted for baseline characteristics, which included standard controls of age, sex at birth, region, race, year of index date, and baseline Quan-CCI, with the addition of other variables that may have also affected differences in adherence between the two cohorts such as cardiopulmonary disease (CPD), peripheral vascular disease, hypertension, atrial fibrillation (AF), metastatic cancer, use of corticosteroids, and use of antiplatelets.

Results

The Acentrus EMR database contained 3712 patients with ≥2 CLL/SLL diagnoses. In total, 2824 patients met the study inclusion/exclusion criteria (Figure 1). Among them, 1374 and 140 patients initiated 1L ibrutinib and 1L acalabrutinib, respectively, between January 1, 2018, and November 30, 2020.

Patient Baseline Characteristics

Among the ibrutinib and acalabrutinib cohorts, respectively, the mean age was 70.7 and 72.1 years (*P*=0.109), 35.7% and 42.9% were female (*P*=0.095), the mean (median) length of follow-up time was 32.0 (33.2) and 23.8 (22.2) months, and the mean (median) LOT duration was 27.5 (28.9) and 20.7 (21.1) months (Table 1 and Table 2). US region varied between ibrutinib and acalabrutinib cohorts (South: 27.8% vs 41.4% [*P*<0.001]; Midwest: 26.1% vs 16.4% [*P*=0.012]). The mean Quan-CCI was 3.0 for ibrutinib and acalabrutinib (*P*=0.707) and a higher proportion of patients in the ibrutinib cohort had hypertension (37.8% vs 29.3%; *P*=0.046) in the baseline period. Baseline corticosteroid use was lower in the ibrutinib cohort (13.7% vs 25.0%; *P*<0.001).

