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METHOD

Fixed-duration ibrutinib-venetoclax for first-line treatment of patients with chronic lymphocytic leukemia: the REALITY-WW prospective real-world study cohort

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ABSTRACT

The fixed-duration combination of ibrutinib and venetoclax has shown significant benefits in the first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) through clinical studies with follow-up extending up to 5.5 years. However, there remains an important gap in real-world data regarding efficacy and tolerability outcomes of this regimen outside of clinical trial settings. The REALITY-Worldwide study has been initiated as a prospective observational study aimed at understanding the usage, factors for therapy decision, and clinical response of first-line fixed-duration ibrutinib-venetoclax in routine clinical practice. The primary endpoint is physician-assessed overall response rate according to 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. Secondary endpoints and outcomes of interest include duration of response, progression-free survival, overall survival, time to next treatment, tumor lysis syndrome risk, adverse events, patient-reported outcomes, factors associated with physician decision to initiate fixed-duration ibrutinib-venetoclax in clinical practice, medical resource utilization, and patient-reported outcomes. The study aims to enroll approximately 200 patients across Europe, the Middle East, and Latin America. A pooled analysis will include subsets of data collected from REALITY-WW and the ongoing multicenter REALITY-2 study in Germany.

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CLL/SLL; ibrutinib-venetoclax; mechanism of action; prospective; REALITY-WW; real-world

1. Background

1.1. Overview of disease state

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most prevalent adult leukemia in Western countries [1]. All patients who meet the 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria should be offered treatment [2].

CLL and SLL are characterized by an abnormal, uncontrolled growth and accumulation of malignant B lymphocytes that can be found in the blood, bone marrow, lymph nodes, and spleen [3,4]. Importantly, the B-cell receptor signaling pathway and B-cell lymphoma 2 (BCL-2) family of anti-apoptotic proteins are functional in the pathobiology of CLL/SLL [4]. Bruton's tyrosine kinase (BTK) plays a pivotal role in the B-cell receptor and other signaling pathways, which are required for the survival, proliferation, and migration of normal B cells and CLL/SLL cells [3–5]. Ibrutinib is a selective and irreversible inhibitor of BTK [6]. Through inhibition of BTK, ibrutinib disrupts this signaling pathway, leading to the displacement of B cells from nurturing lymphoid microenvironments and ultimately inducing programmed cell death [5,6]. The importance of BTK inhibition in the clinical setting was demonstrated by the achievement of long-term progression-free survival (PFS) and overall survival (OS) with once-daily oral ibrutinib 420 mg monotherapy in patients with CLL/SLL versus chlorambucil standard chemotherapy or immunotherapy in both the first-line setting and in patients with relapsed/refractory disease [7,8]. Subsequently, ibrutinib 420 mg/day was approved in both indications in Europe, the United States, and other countries and regions as monotherapy for CLL/SLL, including older patients (aged 65 years or older) [9] and patients with high-risk genetic abnormalities (chromosome 17p13.1 deletion) [10].

The RESONATE-2 (NCT01722487) phase 3 study with up to 10 years of follow-up demonstrated improved PFS and OS with continuous ibrutinib versus standard chemotherapy or chemoimmunotherapy in patients with previously untreated CLL/SLL [11]. In addition, real-world studies in Germany [12], Italy [13], Sweden [14], and the United States [15] have demonstrated favorable clinical outcomes of continuous ibrutinib monotherapy for CLL/SLL in both the first-line and subsequent treatment settings.

While continuous BTK inhibition is an established standard of care in CLL/SLL treatment, clinical practice guidelines now recommend time-limited treatment options when their efficacy is comparable with continuous BTK inhibition. By opting for time-limited treatments with similar efficacy, healthcare

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Article highlights

Background
- The treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has been advanced significantly with the introduction of the Bruton's tyrosine kinase inhibitor ibrutinib and the B-cell lymphoma 2 inhibitor venetoclax.
- Combination therapy with fixed-duration (FD) ibrutinib-venetoclax results in synergistic cytotoxicity, leading to faster and more extensive CLL/SLL cell apoptosis compared with either drug alone.
- Multiple clinical studies have demonstrated the efficacy and safety of FD ibrutinib-venetoclax in the first-line treatment of CLL/SLL.
- Mutations in *BTK*, *BCL2*, or *PLCG2* have not been detected in first relapse after treatment with FD ibrutinib-venetoclax, which makes the retreatment with one or both drugs feasible.

Rationale
- There is a need for real-world data showing the use and clinical outcomes of FD ibrutinib-venetoclax outside of clinical trial settings. These data may help guide healthcare providers to make informed decisions about treatment options for best patient outcomes.

