NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA partial review of TA663) [ID6291]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA partial review of TA663) [ID6291]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from AbbVie:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. CLL Support Charity
   b. Leukaemia Care. Submission also submitted on behalf of Blood Cancer UK, Leukaemia UK and Lymphoma Action
   c. UK CLL Forum & British Society of Haematology
      i. UK CLL Forum letter to NICE

4. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science (BCEIS)

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA part review of TA663) [ID6291]

Company evidence submission

July 2025

File name	Version	Contains confidential information	Date
ID6291_Ven+O_CLL_Company_Submission_[REDACTED]	**REDACTED**	**No**	**22 July 2025**

Contents

Tables

Figures

Abbreviations

ADCC	antibody-dependent cell cytotoxicity
AEPI	adverse events of particular interest
BCL2	B cell leukaemia/lymphoma 2
BR	bendamustine and rituximab
BNF	British National Formulary
BSH	British Society of Haematology
CDF	Cancer Drugs Fund
CI	confidence interval
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukaemia
CLL-IPI	International Prognostic Index for Chronic Lymphocytic Leukemia
CR	complete remission
CTC	common toxicity criteria
CTCAE	common terminology criteria for adverse events
CV	cardiovascular
DSA	deterministic sensitivity analysis
DSMB	data safety monitoring board
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FCR	fludarabine, cyclophosphamide and rituximab
FISH	fluorescent in-situ hybridisation
HCP	healthcare professional
HCRU	healthcare resource utilisation
HR	hazard ratio
HRQoL	health-related quality of life
I+Ven	ibrutinib + venetoclax
I+Ven+O	ibrutinib + venetoclax + obinutuzumab
ICER	incremental cost-effectiveness ratio
Ig	immunoglobulin
IGHV	immunoglobulin heavy-chain variable region gene
IPD	individual patient data
IQR	interquartile range
ITC	indirect treatment comparison
ITT	intention-to-treat

IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MAIC	matching-adjusted indirect comparison
MOMP	mitochondrial outer membrane permeabilisation
MRD	minimal residual disease
O-Clb	obinutuzumab + chlorambucil
ORR	overall response rate
OS	overall survival
PD	progressed disease
PDS	personal demographics service
PF	progression-free
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
PV	prognostic variable
QALY	quality-adjusted life year
QoL	quality of life
SACT	systemic anti-cancer therapy
SAE	serious adverse event
SCIT	standardised chemoimmunotherapy
SLR	systematic literature review
STC	simulated treatment comparison
TEAE	treatment-emergent adverse event
TEM	treatment effect modifier
TLS	tumour lysis syndrome
TTNT	time to next treatment
uMRD	undetectable MRD
VAS	visual analogue scores
Ven+O	venetoclax + obinutuzumab
Ven+R	venetoclax + rituximab

Executive summary

Background

This is a Cancer Drugs Fund (CDF) exit submission for TA633.[1] During the initial appraisal (2020), AbbVie submitted in three sub-populations of untreated chronic lymphocytic leukaemia (CLL) in line with the marketing authorisation:

- Population 1: with 17p deletion or *TP53* mutation
- Population 2: without 17p deletion or *TP53* mutation and for whom fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine with rituximab (BR) is unsuitable
- Population 3: without 17p deletion or *TP53* mutation and for whom FCR or BR is suitable

Populations 1 and 2 were recommended for routine commissioning, and Population 3 was recommended for use in the CDF, pending final readout of the CLL13 trial. However, in the past five years since the initial appraisal, the CLL landscape has changed considerably with chemo-immunotherapies (FCR and BR) being superseded by targeted treatments like venetoclax + obinutuzumab (Ven+O) and ibrutinib + venetoclax (I+Ven) in clinical practice and within national guideline recommendations, shifting treatment decisions away from a patient's 'fitness' for chemo-immunotherapies (TA891, 2023).[2]

Disease Overview

CLL is a blood cancer of unknown aetiology characterised by over-proliferation of mature $CD5^+$ B cells.[3] CLL has a substantial detrimental impact on patients' quality of life (QoL), due to the high symptom burden, treatment-associated toxicity and the emotional impact of living with an incurable illness.[4-8]

Current treatment pathway (**Population 3**)

The aim of treatment is to achieve durable remission with long lasting periods of progression-free survival (PFS), whilst minimising toxicities from treatment.[9] As described above, patients with untreated CLL without 17p deletion or *TP53* mutation, for whom FCR or BR would have been suitable, no longer receive FCR

or BR; instead they receive targeted treatments such as I+Ven and Ven+O (via the CDF). This has been validated with UK Clinical experts and NHSE.[10] During AbbVie consultations with UK clinical experts, they stated their strong preference to continue to have the choice between I+Ven and Ven+O in this population as it facilitates tailoring of treatment based on patient needs.[10] For example, patients with cardiac comorbidities or at risk of cardiovascular (CV) adverse events (AEs) are often offered Ven+O due to the known association of Bruton's tyrosine kinase inhibitors (BTKis) such as ibrutinib with CV AEs.

Clinical Efficacy of Ven+O

- Relevant evidence for the clinical efficacy of Ven+O in Population 3 is derived from the phase 3 clinical trial, CLL13 (NCT02950051). Secondary evidence is provided by the SACT report, which covers data collected during the CDF data collection period (from 10/11/2020 to 31/10/2022).
- CLL13 demonstrated that at a median follow-up of 63.8 months, PFS was superior for Ven+O compared with SCIT (median not reached [NR] vs 61.2 months; $p<0.001$).[11]
- The efficacy of Ven+O is supported by the SACT report. Of the [redacted]% of patients that had completed treatment, [redacted]% completed treatment as prescribed. Median overall survival (OS) was not reached, with an OS of [redacted] at 24 months.[12]

Clinical Safety of Ven+O

- CLL13 demonstrated that Ven+O is well tolerated by fit patients with untreated CLL and no del(17p)/ *TP53* mutation. The most frequently reported treatment-emergent serious adverse events with maximum CTC grade ≥ 3 in patients treated with Ven+O were infusion-related reactions ([redacted]), pneumonia ([redacted]) and tumour lysis syndrome ([redacted]).[13] This tolerable safety profile is supported by the treatment adherence observed in the SACT report.[12]

Comparative Efficacy (Ven+O vs I+Ven)

- Relevant evidence for the clinical efficacy of I+Ven in Population 3 is derived from the phase 3 clinical trial, CAPTIVATE (NCT02910583)
- In the absence of a head-to-head trial, an unanchored matching-adjusted indirect comparison (MAIC) was performed to compare CLL13 (Ven+O) with aggregate data from CAPTIVATE (I+Ven).
- The MAIC suggests Ven+O is numerically better than I+Ven with improvements in both PFS (HR [redacted], 95% CI [redacted]) and OS (HR [redacted], 95% CI [redacted]). However, the confidence intervals were wide and the benefit for Ven+O was not statistically significant.

Cost-effectiveness

- A cost-utility analysis was performed using a partitioned survival model (PSM) structure in line with previous NICE technology appraisals (TAs), including TA663. In the cost-utility analysis, Ven+O was associated with 0.37 incremental QALYs and a **cost saving** of [redacted] [at venetoclax PAS price] compared with I+Ven. As such, Ven+O returned a dominant ICER.

Cost-comparison scenario

- Clinical expert feedback on the MAIC suggests Ven+O and I+Ven outcomes appear comparable. Furthermore, clinical expert feedback based on NHS clinical practice is that in the absence of randomised comparative data, outcomes of Ven+O and I+Ven are similar. Therefore, AbbVie undertook a cost-comparison analysis.
- The cost comparison shows Ven+O would be cost-saving for the NHS vs. I+Ven by [redacted] [at venetoclax PAS price].

Conclusions

Patients without 17p deletion or *TP53* mutation and for whom in the past FCR or BR would have been suitable, are now successfully and routinely being treated with Ven+O via the CDF and I+Ven. Patients and clinical experts value the

availability of both treatments as it offers them choice and the tailoring of treatment based on patient needs. The cost-utility and cost-comparison analyses both demonstrate that Ven+O is **cost-saving** compared with I+Ven.

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

Background and Context

The treatment landscape has changed considerably since venetoclax in combination with obinutuzumab (Ven+O) first gained marketing authorisation in the UK. In 2019, AbbVie submitted Ven+O to NICE in three sub-populations of untreated CLL, in line with the marketing authorisation:

- Population 1: adults with untreated chronic lymphocytic leukaemia (CLL) who have a 17p deletion or *TP53* mutation, or
- Population 2: adults where there is no a 17p deletion or *TP53* mutation and for whom fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine with rituximab (BR) is unsuitable.[1]
- Population 3: adults where there is no 17p deletion or *TP53* mutation and for whom FCR or BR is suitable.[1]

Populations 1 and 2 were recommended for routine commissioning, and population 3 was recommended for use in the CDF, pending final readout of the CLL13 trial. However, in the five years since the initial appraisal, the landscape has changed considerably with chemo-immunotherapies (FCR and BR) no longer routinely used and being superseded by targeted treatments such as ibrutinib + venetoclax (I+Ven) (TA891, 2023)[2].

Decision Problem

This submission focuses on the indication reimbursed via the CDF (Population 3 above) with the aim of achieving routine commissioning. However, the treatment landscape no longer delineates by suitability for FCR/BR as the use of these standard chemoimmunotherapy (SCIT) agents has been superseded by both Ven+O

(via the CDF) and ibrutinib + venetoclax (I+Ven), which is reimbursed in all three populations mentioned above (TA891).[2,9,14] Therefore, as described during the scoping stage for this appraisal, AbbVie consider that I+Ven is the only relevant comparator given changes in the treatment landscape based on clinical expert feedback, guidelines and prior NICE technology appraisals:

- **BR**: Per the 2022 British Society for Haematology (BSH) Guidelines which no longer recommend the use of BR in CLL patients, BR should not be a comparator.[9] Through personal communication with the authors of the BSH CLL guideline authors, [redacted].[15] This aligns with the I+Ven appraisal (TA891) that noted that BR is 'rarely used in clinical practice and is no longer recommended in the 2022 BSH guidelines.'[2] This was validated by AbbVie in UK clinical expert consultations.[10]

- **FCR**: FCR is no longer considered a relevant comparator, given advice from several clinical engagements and an advisory board with clinicians across England who agreed that FCR is no longer used in practice.[10] Additionally, in TA891 the clinical experts and NHS England representatives noted that FCR and BR "are hardly used."[2] Furthermore, the latest ESMO guidelines no longer recommend FCR as a treatment option where targeted therapies are reimbursed, which includes the UK.[14] Through personal communication with the CLL BSH guideline authors, updated guidelines from the [redacted] are expected to be published imminently, [redacted].[15] Per TA891 in 2022, the CLL Forum and the BSH state that Ven+O has displaced chemoimmunotherapy as the preferred front-line treatment.[2] Patient safety demands that when there are newer, more effective, and safer treatments, that these are favoured over scarcely used, outdated, unsafe treatments. SCIT not only faces concerns regarding toxicity and the risk of secondary malignancies—for example, in TA891 it was noted that FCR can have an 'extremely negative impact on patients'—but its use has been superseded by targeted agents.[2]

Considering the evolution to the treatment landscape described above, AbbVie therefore, propose that the wording of the target population be changed to ‘fit patients with untreated chronic lymphocytic leukaemia when there is no 17p deletion or *TP53* mutation.’ AbbVie wish to clarify that this amendment to the wording does not impact the patient cohort being appraised, as this was the cohort previously considered suitable for FCR/BR (hereby denoted by ‘fitness’).

Throughout the rest of the submission document, Population 3 (the population of interest) will be referred to as: **fit patients with untreated CLL and no del(17p)/ *TP53* mutation** (who would previously have been considered suitable for treatment with SCIT).

The decision problem for this submission is outlined in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation and for whom FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) is suitable	Fit patients with untreated chronic lymphocytic leukaemia when there is no 17p deletion or *TP53* mutation	This wording reflects the evolution in the treatment pathway for patients with untreated CLL, though does not impact the patient cohort being appraised, as this is the same cohort previously considered suitable for FCR/BR.
Intervention	Venetoclax with obinutuzumab	Venetoclax with obinutuzumab (Ven+O)	Not applicable
Comparator(s)	• Bendamustine plus rituximab (BR) • Fludarabine with cyclophosphamide and rituximab (FCR) • Ibrutinib plus venetoclax • Acalabrutinib with venetoclax with or without obinutuzumab (subject to ongoing NICE evaluation)	Ibrutinib with venetoclax (I+Ven)	As detailed in Section 1.1 and Section 1.3.5.1, use of FCR and BR as 1L treatment for CLL in the UK is rare and has declined over time.[2] [redacted] Acalabrutinib with venetoclax with or without obinutuzumab is not considered a relevant comparator as it is not established practice in the NHS due to its ongoing NICE appraisal.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment	Primary endpoints: • Progression-free survival (PFS) • Undetectable minimal residual disease (uMRD) in peripheral blood	Not applicable

	• Health-related quality of life	Secondary endpoints: • uMRD in bone marrow • Overall survival • Response rate • Adverse events (AEs) • Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Cost-utility analysis in the base case (expressing cost-effectiveness in terms of incremental QALYs), and cost-comparison analysis as a scenario. The existing commercial agreement for venetoclax is considered. PAS prices are not known for obinutuzumab and ibrutinib; therefore, these are costed at list price	Not applicable

AE, adverse event; BR, bendamustine, rituximab; BSH, British Society for Haematology; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide, rituximab; MRD, minimal residual disease; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year;

1.2 Description of the technology being evaluated

Details of the technology being appraised in this submission are summarised in Table 2. The summary of product characteristics and the UK public assessment report are provided in Appendix A.

Table 2. Technology being evaluated

UK approved name and brand name	Venetoclax with obinutuzumab (Ven+O) Venclyxto® with Gazyvaro®
Mechanism of action	Venetoclax is a small, and highly selective orally bioavailable molecule that was designed to target specifically the BH3 domain of BCL2. As a BH3 mimetic, venetoclax displays a high affinity to the BH3-binding groove of BCL2 and is able to displace pro-apoptotic BH3-only proteins (e.g., BIM) bound to BCL2. Therefore, free BH3-only proteins can activate apoptotic effectors (BAX and BAK) or inhibit other anti-apoptotic members (MCL-1). Therefore, venetoclax triggers and restores apoptosis in tumour cells by releasing pro-apoptotic proteins from BCL2.[16] Obinutuzumab is a humanised anti-CD20 monoclonal antibody. CD20 is found on the surface of B cells, and targeting by obinutuzumab promotes antibody-dependent cell cytotoxicity by natural killer cells[17] and directly activates intracellular death signalling pathways.
Marketing authorisation	Venetoclax and obinutuzumab has received marketing authorisation via the Medicines & Healthcare products Regulatory Agency (MHRA) (March 2020)[18]
Indications and any restriction(s) as described in the summaries of product characteristics (SmPCs)	Venetoclax in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. Approved venetoclax (Venclyxto®) combination therapies that are **not** relevant to this submission: Venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. Venetoclax monotherapy is indicated for the treatment of CLL: • in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or • in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Venetoclax in combination with a hypomethylating agent or low-dose cytarabine is indicated for the treatment of adult

	patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.[18]
Method of administration and dosage	Venetoclax is administered orally as a film coated tablet. The daily regimen is initiated on day 22 of Cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of Cycle 12. Obinutuzumab is administered intravenously for 6 cycles[18]: • 100 mg on Day 1 and 900 mg on Day 2 (or 1000 mg on Day 1) of Cycle 1 • 1000 mg on Days 8 and 15 of Cycle 1 • 1000 mg on Day 1 of Cycles 2–6
Additional tests or investigations	There are no additional tests required for Ven+O compared with I+Ven. Prior to initiating venetoclax treatment, tumour burden assessment, including radiographic evaluation (e.g., CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed, and pre-existing abnormalities corrected.
List price and average cost of a course of treatment	Confirmed list price of venetoclax: • 10mg tablets (pack of 14) = £59.87 • 50mg tablets (pack of 7) = £149.67 • 100mg tablets (pack of 7) = £299.34 • 100mg tablets (pack of 14) = £598.68 • 100mg tablets (pack of 112) = £4,789.47 Confirmed list price of obinutuzumab: • 1000mg/40ml vial for infusion (pack of 1) = £3,312.00 The cost of an entire course of treatment with Ven+O assuming 100% treatment compliance is £79,786.24.
Patient access scheme/commercial arrangement (if applicable)	There is a simple discount patient access scheme (PAS) for venetoclax, which entails providing a discount of [redacted]% on the list price for venetoclax. The cost of Ven+O for the entire treatment duration, assuming 100% treatment compliance and accounting for this PAS, is £[redacted] A confidential PAS is also available for obinutuzumab. However, the figure for the average cost of Ven+O above does not include the PAS price of obinutuzumab as this is confidential and unknown to AbbVie.

AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CT, computerised tomography; PAS, patient access scheme

1.3 Health condition and position of the technology in the treatment pathway

Disease overview

- CLL is a blood cancer characterised by over-proliferation of mature CD5+ B cells.[3] Survival and proliferation of CLL cells is facilitated via various signalling pathways, in particular, enhanced B cell receptor signalling.[19] The majority of patients with CLL present asymptomatically or with non-specific symptoms; however, as CLL progresses, patients experience a range of debilitating symptoms that have a substantial detrimental impact on patients' QoL.[4-8] In addition to the high symptom burden, the emotional toll of living with an incurable illness poses a profound challenge that deeply impacts patients' lives.[4-8]
- In the UK, the mean reported yearly incidence of CLL between 2017 and 2019 was 3,952, equating to 6.0 cases per 100,000.[20] Of these, around two thirds of patients require treatment.[21] Approximately 980 people die of CLL per year in the UK.[22]

Current treatment pathway

- Treatment aims to achieve durable remission with long lasting periods of progression-free survival, whilst minimising toxicities from treatment.[9]
- For fit patients with non-*TP53*-/del(17p) untreated CLL, the current BSH guidelines (2022) recommends 1L treatment with Ven+O, where accessible via the CDF or other funding streams.[9] NICE has also approved I+Ven and SCIT in this population; however, SCIT is no longer recommended in this population and has been superseded by Ven+O and I+Ven (the only relevant comparator), as is detailed in updated ESMO and soon to be published [redacted].[2,10,14,15]
- Without the reimbursement of Ven+O, formerly SCIT-suitable patients with non-*TP53*-/del(17p) untreated CLL have only one targeted therapy approved by NICE: I+Ven. This leaves patients and clinicians with no alternative treatment options, preventing tailoring of treatment based on patient needs, particularly for those with cardiac comorbidities or those at risk of CV AEs.[23-25]

Supersession of FCR/BR by targeted therapies in UK clinical practice

- Clinicians prefer to use targeted therapies over outdated SCIT due to the improved PFS demonstrated by targeted therapies in clinical trials, as well as an improved safety profile given the concerns regarding toxicity and the risk of secondary malignancy associated with SCIT.[10,11,25-28,9,29] Further multiple recent clinical trials have not included SCIT as a comparator, reinforcing the change in treatment landscape.[30-32]

- In addition, NICE has also acknowledged that use of SCIT is rare in the UK,[2] which is strongly supported by clinical engagements conducted by AbbVie.[10,33] Finally, the supersession of FCR/BR by targeted therapies is reflected in the updated ESMO [redacted] treatment guidelines whereby FCR/BR are no longer recommended as treatment options when targeted treatment options are available.[14,15]

Venetoclax + obinutuzumab

- Ven+O is the preferred treatment option for patients in this population; not only according to BSH guidelines, but also clinicians, who have almost 5 years of experience of using Ven+O from the point of its entry into the CDF in 2020.[1,9,10] Additionally, as pointed out by CLL Support, Ven+O provides a valuable treatment option and it is important it remains available to patients and clinicians.[34] Under current guidelines, 1L Ven+O treatment represents the only opportunity to use obinutuzumab for this population, taking advantage of its efficacy as the most effective anti-CD20 therapy in CLL.[35] Without Ven+O for 1L treatment, obinutuzumab will not be available for this population at any stage of their CLL.

1.3.1 Disease background

Chronic lymphocytic leukaemia (CLL) is a blood cancer characterised by over proliferation of mature $CD5^+$ B cells. Malignancy is usually in the blood, bone marrow and lymphoid tissues, such as the spleen and lymph nodes.[3] In the lymphoid tissues, CLL cells receive signals from a variety of surrounding cells, including monocyte-derived cells, stromal cells and supportive T-cells.[3,36-38] These signals stimulate various intracellular signalling pathways activated by the B-cell receptor (BCR), including the mTOR, JNK, ERK/MAPK and NF-κB signalling pathways. These pathways promote survival, proliferation, disease progression and drug resistance.[3,19,37,38]

Enhanced BCR signalling is a key feature of CLL. The BCR regulates apoptosis, a form of programmed cell death, via the NF-κB signalling pathway, and promotes the differentiation and proliferation of B cells.[19] The NF-κB pathway activates anti-apoptotic BCL-2 proteins that prevent cell death, a hallmark of cancer cells.[37,39] This role in promoting B cell proliferation and preventing cell death makes the BCR a strong therapeutic target in CLL.

Although its role in BCR signalling remains unclear, the surface glycoprotein CD20 has emerged as a target for the treatment of mature B cell malignancies.[3] CD20 is thought to be required for efficient BCR signalling in B cells,[40] and physical and functional interaction has been reported between CD20 and MHCII and CD40 – proteins, critical for B- and T-cell interactions.[40,41] Though mature B cells express CD20, the majority of haematopoietic cells do not, rendering CD20 a target for CLL treatments, including the monoclonal antibody, obinutuzumab.[3]

1.3.2 Epidemiology and risk factors

CLL is the most common lymphoproliferative disease in Western countries, representing 25-30% of leukaemia cases.[42] There were approximately 100,000 cases of CLL in 2019, globally,[43] and an incidence of $\leq$ 5/100,000.[44] Incidence has increased worldwide over the past three decades,[43] and specifically by 16% in the UK between 1993 and 2019.[20] In the UK, the mean reported yearly incidence between 2017 and 2019 was 3,952, equating to 6.0 cases per 100,000.[20] The older population is most affected, with 41% of new CLL cases diagnosed in people aged ≥ 75 years.[20] Men are also disproportionately affected: there are approximately twice as many cases in males compared to females.[45]

Risk factors associated with CLL include sex, age, obesity, environmental factors (e.g. exposure to chemicals or smoking), and genetic factors, with a nine-fold increased risk of developing CLL in family members.[46,47] Increases in the prevalence of risk factors, such as increased obesity rates and increased exposure to certain chemicals used in agriculture, are thought to be possibly responsible for the increased incidence of CLL.[46,48]

Approximately 980 people die of CLL per year in the UK, of which ~60% are male, and ~80% occur in people over 75 years old.[22] This reflects the higher incidence and lower survival for CLL in older patients. Prognostic factors for CLL include how advanced the disease is, as well as patient age and genetic changes in the leukaemia cells.[49]

Chromosomal deletions are carried by approximately 80% of patients with CLL.[50] Some of these mutations are associated with worse prognoses.[50] A deletion in the p arm of chromosome 17 (17p13, also known as del17p), is associated with the poor median survival and response to therapy.[50,51] This mutation affects the *TP53* gene, a tumour suppressor gene involved in the DNA damage repair to restore genome integrity, and thought to be responsible for reduced drug response.[50] *TP53* mutations also can be present independently of 17p13, occurring in approximately 10% of patients who start their first line of CLL treatment.[50] Patients with ≥ 3 chromosomal aberrations are considered to have a complex karyotype, which may also have adverse prognostic significance.[49]

Other prognostic factors include the expression of a mutated or unmutated form of the immunoglobulin heavy-chain variable region gene (*IGHV*), with the former associated with better prognosis.[47,51-53]

1.3.3 Clinical presentation

The majority of patients with CLL are asymptomatic at presentation, with diagnosis occurring during a routine blood test, or they may present with non-specific symptoms such as fatigue, weight loss, night sweats, fever or swollen lymph nodes.[6,54] When the disease is advanced, patients experience a range of symptoms including extreme weakness and shortness of breath (due to anaemia), increased number of infections (due to neutropenia) and excessive bruising or bleeding (due to thrombocytopenia).[6] These symptoms are caused by excessive proliferation and survival of CLL cells, overcrowding other healthy blood cells, impairing their development and growth in the bone marrow and impeding their functions.[49,55]

Diagnosis of CLL requires detection of ≥ 5 × 10^9/L B lymphocytes in the peripheral blood sustained over a 3-month period, with confirmation of B cell clonality demonstrated using flow cytometry.[49] Further diagnostic work up of CLL patients consists of examination of prognostic markers, including chromosome status in lymphocytes by cytogenic and fluorescent in-situ hybridisation (FISH) testing, analysis of *TP53* and *IGHV* status, immunoglobulin (Ig) tests to determine circulating antibody levels for fighting infection, and the Direct Coombs test, which measures

whether CLL cells are producing antibodies that target and damage red blood cells.[49,56]

The severity of CLL is determined according to either the Rai or Binet staging systems. The Rai system, most commonly used in the US,[57] stages CLL into five categories representing three risk-factor groups: low, intermediate and high-risk.[57] The Binet system, commonly used in Europe, follows three stages: A, B and C (Table 3).[57]

In addition to these staging systems, systems have been proposed encompassing patient age and the aforementioned prognostic markers to further define disease risk, such as the CLL international prognostic index (CLL-IPI).[49]

Table 3. Disease staging for CLL

Binet staging		
Stage		**Definition**
Low risk (A)		< 3 involved lymphoid sites† Haemoglobin ≥ 100 g/L and platelets ≥ 100 × 10^9/L
Intermediate risk (B)		≥ 3 involved lymphoid sites† Haemoglobin ≥ 100 g/L and platelets ≥ 100 × 10^9/L
High risk (C)		Haemoglobin < 100 g/L and platelets < 100 × 10^9/L
Rai staging		
Stage		**Definition**
Low risk	Rai 0	Lymphocytosis > 5 × 10^9/L
Intermediate risk	Rai I	Lymphocytosis and lymphadenopathy
	Rai II	Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy
High risk	Rai III	Lymphocytosis, haemoglobin < 110g/L (6.83 mmol/L) with/without lymphadenopathy
	Rai IV	Lymphocytosis and platelets < 100 × 10^9/L with/without lymphadenopathy/organomegaly

† Areas considered: cervical, axillary, inguinal lymphadenopathy (uni- or bilateral), spleen and liver. Involvement is judged by physical exam, independent of imaging studies.
Adapted from Eichhorst et al. 2021[29]

1.3.4 Disease burden

CLL has a substantial detrimental impact on patients' health-related quality of life (HRQoL), due to the high symptom burden, treatment-associated toxicity and the emotional impact of living with an incurable illness.[4-8]

In the early stages of CLL, patients can be asymptomatic but can, over time, experience fatigue, weight loss, chills, fever, night-sweats and swollen lymph nodes.[6] As the disease progresses, patients may experience more burdensome symptoms, including greater fatigue, weakness, shortness of breath due to anaemia, excessive bruising and bleeding due thrombocytopenia and greater risk of infection due to neutropenia.[5,6] Patients with CLL are reported to have substantially worse HRQoL than the general population in terms of fatigue, anxiety, physical functioning, social functioning, sleep disturbance and pain interference.[4]

Further, patients with CLL have significantly reduced emotional wellbeing than the general population ($p < 0.001$), and patients with other cancers ($p < 0.001$).[5] Factors associated with lower overall QoL include the severity of co-morbidities, older age, and fatigue.[5] There is also significant emotional impact on patients from living with an incurable illness; in a US-based self-reported patient survey, 72% of patients were worried about their disease relapsing or progressing, and 96% of patients stated that delaying disease progression was their priority.[7] Similarly, patients experience mental health issues due to the uncertainty surrounding when their disease may relapse.[7] Younger patients ($\leq$ 60 years old) diagnosed with CLL are more likely to suffer from anxiety and depression and have a reduced emotional and social quality of life.[58] The quality of life of friends, family and other caregivers is also often affected, as CLL patients often require support to perform everyday activities.[59]

In a survey using time trade-off methodology to measure the UK public's perceptions of nine health states representing CLL treatment lines or disease stages, PFS without therapy was rated as the most positive health state. Conversely, relapsed lines of treatment represented the greatest burden, highlighting the value of maintaining PFS.[60]

CLL is associated with a considerable healthcare resource utilisation (HCRU) burden.[61] A systematic review of the economic burden of CLL found that healthcare costs are primarily driven by treatment and hospitalisation-related costs, AE management, and disease progression.[4] Treatments with targeted therapies are associated with lower HCRU costs, although patients with CV events after treatment with ibrutinib were noted to have higher HCRU than those without CV events.[4]

Aside from the economic burden of treatments, CLL patients with cytopenia often require treatment for these symptoms, increasing healthcare resource use. Patients with neutropenia and hypogammaglobulinaemia often require prophylactic treatments to mitigate the risk of infection, including the use of antimicrobials and immunoglobulin replacement therapy.[57,62,63] Anaemia treatment ranges from supportive care to the use of erythropoietic agents and blood transfusions.[64] Similarly, thrombopoietin receptor agonists have been advised for treatment of autoimmune cytopenia, as has immunosuppressive treatment such as with corticosteroids.[29,65]

Finally, in a study of the burden of CLL on patients' QoL, 12% of patients reported being medically disabled when describing their employment status, almost 80% of whom attributed their disability to CLL.[5] As the majority of patients in this study were < 60 years old,[5] this suggests that improving the treatment options for fit patients may allow some to continue working. This may alleviate some economic burden both through reducing the need for disability support and increasing economic participation.

1.3.5 Current treatment pathway

As CLL is incurable, and early interventions have not demonstrated improved survival in asymptomatic CLL patients,[66,67] treatment of early stage CLL follows a strategy of 'active monitoring', with treatment initiated in patients who satisfy the 2018 iwCLL criteria for progressive or symptomatic disease.[49] Approximately two thirds of patients experience disease progression at some stage, requiring treatment.[21]

The overall aim of treatment for CLL is to achieve a durable remission with long lasting periods of PFS and extended OS, whilst also minimising side effects and toxicities from treatment.[9] Response to treatment is typically assessed at least two months after completion of therapy with complete and differential blood counts, physical examination, and evaluation of bone marrow conducted in cases with cytopenia.[49] The extent of response is defined using parameters pertaining to lymphoid tumour load and constitutional symptoms, such as lymphadenopathy, splenomegaly and hepatomegaly, and parameters pertaining to the hematopoietic system, including platelet, neutrophil and haemoglobin counts.[49]

Extent of remission is also measured as the presence of minimal residual disease (MRD) or undetectable MRD (uMRD), categorised clinically as 1 CLL cell per 10,000 (10^4) leukocytes in the blood or bone marrow.[68] Achieving uMRD is associated with longer remission periods and survival,[69,70] and an uMRD of < 10^{-4} in peripheral blood at the cessation of treatment is indicative of treatment efficacy.[71] MRD is primarily used as an endpoint in clinical trials, although its importance in clinical practice is increasing.[72,73]

Treatment strategies vary according to prognostic and predictive factors, including genetic abnormalities, patients' fitness or comorbidities, concomitant medication, and prior treatment.[9,14] Comorbidities are common due to the age profile of patients;[74] however, there is no formal comorbidity assessment tool to determine fitness of patients for chemotherapy.[65] An advisory board of UK-based clinicians organised by AbbVie found that end-of-bed assessments of patient fitness are used to inform selection of first-line therapy.[10] Treatment guidelines in the UK and Europe are dictated by the most recent British Society of Haematology (BSH) guidelines,[9] published in 2022 ([redacted]), and the European Society for Medical Oncology (ESMO) guidelines, published in 2024.[14]

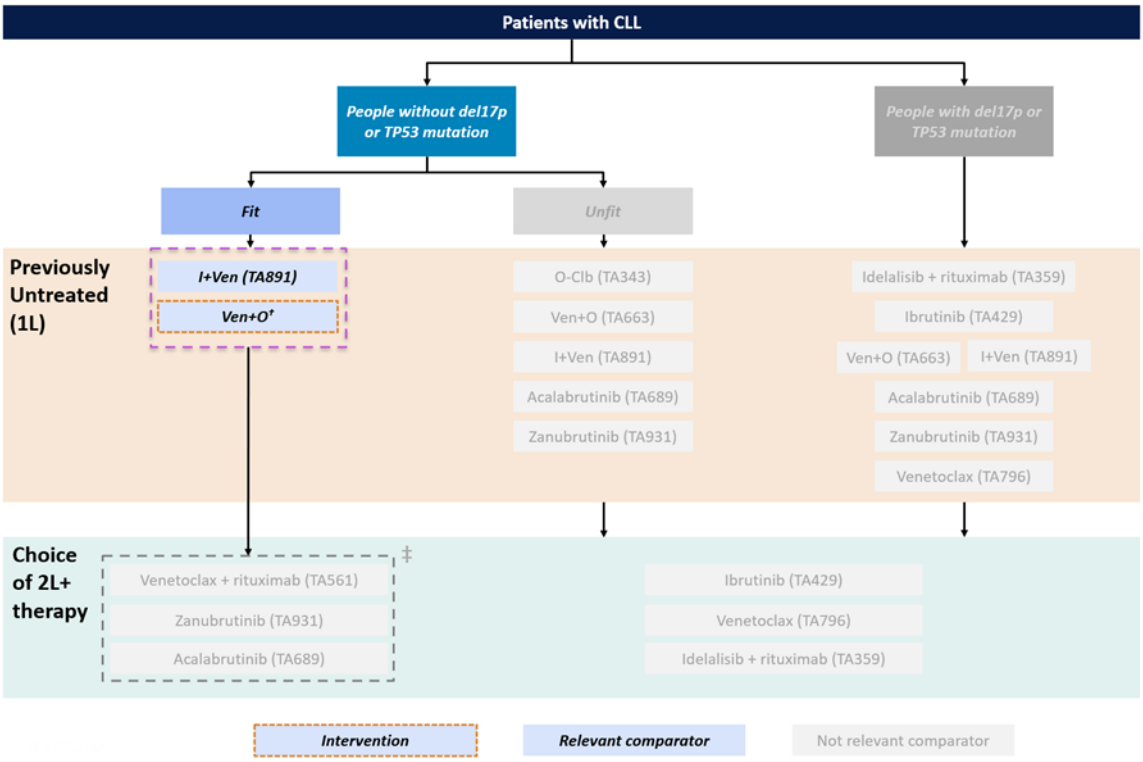
For fit patients with untreated CLL and no del(17p)/ *TP53* mutation, the BSH recommends 1L treatment with targeted therapies, including Ven+O where accessible via the CDF or other funding streams.[9] Since the approval of Ven+O for this population, use of SCIT treatments has considerably declined, and is avoided by

clinicians (Section 1.3.5.1). [redacted][15] In agreement, the ESMO guidelines state that time-limited SCIT treatments, such as FCR, should only be considered in certain patients and only if targeted therapies are not reimbursed.[14]

Time to relapse is dependent on several aspects, including prognostic factors, previous treatment and genotype.[75,76] Relapse results in re-initiation of treatment, and may occur multiple times throughout a patient's lifetime,[9] resulting in increased hospital visits,[77] further exposure to the adverse effects of subsequent treatments, and increased risk of complications due to the development of comorbidities as patients age, and worsening QoL.[4,76,78] The duration of remission (DOR) after 1L therapy may influence the choice of 2L therapy, according to clinicians interviewed by AbbVie, who stated that if long remission was seen with fixed-duration 1L therapy, they might then consider another fixed-duration treatment at 2L.[10]

Figure 1 displays the current treatment pathway as outlined in previous NICE technology appraisals, which best represents current UK clinical practice.[1,2,79-85] Of note, I+Ven and Ven+O (including the population in the CDF) are the only treatments recommended in all sub-populations of previously untreated CLL.

Figure 1. Treatment pathway in UK clinical practice for fit CLL patients without TP53/del17p



† Venetoclax + obinutuzumab is available for patients in this population via the CDF in England and Northern Ireland, and through a different funding scheme in Wales.
‡ Relevant 2L+ treatments for the target population were identified by UK clinical experts who added that duration of response to 1L therapy determines the 2L treatment rather than the type of 1L therapy. This is consistent with ESMO guidelines.[14] The Evidence Assessment Group (EAG) for a recent NICE appraisal (TA931) outlined that the definition of patient fitness is subjective and driven by patient characteristics such as age and CIRS score rather than eligibility for specific treatments, in line with recent declines in use of chemotherapy regimens in clinical practice.[79]
1L, first-line; 2L, second-line; BR, bendamustine and rituximab; CDF, Cancer Drugs Fund; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; I+Ven, ibrutinib + venetoclax; Ven+O, venetoclax + obinutuzumab
Adapted from NICE TA931 committee slides[79]

1.3.5.1 Supersession of FCR/BR by targeted therapies in UK clinical practice

NICE have previously acknowledged that use of FCR and BR as 1L treatment for CLL in the UK is rare and has declined over time.[2] Indeed, [redacted] the [redacted] ESMO guidelines no longer recommend FCR or other chemotherapy-based treatments when targeted agents are available.[14,15]

Targeted therapies are preferred to SCIT due to their improved efficacy. In addition, SCIT faces concerns regarding toxicity and the risk of secondary malignancy.[9,29]

Toxicities associated with SCIT include profound immunosuppression, prolonged cytopenia, and a 5-10% risk of therapy-related myelodysplasia (MDS).[86,87] Even among fit patients, approximately three times as many patients discontinue SCIT due to AEs, and more patients experience secondary neoplasms, compared with Ven+O (Table 8).[26] Further, in the ESMO guidelines, it is recommended that clinicians discuss the risks of secondary malignancies associated with SCIT with patients during treatment selection.[14] A large-scale, cross country, European study analysing 25,814 newly diagnosed patients with CLL found that the probability of developing a secondary malignancy within four years of starting FCR therapy ranged between 28.0% and 36.8%.[88]

Aligned with the updated ESMO [redacted] guidelines, clinical engagements conducted by AbbVie confirm that FCR and BR are no longer routinely used in clinical practice[10]:

- **Advisory board feedback:**
    - Advisory board feedback based on seven UK-based consultants is that FCR and BR are no longer the preferred first-line treatment option, regardless of CLL sub-population, and instead there is a preference for selecting targeted therapies.
- **NHSE CDF Clinical lead feedback**
    - Recent (March 2025) feedback from the NHSE CDF Clinical lead is that FCR and BR is no longer used for 1L patient with CLL. This is similar to feedback given and accepted by the committee in TA891 (as referenced below).[2]
- **Individual clinical consultations (four clinical experts):**
    - The NHSE CDF Clinical lead's stance is supported through individual consultations with three UK based clinical experts in November 2024 and one in June 2025.
    - One consultant haemato-oncologist stated they would be "very shocked if anyone has given FCR in the last 2/3/4 years."

- When asked to consider the relevant treatment comparator for fit patients, all consultants agreed that VenI was the relevant comparator. Three consultants were asked what treatment they would use in a world without Ven+O; all three consultants said that if Ven+O was not available they would use I+Ven and not SCIT.

Consistent with the clinical opinions above, the technology appraisal guidance for I+Ven (TA891) states that "BR and FCR are ***hardly used*** [in clinical practice in England]". Since TA891, I+Ven has largely superseded FCR/BR chemotherapy as the only 1L treatment used by clinicians, other than Ven+O via the CDF, for fit patients with untreated CLL and no del(17p)/ *TP53* mutation.[1,2,9]

In line with the NICE technology evaluations manual, this company submission considers how the treatment pathway has evolved since TA663 and views only I+Ven as a relevant comparator.[89]

1.3.6 Limitations in current treatment pathway

With the supersession of SCIT use by targeted therapies, and the recommendation for using targeted therapies over SCIT in clinical guidance (Section 1.3.5.1), I+Ven represents the only relevant 1L treatment routinely recommended by NICE, other than Ven+O (via the CDF), for fit patients with untreated CLL and no del(17p)/ *TP53* mutation.[1,2,9]

Treatment with I+Ven is associated with a number of AEs, including cytopenias, bruising, arthralgia, nausea/vomiting and diarrhoea.[24,25,90] Of particular note is the association with CV side effects, which are a deciding factor for clinicians when administering a BTKi-based therapy such as I+Ven.[91,92] Indeed, the British National Formulary (BNF) advises that older patients, patients with cardiac comorbidities, or those with Eastern Cooperative Oncology Group (ECOG) performance status (a commonly used measure of fitness) ≥ 2, are at increased risk of CV events, including those that are fatal.[93] As such, healthcare professionals (HCPs) are advised to evaluate patients' cardiac history and function before initiating therapy,[94] considering alternatives in those at higher risk. Furthermore, monitoring cardiac function is

advised, with discontinuation in patients with more severe cardiac failure or arrhythmia, and temporary or permanent treatment cessation in patients with new or worsening cardiac failure or arrhythmias.[92]

In the fixed-duration cohort of the I+Ven pivotal trial, CAPTIVATE (NCT02910583), 59% of patients not using concomitant anticoagulants experienced bleeding events of any grade. 4% of all patients in the trial experienced atrial fibrillation of any grade, and 6% of patients experienced grade 3 or 4 hypertension, the second most common grade 3 or 4 AE after neutropenia (33%).[24] Furthermore, an association between pre-existing CV disease and CV events during BTKi therapy has been demonstrated.[91]

The incidence of CV side effects observed in studies of BTKis have led to the recommendation of CV assessments prior to, and during BTKi treatment,[93] likely increasing resource use through outpatient monitoring. Concordantly, clinical and patient experts advise that CV comorbidities can prevent patients from taking ibrutinib-based therapies.[1] Despite the fixed duration of ibrutinib treatment, the onset of CV events are likely to occur in the first 6-12 months, with hypertension, atrial fibrillation and ventricular arrhythmias potentially occurring within the first 12 months, and heart failure occurring within 3 years.[91]

There is, therefore, a significant need for tolerable and effective alternative treatment options for fit patients with untreated CLL and no del(17p)/ *TP53* mutation, offering patients a choice in their treatment, and individualising treatment based on underlying comorbidities. Reimbursement of Ven+O would offer clinicians a simplified treatment pathway for CLL, where clinicians would no longer have to consider the fitness of a patient when deciding treatment (given Ven+O routine reimbursement in the rest of the 1L CLL population). Maintaining and expanding access to Ven+O is of additional importance for patients who are not suitable for I+Ven (see section 1.3.6).[9,14]

1.3.7 Positioning of Ven+O

Given the limited recommended treatment options available for fit patients with untreated CLL and no del(17p)/ *TP53* mutation, Ven+O represents an effective and tolerable treatment option. Furthermore, the treatment is recommended for use by the BSH and ESMO,[9,14] and is actively being used by patients in the UK via the CDF,[12] with positive outcomes as described in the SACT report (Section 2.6.4). As noted by the CLL Support Charity during the scoping period for this appraisal, Ven+O represents a "valuable treatment option for CLL patients and it is urgent and important that it remains available."[34]

Ven+O presents an alternative treatment to I+Ven for the 1L treatment of CLL in fit patients with untreated CLL and no del(17p)/ *TP53* mutation (Figure 1). It provides an effective and tolerable treatment in a patient population who currently have limited treatment options. Under current guidelines, 1L Ven+O treatment represents the only opportunity to use obinutuzumab for this population.[9] Without Ven+O for 1L treatment, obinutuzumab will not be available for this population at any stage.

1.4 Equality considerations

It is not considered that this appraisal will exclude any people protected by equality legislation; or lead to a recommendation that would have a different impact on people protected by equality legislations than on the wider population; or lead to recommendations that would have an adverse impact on people with a particular disability.

2 Clinical effectiveness

Clinical overview

- Relevant evidence for the clinical efficacy of Ven+O in fit patients with untreated CLL and no del(17p)/ *TP53* mutation (who would previously have been considered suitable for treatment with SCIT) is derived from the phase 3 clinical trial, GAIA/CLL13 (NCT02950051),[11,26,27] hereafter referred to as CLL13, and a RWE report using NHS England's systemic anti-cancer therapy dataset (hereafter referred to as the SACT report).[12]
- CLL13 reported rates of uMRD in peripheral blood (PB) and in bone marrow, PFS, OS, TTNT, clinical response, and measures of QoL,[26,27] whereas SACT reported OS only.[12]

Efficacy

- For completeness, AbbVie describe observed outcomes for Ven+O and SCIT in this section; however, we emphasise that although SCIT is a comparator within the CLL13 trial, it is no longer considered a relevant treatment in UK clinical practice.
  - **PFS**: At a median follow-up of 63.8 months, PFS was superior for Ven+O compared with SCIT (median not reached vs 61.2 months; p<0.001), with estimated 5-year PFS rates of 69.8% vs 50.7% respectively.[11]
  - **OS**: Overall survival did not differ significantly between the treatment groups, and no treatment group reached median OS. Five-year OS rates were 93.6% for Ven+O and 90.7% for SCIT.[11]
  - **TTNT**: At a median follow-up of 63.8 months, time to next treatment was significantly longer in patients treated with Ven+O compared with patients treated with SCIT (HR 0.43 [97.5% CI: 0.27–0.68], p<0.001).[11]
  - **uMRD**: At month 15, a significantly higher percentage of patients treated with Ven+O displayed uMRD in PB compared with patients treated with SCIT (86.5% [97.5% CI 80.6; 91.1] vs. 52.0% [97.5% CI 44.4; 59.5], p<0.001).[27]
  - **CR**: At month 15, a greater proportion of patients treated with Ven+O (130 of 229 patients [56.8%]) achieved CR, as defined in the iWCLL guidelines, than in those treated with SCIT (71 of 229 patients [31.0%]).[27]
- The efficacy of Ven+O is supported by the SACT report. Of the [redacted]% of patients that had completed treatment, [redacted]% completed treatment as prescribed. Median OS was not reached, with an OS of [redacted] at 24 months.[12]

Indirect treatment comparison

- To compare Ven+O with other treatments approved for this population, an unanchored MAIC was conducted using results from the CAPTIVATE (NCT02910583) trial of I+Ven.

- In the MAIC, Ven+O demonstrated numerical improvements in both PFS and OS compared with I+Ven, and additional improvement in complete remission.
    - **PFS:** [redacted], **OS:** [redacted]

Safety

- CLL13 demonstrated that Ven+O is well tolerated by fit patients with untreated CLL and no del(17p)/ *TP53* mutation. The most frequently reported treatment-emergent serious adverse events with maximum CTC grade ≥ 3 in patients treated with Ven+O were infusion-related reactions ([redacted]), pneumonia ([redacted]), tumour lysis syndrome ([redacted]), thrombocytopenia ([redacted]), and febrile neutropenia ([redacted]).[13] This manageable safety profile is supported by the treatment adherence observed in the SACT report.[12]

Conclusions

- Aside from Ven+O via the CDF, fit patients with untreated CLL and no del(17p)/ *TP53* mutation have a single viable therapy option: I+Ven (Section 1.3.5 and 1.3.6).
- The MAIC comparing Ven+O and I+Ven demonstrated numerical improvements for Ven+O in both PFS and OS.
- Ven+O's alternative mechanism of action offers a much-needed novel targeted treatment for this population, especially given that some patients are not suitable for BTKi-based treatments.[23,24] Clinical experts report that Ven+O is used frequently for 1L CLL management. Routine commissioning will ensure continued access to Ven+O, maintaining choice for patients based on their individual needs.

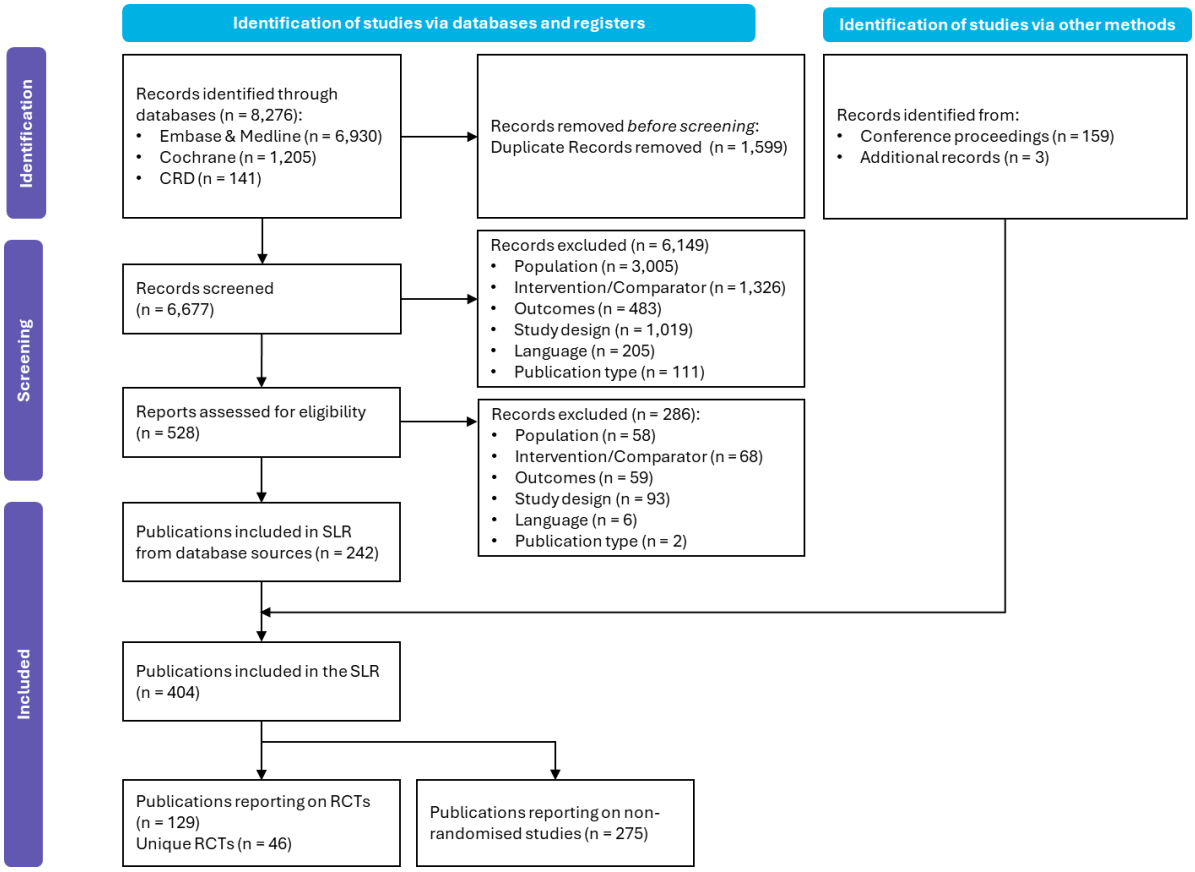
2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical and economic (non-clinical) evidence for the treatment of fit patients with untreated CLL and no del(17p)/*TP53* mutation (who would previously have been considered suitable for treatment with SCIT).