Treatment Adherence

Overall, at 6 months, patients on ibrutinib had a 58–76% higher likelihood of staying adherent as compared to patients on acalabrutinib, with a similar trend observed for the entire LOT (ibrutinib 50–53% more likely to be adherent).
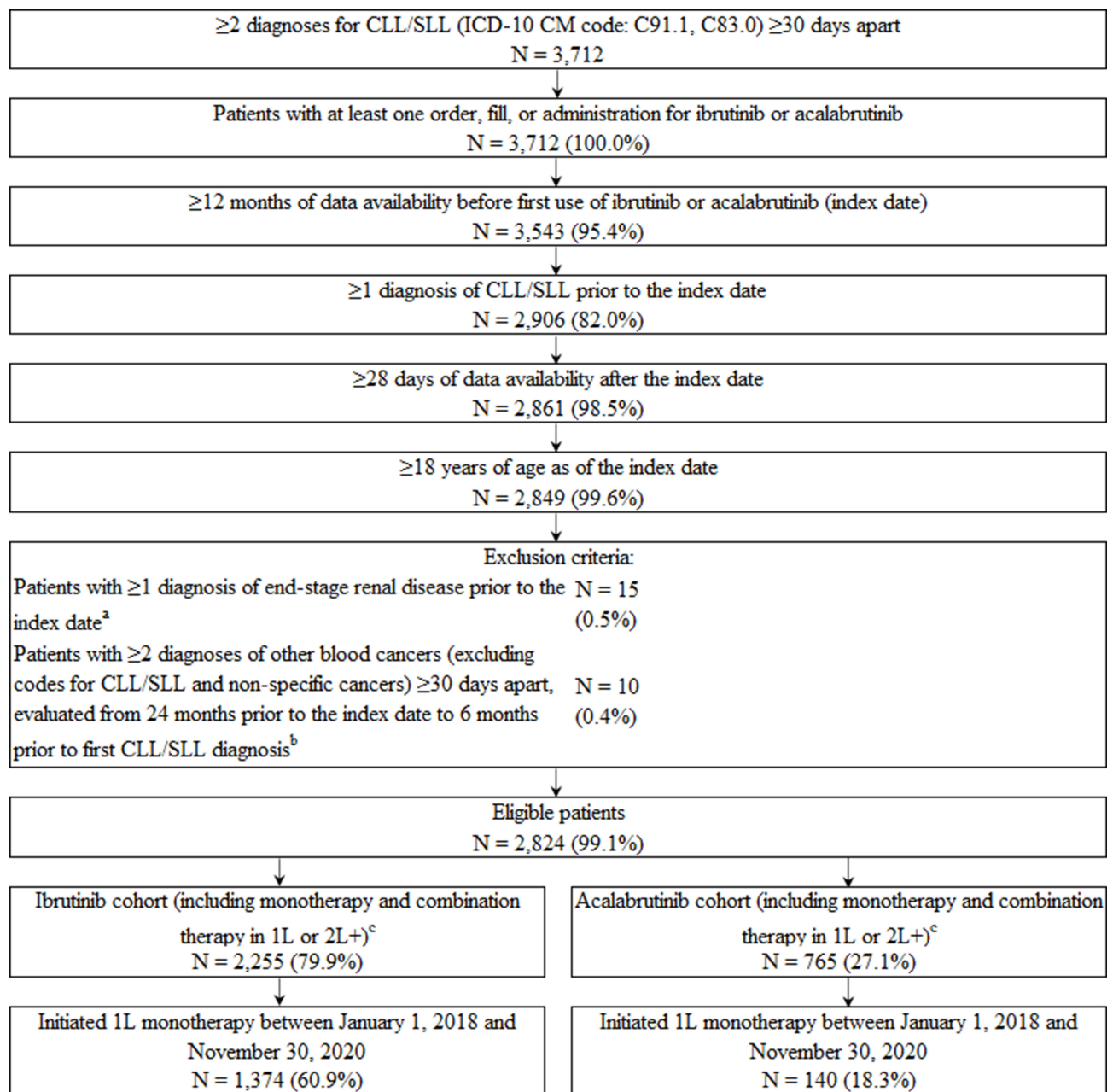
Figure 1 Identification of CLL/SLL patients treated with ibrutinib or acalabrutinib.
Notes: [a]ICD-10 CM code; N18.6. [b]ICD-10 CM codes: C81-C82, C83.1-C83.7, C84, C85.2, C86, C88, C90, C91.0, C91.2-C91.6, C91.A, C92-C93, C94.0-C94.4, C95.0, and C96. [c]Patients may use both acalabrutinib and ibrutinib. As such, the cohorts are not mutually exclusive at this step of the patient selection.
Abbreviations: 1L, first line; 2L+, second or later line; CLL, chronic lymphocytic leukemia; ICD-10 CM, International Classification of Diseases, Tenth Revision, Clinical Modification; SLL, small lymphocytic lymphoma.

Based on the proportion of patients with a PDC ≥ 80%, during the first 3, 6, 9, and 12 months of the LOT, and over the entire LOT duration, ibrutinib-treated patients were consistently more adherent than acalabrutinib-treated patients. ORs for the time points considered ranged from 1.04 to 1.76 (Figure 2). Results were statistically significant at 6 months into the LOT with 75.9% and 63.6% of patients adherent in the ibrutinib and acalabrutinib cohorts, respectively (OR: 1.76, P=0.008), and over the entire LOT duration, with 53.0% and 41.4% of patients adherent (OR: 1.53, P=0.021). Mean PDC for ibrutinib-treated patients was also higher than for acalabrutinib-treated patients at all time points (MD range of 0.03 to 0.07), with results reaching statistical significance at 6 months (0.85 for ibrutinib vs 0.77 for

Table 1 Baseline Demographic and Clinical Characteristics Evaluated in the 12-Month Baseline Period