Study design
- REALITY-WW is a prospective observational study aimed at understanding the usage, factors for therapy decision, and clinical response of FD ibrutinib-venetoclax in routine clinical practice.
- Eligible patients will have a confirmed diagnosis of CLL/SLL requiring first-line treatment according to 2018 International Workshop on Chronic Lymphocytic Leukemia criteria.
- Enrolled patients will receive a 3-cycle lead-in of ibrutinib 420 mg/day. The venetoclax dose will be escalated weekly from 20 to 400 mg/day over 5 weeks from Cycle 4. Patients will receive all-oral FD ibrutinib 420 mg/day plus venetoclax 400 mg/day for 12 treatment cycles.
- The primary endpoint is overall response rate by the end of 15 treatment cycles (approximately week 60).

providers can potentially enhance patient outcomes while minimizing long-term complications associated with continuous therapy [16].

Venetoclax is a selective inhibitor of the anti-apoptotic protein BCL-2 that rapidly induces apoptosis in CLL/SLL cells [17–19]. Recently, combinations of targeted therapies have emerged that could potentially improve efficacy with reduced toxicity [20]. Preclinical studies have shown that combining ibrutinib with venetoclax produces synergistically greater cytotoxicity against CLL cells than either drug alone (Figure 1) [17,18,21–24].

All-oral, FD ibrutinib-venetoclax is approved for first-line treatment of CLL/SLL in 78 countries across Asia, Europe, the Middle East, and South America, as well as Australia, Canada, and New Zealand [25,26], with ongoing discussions and evaluations in other jurisdictions. The approval was based on the efficacy and safety of FD ibrutinib-venetoclax for patients with previously untreated CLL demonstrated in the phase 2 CAPTIVATE (NCT02910583) and phase 3 GLOW (NCT03462719) clinical studies [23,27–31]. The CAPTIVATE study, which examined first-line FD ibrutinib-venetoclax in relatively young and fit patients (median age 60 years) with CLL, showed that this combination provided deep remission, including high bone marrow undetectable minimal residual disease (uMRD) rates in patients with high-risk disease features, such as del(17p) or *TP53* mutation, del(11q), and unmutated IGHV gene [25]. At 5.5 years, PFS and OS rates were 60% and 96%, respectively. With up to 5.5 years of follow-up, median PFS and median time to next treatment was still not reached with FD ibrutinib-venetoclax and the safety profile was still manageable and unchanged from previous reports [29]. Notably, the estimated 5.5-year rate of freedom from next-line treatment was 69% [29]. In a pooled analysis of the GLOW and CAPTIVATE studies, OS for patients with CLL/SLL treated with FD ibrutinib-venetoclax in the first-line setting was comparable with an age-matched general European