Searches for relevant publications were conducted in the MEDLINE, Embase, Cochrane, and the Centre for Reviews and Dissemination databases, and conference proceedings. These searches were initially conducted in December 2018, with updates performed in July 2019, September 2020, December 2022, February 2024 and February 2025. The updated searches run in December 2022, February 2024 and February 2025 only summarised evidence from RCTs as it was concluded that a critical mass of clinical evidence had been reached, and therefore, the data extraction and reporting focused only on RCTs, which are presented in the report. A total of 46 RCTs were identified from 129 publications, as were 275 non-randomised studies. Full details of the review are given in Appendix B.

A PRISMA diagram for the search of clinical literature is presented in Figure 2.

Figure 2. PRISMA diagram for clinical SLR



CRD, Centre for Reviews and Dissemination; RCT, randomised controlled trial; SLR, systematic literature review

2.2 List of relevant clinical effectiveness evidence

During the SLR, the CLL13 trial was identified as the only relevant trial providing evidence to support the effectiveness of Ven+O for the treatment of untreated CLL in fit patients with untreated CLL and no del(17p)/*TP53* mutation.

The efficacy and safety of Ven+O have previously been explored in the CLL14 trial, which was used to inform the TA663 submission and marketing authorisation (Table 4). However, as this trial was conducted in a different patient population to that considered in this submission, namely unfit patients with comorbidities defined as a cumulative illness rating scale (CIRS) > 6, the CLL14 trial is not considered relevant to inform this submission, given that the CLL13 trial aligns with the population of interest in the decision problem.

Table 4. Patient populations in the CLL13 and CLL14 trials

Trial	Population	Marketing Authorisation	Presented to NICE
CLL14	Unfit patients	Used to gain marketing authorisation across both fit and unfit population	Used to support TA663, which recommended unfit population and any patients with del17p or *TP53* mutations for routine commissioning but fit population for CDF pending readout off CLL13
CLL13	Fit patients	N/A	Focus of this submission to exit the CDF

CDF, Cancer Drugs Fund

CLL13 was a phase 3, multicentre, randomised, prospective open label trial evaluating the safety and efficacy of Ven+O, I+Ven+O, and Ven+R compared with SCIT, in fit patients with previously untreated CLL without del17p or *TP53* mutations.[26] Fitness was defined by a CIRS score ≤6 and a normal creatinine clearance ≥70ml/min.[26]

Pursuant to TA663, and pending data readout from CLL13, Ven+O was commissioned via the CDF to facilitate managed access and additional data collection to resolve uncertainty on the OS evidence supporting Ven+O in fit patients with untreated CLL and no del(17p)/ *TP53* mutation.[1] The real-world evidence on the effectiveness of Ven+O was compiled from the routinely collected SACT dataset.[12]

Table 5. Clinical effectiveness evidence

Study	CLL13 (NCT02950051)	SACT data cohort study
Study design	Phase III prospective, multicentre, open-label, randomised trial	SACT data cohort study
Location	159 sites in ten countries in Europe and the Middle East	NHSE trusts
Population	Fit patients with previously untreated CLL without del17p or *TP53* mutation (Fit patients defined by a CIRS score ≤6 and a normal creatinine clearance ≥70ml/min)	Patients receiving venetoclax with obinutuzumab for untreated CLL via the CDF
Intervention(s)	Ven+O I+Ven+O Ven+R	Ven+O
Comparator(s)	Standard chemoimmunotherapy: • FCR (patients up to and including 65 years old) • BR (patients older than 65 years) I+V+O and Ven+R are not licensed or funded in the UK for previously untreated patients and therefore, not included as comparators	Not applicable
Indicate if study supports application for marketing authorisation (yes/no)	No	No
Reported outcomes specified in the decision problem	• Investigator-assessed PFS • Investigator-assessed overall response-rate • Investigator-assessed complete response-rate • OS • Adverse effects of treatment • HRQoL	• Treatment duration • OS
All other reported outcomes	• MRD response rate measured by flow cytometry in peripheral blood and bone marrow • Duration of response • Event-free survival • Time to next treatment	• Sensitivity analysis of treatment duration and OS in patients with ≥ 6 months follow-up

BR, bendamustine + rituximab; CLL-IPI, International Prognostic Index for chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide, rituximab; HRQoL, health related quality of life; I+Ven+O, ibrutinib + venetoclax + obinutuzumab; MRD, minimal residual disease, NHSE, NHS England; OS, overall survival; PFS, progression-free survival; TP53, tumour protein p53; Ven+R, venetoclax + rituximab; Ven+O, venetoclax + obinutuzumab
Source: CLL13 trial protocol,[95] Eichhorst et al. 2023,[27] SACT report[12]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

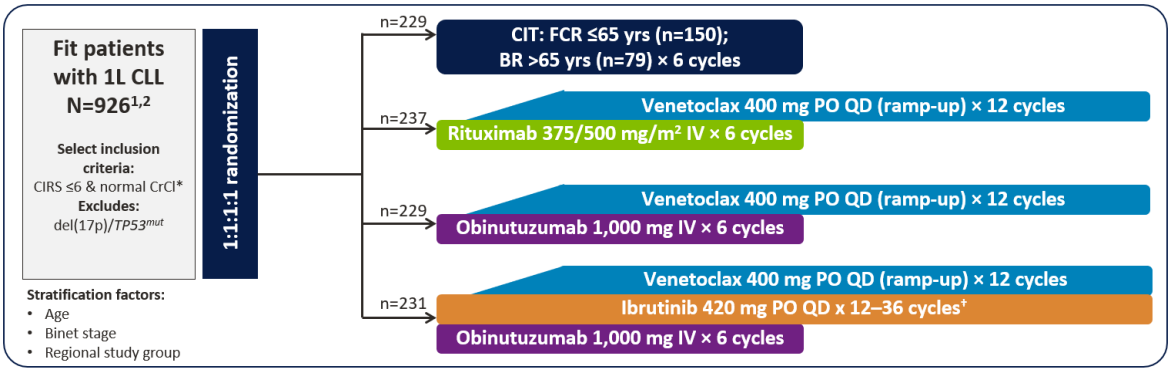
2.3.1 CLL13 study design

CLL13 was a phase 3, multicentre, randomised, prospective open-label trial evaluating the safety and efficacy of venetoclax regimens Ven+O, I+Ven+O and Ven+R compared with SCIT (FCR and BR) in fit patients with previously untreated CLL without del17p or *TP53* mutation.[26] The trial was conducted across 159 sites in ten countries in Europe and the Middle East.

The co-primary objectives were to assess the negativity rate of MRD measured by flow cytometry in peripheral blood (PB) at Month 15 in patients receiving Ven+O compared with SCIT, and to assess progression-free survival (PFS) in patients receiving I+Ven+O compared with patients receiving SCIT. Key secondary endpoints included assessment of PFS pairwise between patients treated with each regimen, including Ven+O vs SCIT.[26]

Patients (n = 926) were randomised 1:1:1:1 to either SCIT, Ven+O, Ven+R or I+Ven+O. Randomisation was stratified according to age (≤ 65 vs > 65), Binet stage at screening (A, B or C), and geographic region. In the SCIT arm, patients ≤ 65 years received FCR, whereas those > 65 years received BR.[26]

Figure 3. CLL13 study design



28-day cycles; * Normal CrCl defined as ≥70 mL/min; † Continuation of ibrutinib up to cycle 36 allowed if MRD still detectable (80% received 12–15 cycles).
BM, bone marrow; BR, bendamustine + rituximab; CIRS, cumulative illness rating scale; CIT, chemoimmunotherapy; CrCl, creatinine clearance; EFS, event-free survival; FCR, fludarabine + cyclophosphamide + rituximab; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; PB, peripheral blood; Ven, venetoclax

The Ven+O arm of CLL13 is applicable for the target population of this appraisal (fit patients with untreated CLL and no del(17p)/*TP53* mutation) who currently have limited availability of reimbursed therapies.

2.3.1.1 Study treatments

Treatments administered in CLL13 relevant to this submission (albeit FCR/BR are no longer relevant to the UK as described in Section 1.3.5.1), and their associated regimen, are summarised in Table 6.

Table 6. Study treatments administered in CLL13†

Ven+O	Ven+O treatment consisted of 12 cycles, each with a duration of 28 days. During the first cycle obinutuzumab was administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of cycles 2-6. • Obinutuzumab IV infusion: Cycle 1: Day 1: obinutuzumab 100 mg; Day 1 (or 2): obinutuzumab 900 mg; Day 8: obinutuzumab 1000 mg; Day 15: obinutuzumab 1000 mg Cycles 2-6: Day 1: obinutuzumab 1000 mg The first infusion of obinutuzumab could be administered at the full dose (1000 mg) on day 1 of the first cycle if the infusion of a test-dosage of 100 mg was well tolerated by the patient. Alternatively, if the first 100 mg infusion on day 1 was not tolerated well, the remaining 900 mg of the first dose was to be administered on day 2. • Venetoclax was administered daily with a slow dose escalation of venetoclax started on day 22 of cycle one. Cycle 1: Days 22-28: venetoclax 20 mg (2 tablets at 10 mg) Cycle 2: Days 1-7: venetoclax 50 mg (1 tablet at 50 mg); Days 8-14: venetoclax 100 mg (1 tablet at 100 mg); Days 15-21: venetoclax 200 mg (2 tablets at 100 mg); Days 22-28: venetoclax 400 mg (4 tablets at 100 mg) Cycles 3-12: Days 1-28: venetoclax 400 mg (4 tablets at 100 mg) Due to the risk of adverse events, especially tumour-lysis-syndromes (TLS), the dose of venetoclax was increased slowly every week until the final dose of 400 mg was reached (ramp-up). On days with administration of both venetoclax and obinutuzumab, oral intake of venetoclax was followed by intravenous (IV) administration of obinutuzumab.

Standardised chemotherapy (FCR/BR)	**FCR** Patients ≤ 65 years received 6 cycles of fludarabine, cyclophosphamide and rituximab, each cycle with a duration of 28 days. • Fludarabine was administered intravenously on days 1-3 (cycle 1-6) at a dosage of 25 mg/m^2. • Cyclophosphamide was administered intravenously on days 1-3 (cycle 1-6) at a dosage of 250 mg/m^2. • Rituximab was administered intravenously before the application of chemotherapy at a dosage of 375 mg/m^2 in the first cycle and at a dosage of 500 mg/m^2 in cycles 2-6, with premedication according to clinical practice of the participating sites. **BR** Patients > 65 years received 6 cycles of bendamustine and rituximab, each cycle with a duration of 28 days. • Bendamustine was administered intravenously on days 1 and 2 (cycle 1-6) at a dosage of 90 mg/m^2. • Rituximab was administered intravenously before the application of chemotherapy at a dosage of 375 mg/m^2 in the first cycle and at a dosage of 500 mg/m^2 in cycles 2-6 with premedication according to the clinical practice of the participating sites.

† Treatments denoted here include only those approved by NICE for untreated CLL in patients without del17p or *TP53* mutation.
BR, bendamustine + rituximab; CLL, chronic lymphocytic leukaemia; I+Ven+O, ibrutinib + venetoclax + obinutuzumab; IV, intravenous; FCR, fludarabine, cyclophosphamide, rituximab; MRD, minimal residual disease; TLS, tumour lysis syndrome; Ven+R, venetoclax + rituximab; Ven+O, venetoclax + obinutuzumab
Source: CLL13 trial protocol[95]

2.3.1.2 Eligibility criteria

A summary of the key eligibility criteria for CLL13 is presented in Table 7.

Table 7. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
1. Documented CLL requiring treatment according to iwCLL criteria.[96] 2. Age at least 18 years. 3. Life expectancy ≥ 6 months. 4. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements. 5. Adequate bone marrow function indicated by a platelet count >30x10^9/l (unless directly attributable to CLL infiltration of the bone marrow, proven by bone marrow biopsy) 6. GFR ≥70ml/min directly measured with 24hr urine collection, calculated according to the modified formula of Cockcroft and Gault *(for men: GFR ≈ ((140 - age) x bodyweight) / (72 x creatinine), for women x 0, 85) or an equally accurate method*. *For patients with creatinine values within the normal range the calculation of the clearance is not necessary. Dehydrated patients with an estimated creatinine clearance less than 70 ml/min may be eligible if a repeat estimate after adequate hydration is > 70 ml/min.* 7. Adequate liver function as indicated by a total bilirubin ≤ 2 x, AST/ALT ≤ 2.5 x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome. 8. Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every month until 12 months after last treatment cycle), negative testing for hepatitis C RNA within 6 weeks prior to registration. 9. Eastern Cooperative Oncology Group Performance Status (ECOG) performance status 0-2.	1. Any prior CLL-specific therapies (except corticosteroid treatment administered due to necessary immediate intervention; within the last 10 days before start of study treatment, only dose equivalents up to 20 mg prednisolone are permitted) 2. Transformation of CLL (Richter's transformation). 3. Decompensated haemolysis, defined as ongoing haemoglobin drop in spite of prednisolone or intravenous immunoglobulins (IVIG) being administered for haemolysis. *Prior treatment with rituximab even for other indications than CLL is not permitted.* 4. Detected del17p or *TP53* mutation. 5. Patients with a history of PML. 6. Any comorbidity or organ system impairment rated with a single CIRS (cumulative illness rating scale) score of 4 (excluding the eyes/ears/nose/throat/larynx organ system), a total CIRS score of more than 6 or any other life-threatening illness, medical condition or organ system dysfunction that, in the investigator´s opinion, could compromise the patients safety or interfere with the absorption or metabolism of the study drugs (e.g. inability to swallow tablets or impaired resorption in the gastrointestinal tract). 7. Urinary outflow obstruction. 8. Malignancies other than CLL currently requiring systemic therapies, not being treated with curative intent before (unless the malignant disease is in a stable remission due to the discretion of the treating physician) or showing signs of progression after curative treatment. 9. Uncontrolled or active infection. 10. Patients with known infection with human immunodeficiency virus (HIV).

	11. Requirement of therapy with strong CYP3A4 and CYP3A5 inhibitors/inducers. 12. Anticoagulant therapy with warfarin or phenoprocoumon *(alternative anticoagulation is allowed (e.g. DOACs), but patients must be properly informed about the potential risk of bleeding under treatment with ibrutinib).* 13. History of stroke or intracranial haemorrhage within 6 months prior to registration. 14. Use of investigational agents which might interfere with the study drug within 28 days prior to registration. 15. Vaccination with live vaccines 28 days prior to registration. 16. Major surgery less than 30 days before start of treatment. 17. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, known sensitivity or allergy to murine products. 18. Known hypersensitivity to any active substance or to any of the excipients of one of the drugs used in the trial. 19. Pregnant women and nursing mothers. 20. Fertile men or women of childbearing potential unless: a. surgically sterile or ≥ 2 years after the onset of menopause b. willing to use two methods of reliable contraception including one highly effective contraceptive method (Pearl Index <1) and one additional effective (barrier) method during study treatment and for 18 months after the end of study treatment. 21. Legal incapacity. 22. Prisoners or patients who are institutionalised by regulatory or court order. 23. Persons who are in dependence to the sponsor or an investigator.

ALT, Alanine transaminase; AST, Aspartate transaminase; CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukaemia; DOAC, direct oral anticoagulants; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; HBV, hepatitis B virus; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; RNA, ribonucleic acid; *TP53*, tumour protein p53; ULN, upper limit of normal

Source: CLL13 trial protocol[95]

2.3.2 SACT report design

NICE previously appraised the clinical and cost effectiveness of Ven+O for untreated CLL and made a positive recommendation for patients considered unfit, but recommended the commissioning of Ven+O through the CDF to allow a period of managed access for patients considered to be fit.[12] This period has facilitated evidence on the real-world treatment effectiveness of Ven+O in the CDF population by NHS England using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.[12]

The SACT report only contains real world evidence considering patients approved for Ven+O treatment via the CDF. Ven+O treatment was administered per their respective SmPCs, as detailed in Table 6 above.[12,18,97]

2.3.2.1 Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for Ven+O for the treatment of untreated CLL in the CDF. Patient NHS numbers were used to link Blueteq® applications to the National Disease Registration Service's (NDRS) routinely collected SACT data to provide SACT treatment history.

Between 10 November 2020 and 31 October 2022, 542 applications for Ven+O were identified in the Blueteq® system. Following appropriate exclusions (patients with duplicate applications, patients who were not included in the SACT and patients who did not receive treatment), 483 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS).

2.3.2.2 Eligibility criteria

A summary of the key eligibility criteria for the SACT report is presented in Table 8.

Table 8 Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Application is made for the initiation of systemic anti-cancer therapy with venetoclax in combination with obinutuzumab by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy • Patient has chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) • Patient has symptomatic disease which requires systemic therapy • Patient has a performance status of 0 or 1 or 2 • In the absence of this venetoclax plus obinutuzumab treatment option, the patient would otherwise have been treated with the combination of fludarabine, cyclophosphamide and rituximab (FCR) or the combination of bendamustine and rituximab (BR)† • Patient has been prospectively assessed for the risk of the development of tumour lysis syndrome with venetoclax and that appropriate risk mitigation strategies have been put in place • Patient has been assessed specifically for potential drug interactions with venetoclax • Patient has been tested for 17p deletion and *TP53* mutation and the results are negative • Patient has not received any previous systemic therapy for CLL/SLL	• Patient has del17p or *TP53* mutation • Patient has received previous systemic therapy for CLL/SLL

† This was prior to I+Ven reimbursement, hence was appropriately worded in the managed access agreement, but no longer reflects the current treatment pattern for this population.
Source: SACT report.[12] This text has been lifted directly from the published SACT report, as presented by the NHS.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1.1 Statistical analysis in CLL13

A description of the statistical analyses and definition of study groups in CLL13 are shown in

Table 9.

Table 9. CLL13 statistical analysis and definition of study groups

	CLL13
Analysis populations	**Intention-to-Treat (ITT):** all randomised patients regardless of whether they received any of the study treatment or not. Patients were assigned to treatment groups and analysed as randomised. The ITT population was used for analysis of all study endpoints except safety. **Safety population:** all patients enrolled in the study who received at least one dose of one component of the treatment. The safety population was used for evaluating the safety endpoints. Patients in this population were analysed by what they have received, and not as originally randomised.
Statistical analysis of primary endpoints	The first co-primary efficacy endpoint is the MRD negativity rate in PB at month 15 for the comparison of Ven+O versus SCIT. At this specific time point, patients were classified according to their MRD level. The MRD negativity rate in PB at month 15 was defined as the proportion of MRD negative patients at month 15 based on the ITT population. MRD negativity was defined as <1 CLL-cell among 10,000 leukocytes analysed [0.01% or < 10^{-4}]. MRD measurement for co-primary efficacy endpoint was based on assessment performed centrally by multi-colour-flow cytometry in the GCLLSG lab in Kiel. According to the ITT principle, all patients without any MRD PB sample at month 15 were kept and labelled as 'non-evaluable' in the analysis. The MRD negativity rate of Ven+O and SCIT was compared using the Cochran-Mantel-Haenszel test stratified by age and Binet stage. Rates and 97.5% CIs are reported for each study arm. The MRD co-primary endpoint was analysed as soon as all randomised patients had achieved the landmark month 15 after randomisation. Thus, final MRD analysis took place as soon as the last patient randomised reached the 15-month time point and all MRD samples were analysed. Additionally, comparisons of MRD negativity rate in PB at month 15 were performed for other study arms. The second co-primary efficacy endpoint was the investigator-assessed PFS for the comparison of I+V+O versus SCIT, defined as the time from randomisation to the first occurrence of progression or relapse (determined using standard iWCLL guidelines [2008]), or death from any cause, whichever occurred first. For patients who had not progressed, relapsed, or died at the time of analysis, PFS was censored on the date of the last tumour assessment. If no tumour assessments were performed after the baseline visit, PFS was censored at the time of randomisation + 1 day. All patients including patients who discontinued all components of study therapy prior to disease progression (e.g., for toxicity) continued on study and were followed for progressive disease and survival regardless of whether or not they subsequently received new anti-leukemic therapy. In case of initiation of subsequent anti-leukaemic treatment without documented disease progression, patients were censored at last tumour assessment prior to start of subsequent therapy. Sensitivity analyses utilising different schemes for censoring were performed in terms of sensitivity of the primary analysis of PFS and are described in the statistical analysis plan.

Statistical analysis of secondary endpoints	Secondary time-to-event and rate-based endpoints were analysed using the same statistical methods described for the primary analyses, including pairwise comparisons of the efficacy of the other treatment regimens. PFS comparisons between other treatment regimens were to be performed at time of PFS interim analysis, only if the data safety monitoring board (DSMB) confirmed that the results of the PFS interim analysis were statistically significant, robust and reliable with regard to the pre-specified significant boundary, and the DSMB recommended conducting the primary analysis of the co-primary endpoint PFS. To ensure type 1 error control for statistical testing, a hierarchical test sequence according to Lehmacher et al. 2000 was to be considered.[98] The timepoint of the PFS interim analysis was reached once either 65% of the total of 213 PFS events occurred (i.e. 138 PFS events, projected at month 49) or 61 months after FPI, whichever occurred first.
Statistical analysis of safety endpoints	Safety parameters were analysed on the safety population. The recent updated version of NCI Common Terminology Criteria for AEs (NCI-CTCAE) was used for assessing the severity of AEs. Classifications were performed using the Medical Dictionary for Regulatory Activities classification system (MedDRA preferred term). Presentations of AEs included a complete-case and a per-patient analysis. Relative frequencies were displayed for categorical variables. For continuous variables descriptive statistics including median, mean, minimum, maximum, and standard deviation were used.
Sample size and power calculation	The co-primary endpoints MRD negativity rate and median PFS were used to determine the sample size of the study assuming 80% power and two-sided significance level of 5% (split equally 2.5% | 2.5% to allow for two co-primary endpoints). The following requirements are given to perform a hypothesis test for clinically relevant superiority in the co-primary endpoint PFS: • Log-rank test at the two-sided 0.025 significance level • Median PFS for SCIT = 48 months • 80% power to detect a hazard ratio HR = 0.649 for the comparison I+Ven+O versus SCIT with median PFS for I+Ven+O increased to 74 months • Exponential distribution of PFS • One interim analysis for assessing efficacy as soon as either 65% of PFS events occurred (across the total trial population) or 61 months after FPI. PFS was tested at the significance level determined using the Lan-DeMets alpha spending function with an O`Brien-Fleming boundary so that the overall two-sided type I error rate will be maintained at 0.025 level. Further, a non-binding futility boundary is included. Based on these assumptions 213 PFS events are required for the final PFS analysis. Assuming non-linear accrual of 460 patients [230 patients for SCIT and 230 patients for I+Ven+O] over 33 months, the 213 events will be reached 72 months after FPI. In terms of timely completion, the final PFS will be conducted as soon as either 213 PFS events occurred or 73 months after FPI. The MRD negativity rate in PB at months 15 for the SCIT arm was assumed to be 30%. It was assumed to improve this rate to at least 50% with the Ven+O regimen resulting in a clinically relevant increase of the absolute percentage difference of at least 20%. With these determined study parameters, a two-sided two-sample $\chi 2$-test of rates with an overall significance level of $\alpha = 2.5\%$ will adhere $(1 - \beta) \approx 98.7\%$ power to detect a 20% difference if the total number of patients is 460 [230 patients for SCIT and 230 patients for Ven+O].

	To enable balanced comparisons between all treatment arms, equal recruitment of all arms will be considered. The total number of patients to be randomised is therefore 920. Sample size calculations were performed with EAST 6 software.
Handling of missing data and participant withdrawals	The proportion of patients for whom data are missing are described with respect to the ITT population. Patients with missing response assessment were kept and labelled as 'non-responder' in the analysis.

FPI, first patient randomised; ITT, intention-to-treat; iWCLL, International Workshop on Chronic Lymphocytic Leukemia; I+Ven+O, ibrutinib + venetoclax + obinutuzumab; LPI, last patient randomised; MRD, minimal residual disease; NCI-CTCAE, NCI Common Terminology Criteria for AEs; PB, peripheral blood; PFS, progression-free survival; SCIT, standardised chemoimmunotherapy; Ven+O, venetoclax + obinutuzumab
Source: CLL13 SAP and protocol[95,99]

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from the CLL13 trial, including the CSR and publications.[11,13,26,27] Quality assessment of CLL13 is presented in Table 10. The quality assessment was conducted based on the Centre for Reviews and Dissemination's (CRD's) guidance. Additional detail is provided in Appendix B.

Table 10. Quality assessment results for CLL13

	CLL13
Was randomisation carried out appropriately?	Yes – patients were randomised 1:1:1:1 by an interactive voice and web response system (IXRS), across four treatment groups. Randomisation was stratified according to trial group, age (≤ 65 or > 65 years), and Binet stage before initiation of therapy (A, B, C) and region.
Was the concealment of treatment allocation adequate?	No – as is common practice in oncology trials, the study was open label as a safety measure so that prompt and accurate assessment of the unique toxicities associated with study treatments could be conducted. Investigators and patients were not masked to treatment assignments, and neither was an independent data and safety monitoring lead, nor the DSMB.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – baseline characteristics were well balanced between the treatment groups (Table 12).
Were the care providers, participants and outcome assessors blind to treatment allocation?	No – the study was open label as a safety measure, which is typical for clinical trials in oncology. Blinding of investigators and patients would not have been possible due to differences in the nature and schedules of treatments (Table 6).
Were there any unexpected imbalances in dropouts between groups?	No – a similar number of patients discontinued in each treatment arm (Table 11).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all trial outcomes are reported within the CSRs provided.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – this was appropriate. The ITT population was used for evaluation of all efficacy endpoints. Where responses were not assessable, patients were counted as missing (Table 9).

AE, adverse event; CSR, clinical study report; DSMB, Data and Safety Monitoring Board; FCR, fludarabine, cyclophosphamide and rituximab; ITT, intention-to-treat; IXRS, interactive voice and web response system; IV, intravenous; SCIT, standardised chemoimmunotherapy; Ven+O, venetoclax + obinutuzumab
Source: CLL13 SAP and protocol,[95,99] Fürstenau et al. 2024[26]

The clinical effectiveness evidence of Ven+O provided in this submission is derived from the CLL13 trial. The trial was mostly conducted in Europe, with 96% of patients randomised being treated at European centres (Table 12). As such, clinical experts considered the trial generalisable to UK clinical practice.[10] Further subgroup analyses using CLL13 data demonstrate that Ven+O treatment resulted in a statistically significant improvement in PFS for both ≤ 65 year-old patients (HR 0.54, 95% CI 0.31; 0.93) and for > 65 year-old patients (HR 0.29, 95% CI 0.15; 0.55) compared with SCIT (Section 2.6.2).[27] Furthermore, the OS outcomes of CLL13

align with those observed in the SACT report, which demonstrates the effectiveness of Ven+O in this population within UK clinical practice.[12]

2.6 Clinical effectiveness results of the relevant studies

2.6.1 CLL13: patient disposition and baseline characteristics

During CLL13, 1,080 patients were screened, and 926 were randomised 1:1:1:1 to each of the four treatment arms (Ven+O n=229, I+Ven+O n=231, Ven+R n=237, SCIT n=229)[17]. Patient disposition, including reasons for discontinuation, are presented in Table 11.

Table 11 Patient disposition

	Ven+O	I+Ven+O	Ven+R	SCIT
Randomised	229	231	237	229
Received study treatment	228	231	237	216
Did not receive study treatment	1	0	0	13
Withdrew consent	0	0	0	11
Other reasons	0	0	0	2
Died before receiving study treatment	1	0	0	0
Discontinuations				
Discontinued study treatment per protocol	214	200	219	176
Discontinued study treatment early	14	31	18	40
Progressive disease	3	0	4	2
Death	1	2	1	0
Adverse event	9	27	11	32
Non-compliance	1	0	0	2
Other reasons	0	2	2	4
Discontinued Ven per protocol, but discontinued ibrutinib before cycle 12	NA	16	NA	NA
Lost to follow up				
Total	14	17	14	41
Death	11	11	9	17
Patient withdrawal	3	4	0	17

Non-compliance	0	0	2	2
Other reasons	0	2	3	5
In follow-up as of data-cut off†	215	214	223	188

†Data reported here is from the January 2023 data cut
I+Ven+O; ibrutinib + venetoclax + obinutuzumab; SCIT, standardised chemoimmunotherapy; Ven+O, venetoclax + obinutuzumab; Ven+R, venetoclax + rituximab
Adapted from Fürstenau et al. 2024[26]

Baseline characteristics were generally similar across all treatment arms (Table 12). Median age of patients in the Ven+O and SCIT arms was 62 and 61 years, respectively. This was similar to the median age of patients in the SACT report (61 years), further supporting the relevance of the trial population to the target population.[12] In CLL13, females represented 25.3% of Ven+O patients and 28.8% of SCIT patients. Patients displayed similarity across measures of fitness, with the mean CIRS score for both Ven+O and SCIT patients being 2.3, and similar proportions of patients in each CLL-IPI category.[26]

Severity of CLL was quantified by Binet stage. In the Ven+O arm, 25.3%, 39.7% and 34.9% of patients categorised as Binet stage A, B and C, respectively. Similarly, in the SCIT arm, 27.5%, 36.7% and 35.8% of patients were staged as above. Bulky disease (lymph nodes ≥ 5 cm) was present in 29.1% of Ven+O patients and 31.1% of SCIT patients. Genetic abnormalities, pertinent to CLL prognosis, were broadly similar across trial arms.[26]

Table 12. CLL13 baseline patient characteristics across treatment groups

Baseline characteristics by treatment arm	Ven+O (N = 229)	I+Ven+O (N = 231)	Ven+R (N = 237)	SCIT (N = 229)	Total (N = 926)
Age (years)					
Median age (range)	62 (31–83)	60 (30–84)	62 (27–84)	61 (29–84)	—
≤ 65, N (%)	147 (64.2)	148 (64.1)	152 (64.1)	150 (65.5)	597 (64.5)
> 65, N (%)	82 (35.8)	83 (35.9)	85 (35.9)	79 (34.5)	329 (35.5)
Sex					
Male, N (%)	171 (74.7)	158 (68.4)	175 (73.8)	163 (71.2)	667 (72.0)
ECOG					
ECOG performance status score of 0, N (%)	165 (72.1)	163 (70.6)	172 (72.6)	164 (71.6)	—
Geographic location					
Europe	224 (97.8)	220 (95.2)	226 (95.4)	222 (96.9)	892 (96.3)
Middle East	5 (2.2)	11 (4.8)	11 (4.6)	7 (3.1)	34 (3.7)
Time between first diagnosis and randomisation (months)					
Median	27.7	28.7	32.9	26.7	29.0
IQR	8.3-62.0	9.4-58.6	9.7-62.1	9.2-59.1	9.1-59.9
CIRS score					
Median	2	2	2	2	2
Mean (SD)	2.3 (1.9)	2.5 (2.0)	2.4 (2.0)	2.3 (1.9)	2.4 (1.9)
CIRS score, N (%)					
≤ 1	90 (39.3)	84 (36.4)	94 (39.7)	93 (40.6)	361 (39.0)
> 1	139 (60.7)	147 (63.6)	143 (60.3)	136 (59.4)	565 (61.0)

Tumour lysis syndrome risk category, n/N (%)					
Low	31/211 (14.7)	28/226 (12.4)	23/220 (10.5)	31/214 (14.5)	—
Intermediate	127/211 (60.2)	154/223 (68.1)	146/220 (66.4)	132/214 (61.7)	—
High	53/211 (25.1)	44/226 (19.5)	51/220 (23.2)	51/214 (23.8)	—
Binet stage, N (%)					
Stage A	58 (25.3)	63 (27.3)	61 (25.7)	63 (27.5)	245 (26.5)
Stage B	91 (39.7)	84 (36.4)	92 (38.8)	84 (36.7)	351 (37.9)
Stage C	80 (34.9)	84 (36.4)	84 (35.4)	82 (35.8)	330 (35.6)
Rai stage n/N (%)					
0	13/228 (5.7)	7/230 (3.0)	8/237 (3.4)	7/227 (3.1)	—
I or II	122/228 (53.5)	121/230 (52.6)	124/237 (52.3)	113/227 (49.8)	—
III or IV	93/228 (40.8)	102/230 (44.3)	105/237 (44.3)	107/227 (47.1)	—
Creatinine clearance (Cockroft-Gault) (ml/min)					
Median	86.3	86.2	84.5	86.3	85.7
IQR	72.6-108.6	72.9-98.7	71.2-102.8	73.4-104.6	72.7-102.5
Missing information, N (%)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cytogenetic subgroup by hierarchical order, N (%)					
Del17p	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Del11q	44 (19.2)	32 (13.9)	45 (19.0)	41 (17.9)	162 (17.5)
Trisomy 12	47 (20.5)	35 (15.2)	34 (14.3)	34 (14.8)	150 (16.2)
No abnormalities	44 (19.2)	59 (25.5)	45 (19.0)	53 (23.1)	201 (21.7)
Del13q	94 (41.0)	105 (45.5)	113 (47.7)	101 (44.1)	413 (44.6)

IGHV mutational status, N (%)					
Unmutated	130 (57.0)	123 (53.2)	134 (56.5)	131 (57.2)	518 (56.0)
Mutated	89 (39.0)	101 (43.7)	95 (40.1)	95 (41.5)	380 (41.1)
Not evaluable	9 (3.9)	7 (3.0)	8 (3.4)	3 (1.3)	27 (2.9)
Missing information	1 (0.4)	0 (0.)	0 (0.0)	0 (0.0)	1 (0.1)
Beta$_2$-microglobulin					
Median (range)	4.0 (2.0-16.2)	4.1 (1.3-11.9)	3.9 (1.7-11.4)	4.2 (1.4-15.5)	—
>3.5 mg/litre, n/N (%)	136/227 (59.9)	146/229 (63.8)	150/236 (63.6)	155/228 (68.0)	—
CLL-IPI risk group, N (%)					
Low	32 (14.7)	36 (16.2)	39 (17.1)	36 (16.0)	143 (16.0)
Intermediate	76 (35.0)	85 (38.3)	66 (28.9)	67 (29.8)	294 (33.0)
High	109 (50.2)	101 (45.5)	123 (53.9)	122 (54.2)	455 (51.0)
Very High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing information	12 (5.2)	9 (3.9)	9 (3.8)	4 (1.7)	34 (3.7)
Complex karyotype, N (%)					
< 3 aberrations	182 (83.5)	196 (87.9)	187 (81.0)	177 (79.4)	742 (82.9)
≥ 3 and < 5 aberrations	25 (11.5)	21 (9.4)	34 (14.7)	30 (13.5)	110 (12.3)
≥ 5 aberrations	11 (5.0)	6 (2.7)	10 (4.3)	16 (7.2)	43 (4.8)
Missing information	11 (4.8)	8 (3.5)	6 (2.5)	6 (2.6)	31 (3.3)

Bulky disease, N (%)					
All measurable lymph nodes with the largest diameter < 5 cm	156 (70.9)	163 (72.8)	165 (72.1)	153 (68.9)	637 (71.2)
Any measurable lymph node with the largest diameter ≥ 5 cm & < 10 cm	48 (21.8)	47 (21.0)	48 (21.0)	50 (22.5)	193 (21.6)
Any measurable lymph node with the largest diameter ≥ 10 cm by CT/MRI scan	16 (7.3)	14 (6.3)	16 (7.0)	19 (8.6)	65 (7.3)
Missing information	9 (3.9)	7 (3.0)	8 (3.4)	7 (3.1)	31 (3.3)

CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukaemia; CLL-IPI, International Prognostic Index for Chronic Lymphocytic Leukemia; CT, computed tomography; IGHV, immunoglobulin heavy chain gene; IGHV, immunoglobulin heavy-chain variable region gene; IPI, international prognostic index; IQR, interquartile range; MRI, magnetic resonance imaging
Source: Eichhorst et al. 2023[27], Fürstenau et al 2024.[26]

2.6.2 CLL13: efficacy results

Efficacy results presented below are based on the January 2023 (Fürstenau et al. 2024) data cut, representing median 50.7 months of follow-up and the February 2024 (Fürstenau et al. 2025) data cut, representing median 63.8 months of follow-up, with the exception of MRD results which are based on the February 2021 (Eichhorst et al. 2023) data cut.

CLL13 is an Investigator Sponsored Study conducted by the German CLL Study Group who owns the Individual Patient Data (IPD), which AbbVie requested to support this submission.

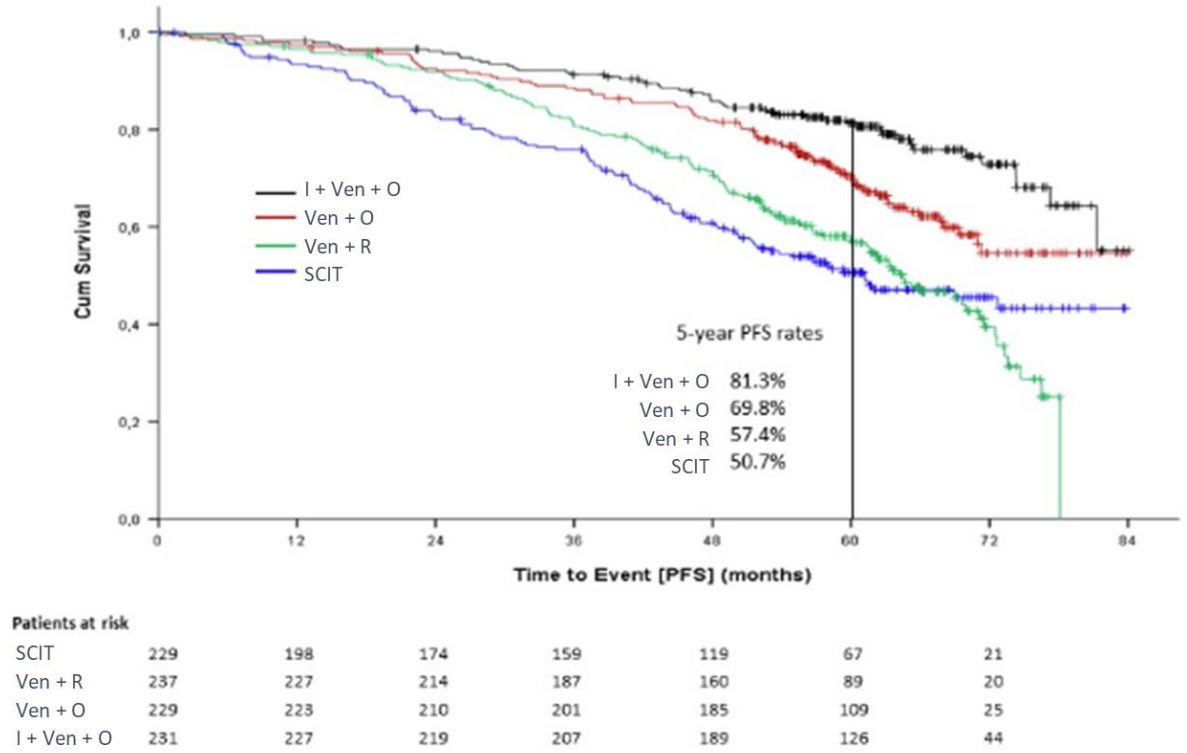
Although results for Ven+R and I+Ven+O are included within this submission, these treatments are not licenced in UK clinical practice for 1L CLL. For completeness, AbbVie describe observed outcomes for Ven+O and SCIT in this section; however, while SCIT is a comparator within the CLL13 trial, it is no longer considered a relevant treatment in UK clinical practice, as detailed throughout Section 1.

2.6.2.1 Progression-free survival (PFS)

Treatment of CLL aims to achieve durable remission, reducing patient symptom burden.[9] Progression-free survival represents a key indicator of treatment efficacy and is routinely assessed and formally recognised in clinical trials.[49]

At a median follow-up of 63.8 months, PFS was superior for Ven+O compared with SCIT (median not reached [NR] vs 61.2 months; p<0.001). PFS data from the ITT population of CLL13 is presented in Figure 4.[11]

Figure 4. PFS in the CLL13 ITT population



CIT, chemoimmunotherapy; GIV, I+Ven+O; GV, Ven+O; RV, Ven+R

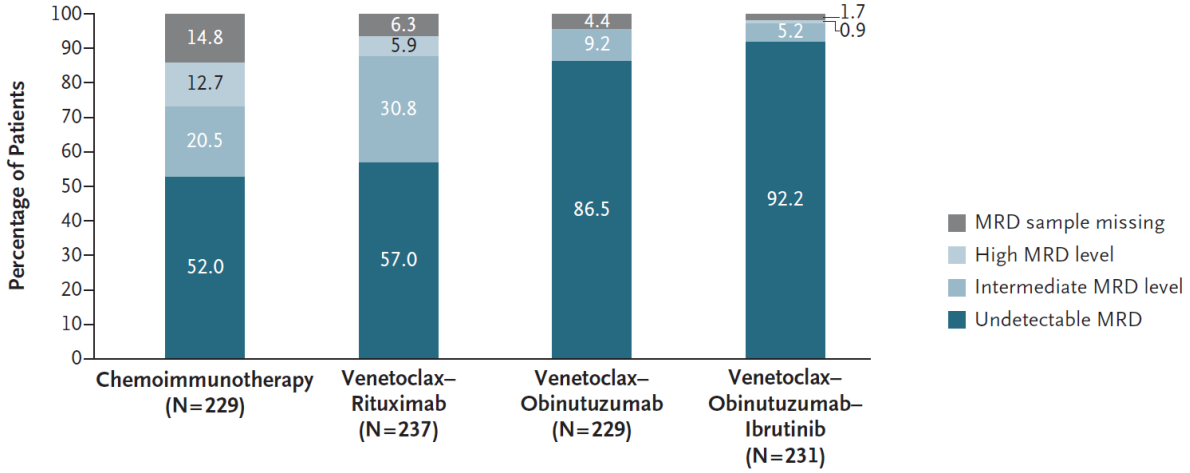
Source: Adapted from Furstenau et al. 2025[11]

2.6.2.2 MRD negativity rate in PB at month 15

Undetectable MRD rate is associated with longer periods of remission and PFS, hence is considered a good surrogate endpoint for these outcomes.[72,100,101]

At month 15, a significantly higher percentage of patients treated with Ven+O displayed uMRD in PB compared with patients treated with SCIT (86.5% [97.5% CI, 80.6 to 91.1] vs. 52.0% [97.5% CI, 44.4 to 59.5]; p<0.001) (Figure 5).[27]

Figure 5. MRD in peripheral blood at month 15 measured by flow cytometry

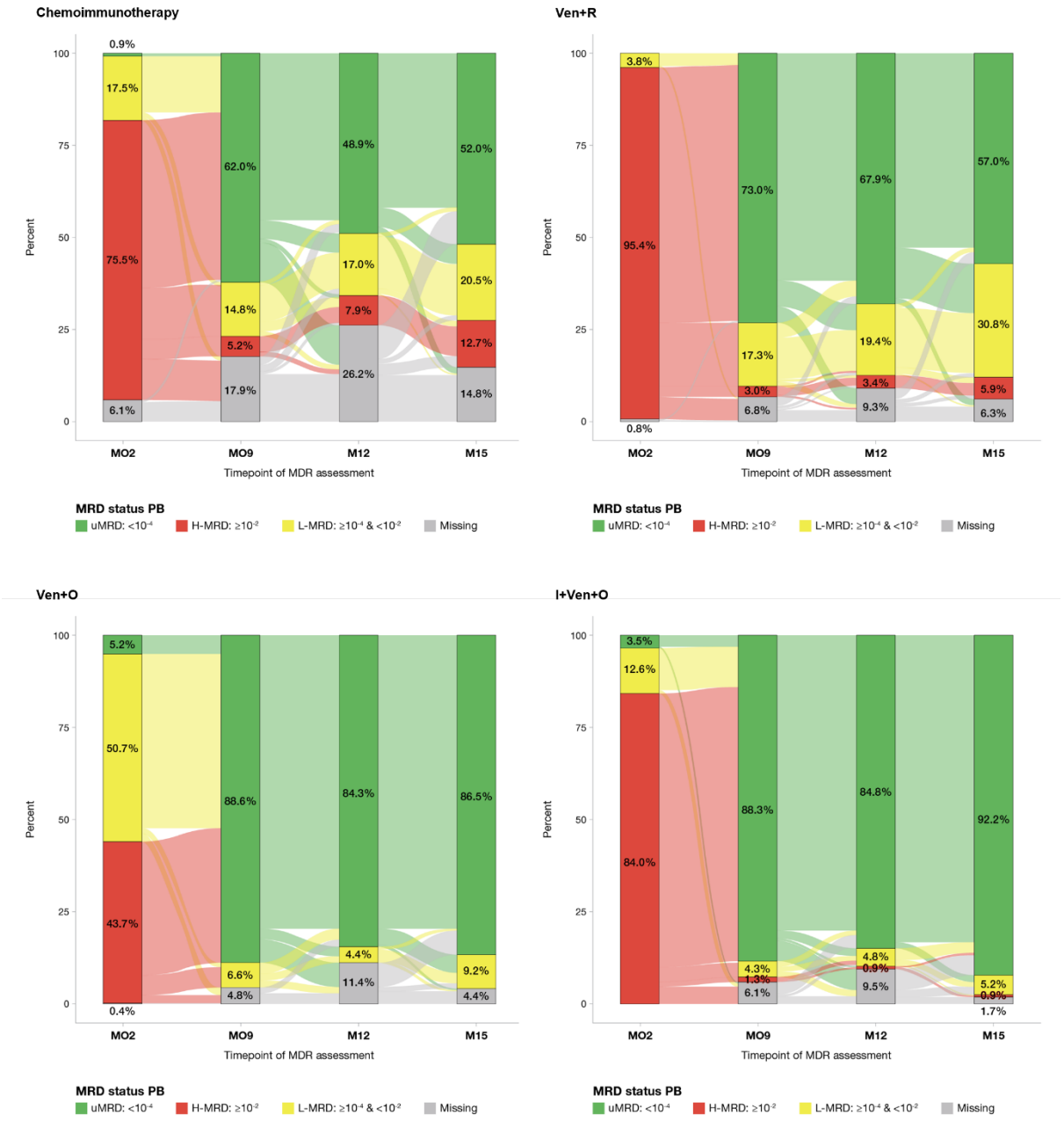


Abbreviations: MRD, minimal residual disease
Source: Eichhorst et al. 2023[27]

2.6.2.3 MRD levels measured in peripheral blood (PB) by flow cytometry at different time points

Patients treated with Ven+O demonstrated a higher rate of uMRD in PB than patients treated with SCIT at months 2, 9, 12 and 15 (Figure 6).[27] By month 9, 88.6% of Ven+O patients achieved uMRD, compared with 62% of patients treated with SCIT, with > 84% of patients treated with Ven+O maintaining uMRD in subsequent follow-ups, compared with 48.9% and 52.0% of patients treated with SCIT achieving uMRD at months 12 and 15, respectively.[27]

Figure 6. MRD by flow in peripheral blood during therapy for each treatment



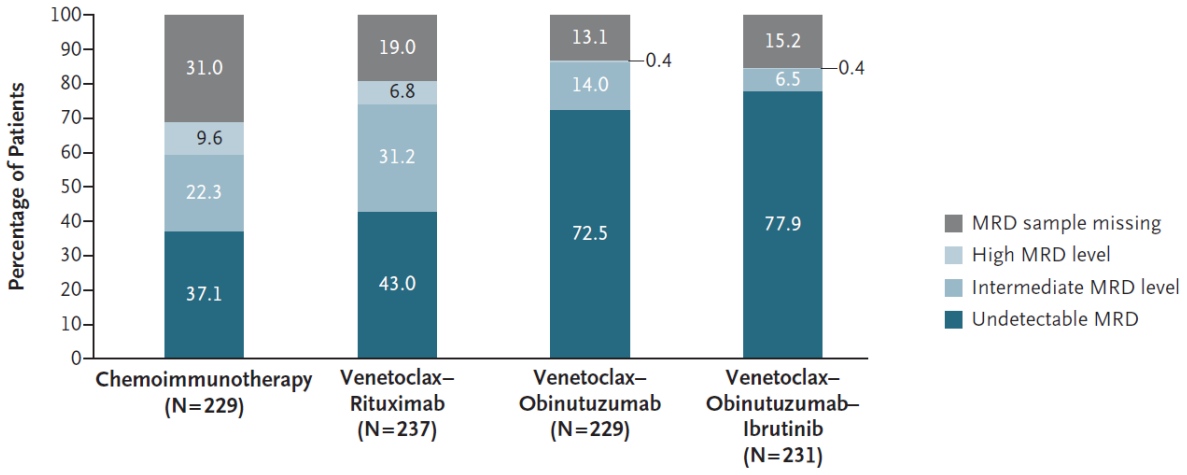
MRD, minimal residual disease; PB, peripheral blood; uMRD, undetectable minimal residual disease
Source: Eichhorst et al. 2023[27]

2.6.2.4 MRD levels in bone marrow

To further assess response, bone marrow biopsy and measurement of MRD was requested only for patients with a clinical complete remission (defined according to iWCLL guidelines).[96] At the February 2021 data cut, bone marrow biopsies had been requested for 69.0% of patients in the SCIT arm, and 86.9% of patients in the Ven+O arm.[27]

A higher proportion of patients treated with Ven+O achieved uMRD in bone marrow than patients treated with SCIT (166 of 229 patients [72.5%] and in 85 of 229 patients [37.1%], respectively) (Figure 7).[27]