	Ibrutinib N = 1374	Acalabrutinib N = 140
Demographics[a]		
Age at index date, mean ± SD [median]	70.7 ± 10.1 [71.0]	72.1 ± 9.4 [73.5]
Female, n (%)	491 (35.7)	60 (42.9)
Insurance coverage, n (%)[b]		
Medicare	382 (27.8)	43 (30.7)
Managed Care	135 (9.8)	11 (7.9)
Medicaid	22 (1.6)	0 (0.0)
Other	554 (40.3)	55 (39.3)
Unknown	281 (20.5)	31 (22.1)
US region, n (%)		
West	434 (31.6)	49 (35.0)
South	382 (27.8)	58 (41.4)
Midwest	359 (26.1)	23 (16.4)
Northeast	46 (3.3)	2 (1.4)
Unknown	153 (11.1)	8 (5.7)
Race, n (%)		
White	551 (40.1)	51 (36.4)
Black	63 (4.6)	4 (2.9)
Asian	43 (3.1)	1 (0.7)
Unknown	717 (52.2)	84 (60.0)
Clinical Characteristics[c]		
Quan-CCI, mean ± SD [median][d]	3.0 ± 1.6 [2.0]	3.0 ± 1.7 [2.0]
Chronic pulmonary disease, n (%)	157 (11.6)	20 (14.5)
Peripheral vascular disease, n (%)	101 (7.4)	7 (5.1)
Patients with pre-existing cardiovascular comorbidities, n (%)		
Hypertension	520 (37.8)	41 (29.3)
Atrial fibrillation	108 (7.9)	17 (12.1)
Metastatic cancer, n (%)	38 (2.8)	4 (2.9)
Use of corticosteroids, n (%)	188 (13.7)	35 (25.0)
Use of antiplatelets, n (%)	90 (6.6)	9 (6.4)

Notes: [a]Demographic characteristics were evaluated on the date of treatment initiation. [b]Insurance coverage type is identified by selecting the payer record closest to index date. [c]Evaluated in the up to 12-month baseline period, excluding the date of treatment initiation. [d]Reference: Quan H, Li B, Couris et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–682.
Abbreviations: Quan-CCI: Quan-Charlson Comorbidity Index; SD: standard deviation; US: United States.

acalabrutinib; MD: 0.07, *P*=0.010), 9 months (0.80 for ibrutinib vs 0.73 for acalabrutinib; MD: 0.07, *P*=0.017), and over the entire LOT duration (0.69 for ibrutinib vs 0.62 for acalabrutinib; MD: 0.07, *P*=0.034) (Table 2).

Similar outcomes were observed using MPR to measure adherence. Based on the proportion of patients with an MPR of ≥80%, ibrutinib-treated patients were more adherent than acalabrutinib-treated patients during the first 3, 6, 9, and 12 months of the LOT, and over the entire LOT duration. ORs for the time points considered ranged from 1.03 to 1.58 (Figure 3). Results were statistically significant at 6 months with 76.8% and 66.9% of patients adherent in the ibrutinib and acalabrutinib cohorts, respectively (OR: 1.58, *P*=0.036), and over the entire LOT duration, with 58.7% and 47.1% of patients adherent (OR: 1.50, *P*=0.027). Mean MPR for ibrutinib-treated patients was also higher than for acalabrutinib-treated patients at all time points (MD range of 0.03 to 0.06), with results reaching statistical significance at 6 months (0.85 for ibrutinib vs 0.78 for acalabrutinib; MD: 0.06, *P*=0.016), and 9 months (0.82 for ibrutinib vs 0.75 for acalabrutinib; MD: 0.06, *P*=0.041) (Table 2).

Table 2 Comparison of Mean Adherence Between Patients Treated with 1L Ibrutinib and Acalabrutinib

Mean ± SD [median]	Ibrutinib N = 1374	Acalabrutinib N = 140	Adjusted Mean Difference (95% CI)[a]	P-value[a]
Line of therapy duration, months	27.5 ± 13.6 [28.9]	20.7 ± 10.1 [21.1]	-	-
PDC	0.69 ± 0.34 [0.85]	0.62 ± 0.36 [0.66]	0.07 (0.00, 0.13)	0.034*
MPR	0.72 ± 0.35 [0.97]	0.65 ± 0.37 [0.78]	0.06 (0.00, 0.12)	0.055
Patients with ≥3 months line of therapy	N = 1358	N = 139		
PDC	0.90 ± 0.22 [1.00]	0.87 ± 0.26 [1.00]	0.03 (−0.01, 0.07)	0.110
MPR	0.91 ± 0.22 [1.00]	0.87 ± 0.26 [1.00]	0.03 (0.00, 0.07)	0.086
Patients with ≥6 months line of therapy	N = 1222	N = 121		
PDC	0.85 ± 0.28 [1.00]	0.77 ± 0.32 [1.00]	0.07 (0.02, 0.12)	0.010*
MPR	0.85 ± 0.28 [1.00]	0.78 ± 0.32 [1.00]	0.06 (0.01, 0.12)	0.016*
Patients with ≥9 months line of therapy	N = 1175	N = 118		
PDC	0.80 ± 0.30 [1.00]	0.73 ± 0.35 [0.94]	0.07 (0.01, 0.13)	0.017*
MPR	0.82 ± 0.30 [1.00]	0.75 ± 0.35 [1.00]	0.06 (0.00, 0.12)	0.041*
Patients with ≥12 months line of therapy	N = 1139	N = 111		
PDC	0.78 ± 0.32 [1.00]	0.70 ± 0.36 [0.89]	0.06 (0.00, 0.12)	0.057
MPR	0.79 ± 0.32 [1.00]	0.73 ± 0.36 [0.99]	0.05 (−0.01, 0.11)	0.129