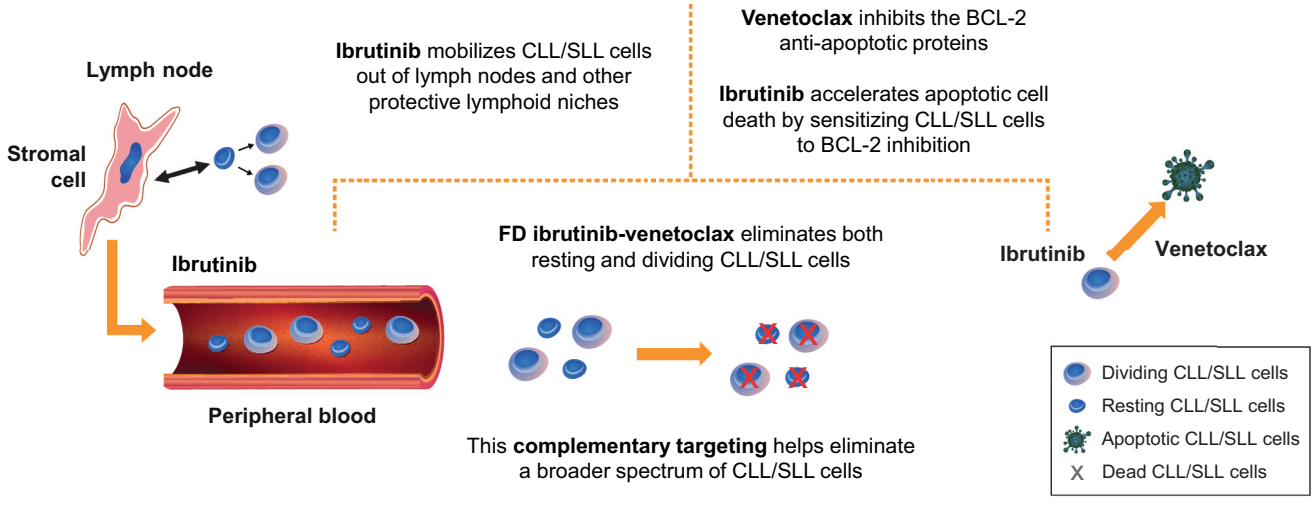

Figure 1. Synergistic mechanism of action of ibrutinib and venetoclax in CLL/SLL. The figure illustrates the complementary actions of ibrutinib and venetoclax in CLL/SLL treatment. CLL and SLL are the same disease, but CLL cells are found mostly in the blood and bone marrow while SLL cells are found mostly in the lymph nodes [24]. Protective lymphoid niches for CLL/SLL cells are complex microenvironments composed of diverse cell types and signaling pathways that play a crucial role in the survival and proliferation of CLL/SLL cells [21]. These niches are primarily located in the bone marrow and lymph nodes, where CLL/SLL cells interact with various stromal cells. Ibrutinib decreases CLL/SLL cell proliferation and mobilizes CLL/SLL cells from protective lymphoid niches into peripheral blood, increasing their dependence on BCL-2. The CLL/SLL cells then become more sensitive to venetoclax-induced apoptosis [17]. Ibrutinib primarily targets dividing CLL/SLL cells, while venetoclax is more effective against resting CLL/SLL cells [22]. The combination therapy with FD ibrutinib-venetoclax results in synergistic cytotoxicity, leading to faster and more extensive CLL/SLL cell apoptosis compared with either drug alone [18,22,23,29].

Abbreviations: BCL-2, B-cell lymphoma 2; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FD, fixed-duration.

population, including subpopulations of patients aged ≥65 years and < 65 years [32]. This analysis also showed that estimated OS was similar to an age-matched European population regardless of the IGHV mutational status.

While the clinical benefit of FD ibrutinib-venetoclax has been established in CLL/SLL in clinical studies, prospective real-world evidence is limited, creating a gap in clinical outcomes data with FD ibrutinib-venetoclax in routine clinical practice. Recently, initial results of the LI+VE real-world observational study of FD ibrutinib-venetoclax reported favorable clinical outcomes for 81 patients with previously untreated CLL/SLL in clinical practice in Spain [33]. The REALITY-Worldwide (WW) study will prospectively investigate efficacy and safety outcomes of FD ibrutinib-venetoclax treatment in patients with previously untreated CLL/SLL in routine clinical practice in Europe, the Middle East, and Latin America.

1.2. REALITY-WW study

REALITY-WW is an international, multicenter, prospective observational study to describe the management of patients with previously untreated CLL/SLL, using FD ibrutinib-venetoclax in a real-world setting. The main aim of this study is to gain insights on the usage, factors for treatment decision, and effectiveness and clinical response of FD ibrutinib-venetoclax in routine clinical practice. Participating sites will be hospitals and other medical institutions treating and managing patients with CLL/SLL using FD ibrutinib-venetoclax treatment within routine clinical practice.

Participants will be adult patients with a confirmed diagnosis of CLL/SLL requiring first-line treatment per iwCLL 2018 criteria [2] using FD ibrutinib-venetoclax treatment in routine clinical practice. The decision to start treatment with FD ibrutinib-venetoclax must have been taken prior to and independent of the patient's enrollment in the study. Prior to data collection, all patients must sign an informed consent form (ICF)/participation agreement, allowing data collection and source data verification in accordance with local requirements. Data collection will include patient characteristics, efficacy and treatment response, safety, reasons for treatment decisions, treatment details, and health-related quality of life. Additionally, possible associations between patient characteristics and clinical outcomes will be explored. The primary data source will be the medical records of each participating patient; data collection will start at baseline, after the ICF is signed and within 30 days before initiation of FD ibrutinib-venetoclax treatment for the first participating patient. The end of the study will be the last documented data collection point in the study for the last participating patient. Approximately 200 patients will be enrolled in Europe, the Middle East, and Latin America.

1.3. Study design

REALITY-WW will comprise two phases: a treatment phase and a follow-up phase (Figure 2). The dosing schedule is detailed per label, with a 3-cycle lead-in of ibrutinib 420 mg/day followed by 12 cycles of FD ibrutinib-venetoclax, with venetoclax dose ramp-up from 20 to 400 mg over 5 weeks from cycle 4. Subsequent data collection will be performed at patient visits conducted within local routine clinical practice every 3 cycles (approximately every 12 weeks [±4 weeks] or as per routine clinical practice). The treatment phase will continue until discontinuation of ibrutinib or venetoclax at the end of FD ibrutinib-venetoclax treatment. In the follow-up phase, after the end of the treatment phase, data collection will continue to be performed at patient visits conducted within local routine clinical practice (approximately every 12 weeks [±4 weeks] or