Figure 7. MRD in bone marrow at final restaging

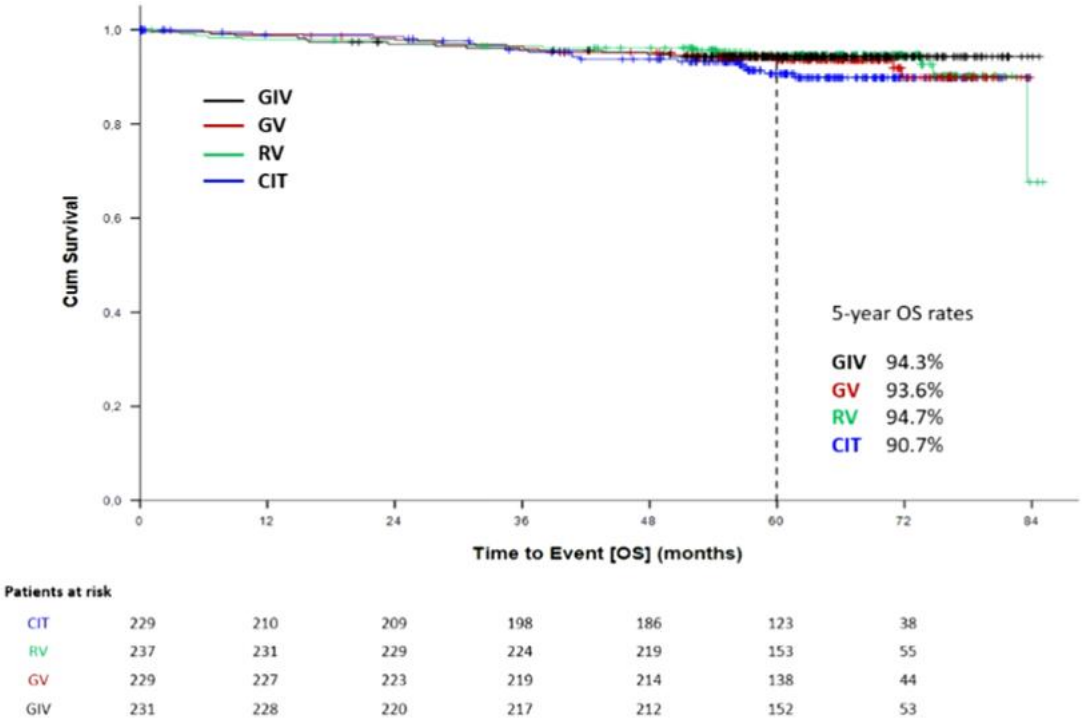


Abbreviations: MRD, minimal residual disease
Source: Eichhorst et al. 2023[27]

2.6.2.5 Overall survival

Overall survival did not differ significantly between the treatment groups, and no treatment group reached median OS. After 5 years of follow-up, OS rate was 93.6% in patients treated with Ven+O, and 90.7% in patients treated with SCIT (Figure 8).[11]

Figure 8. Overall survival from CLL13



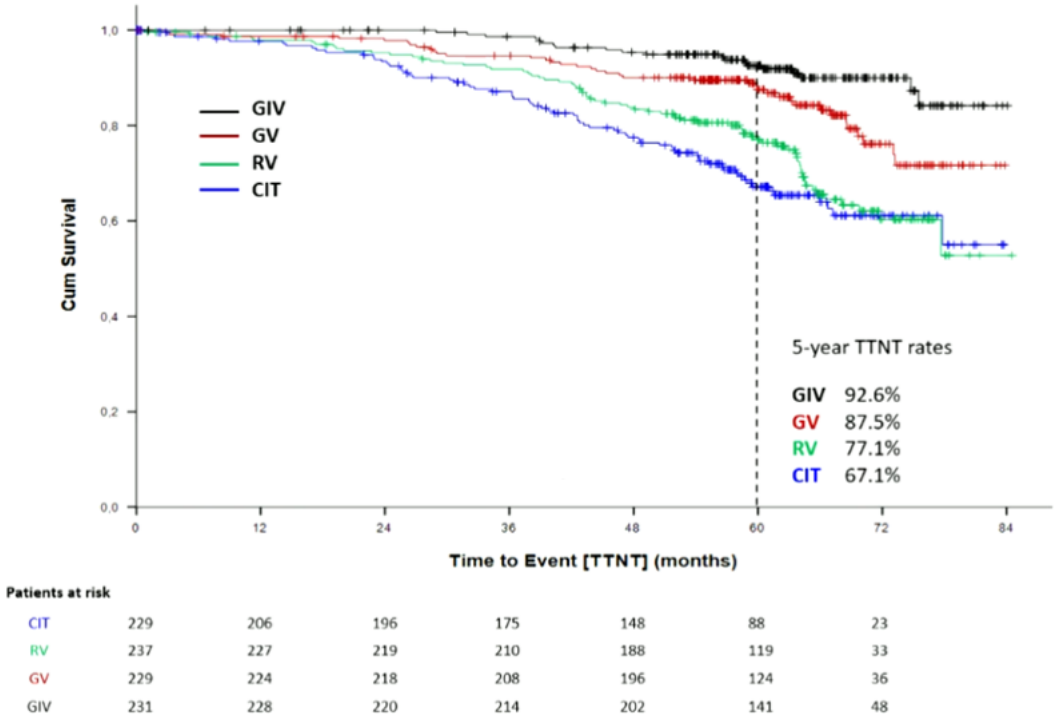
CIT, chemoimmunotherapy; GIV, I+Ven+O; GV, Ven+O; RV, Ven+R

Source: Adapted from Fürstenau et al. 2025[11]

2.6.2.6 Time to next treatment

After five years of follow-up, time to next treatment was significantly longer in patients treated with Ven+O compared with patients treated with SCIT (HR 0.43 [97.5% CI: 0.27; 0.68], log-rank p<0.001) (Figure 9).[11]

Figure 9. Time to next treatment from CLL13



Patients at risk

CIT	229	206	196	175	148	88	23
RV	237	227	219	210	188	119	33
GV	229	224	218	208	196	124	36
GIV	231	228	220	214	202	141	48

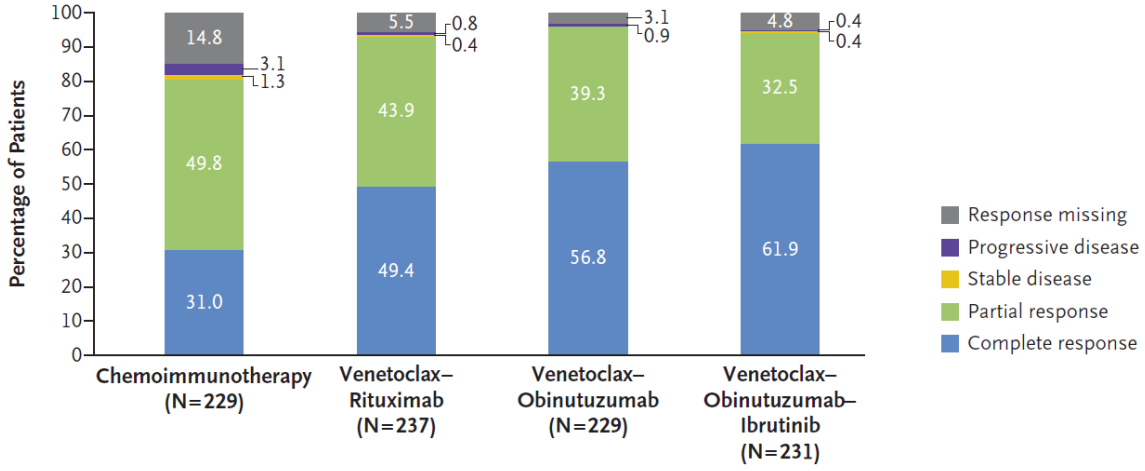
CIT, chemoimmunotherapy; GIV, I+Ven+O; GV, Ven+O; RV, Ven+R

Source: Adapted from Fürstenau et al. 2025[11]

2.6.2.7 Clinical response at month 15 according to iWCLL criteria

At month 15, a greater proportion of patients treated with Ven+O (130 of 229 patients [56.8%]) achieved complete response (as defined in the iWCLL guidelines) than in those treated with SCIT (71 of 229 patients [31.0%]) (Figure 10).[27]

Figure 10. Clinical response at month 15 according to iWCLL criteria

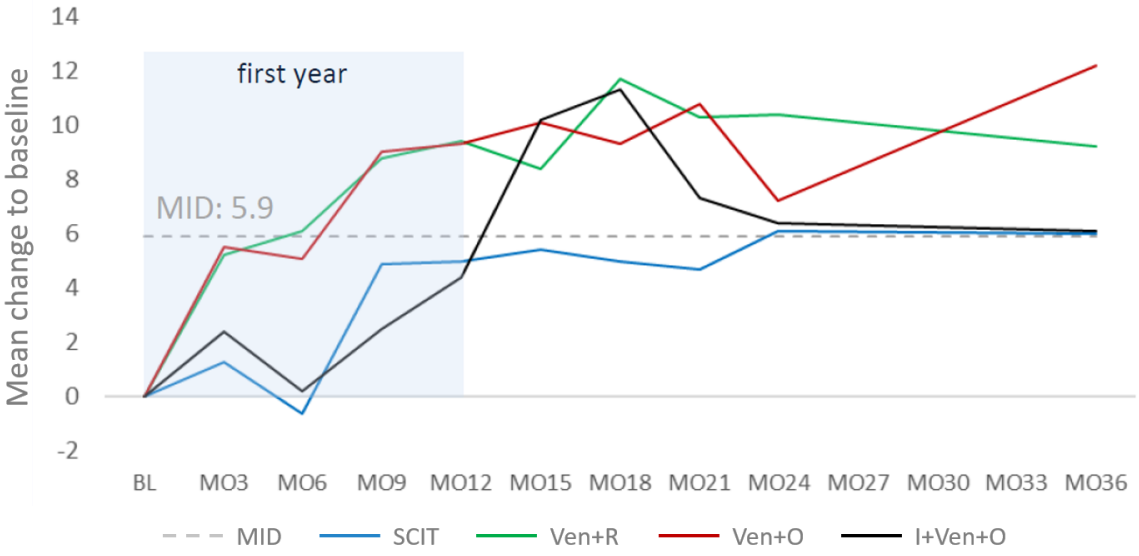


Source: Eichhorst et al. 2023[27]

2.6.2.8 *EORTC QLQ-C30*

Exploratory analysis of patient reported QoL was conducted using the EORTC QLQ-C30 survey (European Organisation for Research and Treatment of Cancer Quality of Life Group Core). QoL improved shortly after treatment initiation with Ven+O (reached by month 9) and the benefit was maintained throughout the study, while improvements greater than the minimal important difference (MID) in mean change in global health status from baseline was reached later with SCIT (reached at month 24). Ven+O patients maintained a greater mean change in baseline in global health status compared with that of SCIT patients across all timepoints (Figure 11).[102]

Figure 11 **Mean change from baseline in global health status**



MID, minimal important difference
Source: Adapted from Furstenau et al. 2024[102]

2.6.3 SACT report: patient demographics and baseline characteristics

Of patients included in the SACT report, [redacted]% of patients were male. Median age of males and females was [redacted] and [redacted] years, respectively. The most common age range was [redacted] years old ([redacted]% of patients), and the most common performance status was [redacted] ([redacted]%) (Table 13).[12]

Table 13. Patient characteristics from the SACT report

		Frequency (N)	%
Gender	Male	[redacted]	[redacted]
	Female	[redacted]	[redacted]
Age	<40	[redacted]	[redacted]
	40 to 49	[redacted]	[redacted]
	50 to 59	[redacted]	[redacted]
	60 to 69	[redacted]	[redacted]
	70 to 79	[redacted]	[redacted]
	80+	[redacted]	[redacted]
Performance status at the start of regimen	0	[redacted]	[redacted]
	1	[redacted]	[redacted]
	2	[redacted]	[redacted]
	3	[redacted]	[redacted]
	4	[redacted]	[redacted]
	Missing	[redacted]	[redacted]

Adapted from NHS England SACT report[12]

Of the patients who have ended treatment, the majority ([redacted]%) completed their treatment as prescribed (Table 14).[12]

Table 14 Treatment outcomes for patients that have ended treatment

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – completed as prescribed	[redacted]	[redacted]
Stopped treatment – no treatment in at least 3 months	[redacted]	[redacted]
Stopped treatment – acute toxicity	[redacted]	[redacted]
Stopped treatment – patient choice	[redacted]	[redacted]
Stopped treatment – died not on treatment	[redacted]	[redacted]
Stopped treatment – palliative, patient did benefit	[redacted]	[redacted]
Stopped treatment – progression of disease	[redacted]	[redacted]
Stopped treatment – died on treatment	[redacted]	[redacted]
Stopped treatment – other comorbidity	[redacted]	[redacted]
Stopped treatment – COVID	[redacted]	[redacted]
Total	[redacted]	[redacted]

Adapted from NHS England SACT report[12]

2.6.4 SACT report: overall survival

Median follow-up was [redacted] months ([redacted] days). As was the case in CLL13, median OS in the SACT report was [redacted], with OS at [redacted]% after 24 months (Table 15). This was similar to the OS for Ven+O patients at 24 months in CLL13, at [redacted]% (Figure 8).[27] Overall survival at 6 month intervals, and Kaplan–Meier survival and associated data is displayed in Table 15, and Figure 12 and Table 16, respectively. In routine NHS practice, these survival outcomes demonstrate that Ven+O is a highly effective treatment for fit patients with untreated CLL and no del(17p)/ *TP53* mutation.

Table 15. Overall survival at 6, 12, 18 and 24-month intervals from SACT report

Time period	OS (%)
6 months	[redacted]
12 months	[redacted]
18 months	[redacted]
24 months	[redacted]

OS, overall survival
Adapted from NHS England SACT report[12]

Figure 12. Kaplan–Meier survival plot (N=[redacted])

Source: NHS England SACT report[12]

Table 16 Patients at risk, censored, events

Time intervals (months)	0–27	3–27	6–27	9–27	12–27	15–27	18–27	21–27	24–27
Number at risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from NHS England SACT report[12]

2.7 Subsequent treatments used in the relevant studies

As the CLL13 trial was not performed or owned by AbbVie, information relating to subsequent treatment lines in the trial is limited to what has been published and is publicly available.

As reported in Fürstenau et al., 2025, at five years of follow-up, of the 177 patients who received subsequent therapies for CLL, 91 (51.4%) received BTKi-based therapies, 45 (25.4%) venetoclax-based treatments, 31 (17.5%) venetoclax + BTKi and 7 (4.0%) CIT as second-line treatments.[11]

2.8 Subgroup analysis

During the CLL13 trial, prespecified subgroup analysis of PFS was conducted considering factors pertinent to the patient prognosis:[26]

- age (≤ 65 years vs > 65 years)
- Binet stage
- cytogenetic subgroup
- *IGHV* mutation status
- CLL-IPI risk group
- complex karyotype

Analysis of subgroups demonstrates results largely consistent with the overall population, and are reported in the Eichhorst et al. 2023 and Furstenau et al. 2024 publications.[26,27]

2.9 Meta-analysis

Not applicable.

2.10 Indirect and mixed treatment comparison

Summary of ITC

- As no direct trial evidence for the comparative efficacy of Ven+O versus I+Ven is available, an ITC was required to inform the relative efficacy estimates.
- An unanchored MAIC was conducted in line with the approach outlined in Signorovitch et al. (2012),[103] and considering the methods described in NICE DSU TSD 18.[104]
- Evidence to conduct the MAIC was derived from CLL13 trial (for Ven+O) and from the CAPTIVATE trial (for I+Ven).
- A heterogeneity assessment comparing CLL13 and CAPTIVATE was performed that concluded that an unanchored, population-adjusted indirect comparison would be appropriate.
- As the CLL13 trial is not owned by AbbVie, the company have limited access to IPD; therefore, the MAIC is performed using the latest data cut where AbbVie have access to IPD (CLL13 4-year follow-up, with related publication by Fürstenau et al. 2024).[26]
- Key prognostic variables and treatment effect modifiers were identified through a targeted literature review (including previous NICE appraisals in CLL), empirical analyses of CLL13 outcomes, and engagement with clinical experts experienced in treating patients with CLL.
- The effective sample size of the Ven+O arm was well-preserved in the population-adjusted analysis, with 84% preservation (n=158.01) of the sample size compared with the unadjusted analysis.
- In the population-adjusted analyses, Ven+O demonstrates a numerical improvement in PFS and OS compared with I+Ven:
  - Patients treated with Ven+O have a [redacted]% lower risk of experiencing disease progression compared with patients who receive I+Ven, though this treatment benefit is not statistically significant ([redacted]).
  - Patients treated with Ven+O have a [redacted]% lower risk of death compared with patients who receive I+Ven, however this treatment benefit is not statistically significant ([redacted]).

2.10.1 Evidence base

2.10.1.1 Identification and selection of studies

An SLR was conducted to support the identification of relevant clinical evidence for comparators with which to compare the efficacy of Ven+O. Records were excluded based on trial design and the interventions being investigated. Of the 11 remaining records, one clinical trial (GLOW) was identified that evaluated the efficacy of I+Ven, the key comparator of interest. However, this trial was not in the population of interest i.e. fit patients with untreated CLL and no del(17p)/ TP53 mutation and was therefore excluded. The CLL13, FLAIR and CAPTIVATE trials were subsequently identified following an SLR update and a grey literature review.

FLAIR is a phase 3 randomised, controlled, open-label study of I+Ven vs ibrutinib monotherapy vs. FCR. Patients had to be considered fit for FCR to enrol in the FLAIR trial. Moreover, the FLAIR study assesses the effect of MRD guided I+Ven, with a minimum of 2 years and maximum of 6 years of I+V, which substantially differs from the I+Ven marketing authorisation and how it is currently used in NHS clinical practice (i.e. I+Ven is recommended, within is marketing authorisation, for 15 months fixed treatment duration).[92,105,106] Since this would bias results for which no adjustment can be made, the FLAIR study was excluded from the ITC analyses.

CAPTIVATE *was* included, as it was the only available evidence of I+Ven for fit patients with untreated CLL and no del(17p)/*TP53* mutation.[24,107] Furthermore, in TA891, CAPTIVATE was the main evidence submitted to NICE for the fit population.

2.10.1.2 Overview of selected studies

Evidence to conduct the MAIC was derived from the CLL13 phase 3 trial (for Ven+O) and from the CAPTIVATE (NCT02910583) phase 2 trial (for I+Ven).

As previously described, CLL13 was a phase 3, multicentre, randomised, prospective open-label trial evaluating the safety and efficacy of venetoclax regimens Ven+O, I+Ven+O and Ven+R compared with SCIT in fit patients with previously untreated CLL without del17p or *TP53* mutations.[26]

As the CLL13 trial is not owned by AbbVie, the company have limited access to IPD; therefore, the MAIC is performed using the data from 4-year follow-up (published in Fürstenau et al. 2024)[26], to which AbbVie have access to some IPD, rather than the newly published 5-year data (published at the European Haematology Association meeting in Fürstenau et al. 2025), for which AbbVie have no access to IPD.[11]

CAPTIVATE was a phase 2, multicentre, randomised, two-cohort, prospective clinical trial evaluating the safety and efficacy of I+Ven in patients with previously untreated CLL. The fixed duration cohort was relevant for this comparison as this best reflects the dosing regimen for I+Ven in the UK.[24]

2.10.1.3 Assessment of heterogeneity

A heterogeneity assessment comparing CLL13 and CAPTIVATE was performed to determine whether an unanchored, population-adjusted indirect comparison would be feasible. Table 17 shows an overview of the main study characteristics for CLL13 and CAPTIVATE.

Table 17. Comparison of general study characteristics between CLL13 and CAPTIVATE for MAIC

Study	**CLL13** NCT02950051	**CAPTIVATE** NCT02910583
Trial	Standard Chemoimmunotherapy (FCR/BR) versus rituximab + venetoclax (Ven+R) versus obinutuzumab + venetoclax (Ven+O) versus obinutuzumab + ibrutinib + venetoclax (I+Ven+O) in fit patients with previously untreated CLL without del(17p) or *TP53* mutation	Ibrutinib Plus venetoclax in Subjects with Treatment-naïve Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma (CLL/SLL)
Data cuts available to AbbVie	**Patient level data:** January 2023, representing median follow-up of 50.7 months.[26] **Summary data:** June 2025 EHA conference presentation, representing median follow-up of 63.8 months [not used in MAIC].[11] February 2021 Eichhorst publication with 15-month MRD outcomes [not used in MAIC].[27]	**Patient level data:** None **Summary data:** Wierda et al. and Tam et al. publications.[24,107,108] ITC analysis based on: • OS and PFS Data: Maximum follow-up 66 months (median follow-up 61.2 months) • CR and ORR: maximum follow-up of 27 months

Interventions of interest	Ven+O	I+Ven FD cohort
Study design	Phase 3, open-label, randomised study	Phase 2, open-label, single-arm cohort
Eligibility criteria	Adult patients with previously untreated, advanced CLL that warranted treatment according to the International Workshop on CLL 2008 (iWCLL) criteria Low burden of coexisting conditions (a score of ≤6 on the CIRS Scale) Normal creatinine clearance (≥70 ml per minute) ECOG PS score of 0 to 2 Exclusion: Detection of del(17p) or *TP53* mutations	Adult patient (≤70 years) with previously untreated CLL or SLL requiring treatment by IWCLL 2008 ECOG PS score of 0 to 2; and adequate hepatic, renal (CrCl) ≥60 mL/min), and haematologic function

CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine, cyclophosphamide and rituximab; FD, fixed duration; iWCLL, International Workshop on CLL; SLL, small lymphocytic lymphoma

Population

There are three key differences across CLL13 and CAPTIVATE, namely age, patients with del(17p) or *TP53* mutations, and patients with small lymphocytic lymphoma (SLL).

Firstly, CAPTIVATE included patients with SLL (8%), who were excluded from CLL13. CLL and SLL differ in their primary tumour location but are considered the same disease due to the immunophenotypes of the tumours.[29] There are multiple examples of trials where both CLL and SLL are enrolled as if a single disease and there is no distinction in management of the entities.[109-112] Therefore, it was assumed that the efficacy is similar irrespective of whether a patient has SLL/CLL.

Secondly, whereas participation in the CAPTIVATE trial was restricted to patients aged ≤70 years, the patient population of CLL13 did not exclude patients aged >70 years. Thus, to ensure comparability in the MAIC, the CLL13 patient population was restricted to the population ≤70 years of age to align with the CAPTIVATE population. As detailed previously, it was assumed the CLL13 (≤70 yrs) and CAPTIVATE populations had comparable fitness, in line with clinical feedback. Patient baseline characteristics for the restricted CLL13 population ≤70 years of age and the CAPTIVATE population are shown in Table 18.

Finally, the primary distinction across CLL13 and CAPTIVATE concerned the inclusion of patients with del(17p) or *TP53* mutations (17% in CAPTIVATE) who were excluded from the CLL13 trial. Although 17% of CAPTIVATE patients were known to have del(17p)/*TP53* mutation, clinical experts considered CAPTIVATE, like CLL13, to be sufficiently representative of the UK patient population.[10]

Table 18. Baseline characteristics in the restricted (≤70 years) CLL13 subgroup and the CAPTIVATE ITT population

Baseline characteristics	CLL 13 Ven+O (≤70 years)	CAPTIVATE (≤70 years)
All patients, N	[redacted]	**159**
Median age (years) (range)	[redacted]	60 (33-71)
≥ 65 years, N (%)	[redacted]	45 (28)
Male gender, N (%)	[redacted]	106 (67)
Race, N (%)		
White	[redacted]	147 (92.5)
Non-White	[redacted]	12 (7.5)
ECOG PS, N (%)		
0	[redacted]	110 (69)
1	[redacted]	49 (31)
2	[redacted]	0 (0)
IGHV mutation status, N (%)		
Unmutated	[redacted]	89 (56)
Mutated	[redacted]	66 (42)
Not evaluated	[redacted]	0 (0)
Missing	[redacted]	4 (3)
Rai		
0/I/II	[redacted]	113 (71)
III/IV	[redacted]	44 (28)
Missing	[redacted]	2 (1)
Anaemia at baseline (Hb ≤ 11 g/dL)	[redacted]	37 (23)
Thrombocytopenia at baseline (PLC ≤ 100 x 10^9 /L)	[redacted]	21 (13)
Neutropenia at baseline (ANC ≤ 1.5 x 10^9 /L)	[redacted]	13 (8)
Bulky disease		
< 5 cm	[redacted]	111 (70)
≥ 5 cm	[redacted]	48 (30)

≥ 10 cm	[redacted]	5 (3)
Unknown/Missing	[redacted]	0 (0)
Cytogenetic subgroup (per Dohner hierarchy)		
Deletion 17p	[redacted]	20 (13)
Deletion 11q	[redacted]	28 (18)
Trisomy 12	[redacted]	23 (14)
No abnormalities	[redacted]	33 (21)
Deletion in 13q	[redacted]	54 (34)
Unknown	[redacted]	1 (1)
Complex karyotype		
Yes (≥ 3 abnormalities)	[redacted]	31 (19)
No	[redacted]	102 (64)
Unknown	[redacted]	26 (16)

Numbers may not sum to 100% due to rounding
All entries in red font were considered to be different across the CLL13 and CAPTIVATE trials, classified by ≥10% difference.
ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat;

As no baseline characteristics were available for the CAPTIVATE subgroup without del(17p) and/or *TP53* mutation, clinical experts suggested it would be reasonable to compare the baseline characteristics of CAPTIVATE including patients including del(17p) and/or TP53 mutation.[10] This assumption is considered further within the uncertainties section (Section 2.10.4).

Overall, notwithstanding the exclusion of del(17p) and/or *TP53* mutation in the CLL13 population, baseline characteristics between the restricted ≤70 years CLL13 population and the CAPTIVATE ITT population were comparable. The most prominent differences (determined by ≥10% difference; see Table 18) were observed for Rai staging, anaemia, 13q deletion proportions, and complex karyotype (CK). Less prominent differences are observed in gender ([redacted]%), ECOG PS ([redacted]%), bulky disease ([redacted]%), and *IGHV* mutation status ([redacted]%).

Outcomes

The median follow-up in CAPTIVATE at the time of analysis spans 61 months, whereas the median follow-up for the CLL13 IPD used in the MAIC is 50.7 months.[11,13,24,26,107] Thus, the follow-up for CLL13 is slightly shorter compared with CAPTIVATE. For patients treated with I+Ven in the CAPTIVATE study, reported

outcomes included investigator-reported PFS and OS as well as CR and ORR data. PFS and OS KM data were available for maximum follow-up of 61 months, whereas both ORR and CR data were available for a maximum follow-up of 27 months. For CLL13, IPD data was available for PFS, OS, CR and ORR for a maximum follow-up of 50.7 months.[26]

A challenge identified for both studies was the immaturity of the OS data. For all analyses, OS curves plateau above 95%, with the majority of patients censored as opposed to experiencing an OS event.

Study design

The most important difference between the two studies was that CLL13 is a phase 3 randomised controlled trial whereas CAPTIVATE is phase 2 single arm trial. Given the absence of a common comparator between the two studies, unanchored methods were required to perform the indirect comparison.

Conclusion of heterogeneity assessment

It was concluded from the heterogeneity assessment that an unanchored, population-adjusted indirect comparison is recommended and feasible. To ensure comparability, the CLL13 patient population was restricted to the population ≤70 years of age to align with the CAPTIVATE population.

2.10.2 Methodology of the ITC

Since there was no common comparator between CLL13 and CAPTIVATE, an unanchored MAIC was conducted in line with the approach outlined in Signorovitch et al. (2012),[103] and considering the methods described in NICE DSU TSD 18.[104] Unanchored indirect comparisons do not rely on the presence of a common comparator, and, as per NICE Technical Support Document 18, suggests that the use of population adjustment in unanchored indirect comparisons requires that absolute outcomes can be reliably predicted from covariates.[104]

In brief, MAIC is a population-adjusted treatment comparison method designed to allow the comparison between outcomes originating from IPD from the

manufacturer's trial and aggregate outcomes published for the comparator where no common comparator exists between the two studies, while accounting for differences in clinically relevant treatment effect modifiers (TEMs) and prognostic variables (PVs) in trial populations. Baseline characteristics are reweighted based on the TEM and PVs, and efficacy of treatment is recalculated. Therefore, it is necessary to establish which patient characteristics are known TEM or PV, or can be plausibly considered as TEM/PV, and whether these variables are in substantial imbalance between the trials being considered.

2.10.2.1 Feasibility assessment of ITC approach

Both matching-adjusted indirect comparisons (MAICs) and simulated treatment comparison (STC) aim to adjust for differences in population characteristics between data sources when head-to-head trials do not exist, but each offer slightly different methodologies. In this case, the MAIC approach was preferred over STC for several key reasons, described below.

- STC based parametric or semiparametric regression analyses rely on the number of events (not the number of patients) to determine the degrees of freedom; the lower the number of events, the lower the number of predictors that can be included in the model. As such, this method would not have been appropriate in this submission due to the small number of OS events recorded in the CLL13 study, which in turn would reduce the number of predictors that could be included in the model.
- MAICs are the preferred method of analysis when analysing time-to-event data for a single target comparator (or single RWE database) across multiple treatment outcomes, whereas STCs are more appropriate for analyses against multiple comparators.
- Conducting an STC on time-to-event outcomes requires a parametric distribution (e.g. exponential, Weibull, etc.) of the best fit to be specified for the outcome, and an assessment performed regarding whether the same distribution is applicable to both arms of the analysis.[113] The choice of the parametric distribution in an STC is a critical assumption, and misspecification

of the parametric distribution can lead to biased results. The choice of the parametric curve for the STC would introduce another layer of uncertainty next to the additional aspects of a correct specification of the outcome model and the assumption that the relationship between baseline covariates and the outcome is the same in both studies.

2.10.2.2 Selection of treatment-effect modifiers and prognostic variables

The underlying assumption of an unanchored MAIC is that all PVs and TEMs can be adjusted for; therefore relevant TEMs and PVs were selected through a targeted literature review (TLR), empirical analyses, and expert validation.[104]

Selection from literature

A TLR was performed to identify relevant TEMs and PVs reported in published literature, as any imbalance in TEMs and/or PVs between CLL13 and CAPTIVATE would require adjustment. A desk search was conducted to identify published ITCs, diagnostic guidelines, prognostic factor studies, and HTA submissions in CLL. The publications were reviewed and assessed for commonly reported PVs and potential TEMs, with the most important factors for the population of interest being[49,114-116]:

- Unmutated/mutated immunoglobulin heavy chain gene (*IGHV*)
- Del17p or *TP53* mutation
- β_2-macroglobulin
- Rai/Binet stage
- Age
- Sex
- ECOG performance status (PS)
- Fitness
- CIRS
- Creatine clearance

Empirical analyses

Empirical analyses were conducted using OS and PFS data from CLL13 patients to identify potential TEMs and PVs. To estimate PVs, Cox regression models were fitted including baseline characteristics as covariates. For TEMs, interaction terms were included in the regression models for patient characteristics with treatment. Coefficients showing a p-value smaller or equal to 0.25 were considered potential TEMs or PVs as per recommendations from Hosmer & Lemeshow (2011).[117]

While SCIT is not a treatment of interest in the ITC as it has largely been superseded by I+Ven since TA891 (Section 1.3.5.1), the SCIT population from the CLL13 trial was used to identify variables that can potentially modify the treatment effect. For the TEMs analyses, all Ven+O and SCIT patients ≤70 years of age were included. Within the SCIT population, this resulted in the inclusion of patients receiving BR aged 65-70 years of age. To assess any potential bias in the interaction analysis for TEMs due to the inclusion of BR patients, patient characteristics were compared prior to the analyses. Although the subgroup of BR patients (n = 38) showed some differences in characteristics (e.g., ECOG PS, anaemia, bulky disease ≥10 cm, del11q, trisomy 12, and 'no abnormalities' cytogenetic risk groups) compared with the Ven+O CLL13 restricted and CAPTIVATE populations, any of these differences can be primarily attributed to the small sample size and bias in concerning an older population inherently due to the placement of BR in the CLL treatment algorithm.

Baseline characteristics of CLL13 patients included in the TEMs analyses were assessed as both FCR (≤65 years) and BR patients (>65-≤70 years) were included in the CIT cohort. No meaningful differences in baseline characteristics were observed when compared across the SCIT subgroups and when compared with the Ven+O population restricted to ≤70 years of age. Therefore, for the final selection of TEMs, all Ven+O and CIT patients ≤70 years of age were included.

When fitting Cox regression models for PV selection, all variables but sex and neutropenia were found to be potential PVs for PFS and/or OS in the cohort ≤ 70 years of age for a $p \leq 0.25$ (Table 19). This p value threshold was used given the small sample size for posing hypotheses about which variables are potential effect

modifiers and should be considered in the matching. As can be seen in the forest plots in Figure 13 and Figure 14, the small number of patients in the missing variable groups (e.g., IGHV, bulky disease and Rai) resulted in extremely wide confidence intervals as well as a very small number of events for OS. A similar effect was seen in the univariate analysis for CR. The number of variables that were found to be TEMs in the empirical analyses was considerably fewer including ECOG, bulky disease and FISH for PFS while none of the variables reported a $p \leq 0.25$ for OS.

Table 19. Results of the Interaction (TEM) and Univariate (PV) Analyses

Variable	Reference Category	PV-HR ≤ 70 y PFS	PV-HR ≤ 70y OS	TEM-HR ≤ 70 y PFS	TEM-HR ≤ 70y OS	Include as matching variable
Age (>60y)	Age ≤60y	[redacted]	[redacted]	[redacted]	[redacted]	✓
Sex male	Female	[redacted]	[redacted]	[redacted]	[redacted]	
ECOG ≥1	ECOG 0	[redacted]	[redacted]	[redacted]	[redacted]	✓
Rai-III/IV	Rai-0/I/II	[redacted]	[redacted]	[redacted]	[redacted]	✓
Rai-missing		[redacted]	[redacted]	[redacted]	[redacted]	✓
Bulky disease (>= 5cm)	Bulky disease (>= 5cm): No interaction	[redacted]	[redacted]	[redacted]	[redacted]	✓
Bulky disease (>= 5cm): Missing		[redacted]	[redacted]	[redacted]	[redacted]	
Bulky disease (>= 10cm): Yes interaction	Bulky disease (>= 10cm): No interaction	[redacted]	[redacted]	[redacted]	[redacted]	✓
Bulky disease (>= 10cm): Missing interaction		[redacted]	[redacted]	[redacted]	[redacted]	
Anaemia	No anaemia	[redacted]	[redacted]	[redacted]	[redacted]	✓
Thrombocytopenia	No thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	✓
Neutropenia	No neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	
IGHV mutated	IGHV unmutated	[redacted]	[redacted]	[redacted]	[redacted]	✓
IGHV unknown		[redacted]	[redacted]	[redacted]	[redacted]	
FISH: Del11q	FISH normal	[redacted]	[redacted]	[redacted]	[redacted]	✓
FISH: Trisomy 12		[redacted]	[redacted]	[redacted]	[redacted]	✓
FISH: Del 13q		[redacted]	[redacted]	[redacted]	[redacted]	✓

FISH: Unknown		[redacted]	[redacted]	[redacted]	[redacted]	
Complex karyotype: Yes	Complex karyotype: No	[redacted]	[redacted]	[redacted]	[redacted]	✓
Complex karyotype: Unknown		[redacted]	[redacted]	[redacted]	[redacted]	

Variables listed in red were statistically significant with a p-value ≤ 0.25
Zero entries were rounded from non-zero entries smaller than a power e-04.
FISH, fluorescent in-situ hybridisation; IGHV, immunoglobulin heavy-chain variable region gene; OS, overall survival; PFS, progression-free survival; PV, prognostic variable; TEM, treatment effect modifier

Figure 13. Forest plot for prognostic factors of PFS relative to their reference group

Variables with HR of 0 that subsequently produced CIs including infinity were set to the maximum of the upper bound.
Arrows indicate CIs extending past the x-axis
CKT, complex karyotype; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in-situ hybridisation; IGHV, immunoglobulin heavy-chain variable region gene; OS, overall survival; PFS, progression-free survival; PV, prognostic variable; TEM, treatment effect modifier

Figure 14. Forest plot for prognostic factors of OS relative to their reference group

Variables with HR of 0 that subsequently produced CIs including infinity were set to the maximum of the upper bound. Arrows indicate CIs extending past the x-axis
CKT, complex karyotype; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in-situ hybridisation; IGHV, immunoglobulin heavy-chain variable region gene; OS, overall survival; PFS, progression-free survival; PV, prognostic variable; TEM, treatment effect modifier

Clinical Expert Validation

AbbVie engaged with UK clinical experts in the field of CLL to identify potential TEMs & PVs.[10] The covariates considered for validation were based on the availability of variables in CLL13 and CAPTIVATE. As such, CIRS and Binet staging were considered relevant but not included in the final selection because they were not uniformly available in both trials. *IGHV* mutation status, bulky disease, FISH and complex karyotype were consensually considered important variables for matching. Age, Sex, ECOG PS, and Rai staging were considered to be of secondary importance. Please note, both Rai and Binet staging measure the development of CLL in a patient,[9,29] and as Rai was available for both CLL13 and CAPTIVATE it was

used as part of an extended set of variables in the scenario analyses. As a result, the clinical validation yielded a final set of recommended matching factors including:

- *IGHV* mutation status
- Bulky disease
- FISH
- CK

An extended set of variables was recommended to be investigated in scenario analyses comprising:

- IGHV mutation status
- Bulky disease
- FISH
- CK
- Age
- ECOG PS
- Rai staging

Final selection of analyses

The quantitative assessment and clinical validation informed the final selection of the matching variables for the base case analysis. The set of matching variables used for the base case analysis is presented in Table 20. Sensitivity analyses for the MAIC were performed and are presented in Appendix J.

Table 20. Approach to unanchored MAIC

Approach	Outcomes	Ven+O evidence base[26]	I+Ven evidence base - Wierda et al.(2024)[108] AND Tam et al.(2022)[24]	Matching factors
Clinical expert selection approach	PFS, OS, CR, ORR	CLL13 ≤70 Ven+O IPD	CAPTIVATE 61.2-month follow-up data – ITT KM curve for PFS and OS CAPTIVATE 27-month follow-up data from Tam et al.(2022) for CR and ORR	*IGHV*, FISH, bulky disease, complex karyotype

CR, complete response; FISH, fluorescent in-situ hybridisation; FU, follow-up; IGHV, immunoglobulin heavy-chain variable region gene; IPD, individual patient data; ITT, intention to treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

2.10.2.3 Propensity score weighting

The weights estimated for matching reflect the inverse odds of individual CLL13 patients being included in CAPTIVATE. These resulting weights were then used to obtain statistically similar populations after which outcomes could be meaningfully compared. Effectively, patients who were more likely to be among the target aggregate population (given their characteristics) were assigned higher weights in the analysis and vice versa. Propensity score weighting was performed using a logistic (logit) regression model:

$$\log(w_{it}) = \alpha_0 + \alpha_1^T X_{it}$$

with X_{it} as the effect modifying or prognostic covariate for the i-th individual receiving the treatment of interest. However, given that for CAPTIVATE, only aggregate data was available, an $\hat{\alpha}1$ can be estimated according to the method of moments.[103,104] Subsequently, the weights exactly balanced the mean values of the covariates included.[104] The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. The propensity score matching method was used to generate 1:1 matched pairs between the Ven+O arm in CLL13 and CAPTIVATE patients, based on the identified matching variables (Section 2.10.2.1), creating a balanced cohort between the two studies.

2.10.2.4 Rescaled weights

To assess the uniformity of the weights, histograms of the rescaled weights were produced, where the rescaled weights were calculated according to the following formula:

$$Rescaled\ weights = \frac{weight_i}{\sum_{i=1}^{n} weight_i} \times N$$

where N is the number of subjects in the Ven+O arm. These rescaled weights can then be interpreted such that if a patient has a weight > 1 they contribute more compared to the original data whereas a weight < 1 implies that a patient contributes less compared to the original data. When the estimated weights are extreme, the overlap between populations is small which indicates little statistical information is present in the reweighted cohorts. Moreover, the reweighted baseline characteristics of the Ven+O CLL13 arm were compared to the aggregated baseline characteristics of CAPTIVATE.

2.10.2.5 Effective sample size

The impact of reweighting is that there is less statistical information in the reweighted trial data, which was reflected in the ESS. The ESS is presented alongside the results of the MAICs and was computed according to the following formula[104]:

$$ESS = \frac{(\Sigma\ weights)^2}{\Sigma(weights^{\,2})}$$

A small ESS can indicate that the estimated weights are highly variable due to a lack of population overlap between the two studies resulting in the presence of extreme weights. When the statistical power to detect differences between treatments is limited due to a small ESS, the relative treatment effects can become inflated as they depend on a small number of individuals.[103] It has been suggested that an ESS less than n=~35 results in biased estimates.[118]

2.10.2.6 Outcome Assessment

In the final step, as per NICE DSU TSD recommendations, outcomes were estimated on the transformed linear predictor scale (e.g., using a log link).[104] As the aim was to compare treatment A vs. B in a certain population p (e.g., CAPTIVATE):

$$\Delta_{AB(p)} = g\left(Y_{B(p)}\right) - g\left(Y_{A(p)}\right)$$

Where the estimation of the treatment-effect of B (I+Ven) $\left(Y_{B(p)}\right)$ is based on aggregate data and the estimation of treatment-effect A (e.g. Ven+O) $\left(Y_{A(p)}\right)$ is based on reweighted IPD.

2.10.2.6.1. Progression-free Survival and Overall Survival

2.10.2.6.1.1. Kaplan–Meier Data

Weighted Ven+O Kaplan–Meier curves, denoted as 'weighted' as these account for the adjustment of matching factors, were plotted for PFS and OS using the CLL13 weighted IPD data. These Kaplan–Meier curves were then compared to the unweighted (observed KMs directly from the CLL13 IPD for the full Ven+O ITT) Ven+O curves and the CAPTIVATE curves to determine deviations after adjusting for PVs and TEMs. For the CAPTIVATE study, pseudo-IPD were recreated by digitising the Kaplan–Meier curves for the endpoints in question. Digitisation involved extracting graphed PFS and OS curves by digitally approximating the published curves and subsequently correcting for any discrepancies in the approximation. Mapping the published Kaplan–Meier survival curves to pseudo-IPD followed the methodology as described by Guyot et al. 2012.[119]

2.10.2.6.1.2. Cox Proportional Hazard Model

Hereafter, Cox proportional hazard (PH) models were fitted to estimate the HRs for PFS, and OS while including the weights in the analyses.

$$h(t) = h_0(t)^{\beta_1 x_{i1}\widehat{w}_i + \cdots \beta_k x_{ik}\widehat{w}_i}$$

The indirect treatment effects, p-values, and 95% CIs for the MAIC results were estimated and compared to the results from the naïve comparison. To account for the inclusion of weights (i.e. for the weighted Kaplan–Meier curves of CLL13

compared to Kaplan–Meier curves of CAPTIVATE), standard errors were estimated using a robust sandwich estimator.

2.10.2.6.2. Complete Remission and Overall Response Rate

For the ORR and CR, a generalised linear model (GLM) was fitted to model the ORs and their accompanying 95% CIs. To estimate the weighted ORs for ORR and CR, the 'glm' function in R (Binomial family and a logit link function) with a robust variance estimator from the sandwich package were used.

$$logit(\mu_i) = \beta_0 + \beta_1 X_1 \widehat{w}_i + \cdots + \beta_k X_k \widehat{w}_i$$

the weights $\widehat{w}_i$ were included in the GLM to adjust for any imbalances in TEMs and PVs. The ORR and CR were compared to the naïve (unweighted) treatment-effect to assess the impact of weighting.

2.10.3 Results

2.10.3.1 Assessment of matching

Matching was assessed based on evaluation of the rescaled matching weights, a summary table containing the ESS, and finally an overview of the reweighted baseline characteristics (Figure 15, Table 21, and Table 22).

Propensity score weighting algorithms converged, and the diagnostics of weights based on histogram and summary statistics do not reveal any issues with no extreme weights (>6) upon matching (Figure 15). The effective sample size (ESS) was 158.01 (84.05%) upon matching of selected variables.

As illustrated in Figure 15, most patients have been assigned a weighting of ~1, demonstrating a similarity between CLL13 and CAPTIVATE trial populations.

Figure 15. Distribution of matching weights

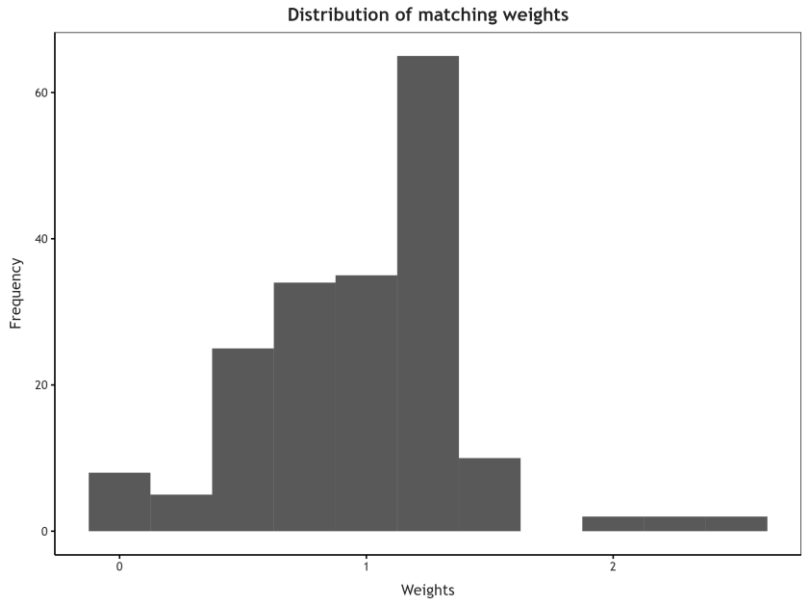


Table 21. Estimation of propensity score weights

Attribute	Value
ESS	158.01
% of original sample size	84.05
Min	0.00
1st quartile	0.68
Median	1.08
Mean	0.99
3rd quartile	1.20
Max	2.52

ESS, effective sample sizes

2.10.3.2 Population characteristics

Table 22 displays the population characteristics before and after weighting.

Table 22 Population characteristics before and after population-adjusting

Treatment effect modifier	CLL13		CAPTIVATE
	Unweighted	Weighted	
Bulky disease (>= 5cm): No	[redacted]	[redacted]	69.81
Bulky disease (>= 5cm): Yes	[redacted]	[redacted]	30.19
Bulky disease (>= 10 cm): No	[redacted]	[redacted]	96.86
Bulky disease (>= 10 cm): Yes	[redacted]	[redacted]	3.14

FISH: Del11q	[redacted]	[redacted]	17.61
FISH: Trisomy 12	[redacted]	[redacted]	14.47
IGHV unmutated	[redacted]	[redacted]	55.97
IGHV mutated	[redacted]	[redacted]	41.51
IGHV unknown	[redacted]	[redacted]	2.52
Complex karyotype: Yes	[redacted]	[redacted]	22.64[†]
Complex karyotype: No	[redacted]	[redacted]	73.58[†]
Complex karyotype: Unknown	[redacted]	[redacted]	3.78[†]

Data for median/percentage is displayed for each treatment effect modifier.
[†] In the CAPTIVATE study, the distribution of patients with complex karyotype was adjusted to match the six patients with unknown status, similar to the CLL13 study. Initially, 26 patients in CAPTIVATE had an unknown complex karyotype status. To align with the six unknowns, the remaining 20 patients (26 - 6) were redistributed into "yes" and "no" categories based on the distribution observed in the complete cases. In these complete cases, 23.3% had a complex karyotype, while 76.7% did not. This adjusted distribution was applied, maintaining 6 out of 159 patients (3.78%) in the unknown category. For the "Yes" category, 23.3% of 96.2% (i.e., 100% - 3.8%) equates to 22.4%, resulting in approximately 36 patients (22.4% × 159 = 35.64). For the "No" category, 76.7% of 96.2% is 73.8%, translating to approximately 117 patients (73.8% × 159 = 117.45). Thus, after rescaling, 22.64% (36/159) of patients were in the "Yes" category, and 73.58% (117/159) were in the "No" category.
ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in-situ hybridisation; IGHV, immunoglobulin heavy-chain variable region gene

2.10.3.3 Progression-free survival

The weighted and unweighted PFS Ven+O KM curves are displayed alongside the I+Ven PFS (digitised) KM curve in Figure 16. The weighted and unweighted PFS KM curves for Ven+O were closely aligned with the exception of the tail at 66 months which coincides with very few numbers at risk. This suggests that, when estimated in the CAPTIVATE population, Ven+O PFS might be slightly better. The potential benefit of Ven+O delaying progression over I+Ven is visible with both the weighted and unweighted curves lying above the I+Ven curve for most of the follow-up period.

Figure 16. PFS Kaplan–Meier curves for unweighted and weighted Ven+O, and digitised I+Ven

Ven+O follow-up is 72 months
PFS, progression-free survival

The beneficial effect of Ven+O over I+Ven is reflected in the naïve comparison and MAIC-weighted PFS HRs for Ven+O vs I+Ven, which are [redacted] and [redacted], respectively (Table 23).

Table 23. Cox PH model summaries for PFS

Scenario	Comparison	HR (95% CI)	P-value
Naïve comparison	Unweighted Ven+O vs I+Ven	[redacted]	[redacted]
Weighted	Weighted Ven+O vs I+Ven	[redacted]	[redacted]

CIs were estimated using a robust sandwich estimator
Ven+O follow-up is 72 months in both PFS and OS analyses.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

This suggests Ven+O delays progression compared to I+Ven, albeit non-statistically significant as the 95% CIs cross the line of equivalence. The impact of matching was minimal, suggesting that the matched variables have a minor effect on the PFS outcome, and that the effect estimated in the CLL13 cohort is already closely aligned with that estimated for a CAPTIVATE population.

2.10.3.4 Overall survival

Similar results were observed for OS. The MAIC-weighted and unweighted OS Ven+O Kaplan–Meier curves are displayed alongside the I+Ven OS (digitised) Kaplan–Meier curve in Figure 17. With the small number of OS events, any difference between the unweighted and weighted curves is indiscernible. A potential benefit of Ven+O delaying progression over I+Ven is visible in the first half of the follow-up period, with both the weighted and unweighted curves lying slightly above the I+Ven curve. However, the number of events is very small and this should be taken into account when interpreting these Kaplan–Meier curves.

Figure 17. OS Kaplan–Meier curves for unweighted and weighted Ven+O and digitised I+Ven

Ven+O follow-up is 72 months
OS, overall survival

Table 24 shows the HR of Ven+O vs I+Ven for both the unweighted and weighted CLL13 populations. The unweighted OS HR for Ven+O vs I+Ven is [redacted], suggesting beneficial OS for Ven+O compared to I+Ven. In the MAIC-adjusted analysis, matching increases the beneficial effect of Ven+O over I+Ven with a reduced OS HR of [redacted]; however, neither of the estimated HRs are statistically significant and confidence intervals are wide.