Notes: [a]Mean differences and p-values were estimated using ordinary least squares regression models adjusted with the following variables: age, sex at birth, region, race, year of index date, Quan-Charlson Comorbidity Index, chronic pulmonary disease, peripheral vascular disease, hypertension, atrial fibrillation, metastatic cancer, use of corticosteroids, and use of antiplatelets. A mean difference >0 indicates higher adherence for ibrutinib. * indicates P-value <0.05.
Abbreviations: 1L, first line; CI, confidence interval; MPR, medication possession ratio; PDC, proportion of days covered; SD, standard deviation.

Discussion

For chronic diseases like CLL/SLL requiring continuous BTKi therapy, several factors can impact adherence, and sustained medication adherence is needed to achieve optimal outcomes. Thus, it becomes imperative to understand real-world adherence patterns with continuous BTKi therapies. This real-world study compared treatment adherence of patients in the US diagnosed with CLL/SLL who were treated with once-daily ibrutinib or twice-daily acalabrutinib in 1L. Using PDC and MPR as measures of adherence, results show that at 6 months and during the entire LOT, patients on ibrutinib had >50% higher likelihood of staying adherent compared to patients on acalabrutinib, with consistently higher adherence at all other time points evaluated as well.

To our knowledge, this is the first real-world study comparing treatment adherence among BTKis in 1L patients with CLL. Real-world adherence to ibrutinib has been previously characterized, but in different settings. One retrospective chart review study found that among patients treated at North Carolina Cancer Hospital for at least 6 months, the mean adherence rate measured by MPR was 91.7% (range: 84.4% to 100%).[32] A second follow-up study reported a mean PDC of 95% (range: 65–100%) among patients treated with ibrutinib for at least 6 months.[33] The mean PDC and MPR reported in the current study for patients treated with ibrutinib with at least 6 months of LOT duration were similarly high at 85% and may be more generalizable, as the data came from a larger cohort of 1374 patients treated with ibrutinib in 15 academic and 12 non-teaching hospital systems across 15 US states (compared to only 32–149 patients from one or two centers).