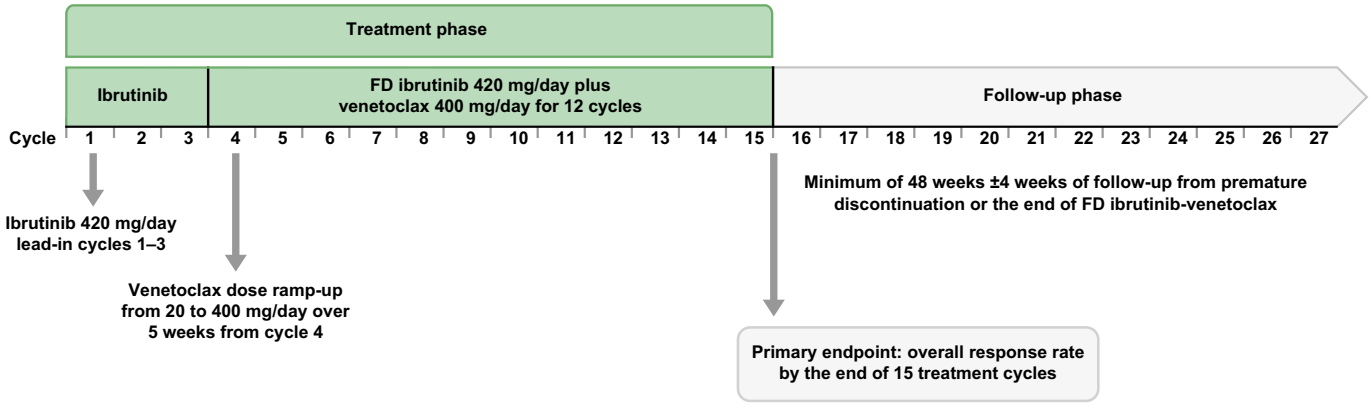

Figure 2. REALITY-WW study design. Data collection will start at baseline, after the informed consent form is signed and within 30 days before initiation of FD ibrutinib-venetoclax treatment for the first participating patient. Data will be collected at patient visits conducted within local routine clinical practice every 3 cycles (approximately every 12 weeks [±4 weeks] or as per routine clinical practice). The treatment begins with a 3-cycle lead-in of ibrutinib 420 mg/day. Each cycle is 28 days. The venetoclax dose will be escalated weekly from 20 to 400 mg/day over 5 weeks from cycle 4. Patients will receive all-oral FD ibrutinib 420 mg/day plus venetoclax 400 mg/day for 12 cycles (cycle 4 through cycle 15). The treatment phase will continue until discontinuation of ibrutinib or venetoclax or the end of FD ibrutinib-venetoclax treatment. The primary endpoint is overall response rate by the end of 15 treatment cycles (approximately week 60). Adverse event collection starts with the first use of ibrutinib within the study. Tumor lysis syndrome risk categories will be collected at baseline and after the ibrutinib lead-in period. Follow-up starts as soon as the patient permanently discontinues FD ibrutinib-venetoclax treatment at the physician's discretion. In the follow-up phase, data collection will continue at patient visits conducted within local routine clinical practice (approximately every 12 weeks [±4 weeks]) or until documentation of the subsequent CLL/SLL treatment or the end of the study, whichever comes first. The end of the study will be the last documented data collection point within the study for the last participating patient.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FD, fixed-duration.

until documentation of the subsequent CLL/SLL treatment or at the end of the study, whichever comes first. The overall duration of the study is expected to be approximately 4 years, with approximately 1.5 years enrollment, up to 15 cycles of FD ibrutinib-venetoclax treatment as per standard of care, and up to approximately 1 year of follow-up.

1.4. Eligibility criteria

Participating physicians will assess patients to determine their eligibility for data collection within the study based on the eligibility criteria. Key eligibility criteria are: patients aged ≥18 years (or the higher legal age of majority in the jurisdiction in which the study is taking place) at the time of informed consent with confirmed diagnosis of CLL/SLL requiring treatment according to iwCLL 2018 guidelines; intention of treatment with FD ibrutinib-venetoclax according to the approved indication; patient has signed an ICF/participation agreement allowing data collection and source data verification in accordance with local requirements; patient is able to read, understand, and complete the patient-reported outcome (PRO) instruments and comply with completion of all PRO instruments. Patients who received prior treatment for CLL or an investigational medicinal product within 30 days before the start of the study or are currently enrolled or plan to participate in an investigational clinical trial in CLL/SLL (participation in a non–Janssen-sponsored non-interventional study or registry is allowed) are excluded. Patients with any restrictions or limitations preventing treatment with FD ibrutinib-venetoclax as per the current approved label of ibrutinib or venetoclax in each site country, if applicable, are also excluded. Participating sites will be encouraged to enroll patients in a consecutive manner when patients come for their regular visit within routine clinical practice, to minimize bias in patient selection. All eligible patients should be offered enrollment for data collection within the study.