Table 24. Cox PH model summaries for OS

Scenario	Comparison	HR (95% CI)	P-value
Naïve comparison	Unweighted Ven+O vs I+Ven	[redacted]	[redacted]
Weighted	Weighted Ven+O vs I+Ven	[redacted]	[redacted]

CIs were estimated using a robust sandwich estimator
Ven+O follow-up is 72 months in both PFS and OS analyses
CI, confidence interval; HR, hazard ratio; OS, overall survival

2.10.3.5 Complete remission (CR)

CR for CAPTIVATE was assessed at 27 months. The unweighted CR rate of Ven+O ([redacted]%) and weighted CR rate ([redacted]%) are comparable to the CAPTIVATE CR rate of 52.2% (Table 25) resulting in odds ratios close to 1 ([redacted] and [redacted]) respectively.

Table 25. Complete remission summaries

Weighting	CR Rate (95% CI) (%)	Odds ratio (95% CI)	Odds ratio p-value
CAPTIVATE	52.2 (44.4 – 60.0)	Reference	-
Unweighted CLL13	[redacted]	[redacted]	[redacted]
Weighted CLL13	[redacted]	[redacted]	[redacted]

Odds ratio < 1 means Ven+O provides greater benefit compared with I+Ven
CI, confidence interval; CR, complete response

2.10.3.6 Overall response

Like CR, ORR for CAPTIVATE was assessed at 27 months. The unweighted ORR ([redacted]) and weighted ORR ([redacted]) for Ven+O were closely aligned and comparable to the CAPTIVATE ORR (96.2 [93.2 –99.2]) (Table 26). The odds ratios are associated with very wide confidence intervals and therefore significant uncertainty.

Table 26. Overall response summaries

Weighting	OR Rate (95% CI)	Odds ratio (95% CI)	Odds ratio p-value
CAPTIVATE	96.2 (93.2 –99.2)	Reference	-
Unweighted CLL13	[redacted]	[redacted]	[redacted]
Weighted CLL13	[redacted]	[redacted]	[redacted]

Odds ratio < 1 means Ven+O provides greater benefit compared with I+Ven
CI, confidence interval; MAIC, matching-adjusted indirect comparison; OR, overall response

2.10.4 Uncertainties in the indirect treatment comparisons

Although the analyses adhered to best-practice guidelines, several limitations were identified.

Firstly, AbbVie do not have access to IPD for the CAPTIVATE trial and hence were unable to perform alternative approaches to propensity score matching which require IPD for both trials within the comparison (e.g. inverse probability of treatment weighting [IPTW]). In addition, as the CLL13 trial is not owned by AbbVie, the company have only have access to IPD for specific data cuts; therefore, the MAIC is performed using the latest data-cut for which AbbVie had access to the IPD (the 4-year follow-up, for which the respective publication is Fürstenau et al. 2024) rather than the most recent data reported in Fürstenau et al. 2025.[11,26] As noted by clinical experts, this is not expected to have any undue influence on outcomes as the Kaplan-Meier curves demonstrated only minimal changes between the 4-year and 5-year follow-up periods.[10,11,26]

Secondly, although the CLL13 and CAPTIVATE trials were broadly comparable (Section 2.10.1.3), some differences in the trial populations were noted, and have been discussed. Namely, there were some differences between the eligibility criteria of CAPTIVATE and CLL13. Where CAPTIVATE included adult patients ≤ 70 years old, CLL13 included patients ≥ 18 years old. As such, the Ven+O evidence base was restricted to CLL13 patients ≤ 70 years old for the MAIC.

Further, in CLL13, no distinction was made between patients with CLL or SLL (differing by primary tumour location but considered the same disease due to their immunophenotypes), whereas this was considered in CAPTIVATE. Given this, efficacy was assumed to be similar for both CLL and SLL.

In the MAIC, due to data limitations (i.e. a lack of baseline characteristics for CAPTIVATE without del17p and TP53 mutations), adjustments were not made for patients with/without del17p or *TP53* mutations, the presence of which are often associated with other unfavourable prognostic markers.[10,120,121] Therefore, removing patients with *TP53* mutations from the CAPTIVATE data means that other

unfavourable markers may also be removed. Given the similarity in baseline characteristics of the ITT populations between the two trials, the removal of TP53 patients from CAPTIVATE could result in a fitter, healthier patient population in CAPTIVATE compared with CLL13. Despite this, Ven+O displays better outcomes compared with fixed dose I+Ven, when the population characteristics are broadly similar (i.e. untreated fit CLL patients with no del17p/TP53 mutations), at the ~5-year timepoint (CLL13 5-yr PFS [no del17p/*TP53*] = 69.8%; CAPTIVATE FD cohort 5.5-year PFS [no del17p/*TP53*] = 66%).[11,107]

Finally, the underlying assumption of unanchored ITCs is that all TEMs and PVs are included and that all imbalances are accounted for. However, it is generally acknowledged that this assumption rarely holds due to limitations in reporting and the desire to preserve ESS and thus some risk of residual bias remains. In these analyses there were two potential PVs/TEMs (CIRS and Binet staging) that were not included as they were not available in both CAPTIVATE and CLL13.

To explore the impact of uncertainties on the MAIC analyses, sensitivity analyses were performed as described in Appendix J which show that outcomes remain similar when extending the matching variables.

2.10.5 Conclusions of the ITC

An unanchored MAIC was performed estimating the relative efficacy of Ven+O vs I+Ven in fit patients with untreated CLL and no del(17p)/*TP53* mutation.

When compared with I+Ven, Ven+O demonstrates numerical PFS improvement, with a HR of [redacted], though this benefit is not statistically significant. These findings remained consistent when extending the matching variables included in the scenario analyses (Appendix J).

For OS, the HR of [redacted] for Ven+O vs I+Ven suggested a beneficial treatment effect for Ven+O. However, the confidence intervals were wide and therefore the benefit for Ven+O was not statistically significant. This can be attributed to the absolute number of events for OS remaining low for both CLL13 and CAPTIVATE in younger patients despite the length of follow-up.

2.11 Adverse reactions

During the CLL13 trial, an independent data and safety monitoring board reviewed safety data on a regular basis and were not masked to treatment assignment.[95] Safety analyses were performed in the safety population, defined as all patients who had received at least one dose of study treatment.

Serious adverse events (SAEs) were reported from the first dose of study medication until the end of the study, while AEs were reported from first dose of study medication until 28 days after the end of treatment. Adverse events were assessed and reported according to Common Terminology Criteria for Adverse Events (version 4.0) and the MedDRA classification system.[95]

As outlined in Fürstenau et al., treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred within 84 days after the last dose of study treatment or initiation of next treatment for CLL, whichever was earlier, with the exception of secondary malignancies and deaths, which were assigned as treatment-emergent without any time limitations. Association of adverse events and deaths with treatment was determined by local investigators.[26]

2.11.1.1 Treatment-emergent SAE with maximum CTC grade ≥ 3

The frequency of patients with TESAEs was numerically higher in the SCIT arm ([redacted]) compared with the Ven+O arm ([redacted]).[13]

The most frequently reported treatment-emergent serious adverse events with maximum CTC grade ≥ 3 in patients treated with Ven+O were infusion-related reactions ([redacted]), pneumonia ([redacted]), tumour lysis syndrome ([redacted]), thrombocytopenia ([redacted]), and febrile neutropenia ([redacted]).[13] TESAEs maximum CTC grade ≥ 3 and incidence ≥ 1% in any arm are presented in Table 27.[13]

Section 3.4.4 compares the incidence of TESAEs for Ven+O with I+Ven and displays generally minor differences between both regimens, indicating their comparable

tolerability. The higher incidence of neutropenia in patients treated with I+Ven is aligned with clinical expert opinion.[10]

Table 27. Treatment-emergent serious adverse events (TESAE) with maximum CTC grade ≥ 3 and incidence ≥ 1% in any arm

	Ven+O N = 228	SCIT N = 216
Patients with ≥ 1 TESAE, N (%)	[redacted]	[redacted]
Blood and lymphatic system disorders		
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
General disorders and administration site conditions		
Pyrexia	[redacted]	[redacted]
Infections and infestations		
Febrile infection	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Injury, poisoning and procedural complications		
Infusion related reaction	[redacted]	[redacted]
Metabolism and nutrition disorders		
Tumour lysis syndrome	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Basal cell carcinoma	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]
Richter's syndrome	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]

CTC, common toxicity criteria; SCIT, standardised chemoimmunotherapy; TESAE, treatment-emergent serious adverse event
Source: CLL13 Priority 1 analyses[13]
Note: the percentages have been calculated using the total N number as the denominator

2.11.1.2 Adverse events of particular interest (AEPIs) of any CTC grade

Adverse events of particular interest (AEPI) were documented until the patient receives new CLL treatment or is considered as end of study and not only during

treatment.[95] The frequency of patients with any grade AEPIs was numerically higher in the Ven+O arm ([redacted]) compared with the SCIT arm ([redacted]).[13]

The most frequently reported AEPIs were nasopharyngitis ([redacted] in the Ven+O arm and [redacted] in the SCIT arm), and COVID-19 ([redacted] in the Ven+O arm and [redacted] in the SCIT arm). AEPIs of any CTC grade with an incidence ≥ 5% in the Ven+O arm are presented in Table 28.

Table 28. Adverse events of particular interest (AEPI) of any CTC grade where incidence ≥ 5% in the Ven+O arm

	Ven+O N = 228	SCIT N = 216
Patients with ≥ 1 AEPI, N (%)	[redacted]	[redacted]
General disorders and administration site conditions		
Influenza like illness	[redacted]	[redacted]
Infections and infestations		
Bronchitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Investigations		
Neutrophil count decreased	[redacted]	[redacted]

Percentages have been calculated using the total N number as the denominator
AEPI, adverse event of particular interest; CTC common toxicity criteria; SCIT, standardised chemoimmunotherapy
Source: CLL13 Priority 1 analyses[13]

2.12 Interpretation of clinical effectiveness and safety evidence

2.12.1 Principal findings of the clinical evidence base

Having been recommended via the CDF for 1L treatment of fit patients with untreated CLL and no del(17p)/*TP53* mutation, Ven+O is proposed to be recommended for routine commissioning. This patient population currently only have access to two effective treatment non-chemotherapy regimens; I+Ven, which combines a BCL2 inhibitor and a BTKi,[2] and Ven+O, which combines targeting of BCL2 and CD20.[1] Ven+O's alternative mechanism of action offers an alternative and targeted treatment for this population, with the only opportunity to use obinutuzumab within the pathway, especially given that some patients are not suitable for BTKi-based treatments.[23,24]

As outlined previously, clinical experts have detailed their frequent usage of Ven+O in fit patients with untreated CLL and no del(17p)/*TP53* mutation since its entrance into the CDF almost 5 years ago, having become a primary choice in the 1L treatment pathway. Approval for use via routine commissioning will ensure continued access to a well-tolerated, efficacious treatment whilst maintaining choice for patients based on their individual needs.

The phase 3, multicentre RCT CLL13 demonstrated the efficacy, safety and tolerability of Ven+O in fit patients with untreated CLL and no del(17p)/ *TP53* mutation. The trial was robust, and considers patient populations relevant to UK clinical practice.[26] At a median follow-up of 50.7 months (IQR 44.6-57.9), patients in the Ven+O group displayed a significantly longer PFS than those in the SCIT group (HR 0.47, 97.5% CI 0.32–0.69; p<0.0001).[26] Furthermore, Ven+O demonstrated a long-term response, with significantly longer TTNT in patients treated with Ven+O compared with patients treated with SCIT (HR 0.34 [97.5% CI: 0·20–0.60], log-rank p<0.0001).[26] No new safety concerns were detected with longer follow-up and were comparable to those observed in comparable trials in alternative CLL populations.

Since the approval of Ven+O for fit patients with untreated CLL and no del(17p)/ *TP53* mutation via the CDF, RWE has been accumulated from patients treated in England, providing a relevant, additional source of OS data from which to validate the performance of Ven+O in clinical practice. The OS outcomes of CLL13 align with those observed in the SACT report, which demonstrates the effectiveness of Ven+O in this population within UK clinical practice [12]

A MAIC of Ven+O and the only targeted treatment currently used in clinical practice for this population, I+Ven, suggested that Ven+O may provide numerical improvements in OS and PFS compared with I+Ven, though the differences were not statistically significant.

2.12.2 Strengths and limitations of the clinical evidence base

The CLL13 trial provides evidence on the efficacy and safety of Ven+O for the treatment of fit patients with untreated CLL and no del(17p)/*TP53* mutation. The population included in the trial is aligned with the marketing authorisation for Ven+O and the population listed in the final NICE scope. A high proportion of patients enrolled in the CLL13 trial were from European countries (96.3%).[27] Likewise, the outcomes of the CLL13 trial are supported by those from the SACT report, which provides direct RWE from the UK patient population who would receive Ven+O if it were approved for routine commissioning.

The clinical evidence presented as part of this submission has been derived from a recent SLR that was conducted according to the principles of systematic reviewing published in the Cochrane handbook.[122] The clinical SLR identified the pivotal clinical trial CLL13 as the primary evidence source. The results of the CLL13 trial are relevant to the decision problem outlined in the NICE scope, specifically the population of interest.

Due to an absence of direct trial evidence comparing Ven+O with I+Ven, a MAIC was conducted to generate comparative efficacy evidence. Since there was no common comparator between CLL13 and CAPTIVATE, an unanchored MAIC was conducted in line with the approach outlined in Signorovitch et al. (2012),[103] and

considering the robust methods described in NICE DSU TSD 18,[104] which suggests that the use of population adjustment in unanchored indirect comparisons requires that absolute outcomes can be reliably predicted from covariates.[104] This resulted in a high-quality analysis, providing the best estimates for comparative efficacy that could be conducted using the data available. In the MAIC, Ven+O demonstrated a beneficial PFS with a HR of [redacted] and a beneficial OS with a weighted HR of [redacted].

2.13 Ongoing studies

An additional trial, CRISTALLO (NCT04285567), investigating the effectiveness of Ven+O compared with SCIT in patients with untreated CLL without del17p or *TP53* mutations, is also ongoing. The CRISTALLO trial is being performed at 40 sites across Europe, Australia and the United States, and the baseline age of participants closely matches that in CLL13. Preliminary results are supportive of the efficacy and safety of Ven+O as observed in CLL13. In CRISTALLO, at a median duration of follow-up of 32 months, fewer patients had progressed or died with Ven+O compared with SCIT.[123] This observation is aligned with the outcomes in CLL13. Further, the 2-year PFS rate of 95.7% for Ven+O in CRISTALLO aligns closely with the 2-year PFS rate for Ven+O of 92.5% observed in CLL13, emphasising the reproducibility of survival outcomes for Ven+O between these independent clinical trials.[26,123] As with CLL13, CRISTALLO is an investigator sponsored study and therefore AbbVie does not have access to the data.

3 Cost effectiveness

The objective of this analysis was to evaluate the cost-effectiveness of Ven+O in fit patients with untreated CLL and no del(17p)/ *TP53* mutation (who would previously have been considered suitable for treatment with SCIT). **The analysis compares Ven+O with a I+Ven which is considered the only relevant comparator for this appraisal.**

- A three-state PSM was developed including: Progression-free, Progressed-disease, and Death states.

Survival analyses

- MAIC-adjusted KM survival data for Ven+O from CLL13 are extrapolated to a lifetime horizon using the recommendations provided in NICE DSU TSD14.[124] Base case parametric distributions were based on visual fit, fit statistics and clinical plausibility.
- The HRs calculated in the MAIC (Section 2.10) are applied to the MAIC-adjusted Ven+O Kaplan–Meier curves to derive outcomes for the I+Ven arm using the guidance described in NICE DSU TSD 14.[124]
- Time on treatment for Ven+O and I+Ven was protocol-driven, as per the CLL13 and CAPTIVATE trials.

Cost and utility inputs

- The analysis considered treatment acquisition costs for first-line and subsequent treatments[93,125,126], treatment administration costs and healthcare resource use[127], terminal care costs[128], and TLS and AE management costs[2,10].
- Due to utility data not being available from CLL13 and the paucity of HRQoL data regarding fit patients, the Hancock et al publication (used in TA119, TA174 and TA193) was chosen to inform the PF and PD utility values used in the analysis.[129-132]

Cost-effectiveness results

- All cost-effectiveness results presented within this submission use the venetoclax PAS price and other therapies at list price.
- In the cost-utility analysis, Ven+O was associated with 0.37 incremental QALYs and a **cost saving** of £[redacted] compared with I+Ven. As such, Ven+O returned a dominant ICER, demonstrating that Ven+O is an effective use of NHS resources.

- The outcomes of this analysis demonstrate that although patients treated with Ven+O must attend appointments for IV infusion of obinutuzumab, this patient and system burden is offset by the lower acquisition costs of obinutuzumab compared with ibrutinib, in addition to the reduced requirement for cardiac monitoring in a hospital setting for Ven+O compared with I+Ven.

- The PSA results are similar to the base-case results, demonstrating the model is robust to uncertainty. From the DSA, the model is most sensitive to the cohort starting age and the time horizon; a result of a shortened time horizon reducing QALY benefits with minimal cost impact.

Cost Comparison Scenario

- Clinical expert feedback on the MAIC suggests Ven+O and I+Ven outcomes appear comparable.[10] Furthermore, clinical expert feedback based on NHS clinical practice is that the outcomes of Ven+O and I+Ven are similar. Therefore, AbbVie undertook a cost-comparison analysis.
- The cost comparison shows Ven+O would be cost saving for the NHS vs. I+Ven by [redacted] [at venetoclax PAS price and not including 3.5% discounting on costs].

The cost-utility and cost-comparison analyses both demonstrate that Ven+O is cost saving compared to I+Ven in fit patients with untreated CLL and no del(17p)/ *TP53* mutation.

3.1 Published cost-effectiveness studies

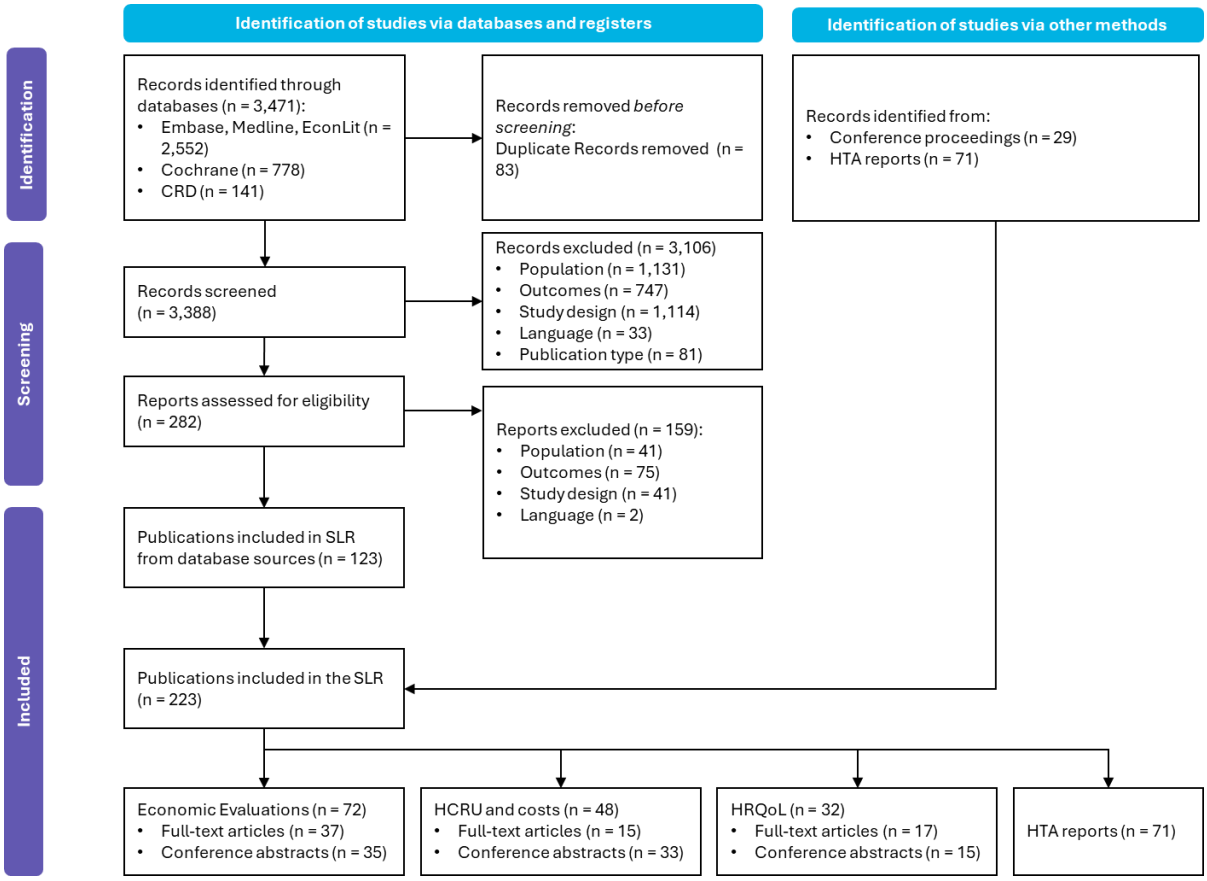
In line with the NICE technology evaluations manual, an SLR was conducted to identify all relevant cost-effectiveness studies in CLL. The SLR was conducted in alignment with the CRD's guidance for systematic reviews,[133] the Cochrane Handbook for Systematic Reviews,[122] PRISMA guidelines,[134] and requirements set out by NICE.[89] Details of the SLR are provided in Appendix E.

In brief, electronic databases (Embase, Medline and EconLit) were searched from inception to 12 December 2018, and subsequently updated on five occasions, the most recent update being on 06 February 2025. In addition, the conference proceedings from 2020 to 2024 and websites of European and North American HTA organisations were searched. Additional searches were performed on the websites of HTA authorities to retrieve critical appraisals and key learnings from previous assessments. To identify relevant articles, search terms for CLL were used in the websites' search engines. HTA authorities considered for inclusion in the SLR were:

- All Wales Medicines Strategy Group (AWMSG)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Haute Autorité de Santé (HAS)
- National Centre for Pharmacoeconomics (NCPE)
- National Institute for Health and Care Excellence (NICE)
- Norwegian Medicines Agency (NoMA)
- Folkehelseinstituttet (FHI)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Scottish Medicines Consortium (SMC)
- Tandvårds- och läkemedelsförmånsverket (TLV)
- Zorginstituut Nederland (ZiNL).

A PRISMA diagram for the search of economic evaluations, HCRU and costs, and HRQoL is presented in Figure 18.

Figure 18. PRISMA flow diagram for economic SLR



CRD, Centre for Reviews and Dissemination; HCRU, healthcare resource utilisation; HRQoL, health-related quality of life; HTA, health technology assessment; SLR, systematic literature review

The outcomes of the economic search are presented in Appendix F.

3.2 Economic analysis

The economic case presented in this submission is based on a conventional cost utility analysis, assessing the use of Ven+O for the treatment of fit patients with untreated CLL and no del(17p)/ *TP53* mutation (who would previously have been considered suitable for treatment with SCIT). A cost-comparison scenario is also presented.

3.2.1 Patient population

The model considers the target population as defined in the final scope (Table 1). Baseline mean age and gender distribution are used to estimate age- and gender-specific mortality of the general population (Table 29).

Table 29. Population baseline characteristics

Parameter	Value	Source
Mean age (SD), years	60.9 (10.0)	CLL13, Fürstenau et al. 2024[26]
Male proportion, %	74.7	CLL13, Fürstenau et al. 2024[26]

SD, standard deviation

3.2.2 Model structure

In line with previous appraisals in CLL, including the original appraisal for Ven+O (TA663), a partitioned survival model (PSM) structure is used to estimate the cost-effectiveness of Ven+O compared with I+Ven.[1,80,83-85] The cost-effectiveness model has been developed in line with NICE guidelines related to the methods of technology appraisals.[89]

The model adopts three health states:

- Progression-free (PF): includes patients who are alive and whose disease has not progressed
- Progressed disease (PD): includes patients who are alive but whose disease has progressed
- Death: includes patients who have died either from disease or other causes

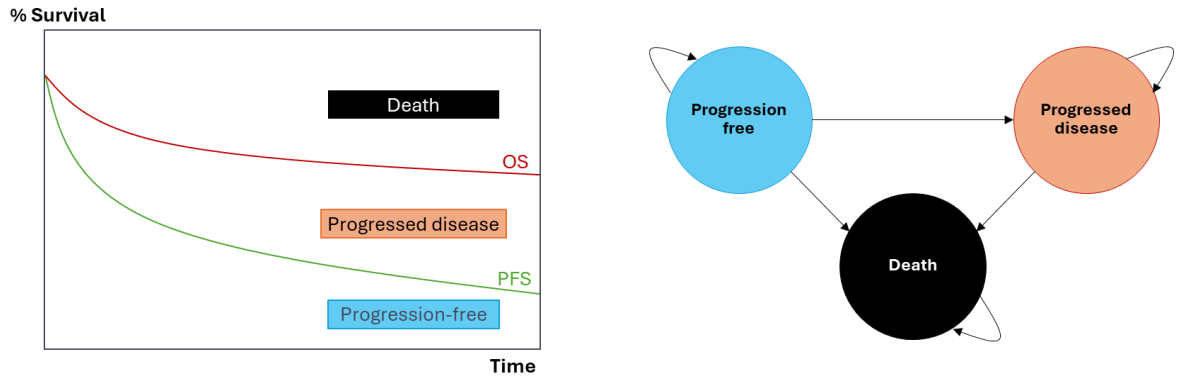
This three-state PSM structure was selected because it offers a data-driven, flexible approach that is well-established in economic modelling of oncological diseases (Table 30). In particular, PSMs have the advantage of directly incorporating observed survival data (such as PFS and OS), which reduces the uncertainty that can arise when estimating separate transition probabilities required in a state-transition model. This approach minimises reliance on additional assumptions about intermediate health state transitions—a significant benefit when intermediate endpoint data are limited. Further, the data required for a PSM analysis are aligned with the disease pathway of CLL (i.e. disease progression and death) and aligned with the measured endpoints from the CLL13 trial.

In the PSM, the proportion of patients within each health state is determined by OS and PFS curves via an area-under-the-curve approach using data from the CLL13 trial, with outcomes being modelled following adjustments performed via the MAIC

described in Section 2.10. As illustrated in Figure 19, the PFS curve determines the proportion of patients remaining alive and progression-free, and the OS curve determines the proportion of patients that are alive (irrespective of their progression status). The difference between the PFS and OS curves informs the proportion of patients that are alive post-progression.

Background mortality is incorporated in survival extrapolations to ensure that the OS of patients within the model does not exceed the survival of an age- and sex-matched population within the UK (Section 3.3.2.3.1).

Figure 19. Survival curves informing the proportion of patients per health state



OS, overall survival; PFS, progression-free survival

Patients accrue costs and utilities for each cycle they spend in each state (excluding death) and the model is run over a defined number of cycles, allowing an estimate of total costs and quality-adjusted life years (QALYs) for the cohort over the specified time horizon. The direct healthcare costs include treatment acquisition costs, administration costs, healthcare resource costs per health state, costs of subsequent treatment following treatment discontinuation, AE management costs, and costs of terminal care.

3.2.2.1 Time horizon

NICE guidelines recommend that the time horizon is sufficiently long to reflect any differences in costs or outcomes between the technologies that are being compared; therefore, a lifetime horizon is considered in the base case analysis.[89] With a mean age at the start of the model of 60.9 years, as informed by the cohort receiving

treatment with Ven+O in the CLL13 trial, this leads to a lifetime horizon spanning 39.1 years, for a maximum patient age in the model of 100 years.

3.2.2.2 Cycle length

The model adopts a cycle length of 28 days which is considered sufficient to accurately capture the clinical outcomes reported for CLL patients from the CLL13 trial. Further, this cycle length is consistent with the dosing schedules of Ven+O and I+Ven. A half-cycle correction is applied to QALYs and disease management costs, but not treatment acquisition costs as it is assumed that patients who start treatment in a given cycle will incur the full cost of the drug (in line with the dosing regimen). This adjustment simplifies calculations while ensuring more accurate estimates of costs and QALYs, helping to avoid overestimations due to timing discrepancies.

3.2.2.3 Perspective and discounting

The model adopts a National Health Service (NHS) and Personal Social Services (PSS) perspective, with costs and health-related utilities discounted at 3.5% per annum in accordance with the NICE reference case.[89]

Table 30 summarises the key features of the economic analysis in comparison with previous appraisals in CLL.

Table 30. Features of the economic analysis†

Factor	Previous appraisals in CLL						Current appraisal	
	TA561 Ven+R[85]	TA663 Ven+O[1]	TA689 Acalabrutinib[81]	TA796‡ Ven[84]	TA891 I+Ven[2]	TA931 Zanubrutinib[79]	Chosen approach	Description
Model structure	Partitioned survival analysis in the base case and a cost-comparison scenario§	Partitioned survival analysis	3-state semi-Markov	Partitioned survival analysis	4-state semi-Markov	3-health state semi-Markov	Partitioned survival analysis Cost comparison Scenario	Aligned with previous NICE TAs, disease pathway of CLL and the endpoints of the CLL13 trial. Cost-comparison scenario aligned with TA561
Time horizon	Lifetime (30 years)	Lifetime (30 years)	Lifetime (30 years)	10 years	Lifetime (40 years)	Lifetime (30 years)	Lifetime (39.1 years)	Aligned with NICE reference case, with the aim to fully capture lifetime costs and benefits
Cycle length	28 days (with half-cycle correction	28 days (with half-cycle correction)	28 days (with half-cycle correction)	NR	28 days (with half-cycle correction)	28 days (with half-cycle correction)	28 days (with half-cycle correction)	Consistent with the dosing schedule of Ven+O and I+Ven
Discount rate	3.5% (costs and outcomes)	3.5% (costs and outcomes)	3.5% (costs and outcomes)	NR	3.5% (costs and outcomes)	3.5% (costs and outcomes)	3.5% (costs and outcomes)	Consistent with NICE reference case
Health effect measures	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Consistent with NICE reference case

† As detailed in Section 1.3.5, only I+Ven is considered a relevant comparator for this appraisal. Other appraisals listed here have focused on subsequent lines of therapy for CLL.
‡TA796 is an update from TA487, for which the committee papers are not available on the NICE website. There are details around methodology which are not reported in the TA796 publication
§ The EAG stated that "estimates from the cost-effectiveness analyses range from venetoclax plus rituximab being less costly and more effective to it being less costly and less effective, when compared with ibrutinib. Although it is uncertain how effective venetoclax is compared with ibrutinib, a cost-comparison analysis shows that venetoclax plus rituximab is considered to be a cost-effective use of NHS resources and it is recommended for routine use in the NHS"
BNF, British National Formulary; eMIT, drugs and pharmaceuticals electronic market information tool; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; TA, technology appraisal

3.2.3 Intervention technology and comparators

3.2.3.1 Intervention

As described in Section 1, the intervention of interest in this appraisal is Ven+O. Treatment with Ven+O treatment consists of 12 cycles (12 cycles of Ven and 6 cycles of O), each with a duration of 28 days.

Venetoclax is an oral tablet and is delivered with an initial dose escalation:

- Cycle 1, Day 22–28: 20 mg daily
- Cycle 2, Day 1–7: 50 mg; Day 8–14: 100 mg; Day 15–21: 200 mg; Day 22–28: 400 mg
- Cycle 3–12, Day 1–28: 400 mg daily

Venetoclax is given for a fixed treatment duration until the end of Cycle 12 based on the clinical trial protocol requirements.[95]

Obinutuzumab is administered as an intravenous infusion. The recommended dosage is 1000 mg administered over Days 1 (100mg) and 2 (900mg) [or 1000 mg administered in full on Day 1 if no modifications of the infusion rate or interruptions during the first 100 mg], 1000 mg on Day 8 and Day 15 of treatment Cycle 1, followed by 1000 mg on Day 1 of treatment Cycles 2–6. Obinutuzumab is given for a fixed treatment duration which is until end of Cycle 6 based on the clinical trial protocol.[95]

Ven+O is routinely commissioned in all untreated CLL patient populations apart from fit patients with untreated CLL and no del(17p)/ *TP53* mutation where it is reimbursed via the CDF (TA663).[1] According to clinical expert opinion, Ven+O has become the standard of care for patients with untreated CLL.[10]

3.2.4 Comparator

As detailed in Section 1.3.5.1 and in line with the NICE technology evaluations manual, this company submission considers how the treatment pathway has evolved since TA663 and views only I+Ven as a relevant comparator.[89]

Treatment with I+Ven consisted of 15 cycles, each with a duration of 28 days.

Ibrutinib is an oral tablet administered daily. The recommended dosage is 420 mg on Days 1–28 for a fixed treatment duration of 15 cycles. Treatment with venetoclax begins on Day 1 of treatment Cycle 4 as per the dose escalation regimen outlined above.[18,92]

3.3 Clinical parameters and variables

3.3.1 Evidence synthesis

Evidence to describe the characteristics of the patient population and the effectiveness of Ven+O was primarily derived from the CLL13 trial, a phase 3, multicentre, randomised, prospective open-label trial evaluating the safety and efficacy of venetoclax regimens compared with SCIT in fit patients with previously untreated CLL without del17p or *TP53* mutation.[26] An uMAIC using data obtained from CAPTIVATE was conducted to derive survival outcomes for I+Ven as described in Section 2.10.

3.3.2 Survival analysis

As described in Section 3.2.2, at each model cycle the proportion of patients in the PFS, PD, and Death states are derived from MAIC-adjusted PFS and OS curves based on CLL13 trial data. As the modelled time horizon extends beyond the CLL13 follow-up period, these survival curves are extrapolated using parametric distributions to project health-state distributions over time.

3.3.2.1 Assessing the proportional hazards assumption

The proportional hazards assumption (PHA) was assessed using the MAIC-adjusted Ven+O survival curves presented in Section 2.10.3 to determine whether a constant HR could be applied to the Ven+O curve to extrapolate long-term outcomes for I+Ven, or whether alternative methods should be considered. Four assessments were conducted:

- Visual inspection of Kaplan–Meier (KM) curves for Ven+O and I+Ven (Section 2.10.3). Crossing of KM curves might indicate that the hazard for one

treatment group is higher at some times and lower at others, violating the PH assumption.

- Visual inspection of log-cumulative hazards against log-time. Approximately, parallel lines indicate the PHA holds, while non-parallel or crossing lines suggest it does not.

- Visual inspection of Schoenfeld residuals. These residuals reflect the difference between observed covariates and expected value over time, with a plot centred around zero and showing no trend supporting the PHA.

- The Grambsch and Therneau test. This evaluates the relationship between Schoenfeld residuals and survival time, with a significant p-value ($p<0.05$) indicating a violation of the PHA.

The results of these tests are described in Table 31.

Table 31. Assessing the PHA for Ven+O compared with I+Ven

Scenario	Outcome	Log-cumulative hazard plots	Schoenfeld residuals plot†	Grambsch-Therneau test‡	PHA violated?	HR applied	p-value
Ven+O vs I+Ven	OS	Crossing	Slight trend	p = 0.766	Unclear	[redacted]	[redacted]
	PFS	Multiple crossings	No time-varying trend	p = 0.737	No	[redacted]	[redacted]

† If p-value > 0.05, no evidence to reject PHA
‡ if the covariate is time-independent, no evidence to reject PHA
HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PHA, proportional hazards assumption

As described in Table 31, statistical tests for PHA between Ven+O and I+Ven remain inconclusive; with a fairly small sample size it is unlikely that the tests are powered to detect whether or not PH is supported. This is partially a consequence of the output of the MAIC, which demonstrated that Ven+O was numerically superior to I+Ven, albeit with HR confidence intervals crossing 1, thus providing rationale for very similar hazards over time and the meeting, touching or brief crossing of the log-cumulative hazard plots (Figure 20). Further, the slight trend in the Schoenfeld residuals plot for OS can be explained by the low number of events for this endpoint (Figure 21). Moreover, published literature confirms that uMRD is a known clinical

indicator of long-term survival outcomes in patients with CLL, driven by the venetoclax component of Ven+O and I+Ven and thus contributing to the similar hazard profile.[72,135] Based off this, the assumption of constant hazards was clinically validated via two individual consultations, whereby it was confirmed that treatment effect of Ven+O and Ven+I is proportionate and therefore the PHA is appropriate.

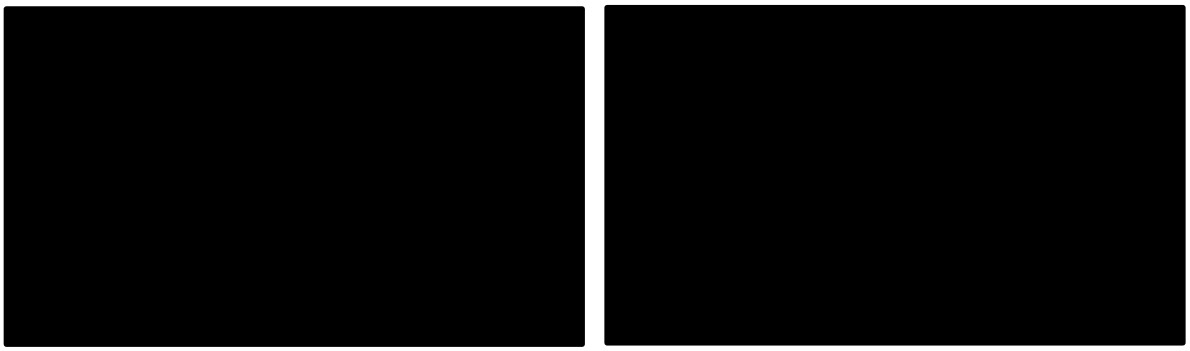
Figure 20. Log-cumulative hazard plots of MAIC-adjusted Ven+O and I+Ven

OS **PFS**

PFS, progression-free survival; OS, overall survival

Figure 21. Schoenfeld residuals of MAIC-adjusted Ven+O and I+Ven

OS **PFS**



PFS, progression-free survival; OS, overall survival

Based on the rationale provided, particularly the inclusion of Ven in both treatment arms, the company believe it appropriate to model the hazards between Ven+O and I+Ven proportionally in the base case analysis and, in line with the guidance within TSD14, apply constant HRs for long-term extrapolations of OS and PFS.[124] This approach also reduces the number of estimated degrees of freedom compared with using independent models, which would lead to a broad range of results that would

be unsuitable for decision-making. For completeness, a description of an independent modelling approach is presented in Appendix K.

3.3.2.2 Extrapolation of survival outcomes

To extrapolate survival outcomes over the lifetime horizon, standard parametric curves (exponential, gamma, generalised gamma, Gompertz, log-normal, log-logistic, and Weibull) were fitted to the MAIC-adjusted PFS and OS Ven+O curves from CLL13 as per NICE TSD14.[124]

Curve selection was performed according to the following criteria presented in TSD14, namely:

- Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to test the relative fit of each parametric model, while also penalising overfitting to observed data. Models with an AIC or BIC difference of ≤2 were considered statistically comparable.[136]

- Each curve was visually compared against the Kaplan–Meier data to evaluate the fit. Parametric distributions that deviated substantially or produced implausible projections were discounted.

- Plausibility of predictions across the unobserved period up to 40 years (maximum patient age of 100 years in the model) were validated with clinicians and against literature.[124,137]

In the base-case analysis, PFS and OS outcomes for I+Ven are derived by applying the MAIC-adjusted HRs to the adjusted Ven+O data, ensuring comparability between treatment arms in the population in the decision problem.

3.3.2.3 Overall survival

Parametric distributions were applied to the MAIC-adjusted Ven+O OS data from CLL13 using the methodology described in Section 3.3.2.2. The generalised gamma distribution did not converge and was therefore excluded from the analyses.

Short-term extrapolations of the fitted distributions are plotted against the observed data in Figure 22.

Figure 22. Kaplan–Meier curve of Ven+O OS data and fitted parametric distributions extrapolated to 72 months

OS, overall survival

The AIC and BIC scores of the fitted standard parametric distributions are presented in Table 32. Based on both the AIC and BIC, the exponential distribution appears to be the best fitting distribution. The AIC values of all other distributions are similar to the exponential AIC, though slightly more variation between distributions is observed for BIC values. However, all of these are plausible in terms of best statistical fit as they are within 4 points of the AIC.

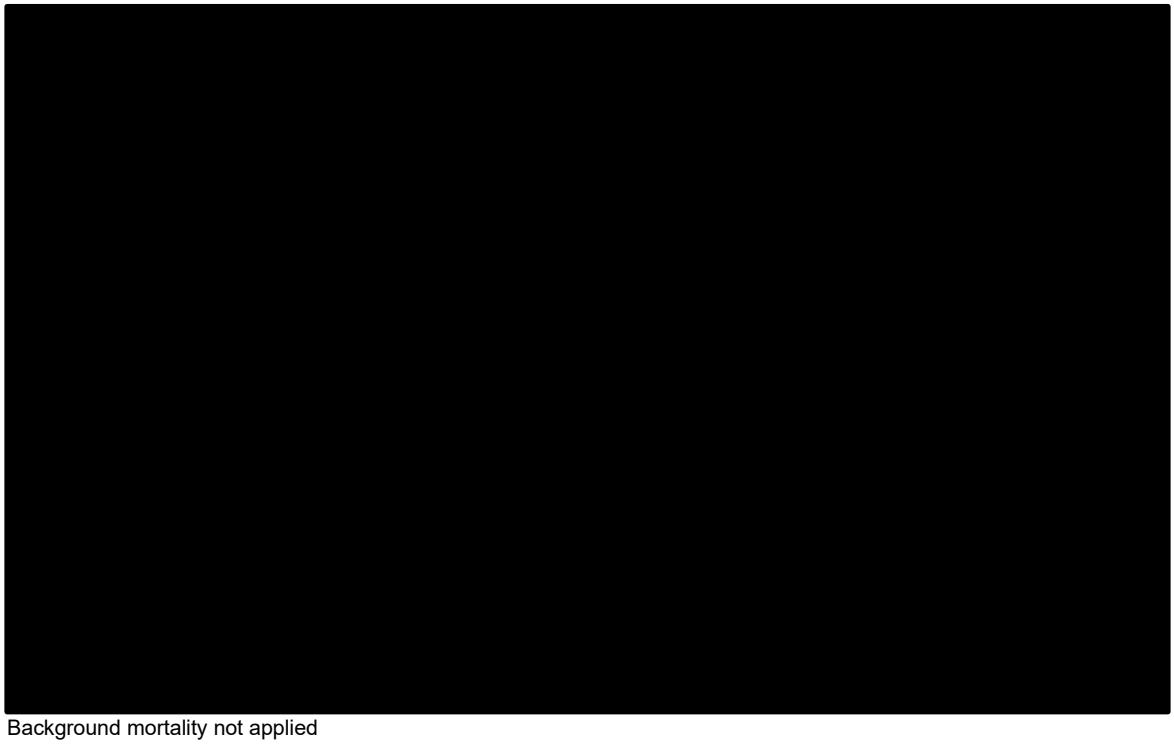
Table 32. AIC and BIC values of standard parametric distributions fit to Ven+O OS data

Distribution	AIC	BIC
Exponential	*96.8*	*100.0*
Gamma	97.3	103.6
Gompertz	98.3	104.6
Log-logistic	97.4	103.7
Log-normal	97.0	103.2
Weibull	97.4	103.7

Best-fitting distributions are in italics and highlighted in green.
AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

In the long-term extrapolations, considerable variation is observed across the distributions (Figure 23 and Table 33). The exponential distribution has an extremely gradual slope resulting in the overly optimistic prediction that only ~20% of patients will die due to CLL after 40 years (without accounting for background mortality). In contrast, the Gompertz distribution results in 100% of CLL related mortality after ~20 years (also without accounting for background mortality) which is overly conservative. The remaining distributions present long-term extrapolations between the Gompertz and exponential distributions.

Figure 23. Kaplan–Meier curve of Ven+O OS data and fitted parametric distributions extrapolated to a lifetime horizon



Background mortality not applied
KM, Kaplan–Meier; OS, overall survival; Ven+O, venetoclax + obinutuzumab

Table 33. Landmark estimates Ven+O OS data

Distribution	12 months	24 months	48 months	60 months	120 months
Observed[†] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†] MAIC-adjusted Kaplan–Meier data from CLL13 after median 50.7 months of follow-up
CI, confidence interval; NR, not reached; OS, overall survival

Overall, the preferred distribution for OS has been selected through a holistic consideration of visual fit, statistical fit and the clinical plausibility of long-term extrapolations. On balance, the log-logistic distribution is considered the most appropriate as it produces clinically plausible outcomes at the 10 year timepoint, while providing an acceptable visual and statistical fit to observed data from CLL13;

however, the statistical and visual fit of all distributions is extremely close with the exception of the Gompertz and exponential distributions which are clinically implausible. Through clinical validation, it was established that CLL patients would have slightly worse survival compared to the general population due to potential secondary illnesses such as Richter's transformation, secondary malignancy, and infection; however, CLL patient survival would not be as low as the Gompertz distribution survival estimates. As will be discussed in Section 3.3.2.3.1, the overly optimistic distributions are capped by general population mortality in the model. Therefore, the log-logistic distribution has been chosen based on the best visual and statistical fit in the shorter term (up to 10 years), with the longer-term survival in the model capped by general population mortality.

3.3.2.3.1. Background mortality

To account for death due to other causes, the OS estimates from MAIC-adjusted curves are corrected for background mortality under the assumption that the age- and sex-adjusted mortality risk (i.e. hazard rate) of CLL patients can never be lower than the age- and sex-adjusted mortality risk of the general population (Figure 24). Estimates of the general population mortality (i.e. mortality not related to the disease) are taken from the most recent life tables reported by the Office of National Statistics for the year 2021-2023 for England and Wales.[138]

In cases where the mortality risk with the chosen OS curve is lower than the mortality risk of the general population, the mortality risk of the patient is assumed to equal the risk of the age- and sex-matched peers in the general population. The general population mortality was adjusted by the baseline mean age and sex ratio of the CLL13 population. This approach ensures the model does not underestimate true mortality while avoiding double-counting risks and so provides a more realistic reflection of patient survival.

Figure 24. Applying background mortality to extrapolated Ven+O OS curves

OS, overall survival

3.3.2.4 Progression-free survival

As for OS, standard parametric distributions were fitted to the MAIC-adjusted Ven+O curves derived using the weights from the MAIC. The preferred distribution was selected according to visual fit, and statistical fit (AIC, BIC) and plausibility of long-term outcomes.

Short-term extrapolations of the fitted distributions are plotted against the observed data in Figure 25. All models show good visual fit when compared with the observed Kaplan–Meier curve except for the exponential distribution.

Figure 25. Kaplan–Meier curve of Ven+O PFS data and fitted parametric distributions extrapolated to 72 months

PFS, progression-free survival

The AIC and BIC scores of the fitted standard parametric distributions are presented in Table 34. Based on both the AIC and BIC, the Gompertz distribution appears to have the best fit, with the gamma, log-logistic, and Weibull distributions having comparable AIC and BIC scores. The generalised gamma has a comparable AIC value but was penalised in the BIC due to its additional parameter and additional complexity.

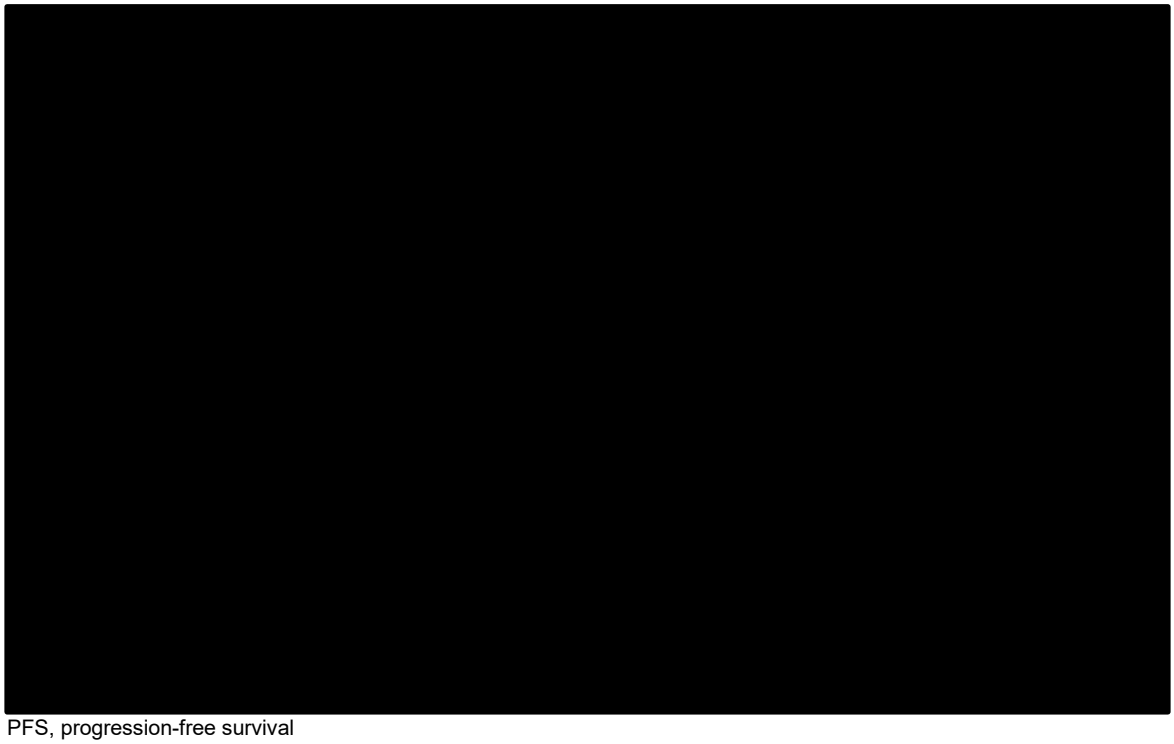
Table 34. AIC and BIC values of standard parametric distributions fit to Ven+O PFS data

Distribution	AIC	BIC
Exponential	776.2	779.3
Gamma	757.9	764.1
Generalised gamma	758.1	767.4
Gompertz	*756.4*	*762.7*
Log-logistic	757.6	763.8
Log-normal	761.6	767.8
Weibull	756.7	763.0

Best-fitting distributions are in italics and highlighted in green.
AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Long-term extrapolations of the fitted distributions are plotted against the observed data in Figure 26 and presented in Table 35.