Our finding that treatment adherence was higher among patients treated with once-daily ibrutinib than those treated with twice-daily acalabrutinib is consistent with what has been observed for the treatment of other chronic diseases. A meta-analysis investigating dosing frequency and medication adherence across 51 studies of various chronic disease states reported a statistically significant relationship between medication adherence and dosing frequency, where patients treated for chronic diseases are more adherent to treatments that require less frequent dosing.[34] Specifically, regimen adherence was 13.5% lower among patients on twice-daily treatment regimens than those on once-daily regimens.[34] These findings are likely associated with the convenience of having to take a treatment less frequently.[35]
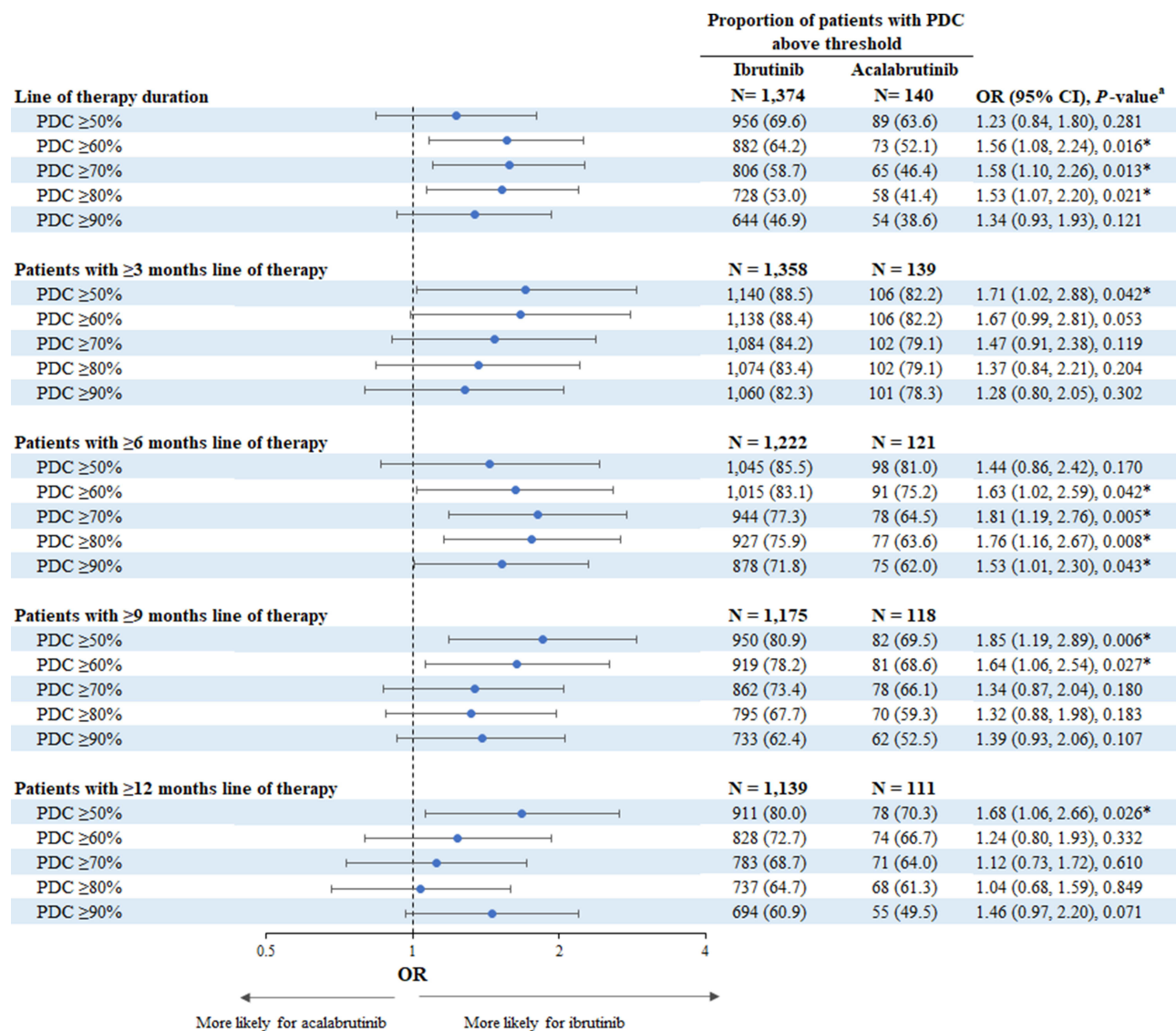
Figure 2 Comparison of PDC above thresholds between patients treated with 1L ibrutinib or acalabrutinib.
Notes: [a]ORs and their associated 95% CIs and *P*-values were estimated using logistic regression models adjusted with the following variables: age, sex at birth, region, race, year of index date, Quan-Charlson Comorbidity Index, chronic pulmonary disease, peripheral vascular disease, hypertension, atrial fibrillation, metastatic cancer, use of corticosteroids, and use of antiplatelets. An OR >1 indicates a higher proportion of patients above the PDC threshold for ibrutinib. *Indicates *P*-value <0.05.
Abbreviations: 1L, first line; CI, confidence interval; OR, odds ratio; PDC, proportion of days covered.