1.5. Study endpoints & outcome measures

The study objectives and endpoints are described in Table 1. The primary endpoint is best overall response rate (ORR) at end of 15 treatment cycles, defined as the proportion of participants who achieve partial response (PR) or better response (complete response [CR], CR with incomplete hematologic recovery [CRi], or partial response with lymphocytosis [PR-L], per the iwCLL 2018 treatment criteria) over the course of the study, as assessed by the investigator. Secondary endpoints and outcomes of interest include duration of response, PFS and OS (if sufficient data are available), MRD negativity rates, time to next treatment, tumor lysis syndrome (TLS) risk, adverse events, factors associated with physician decision to initiate FD ibrutinib-venetoclax in routine clinical practice, medical resource utilization, and PROs. PROs available within routine clinical practice will be collected using the Quality-of-Life Questionnaire-CLL17 (QLQ-CLL17). Outcomes will be analyzed for subgroups based on patients aged ≥65 years and < 65 years at baseline and patients' IGHV mutational status.

1.6. Assessments

A summary of the clinical response assessments is shown in Table 2. The physicians responsible for response assessments are hematologists with expertise in CLL/SLL management. ORR is investigator-assessed by the proportion of patients achieving the best response of complete or partial response (including CR [if imaging is available], CRi, PR, or PR-L), per iwCLL 2028 criteria. Safety assessments will be recorded in the case report form (CRF) for the protocol-defined data collection

Table 1. REALITY-WW study objectives and endpoints.

Primary objective	Primary endpoint
Describe the effectiveness of FD ibrutinib-venetoclax treatment in routine clinical practice	Overall response rate by the end of 15 treatment cycles (approximately Week 60) in a real-world setting, per physician's assessment based on iwCLL 2018 criteria (proportion of patients achieving the best response of complete or partial response, including CR [if imaging available], CRi, PR, or PR-L)
Secondary objectives	**Secondary endpoints and outcomes and measures of interest**
Further describe the clinical response and effectiveness of FD ibrutinib-venetoclax treatment in routine clinical practice	Overall response rate (proportion of patients who achieve CR, CRi, PR, or PR-L) by the end of 3, 6, 9, and 12 treatment cycles
	Duration of response
	Progression-free survival
	Overall survival
	Measurable residual disease in peripheral blood, bone marrow aspirate, and/or lymph nodes (if collected in clinical practice at one or more time points)
	Treatment interruption/discontinuation and dose adjustments (time on treatment, time to treatment discontinuation, and time to next treatment)
Describe the safety of FD ibrutinib-venetoclax treatment	Adverse events, serious adverse events, and special situations
	Tumor lysis syndrome risk (absolute lymphocyte count and lymph node diameter) at baseline and after 3 cycles of ibrutinib lead-in
	Hospitalization rate for venetoclax ramp-up
Describe patient-reported outcomes	EORTC QLQ-CLL17
Describe medical resource utilization	Days in hospital and emergency room visits, other than due to a serious adverse event
Understand the factors relevant for the treating physician's decision of FD ibrutinib-venetoclax treatment	Factors affecting treating physician's decision of FD ibrutinib-venetoclax treatment in routine clinical practice
	Factors affecting patient's decision to accept or continue with proposed treatment
	Patient baseline characteristics to explore associations with physician's treatment decisions

Abbreviations: CR, complete response; CRi, complete response with incomplete hematologic recovery; EORTC, European Organization for Research and Treatment of Cancer; FD, fixed-duration; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PR, partial response; PR-L, partial response with lymphocytosis.

Table 2. REALITY-WW study assessments.

Endpoints and outcomes	Assessment
Response rates	• Overall response rate (CR, CRi, PR, and PR-L) by the end of 3, 6, 9, and 12 treatment cycles • CR rate (if imaging available), CRi rate, PR rate, and PR-L rate by the end of 3, 6, 9, 12, and 15 treatment cycles
Duration of response	• Defined as time (in months) from the first date of achieving complete or partial response (including CR, CRi, PR, or PR-L) to the date of first documented evidence of progressive disease or death[†]
Progression-free survival	• Measured from the start of FD ibrutinib-venetoclax treatment to documented disease progression, relapse, or death due to any cause[†]
Overall survival	• Measured from the start of FD ibrutinib-venetoclax treatment to date of death due to any cause[‡]
Minimal residual disease	• Proportions of patients with MRD in peripheral blood or bone marrow aspirate by the end of 3, 6, 9, 12, and 15 treatment cycles (if collected in clinical practice at one or more time points)
Time to treatment discontinuation	• Defined as the time from the start of FD ibrutinib-venetoclax treatment to the premature discontinuation of ibrutinib or venetoclax (whichever is earlier)[§]
Treatment interruption	• Proportion of patients with treatment interruption, discontinuation, or dose adjustments of FD ibrutinib-venetoclax treatment, with reasons for the change in treatment
Time on treatment	• Defined as the time from the start of FD ibrutinib-venetoclax treatment to the time of the end of treatment (whether this is a premature or regular end of treatment)
Time to next treatment	• Measured from the start of FD ibrutinib-venetoclax treatment to the start of subsequent CLL/SLL treatment[¶]
Patient baseline characteristics	• Genetic factors, age, comorbidities/Cumulative Illness Rating Scale score, and ECOG performance status
Patient reported outcomes	• Change from baseline of EORTC QLQ-CLL17 (multi-item scales) throughout the study[#]
Factors relevant to the treating physician's decision to use FD ibrutinib-venetoclax	• Based on the Physician's Treatment Decision Questionnaire
Factors affecting the patient's decision to accept or continue with the proposed treatment	• Based on physician's impression of their patient, documented using the Physician's Treatment Decision Questionnaire