Figure 26. Kaplan–Meier curve of Ven+O PFS data and fitted parametric distributions extrapolated to a lifetime horizon



PFS, progression-free survival

Table 35. Landmark estimates Ven+O PFS data

Distribution	12 months	24 months	48 months	60 months	120 months
Observed[†] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†] MAIC-adjusted Kaplan–Meier data from CLL13 after median 50.7 months of follow-up
CI, confidence interval; NR, not reached; PFS, progression-free survival

The exponential distribution provides the most optimistic (and implausible) extrapolations due to its underlying assumption that the hazard remains constant over time. In contrast, the Gompertz distribution is much more pessimistic and consistent with the increasing monotonic shape of the observed Kaplan–Meier curve. Further, all distributions except for exponential and log-normal have a 5-year PFS landmark estimate which aligns closely with the estimated 5-year PFS landmark outcome of 68.4% observed in the five-year follow up data of CLL13.[11]

In conclusion, based on the AIC and BIC statistics, the Gompertz distribution appears to have the best fit to the MAIC-weighted Kaplan–Meier data, with the Gamma, log-logistic, and Weibull distributions having comparable and therefore plausible AIC and BIC scores. Indeed, each of these curves provide a good visual fit to the Kaplan–Meier curve, with Gompertz appearing to fit the best. However, engagement with clinical experts when validating the model found that 10-year PFS rates of ~20-30% were noted as being most plausible. As such, the Weibull distribution was selected for modelling PFS outcomes for Ven+O as it results in conservative but clinically appropriate long-term survival estimates which are aligned with the recently published observed outcomes at 5-year follow-up.[11]

3.3.2.5 Time on treatment

In CLL13, patients were treated with Ven+O for twelve 28-day cycles as per the study protocol. Observed time on treatment data for the safety population of CLL13 are used to model Ven+O time on treatment in the analysis. In contrast, the dosing regimen for I+Ven is fifteen 28-day cycles, which is three cycles longer than the dosing regimen of Ven+O; therefore, applying a scaled time-on-treatment curve derived from CLL13 would not be universally appropriate. Instead, time-to-discontinuation (TTD) for I+Ven has been modelled using outcomes from the CAPTIVATE trial, which reported that 92% of patients completed the full 15 cycles of treatment.[24] The following approach is taken to model time on treatment for I+Ven:

- For the first three cycles (ibrutinib lead-in phase), all 159 patients commenced treatment. During this phase, six patients discontinued treatment, leaving 153 patients to proceed to the combination therapy (I+Ven) phase. This results in 100% of patients remaining on treatment in cycles 1–3, dropping to 96.2% (153/159) at the start of cycle 4.

- From cycle 4 onwards, the TTD is modelled as a linear decline, starting at 96.2% and reaching 92.0% (147/159) by cycle 15, consistent with the proportion of patients who completed the full course of treatment. This linear approach assumes an even distribution of discontinuation events during the combination phase, given the absence of precise cycle-specific data.

- By the end of cycle 15, the model reflects the 92% completion rate observed in the CAPTIVATE trial, and 0% thereafter in line with the fixed treatment duration for I+Ven and an assumption of no dosing delays.

3.3.3 Adverse events

The analysis considers the unit costs and resource use associated with grade 3 or 4 adverse reactions (Table 36) that occurred in ≥5% of the patients in the CLL13 trial or were included in TA891 (for which inputs were available). Due to limitations in the availability of adverse event incidence data for I+Ven in a comparable patient population—and the extensive redactions in TA891—AbbVie has had to make

simplifying assumptions when reporting incidence rates. Specifically, it was assumed that the CAPTIVATE and GLOW study populations would exhibit similar adverse event profiles, despite differences in their patient characteristics.

Table 36. Incidence of adverse events of grade 3 or 4 for Ven+O and I+Ven

AE	Ven+O	I+Ven
Anaemia	[redacted]	0.0%
Diarrhoea	[redacted]	3.1%
Infections (UTI)	[redacted]	8.2%
Infusion related reaction	[redacted]	0.0%
Neutropenia	[redacted]	32.7%
Pneumonia	[redacted]	2.0%
Thrombocytopenia	[redacted]	5.7%
Atrial fibrillation	[redacted]	1.3%
Cardiac failure	[redacted]	3.8%
Hypertension	[redacted]	5.7%
Hyponatraemia	[redacted]	5.7%
Tumour lysis syndrome	[redacted]	0.0%

TESAE incidence for Ven+O sourced from CLL13.[13] AE incidence for I+Ven sourced from TA891.[2]
AE, adverse event; TESAE, treatment-emergent serious adverse event; UTI, urinary tract infection

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life studies

In line with NICE requirements and because no utilities were available from the CLL13 trial, an SLR was conducted to identify HRQoL studies for the treatment of first-line CLL. A full description of SLR methodology and outcomes is provided in Appendix F. A brief overview is provided below.

In brief, electronic databases (Embase, Medline and EconLit) were searched from inception to 12 December 2018, and subsequently updated on five occasions, the most recent update being on 06 February 2025. Grey literature searches have continued to be performed to ensure any more recent publications are captured and considered. Publications describing health state utility values and disutility values for fit patients with untreated CLL and no del(17p)/ *TP53* mutation were included.

In total, 32 studies were identified including 6 conference abstracts. The majority of studies collected HRQoL data through questionnaires provided to CLL patients, while 3 studies collected HRQoL scores for CLL health states from the general public. The most common instrument used was EORTC QLQ-C30 (n=16), followed by EQ-5D (n=5) and QLQ-CLL16 (n=5).

The PRISMA diagram is included in Figure 18. Eligible studies are described in Appendix F.

3.4.2 Health-related quality-of-life data from clinical trials

As patient-level HRQoL data was not available from the CLL13 trial, utility analyses could not be performed in a CLL13 population. Therefore, the utilities in the model are based on prior NICE technology appraisals in CLL. Table 37 presents a summary of the utility values that were sourced from previous NICE technology appraisals.

The populations considered in the previous NICE appraisals are broader than the population considered in the CLL13 trial i.e., these populations do not specify whether patients are fit or unfit. In addition, some appraisals consider patients who have been previously treated and those who have different tumour mutation status.

Table 37. Summary of utility values from previous NICE technology appraisals

NICE technology appraisal	Population considered	Progression status	Utility value	Source
TA891	Untreated CLL in adults	Progression free first-line (PF1L)	0.86 (FCR-suitable)	GLOW trial adjusted to FCR-suitable population
		Progression free second line (PF2L)	0.63 (FCR-suitable)	TA689 (derived from Holzner et al, 2004)[139]
		Post-progression (PP)	0.63 (FCR-suitable)	TA689 (derived from Holzner et al, 2004)[139]
TA343	Adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable	Progression free on oral treatment	0.71	Utility elicitation study of general UK public[60]
		Progression free on IV treatment	0.67	
		Progression free on initial therapy with increased hospital visits	0.55	
		Progression free after initial treatment completed	0.82	
		Progressed disease	0.60	
TA561	Chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy	Progression free	0.748	TA487 (later updated to TA796) & TA359
		Progressed disease	0.60	
TA487/TA796	Patients with CLL with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or Patients without a 17p deletion or TP53 mutation, and whose disease has progressed after both	Progression free	0.748	As per ERG and NICE committee recommendation
		Progressed disease	0.60	

	chemo-immunotherapy and a B-cell receptor pathway inhibitor.			
TA359	Untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation, or for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.	Progression free (comparator)	0.75	Study 116 EQ-5D data
		Intervention treatment utility effect	0.07	
		Progression free off treatment	0.80	TA193
		Progressed disease	0.60	
TA193	Relapsed or refractory CLL excluding patients that are refractory to fludarabine or have been previously treated with rituximab	Progression free	0.80	Hancock et al, 2002[132]
		Progressed disease	0.60	
TA174	First line treatment of CLL where FCR is considered appropriate	Progression free	0.80	Hancock et al, 2002[132]
		Progressed disease	0.60	

BR, bendamustine and rituximab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide, rituximab; PF1L, progression-free on first-line treatment; PF2L, progression-free on second-line treatment

3.4.3 Health-related quality-of-life data used in the cost-effectiveness analysis

Given that there is limited publicly available data regarding fit patients, the Hancock et al publication (used in TA174) was chosen to inform the PF and PD utility values used in the model.[132] In previous submissions, the utility value for PFS is lower (e.g., TA561 and TA487) as the population does not solely include fit patients. This analysis assumes that fit patients would have a higher utility than unfit patients. Given that the utility values derived from Hancock et al have been accepted in previous appraisals (TA119, TA174 and TA193), the utility estimate for PFS (0.80) is considered appropriate.[129-132] In addition, the PD utility health state of 0.60 is consistent with all the previous TAs listed and was considered appropriate for using in the model.

The Hancock publication estimated utility values based on HRQoL estimates undertaken by Holzner et al on 81 patients with CLL who had a median age of 68 years.[132,139] The age of this cohort is substantially higher than the mean age within this analysis, necessitating age-dependent utility adjustment using the methodology described in Section 3.4.6.[139,140]

Table 38 presents the base case utility values used in the model.

Table 38. Utility values used in the model

Health state	Utility value	Justification
PFS	0.80	TA174 (Hancock et al, 2002)[130,132]
PD	0.60	TA174 (Hancock et al, 2002)[130,132]

PD, progressed disease; PFS, progression-free survival

3.4.4 Adverse reactions

Adverse event disutility values and duration of adverse events are used to assess the impact of adverse events on QALYs. The disutility value per adverse event is multiplied with its duration to calculate a QALY decrement. The QALY decrement is applied during the first model cycle as all adverse events are assumed to occur

during the initial treatment phase. The parameters for each adverse event have been sourced from previous NICE technology appraisals.[141]

Adverse event disutilities applied within the model are summarised in Table 39.

Table 39. Adverse event QALY decrement inputs

Adverse event	Disutility (positive)	Duration (days)	QALY decrement
Anaemia	0.090	23.21	0.006
Diarrhoea	0.200	3.00	0.002
Infections (UTI)	0.220	14.00	0.008
Infusion related reaction	0.200	3.50	0.002
Neutropenia	0.160	15.09	0.007
Pneumonia	0.195	18.21	0.010
Thrombocytopenia	0.110	23.21	0.007
Atrial fibrillation	0.220	14.00	0.008
Cardiac failure	0.220	14.00	0.008
Hypertension	0.220	14.00	0.008
Hyponatraemia	0.220	14.00	0.008
Tumour lysis syndrome	0.000	23.21	0.000

Source: NICE TA746[141]
QALY, quality adjusted life year; UTI, urinary tract infection

3.4.5 IV treatment disutility

An IV treatment disutility factor of -0.04 is applied for 1L treatments to account for the impact of IV administration on patient HRQoL.[80] The disutility is applied for each cycle during which IV administration occurs and is scaled to reflect the number of IV administrations given per cycle for the specific treatment regimen. This ensures that the frequency and burden of IV treatment are appropriately incorporated into the model.

3.4.6 Age adjustment

In the economic evaluation, QALYs are derived by multiplying the time spent in each health state by the health state utility values associated with that state. To account for age-related deterioration in QoL, the model applies an adjustment factor to all health state utility values, in line with NICE DSU recommendations. This age-related

adjustment factor is derived by calculating the ratio of general population utility at each model timestep to the baseline utility. The factor is applied consistently across all health state utility values to reflect gradual reductions in HRQoL over time.

Depending on the starting age, the age-adjusted utility has been implemented in the model using the methodology provided within the Hernandez-Alava 2023 publication.[140]

3.5 Cost and healthcare resource use identification, measurement and valuation

Section 3.1 and Appendix G describe how relevant cost and healthcare resource data were identified.

In total, 48 studies were identified for resource use and costs outcomes within first-line CLL patients, of which 15 were full text studies and the remaining 33 were conference abstracts. The most reported resource use parameter was outpatient visits, followed by hospitalisations, and general practitioner (GP) visits.

The PRISMA diagram is included in Figure 18. Eligible studies are described in Appendix G.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Drug acquisition costs

Drug acquisition costs for Ven+O and I+Ven are sourced from the British National Formulary (BNF) and provided in Table 40.[93,125,126] The analysis considers the PAS available for venetoclax but does not consider the commercial discounts available for obinutuzumab or ibrutinib as these are confidential and unknown.

Table 40. Acquisition costs of the intervention and comparator technologies

	Drug	Dose per tablet or vial	Units per package	Cost per package	Price per mg
Ven+O	Venetoclax, Tablet	10 mg	14	£59.87	£0.43
		50 mg	7	£149.67	£0.43
		100 mg	112	£4,789.47	£0.43
	Obinutuzumab, IV	1000mg	1	£3,312.00	£3.31
I+Ven	Venetoclax, Tablet	10 mg	14	£59.87	£0.43
		50 mg	7	£149.67	£0.43
		100 mg	112	£4,789.47	£0.43
	Ibrutinib, Tablet, mg	140 mg	28	£1,430.80	£0.37
		280 mg	28	£2,861.60	£0.37
		420 mg	28	£4,292.40	£0.37
		560 mg	28	£5,723.20	£0.37

Source: British National Formulary[142]
IV, intravenous

In line with TA891, this analysis considered minor reductions in dose intensity among treatment options, reflecting observed declines in dose intensity in clinical trials.[2] A dose intensity of [redacted]% is applied for venetoclax in both the Ven+O and I+Ven arms, while a dose intensity of [redacted]% is applied for obinutuzumab in Ven+O based on CLL13, and 94.5% for ibrutinib in I+Ven (consistent 5.7% of patients with dose reductions due to TEAEs in CAPTIVATE), based on the RESONATE-2 value presented in TA891.[2,13]

3.5.1.2 Drug administration costs

Drug administration costs are sourced from NHS reference costs 2023-2024 and are presented in Table 41.[127] It is assumed that there is no cost associated with oral administration, which is in line with previous NICE technology appraisals.[1,81,141]

Table 41. Drug administration costs

Administration route	Cost	Source
IV	£430.24	NHS reference costs code (2023-2024)[127]: SB15Z
Rapid IV	£403.52	NHS reference costs code (2023-2024)[127]: SB12Z + £9.35 dispensing fee
Oral	£0.00	Assumption in line with TA663, TA689 & TA746.[1,81,141]

Source: NHS reference costs code (2023-2024)[127]
IV, intravenous

3.5.1.3 Subsequent treatment use

Patients may proceed onto subsequent treatment upon entry in the PD health state. All patients in the PD health state are eligible for treatment with subsequent therapy. Subsequent treatment costs are included for each treatment arm and are calculated based on three key inputs:

- The treatment regimens received
- The duration patients remain on subsequent treatment
- The timing at which patients switch to the next treatment line

UK clinical experts were consulted to inform the treatment regimens received and the duration of subsequent treatment. From this, the proportion of patients receiving each subsequent treatment was determined (Table 42).[10] As subsequent treatments are modelled as 2L+ in the PD state, rather than 2L specifically, it is assumed that all patients will eventually receive all relevant subsequent treatment options; therefore, the proportion of subsequent treatments is equal between arms. Additionally, clinical feedback via individual consultations has informed that duration of response to 1L treatment drives choice of 2L treatment, rather than the 1L treatment itself.

To inform the timepoint at which patients switch to the next line of treatment, a time-to-next-treatment (TTNT) approach would typically be considered. However, TTNT data were not collected in the CAPTIVATE trial for I+Ven, and applying TTNT data from the MAIC-adjusted Ven+O data is inappropriate given the differences in

treatment durations—patients on Ven+O receive 12 cycles compared with 15 cycles for I+Ven.

Instead, the model tracks changes in state occupancy over successive cycles. In each cycle, the net increase in the occupancy of the PD and death states is used to capture the incidence of patients transitioning to subsequent treatment, while accounting for mortality. The net number of patients transitioning to subsequent treatment in cycle t is calculated as:

$$\Delta ST_t = (PD_t - PD_{t-1}) + (Death_t - Death_{t-1})$$

The change in deaths is added because any patient who progresses to PD and then dies in the same cycle would never contribute to a net rise in the PD count. By adding deaths back in, it captures those who transition from PD to death and avoids underestimating how many actually entered the PD state (i.e. it applies costs to those entering PD as a one-off cost).

The weighted cost of treatment—reflecting the proportions of patients receiving each subsequent regimen—is then applied to ΔST_t. Specifically, it is based on the mean time on subsequent treatment, from which the total number of cycles per subsequent treatment is calculated. Then, for each cycle, the average drug acquisition cost and the average administration cost are determined based on the dosing regimens and cost data. Multiplying the sum of these per-cycle costs by the total number of cycles gives the per patient subsequent treatment cost. The overall cost over the time horizon is determined by summing across the cycle costs:

$$Total\ Subsequent\ Treatment\ Cost = \sum_{t=1}^{T} (L \times \Delta_{ST,t})$$

Where L is the weighted cost per patient.

The proportion of patients receiving each subsequent treatment is presented in Table 42 and the mean time on subsequent treatment is presented in Table 43.

Table 42. Proportion of subsequent treatments following Ven+O and I+Ven

Treatment arm	Acalabrutinib	Ibrutinib	Zanubrutinib	Ven+R
Ven+O	38.54%	0.00%	36.46%	25.00%
I+Ven	38.54%	0.00%	36.46%	25.00%

Source: Clinical input[10]

Table 43. Mean time on subsequent treatments

Subsequent Treatment	Mean time on subsequent treatment (months)	Total number of cycles
Acalabrutinib	39	42
Zanubrutinib	46.8	51
Ven+R	24.4	27

Source: Clinical input[10]

Drug acquisition costs for subsequent treatments are sourced from the BNF and provided in Table 44.

Table 44. Acquisition costs of subsequent treatments

Treatment		Dose per tablet or vial	Units per package	Cost per package	Price per mg
Acalabrutinib, Tablet		100 mg	60	£5,059.00	£0.84
Zanubrutinib, Tablet		80 mg	120	£4,928.65	£0.51
Ven+R	Venetoclax, Tablet	10 mg	14	£59.87	£0.43
		50 mg	7	£149.67	£0.43
		100 mg	112	£4,789.47	£0.43
	Rituximab, IV	500 mg	1	£785.84	£1.57

Source: British National Formulary[142]
IV, intravenous

3.5.2 Intervention and comparators' healthcare resource use and associated costs

The cost per health state considers the healthcare resource use in each cycle (e.g. oncologist appointments, computerised tomography [CT] scans) and additional treatments required, including subsequent treatments post-progression.

The resource use categories and annual frequencies applied in the analysis are sourced from TA891 and outlined in Table 45.[2]

Table 45. Progression free and post-progression resource use frequency

Resource use	Annual pre-progression frequency	Annual post-progression frequency	Per cycle pre-progression frequency	Per cycle post-progression frequency
Full blood count	5.0	7.0	0.39	0.53
Chest X-ray	1.0	1.0	0.07	0.07
Bone marrow exam	0.0	1.0	0.00	0.07
LDH	2.0	3.0	0.16	0.23
Haematologist visit	4.0	5.0	0.30	0.39
CT scan	0.2	2.0	0.02	0.16
Biochemistry test: renal - Urea and electrolytes test (UE test)	4.0	7.0	0.30	0.53
Biochemistry test: liver function test	4.0	7.0	0.30	0.53
Immunoglobulins Blood Test	1.0	1.0	0.07	0.07
Inpatient non-surgical/medical visit	1.0	2.0	0.07	0.16
Full blood transfusion	0.0	1.0	0.39	0.07

Source: NICE TA891[2]
CT, computerised tomography; ECG, electrocardiogram; LDH, lactate dehydrogenase; UE, urea and electrolytes

The most recent National Schedule of NHS Costs (2023-2024) are used to inform the routine care and monitoring costs detailed in Table 46.[127]

Table 46. Routine care and monitoring costs used in the model

Resource use	Cost	Source – NHS reference costs (2023-2024)[127]
Full blood count	£3.10	NHS reference costs code: DAPS05
Chest X-ray	£50.06	NHS reference costs code: RD97Z
Bone marrow exam	£740.05	NHS reference costs code: SA33Z
LDH	£1.53	NHS reference costs code: DAPS04
Haematologist visit	£184.09	NHS reference costs code: Outpatient Attendances Data: 303- Clinical haematology
CT scan	£113.66	NHS reference costs code: Weighted average of RD20A (£113) and RD21A (£116)
Biochemistry test: renal - Urea and electrolytes test (UE test)	£1.53	NHS reference costs code: DAPS04

Biochemistry test: Liver function test	£1.53	NHS reference costs code: DAPS04
Immunoglobulins Blood Test	£3.10	NHS reference costs code: DAPS05
Inpatient non-surgical/medical visit	£561.72	NHS reference costs code: Weighted average of day case, Chronic Lymphocytic Leukaemia, including Related Disorders, SA32A (£408), SA32B (£438), SA32C (£459) and SA32D (£403) = £418.72 PSSRU 2021: Medical consultant hour + qualification costs = £143
Full blood transfusion	£398.79	NHS reference costs code: SA44A

Source: NHS reference costs (2023-2024)[127] and PSSRU 2021[143]
CT, computerised tomography; ECG, electrocardiogram; LDH, lactate dehydrogenase; PSSRU, Personal Social Services Research Unit; UE, urea and electrolytes

3.5.3 Management of tumour lysis syndrome

The costs associated with the management and monitoring of TLS are included in the analysis. The risk of TLS based on tumour burden was determined by clinical experts. Total costs are determined by the TLS risk category and associated management strategies based on clinical input (Table 47).

Table 47. TLS monitoring by level of tumour burden

TLS risk	Low tumour burden	Medium tumour burden	High tumour burden†
TLS management	Oral hydration and allopurinol	Oral or IV hydration and allopurinol	Oral hydration and IV hydration and allopurinol. Rasburicase is considered if baseline uric acid is elevated
TLS monitoring	Outpatient	Outpatient (a percentage is monitored as high risk, e.g. reduced renal function[18])	Ambulatory care/inpatient

† These requirements only apply for the first dose of 20mg and 50mg, rather than the entire five week ramp-up.[18]
IV, intravenous; TLS, tumour lysis syndrome

The proportions of patients in each TLS risk category are derived from Fürstenau et al, Tam et al and clinical input .[24,144] Engagement with UK clinical experts indicated that 20–30% of patients with medium tumour burden typically require high-risk management. The proportion of patients in each TLS risk category was calculated as described in Table 48.[10]

Table 48. Proportions of patients in each TLS risk category after debulking

	TLS risk			
	Low tumour burden	Medium tumour burden	High tumour burden	Missing
Sourced from published literature				
Ven+O	61.0%	21.0%	7.0%	11.0%
I+Ven	29.0%	67.0%	1.0%	4.0%
Normalised to account for patients with missing TLS risk				
Ven+O	68.5%	23.6%	7.9%	-
I+Ven	29.9%	69.1%	1.0%	-
Adjusted to account for 25% of patients with medium tumour burden being treated as high risk				
Ven+O	68.5%	17.7%	13.8%	-
I+Ven	29.9%	51.8%	18.3%	-

Proportions based on Fürstenau et al. 2021 and Tam et al. 2022.[24,144]

Monitoring costs for TLS are applied based on the risk-adjusted distribution of Ven+O and I+Ven, and the unit costs outlined previously. For each risk category, the specific components of TLS prophylaxis (e.g., hydration, lab tests, rasburicase) are included, with inpatient costs applied for high-risk patients as necessary. Unit costs for TLS monitoring have been sourced from NHS reference costs and relevant treatment list prices.[127] The associated one-off monitoring costs for TLS are then calculated based on the proportions of low, medium and high-risk patients (Table 48), and applied in the first model cycle (Table 49).

Table 49. One-off monitoring costs for TLS

Treatment arm	Cost (£)
Ven+O	£477.91
I+Ven	£498.18

TLS, tumour lysis syndrome

3.5.4 Terminal care costs

Costs associated with terminal care are sourced from Round et al. and inflated to a 2024 value.[128,141] A terminal care cost of £9,007.92 is applied as a one-off cost upon entry into the death health state.

3.5.5 Adverse reaction unit costs

The analysis considers the unit costs and resource use associated with grade 3 or 4 adverse reactions that occurred in ≥5% of the patients in the CLL13 trial or were included in TA891 (Table 36).[2]

The total costs of managing adverse events are calculated through summing the multiplication of the AE incidence presented in Section 3.3.3 with the associated costs presented in Table 50. These costs are applied as a one-off expense in the first cycle, ensuring that the management costs for adverse events are incurred only once at the initiation of treatment.

Table 50. Adverse event costs applied within the economic evaluation

AE	Cost (£)	SE	Reference
Anaemia	£387.49	£77.50	NICE TA891
Diarrhoea	£598.88	£119.78	NICE TA891
Infections (UTI)	£1,812.65	£362.53	NICE TA891
Infusion related reaction	£1,934.59	£386.92	NICE TA891
Neutropenia	£1,861.74	£372.35	NICE TA891
Pneumonia	£1,989.50	£397.90	NICE TA891
Thrombocytopenia	£1,996.72	£399.34	NICE TA891
Atrial fibrillation	£1,074.67	£214.93	NICE TA891
Cardiac failure	£2,176.26	£435.25	NICE TA891
Hypertension	£678.83	£135.77	NICE TA891
Hyponatraemia	£1,518.53	£303.71	NICE TA891
Tumour lysis syndrome	£1,458.68 (Ven+O) / £1,523.47 (I+Ven)	£291.74 (Ven+O) / £304.69 (I+Ven)	Calculated using BNF, PSSRU and NHS reference costs

AE management costs and incidence for I+Ven sourced from TA891.[2] AE incidence for Ven+O sourced from CLL13.[13]
AE, adverse event; SE, standard error; UTI, urinary tract infection

3.5.6 Miscellaneous unit costs and resource use

Clinical expert opinion and published good practice guidelines have indicated that patients treated with I+Ven are expected to require cardiac monitoring due to reported ibrutinib cardiotoxicities.[10,23] Patients treated with I+Ven are expected to require five electrocardiograms (ECGs) in the first year of treatment (one at baseline

and every three months thereafter), where each ECG incurs an outpatient cost of £176.40 (NHS reference costs 2023-2024: EY51Z). [23,127] The total cost for cardiac monitoring is applied to the I+Ven arm in the first model cycle. No cardiac monitoring is required for patients treated with Ven+O.[10]

3.6 Severity

It is not anticipated that Ven+O would qualify for a severity modifier in this indication.

3.7 Uncertainty

While every effort has been made to ensure the robustness and accuracy of this analysis, some residual uncertainties remain:

- **Survival outcomes** - While the low numbers of OS events in the CLL13 trial demonstrate the efficacy of Ven+O as a treatment option for patients with untreated CLL, this introduces uncertainty in long-term extrapolations of survival outcomes which become increasingly uncertain and sensitive to the choice of parametric models. In spite of this, AbbVie believe that a partitioned survival remains the most appropriate modelling approach for comparing Ven+O and I+Ven, as explained in Section 3.2.2, and that the application of HRs to determine the efficacy of I+Ven ensures that the relative treatment efficacy is captured.

- **Indirect treatment comparison** - The key uncertainties associated with the MAIC are described in Section 2.10. Nonetheless, AbbVie have presented a cost-effectiveness analysis against I+Ven informed by the outputs from this MAIC.

- **Utility analysis** - Utility analyses could not be performed on CLL13 trial data due to data access limitations and consequently published literature has been used to inform the health state specific utility values in the model. While the use of utility outcomes from CLL13 would be preferred, this does not present a significant limitation as the analysis incorporates utility values accepted in previous appraisals.[130,131]

- **Acquisition costs for obinutuzumab and ibrutinib** - Confidential commercial agreements are in place for both ibrutinib and obinutuzumab. Consequently, this analysis results in cost-effectiveness estimates that may not accurately reflect the costs saved/incurred by NHS England.

3.7.1 Summary of base-case analysis inputs

A summary of all values used in the base case analysis is presented in Table 51.

Table 51. Summary of variables applied in the base case analysis

Variable	Value	Measurement of uncertainty and distribution	Section
Baseline parameters			
Baseline parameters	Table 29	Beta for % male Normal for age	3.2.1
Survival functions			
OS extrapolation for Ven+O	Log-logistic	Distribution-specific	3.3.2.3
PFS extrapolation for Ven+O	Weibull	Distribution-specific	3.3.2.4
Time on treatment	Protocol-driven	NA	3.3.2.5
Hazard ratios	Table 31	Log-normal	3.3.2.1
Clinical parameters			
Adverse event rates	Table 36	Normal	3.3.3
Utilities	Table 38 Table 39	Normal	3.4.3
Costs			
Treatment acquisition	Table 40	Gamma	3.5.1.1
Drug administration	Table 41	Gamma	3.5.1.2
Subsequent treatments	Table 42 Table 43 Table 44	Standardised Beta	3.5.1.3
Healthcare resource use	Table 45 Table 46 Table 47 Table 49	Normal for frequencies Gamma for costs	3.5.2 3.5.3 3.5.4 3.5.6
AE costs	Table 50	Gamma	3.5.5

3.7.2 Assumptions

A summary of the model assumptions is presented in Table 52.

Table 52. Summary of assumptions

Assumption/ limitation	Details	Rationale
Ibrutinib and obinutuzumab acquisition costs	The list prices for ibrutinib and obinutuzumab are applied within the analysis as their confidential discounts are unknown.	The confidential discounts for ibrutinib and obinutuzumab are confidential and unknown.
Half-cycle correction	It is assumed that this approach sufficiently corrects for the fact that drug administrations are given at day one of each cycle, while half-cycle correction assumes this happens half-cycle.	Simplifies calculations while ensuring accurate estimates of costs and QALYs, avoiding overestimation of benefits or costs due to timing discrepancies.
Lifetime horizon	A ~40-year lifetime horizon is used to capture all relevant costs and benefits for a chronic disease like CLL. Model also assumes the cohort does not live past 100 years of age (based on mean baseline age).	Ensures all relevant costs and benefits are captured for a chronic, progressive disease like CLL, where patients may live for decades with or without treatment. The assumption that no patient lives beyond 100 years is consistent with life table data and avoids unnecessary extrapolation beyond plausible limits.
Adverse events	Both costs and QALY losses due to adverse events are incurred in the first model cycle	Adverse events primarily occur during the initial treatment phase; this assumption simplifies implementation while reflecting their early impact.
Efficacy - Time on treatment	Time on treatment was protocol driven where Ven+O was given for 12 cycles. For I+Ven, modelling reflects the CAPTIVATE trial's observed treatment completion patterns.	Observed data ensures accuracy for fixed-duration regimens, while CAPTIVATE data provides the best available evidence for I+Ven due to a lack of direct trial data for Ven+O.
Subsequent treatments	Subsequent treatment costs are applied to all those who enter the PD health state	Patients may receive treatment with subsequent therapy following initial treatment with first-line therapy
Efficacy – I+Ven	PFS for I+Ven is informed by the HR derived from a MAIC.	Reflects the best available evidence comparing I+Ven to Ven+O, given the absence of direct head-to-head trials.
Utilities	Quality of life data from CLL13 trial is unavailable to conduct utility analysis. Therefore, in the absence of this data, literature was used to inform utility values in the model.	Relies on accepted utility values from previous NICE appraisals, ensuring alignment with established standards and available evidence for CLL.
TLS prophylaxis calculations	TLS prophylaxis is modelled based on patient stratification into low, medium, and high-risk categories, with associated costs reflecting the	Simplifies cost calculations by focusing on the highest-risk period (treatment initiation) while accounting

	intensity of monitoring and treatments required (e.g., hydration, allopurinol, rasburicase). TLS prophylaxis costs are applied as a one-off in the first cycle for Ven+O and I+Ven.	for variations in clinical risk and standard monitoring practices.
Probabilistic sensitivity analysis	PSA is conducted assuming independent distributions for most parameters, with uncertainty in survival extrapolations accounted for through sampling.	Allows assessment of parameter uncertainty in the model while maintaining computational feasibility and capturing key sources of variability in cost-effectiveness.

CLL, chronic lymphocytic leukaemia; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PP, post-progression; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TLS, tumour lysis syndrome

3.8 Base-case results

In the base case cost-utility analysis with OS and PFS, the model predicts total discounted costs associated with Ven+O accrued over the modelled time horizon to be £[redacted] (with venetoclax PAS applied), which was lower than costs accrued for I+Ven (incremental: -£[redacted]). As illustrated in Table 53, this cost saving for Ven+O is primarily driven by its lower treatment acquisition costs in the first line compared with I+Ven.

Table 53. Cost-breakdown of Ven+O compared with I+Ven

Outcome	Ven+O	I+Ven	Incremental
Acquisition (1L)	[redacted]	[redacted]	[redacted]
Administration (1L)	[redacted]	[redacted]	[redacted]
TLS Prophylaxis	[redacted]	[redacted]	[redacted]
TRAE	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition	[redacted]	[redacted]	[redacted]
Subsequent treatment administration	[redacted]	[redacted]	[redacted]
Disease management (PFS)	[redacted]	[redacted]	[redacted]
Disease management (PD)	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Analysis performed using venetoclax PAS price and other therapies at list price
1L, first-line; PD, progressed disease; PFS, progression-free survival; TLS, tumour lysis syndrome; TRAE, treatment-related adverse event

The base case cost-utility analysis also considers the life years gained and quality-of-life with each therapy. The outcomes of this analysis are presented in Table 54. The cost-utility analysis predicted mean undiscounted LYs of 21.5 for I+Ven,

correlating to 9.5 discounted QALYs. In comparison, treatment with Ven+O is expected to yield an additional 0.37 discounted QALYs compared with I+Ven. Accordingly, Ven+O presents a dominant treatment option compared with I+Ven by achieving greater health benefits at lower costs, demonstrating that Ven+O can be considered a cost-effective use of NHS resources if established as part of routine commissioning.

Table 54. Base-case results

	Total			Incremental			
Technologies	**Costs (£)**	**LYs**	**QALYs**	**Costs (£)**	**LYs**	**QALYs**	**ICER (£/QALY)**
Ven+O	[redacted]	22.35	9.85	[redacted]	0.83	0.37	Dominant
I+Ven	[redacted]	21.51	9.48	-	-	-	-

Analysis performed using venetoclax PAS price and other therapies at list price
Costs and QALYs discounted; LYs undiscounted
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

A summary of net monetary benefit (NMB) and net health benefit (NHB) outcomes in the base case is provided in Table 55.

Table 55. Incremental net benefit results in the base case analysis

Incremental net monetary benefit (NMB) at £30,000	Incremental net health benefit (NHB) at £30,000
[redacted]	[redacted]

Analysis performed using venetoclax PAS price and other therapies at list price
NHB, net health benefit; NMB, net monetary benefit

Clinical outcomes from the model and disaggregated results of the base-case incremental cost effectiveness analysis are presented in Appendix H.

3.9 Exploring uncertainty

3.9.1 Probabilistic sensitivity analysis

NICE guidelines state the number of iterations should be chosen such that stochastic results converge towards an equilibrium.[89] Therefore, the probabilistic sensitivity analysis (PSA) assesses model uncertainty by varying model parameters simultaneously over 1,000 iterations to estimate the range of possible outcomes.

The distribution chosen for each parameter included in the probabilistic sensitivity analysis PSA (and DSA) is based on the recommendations provided in Briggs et al. (2006).[145] Correlated parameters (such as shares) are modelled through a Dirichlet distribution where applicable.

Where available, the parameters for the distributions in the PSA were derived from the deterministic value and the SE from these deterministic input estimates. In absence of estimates of variance, an SE level of 20% was assumed in line with prior NICE submissions.

The findings are presented by means of the cost-effectiveness acceptability curve and a scatter plot of the incremental cost versus the incremental QALYs. Mean total costs, mean total QALYs, and the mean probabilistic ICER are presented for/versus I+Ven in Table 56.

3.9.1.1 Probabilistic sensitivity analysis results

In the PSA, the model samples values from distributions around the means of input parameters using both the mean and SE of parameters to derive an estimated value using an appropriate distribution.

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for Ven+O compared with I+Ven, arising from 1,000 simulations of the model with all parameters sampled, are presented in Figure 27 and Figure 28.

Figure 27. Cost-effectiveness scatter plot for Ven+O versus I+Ven

Analysis performed using venetoclax PAS price and other therapies at list price
ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years; WTP, willingness to pay

Figure 28. Cost-effectiveness acceptability curve for Ven+O versus I+Ven

Analysis performed using venetoclax PAS price and other therapies at list price
WTP, willingness to pay

The results of the probabilistic sensitivity using the base case settings are presented in Table 56.

Table 56. Probabilistic base-case results

Technologies	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Ven+O	[redacted]	8.32	[redacted]	0.42	Dominant
I+Ven	[redacted]	7.90	-	-	-

Analysis performed using venetoclax PAS price and other therapies at list price
Costs and QALYs discounted; LYs undiscounted
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Based on these analyses, the probability that Ven+O is cost-effective versus I+Ven is [redacted]% at a willingness-to-pay (WTP) threshold of £30,000/QALY gained, strengthening the conclusion that Ven+O provides a cost-effective use of NHS resources compared with I+Ven.

3.9.2 Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) is a form of one-way sensitivity analysis that adjusts each parameter one at a time to assess the impact of uncertainty around individual input parameters on the incremental costs, incremental QALYs and ICER. Where available, lower and upper bounds for the DSA were determined by the SE from input estimates. In absence of estimates of variance, an SE level of 10% was assumed. An overview of the parameters varied within the DSA is presented in Appendix L.

3.9.2.1 Deterministic sensitivity analysis results

Results of the DSA are presented in Figure 29 and demonstrate the impact of specific parameters on ICER estimates.

Figure 29. DSA tornado plot for Ven+O versus I+Ven

Analysis performed using venetoclax PAS price and other therapies at list price

The parameters with the greatest impact on the ICER are the baseline age of patients starting the model and the time horizon considered by the analysis. This is a consequence of a shortened time horizon leading to reduced time for QALY benefits of Ven+O compared with I+Ven to be realised, with minimal impact on costs. The remaining parameters had a minimal impact on ICER estimates.

3.9.3 Scenario analysis

3.9.3.1 Cost-comparison analysis

Whereas a cost-utility analysis considers the incremental costs of an intervention in the context of differences in patient survival and quality-of-life, a cost-comparison assumes comparable efficacy and considers only the difference in treatment costs and disease management between the intervention and comparator(s).

Clinical feedback sought by AbbVie revealed that expert clinicians noted efficacy outcomes between Ven+O and I+Ven appear comparable. Given that clinicians have been using Ven+O in NHS clinical practice for almost five years since its entry into the CDF and I+Ven as part of routine commissioning for over two years, their knowledge and experience of Ven-based regimen's treatment efficacy in real world practice is invaluable.

Section 3.2 of the NICE Methods Guide, states that “a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication.”[146] As such, AbbVie have performed a scenario analysis to compare Ven+O with I+Ven, assuming equal efficacy given the feedback from clinical experts and to address any uncertainty associated with the MAIC results.[10] For simplicity of interpretation, AbbVie have provided a separate straightforward cost-comparison model.

The cost-comparison analysis considered treatment acquisition costs for first-line and subsequent treatments (sourced from the BNF)[93,125,126], treatment administration costs and healthcare resource use (sourced from the NHS Schedule of Costs 2023-2024)[127], terminal care costs (sourced from Round et al.)[128], and costs associated with the management of TLS and AEs (informed by clinical input and TA891).[2,10]

The results of the cost-comparison analysis are presented in Table 57 and demonstrate that the total lifetime cost for Ven+O is £[redacted] compared with £[redacted] for I+Ven, resulting in an incremental cost of -£[redacted]. As in the cost-utility analysis, this cost saving for Ven+O is primarily driven by its lower treatment acquisition costs in the first-line setting compared with I+Ven.

Table 57. Summary of cost-comparison analysis scenario

Outcome	Ven+O	I+Ven	Incremental
Acquisition (1L)	[redacted]	[redacted]	[redacted]
Administration (1L)	[redacted]	[redacted]	[redacted]
TLS Prophylaxis	[redacted]	[redacted]	[redacted]
TRAE	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition	[redacted]	[redacted]	[redacted]
Subsequent treatment administration	[redacted]	[redacted]	[redacted]
Disease management (PFS)	[redacted]	[redacted]	[redacted]
Disease management (PP)	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Analysis performed using venetoclax PAS price and other therapies at list price
Results presented are undiscounted
1L, first-line; PFS, progression-free survival; PP, post-progression; TLS, tumour lysis syndrome; TRAE, treatment-related adverse event

3.10 Subgroup analysis

Per the final scope, there are no subgroups for this submission which should be considered separately to the main population.

3.11 Benefits not captured in the QALY calculation

As detailed previously, clinical feedback has indicated that that Ven+O acts as the standard of care for first-line treatment of CLL. The key benefit of Ven+O compared with I+Ven is the cost saving it provides to the healthcare system. These savings may be repurposed to facilitate wider care provision and developments to service infrastructure.

Access to obinutuzumab for disease management

Under current guidelines, first-line treatment with Ven+O treatment represents the only opportunity to use obinutuzumab for this population, taking advantage of its efficacy as the most effective anti-CD20 therapy indicated in CLL.[9,147] There is significant unquantifiable benefit in clinicians having a choice of which targeted therapy to use in the first line setting, particularly because without Ven+O as a first-

line option, obinutuzumab will not be available for this population at any later stage in their treatment pathway.

Alternative to ibrutinib as a first-line therapy with reduced HCRU

As described in Section 1.3.6, treatment with I+Ven is associated with a number of moderate-to-severe AEs, including bruising, arthralgia, nausea/vomiting and diarrhoea.[24,25] Of particular note is the association with CV side effects, which are a deciding factor for clinicians when administering I+Ven.[91,92] Good Practice Guidelines published by the BSH recommend monitoring the cardiac function in patients receiving I+Ven through ECGs prior to, and during ibrutinib treatment.[23] Discontinuation is recommended in patients with more severe cardiac failure or arrhythmia, and temporary or permanent treatment cessation in patients with new or worsening cardiac failure or arrhythmias.[93] This reduced requirement for serial cardiac monitoring compared with I+Ven is expected to provide a meaningful reduction in healthcare resource use on patients, carers and overall healthcare system capacity, as well as ensuring patients have a choice of targeted treatments. While this reduction in healthcare resource use is considered within the QALY calculation from a financial perspective, the benefits of increased system capacity and reduced expenditure for first-line treatment of patients with CLL cannot fully be captured by traditional cost-effectiveness analyses.

In summary, Ven+O provides an effective, targeted first-line treatment for the target population of this appraisal.[10]

3.12 Validation

The model structure is identical to that presented to NICE for TA663, which was considered by the EAG and Committee to be suitable for decision-making.[1] Where required, key model assumptions are based on feedback from clinical experts with experience in treating patients with CLL and health economic experts with experience supporting oncology submissions.

3.12.1 Clinical validation

In order to obtain clinical opinion in advance of this submission, AbbVie organised consultations with seven consultant haematologists based around the UK and who are experienced in treating patients with CLL. These discussions included validation of the clinical care pathway for patients receiving first-line therapy, use of subsequent therapies, management of TLS, and cardiac monitoring in patients treated with I+Ven. The outputs of these discussions were implemented within the company's base case analysis.

3.12.2 Technical validation

In alignment with best practice, validation of the economic model structure was conducted prior to submission by a health economist independent of the project team and a second external health economics expert with particular expertise in HTA and decision making. These validation processes aimed to ensure that a high degree of transparency was maintained throughout the model and so adaptations were carried out where necessary to ensure the validity of assumptions made and methodologies undertaken within the cost-effectiveness model.

3.12.3 Verification of cost-effectiveness analysis

Verification was undertaken to assess and review the following:

- Assess the major spreadsheet calculations and Visual Basic for Applications (VBA) subroutines for accuracy and ensure they operate as intended.
- Review of model equations and parameters against their source, to ensure that there are no transcription errors.
- Review of input derivation and implementation, to ensure that these were derived and implemented correctly.
- Sensitivity and extreme value analysis: the model has been run under a variety of scenarios, under simplified assumptions and utilising extreme model inputs to ensure model output is internally consistent and that the direction and magnitude of model outputs behave as expected.

- Internal validation was undertaken on clinical data used to inform model inputs and methodologies to assess the appropriate interaction of the model's components, within the context of their ability to accurately reproduce observed outcomes.

3.13 Interpretation and conclusions of economic evidence

3.13.1 Strengths and limitations of the analysis

Model structure

The model adopts a PSM structure to capture the clinical benefits of Ven+O in patients with CLL. This is aligned with prior NICE technology appraisals (including TA663) and has the advantage of directly incorporating observed survival data from CLL13, reducing the uncertainty that can arise when estimating separate transition probabilities in a state-transition model, as detailed in Section 3.2.2.

CLL13

As described in Section 2.5, the CLL13 trial was mostly conducted in Europe, and clinical experts considered the trial generalisable to UK clinical practice.[10] Further, clinical experts supported the identification of matching variables considered to be TEMs or PVs within the MAIC. Therefore, both the survival data from CLL13 and outcomes of the MAIC, including the conclusion of clinical similarity for Ven+O and I+Ven, can be considered relevant to UK clinical practice.

As detailed in NICE DSU TSD14,[124] the validity of the PHA was tested to determine whether this approach could be used to model outcomes for I+Ven. Based on the outputs of the MAIC and feedback from clinical experts that Ven+O and I+Ven can be considered clinically comparable in terms of efficacy outcomes, the base case analysis models the outcomes for I+Ven by applying a HR, reducing the number of estimated degrees of freedom compared with using independent models which may lead to outcomes unsuitable for decision-making.

3.13.2 Cost-utility analysis

In the cost-utility analysis, Ven+O was associated with 0.37 incremental QALYs and -£[redacted] incremental costs compared with I+Ven. As such, Ven+O returned a **dominant** ICER, demonstrating that Ven+O was comfortably below the threshold that NICE usually considers to be acceptable use of NHS resources. This **cost saving** for Ven+O is primarily driven by its lower treatment acquisition costs in the first-line setting compared with I+Ven.

The outcomes of this analysis demonstrate that although patients treated with Ven+O must attend appointments for IV infusion of obinutuzumab, this patient and system burden is offset by the lower acquisition costs of obinutuzumab compared with ibrutinib, and reduced requirement for cardiac monitoring in a hospital setting for Ven+O compared with I+Ven. Further, the comparable tolerability profiles of Ven+O and I+Ven emphasises the limited impact on overall resource use for Ven+O if established as part of routine commissioning.

The model was robust to parameter uncertainty with the mean PSA results lying close to the deterministic results for the base-case.

3.13.3 Cost-comparison scenario analysis

In the cost-comparison scenario, Ven+O incurs lower total costs (£[redacted]) compared with I+Ven (£[redacted]) and results in a **cost saving** of £[redacted] when the venetoclax PAS is considered. As in the base case analysis, this cost saving is predominantly driven by its lower treatment acquisition costs in the first-line setting. Therefore, Ven+O presents an acceptable use of NHS resources.

3.13.4 Conclusion

The results of the MAIC (Section 2.10) demonstrate that Ven+O is more efficacious than I+Ven, with the coinciding cost-effectiveness results showing dominance of Ven+O over I+Ven. However, given the well-valued clinical feedback noting that Ven+O and I+Ven outcomes appear comparable, a cost-comparison scenario has been presented to support this feedback. While patients treated with Ven+O must attend appointments for IV infusion of obinutuzumab, both the patient and system

burdens are offset by the lower acquisition costs of obinutuzumab compared with ibrutinib and reduced requirement for cardiac monitoring in a hospital setting for Ven+O compared with I+Ven. Therefore, Ven+O is a cost-saving treatment for fit patients with untreated CLL and no del(17p)/*TP53* mutation.

Routine commissioning for Ven+O will ensure that both patients and clinicians have the choice to individualise treatment, offering the only opportunity for patients to access obinutuzumab in the fit 1L no del(17p)/*TP53* mutation treatment pathway. Ven+O has become a primary choice in treating this population over the last 4+ years since it was made available via the CDF, offering an alternative and efficacious targeted treatment.

4 References

1. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [TA663]. 2020; Updated 09/12/2020. Available from: https://www.nice.org.uk/guidance/ta663/chapter/3-Committee-discussion [accessed 05/02/2024].
2. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [TA891]. 2023; Updated 31/05/2023. Available from: https://www.nice.org.uk/guidance/ta891/chapter/1-Recommendations [accessed 10/07/2025].
3. Kikushige Y. Pathogenesis of chronic lymphocytic leukemia and the development of novel therapeutic strategies. J Clin Exp Hematop. 2020;60(4):146-58.
4. Waweru C, Kaur S, Sharma S, et al. Health-related quality of life and economic burden of chronic lymphocytic leukemia in the era of novel targeted agents. Current Medical Research and Opinion. 2020;36(9):1481-95.
5. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. Br J Haematol. 2007;139(2):255-64.
6. American Cancer Society. Signs and symptoms of chronic lymphocytic leukemia. 2018; Updated 10/05/2018. Available from: https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html [accessed 30/01/2024].
7. Price M, Ravelo A, Sae-Hau M, et al. Patient-reported disease burden in chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and follicular lymphoma: Results from a national patient advocacy survey. Journal of Clinical Oncology. 2019;37(15_suppl):e18198-e.
8. Lien PW, Jawaid D, Emechebe N, et al. EE124 Real-World Mental Health Burden in Patients With Chronic Lymphocytic Leukemia. Value in Health. 2024;27(6):S80.
9. Walewska R, Parry-Jones N, Eyre TA, et al. Guideline for the treatment of chronic lymphocytic leukaemia. Br J Haematol. 2022;197(5):544-57.
10. AbbVie UK. Engagement with UK clinical experts (2022-2025).
11. Fürstenau M, Robrecht S, Tresckow Jv, et al. THE TRIPLE COMBINATION OF VENETOCLAX-IBRUTINIB-OBINUTUZUMAB PROLONGS PROGRESSION-FREE SURVIVAL COMPARED TO VENETOCLAX-CD20-ANTIBODY COMBINATIONS AND CHEMOIMMUNOTHERAPY IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA: FINAL ANALYSIS FROM THE PHASE 3 GAIA/CLL13 TRIAL. 2025. Available at: https://library.ehaweb.org/eha/2025/eha2025-congress/4159268/moritz.frstenau.the.triple.combination.of.venetoclax-ibrutinib-obinutuzumab [Accessed 05/06/2025].
12. National Disease Registration Service. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia in people without del(17p)/TP53 mutation and for whom FCR and BR are suitable – data review. 2023.