Adherence to a prescribed treatment regimen is a key component of the management of chronic diseases. High adherence to treatment has been associated with longer time to disease progression,[24] fewer acute or adverse events,[36,37] and overall increased quality of life.[38] In a retrospective analysis of a phase 3 clinical trial for ibrutinib, patients missing ≥8 consecutive days of medication were associated with a shorter median PFS.[24] More generally, one meta-analysis across 63 chronic disease studies showed that adherence to treatment reduces the risk for a null or poor treatment outcome by 26% relative to nonadherence, and the odds of a good outcome were almost three times higher for adherent patients.[39] Additionally, the economic costs of treatment nonadherence are high, with an estimated US $100 to $300 billion avoidable health-care costs attributed to medication nonadherence annually.[40,41] Thus, treatments requiring less frequent dosing such as ibrutinib that are associated with higher patient adherence, and that offer the option of dose flexibility[6] may result in more favorable patient outcomes and reduced health-care costs relative to their twice-daily counterparts, which require more frequent administration.
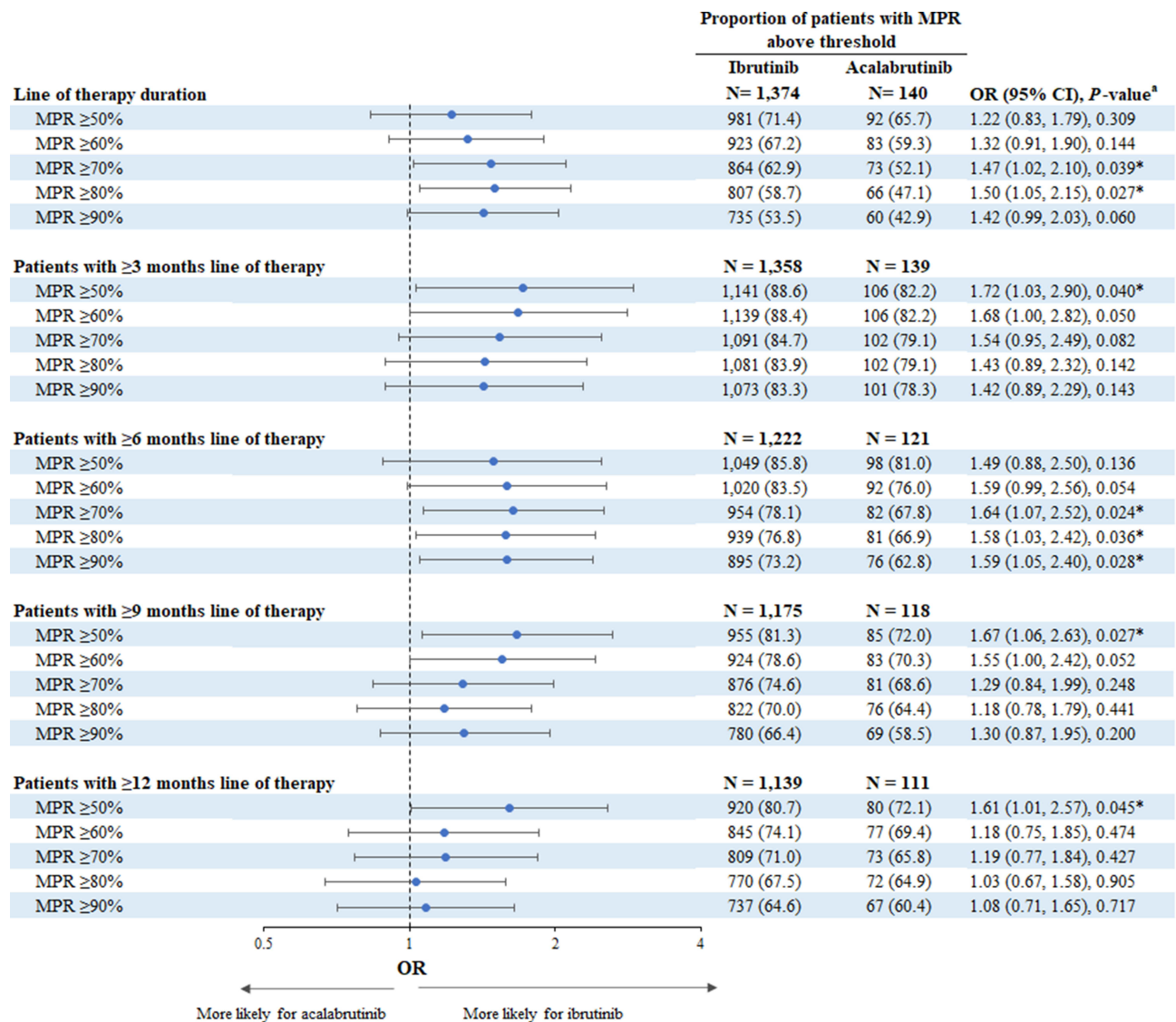
	Proportion of patients with MPR above threshold		
	Ibrutinib	**Acalabrutinib**	
Line of therapy duration	**N= 1,374**	**N= 140**	**OR (95% CI), P-value[a]**
MPR ≥50%	981 (71.4)	92 (65.7)	1.22 (0.83, 1.79), 0.309
MPR ≥60%	923 (67.2)	83 (59.3)	1.32 (0.91, 1.90), 0.144