[†]Patients who are progression free and alive will be censored at the date of last disease assessment.
[‡]If the patient is alive or the vital status is unknown, the patient will be censored at the date last known to be alive.
[§]For patients who do not prematurely discontinue the treatment, time to treatment discontinuation is censored at the last dose date of the treatment.
[¶]For patients who do not switch to subsequent CLL/SLL treatment, time to next treatment is censored at the last follow-up date.
[#]Responses are measured on a 4-point scale ranging from 1 (not at all) to 4 (very much). The scores are transformed to give a rating from 0 to 100.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; CRi, complete response with incomplete hematologic recovery; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; FD, fixed-duration; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; PR, partial response; PR-L, partial response with lymphocytosis.

period and in the patient's source medical records, regardless of seriousness or causality. Adverse event collection starts with the first use of ibrutinib within the study and will apply to all adverse events, regardless of seriousness, that occur within 30 days after the patient's last use of ibrutinib within the study or until the end of the study if sooner. Clinical laboratory test results will be obtained as part of the patient's usual standard of care. TLS risk categories will be collected at baseline and after the ibrutinib lead-in period (usually the first 12 weeks of ibrutinib-venetoclax treatment). TLS risk categories are defined as high (any lymph node with largest diameter ≥10 cm or any lymph node with the largest diameter ≥5 cm and absolute lymphocyte count [ALC] ≥25 G/L), intermediate (any lymph node ≥5 cm to < 10 cm or ALC ≥25 G/L), or low (all lymph nodes < 5 cm and ALC < 25 G/L).

Patients will be asked to complete the QLQ-CLL17 [34] health-related quality-of-life questionnaire at baseline, every 3 cycles during the treatment phase until the end of treatment, and every 8 to 16 weeks during the follow-up phase. The QLQ-CLL17, which is composed of 17 questions [34], was developed to specifically assess the health status of patients with CLL/SLL. There are three multi-item scales pertaining to: symptom burden due to disease and/or treatment (six items), physical condition/fatigue (four items), and worries/fears about health and functioning (seven items, of which two are conditional). The questionnaire contains an instruction section and will be provided in the local language, and completion usually takes less than 10 minutes. Where not available, participating physicians will be asked to obtain these PROs from patients participating in this study. Responses will be directly entered by the patient using paper sheets at each applicable occasion. Where possible and in accordance with local clinical practice, PROs should be completed before other assessments. Data collected on an paper sheets will be handled as source data and entered in the CRF by the site staff.

Physicians will be asked to complete the Physician's Treatment Decision Questionnaire (Supplementary Table) at baseline, before the start of treatment for each individual patient. Factors affecting the decision to start FD ibrutinib-venetoclax treatment will be recorded from the questionnaire, together with dosing details of the FD ibrutinib-venetoclax treatment. The physician will document the factors determining why the patient has chosen FD ibrutinib-venetoclax treatment, including an indication of whether the patient had influenced the treatment decision or not, the patient age, comorbidities, disease characteristics, social circumstances, and efficacy and safety profile. Where applicable, hospitalization (i.e., days in hospital) and emergency department visits

(with reason for admission/emergency department visit) following exposure to ibrutinib will be documented for events that occur after the first use within the study and within 30 days after the patient's last documented use of ibrutinib or until the end of the study, irrespective of seriousness or causality (e.g., TLS prophylaxis). The hospitalization rate and reasons for admission for venetoclax ramp-up will be recorded. The physician questionnaires will allow clinicians and healthcare providers to gain insight into the drivers of treatment decisions across large patient populations with CLL/SLL. The most common reasons for selection of ibrutinib-venetoclax will be reported. The results will not be averaged, but subgroup analysis may be performed for patients aged > 70 years and patients' ECOG status at baseline.

1.7. Statistical analyses

The REALITY-WW study plans to enroll 200 patients considering pragmatic factors, including a varied ORR in a real-world observational study. A screen failure rate of 10% was assumed based on data science on similar real-world studies in hematology. The expected sample size of at least 180 treated patients will provide sufficient statistical power to estimate the ORR with adequate confidence level across various scenarios. Higher statistical power could be achieved if the actual screen failure rate is lower than 10%. A sample size of 180 treated patients achieves approximately 93% power to detect a 10% difference in ORR using a two-sided exact test at a significance level (alpha) of 0.05, assuming an ORR of 85% versus 75%. ORR will be summarized with frequency (%), and two-sided 95% confidence intervals (CIs) will be calculated using the normal approximation.