13. Deutsche Studiengruppe. CLL13 (GAIA) Priority 1 analyses for AbbVie (Jan 2023 data cut-off) v1.0. 2023.
14. Eichhorst B, Ghia P, Niemann C, et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Annals of Oncology. 2024;35(9):762-8.
15. British Society for Haematology. Guideline for the treatment of chronic lymphocytic leukaemia [in review, expected 2025]. 2025.
16. Mihalyova J, Jelinek T, Growkova K, et al. Venetoclax: A new wave in hematooncology. Experimental Hematology. 2018;61:10-25.
17. Rafiq S, Butchar JP, Cheney C, et al. Comparative Assessment of Clinically Utilized CD20-Directed Antibodies in Chronic Lymphocytic Leukemia Cells Reveals Divergent NK Cell, Monocyte, and Macrophage Properties. The Journal of Immunology. 2013;190(6):2702-11.
18. MHRA. Venclyxto 10 mg film-coated tablets - Summary of Product Characteristics. 2025.
19. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. Blood. 2012;120(6):1175-84.
20. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence#heading-Zero [accessed 07/02/2024].
21. CLL Support. About CLL, SLL and MBL. Available from: https://cllsupport.org.uk/information-support/about-cll/
22. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) mortality statistics. 2022. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/mortality.
23. Tang CPS, Lip GY, McCormack T, et al. Management of cardiovascular complications of Bruton tyrosine kinase inhibitors. British Journal of Haematology. 2022;196(1):70-8.
24. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood, The Journal of the American Society of Hematology. 2022;139(22):3278-89.
25. Kater AP, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. NEJM evidence. 2022;1(7):EVIDoa2200006.
26. Fürstenau M, Kater AP, Robrecht S, et al. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2024;25(6):744-59.
27. Eichhorst B, Niemann Carsten U, Kater Arnon P, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2023;388(19):1739-54.
28. Al-Sawaf O, Robrecht S, Zhang C, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. Blood. 2024;144(18):1924-35.

29. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2021;32(1):23-33.
30. clinicaltrials.gov. Ibrutinib Monotherapy Versus Fixed-duration Venetoclax Plus Obinutuzumab Versus Fixed-duration Ibrutinib Plus Venetoclax in Patients with Previously Untreated Chronic Lymphocytic Leukaemia (CLL) (CLL17). 2025. Available at: https://clinicaltrials.gov/study/NCT04608318 [Accessed 07/07/2025].
31. Roeker LE, Woyach JA, Cheah CY, et al. Fixed-duration pirtobrutinib plus venetoclax with or without rituximab in relapsed/refractory CLL: the phase 1b BRUIN trial. Blood. 2024;144(13):1374-86.
32. Shadman M, Kater AP, Woyach JA, et al. CELESTIAL-TNCLL: An ongoing, open-label, multiregional, phase 3 study of sonrotoclax (BGB-11417) + zanubrutinib vs venetoclax + obinutuzumab for treatment-naïve (TN) CLL. Journal of Clinical Oncology. 2024;42(16_suppl):TPS7087-TPS.
33. IQVIA. Chronic Lymphocytic Leukaemia (CLL) Therapy Tracker Summary Report. 2024.
34. National Institute for Health and Care Excellence. Consultation comments on the draft remit and draft scope for the technology appraisal of venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (Managed access partial review of TA663) [ID6291]. 2025. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta11495/documents [Accessed 08/07/2025].
35. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions. New England Journal of Medicine. 2014;370(12):1101-10.
36. de Weerdt I, Hofland T, de Boer R, et al. Distinct immune composition in lymph node and peripheral blood of CLL patients is reshaped during venetoclax treatment. Blood advances. 2019;3(17):2642-52.
37. van Attekum MH, Eldering E, Kater AP. Chronic lymphocytic leukemia cells are active participants in microenvironmental cross-talk. haematologica. 2017;102(9):1469.
38. Ten Hacken E, Burger JA. Microenvironment interactions and B-cell receptor signaling in Chronic Lymphocytic Leukemia: Implications for disease pathogenesis and treatment. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2016;1863(3):401-13.
39. Hanahan D, Weinberg Robert A. Hallmarks of Cancer: The Next Generation. Cell. 2011;144(5):646-74.
40. Pavlasova G, Mraz M. The regulation and function of CD20: an “enigma” of B-cell biology and targeted therapy. haematologica. 2020;105(6):1494.
41. Léveillé C, Al-Daccak R, Mourad W. CD20 is physically and functionally coupled to MHC class II and CD40 on human B cell lines. European journal of immunology. 1999;29(1):65-74.
42. Ghia P, Ferreri AJ, Caligaris-Cappio F. Chronic lymphocytic leukemia. Critical reviews in oncology/hematology. 2007;64(3):234-46.

43. Yao Y, Lin X, Li F, et al. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. Biomed Eng Online. 2022;21(1):4.
44. National Cancer Institute. Cancer Stat Facts: Leukaemia - Chronic Lymphocytic Leukemia (CLL). Available from: https://seer.cancer.gov/statfacts/html/clyl.html [accessed 29/01/2024].
45. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. American Journal of Hematology. 2017;92(9):946-65.
46. Wu S-J, Huang S-Y, Lin C-T, et al. The incidence of chronic lymphocytic leukemia in Taiwan, 1986-2005: a distinct increasing trend with birth-cohort effect. Blood, The Journal of the American Society of Hematology. 2010;116(22):4430-5.
47. Lymphoma Coalition. Chronic Lymphocytic Leukaemia: Global Subtype Report. 2017.
48. Cancer Research UK. Risks and causes of chronic lymphocytic leukaemia (CLL). 2024. Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/risks-causes [Accessed
49. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-60.
50. Gaidano G, Rossi D. The mutational landscape of chronic lymphocytic leukemia and its impact on prognosis and treatment. Hematology 2014, the American Society of Hematology Education Program Book. 2017;2017(1):329-37.
51. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010;28(29):4473-9.
52. Rossi D, Gaidano G. The clinical implications of gene mutations in chronic lymphocytic leukaemia. British Journal of Cancer. 2016;114(8):849-54.
53. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. Lancet. 2018;391(10129):1524-37.
54. Muchtar E, Kay NE, Parikh SA. Early intervention in asymptomatic chronic lymphocytic leukemia. Clin Adv Hematol Oncol. 2021;19(2):92-103.
55. Devi A, Thielemans L, Ladikou EE, et al. Lymphocytosis and chronic lymphocytic leukaemia: investigation and management. Clinical Medicine. 2022;22(3):225-9.
56. MacMillan Cancer Support. Chronic lymphocytic leukaemia. 2022. Available from: https://www.macmillan.org.uk/cancer-information-and-support/leukaemia/chronic-lymphocytic-leukaemia-cll [accessed 29/01/2024].
57. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. Nat Rev Dis Primers. 2017;3:16096.
58. Levin TT, Li Y, Riskind J, et al. Depression, anxiety and quality of life in a chronic lymphocytic leukemia cohort. Gen Hosp Psychiatry. 2007;29(3):251-6.
59. Wright KB, Bylund CL, Bagautdinova D, et al. Caring for an individual with chronic lymphocytic leukemia (CLL): understanding family caregivers'

perceptions of social support, caregiver burden, and unmet support needs. Journal of Cancer Education. 2024;39(2):180-5.
60. Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leukemia & lymphoma. 2015;56(5):1320-6.
61. Lafeuille M-H, Vekeman F, Wang S-T, et al. Lifetime costs to Medicare of providing care to patients with chronic lymphocytic leukemia. Leukemia & lymphoma. 2012;53(6):1146-54.
62. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia, Gale RP, Chapel HM, et al. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. The New England journal of medicine. 1988;319(14):902-7.
63. Spadaro G, Pecoraro A, De Renzo A, et al. Intravenous versus subcutaneous immunoglobulin replacement in secondary hypogammaglobulinemia. Clinical Immunology. 2016;166:103-4.
64. Schrijvers D, De Samblanx H, Roila F. Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use. Annals of Oncology. 2010;21:v244-v7.
65. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. British Journal of Haematology. 2018;182(3):344-59.
66. Hoechstetter MA, and Wendtner C-M. Clinical trials in early-stage CLL: what has been learned and what's next? Leukemia & lymphoma. 2025;66(3):378-88.
67. Langerbeins P, Zhang C, Robrecht S, et al. The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia. Blood, The Journal of the American Society of Hematology. 2022;139(2):177-87.
68. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021;96(12):1679-705.
69. Kovacs G, Robrecht S, Fink AM, et al. Minimal Residual Disease Assessment Improves Prediction of Outcome in Patients With Chronic Lymphocytic Leukemia (CLL) Who Achieve Partial Response: Comprehensive Analysis of Two Phase III Studies of the German CLL Study Group. J Clin Oncol. 2016;34(31):3758-65.
70. Böttcher S, Ritgen M, Fischer K, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. J Clin Oncol. 2012;30(9):980-8.
71. Davids MS, Lin KH, Mohamed AI, et al. Measurable residual disease-driven treatment in first-line chronic lymphocytic leukaemia. Br J Haematol. 2025;206(1):33-43.
72. Stumpf J, Al-Sawaf O. Chronic Lymphocytic Leukemia: Time-Limited Therapy in the First-Line Setting and Role of Minimal Residual Disease. Current Oncology Reports. 2024;26(2):136-46.
73. Rhodes JM, Lopez CA, Barrientos JC. MRD-directed therapy in CLL: ready for prime time? Hematology. 2023;2023(1):413-20.

74. Villavicencio A, Solans M, Zacarías-Pons L, et al. Comorbidities at diagnosis, survival, and cause of death in patients with chronic lymphocytic leukemia: a population-based study. International journal of environmental research and public health. 2021;18(2):701.
75. Odetola O, Ma S. Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL). Current Hematologic Malignancy Reports. 2023;18(5):130-43.
76. Bennett R, Seymour JF. Update on the management of relapsed/refractory chronic lymphocytic leukemia. Blood Cancer J. 2024;14(1):33.
77. De Nigris E, Yang X, Zanardo E, et al. Healthcare resource utilization and costs of chronic lymphocytic leukemia/small lymphocytic lymphoma patients who relapse or are refractory to ibrutinib. Future Oncology. 2024;20(35):2723-35.
78. Steingrímsson V, Lund SH, Dickman PW, et al. Survival, causes of death, and the prognostic role of comorbidities in chronic lymphocytic leukemia in the pre-ibrutinib era: A population-based study. Eur J Haematol. 2022;108(2):145-53.
79. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia [TA931]. 2023; Updated 22/11/2023. Available from: https://www.nice.org.uk/guidance/ta931/chapter/1-Recommendations [accessed 07/02/2024].
80. National Institute for Health and Care Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia [TA343]. 2015; Updated 02/06/2015. Available from: https://www.nice.org.uk/guidance/ta343/chapter/1-Guidance [accessed 07/02/2024].
81. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia [TA689]. 2021; Updated 21/04/2021. Available from: https://www.nice.org.uk/guidance/ta689/chapter/1-Recommendations [accessed 06/02/2024].
82. National Institute for Health and Care Excellence. Idelalisib for treating chronic lymphocytic leukaemia. 2015. Available at: https://www.nice.org.uk/guidance/ta359 [Accessed 07/02/2024].
83. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation [TA429]. 2017. Available at: https://www.nice.org.uk/guidance/ta429 [Accessed 11/05/2025].
84. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia [TA796]. 2022. Available at: https://www.nice.org.uk/guidance/ta796 [Accessed 11/05/2025].
85. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia [TA561]. 2019. Available at: https://www.nice.org.uk/guidance/ta561 [Accessed 11/05/2025].
86. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005;23(18):4079-88.

87. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008;112(4):975-80.
88. Kósa F, Nečasová T, Špaček M, et al. Secondary malignancies and survival of FCR-treated patients with chronic lymphocytic leukemia in Central Europe. Cancer Med. 2023;12(2):1961-71.
89. National Institute for Health and Care Excellence. NICE Health Technology Evaluations: The Manual [PMG36]. 2022. Available at: https://www.nice.org.uk/process/pmg36 [Accessed 28/01/2025].
90. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. New England Journal of Medicine. 2019;380(22):2095-103.
91. Quartermaine C, Ghazi SM, Yasin A, et al. Cardiovascular Toxicities of BTK Inhibitors in Chronic Lymphocytic Leukemia: JACC: CardioOncology State-of-the-Art Review. JACC: CardioOncology. 2023;5(5):570-90.
92. MHRA. Imbruvica 280 mg film-coated tablets - Summary of Product Characteristics. 2024.
93. British National Formulary. Ibrutinib [Specialist drug] - Medicinal Forms. 2024.
94. Tang CPS, Lip GYH, McCormack T, et al. Management of cardiovascular complications of bruton tyrosine kinase inhibitors. British Journal of Haematology. 2022;196(1):70-8.
95. University of Cologne. Trial Protocol: A Phase 3 Multicenter, Randomized, Prospective, Open-Label Trial of Standard Chemoimmunotherapy (FCR/BR) Versus Rituximab Plus Venetoclax (RVE) Versus Obinutuzumab (GA101) Plus Venetoclax (GVe) Versus Obinutuzumab (GA101) Plus Ibrutinib Plus Venetoclax (GIVe) in Fit Patients With Previously Untreated Chronic Lymphocytic Leukaemia (CLL) Without Del(17p) or TP53 Mutation. 2021.
96. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
97. MHRA. Gazyvaro 1,000 mg concentrate for solution for infusion - Summary of Product Characteristics. 2023. Available at: https://mhraproducts4853.blob.core.windows.net/docs/de8a2c57a8e71dd02f7fc8c84dd418279cc00e4e [Accessed 03/04/2025].
98. Lehmacher W, Kieser M, Hothorn L. Sequential and multiple testing for dose-response analysis. Drug Information Journal. 2000;34(2):591-7.
99. Deutsche Studiengruppe. CLL13 STATISTICAL ANALYSIS PLAN –PRIMARY ENDPOINTS ANALYSIS. 2021.
100. Rios-Olais FA, McGary AK, Tsang M, et al. Measurable residual disease and clinical outcomes in chronic lymphocytic leukemia: a systematic review and meta-analysis. JAMA oncology. 2024.
101. Simon F, Ligtvoet R, Robrecht S, et al. End point surrogacy in first-line chronic lymphocytic leukemia. Journal of Clinical Oncology. 2024:JCO. 24.01192.
102. Fürstenau M, Rotbain EC, Eurelings L, et al. Patient-Reported Quality of Life Outcomes with Venetoclax-Based First-Line Combinations in CLL: An Analysis from the Phase 3 GAIA/CLL13 Trial. 66th ASH annual meeting, 2024, San Diego, Publication Number: 3238. 2024.

103. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value in Health. 2012;15(6):940-7.
104. Phillippo D, Ades T, Dias S, et al. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
105. Munir T, Cairns DA, Bloor A, et al. Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease. N Engl J Med. 2024;390(4):326-37.
106. Munir T, Girvan S, Cairns DA, et al. Measurable Residual Disease-Guided Therapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2025.
107. Wierda W, Barr P, Allan J, et al. FINAL ANALYSIS OF FIXED-DURATION IBRUTINIB + VENETOCLAX FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL) IN THE PHASE 2 CAPTIVATE STUDY. 2025. Available at: https://library.ehaweb.org/eha/2025/eha2025-congress/4159233/paolo.ghia.final.analysis.of.fixed-duration.ibrutinib.2B.venetoclax.for.chronic.html?f= [Accessed 09/07/2025].
108. Wierda WG, Jacobs R, Barr PM, et al. Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Up to 5.5 years of follow-up in the phase 2 CAPTIVATE study. Journal of Clinical Oncology. 2024;42(16_suppl):7009-.
109. Clinicaltrials.gov. A Study of the Combination of Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab for the First-line Treatment of Participants With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) (GLOW). 2025. Available at: https://www.clinicaltrials.gov/study/NCT03462719 [Accessed 10/07/2025].
110. Clinicaltrials.gov. A Study of Zanubrutinib (BGB-3111) Versus Ibrutinib in Participants With Relapsed/Refractory Chronic Lymphocytic Leukemia (ALPINE). 2025. Available at: https://clinicaltrials.gov/study/NCT03734016 [Accessed 10/07/2025].
111. Clinicaltrials.gov. Acalabrutinib, Venetoclax, and Obinutuzumab for Initial Therapy of CLL (AVO). 2024. Available at: https://www.clinicaltrials.gov/study/NCT03580928 [Accessed 10/07/2025].
112. Clinicaltrials.gov. Open-label Phase 3 BTK Inhibitor Ibrutinib vs Chlorambucil Patients 65 Years or Older With Treatment-naive CLL or SLL (RESONATE-2). 2025. Available at: https://clinicaltrials.gov/study/NCT01722487 [Accessed 10/07/2025].
113. Macabeo B, Quenéchdu A, Aballéa S, et al. Methods for Indirect Treatment Comparison: Results from a Systematic Literature Review. J Mark Access Health Policy. 2024;12(2):58-80.
114. CADTH. Clinical Report - Venetoclax (VENCLEXTA) (AbbVie Corporation) Indication: In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are fludarabine ineligible. 2020. Available from: https://www.cadth.ca/sites/default/files/pcodr/Reviews2020/10212Venetoclax

ObinutuzumabCLL_fnCGR_REDACT_EC_Post17Nov2020_final.pdf [accessed 31 May].
115. Davids MS, Waweru C, Le Nouveau P, et al. Comparative Efficacy of Acalabrutinib in Frontline Treatment of Chronic Lymphocytic Leukemia: A Systematic Review and Network Meta-analysis. Clinical Therapeutics. 2020;42(10):1955-74.e15.
116. Owen C, Banerji V, Johnson N, et al. Canadian evidence-based guideline for frontline treatment of chronic lymphocytic leukemia: 2022 update. Leukemia Research. 2023;125:107016.
117. Hosmer Jr DW, Lemeshow S, May S. Applied survival analysis: regression modeling of time-to-event data: John Wiley & Sons; 2011.
118. Ishak KJ, Chandler, C., Liu, F.F., Klijn, S. . Can Low Effective Sample Size in Matching-Adjusted Indirect Comparisons (MAICS) Lead to Bias? Findings From a Simulation Study. ISPOR; November 17-20; Barcelona, Spain: ISPOR Europe; 2024.
119. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
120. Malcikova J, Pavlova S, Baliakas P, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia—2024 update. Leukemia. 2024:1-14.
121. Griffin R, Wiedmeier-Nutor JE, Parikh SA, et al. Differential prognosis of single and multiple TP53 abnormalities in high-count MBL and untreated CLL. Blood Adv. 2023;7(13):3169-79.
122. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA,. Cochrane Handbook for Systematic Reviews of Interventions 2022; Updated February 2022. Available from: www.training.cochrane.org/handbook.
123. Sharman JP, Laurenti L, Ferrant E, et al. CRISTALLO: Results from a Phase III Trial of Venetoclax-Obinutuzumab Versus Fludarabine, Cyclophosphamide and Rituximab or Bendamustine-Rituximab in Patients with Untreated Chronic Lymphocytic Leukemia without Del (17p) or TP53 Mutations. Blood. 2024;144:3237.
124. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.
125. British National Formulary. Venetoclax [Specialist drug] - Medicinal Forms. 2024.
126. British National Formulary. Obinutuzumab [Specialist drug] - Medicinal Forms. 2024.
127. NHS England. National Cost Collection Data 2023/24: National Schedule of NHS costs. 2025. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Accessed 03/04/2025].
128. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.
129. National Institute for Health and Care Excellence. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia [TA119]. 2007. Available at: https://www.nice.org.uk/guidance/ta119 [Accessed 09/06/2025].

130. National Institute for Health and Care Excellence. Rituximab for the first-line treatment of chronic lymphocytic leukaemia [TA174]. 2009; Updated 22/07/2009. Available from: https://www.nice.org.uk/guidance/ta174/chapter/1-Recommendations [accessed 06/02/2024].
131. National Institute for Health and Care Excellence. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia [TA193]. 2010. Available at: https://www.nice.org.uk/guidance/ta193 [Accessed 29/05/2025].
132. Sarah Hancock BW, Chris Hyde Fludarabine as first line therapy for chronic lymphocytic leukaemia. A West Midlands Health Technology Assessment Collaboration report Department of Public Health and Epidemiology, Univeristy of Birmingham 2002 Contract No.: 42.
133. Centre for Reviews and Dissemination. Systematic Reviews. CRD's guidance for for undertaking reviews in health care. 2009.
134. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
135. Scarfò L, Heltai S, Albi E, et al. Minimal residual disease-driven treatment intensification with sequential addition of ibrutinib to venetoclax in R/R CLL. Blood. 2022;140(22):2348-57.
136. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. Sociological Methods & Research. 2004;33(2):261-304.
137. Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis. 2020.
138. Office for National Statistics. National life tables: UK. 2025. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Accessed 03/04/2025].
139. Holzner B, Kemmler G, Kopp M, et al. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. Eur J Haematol. 2004;72(6):381-9.
140. Hernández-Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022.
141. National Institute for Health and Care Excellence. Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer [TA746]. 2021. Available at: https://www.nice.org.uk/guidance/ta746 [Accessed 17/01/2025].
142. British National Formulary. 2025.
143. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021. 2021. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/ [Accessed 21/05/2025].
144. Fürstenau M, Robrecht S, Zhang C, et al. Comparison of Tumor Lysis Syndrome (TLS) Risk Reduction and Incidence in Different Venetoclax-Based Combinations within the Randomized Phase 3 GAIA (CLL13) Trial. Blood. 2021;138:2639.
145. Briggs. A SM, Claxton. K,. Decision Modelling for Health Economic Evaluation: University of Oxford; 2006.

146. National Institute for Health and Care Excellence. Cost comparison - Addendum to the Guide to the methods of technology appraisal. 2017. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf [Accessed 28/05/2025].
147. Sharman JP, Andorsky D, Melear JM, et al. Debulking eliminates need for hospitalization prior to initiating frontline venetoclax therapy in previously untreated CLL patients: a phase 3b study. Blood. 2019;134:3042.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA part review of TA663) [ID6291]

Summary of Information for Patients (SIP)

July 2025

File name	Version	Contains confidential information	Date
ID6291_Ven+O_CLL_ SIP_[NoCON]	Final	No	22 July 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Venetoclax + Obinutuzumab (Venclyxto® + Gazyvaro®), referred to as Ven+O in this document and the Company Submission

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Ven+O will be used by previously untreated patients with **chronic lymphocytic leukaemia (CLL)** who do not have specific genetic markers (known as a **17p deletion** or ***TP53*** **mutation**) and who would otherwise be suitable for chemotherapy with FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab). This population is identical to the population that Ven+O treatment is currently recommended for via the **Cancer Drugs Fund (CDF)** in a previous submission: TA663.[1] Please note that the population wording here references FCR and BR to align with TA663, however these treatments have since been superseded by targeted therapies (Ven+O and ibrutinib + venetoclax [I+Ven]).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The UK marketing authorisation is a license that enables a drug to be sold; it is only granted after assessing and reviewing all of the evidence for that drug. Venetoclax in combination with obinutuzumab for adult patients with previously untreated CLL received marketing authorisation via the **Medicines & Healthcare products Regulatory Agency (MHRA)**, in March 2020. This is detailed in section B1.2 of the main company submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates with various patient groups supporting people with chronic lymphocytic leukaemia.

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: https://www.abbvie.co.uk/our-company/policies-disclosures.html

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is chronic lymphocytic leukaemia (CLL)?
CLL is a blood cancer with no known cause, where a type of **white blood cell (WBC)** involved in the immune system is overproduced and is dysfunctional or does not work properly.[2]

What are the symptoms of CLL?
Most CLL patients are diagnosed via a blood test, having sometimes experienced symptoms such as fatigue, weight-loss, chills, fever, night-sweats, and swollen lymph nodes.[2] As CLL progresses, symptoms become more severe, with greater fatigue, weakness, shortness of breath, excessive bruising and bleeding, and greater risk of infection.[3] Initially, the patients undergo **active monitoring**, while the disease is mild with few symptoms. However, once the disease becomes 'active' – defined by worsening symptoms and blood test results – patients will start treatment.[4]

How many people have CLL in the UK? Who does it affect?
In the UK, almost 4,000 people are diagnosed with CLL per year, equating to 6 people for every 100,000.[5] The elderly are most affected, with 41% of new cases diagnosed in people 75 years old or over.[5] Males are around twice as likely to get CLL compared with females.[6]

Approximately 980 people die of CLL every year in the UK, around 60% of which are male, and around 80% are over 75 years old.[5]

Risk factors for developing CLL include obesity, old age, genetic factors, and exposure to certain agricultural chemicals,[7] with increases in obesity and use of such chemicals thought to be responsible for increases in CLL cases.[8]

How does it affect patients and their families/friends/care givers?
Beyond direct symptoms, patients' quality of life is reduced. Patients experience higher anxiety, with one patient survey finding that 72% of patients were worried about relapsing after treatment or disease progression, and 96% stating that delaying disease progression was their priority.[9] Patients under active monitoring can experience mental health problems,[10] with younger patients more likely to suffer from anxiety and depression.[11]

Patients' families, friends and caregivers are also affected, as patients with CLL often require support in their everyday activities.[12] As CLL progresses, the carers role changes from emotional support during periods when the disease is well-controlled and there are few symptoms, to both

emotional and physical support during periods when a patient experiences more symptoms. Patients will often need support with daily tasks such as cooking and cleaning, and may need support dealing with any side effects of the medicine they are taking. Patients may need help travelling to medical appointments and listening to the doctor's advice, which can be difficult to absorb when trying to understand a serious medical diagnosis.[13]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

CLL is diagnosed based on the presence of abnormal WBCs in the blood. It is then classified by stage, commonly using a system known as the **Binet system**, in which patients are classified as A: low risk, B: intermediate risk, or C: high risk.[14]

Cells from a patient's blood and bone marrow will be tested to look for changes in certain genes. This helps the doctors decide which treatment is the best for the patient and may help them decide when a patient needs to start treatment.[15] Two of the genetic markers that are tested for are:

- Mutation in the *TP53* gene
- Deletion in chromosome 17, known as del17p, which results in a deletion of the *TP53* gene.

The *TP53* gene produces a protein that repairs **DNA** so that damaged DNA is not passed to new cells. Mutations or a deletion of the *TP53* gene can cause cells to divide uncontrollably.[16]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current treatment pathway

CLL cannot currently be cured, and early treatment for asymptomatic, early stage CLL after diagnosis does not appear to improve survival.[17] Therefore, patients with CLL often have a period of active monitoring, and treatment only starts when patients start to experience worsening symptoms and blood test results.[4]

The treatment used depends on whether the patient has been treated previously (and how successful that treatment was to determine retreatment eligibility), whether the patient's cancer cells have any genetic markers, and whether the patient is fit enough to tolerate certain treatments.[14]

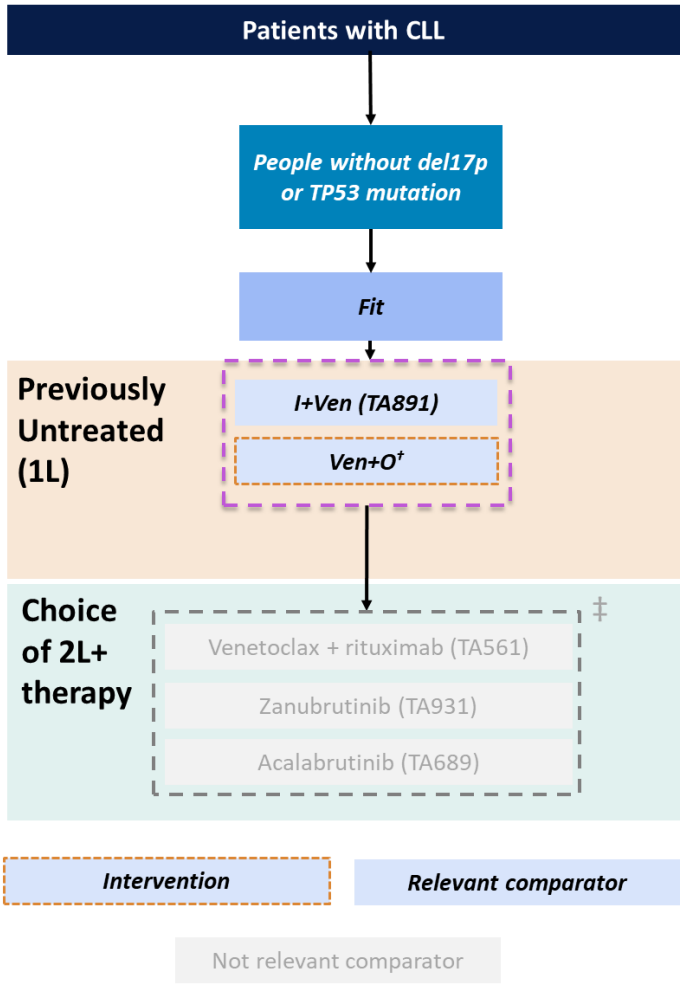


Figure 1. Treatment pathway in UK clinical practice for patients with CLL

Please note that 1L treatments do not include chemoimmunotherapy (CIT) in this diagram as its usage has been superseded by targeted therapies such as Ven+O and I+Ven.[18,19] However, fit patients are those which would have previously been suitable for FCR/BR.

† Venetoclax + obinutuzumab is available for patients in this population via the CDF in England and Northern Ireland, and through a different funding scheme in Wales.

‡ Relevant 2L treatments for the target population were identified by UK clinical experts who added that duration of response to 1L therapy determines the 2L treatment rather than the type of 1L therapy.

The Evidence Assessment Group (EAG) for a recent NICE appraisal (TA931) outlined that the definition of patient fitness is subjective and driven by patient characteristics such as age and CIRS score rather than eligibility for specific treatments, in line with recent declines in use of chemotherapy regimens in clinical practice.[20]

Abbreviations: 1L, first-line; 2L, second-line; BR, bendamustine and rituximab; CDF, Cancer Drugs Fund; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; I+Ven, ibrutinib + venetoclax; Ven+O, venetoclax + obinutuzumab

Adapted from NICE TA931 committee slides[20]

This submission considers patients who have not previously been treated, who do not have certain genetic markers (del17p or *TP53* mutations), and are considered fit. There is no formal tool to assess patient fitness, and clinicians asked by AbbVie agreed that fitness was determined by clinicians, based on their experience. These patients currently have two treatment options: I+Ven and Ven+O, which is currently recommended by NICE for this population via the Cancer Drugs Fund (CDF) and its recommendation for routine use is the focus of this submission.[1] The chemotherapy drugs FCR and BR are also licenced for this population but have been replaced by targeted therapies,[18] such as I+Ven and Ven+O.[21]

I+Ven is a combination of two different targeted therapies. Ibrutinib blocks proteins in cancer cells from sending the signals they need to grow, which causes the cancer cells stop the cells from growing and dividing.[22] Venetoclax blocks the action of a protein called **B-cell lymphoma 2** (**BCL2)**, which is needed by the cancer cells to survive, and so venetoclax kills and slows down their growth. Ultimately, this leads to a reduction in the number of CLL cells in the patient's blood and delays CLL disease progression.[23]

I+Ven is given as tablets, both taken once every day, that can be swallowed by the patient at home. Venetoclax should be taken with or after food, at the same time every day. Patients require regular monitoring while on this treatment. Ibrutinib may be associated with heart problems and alternative anti-CLL therapy should be considered[24,25] for those considered at high risk of these complications, and patients will be required to receive electrocardiogram (ECG) monitoring.[26] Amongst other interventions, cardiac monitoring is advised while on this treatment, with current guidelines recommending that patients receiving I+Ven get up to five ECGs in the first year of treatment (one when they start treatment and one every 3-6 months after that).[26] Patients who develop heart failure or an irregular heartbeat while on this treatment should stop taking the treatment, either temporarily or permanently.[27,28]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

CLL has a significant, detrimental impact on a patient's quality of life, due to the high symptom burden, the potential side effects associated with treatments and the emotional impact of living with a disease that cannot be cured.[7,9,10,29,30]

The quality of life of patients with CLL was studied through the Cancer Support Community's online cancer experience registry, which conducted surveys in 134 patients. More patients with CLL reported experiencing anxiety, fatigue, depression, sleep disturbance and worse physical and social functioning compared with the average American population. Additionally, 62% of patients with CLL indicated that their diagnosis affected their views on their life expectancy, with 41% saying their diagnosis affected their quality of life and 40% saying it affected their finances.[31]

There is a significant impact of having CLL on a patient's mental well-being. In a US-based survey of patients living with a blood cancer, 72% of CLL patients worried about their disease returning or no longer responding to treatment and 96% of CLL patients stated that delaying their disease from progressing was the main goal of their treatment.[9] A survey of 105 patients included in a database of patients with CLL asked patients to rate their anxiety, depression and quality of life. Patients aged under 60 years old reported more depression and worse emotional and social well-being than those over 60 years old. They also had higher levels of anxiety during periods of active monitoring, while they were not receiving treatment for their cancer, than patients aged over 60 years old. Levels of depression and anxiety were equally high in patients who were being monitored while not receiving any treatment compared with those being treated.[11]

There is also a significant burden on the caregivers of patients with CLL, as patients with CLL often require support to perform everyday activities and may require help attending hospital appointments. A total of 575 caregivers of a family member with CLL completed an online survey about the burden of their role, and reported six areas where they needed more support, including financial, emotional, informational (advice or guidance), instrumental (assistance provided to meet needs such as personal care, transport, food preparation), peer (understanding, guidance, and encouragement between caregivers) and communication support.[32]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

In patients with CLL, the bone marrow produces too many abnormal WBCs, which are underdeveloped and do not function properly. These cells rely on a protein called BCL2 for their survival.[33] Venetoclax blocks the action of BCL2 and, in doing so, promotes the deaths of these cells. Ultimately, this leads to a reduction in the number of CLL cells in the patients' blood and delays CLL disease progression.[34,35] Venetoclax blocks the BCL2 protein independently of the p53 tumour suppressor protein, which is produced by the *TP53* gene, and so provides an effective treatment for CLL patients whether they have a genetic mutation in their *TP53* gene or not.[33]

Obinutuzumab is a type of protein called a B-cell specific **antibody**. It travels in the blood and binds to a specific protein called CD20 on the surface of **B-cells**, a type of WBC, including the cancerous cells in CLL. By binding to CD20, obinutuzumab causes direct cell death as well as helps the immune system identify and destroy these cancerous cells.[36-38]

The patient information leaflets can be found here:
Venetoclax: https://www.medicines.org.uk/emc/files/pil.2267.pdf
Obinutuzumab: https://www.medicines.org.uk/emc/files/pil.3279.pdf

The summary of product characteristics can be found here:
Venetoclax: https://www.medicines.org.uk/emc/product/2267/smpc#gref
Obinutuzumab: https://www.medicines.org.uk/emc/product/3279/smpc

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

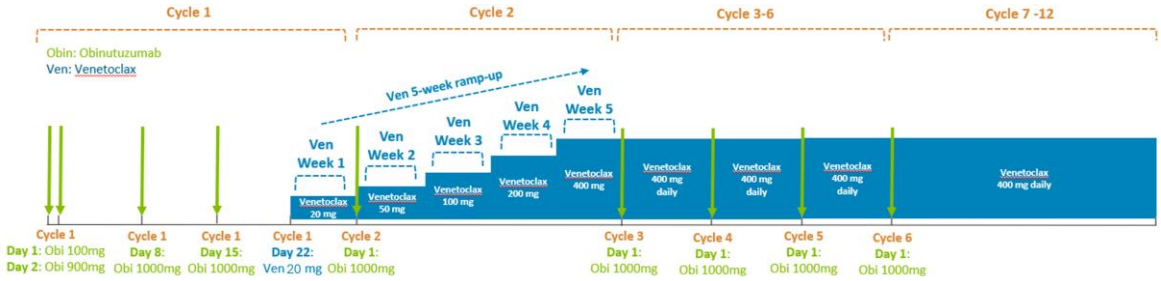
If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of

life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
No, Ven+O is given as a combination of venetoclax and obinutuzumab, however, it is not intended to be used alongside any other medicines for the treatment of adult patients with CLL who had not received any treatment.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Ven+O treatment is taken for 12 cycles, with each cycle consisting of 28 days. Obinutuzumab is given as an infusion into a vein. Treatment starts on day 1 of cycle 1, with a dose of 100 mg on day 1, followed by 900mg which may be administered on day 1 or 2, and then 1000 mg on day 8 and day 15 of cycle 1. For cycles 2 to 6, the dose is 1000 mg on day 1 of each cycle. Obinutuzumab is not given during cycles 7-12 and so patients do not need to go to the hospital to receive obinutuzumab treatment during this time.[39] Venetoclax is given as a tablet, taken once a day, to be swallowed, with or after food. The tablet should be swallowed whole with a glass of water and should not be broken or crushed. The tablet should be taken at the same time every day.[35] Venetoclax treatment starts with a low dose, and the dose is gradually increased over a 5-week period to lower the risk of a side effect called **tumour lysis syndrome**. The dose titration of venetoclax is started on day 22 of cycle 1 as two 10mg tablets and this is continued for the first week of the dose titration schedule (cycle 1, days 22-28). This is followed by taking a 50 mg tablet every day for the second week (cycle 2, days 1-7), a 100 mg tablet every day for the third week (cycle 2, days 8-14), and two 100 mg tablets every day for the fourth week (cycle 2, days 15-21) of the dose titration schedule. After this, patients continue to take four 100mg tablets every day until the end of their treatment (cycle 12).[35,39,40]      **Figure 2. Dosing schedule for Ven+O** Ven+O is given for a fixed duration of 12 cycles (336 days).[39]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The CLL13 clinical trial

The CLL13 (NCT02950051) clinical trial provides evidence regarding how well Ven+O works and its side effects in fit adult patients with CLL who have not had any treatment and who do not have any del17p or *TP53* mutations. There were four treatment groups of patients in the trial; however only those who received Ven+O or standard **chemotherapy** are included in this submission as the treatments given to patients in the other two groups are not licenced for use in the first-line CLL setting in the UK and so are not considered relevant. Patients were put into these groups randomly to ensure the split of patients receiving each treatment was fair. The trial was conducted at 159 hospitals, in 10 countries in Europe and the Middle East.

The CLL13 trial was open label, meaning that the patients and doctors knew which treatments they were receiving. This study design is common in cancer trials given ethical concerns around trials in this disease area, additionally the different treatments have different dosing and schedules and so it may not be possible to hide the treatments patients are receiving. Likewise, this also means doctors are aware which side effects to expect after a given treatment and how to monitor the patient.

There were 926 patients in the trial, 229 patients were given Ven+O and 229 patients were given standard chemotherapy.

To be included in the CLL13 trials, amongst other criteria, patients had to be:

- Adults aged at least 18 years
- Diagnosed with CLL requiring treatment
- Not have a del17p or *TP53* mutation in their cancer cells
- Considered medically fit according to liver and kidney function tests and blood tests
- Previously untreated CLL

SACT Dataset

In 2020, Ven+O was approved for access through the CDF, which allows patients access to promising new treatments while further data is being collected about how effective they are. Data on the use of Ven+O in patients with untreated CLL in the UK through this fund is available in the Systemic Anti-Cancer Therapy (SACT) dataset. This data collection assessed the outcomes of patients receiving the treatment and is not a clinical trial. The 2-year SACT dataset provides information how long patients live after taking Ven+O in a real world setting. [41]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Clinical trial results

The data informing how long patients survive before experiencing any disease progression from the CLL13 trial presented in the submission was taken from the latest available data, from January 2023, which was published in the Fürstenau et al. 2024 publication. During CLL13, **minimal residual disease (MRD)** was measured after 15-months after starting Ven+O treatment and is taken from the Eichhorst et al. 2023 publication (using data collected in February 2021).[42,43]

Treatment with Ven+O aims to reduce the CLL related symptoms a patient experiences over a long period of time whilst decreasing the amount of CLL cells. 81.8% of patients treated with Ven+O were alive after 4 years, with no signs of disease **progression**, compared with 62% of patients treated with standard chemotherapy.

The MRD rate is a measure of the number of cancer cells remaining in a patient's blood and when this is undetectable, it is associated with longer periods of **remission** (where the disease is controlled with a low symptom burden) and survival.[18] 15 months after starting treatment, 86.5% of patients treated with Ven+O had undetectable MRD compared with 52% of patients treated with standard chemotherapy.

Both the improvement in survival and undetectable MRD rate in patients treated with Ven+O compared with those treated with standard chemotherapy were considered to be statistically and clinically meaningful results.

Ven+O compared with I+Ven

There are no clinical trials directly comparing patients treated with Ven+O and those treated with I+Ven, the comparator in this submission. To assess this, a statistical analysis was conducted where patients' response and survival after Ven+O treatment in the CLL13 trial was compared with data from the from the CAPTIVATE (NCT02910583) phase 2 trial, where patients with untreated CLL were treated with I+Ven. This analysis was conducted according to NICE guidelines.

The results of this analysis showed Ven+O to be better than I+Ven, however the results were not statistically significant. Opinions from consultant haematologists suggested that the length of time patients survived without any disease progression was similar between patients treated with Ven+O and those treated with I+Ven. Likewise the overall length of time that patients lived after receiving treatment, was similar between those who received Ven+O and I+Ven.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The quality of life of patients taking Ven+O was investigated in the CLL13 trial and was measured using the **EORTC QLQ-C30** and **EORTC QOL-CLL16** questionnaires.

The EORTC QLQ-C30 consists of 30 questions about different aspects of a patient's quality of life and allows precise description of a patient's experience, including their physical, emotional and social well-being.

The EORTC QOL-CLL16 consists of 16 questions which assess a range of symptoms and issues relating to CLL. These include disease-specific symptoms, treatment side effects, and the impact of CLL on patients' daily functioning and well-being.

Both questionnaires were completed by patients randomised to treatments, before, during and after treatment.

Quality of life improved shortly after patients started treatment with Ven+O and this benefit was maintained throughout the study.[44] Improvements in a patient's physical ability and symptoms were seen within 3 months of starting treatment, and improvements in their social well-being were seen at 9 months. Over a 36-month period, there was a continued improvement in fatigue compared to when the patients started treatment.[44]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Evidence regarding the tolerability of Ven+O was collected during the CLL13 clinical trial, including any side effects of the treatment and any unrelated patient sickness.

The most common serious safety events experienced by patients treated with Ven+O were infusion related reactions, caused by the infusion of the obinutuzumab treatment into a vein. A similar proportion of patients treated with standard chemotherapy also experience site reactions. After this, the most common serious safety events experienced by patients taking Ven+O were pneumonia and tumour lysis syndrome.

Tumour lysis syndrome can be a serious side effect from cancer treatments and is caused when the cancer cells break down too quickly. However, doctors are familiar with these treatments and know to monitor and identify the condition so that it may be treated following established guidelines.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

As Ven+O is given for a fixed time period,[39] this enables patients the chance to experience a prolonged period of time off treatment, reducing the overall burden of treatment whilst keeping the disease under control.

Treatment with Ven+O demonstrated a statistically significant improvement in the rates of survival without any disease progression and with MRD, compared with standard chemotherapy, which suggests that with a one-year fixed treatment duration, Ven+O may result in long, treatment-free periods of remission for patients with CLL. This may improve patient quality of life

by providing the chance the live without the burden of ongoing treatment, the worry about treatment side effects and the opportunity to be out of hospital. Reported in the most recent Leukaemia Care patient survey, 64% of CLL patients would consider it positive if their treatment plan contained a treatment free period or included stopping treatment altogether, with 84% of CLL patients saying they would like a choice of different treatment options.[45]

The provision of treatment options that allow longer-term disease control without ongoing treatment are likely to have positive effects on the caregiver as well as the patient. Delaying disease progression reduces the level of care they need to provide in support to the patient, there is less need for carers to accompany patients to frequent medical appointments, and where patients are able to tolerate their treatment and therefore, experience fewer side effects, less carer support is required to manage the effects of treatment and not just the disease. Time off treatment for the patient, offers the same break for carers, impacting positively on both patient and carer mental health.

The symptoms, disease course, treatment response and tolerance of therapies varies significantly between patients with CLL. Therefore, there is a need for additional effective treatment options with fewer and more tolerable side effects, which offer to improve their quality of life. Ven+O provides an effective treatment option for fit CLL patients with and without del17p or *TP53* mutation, therefore, giving patients the option to start treatment as soon as their disease requires active treatment. Following a prolonged period of active monitoring, this offers a chance to reduce patient and carer anxiety at initiation of treatment.[46,47] CLL patients on active monitoring were found to be significantly more likely to report feeling depressed or anxious more often, or constantly, than patients who had started treatment.[45]

During CLL13, Ven+O demonstrated a manageable safety profile with no new safety concerns compared with previous trials of Ven+O. The benefit of a tolerable side effect profile and the limited treatment duration enables patients to maintain and regain a good quality of life through disease control, potentially resulting in fewer hospital visits and remaining active doing the things they enjoy, demonstrated by their improved wellbeing after completing treatment.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As part of the Ven+O combination, obinutuzumab must be given as an infusion into a vein, which must be done by a healthcare professional in a clinical setting. This requires the patient and their carer to visit this setting 3-4 times in the first month, and once a month for the next 5 months. The infusion may take a long time to administer and can be considered invasive by patients. However, after the first 6 months, obinutuzumab is no longer given, and so patients and carers no longer need to attend a hospital for obinutuzumab treatment.

The main side effects of Ven+O treatment are infusion reactions from the infusion of obinutuzumab, pneumonia and tumour lysis syndrome. These side effects are a common

response to this type of cancer treatment that are monitored for and can be treated with established guidelines.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic model and how does it reflect CLL?

An economic model has been used to assess the value of Ven+O for patients with CLL to the NHS. As statistical analysis suggested that the survival benefits seen in patients treated with Ven+O were either slightly better than or similar to the benefits seen in patients treated with I+Ven, the economic model performs a cost-utility analysis, which considers the cost difference between the two treatments in the context of any differences in their effectiveness outcomes.

As such, the economic model considers the expected costs for treatment with Ven+O and I+Ven over a set time period, including the costs of acquiring the drugs, administration, monitoring and side effect management. For example, costs are applied for each infusion based on published NHS costs, which account for the nurse's time. In addition, costs associated with how CLL is managed and monitored are included in the model. These depend on the response to treatment and any side effects or other health events, which are dependent of disease progression. The model does not include any costs that the patient experiences such as travel to and from hospital. The model considers the costs over a patient's lifetime.

The model considers three patient groups:

- patients who are progression-free, including patients who are alive and whose disease has not progressed,
- patients with progressed disease, who are alive and whose disease has progressed
- patients who have died from either CLL or other causes.

The movement of patients between these groups reflects a patient's real-world experience as their cancer progresses, or is delayed from progressing as a result of an effective treatment. Movement between the groups is modelled using probabilities calculated using survival and

progression data from the CLL13 trial for patients treated with Ven+O and CAPTIVATE trial for patients treated with I+Ven.

Feedback from consultant haematologists on the analysis suggests that Ven+O and I+Ven survival and progression outcomes appear comparable. Additionally, from their experience using these treatments in NHS practice, they also noted that outcomes are comparable. Therefore, AbbVie undertook a cost-comparison analysis, which assumes that survival and progression are equal between treatments, therefore the movement of patients between the groups is equal between Ven+O and I+Ven. The cost-comparison therefore only accounts for any cost differences between the treatments.

Is there any uncertainty in the model?
During the development of an economic model, companies are required to make assumptions where there is a lack of available evidence. For example, in this model there was little published data to inform the next treatment patients would receive if they stopped responding to either Ven+O or I+Ven. Therefore, doctors who were consulted stated that the next therapy should be selected based on the length of time patients responded to treatment opposed to the type of treatment they received. To account for any uncertainty in the model, further analysis was conducted to test some of these assumptions. These analyses were consistent with the results of the main model, so that the results of the model are reliable.

Are there any additional factors to consider?
As patients can already receive Ven+O through the CDF, approval of Ven+O for routine commissioning by NICE would not result in any changes to service provision or add any additional burden to the healthcare system. While patients who received Ven+O need to attend hospital appointments so that obinutuzumab can be administered by infusion, guidelines recommend that patients treated with I+Ven attend hospital appointments for additional cardiac monitoring due to the cardiac side effects linked to ibrutinib.[26] This additional cardiac monitoring is not required for patients treated with Ven+O. Therefore, the service provision required for the administration of obinutuzumab should be offset by the reduced need for cardiac monitoring compared with patients receiving ibrutinib as part of their I+Ven treatment.

The economic modelling conducted during this submission did not consider the burden of caring for a friend or family member with CLL on caregivers, as this is not considered by NICE in their decision making. These caregivers face considerable emotional, practical and financial challenges. Carers often provide transport to-and-from hospital appointments and treatment appointments, which can require time off work and social productivity. Carers also provide emotional support while trying to deal with the emotions surrounding a loved one being seriously ill. Improved survival without any disease progression in patients treated with Ven+O could significantly reduce the burden on caregivers.[32] Time off treatment for the patient offers the same break for carers, impacting positively on both patient and carer mental health.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Routine reimbursement of Ven+O would simplify the treatment pathway for CLL as doctors would no longer need to consider the overall fitness of a patient before deciding treatment because Ven+O would be reimbursed across the untreated CLL population. As Ven+O is given for a fixed duration, it offers patients the chance of prolonged periods without taking treatment and reducing the overall, long-term burden of treatment.