MPR ≥70%	864 (62.9)	73 (52.1)	1.47 (1.02, 2.10), 0.039*
MPR ≥80%	807 (58.7)	66 (47.1)	1.50 (1.05, 2.15), 0.027*
MPR ≥90%	735 (53.5)	60 (42.9)	1.42 (0.99, 2.03), 0.060
Patients with ≥3 months line of therapy	**N = 1,358**	**N = 139**	
MPR ≥50%	1,141 (88.6)	106 (82.2)	1.72 (1.03, 2.90), 0.040*
MPR ≥60%	1,139 (88.4)	106 (82.2)	1.68 (1.00, 2.82), 0.050
MPR ≥70%	1,091 (84.7)	102 (79.1)	1.54 (0.95, 2.49), 0.082
MPR ≥80%	1,081 (83.9)	102 (79.1)	1.43 (0.89, 2.32), 0.142
MPR ≥90%	1,073 (83.3)	101 (78.3)	1.42 (0.89, 2.29), 0.143
Patients with ≥6 months line of therapy	**N = 1,222**	**N = 121**	
MPR ≥50%	1,049 (85.8)	98 (81.0)	1.49 (0.88, 2.50), 0.136
MPR ≥60%	1,020 (83.5)	92 (76.0)	1.59 (0.99, 2.56), 0.054
MPR ≥70%	954 (78.1)	82 (67.8)	1.64 (1.07, 2.52), 0.024*
MPR ≥80%	939 (76.8)	81 (66.9)	1.58 (1.03, 2.42), 0.036*
MPR ≥90%	895 (73.2)	76 (62.8)	1.59 (1.05, 2.40), 0.028*
Patients with ≥9 months line of therapy	**N = 1,175**	**N = 118**	
MPR ≥50%	955 (81.3)	85 (72.0)	1.67 (1.06, 2.63), 0.027*
MPR ≥60%	924 (78.6)	83 (70.3)	1.55 (1.00, 2.42), 0.052
MPR ≥70%	876 (74.6)	81 (68.6)	1.29 (0.84, 1.99), 0.248
MPR ≥80%	822 (70.0)	76 (64.4)	1.18 (0.78, 1.79), 0.441
MPR ≥90%	780 (66.4)	69 (58.5)	1.30 (0.87, 1.95), 0.200
Patients with ≥12 months line of therapy	**N = 1,139**	**N = 111**	
MPR ≥50%	920 (80.7)	80 (72.1)	1.61 (1.01, 2.57), 0.045*
MPR ≥60%	845 (74.1)	77 (69.4)	1.18 (0.75, 1.85), 0.474
MPR ≥70%	809 (71.0)	73 (65.8)	1.19 (0.77, 1.84), 0.427
MPR ≥80%	770 (67.5)	72 (64.9)	1.03 (0.67, 1.58), 0.905
MPR ≥90%	737 (64.6)	67 (60.4)	1.08 (0.71, 1.65), 0.717