Time-to-event endpoints will be analyzed using the Kaplan–Meier product-limit method to estimate the survival distribution and the median time-to-event. In the absence of confirmation of the considered event, the time-to-event will be censored. The estimated survival rates at various time points with 95% CIs, and the number of patients at risk at each time will be reported. Adverse events will be summarized using Medical Dictionary for Regulatory Activities (MedDRA)-coded terms and TLS risk categories will be summarized by frequency tabulations, as available. Continuous endpoints (e.g., QLQ-CLL17 scores) will be summarized using descriptive statistics, including mean and standard deviation or median and range, as applicable. Categorical endpoints (e.g., reasons for therapy decisions made by treating physicians on FD ibrutinib-venetoclax, ORR at different visits, and MRD negativity rate) will be summarized using frequencies and percentages. No formal hypothesis testing is planned for the study. However, the exploratory hypothesis research question is: "Does ibrutinib-venetoclax as a fixed-duration regimen in the first-line treatment of patients with CLL/SLL have comparable ORR and safety profiles to similar patients in clinical trials?"

If a patient is lost to follow-up, every reasonable effort will be made by site personnel to contact the patient and determine the reason for discontinuation. Patients who withdraw from the study will not be replaced. Patients who stop FD ibrutinib-venetoclax treatment will continue to be followed in the study until documentation of the subsequent CLL/SLL treatment or the end of the study, whichever comes first. Missing data will not be replaced but will be handled as "missing" in the statistical evaluation ("observed cases analysis"). Partial dates may be imputed for statistical analyses for specific outcomes. Baseline values will not be carried forward.

1.8. Study sites

Patient enrollment is at 63 sites in five countries in Europe, the middle East, and Latin America.

2. Discussion

The CAPTIVATE and GLOW clinical studies showed that patients with CLL/SLL treated with FD ibrutinib-venetoclax in a first-line setting had high rates of uMRD, high rates of PFS, and durable treatment-free remissions [23,27–31,35]. Moreover, the clinical benefit was demonstrated across various subgroups, including those with high-risk genetic features [29,35,36]. The CAPTIVATE study demonstrated that in patients who experienced disease progression following FD ibrutinib-venetoclax treatment, no resistance-associated mutations were detected in *BTK* or *PLCG2 genes*; and 2 patients had a subclonal *BCL2 A113G* mutation of unclear significance [29]. This finding suggests that FD ibrutinib-venetoclax may potentially reduce the development of resistance mechanisms typically associated with continuous monotherapy with targeted treatment. Furthermore, these results indicate that patients might respond effectively to retreatment with either ibrutinib alone or FD ibrutinib-venetoclax. Consequently, this approach could potentially prolong the clinical benefits derived from these agents. The GLOW study is currently evaluating FD ibrutinib-venetoclax in older, comorbid patients at a median follow-up of 64 months [35].

The REALITY-WW study protocol follows the standard-of-care, on-label approach to treating patients with ibrutinib-venetoclax in the countries selected. The protocol allows physician and patient choice, has wide inclusion criteria to include patients who would not otherwise have been allowed on interventional clinical trials, and consent is obtained after the physician/patient has selected ibrutinib-venetoclax therapy as a treatment choice. Investigators will follow iwCLL 2028 criteria for the diagnosis, treatment, and assessment of patients with CLL/SLL. The sponsor is using a contract research organization to provide separation from patient-level data collection and analysis.

2.1. Rationale for real-world evidence collection

Randomized clinical trials generally provide information on a select group of patients who are chosen based on specific inclusion/exclusion criteria and treated in a controlled manner. In clinical practice, clinicians adopt more varied prescribing patterns in the treatment of a more heterogeneous population of patients. Removing constraints in clinical trials allows real-world studies to provide insights into the use and effectiveness of cancer treatments in real-world practice. Real-world data can guide healthcare providers and policymakers in making informed decisions about resource allocation and

treatment guidelines. Therefore, the non-interventional aspect of this study provides an approach to document the selection of treatments and the observation of interventions in a real-world clinical setting.

There are multiple advantages of the REALITY-WW prospective study design. Compared with a retrospective design, a prospective study can ensure standardized and consistent data gathering, is less likely to have missing data, and makes it easier to follow up with participants for complete information. Moreover, a prospective study design allows researchers to establish the temporal sequence between exposure and outcome. This allows for the identification of relationships between exposures and outcomes and is better suited for studying long-term effects or changes over time.