Treatment with I+Ven is associated with a number of side effects, including cardiac side effects, which influences whether a patient may receive I+Ven.[26] Ven+O provides an alternative treatment option for patients, maintaining patient and clinician choice.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

It is not expected that the provision (or non-provision) of Ven+O within its licensed indication would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation or lead to recommendations that will have adverse impact on people with a particular disability or disabilities.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on CLL may be found here, including the different treatments currently available:

- CLL Support
- Leukaemia Care - The UK's leading leukaemia charity
- Lymphoma Action
- Chronic lymphocytic leukaemia (CLL) | Macmillan Cancer Support
- Chronic lymphocytic leukaemia (CLL) | Cancer Research UK
- Treatment for chronic lymphocytic leukaemia (CLL) | Cancer Research UK
- Chronic lymphocytic leukaemia (CLL) | Blood Cancer UK

Further information on Ven+O may be found here:

- Venetoclax (Venclyxto®) | Macmillan Cancer Support
- Obinutuzumab (Gazyvaro®) | Macmillan Cancer Support
- Information for the public | Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia | Guidance | NICE
- Ventoclax (Venclyxto®) | Information for the Patient

Information on the CLL13 clinical trial may be found here:

- Fürstenau M, Kater AP, Robrecht S, et al. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2024;25(6):744-59.
- Eichhorst B, Niemann Carsten U, Kater Arnon P, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2023;388(19):1739-54.
- Study Details | Standard Chemoimmunotherapy (FCR/BR) Versus Rituximab + Venetoclax (RVe) Versus Obinutuzumab (GA101) + Venetoclax (GVe) Versus Obinutuzumab + Ibrutinib + Venetoclax (GIVe) in Fit Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL) Without Del(17p) or TP53 Mutation | ClinicalTrials.gov

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf

- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

17p deletion: a deletion in chromosome 17, which contains genetic information that produces the p53 protein, which regulates how genetic information is split when cells divide to produce new cells. This deletion means that how cells divide becomes unregulated in cancer cells.

Active monitoring: if a patient does not have any symptoms of chronic lymphocytic leukaemia or their symptoms are not causing any problems, then they may not need treatment straight away. Instead, they will be monitored through regular check-ups and blood tests.

Antibody: a protein in the blood that helps the body's defences by identifying and attaching specific foreign substances including germs.

B-cells: a type of white blood cells that produces proteins that are important to fight infections, known as antibodies.

Binet system: a staging system used to assess how severe a patient's chronic lymphocytic leukaemia is, based on the number of lymphoid tissues involved and the presence of abnormal levels of blood cells, known as anaemia or thrombocytopenia.

Cancer Drugs Fund (CDF): a source of funding for cancer drugs in England, which provides patients access to promising new treatments, before they are reimbursed by NICE, while further evidence is being collected.

Chemotherapy: drugs that are toxic to cells and are used to destroy cancer cells.

Chronic lymphocytic leukaemia (CLL): a rare form of blood cancer that affects B-cells, and may cause swollen glands, unexplained weight loss, a weakened immune system resulting in frequent illness, fatigue and unexplained bleeding and bruises.

Deoxyribonucleic acid (DNA): a chemical that contains genetic information.

EORTC QLQ-C30: is a questionnaire composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/QoL scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties).

EORTC QOL-CLL16: is a 16-item disease specific questionnaire developed specifically to assess health status of patients with CLL. It is comprised of 16 questions that address five domains of HRQoL important in CLL. There are three multi-item scales on: Fatigue (2 items), treatment side effects and disease symptoms (8 items), infection (4 items) and two single item scales on social activities and future health worries. Responses are measured on a 4-point scale ranging from 1

(not at all) to 4 (very much). These scores are transformed to give a rating from 0 (no symptoms or problems) to 100 (severe symptoms or problems)

Marketing authorisation: a license that enables a drug to be sold; it is only granted after assessing and reviewing all of the evidence for that drug.

Medicines and Healthcare products Regulatory Agency: an agency in the Department of Health and Social Care in the UK that is responsible for making sure that medicines and medical devices work and are safe.

Minimal residual disease (MRD): the small number of cancer cells that may remain in a patient's body after treatment that may lead to the cancer returning and the patient experiencing more symptoms, if not detected and managed.

Progression: when cancer cells start to grow again.

Remission: when the symptoms of a disease have become less severe and are not affecting the patient.

***TP53* mutation:** a change in the *TP53* gene that alters the function of the p53 protein that it produces. The p53 protein repairs DNA so that damaged DNA is not passed down into new cells and makes sure that cells with badly damaged DNA do not divide. Mutations of the *TP53* gene can cause cells to divide uncontrollably.

Tumour lysis syndrome: a side-effect of some cancer treatments that occurs when cancer cells break down too quickly and release substances into the blood at a rate that the kidneys cannot remove the substances. Symptoms include nausea, vomiting, diarrhoea, muscle cramps, weakness, fatigue, and seizures. Tumour lysis syndrome can be treated through routine management including the administration of fluids and drugs that help break down these substances or prevent the body from making more of them.

White Blood Cells (WBCs): cells in the immune system that protect the body from infectious diseases and foreign invaders.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [TA663]. 2020; Updated 09/12/2020. Available from: https://www.nice.org.uk/guidance/ta663/chapter/3-Committee-discussion [accessed 10/07/2025].
2. Cancer Research UK. What is chronic lymphocytic leukaemia (CLL)? 2024. Available from: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/about.
3. Cancer Research UK. Symptoms of chronic lymphocytic leukaemia (CLL). 2024. Available from: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/symptoms.

4. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-60.
5. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence#heading-Zero [accessed 07/10/2025].
6. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. American Journal of Hematology. 2017;92(9):946-65.
7. American Cancer Society. Signs and symptoms of chronic lymphocytic leukemia. 2018; Updated 10/05/2018. Available from: https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html [accessed 10/07/2025].
8. Yao Y, Lin X, Li F, et al. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. Biomed Eng Online. 2022;21(1):4.
9. Price M, Ravelo A, Sae-Hau M, et al. Patient-reported disease burden in chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and follicular lymphoma: Results from a national patient advocacy survey. Journal of Clinical Oncology. 2019;37(15_suppl):e18198-e.
10. Lien PW, Jawaid D, Emechebe N, et al. EE124 Real-World Mental Health Burden in Patients With Chronic Lymphocytic Leukemia. Value in Health. 2024;27(6):S80.
11. Levin TT, Li Y, Riskind J, et al. Depression, anxiety and quality of life in a chronic lymphocytic leukemia cohort. Gen Hosp Psychiatry. 2007;29(3):251-6.
12. Wright KB, Bylund CL, Bagautdinova D, et al. Caring for an individual with chronic lymphocytic leukemia (CLL): understanding family caregivers' perceptions of social support, caregiver burden, and unmet support needs. Journal of Cancer Education. 2024;39(2):180-5.
13. Health Tree Foundation for Chronic Lymphocytic Leukaemia. Where Could a CLL Patient Need Support? 2025. Available at: https://healthtree.org/cll/guides/cll-fixed-and-continuous-duration-therapy-guide/cll-caregiver-areas-of-support [Accessed 12/05/2025].
14. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2021;32(1):23-33.
15. Cancer Research UK. Genetic tests on your chronic lymphocytic leukaemia (CLL) cells. 2025. Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/getting-diagnosed/genetic-tests [Accessed 12/05/2025].
16. Marei HE, Althani A, Afifi N, et al. p53 signaling in cancer progression and therapy. Cancer Cell International. 2021;21(1):703.
17. Langerbeins P, Zhang C, Robrecht S, et al. The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia. Blood, The Journal of the American Society of Hematology. 2022;139(2):177-87.
18. Cancer Research UK. Treatment options for chronic lymphocytic leukaemia (CLL). 2025. Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/treatment/decisions [Accessed 09/06/2025].
19. CLL Support. CLL Treatment. 2025. Available at: https://cllsupport.org.uk/information-support/about-cll/cll-treatment/#h-treatment [Accessed 09/06/2025].
20. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia [TA931]. 2023; Updated 22/11/2023. Available from: https://www.nice.org.uk/guidance/ta931/chapter/1-Recommendations [accessed 10/07/2025].

21. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [TA891]. 2023; Updated 31/05/2023. Available from: https://www.nice.org.uk/guidance/ta891/chapter/1-Recommendations [accessed 10/07/2025].
22. Cancer Research UK. Ibrutinib (Imbruvica). 2025. Available at: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/ibrutinib [Accessed 09/06/2025].
23. Cancer Research UK. Venetoclax (Venclyxto). 2025. Available at: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/venetoclax [Accessed 09/06/2025].
24. Macmillan Cancer Support. Ibrutinib and venetoclax. 2025. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/ibrutinib-and-venetoclax [Accessed 09/06/2025].
25. electronic medicines compendium. Package leaflet: Information for the patient (IMBRUVICA). 2024. Available at: https://www.medicines.org.uk/emc/files/pil.10025.pdf [Accessed 10/07/2025].
26. Tang CPS, Lip GYH, McCormack T, et al. Management of cardiovascular complications of bruton tyrosine kinase inhibitors. British Journal of Haematology. 2022;196(1):70-8.
27. British National Formulary. Ibrutinib [Specialist drug] - Medicinal Forms. 2024.
28. MHRA. Imbruvica 280 mg film-coated tablets - Summary of Product Characteristics. 2024.
29. Waweru C, Kaur S, Sharma S, et al. Health-related quality of life and economic burden of chronic lymphocytic leukemia in the era of novel targeted agents. Current Medical Research and Opinion. 2020;36(9):1481-95.
30. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. Br J Haematol. 2007;139(2):255-64.
31. Buzaglo JS, Miller MF, Zaleta AK, et al. Chronic Lymphocytic Leukemia Patient Reported Outcomes and Quality of Life: Findings from the Cancer Experience Registry. Blood. 2017;130(Supplement 1):2122-.
32. Wright KB, Bylund CL, Bagautdinova D, et al. Caring for an Individual with Chronic Lymphocytic Leukemia (CLL): Understanding Family Caregivers' Perceptions of Social Support, Caregiver Burden, and Unmet Support Needs. J Cancer Educ. 2024;39(2):180-5.
33. Lampson BL, Davids MS. The Development and Current Use of BCL-2 Inhibitors for the Treatment of Chronic Lymphocytic Leukemia. Curr Hematol Malig Rep. 2017;12(1):11-9.
34. Macmillan Cancer Support. Venetoclax (Venclyxto®). 2025. Available at: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/venetoclax [Accessed 10/07/2025].
35. electronic medicines compendium. Package leaflet: Information for the patient (Venclyxto). 2025. Available at: https://www.medicines.org.uk/emc/files/pil.2267.pdf [Accessed 10/07/2025].
36. Cancer Research UK. Obinutuzumab (Gazyvaro). 2023. Available at: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/obinutuzumab [Accessed 10/07/2025].
37. Illidge T, Klein C, Sehn LH, et al. Obinutuzumab in hematologic malignancies: Lessons learned to date. Cancer Treatment Reviews. 2015;41(9):784-92.
38. MHRA. Gazyvaro 1,000 mg concentrate for solution for infusion - Summary of Product Characteristics. 2023. Available at: https://mhraproducts4853.blob.core.windows.net/docs/de8a2c57a8e71dd02f7fc8c84dd418279cc00e4e [Accessed 03/04/2025].
39. MHRA. Venclyxto 10 mg film-coated tablets - Summary of Product Characteristics. 2025. Available at:

https://mhraproducts4853.blob.core.windows.net/docs/7684ff182c62a99c80faac1ef82cfff0a11c988e [Accessed 10/07/2025].
40. University of Cologne. Trial Protocol: A Phase 3 Multicenter, Randomized, Prospective, Open-Label Trial of Standard Chemoimmunotherapy (FCR/BR) Versus Rituximab Plus Venetoclax (RVE) Versus Obinutuzumab (GA101) Plus Venetoclax (GVe) Versus Obinutuzumab (GA101) Plus Ibrutinib Plus Venetoclax (GIVe) in Fit Patients With Previously Untreated Chronic Lymphocytic Leukaemia (CLL) Without Del(17p) or TP53 Mutation. 2021.
41. National Disease Registration Service. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia in people without del(17p)/TP53 mutation and for whom FCR and BR are suitable – data review. 2023.
42. Fürstenau M, Kater AP, Robrecht S, et al. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2024;25(6):744-59.
43. Eichhorst B, Niemann Carsten U, Kater Arnon P, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2023;388(19):1739-54.
44. Fürstenau M, Rotbain EC, Eurelings L, et al. Patient-Reported Quality of Life Outcomes with Venetoclax-Based First-Line Combinations in CLL: An Analysis from the Phase 3 GAIA/CLL13 Trial. 66th ASH annual meeting, 2024, San Diego, Publication Number: 3238. 2024.
45. Leukaemia Care. Living with Leukaemia. 2018 Report.
46. Lymphoma Action. The emotional impact of living with lymphoma. Available at: https://lymphoma-action.org.uk/about-lymphoma-living-and-beyond-lymphoma/emotional-impact-living-lymphoma. [Accessed 10/07/2025].
47. Cancer.Net. Leukaemia - Chronic Lymphocytic - CLL: Follow-Up Care. . Available at: https://www.cancer.net/cancer-types/leukemia-chronic-lymphocytic-cll/follow-care [Accessed 10/07/2025].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (Managed access part review of TA663) [ID6291]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
[ID6291] Venetoclax Clarification Questions [REDACTED]	**[REDACTED]**	**Yes**	**29 August 2025**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching (clinical effectiveness)

A1. Company submission (CS), Appendix B. Under 'Date of Searches', it states that: "Additional search updates conducted on 05 December 2022, 12 February 2024, and 06 February 2025 summarised evidence from randomised controlled trials only" (p69). Please confirm:

- whether non-randomised studies were searched for at all update searches
- that potentially eligible non-randomised studies were included throughout the entire screening process at all search updates
- that the 275 non-RCTs which were excluded in the data synthesis is the total number of eligible non-randomised studies from all search updates.

Non-randomised studies were searched in all phases of the clinical SLR and were considered eligible for inclusion in the SLR. However, publications of non-randomised studies were not considered eligible for data extraction in the second, third, fourth and fifth updates of the SLR, because a critical mass of clinical evidence was reached. The 275 non-randomised studies are a result of all SLR iterations.

A2. CS, Appendix B. Please clarify which search strategy the PRISMA flow diagram (Appendix B, Figure 1) is reporting, as the numbers of the search results do not tally with the search results reported in Appendix B, Tables 1 and 2.

The PRISMA flow diagram, as presented in Appendix B – Figure 1, reports the correct number of search results identified across all SLR iterations. In Table 1 of the appendices, the incorrect search line of the original SLR (i.e. S110 instead of S111) was included for the Embase and Medline results identified, therefore, resulting in a different total number of included records for screening. Table 2 in Appendix B only presents the search results of the latest search iteration (Feb 2025).

A corrected version of Table 1 is presented below.

Table 1. Corrected version of Company Submission Appendix B Table 1

Database	Total number of hits retrieved					
	12.12.2018	08.07.2019	17.09.2020	05.12.2022	12.02.2024	06.02.2025
Embase and MEDLINE	4,999	172	325	NA▪	1,135	299
Cochrane CDSR	112	4	5	NA▪	0	0
Cochrane CENTRAL	516	145	100	NA▪	226	87
Cochrane CRD						
• DARE	37	37‡	37‡	NA▪	NA	NA
• NHS EED	28	28‡	28‡	NA▪	NA	NA
• HTA	76	76‡	76‡	NA▪	NA	NA
Cochrane Clinical Answers	NA	NA	0	NA▪	1	0

‡ Searches conducted in Cochrane CRD for SLR run 2019 and 2020 were not counted in the final total hits as these were duplicate records.

A3. CS Appendix B. Please provide the full search strategies for the database searches in Medline, Embase and the Cochrane Library for the original search strategy carried out on 12 December 2018. Please clarify if the update search strategies have changed.

No changes to the search strategies were made over the course of the SLR. Please find the search strategies of the original SLR below.

Table 2. ProQuest – Clinical Search (December 2018)

Topic	Search	Searched for	Results 12 December 2018
Disease	S1	EMB.EXACT("chronic lymphatic leukemia")	36595*
	S2	MESH.EXACT("Leukemia, Lymphocytic, Chronic, B-Cell")	14911*
	S3	EMB.EXACT("B cell leukemia")	6387*
	S4	TI,AB("chronic lymphatic leukemia")	1843°
	S5	TI,AB("chronic lymphatic leukaemia")	1078°
	S6	TI,AB("b cell leukaemia")	185°
	S7	TI,AB("b cell leukemia")	1480°
	S8	TI,AB("chronic lymphocytic leukaemia")	8185*
	S9	TI,AB("chronic lymphocytic leukemia")	38894*
	S10	TI,AB(cll)	37364*
	S11	TI,AB(chronic NEAR/3 lymph* NEAR/3 leuk*)	56869*
	S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	79778*
Treatment setting	S13	TI,AB("previously-untreated")	24204*
	S14	TI,AB(untreat*)	394623*
	S15	TI,AB(un-treat*)	479°
	S16	TI,AB("first-line")	184303*
	S17	TI,AB("first line")	184303*
	S18	TI,AB("1st line")	3535°
	S19	TI,AB(1st-line)	3536°
	S20	TI,AB(1stline)	126°
	S21	TI,AB(frontline)	13917*
	S22	TI,AB("front line")	13986*
	S23	TI,AB(front-line)	15091*
	S24	TI,AB(fit)	290523*
	S25	TI,AB(unfit)	10492*
	S26	TI,AB(un-fit)	11°
	S27	TI,AB("treatment naïve")	26257*
	S28	TI,AB(treatment-naïve)	26270*
	S29	TI,AB("treatment naive")	26257*
	S30	TI,AB(treatment-naive)	26270*
	S31	TI,AB(primary)	3285871*
	S32	TI,AB(initial)	1705529*
	S33	TI,AB("stage B")	5646*
	S34	TI,AB("stage-B")	5646*
	S35	TI,AB("symptomatic")	411932*
	S36	(earl* NEAR/3 chronic AND lymph* AND leuk*)	571°
	S37	(intermediate NEAR/3 chronic AND lymph* AND leuk*)	50°
	S38	(untreated NEAR/5 chronic AND lymph* AND leuk*)	712°
	S39	("first-line" NEAR/5 chronic AND lymph* AND leuk*)	350°
	S40	("first line" NEAR/5 chronic AND lymph* AND leuk*)	350°
	S41	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40	5919651*

Disease and treatment setting	S42	S12 AND S41	16636*
Randomised controlled trial	S43	TI,AB(clinical AND (trial or study or studies))	4228691*
	S44	TI,AB(random*) OR TI,AB,IF(placebo*) OR TI,AB(double NEAR/1 blind*)	2610252*
	S45	TI,AB("RCT")	47936*
	S46	TI,AB(random*AND (trial or study or studies))	12°
	S47	TI,AB(open-label)	104437*
	S48	TI,AB((singl* OR doubl* OR treb* or tripl*) NEAR/1 (blind[*3] OR mask[*3]))	385251*
	S49	TI,AB(placebo[*1])	484790*
	S50	TI,AB(random* NEAR/2 allocated)	64313*
	S51	EMB.EXACT.EXPLODE("Clinical trial")	1562780*
	S52	EMB.EXACT("Controlled clinical trial")	541617*
	S53	EMB.EXACT("Randomized controlled trial")	576486*
	S54	EMB.EXACT.EXPLODE("Randomization")	94423*
	S55	EMB.EXACT("Single blind procedure")	38946*
	S56	EMB.EXACT("Double blind procedure")	161919*
	S57	EMB.EXACT("Crossover procedure")	62439*
	S58	EMB.EXACT("Placebo")	366547*
	S59	EMB.EXACT("Triple blind procedure")	237°
	S60	EMB.EXACT("Multicenter study" OR "Phase 3 clinical trial" OR "Phase 4 clinical trial")	256967*
	S61	EMB.EXACT("Prospective study")	522038*
	S62	MESH.EXACT.EXPLODE("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial") OR MESH.EXACT.EXPLODE("Clinical Trials as Topic")	319373*
	S63	MESH.EXACT.EXPLODE("Random Allocation")	96575*
	S64	MESH.EXACT.EXPLODE("Double-Blind Method")	148336*
	S65	MESH.EXACT.EXPLODE("Single-Blind Method")	25935*
	S66	MESH.EXACT.EXPLODE("Placebos")	34142*
	S67	MESH.EXACT.EXPLODE("Cross-Over Studies")	44071*
	S68	MESH.EXACT.EXPLODE("Prospective Studies")	487301*
	S69	RTYPE("Clinical trial, phase i")	18464*
	S70	RTYPE("Clinical trial, phase ii")	29803*
	S71	RTYPE("Clinical trial, phase iii")	14353*
	S72	RTYPE("Clinical trial, phase iv")	1615°
	S73	RTYPE("Controlled clinical trial")	92767*
	S74	RTYPE("Randomized controlled trial")	471770*
	S75	RTYPE("Multicenter study")	241797*
	S76	RTYPE("Clinical trial")	575326*
	S77	S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76	7982285*
Non-randomised trials	S78	TI,AB("Case control") OR TI,AB(case control NEAR/1 (study OR studies))	262995*
	S79	Cohort NEAR/1 (study OR studies)	626065*
	S80	TI,AB(Cohort analys*)	537800*

	S81	TI,AB(Follow up NEAR/1 (study OR studies))	125787*
	S82	TI,AB(Observational NEAR/1 (stuy OR studies))	264296*
	S83	TI,AB("Cross sectional") OR TI,AB(cross sectional NEAR/1 (study OR studies))	673292*
	S84	TI,AB(Epidemiologic[*1] NEAR/1 (study OR studies))	58202*
	S85	TI,AB(Longitudinal)	501668*
	S86	TI,AB(Retrospective)	1180260*
	S87	EMB.EXACT("Clinical study")	323294*
	S88	EMB.EXACT("Family study")	47646*
	S89	EMB.EXACT("Longitudinal study")	132462*
	S90	EMB.EXACT("Retrospective study")	734284*
	S91	EMB.EXACT("Prospective study") NOT EMB.EXACT("Randomized controlled trials")	522038*
	S92	EMB.EXACT("Cohort analysis")	453917*
	S93	EMB.EXACT("Case control study")	150089*
	S94	EMB.EXACT("Follow up")	1493891*
	S95	EMB.EXACT("Observational study")	172880*
	S96	EMB.EXACT("Epidemiology")	1260713*
	S97	EMB.EXACT("Cross-sectional study")	288180*
	S98	EMB.EXACT("Disease registry")	12496*
	S99	MESH.EXACT("Epidemiologic studies")	7808*
	S100	MESH.EXACT.EXPLODE("Case control studies")	256353*
	S101	MESH.EXACT.EXPLODE("Cohort studies")	1799273*
	S102	MESH.EXACT("Cross-sectional studies")	279232*
	S103	MESH.EXACT("Longitudinal Studies")	118897*
	S104	MESH.EXACT("Retrospective Studies")	718045*
	S105	MESH.EXACT("Prospective Studies")	487301*
	S106	MESH.EXACT("Follow-Up Studies")	602619*
	S107	MESH("Observational Studies")	3394°
	S108	S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107	7720035*
Subtotal	S109	S77 OR S108	12809937*
Total	S110	S42 AND S109	8641*
Total without conference abstracts	S111	S110 NOT DTYPE("conference abstract")	4999*

Table 3. Cochrane library Search (December 2018)

Search Type	Search	Search String	12 December 2018
Population	#1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	380
	#2	chronic AND lymph* AND leuk*	2329
	#3	“chronic lymphocytic leukaemia” OR "chronic lymphocytic leukaemia" OR cll	1420
	#4	untreat* or un-treat* or first-line or "first line" or "1st line" or 1st-line or 1stline or frontline or "front line" or front-line	30,154
	#5	(#1 OR #2 OR #3) AND #4	629

Results per database:	*CDSR*	112
	CENTRAL	516

CDSR (Cochrane Database of Systematic Reviews); CENTRAL (Cochrane Central Register of Controlled Trials)

Table 4. Centre for Reviews and Dissemination search (December 2018)

Search Type	Search	Search String	Result 12 December 2018
Population	#1‡	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	83
	#2‡§	chronic AND lymph* AND leuk*	141
	#3	#1 OR #2	141
Results for databases:		DARE	37
		NHS EED	28
		HTA	76

DARE (Database of Abstracts of Reviews of Effects); EED (NHS Economic Evaluation Database); HTA (Health Technology Assessment database). Searched on 12 December 2018
‡Only 3 fields are available in CRD for their search, §searched in any field

A4. CS Appendix B. Please provide details of the supplemental searches carried out on conference proceedings websites including the search terms used and numbers of included results (CS Appendix B Supplemental Searches).

For the original SLR, update 1, and update 2, separate manual searches were conducted on the websites of the relevant conferences. From update 3 onwards, conference proceedings indexed in Embase were searched using electronic databases (i.e. Embase). For those conferences not covered in Embase, manual searches were conducted on the conference websites. Please find below all search strategies applied. The included conference abstracts are presented in the reference pack.[1]

Conference searches 2018 – 2019

Table 5. American Society of Clinical Oncology (ASCO)

Search Type	Search	Search String	Result 12 December 2018	22 July 2019
Population	1	chronic lymphocytic leukaemia chronic lymphocytic leukemia chronic lymphatic leukaemia chronic lymphatic leukemia "cll"	Combined 3,481	Combined 4,180
	2	1 AND Restricted by site: Meeting Library Publication only	2016: 439 2017: 461 2018: 550	2019: 378
Total			**1,450**	**1,828 (2016-2019)**

https://meetinglibrary.asco.org/. Searched 12 December 2018 and 8 July 2019. Filter: ASCO Annual Meeting.

Table 6. American Society of Haematology (ASH)

Search Type	Search	Search String	Result hits 18 December 2018	22 July 2019
Population	1	Terms & Keywords: chronic lymphocytic leukemia)* AND (Limited to ASH Annual Meeting abstracts)	2016: 355 2017: 329 2018: 341	2019: N/A**
Total			**1,025**	**1,025**

126 (23) 2016 ; Vol 128, Issue 22: 92-5969 December 02, 2016; 128 (22) ; 2017: Vol 130, Issue Suppl 1: 92-5599 (December 07, 2017; 130 (Suppl 1)); November 29, 2018; 132 (Suppl 1) Link: http://www.bloodjournal.org/page/ash-annual-meeting-abstracts
Note: Use Advanced Search engine. *The search engine is limited to a specific number of characters not allowing to search with the same search string as used for ASCO. When using the field “Terms & Keywords” the search engine yields the same results for all variations of the term “chronic lymphocytic leukemia” as used in the ASCO search, hence this search string is simplified to only “chronic lymphocytic leukemia”. **The 61st ASH Annual Meeting will be held December 7-10, 2019.

Table 7. British Society for Haematology (BSH)

Search Type	Search	Search String	Result hits 18 December 2018	22 July 2019
Population	1	chronic lymphocytic leukaemia	2018: 12* 2017: 9** 2016***	2019: 22****
	2	chronic lymphocytic leukemia	2018: 6* 2017: 4** 2016***	2019: 16****
	3	chronic lymphatic leukaemia	2018: 1* 2017: 0** 2016***	2019: 0****
	4	chronic lymphatic leukemia	2018: 0* 2017: 0** 2016***	2019: 0****
	5	CLL	2018: 21* 2017: 84** 2016***	2019: 165****
Total			**137**	**340 (2016-2019)**

*abstract link: https://bshannualmeeting.zerista.com/poster?owner_id=2025677&owner=other&poster_page=1

**Abstract website not found. Figures are estimates based on CTRL+F searches in abstracts published in British Journal of Haematology (2017) 176 Supplement 1. Date of Publication: 1 Mar 2017. Hence these estimates include duplicates.

***In 2016 the BSH did not held an Annual Meeting. Searched 18 December 2018.

**** 2019: https://www.postersessiononline.eu/pr/aula_poster.asp; Figures are estimates based on CTRL+F searches in abstracts published in British Journal of Haematology (2019) 185 Supplement 1. Date of Publication: Mar 2019. Hence these estimates include duplicates.

Table 8. European Hematology Association (EHA)

Search Type	Search	Search String	Result hits 18 December 2018	22 July 2019
Population	1	"chronic lymphocytic leukaemia", "chronic lymphocytic leukemia", "chronic lymphatic leukaemia", "chronic lymphatic leukemia", "cll" *Search terms have been entered individually, results are summed below.	-	-
	2	1 AND (Limited to EHA abstracts)	2018: 406* 2017: 341* 2016: 391*	2019: 351**
Total			**1,138**	**1,489 (2016-2019)**

*The current figures are estimations based on search engine results and contains duplicates as the search engine does not allow to use the Boolean operator OR (https://learningcenter.ehaweb.org/eha/). Results cannot be downloaded from the website in a formalised method, hence the EHA abstract books will be searched manually and relevant abstracts will be manually selected (HemaSphere (2019) 3 Supplement 1; HemaSphere (2018) 2 Supplement S1; Haematologica (2017) 102 Supplement 2; Haematologica (2016) 101 Supplement 1).**2019: searched via https://journals.lww.com/hemasphere/toc/2019/06001

Table 9. European Society for Medical Oncology (ESMO)

Search Type	Search	Search String	Result hits 18 December 2018	22 July 2019
Population	1	chronic lymphocytic leukaemia	2016: 7 2017: 7 2018: 9	2019: N/A*
	2	chronic lymphocytic leukemia	2016: 9 2017: 8 2018: 10	2019: N/A*
	3	CLL	2016: 7 2017: 2 2018: 2	2019: N/A*
	4	Chronic lymphatic leukemia	2016: 8 2017: 4 2018: 6	2019: N/A*
	5	Chronic lymphatic leukaemia	2016: 3 2017: 2 2018: 6	2019: N/A*
Total			**90**	**90 (2016-2019)**

Links to search platform conducted in 2018, 2017, 2016. Please note that these results may include duplicates.
https://oncologypro.esmo.org/Meeting-Resources than go to ESMO 2018 Congress https://oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress
Searched 18 December 2018. *ESMO Congress 2019 will be held at 27 September to 1 October 2019.

Table 10. International Workshop on Chronic Lymphocytic Leukemia (iWCLL)

Search Type	Search	Search String	Result hits 18 December 2018	22 July 2019
Population	1	Manual searches; examples: chronic lymphocytic leukaemia, chronic lymphocytic leukemia, chronic lymphatic leukaemia, chronic lymphatic leukemia	-	
	2	1 AND (Limited to iwCLL 2017 titles)	2017: 50*	2019: N/A**

*Only titles from presentations are available for iwCLL held in 2017. There is no formalised method or search engine to search within the abstract book of the iwCLL 2017 and all results will be manually selected. The current figure is an estimation of relevant titles. http://iwcll2017.org/wp/wp-content/uploads/2016/02/iwCLL-2017_Combined-Abstract-List_5-2-17.pdf
**iwCLL 2019 will be held at 20-23 September 2019.

Conference searches 2020

Table 11. American Society of Clinical Oncology (ASCO)

Search Type	Search	Search String	September 17, 2020
Population	1	chronic lymphocytic leukaemia chronic lymphocytic leukemia chronic lymphatic leukaemia chronic lymphatic leukemia "cll"	
	2	1 AND Restricted by site: Meeting Library Publication only	
Total			*

Searched at: https://meetinglibrary.asco.org/. *ASCO Annual Meeting in 2020 was not held.

Table 12. American Society of Haematology (ASH)

Search Type	Search	Search String	September 17, 2020
Population	1	Terms & Keywords: chronic lymphocytic leukemia)* AND (Limited to ASH Annual Meeting abstracts)	468
Total			**468 (2019-2020)**

Searched at: http://www.bloodjournal.org/page/ash-annual-meeting-abstracts Note: Use Advanced Search engine. *The search engine is limited to a specific number of characters not allowing to search with the same search string as used for ASCO. When using the field "Terms & Keywords" the search engine yields the same results for all variations of the term "chronic lymphocytic leukemia" as used in the ASCO search, hence this search string is simplified to only "chronic lymphocytic leukemia". Results ASH 2020 not yet published during the search.

Table 13. British Society for Haematology (BSH)

Search Type	Search	Search String	September 17, 2020
Population	1	chronic lymphocytic leukaemia	35
	2	chronic lymphocytic leukemia	35
	3	chronic lymphatic leukaemia	0
	4	chronic lymphatic leukemia	0
	5	CLL	33
Total			**105 (2019-2020)**

Searched on the British Journal for Hematology library https://onlinelibrary.wiley.com/journal/13652141 Restricted to abstracts between 07/2019 and 09/2020

Table 14. European Hematology Association (EHA)

Search Type	Search	Search String	September 17, 2020
Population	1	“chronic lymphocytic leukaemia”, “chronic lymphocytic leukemia”, “chronic lymphatic leukaemia”, “chronic lymphatic leukemia”, "cll" *Search terms have been entered individually, results are summed below.	
	2	1 AND (Limited to EHA abstracts)	2020: 4
Total			4

Searched via https://journals.lww.com/hemasphere/pages/currenttoc.aspx Restricted to abstracts and current issue (August 2020: Vol 4; Issue 4)

Table 15. European Society for Medical Oncology (ESMO)

Search Type	Search	Search String	September 17, 2020
Population	1	chronic lymphocytic leukaemia	1
	2	chronic lymphocytic leukemia	5
	3	CLL	4
	4	Chronic lymphatic leukemia	0
	5	Chronic lymphatic leukaemia	0
Total			**2019: 10**

ESMO 2019 Congress results. ESMO 2020 Virtual Congress not held yet at the time of the search. Restricted to abstracts. Searched at: https://oncologypro.esmo.org/Meeting-Resources

Table 16. International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Search Type	Search	Search String	September 17, 2020
Population	1	CLL chronic lymphocytic leukaemia chronic lymphocytic leukemia chronic lymphatic leukaemia chronic lymphatic leukemia	17 3 17 0 0
Total			**37**

Abstracts that were included were from ISPOR 2019-2020 including ISPOR US and Asia-Pacific 2020, excluding ISPOR US held in 2019.
Searched at https://www.ispor.org/heor-resources/presentations-database/search

Table 17. International Workshop on Chronic Lymphocytic Leukemia (iWCLL)

Search Type	Search	Search String	September 17, 2020
Population	1	Manual searches; examples: chronic lymphocytic leukaemia, chronic lymphocytic leukemia, chronic lymphatic leukaemia, chronic lymphatic leukemia	
	2		2019: 135*

Searched at: https://www.iwcll2019.org/wp-content/uploads/2019/09/iwCLL-Abstract-Titles.pdf (iwCLLXVIII 2019 abstract list)

Conference 2020-2024

Table 18. Conference coverage in Embase

Conference	Coverage in Embase (Y/N)			
	2020	2021	2022	2023
ASCO	Y	Y	Y	Y
ASH	Y	Y	Y	N
BSH	Y	Y	Y	Y
EHA	Y	Y	Y	N
ESMO	Y	Y	Y	Y
ISPOR	Y	Y	Y	Y
iWCLL*	N/A	Y	N/A	N

ASCO, American Society of Clinical Oncology; ASH, American Society of Haematology; BSH, British Society for Haematology; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; iWCLL, International Workshop on Chronic Lymphocytic Leukemia; *Bi-annual meeting

Table 19. Conference Search in Embase

Topic	Search	Searched for	February 12, 2024
Disease	S1	EMB.EXACT("chronic lymphatic leukemia")	50116*
	S2	EMB.EXACT("B cell leukemia")	7451*
	S3	TI,AB("chronic lymphatic leukemia")	1659°
	S4	TI,AB("chronic lymphatic leukaemia")	985°
	S5	TI,AB("b cell leukaemia")	230°
	S6	TI,AB("b cell leukemia")	1921°
	S7	TI,AB("chronic lymphocytic leukaemia")	5922*
	S8	TI,AB("chronic lymphocytic leukemia")	32936*
	S9	TI,AB(cll)	33784*
	S10	TI,AB(chronic NEAR/3 lymph* NEAR/3 leuk*)	45571*
	S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	70190*
Treatment setting	S12	TI,AB("previously-untreated")	18563*
	S13	TI,AB(untreat*)	297265*
	S14	TI,AB(un-treat*)	660°
	S15	TI,AB("first-line")	198330*
	S16	TI,AB("first line")	198330*
	S17	TI,AB("1st line")	5826*
	S18	TI,AB(1st-line)	5829*
	S19	TI,AB(1stline)	181°
	S20	TI,AB(frontline)	21449*
	S21	TI,AB("front line")	14534*
	S22	TI,AB(front-line)	15558*
	S23	TI,AB(fit)	243221*
	S24	TI,AB(unfit)	10659*
	S25	TI,AB(un-fit)	16°
	S26	TI,AB("treatment naïve")	32272*
	S27	TI,AB(treatment-naïve)	32290*
	S28	TI,AB("treatment naive")	32272*
	S29	TI,AB(treatment-naive)	32290*
	S30	TI,AB(primary)	2828883*
	S31	TI,AB(initial)	1373397*
	S32	TI,AB("stage B")	4730°
	S33	TI,AB("stage-B")	4730°
	S34	TI,AB("symptomatic")	356291*
	S35	(earl* NEAR/3 chronic AND lymph* AND leuk*)	611°
	S36	(intermediate NEAR/3 chronic AND lymph* AND leuk*)	56°
	S37	(untreated NEAR/5 chronic AND lymph* AND leuk*)	877°
	S38	("first-line" NEAR/5 chronic AND lymph* AND leuk*)	546°
	S39	("first line" NEAR/5 chronic AND lymph* AND leuk*)	546°
	S40	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR	4961869*

		S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39	
Disease and treatment setting	S41	S11 AND S40	17781*
Conferences	S42	CFTI("ASCO" OR "ASH" OR "British Society for Haematology" OR "EHA" OR "ESMO" OR "ISPOR" OR "iWCLL")	271521*
Total and time limit	S43	S41 AND S42 AND (PD(20200917-20240212))	1258°

Table 20. American Society of Haematology (ASH)

Search Type	Search	Search String	February 1, 2024
Population	1	Terms & Keywords: chronic lymphocytic leukemia AND first-line	106
Total			**106**

Searched at: https://ashpublications.org/blood/issue/142/Supplement%201

Table 21. European Hematology Association (EHA)

Search Type	Search	Search String	February 1, 2024
Population	1	CLL in abstract book 2023	~200
Total			**~200**

Searched via abstract book: https://journals.lww.com/hemasphere/Pages/Supplement-Collection.aspx

Table 22. International Workshop on Chronic Lymphocytic Leukemia (iWCLL)

Search Type	Search	Search String	February 1, 2024
Population	1	Manual searches in abstract book; examples: chronic lymphocytic leukaemia, chronic lymphocytic leukemia, chronic lymphatic leukaemia, chronic lymphatic leukemia	~70
Total			~70

Searched at: https://iwcll2023.org/abstracts/

Table 23. Conference Search in Embase

Topic	Search	Searched for	February 6, 2025
Disease	S1	EMB.EXACT("chronic lymphatic leukemia")	52940*
	S2	EMB.EXACT("B cell leukemia")	8001*
	S3	TI,AB("chronic lymphatic leukemia")	2660°
	S4	TI,AB("chronic lymphatic leukaemia")	2660°
	S5	TI,AB("b cell leukaemia")	2672°
	S6	TI,AB("b cell leukemia")	2672°
	S7	TI,AB("chronic lymphocytic leukaemia")	40996*
	S8	TI,AB("chronic lymphocytic leukemia")	40996*
	S9	TI,AB(cll)	36138*
	S10	TI,AB(chronic NEAR/3 lymph* NEAR/3 leuk*)	48024*
	S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	74469*
Treatment setting	S12	TI,AB("previously-untreated")	19564*
	S13	TI,AB(untreat*)	310458*
	S14	TI,AB(un-treat*)	679°
	S15	TI,AB("first-line")	216442*
	S16	TI,AB("first line")	216442*
	S17	TI,AB("1st line")	6256*
	S18	TI,AB(1st-line)	6256*
	S19	TI,AB(1stline)	185°
	S20	TI,AB(frontline)	23957*
	S21	TI,AB("front line")	16632*
	S22	TI,AB(front-line)	16632*
	S23	TI,AB(fit)	258303*
	S24	TI,AB(unfit)	11446*
	S25	TI,AB(un-fit)	18°
	S26	TI,AB("treatment naïve")	35100*
	S27	TI,AB(treatment-naïve)	35100*
	S28	TI,AB("treatment naive")	35100*
	S29	TI,AB(treatment-naive)	35100*
	S30	TI,AB(primary)	3028000*
	S31	TI,AB(initial)	1452830*
	S32	TI,AB("stage B")	5616*
	S33	TI,AB("stage-B")	5616*
	S34	TI,AB("symptomatic")	376230*
	S35	(earl* NEAR/3 chronic AND lymph* AND leuk*)	594°
	S36	(intermediate NEAR/3 chronic AND lymph* AND leuk*)	46°
	S37	(untreated NEAR/5 chronic AND lymph* AND leuk*)	924°
	S38	("first-line" NEAR/5 chronic AND lymph* AND leuk*)	565°
	S39	("first line" NEAR/5 chronic AND lymph* AND leuk*)	565°
	S40	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39	5279815*

Disease and treatment setting	S41	S11 AND S40	19474*
Conferences	S42	CFTI("ASCO" OR "ASH" OR "British Society for Haematology" OR "EHA" OR "ESMO" OR "ISPOR" OR "iWCLL")	311363*
Total and time limit	S43	S41 AND S42 AND (PD(20240212-20250206))	44°

Table 24. American Society of Haematology (ASH)

Search Type	Search	Search String	February 6, 2025
Population	1	Terms & Keywords: chronic lymphocytic leukemia AND first-line	42
Total			**42**

Searched at: https://ash.confex.com/ash/2024/webprogram/start.html

Table 25. European Hematology Association (EHA)

Search Type	Search	Search String	February 6, 2025
Population	1	chronic lymphocytic leukemia (CLL) in abstract book 2024	127
Total			**127**

Searched via abstract book: https://journals.lww.com/hemasphere/Pages/Supplement-Collection.aspx

Table 26. British Society of Haematology (BSH)

Search Type	Search	Search String	February 6, 2025
Population	1	CLL in poster book 2024	39
		CLL in e-poster book 2024	1
Total			**40**

Searched at: https://onlinelibrary.wiley.com/toc/13652141/2024/204/S1

Systematic literature review (clinical effectiveness)

A5. CS, Appendix B. Please provide a list of eligible observational studies, including the full title and reference.

Please find these in the Excel® file in the reference pack.[2]

A6. Please provide PDFs for the following:

A. 129 included RCT publications

Please refer to the reference pack provided with the original submission for these publications. For the EAG's convenience, these references have been re-provided as part of the Clarification Question response.

B. 286 excluded studies

Please find citation details of the excluded studies, and reasons for exclusion, in the reference pack.[3]

C. 275 observational studies

These references have been provided as part of the Clarification Question response by each phase.

Included studies (clinical effectiveness)

A7. CS, section 2.5. Please provide the clinical study report (referred to in section 2.5) and the statistical analysis plan for the CLL13 trial.

The CSR refers to the Priority 1 Analyses document that was provided as part of the additional reference request.[4] A full CSR has not been created by the German CLL Study Group who have ownership and control of the CLL13 trial. The SAP has already been provided as part of the reference pack in the company submission.[5] This has now been re-provided as part of the response to clarification questions.

A8. Please clarify how many UK patients were included in CLL13.

CLL13 was not conducted within the UK and therefore, there were no UK patients within the study. However, a high proportion of patients enrolled in the CLL13 trial were from European countries (96.3%) and therefore their characteristics and associated outcomes are expected to be generalisable to UK clinical practice.[6] This topic was discussed with clinical experts, with whom AbbVie consulted during submission development, and it was confirmed that both patient characteristics and outcomes were consistent with what they would expect from a UK population.

A9. Please clarify what eligibility criteria in CLL13 were used to categorise patients as 'fit'. Please clarify what clinical tests and thresholds were used to define 'fitness'.

When Ven+O originally entered into the CDF, appraisals focused patient fitness based on available chemo-immunotherapy options. Since then, and as explained in the company submission, the treatment pathway has evolved. Targeted therapies have replaced chemo-immunotherapy as the standard of care for all previously untreated CLL patients, as seen with TA891, which reimbursed I+V across all front line CLL regardless of fitness.

In TA891 it was accepted that the FCR- or BR-suitable population cannot be accurately defined in clinical practice in England, and that implementing this criterion, which is essentially related to fitness, is challenging for clinicians.[7] Therefore, whilst our submission focuses on fitness, there is a need to move away from formalising the definition of fitness as this terminology was based on historic use of chemo-immunotherapies.

Per the BSH guidelines there is no formal tool to assess fitness.[8] This was further corroborated by both the company submission in TA891 and the EAG, where both found that there is no standard way for determining patient fitness. Factors which are typically considered include comorbidities, creatinine clearance and previous treatment, regardless of age.

In the absence of a formal tool to assess fitness, the CLL13 trial assessed fitness by the burden of co-existing conditions, assessed using the Cumulative Illness Rating Scale (CIRS), creatinine clearance and Eastern Cooperative Oncology Group (ECOG) performance status.[9]

A10. CS, section 2.3.2.1. The company submission highlights that the Cancer Drugs Fund data collection period occurred from 10/11/2020 to 31/10/2022. The National Disease Registration Service Systemic Anti-Cancer Therapy (SACT) report that data was collected up to February 2023.

- Please clarify whether a more recent data cut can be provided. If not, please explain why no further follow-up is available.

- Please clarify whether additional patients were able to start venetoclax plus obinutuzumab therapy (Ven+O) after the data collection period.

As detailed in the SACT report, [redacted] for venetoclax with obinutuzumab were identified in the Blueteq system.[10]

A snapshot of SACT data was taken on 4 February 2023 and made available for analysis on 13 February 2023 and includes SACT activity up to 31 October 2022.

This confirms that the analysis was run in February on patients whose application for use was entered into the system up until the end of October 2022.

The SACT data collection period was targeted to be aligned with anticipated data cuts from the primary data source stated in the Managed Access Agreement, CLL13. The final data cut for CLL13 was expected to be January 2023 (database lock); however, the January 2023 data cut was in fact the interim analysis used in the submission with a median follow-up of 50.7 months, and the final analysis (to which AbbVie do not have access) was dated January 2024 with a median follow-up of 63.8 months.

Patients were able to start Ven+O after the data collection period, and have continued to benefit from Ven+O.

A11. CS, sections 2.10 and 2.10.1.3. The company submission highlights that "As the CLL13 trial is not owned by AbbVie, the company have limited access to IPD" (p70). It further states "For CLL13, IPD data was available for PFS, OS, CR and ORR for a maximum follow-up of 50.7 months" (p76). Please explain why individual patient data (IPD) was available for some outcomes, but not others such as data on subsequent treatments.

As AbbVie do not own the CLL13 trial, an agreement was formed whereby a limited set of individual patient data (IPD) was able to be provided to allow for the MAIC to be performed.

A summary of the data available from CLL13 is presented in Table 27.

Table 27. Summary of data availability from CLL13

		Source				
		Eichorst 2021[11]	Eichorst 2023[6]	GCLLSG	Furstenau 2024[12]	EHA 2025[13]
Median FU (months):		27.9	38.8	50.7		63.8
IPD	For MAIC – including OS, PFS, CR, ORR	No	No	Yes	No	No
Summary data	OS	No	Yes	Yes	Yes	Yes, no KMs
	PFS	No	Yes	Yes	Yes	Yes, no KMs
Adverse events	Summary	Yes	Yes	Yes	Yes	Yes
	Detailed	No	Yes	Yes	Yes	No
Subsequent treatments		No	No	Yes – see question A16	Limited – see question A16	No

CR, complete response; GCLLSG, German CLL study group; IPD, individual patient data; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

A12. CS, section 3.5.1.1. The company submission reports using dose intensities based on trial data. Please provide details on any dose interruptions or reductions and use of concomitant treatments.

Details regarding treatment exposure in CLL13 are provided in Table 28 as part of additional supportive analyses provided by the German CLL Study Group (GCLLSG). As the original investigators and owners of the CLL13 trial, the GCLLSG have provided this data to support AbbVie in submitting responses to these clarification questions; however, there are no further agreements in place for additional data extraction.[14]

Table 28. Ven+O treatment exposure in CLL13

	Ven+O total	
	Obinutuzumab	Venetoclax
Patients (ITT), N	[redacted]	[redacted]
Dose intensity (%)		
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
IQR	[redacted]	[redacted]
Range	[redacted]	[redacted]
Reduced dose intensity[1], N (%)		
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Time with 0-dose (days)		
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
IQR	[redacted]	[redacted]
Range	[redacted]	[redacted]
Patients with at least one dose modification, N (%)	[redacted]	[redacted]
Patients with at least one dose modification due to AE, N (%)	[redacted]	[redacted]
Patients with at least one dose interruption >7 days, N (%)	[redacted]	[redacted]

[1]Patients have received treatment with reduced dose intensity, if less than 80% of the planned dose was administered
ITT, intention-to-treat population; IQR, inter-quartile range; SD, standard deviation; Ven+O, Venetoclax + Obinutuzumab

Dose intensity is based on the actual treatment duration and is calculated as the quotient of the actual given dose divided by the planned dose of the respective substance. Due to limited access to data from the CLL13 trial, no further details on concomitant treatments are able to be obtained.

A13. CS, section 2.11. The company submission only reports treatment-emergent serious adverse events and adverse events (AEs) of special interest for safety. Please provide overall AEs, and grade 3 and 4 AEs.

The overall AEs and serious AEs are provided in the Priority 1 Analyses document from CLL13 provided in the reference pack for the Company Submission. The grade 3 and 4 AEs have been separated out by the GCLLSG solely for the purpose of this question (per A12). For the EAG's convenience, AbbVie have extracted the relevant data and provided these in the reference pack.[15,16]

A14. CS, section 2. The company submission states "Overall survival did not differ significantly between the treatment groups, and no treatment group reached median OS. Five-year OS rates were 93.6% for Ven+O and 90.7% for SCIT" (p35). Please explain how the absence of statistically significant overall survival (OS) benefit should be interpreted for Ven+O compared to standardised chemoimmunotherapy (SCIT) at 5 years.