OR — axis: 0.5   1   2   4

← More likely for acalabrutinib   More likely for ibrutinib →

Figure 3 Comparison of MPR above thresholds between patients treated with 1L ibrutinib or acalabrutinib.

Notes: [a]ORs and their associated 95% CIs and *P*-values were estimated using logistic regression models adjusted with the following variables: age, sex at birth, region, race, year of index date, Quan-Charlson Comorbidity Index, chronic pulmonary disease, peripheral vascular disease, hypertension, atrial fibrillation, metastatic cancer, use of corticosteroids, and use of antiplatelets. An OR >1 indicates a higher proportion of patients above the PDC threshold for ibrutinib. *Indicates *P*-value <0.05.

Abbreviations: 1L, first line; CI, confidence interval; MPR, medication possession ratio; OR, odds ratio.

This study was subject to certain limitations. For instance, the analyses were based on EMR data, which may contain inaccuracies or omissions; however, these are expected to be random and affect all patients equally and should not bias the conclusions made here. In addition, Acentrus is a provider-based data source in which records are only captured for visits to a network of academic and non-teaching hospital centers included in the Acentrus data. Therefore, any services that patients receive from providers outside of the network are not captured in the database. However, even if patients may change providers to obtain different medications, they tend to obtain all prescriptions for the same medication through a single provider, which allows the analysis of treatment patterns for a specific medication. Prescription fills were assumed to indicate that patients were utilizing their medication; however, patients may not necessarily adhere to the treatment regimen as prescribed. There may also be residual confounding remaining in adjusted analyses due to unmeasured confounders. However, the Acentrus database was rich in demographic and clinical information which, for example, enabled the calculation of the Quan-CCI and reporting of individual comorbidities and use of other medications. This allowed models to be adjusted for many key confounders, which would not be possible in other databases. Of note, in the current study, the number of patients initiated on ibrutinib was much higher than the

number of patients initiated on acalabrutinib, given that the period available for this analysis was from January 1, 2018, to November 30, 2020. However, this was adjusted for in regression analyses by accounting for the year during which treatment was initiated. Additionally, the study used a washout period of 12 months to identify the use of ibrutinib or acalabrutinib in 1L. While this is a common definition used extensively in real-world studies,[42–44] it is possible that patients with longer remission who received a prior line of therapy were included in the sample. However, the expectation would be that these patients, if present, would be balanced between the two groups. Finally, while results may not be generalizable to all patients treated with 1L ibrutinib or acalabrutinib, this real-world study is one of the largest reflecting the experience of patients treated in academic and non-teaching centers, as it covered many sites across the US.

Conclusion

In this real-world study of patients with CLL/SLL in the US treated with once-daily ibrutinib or twice-daily acalabrutinib in 1L, patients who were treated with ibrutinib demonstrated higher adherence to treatment than those treated with acalabrutinib. Specifically, patients on ibrutinib had a >50% higher likelihood of staying adherent compared to patients on acalabrutinib during their LOT. These findings support what is known about the role of lower dosing frequency in achieving higher treatment adherence and better outcomes in patients with chronic diseases. Given the importance of medication adherence in achieving disease control in CLL/SLL (in addition to other factors such as efficacy, tolerability, safety, and past experience treating patients with the medication), dosing frequency may be an important consideration for patients and physicians when considering treatment options in the 1L setting.

Abbreviations

1L, first-line; 2L, second-line; 2L+, second or later-line; AF, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; CPD, cardiopulmonary disease; EMR, electronic medical records; HIPAA, Health Insurance Portability and Accountability Act; KM, Kaplan–Meier; LOT, line of therapy; MD, mean difference; MPR, medication possession ratio; OR, odds ratio; OS, overall survival; PDC, proportion of days covered; PFS, progression-free survival; Quan-CCI, Quan-Charlson Comorbidity Index; SD, standard deviation; SLL, small lymphocytic lymphoma; US, United States.

Data Sharing Statement

The data that support the findings of this study are available from 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 Acentrus, subject to Acentrus' requirements for data access.

Ethics Approval and Informed Consent

The data used in this study were anonymized and comply with the Health Insurance Portability and Accountability Act; therefore, no reviews by an institutional review board were required per Title 45 of CFR, Part 46.101(b)(4).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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