In phase 3 clinical studies, the ORR has been used as the primary endpoint to evaluate response to targeted therapies in CLL/SLL. Given that this observational study aims to review clinical outcomes in the real world, compared with clinical trial data sets, ORR was taken as the primary endpoint. The frequency of data collection (every 3 cycles, approximately every 12 weeks ±4 weeks) in REALITY-WW is compatible with the schedule of visits performed in routine clinical practice, and the duration of follow-up will provide sufficient time to perform follow-up on safety and maintenance of clinical response. Subsets of data collected from REALITY-WW and the ongoing multicenter REALITY-2 study in Germany will be used for a pooled analysis.

3. Conclusion

The treatment of CLL/SLL has advanced significantly with the introduction of the BTK inhibitor ibrutinib and the BCL-2 inhibitor venetoclax [37]. Combining these two drugs in an FD regimen may create a synergistic effect, enhancing their ability to induce cell death. Multiple clinical studies have demonstrated the efficacy and safety of FD ibrutinib-venetoclax in the first-line treatment of CLL/SLL [23,27,28,36,38]. Importantly, treatment with FD ibrutinib-venetoclax can provide improved quality of life, reduced long-term side effects, and increased cost-effectiveness compared with a continuous drug treatment regimen [39]. However, there is a need for real-world data showing the use and clinical outcomes of FD ibrutinib-venetoclax outside of clinical trial settings. REALITY-WW is an international, multicenter, prospective observational study to describe the management of patients with previously untreated CLL/SLL, using FD ibrutinib-venetoclax in a real-world setting. The prospective design of the REALITY-WW study offers several advantages: it enables researchers to implement uniform data collection methods, reduces the likelihood of data gaps, and facilitates more effective participant follow-up to obtain comprehensive information. Furthermore, this approach allows investigators to clearly observe and document the chronological order of events, particularly the relationship between exposure and subsequent outcomes. As the REALITY-WW study progresses, it will provide valuable insights into the effectiveness and safety of FD ibrutinib-venetoclax in a broad patient population, potentially influencing future treatment paradigms for CLL/SLL. Approximately 200 patients will be enrolled in Europe, the Middle East, and Latin America. A combined analysis will be conducted using selected data from two sources: the REALITY-WW study and the ongoing REALITY-2 study, which is being carried out across multiple sites in Germany.

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Author contributions

Boo Messahel, Mohamed Fouad, Claire Kavanagh, Swomya Srikanthan, Christoph Tapprich, and Ping Xu were involved in the design of the study. All authors reviewed the manuscript draft during development, provided comments for revision, and approved the final manuscript. All authors agree to be accountable for all aspects of the work.

Disclosure statement

Talha Munir reports being an advisor and/or consultant for AstraZeneca, Janssen, MorphoSys, Roche, Sobi, and Sunesis, and receiving honoraria and/or travel support from AbbVie, Alexion, AstraZeneca, Gilead, Janssen, Novartis/GSK, Pharmacyclics, Roche, and Sobi; **Danielle Leão** reports being an investigator for ADC Therapeutics, Agios, Astellas, BeiGene, Celltrion, GSK, Daichii Sankyo, Regeneron, Sandoz, and Viracta, being an advisory board member and/or investigator and speaker for AbbVie, Amgen, AstraZeneca, Celgene/Bristol Myers Squibb, Janssen, Knight Therapeutics/United Medical, Libbs/mAxience, Lilly, Novartis, Pfizer, Roche, Sanofi, Takeda, and Zodiac, being an IDMC member for Libbs/mAxience, being a steering committee member for Janssen, and being a speaker for Pint-Pharma; **Boo Messahel** is an employee of Johnson & Johnson and owns stocks in Johnson & Johnson; **Sowmya Srikanthan** is contracted with Johnson & Johnson; **Ping Xu** is an employee of Johnson & Johnson; **Mohamed Fouad** is an employee of Johnson & Johnson and owns stocks/shares in Johnson & Johnson; **Claire Kavanagh** is an employee of Johnson & Johnson; **Christoph Tapprich** is an employee of Johnson & Johnson and owns stocks/shares in Johnson & Johnson and AbbVie; **Oliver Miles** reports steering committee honoraria and travel funding from Janssen; **Adriana Scheliga** reports honoraria from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Johnson & Johnson, Lilly, MSD, Roche, and Takeda, and travel grants from BeiGene and Johnson & Johnson; **Paolo Ghia** reports honoraria from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Galapagos, Janssen, Lilly/Loxo Oncology, MSD, and Roche, and research funding from AbbVie, AstraZeneca, Bristol Myers Squibb, and Janssen.

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Ethical declaration

This study will be performed in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonization and Good Clinical Practice guidelines. Written informed consent will be required and obtained from the participants involved. Applicable local regulatory requirements were followed and the investigators ensured that the study was conducted in full conformity with Regulations for the Protection of Human Subjects of Research.

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