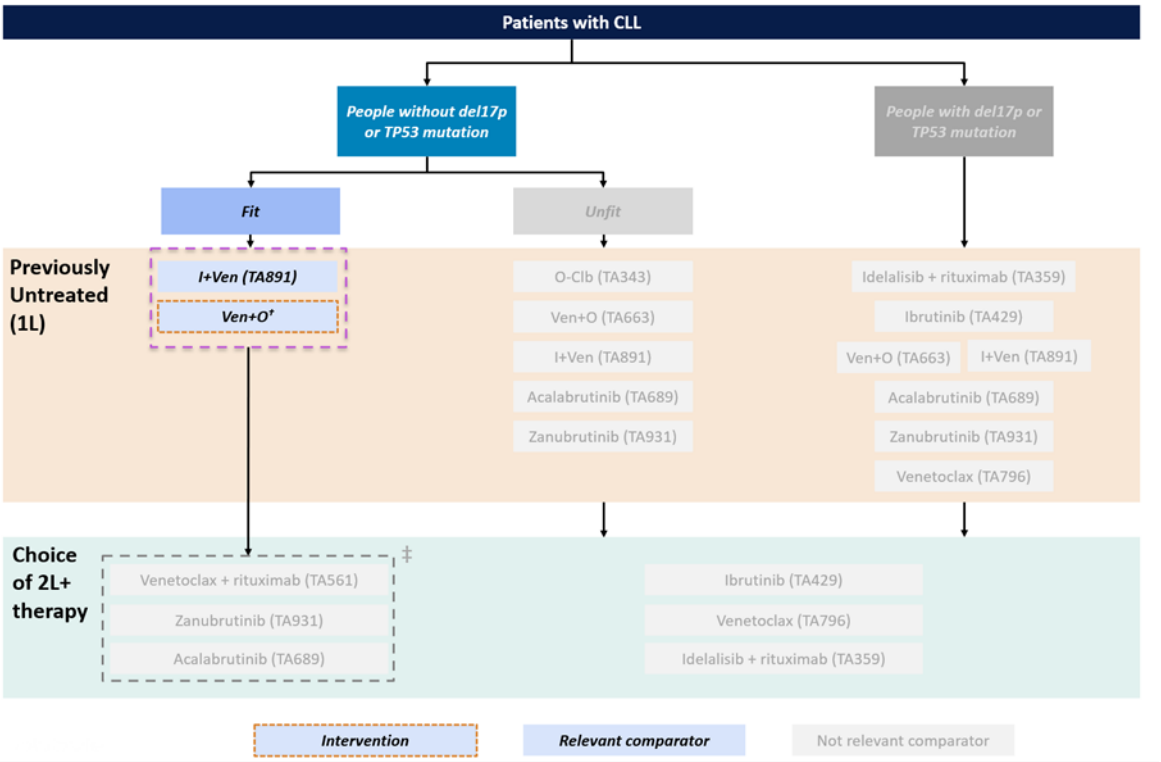
CLL13 demonstrated that at a median follow-up of 63.8 months, PFS was superior for Ven+O compared with SCIT (median not reached [NR] vs 61.2 months; p<0.001).[13] Furthermore, the five-year OS rates were higher for VenO compared to SCIT, albeit not statistically significant. The superior PFS is consistent with the observation across numerous clinical trials in CLL that venetoclax combinations deliver high rates of undetectable MRD and therefore delay progression of the cancer.[4,17-19] Thus, a higher proportion of Ven+O patients are expected to achieve long and durable responses compared with SCIT. Furthermore, patients receiving Ven+O achieve these outcomes without the long-term toxicities associated with SCIT, such as secondary malignancies, which also impact patient quality of life.[20-22] In contrast, a lower proportion of patients receiving FCR would be expected to remain in long-term remission, and would thus require 2L+ treatment.

As outlined in the response to question A16 below, at a median follow-up of 50.7 months (just over 4 years), a higher proportion of patients in the SCIT arm (50 patients) had progressed to second line treatment relative to the Ven+O arm (18 patients).[12]

Figure 1 of the company submission is re-presented below and shows the range of innovative technologies available at 2L+. The main classes of medicines are venetoclax combinations and BTKis, both of which have demonstrated high OS rates. This is consistent with the majority of 2L treatments that patients in the SCIT arm of the CLL13 trial went on to receive based on the 50.7 months follow-up.[12,14] Of

the 50 patents receiving 2L treatment: 22 (44%) received BTKi based treatment and 19 (38%) received venetoclax based treatment [See A16 below]. Thus, notwithstanding the higher 5-year OS rates of Ven+O compared to SCIT, the impact of innovative subsequent treatments is that the 5-year OS rates of other front-line interventions, including SCIT and I+Ven, is expected to be high.

Figure 1. Treatment pathway in UK clinical practice for fit CLL patients without TP53/del17p



† Venetoclax + obinutuzumab is available for patients in this population via the CDF in England and Northern Ireland, and through a different funding scheme in Wales.
‡ Relevant 2L+ treatments for the target population were identified by UK clinical experts who added that duration of response to 1L therapy determines the 2L treatment rather than the type of 1L therapy. This is consistent with ESMO guidelines.[23] The Evidence Assessment Group (EAG) for a recent NICE appraisal (TA931) outlined that the definition of patient fitness is subjective and driven by patient characteristics such as age and CIRS score rather than eligibility for specific treatments, in line with recent declines in use of chemotherapy regimens in clinical practice.[24]
1L, first-line; 2L, second-line; BR, bendamustine and rituximab; CDF, Cancer Drugs Fund; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; I+Ven, ibrutinib + venetoclax; Ven+O, venetoclax + obinutuzumab
Adapted from NICE TA931 committee slides[24]

A15. CS, section 2.3.2.1. Please provide the wording of the questions and the required answers on the Blueteq forms to access Ven+O.

The Blueteq form is hosted on a confidential NHSE Blueteq database, which AbbVie does not have access to.

A16. **PRIORITY QUESTION. CS, section 2.6.** For CLL13, please provide a breakdown of subsequent therapies for Ven+O and SCIT arms.

As explained in the response to question A11 above, information on subsequent therapies is available from the January 2023 data cut, representing a median follow-up of 50.7 months. This is reported in the publication by Fürstenau et al. 2024 and presented in Figure 2 below.[12]

At a median follow-up of 50.7 months (just over 4 years), a higher proportion of patients in the SCIT group (50 patients) had progressed to second line treatment relative to the Ven+O arm (18 patients). Please see the response to question A14, which explains the significance of this observation from the trial.

Figure 2. Sequence of treatments (A) and time to next treatment from the start of second-line treatment (B) in patients with chronic lymphocytic leukaemia-type disease progression (n=111)

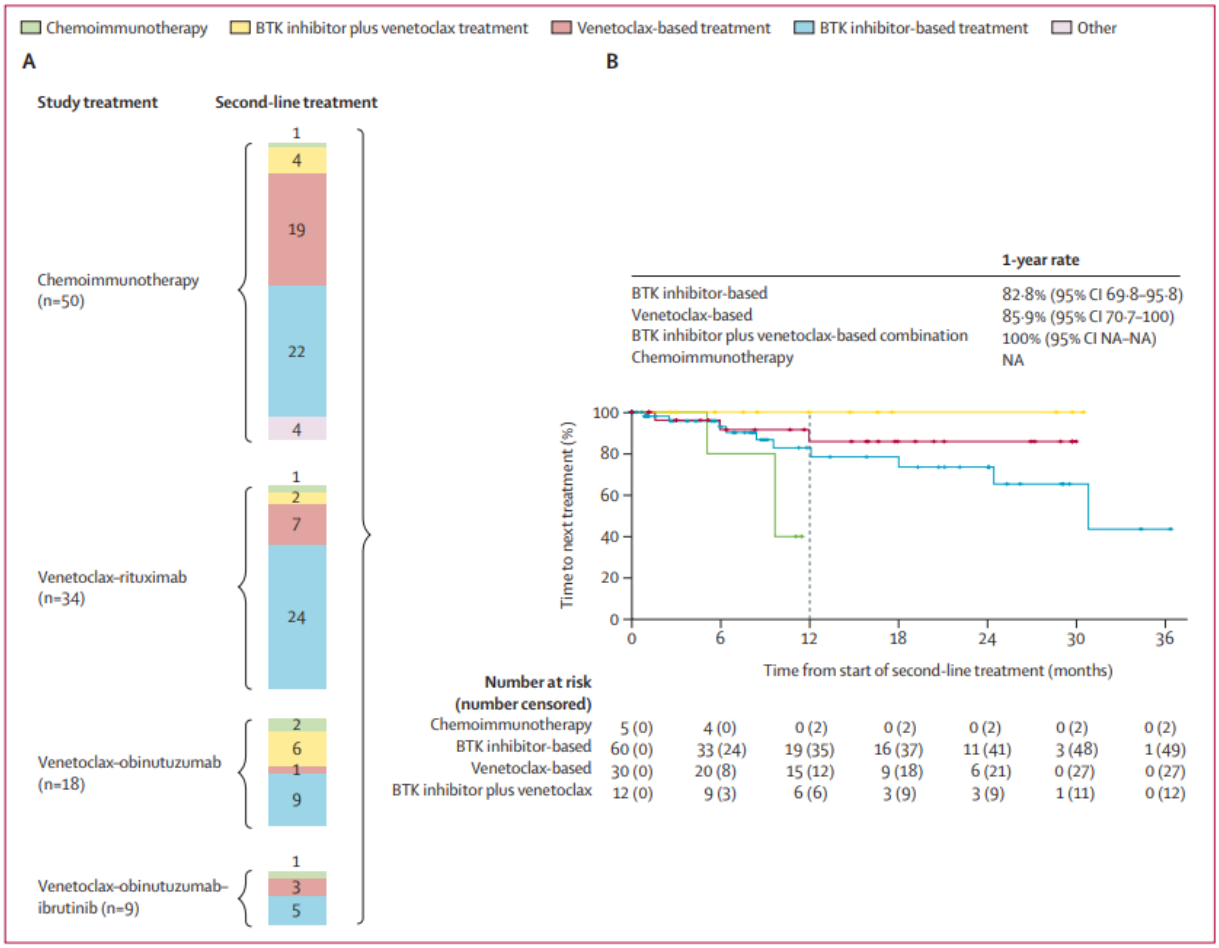


Figure sourced from Furstenau et al 2024.[12]

As stated in the company submission Section 3.5.1.3, clinical feedback reports that choice of treatment in first line does not inform subsequent treatment choice, but that the duration of response to first line treatment is the key consideration informing the next therapy. Additionally, given that all patients are assumed to eventually receive

all relevant subsequent treatments in the economic models, the proportions of patients receiving each subsequent treatment for Ven+O and I+Ven, the only relevant comparator, are assumed to be equivalent.

More granular subsequent treatment data has been obtained for the January 2023 data cut from the GCLLSG solely for the purpose of this question (per A12) and is provided in the reference pack.[25]

Indirect treatment comparison (clinical effectiveness)

A17. **PRIORITY QUESTION. CS, sections 2.10 and 3.3.2.1, Appendix J, Table 50.** Please provide smoothed hazard plots comparing matching-adjusted indirect comparison (MAIC)-weighted CLL13 data under MAIC scenario 4 (Appendix J, Table 50) to CAPTIVATE progression-free survival and OS, along with equivalent information for assessing the proportional hazards assumption as per section 3.3.2.1 in the company submission.

Scenario 4 is the 'fully adjusted' scenario which adjusted for all baseline characteristics, using every treatment effect modifier and prognostic variable as matching factors, as described in Appendix J. The effective sample size for scenario 4 is [redacted], which is [redacted] % of the original sample size. Compared with the base case effective sample size of [redacted] ([redacted]% of the original sample size), this scenario is associated with substantially higher uncertainty.

Table 29. Assessing the proportional hazards assumption for Ven+O versus I+Ven

Scenario	Outcome	Log-cumulative hazard plots	Schoenfeld residuals plot†	Grambsch-Therneau test‡	PHA violated?
Ven+O vs I+Ven	OS	Crossing	Slight trend	p = 0.656	Unclear
	PFS	Multiple crossings	No time-varying trend	p = 0.898	No

† If p-value > 0.05, no evidence to reject PHA

‡ If the covariate is time-independent, no evidence to reject PHA

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PHA, proportional hazards assumption

As shown in Table 29, the results of the proportional hazards assumption (PHA) are inconclusive, given the sample size is smaller than that for the base case MAIC the tests are even less powered to detect whether the PHA is supported. The output of the MAIC for scenario 4 suggested numerical improvements in PFS for Ven+O,

albeit with wide confidence intervals, hence providing rationale for similar hazards over time and the crossing of the log-cumulative hazard plots (Figure 3). The slight, but non-statistically significant, trend in the Schoenfeld residuals plot for OS can be explained by the low number of OS events (Figure 4). As per the base case MAIC, individual consultations confirmed that the treatment effect of Ven+O and I+Ven is proportionate and therefore the PHA holds.

Smoothed hazard plots are provided for PFS and OS in Figure 5. For both PFS and OS, the smoothed hazard plots show that Ven+O and I+Ven maintain low and comparable hazard rates during the initial follow-up period. For OS, at around 30 months, no notable divergence is observed between the two treatments despite a slight increase in hazard for Ven+O. At around 50 months, the hazard for I+Ven rises exponentially in comparison with Ven+O. For PFS, beyond approximately 50 months, the hazard associated with I+Ven increases, diverging from the more stable trajectory of Ven+O. A small cluster of OS events occur between 48 and 54 months in the I+Ven ITT population, having been a relatively steady decline of number at risk prior to 48 months, which could cause the hazard spike. However, it is important to note that the hazard only changes by [redacted] which is very minimal. In conclusion, the smoothed hazard plots support that the PHA between Ven+O and I+Ven may be appropriate.

Figure 3. Log cumulative hazard plot of weighted Ven+O and I+Ven

PFS **OS**

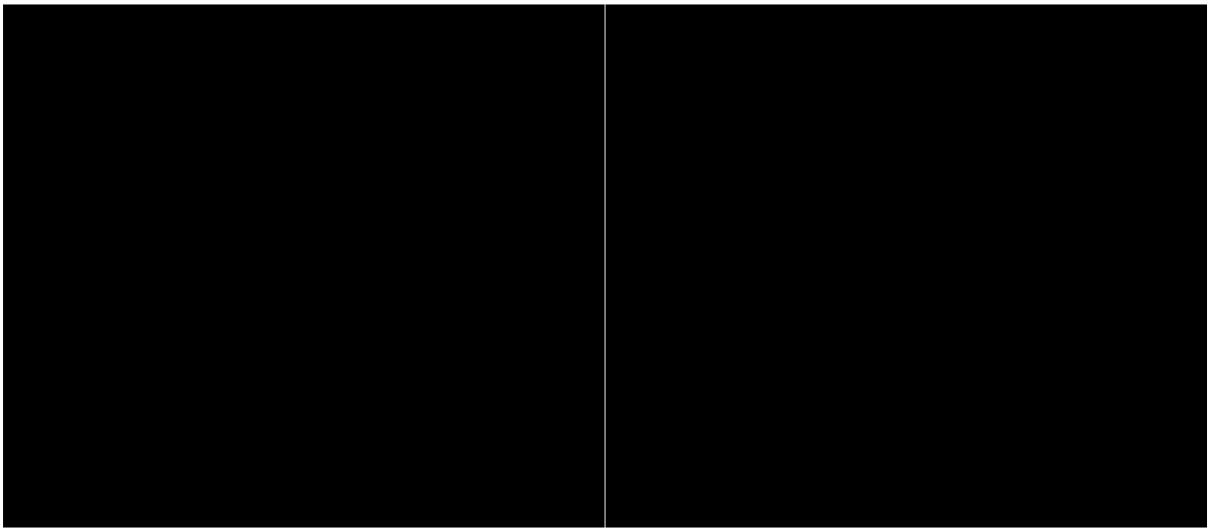


Figure 4. Schoenfeld residuals plot of weighted Ven+O and I+Ven

PFS **OS**

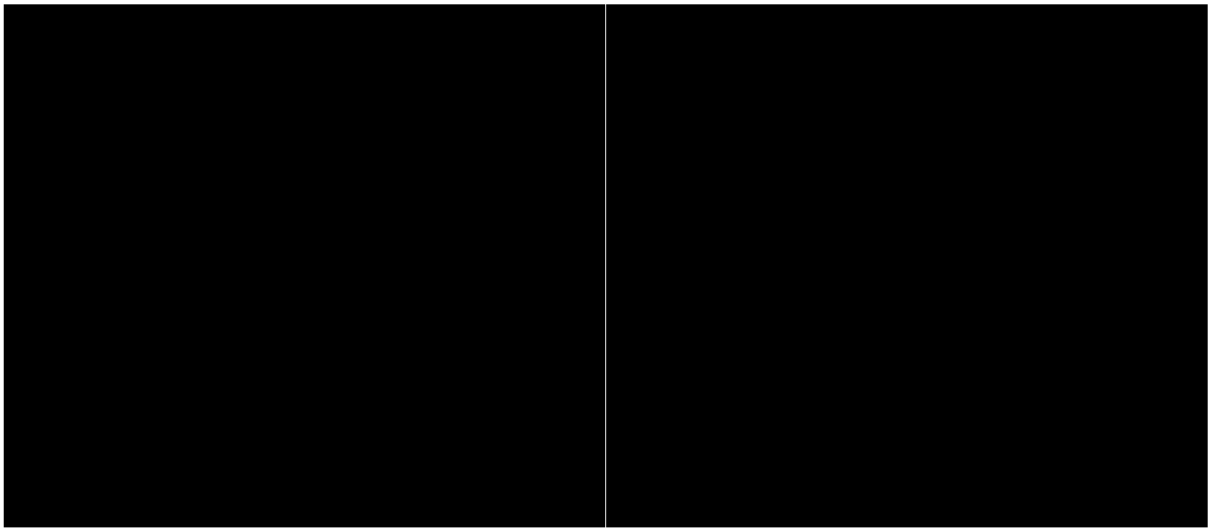
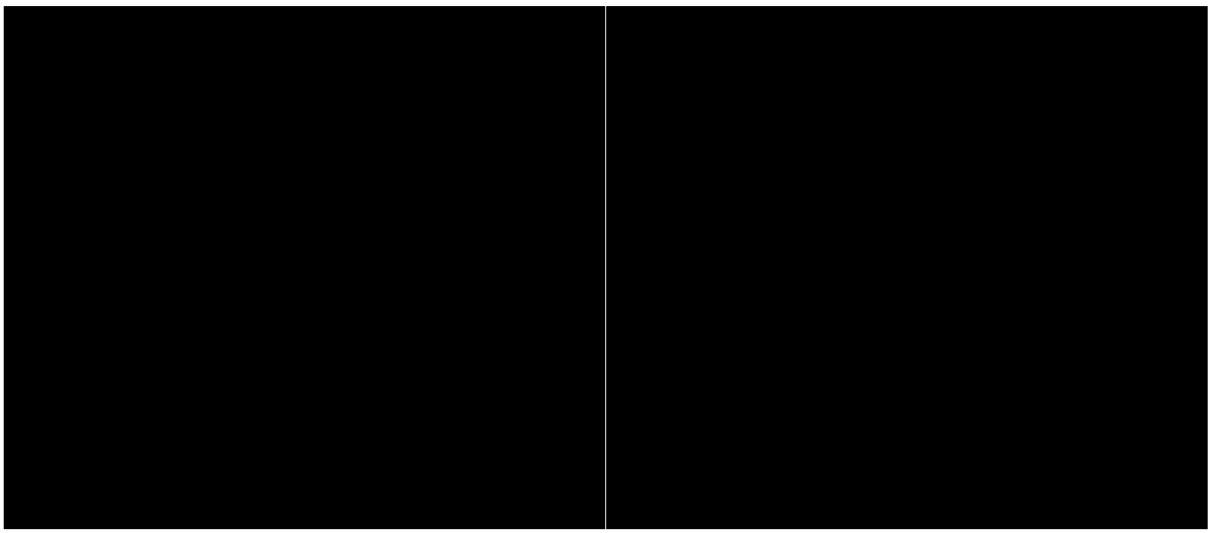


Figure 5. Smoothed hazard plots of weighted Ven+O and I+Ven

PFS **OS**



Section B: Clarification on cost-effectiveness data

Literature searching (cost-effectiveness)

B1. CS, Appendix E. Please provide the full search strategies for the database searches in Medline, Embase and the Cochrane Library for the original search strategy carried out on 12 December 2018. Please clarify if the update searches have changed.

Please find the search strategy of the original SLR below. The search terms have not been adjusted in any of the updates of the SLR.

Table 30. ProQuest economic search (December 2018)

Topic	Search	Searched for	Results 12 December 2018
Disease	S1	EMB.EXACT("chronic lymphatic leukemia")	36595*
	S2	MESH.EXACT("Leukemia, Lymphocytic, Chronic, B-Cell")	14911*
	S3	EMB.EXACT("B cell leukemia")	6387*
	S4	TI,AB("chronic lymphatic leukemia")	1843°
	S5	TI,AB("chronic lymphatic leukaemia")	1078°
	S6	TI,AB("b cell leukaemia")	185°
	S7	TI,AB("b cell leukemia")	1480°
	S8	TI,AB("chronic lymphocytic leukaemia")	8187*
	S9	TI,AB("chronic lymphocytic leukemia")	38894*
	S10	TI,AB(cll)	37370*
	S11	TI,AB(chronic NEAR/3 lymph* NEAR/3 leuk*)	56871*

	S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	79785*
Treatment setting	S13	TI,AB("previously-untreated")	24206*
	S14	TI,AB(untreat*)	394837*
	S15	TI,AB(un-treat*)	485°
	S16	TI,AB("first-line")	184419*
	S17	TI,AB("first line")	184419*
	S18	TI,AB("1st line")	3535°
	S19	TI,AB(1st-line)	3536°
	S20	TI,AB(1stline)	126°
	S21	TI,AB(frontline)	14105*
	S22	TI,AB("front line")	14124*
	S23	TI,AB(front-line)	15257*
	S24	TI,AB(fit)	300510*
	S25	TI,AB(unfit)	10553*
	S26	TI,AB(un-fit)	11°
	S27	TI,AB("treatment naïve")	26260*
	S28	TI,AB(treatment-naïve)	26273*
	S29	TI,AB("treatment naive")	26260*
	S30	TI,AB(treatment-naive)	26273*
	S31	TI,AB(primary)	3304568*
	S32	TI,AB(initial)	1724448*
	S33	TI,AB("stage B")	5650*
	S34	TI,AB("stage-B")	5650*
	S35	TI,AB("symptomatic")	412134*
	S36	(earl* NEAR/3 chronic AND lymph* AND leuk*)	571°
	S37	(intermediate NEAR/3 chronic AND lymph* AND leuk*)	50°
	S38	(untreated NEAR/5 chronic AND lymph* AND leuk*)	712°
	S39	("first-line" NEAR/5 chronic AND lymph* AND leuk*)	350°
	S40	("first line" NEAR/5 chronic AND lymph* AND leuk*)	350°
	S41	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40	5967297*
Disease and treatment setting	S42	S12 AND S41	16638*
Cost effectiveness	S43	EMB.EXACT("Cost effectiveness analysis")	142780*
	S44	MESH.EXACT("Cost-benefit analysis")	74645*
	S45	MESH.EXACT("Economics")	423508*
	S46	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	119284*
	S47	TI(cost NEAR/1 effectiveness)	48901*
	S48	EMB.EXACT("Cost benefit analysis")	82625*
	S49	EMB.EXACT("Economic aspect")	120868*
	S50	EMB.EXACT("Socioeconomics")	138980*
	S51	MESH.EXACT("Economics, pharmaceutical")	2810°
	S52	EMB.EXACT("Health economics")	38939*
	S53	MESH.EXACT("Costs and cost analysis")	46570*
	S54	MESH.EXACT("Value of life")	5626*
	S55	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1043281*
	S56	TI,AB,IF(monte carlo)	109869*
	S57	EMB.EXACT("Probability")	101239*
	S58	MESH.EXACT("Decision Theory" OR "Decision Trees")	11252*
	S59	EMB.EXACT("Decision Tree")	11471*
	S60	MESH.EXACT("Markov chains")	13051*
	S61	EMB.EXACT("Statistical Model")	187394*

	S62	MESH.EXACT("Monte carlo method")	26057*
	S63	EMB.EXACT("Decision Theory")	2779°
	S64	EMB.EXACT("Monte carlo method")	36232*
	S65	TI,AB,IF(markov)	57228*
	S66	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	522005*
	S67	TI,AB,IF(value NEAR/2 (money or monetary))	7429*
	S68	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	85661*
	S69	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2233653*
	S70	MESH.EXACT.EXPLODE("Costs and cost analysis")	219818*
	S71	EMB.EXACT("Economics")	239028*
	S72	EMB.EXACT("Cost")	60409*
	S73	AB,IF(economic model*)	180815*
	S74	MESH.EXACT("Models, economic")	9040*
	S75	EMB.EXACT("Cost utility analysis")	9154*
	S76	TI,AB(cost NEAR/2 effectiveness)	133891*
	S77	TI,AB(cost NEAR/2 utility)	14523*
	S78	TI,AB(cost NEAR/2 benefit)	60856*
	S79	S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78	3588643*
Healthcare cost and resource use	S80	MESH.EXACT("Economics")	423508*
	S81	EMB.EXACT("Economic aspect")	120868*
	S82	EMB.EXACT("Socioeconomics")	138980*
	S83	MESH.EXACT("Economics, pharmaceutical")	2810°
	S84	EMB.EXACT("Health economics")	38939*
	S85	MESH.EXACT("Costs and cost analysis")	46570*
	S86	MESH.EXACT("Value of life")	5626*
	S87	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1043281*
	S88	MESH.EXACT("Hospital costs")	10045*
	S89	MESH.EXACT("Employer health costs")	1087°
	S90	MESH.EXACT("Cost savings")	10962*
	S91	MESH.EXACT("Direct service costs")	1147°
	S92	EMB.EXACT("Financial management")	117324*
	S93	EMB.EXACT("Health care financing")	13395*
	S94	MESH.EXACT.EXPLODE("Budgets")	13408*
	S95	MESH.EXACT.EXPLODE("Economics, medical")	14063*
	S96	TI,AB(Low NEAR/1 cost)	154640*
	S97	MESH.EXACT("Drug costs")	14943*
	S98	MESH.EXACT("Deductibles and Coinsurance")	1678°
	S99	EMB.EXACT("Health care cost")	179313*
	S100	MESH.EXACT("Health expenditures")	18033*
	S101	TI,AB(Cost NEAR/1 variable)	2819°
	S102	EMB.EXACT("Cost of illness")	18510*
	S103	MESH.EXACT("Capital expenditures")	1979°
	S104	MESH.EXACT("Cost allocation")	1988°
	S105	EMB.EXACT("Hospital cost")	20617*
	S106	MESH.EXACT("Cost control")	21278*
	S107	MESH.EXACT.EXPLODE("Economics, hospital")	23189*
	S108	MESH.EXACT("Cost sharing")	2366°

	S109	MESH.EXACT("Cost of illness")	24215*
	S110	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	28718*
	S111	TI,AB(Fiscal OR funding OR financial OR finance)	473995*
	S112	MESH.EXACT.EXPLODE("Fees and charges")	31964*
	S113	EMB.EXACT("Cost minimization analysis")	3362°
	S114	TI,AB(Cost NEAR/1 estimate*)	36595*
	S115	MESH.EXACT("Health care costs")	35902*
	S116	MESH.EXACT("Economics, Nursing")	3949°
	S117	MESH.EXACT("Medical savings accounts")	521°
	S118	EMB.EXACT("Cost control")	67864*
	S119	TI,AB(High NEAR/1 cost)	91613*
	S120	TI,AB(Unit NEAR/1 cost*)	10444*
	S121	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2233653*
	S122	MESH.EXACT.EXPLODE("Costs and cost analysis")	219818*
	S123	EMB.EXACT("Economics")	239028*
	S124	EMB.EXACT("Cost")	60409*
	S125	AB,IF(economic model*)	180815*
	S126	MESH.EXACT("Models, economic")	9040*
	S127	MESH.EXACT("Economics, Dental")	1877°
	S128	EMB.EXACT("Budget")	32340*
	S129	TI,AB,IF(budget*)	115198*
	S130	TI,AB(Productivit*)	156621*
	S131	TI,AB("Health care" AND cost*)	124603*
	S132	TI,AB("Length of stay")	133719*
	S133	TI,AB(Health AND resource)	222030*
	S134	TI,AB(Resource NEAR/2 utili*ation)	29884*
	S135	TI,AB(Hospitali*ation NEAR/2 (rate OR frequency))	24612*
	S136	EMB.EXACT("Productivity")	49619*
	S137	TI,AB(Resource NEAR/3 use)	53937*
	S138	TI,AB(Visit NEAR/3 (inpatient OR outpatient OR ER OR emergency OR GP))	56069*
	S139	TI,AB(Lost AND work* AND day*)	6939*
	S140	S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139	3839404*
HRQoL and utilities	S141	TI,AB(qaly* OR qald* OR qale* OR qtime*)	26034*
	S142	TI,AB(quality adjusted OR adjusted life year*)	99149*
	S143	TI,AB("quality of life" OR qol OR hrqol OR quality NEAR/2 life)	637615*
	S144	TI,AB(health NEAR/5 state)	97958*
	S145	TI,AB(disability adjusted life)	9228*
	S146	TI,AB(daly[*1])	5733*
	S147	TI,AB((index NEAR/3 wellbeing) OR (quality NEAR/3 wellbeing) OR qwb)	1359°
	S148	TI,AB(multiattribute* OR multi attribute*)	10574*

	S149	TI,AB(utility NEAR/3 (score[*1] OR scoring OR valu* OR measur* OR evaluat* OR scale[*1] OR instrument[*1] OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimat* OR elicit* OR disease* OR mean OR cost* OR expenditure[*1] OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculat* OR range* OR increment* OR state OR states OR status))	101028*
	S150	TI,AB(utility OR utilities)	455173*
	S151	TI,AB(disutility OR disutilities)	1353°
	S152	TI,AB(HSUV OR HSUVs)	87°
	S153	TI,AB(health[*1] year[*1] equivalent[*1])	15905*
	S154	TI,AB(hye OR hyes)	140°
	S155	TI,AB("health utility index" OR hui OR hui1 OR hui2 OR hui3)	5291*
	S156	TI,AB(illness state[*1] OR health state[*1])	415996*
	S157	TI,AB(euro qual OR euro qual5d OR euro qol5d OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d)	25338*
	S158	TI,AB(eq-sdq OR eqsdq)	1°
	S159	TI,AB(short form* OR shortform*)	343671*
	S160	TI,AB(sf36* OR sf 36* OR sf thirtysix OR sf thirty six)	57986*
	S161	TI,AB(sf6 OR sf 6 OR sf6d OR sf 6d OR sf six OR sfsix OR sf8 OR sf 8 OR sf eight OR sfeight)	63177*
	S162	TI,AB(sf12 OR sf 12 OR sf twelve OR sftwelve)	33028*
	S163	TI,AB(sf16 OR sf 16 OR sf sixteen OR sfsixteen)	12265*
	S164	TI,AB(sf20 OR sf 20 OR sf twenty OR sftwenty)	19147*
	S165	TI,AB(15D OR 15-D OR 15 dimension)	40237*
	S166	TI,AB(standard gamble* OR sg)	23371*
	S167	TI,AB(time trade off[*1] OR time tradeoff[*1] OR tto OR timetradeoff[*1])	18537*
	S168	TI,AB(rating scal*)	181010*
	S169	TI,AB(linear scal*)	75985*
	S170	TI,AB(linear analog*)	22769*
	S171	TI,AB(visual analog* OR "VAS")	180704*
	S172	EMB.EXACT.EXPLODE("Quality of Life")	469695*
	S173	EMB.EXACT("Value of Life")	1°
	S174	MESH.EXACT("Quality of Life")	168837*
	S175	MESH.EXACT("Quality-Adjusted Life years")	10532*
	S176	MESH.EXACT("Value of Life")	5626*
	S177	S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153 OR S154 OR S155 OR S156 OR S157 OR S158 OR S159 OR S160 OR S161 OR S162 OR S163 OR S164 OR S165 OR S166 OR S167 OR S168 OR S169 OR S170 OR S171 OR S172 OR S173 OR S174 OR S175 OR S176	2470034*
Subtotal	S178	S79 OR S140 OR S177	6442014*
Total	S179	S42 AND S178	1156°

* Duplicates are removed from the search, but included in the result count.
° Duplicates are removed from the search and from the result count.
N/A: Not applicable

Table 31. Cochrane library Search (December 2018)

Search Type	Search	Search String	12 December 2018

Population	#1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	380
	#2	chronic AND lymph* AND leuk*	2329
	#3	“chronic lymphocytic leukaemia” OR "chronic lymphocytic leukaemia" OR cll	1420
	#4	untreat* or un-treat* or first-line or "first line" or "1st line" or 1st-line or 1stline or frontline or "front line" or front-line	30,154
	#5	(#1 OR #2 OR #3) AND #4	629
Results per database:		*CDSR*	112
		CENTRAL	516

CDSR (Cochrane Database of Systematic Reviews); CENTRAL (Cochrane Central Register of Controlled Trials)

Table 32. Centre for Reviews and Dissemination search (December 2018)

Search Type	Search	Search String	Result 12 December 2018
Population	#1‡	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	83
	#2‡§	chronic AND lymph* AND leuk*	141
	#3	#1 OR #2	141
Results for databases:		DARE	37
		NHS EED	28
		HTA	76

DARE (Database of Abstracts of Reviews of Effects); EED (NHS Economic Evaluation Database); HTA (Health Technology Assessment database). Searched on 12 December 2018
‡Only 3 fields are available in CRD for their search, §searched in any field

B2. CS, Appendix E. Please clarify which search strategy the PRISMA flow diagram (Appendix E, Figure 2) is reporting as the numbers of the search results do not tally with the search results reported in Appendix E 1.4, Table 14.

The search results of Table 14 only present the search results from the latest search run (February 2025). The results of the PRISMA Flow diagram presented in Figure 2 present the results of all SLR iterations that have been conducted between 2018-2025.

B3. CS, Appendix E.1.7. Please provide references (and PDFs, if available) of the identified systematic literature reviews of which reference lists were searched for further studies of interest (Selection procedure)

A limited number of relevant SLRs were identified during the individual SLR iterations. A list of SLRs identified that were excluded from the review because they were an SLR, but for which references were checked, are listed in Table 33.

Table 33. SLRs identified that were excluded from the review but for which references were checked

Author	Year	Title	Journal	Volume	Issue	Pages
Skoetz et al.	2012	Alemtuzumab for patients with chronic lymphocytic leukaemia	Cochrane Database of Systematic Reviews: Reviews	NR	Issue 2	NR
Waweru et al.	2020	Health-related quality of life and economic burden of chronic lymphocytic leukemia in the era of novel targeted agents	Current Medical Research and Opinion	-	-	1-15
Golicki, et al.	2020	EQ-5D–Derived Health State Utility Values in Hematologic Malignancies: A Catalog of 796 Utilities Based on a Systematic Review	Value in Health	23	7	953-968
Gao et al.	2022	A systematic review of economic evaluations for the pharmaceutical treatment of chronic lymphocytic leukemia and acute myeloid leukemia	Expert Review of Hematology	15	9	833-847

Model structure

B4. Excel economic PS and CCA models. Please clarify why CLL14 was used to derive mean body weight and mean body height values used in the economic model rather than CLL13.

As discussed in A11, AbbVie do not own the CLL13 trial and therefore, do not have unrestricted access to patient characteristics or outcomes. Baseline characteristics for mean body weight and mean body height from CLL13 were not available to AbbVie, so values from CLL14 were considered an appropriate proxy. As explained in the Company Submission, baseline characteristics for mean body weight and mean body height are used in the economic model to calculate dosage for Ven+R in the subsequent treatment basket.

To address any concerns around the impact of this body surface area (BSA) input on model outputs, AbbVie have undertaken a scenario analysis demonstrating that varying the body surface area has minimal impact on model outcomes by sourcing and applying BSA inputs used in previous NICE appraisals in CLL. Table 34 illustrates the outputs of this scenario in both the partitioned survival model (PSM) and the cost-comparison model.

Table 34. Sensitivity of outputs to varied BSA inputs applied within previous NICE appraisals in CLL

Appraisal	BSA input	Model outcomes for Ven+O and I+Ven comparison			
		PSM			Cost-Comparison
		Inc. Costs	Inc. QALYs	ICER	Inc. Costs
Base case	1.86 m^2	[redacted]	0.37	Dominant	[redacted]
TA891 (I+Ven†)[7]	2.06 m^2	[redacted]	0.37	Dominant	[redacted]
TA931 (Zanubrutinib)[24]	1.92 m^2	[redacted]	0.37	Dominant	[redacted]
TA689 (Acalabrutinib)[26]	1.93 m^2	[redacted]	0.37	Dominant	[redacted]
TA561 (Ven+R)[27]	1.92 m^2	[redacted]	0.37	Dominant	[redacted]

†Input from FCR-suitable population used
BSA, body surface area; ICER, incremental cost-effectiveness ratio; PSM, partitioned survival model; QALY, quality-adjusted life year

In line with the outputs above, the findings of the deterministic sensitivity analysis (DSA) illustrate that neither height nor body weight—which inform BSA through the Dubois formula—are drivers of costs (CS Figure 29). Indeed, of all the 112 parameters sampled in the DSA, mean height (cm) was ranked as the 49th most impactful driver of cost-effectiveness, while mean bodyweight (kg) was ranked 53rd (Table 35).

Table 35. Height and bodyweight are not impactful drivers of cost-effectiveness according to the DSA

Parameter	Incremental costs at lower bound of DSA	Incremental costs at upper bound of DSA	Range between upper and lower bounds	Rank
Mean height (cm)	[redacted]	[redacted]	[redacted]	49
Mean bodyweight (kg)	[redacted]	[redacted]	[redacted]	53

DSA, deterministic sensitivity analysis

In summary, while AbbVie acknowledges general limitations around the use of CLL14 patient characteristics to calculate BSA in the economic models, these inputs are not considered to drive results in these analyses and do not have any undue influence on cost-effectiveness outcomes.

B5. Please confirm if relative survival models were used. If not, please fit these and implement them in the economic models.

AbbVie did not perform relative survival modelling, as this approach is typically used when cause of death data is missing or unreliable in population-based cancer registries, or in clinical trial settings where cause-specific models can be applied using more reliably recorded death information.[28]

AbbVie note that during engagement with clinical experts, clinicians with experience in treating patients with CLL stated that survival for CLL would be approximately 5% lower than patients in the general population. Therefore, AbbVie have performed an additional analysis in which a standardised mortality ratio (SMR) is applied to general population mortality hazard such that patients with CLL have a 5% higher risk of death compared with the general population at each cycle accounting for age and sex.

The outcomes of this analysis in the PSM are presented in Table 36.

Table 36. Scenario analysis: Applying a SMR to general population mortality hazard based on outputs from clinical engagement (PSM)

Scenario	Technologies	Total			Incremental			
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (£/QALY)
Base case (no SMR applied)	Ven+O	[redacted]	22.35	9.85	[redacted]	0.83	0.37	Dominant
	I+Ven	[redacted]	21.51	9.48	-	-	-	-
Scenario where SMR=1.05 applied	Ven+O	[redacted]	22.02	9.77	[redacted]	0.71	0.34	Dominant
	I+Ven	[redacted]	21.31	9.43	-	-	-	-

ICER, incremental cost-effectiveness ratio; LY, life years; PSM, partitioned survival model; QALY, quality-adjusted life year; SMR, standardised mortality ratio

The outputs of this analysis illustrate that varying the approach to survival modelling by applying a general population mortality hazard has limited impact on the model outputs and continue to demonstrate that Ven+O provides greater efficacy than I+Ven and at a lower cost.

When this analysis is performed in the cost-comparison model, the difference in incremental costs between Ven+O and I+Ven compared with the base case is minimal and Ven+O remains a cost-saving treatment option in the target population of this appraisal (Table 37).

Table 37. Scenario analysis: Applying a SMR to general population mortality hazard based on outputs from clinical engagement (Cost-comparison)

Scenario	Technologies	Total Costs (£)	Incremental Costs (£)
Base case (no SMR applied)	Ven+O	[redacted]	[redacted]
	I+Ven	[redacted]	-
Scenario where SMR=1.05 applied	Ven+O	[redacted]	[redacted]
	I+Ven	[redacted]	-

SMR, standardised mortality ratio

Therefore, both the cost-utility and cost-comparison methods presented here illustrate that Ven+O is a cost-effective use of NHS resources in fit patients with untreated CLL who do not have a *TP53* or del(17p) mutation.

B6. **PRIORITY QUESTION.** Please incorporate RWE-based model inputs including survival inputs and baseline characteristics using information from the SACT report to inform Ven+O in the PS model.

The SACT report is provided by NHSE and AbbVie has no further information beyond what has been shared with us. The SACT report has also been shared with the EAG and evidently, there are insufficient inputs to undertake a robust ITC nor implement in the models; there is no IPD available to make any population adjustments in an ITC and no PFS outcomes are available – the importance of PFS is highlighted in A14 and A16. However, the cost-effectiveness results are expected to be similar given that OS is similar between SACT and CLL13.

At the time of entry into the CDF, CLL13 was considered the primary source of evidence and SACT data was collected as secondary evidence. OS was the only reported outcome from SACT, which when compared with the OS from CLL13 displays similarity. OS rates at 24 months as reported by SACT were [redacted]

[redacted], which is comparable to the 3-year OS from CLL13 of 96.3% (the first reported read-out) despite differences in the patient characteristics reported in CLL13 and SACT.

B7. Please add functionality to the PS model to utilise parametric models fitted to the CAPTIVATE PFS and OS data, removing reliance on the PH assumption.

AbbVie had recognised the uncertainty around the dependent modelling approach using the PH assumption performed within the main Company Submission. To address this, an independent modelling scenario was included proactively in Appendix K of the submission package. In this analysis, long-term outcomes for I+Ven were modelled independently of the Ven+O arm using published outcomes from the CAPTIVATE trial, thereby, removing reliance on the PH assumption.

The EAG can perform this analysis using the Survival sheet of the PS model by switching to the 'Independent' option in cells D15 and D28 for PFS and OS, respectively.

For a comprehensive overview of the methodology, including parametric distribution selection and rationale, the EAG is directed to Appendix K of the Company Submission. Key results are summarised below for convenience.

In the independent modelling analysis, the model calculated total discounted costs for I+Ven to be £[redacted], which is £[redacted] higher than for Ven+O, primarily driven by differences in treatment acquisition costs in the first line. The analysis calculated mean undiscounted LYs of 22.34 for I+Ven, correlating to discounted QALYs of 9.83. In comparison, treatment with Ven+O yielded an additional 0.02 discounted QALYs compared with I+Ven. Accordingly, when outcomes for Ven+O and I+Ven were modelled independently, Ven+O remained a dominant treatment option compared with I+Ven by achieving greater health benefits at lower costs (Table **38**).

Table 38. Scenario analysis: Independent modelling

	Total			Incremental			
Technologies	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (£/QALY)
Ven+O	[redacted]	22.35	9.85	[redacted]	0.01	0.02	Dominant
I+Ven	[redacted]	22.34	9.83	-	-	-	-

Analysis performed using venetoclax PAS price and other therapies at list price
Costs and QALYs discounted; LYs undiscounted
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

The outputs of this analysis demonstrate that Ven+O remains a dominant treatment option compared with I+Ven, irrespective of whether survival curves for I+Ven are modelled using the PH assumption or independently using survival data from the CAPTIVATE trial.

Independent modelling was not performed in the cost-comparison scenario as this analysis relies on the assumption that Ven+O and I+Ven provide equal efficacy.

Health-related quality of life

B8. CS, section 3.3.3. Please clarify the source of data for each of the adverse events in Table 36 for ibrutinib + venetoclax (I+Ven) as taken from TA891, that is, CAPTIVATE trial (FCR-suitable) vs. CAPTIVATE (full population) vs. GLOW (I+Ven).

The sources for the incidences of grade 3-4 AEs experienced with I+Ven are presented in Table 36 of the Company Submission and outlined below in Table 39. In the CS, AbbVie acknowledged limitations in the availability of adverse event incidence data for I+Ven in a comparable patient population, and were required to make simplifying assumptions when reporting incidence rates.

Table 39. Source for data of each grade 3 or 4 adverse event for I+Ven presented in Section 3.3.3 of the Company Submission

AE	I+Ven	Source
Anaemia	0.0%	Assumed zero – no reliable input found for grade ≥3 adverse event
Diarrhoea	3.1%	CAPTIVATE (full population) Input sourced from TA891 Appendix F
Infections (UTI)	8.2%	CAPTIVATE (full population) Input sourced from TA891 Appendix F
Infusion related reaction	0.0%	Assumed zero – no reliable input found for grade ≥3 adverse event
Neutropenia	32.7%	CAPTIVATE (full population) Input sourced from TA891 Appendix F
Pneumonia	2.0%	CAPTIVATE (full population) Input sourced from Tam et al. 2022 Supplementary Appendix Table 4
Thrombocytopenia	5.7%	GLOW (FCR-unsuitable population) Input sourced from TA891 Table 49
Atrial fibrillation	1.3%	CAPTIVATE (FCR-suitable population) Input sourced from TA891 Table 48
Cardiac failure	3.8%	GLOW (FCR-unsuitable population) Input sourced from TA891 Table 49
Hypertension	5.7%	CAPTIVATE (FCR-suitable population) Input sourced from TA891 Table 48
Hyponatraemia	5.7%	GLOW (FCR-unsuitable population) Input sourced from TA891 Table 49
Tumour lysis syndrome	0.0%	Assumed zero – not reported as an adverse event in TA891 or Tam et al. publication

AE, adverse event; FCR, fludarabine, cyclophosphamide, and rituximab; UTI, urinary tract infection

Section C: Textual clarification and additional points

C1. CS, Table 18. In Table 18, please clarify what ‘NA’ means?

In this context, NA is intended to mean ‘not available’ as data for these characteristics were not shared with AbbVie.

C2. CS, Table 19. In Table 19, please confirm what is meant by the term “interaction” when used in combination with the bulky disease categories.

There is an error in the categorisation as a result of a copy-paste mistake, which led to the incorrect inclusion of previous conclusions regarding the interaction, and these should be disregarded.

The correct categories pertain to Bulky Disease, which is to be flagged as either "yes," "no," or "missing", for which bulky disease definitions were estimated either for >5cm or >10cm.

The corrected list of disease categories:

- Bulky disease ≥5 cm: yes, Bulky disease: missing, reference: Bulky disease ≥5 cm: no
- Bulky disease ≥10 cm: yes, Bulky disease: missing, Bulky disease ≥10 cm: no

References

1. AbbVie. CLL Conference Proceedings (Grey Literature). 2025.
2. AbbVie UK. CLL SLR - List of Observational Studies. 2025.
3. AbbVie UK. CLL Full-Text Exclusions Citations. 2025.
4. Deutsche Studiengruppe. CLL13 (GAIA) Priority 1 analyses for AbbVie (Jan 2023 data cut-off) v1.0. 2023.
5. Deutsche Studiengruppe. CLL13 STATISTICAL ANALYSIS PLAN –PRIMARY ENDPOINTS ANALYSIS. 2021.
6. Eichhorst B, Niemann Carsten U, Kater Arnon P, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2023;388(19):1739-54.
7. National Institute for Health and Care Excellence. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [TA891]. 2023; Updated 31/05/2023. Available from: https://www.nice.org.uk/guidance/ta891/chapter/1-Recommendations [accessed 10/07/2025].
8. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. British Journal of Haematology. 2018;182(3):344-59.
9. Universität zu Köln. CLL13-trial of the GCLLSG in cooperation with HOVON, Nordic CLL study Group, SAKK, Cancer Trials Ireland and the Israeli CLL Study Group [Trial Protocol]. 2021.
10. Cancer Drugs Fund. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402] - Managed Access Agreement. 2020. Available at: https://www.nice.org.uk/guidance/ta663/documents/final-appraisal-determination-document-2 [Accessed 12/08/2025].
11. Eichhorst B, Niemann C, Kater AP, et al. A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) Vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial. Blood. 2021;138:71.
12. Fürstenau M, Kater AP, Robrecht S, et al. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2024;25(6):744-59.
13. Fürstenau M, Robrecht S, Tresckow Jv, et al. THE TRIPLE COMBINATION OF VENETOCLAX-IBRUTINIB-OBINUTUZUMAB PROLONGS PROGRESSION-FREE SURVIVAL COMPARED TO VENETOCLAX-CD20-ANTIBODY COMBINATIONS AND CHEMOIMMUNOTHERAPY IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA: FINAL ANALYSIS FROM THE PHASE 3 GAIA/CLL13 TRIAL. 2025. Available at: https://library.ehaweb.org/eha/2025/eha2025-congress/4159268/moritz.frstenau.the.triple.combination.of.venetoclax-ibrutinib-obinutuzumab [Accessed 05/06/2025].
14. Deutsche Studiengruppe. CLL13 (GAIA) - Further Analyses for AbbVie NICE Submission. 2025.
15. Deutsche Studiengruppe. CLL13 (GAIA) - Further Analyses for AbbVie NICE Submission - Overall Adverse Events. 2025.

16. Deutsche Studiengruppe. CLL13 (GAIA) - Further Analyses for AbbVie NICE Submission - Serious Adverse Events. 2025.
17. Al-Sawaf O, Robrecht S, Zhang C, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. Blood. 2024;144(18):1924-35.
18. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood, The Journal of the American Society of Hematology. 2022;139(22):3278-89.
19. Arnon P. Kater, Rosemary Harrup, Thomas J. Kipps, et al. The MURANO study: final analysis and retreatment/crossover substudy results of VenR for patients with relapsed/refractory CLL. *Blood* 2025; 145 (23): 2733–2745. doi: https://doi.org/10.1182/blood.2024025525.
20. Kósa F, Nečasová T, Špaček M, et al. Secondary malignancies and survival of FCR-treated patients with chronic lymphocytic leukemia in Central Europe. Cancer Medicine. 2023;12(2):1961-71.
21. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2021;32(1):23-33.
22. Walewska R, Parry-Jones N, Eyre TA, et al. Guideline for the treatment of chronic lymphocytic leukaemia. Br J Haematol. 2022;197(5):544-57.
23. Eichhorst B, Ghia P, Niemann C, et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Annals of Oncology. 2024;35(9):762-8.
24. National Institute for Health and Care Excellence. Zanubrutinib for treating chronic lymphocytic leukaemia [TA931]. 2023; Updated 22/11/2023. Available from: https://www.nice.org.uk/guidance/ta931/chapter/1-Recommendations [accessed 07/02/2024].
25. Deutsche Studiengruppe. CLL13 (GAIA) - Further Analyses for AbbVie NICE Submission - Subsequent Treatments. 2025.
26. National Institute for Health and Care Excellence. Acalabrutinib for treating chronic lymphocytic leukaemia [TA689]. 2021; Updated 21/04/2021. Available from: https://www.nice.org.uk/guidance/ta689/chapter/1-Recommendations [accessed 06/02/2024].
27. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia [TA561]. 2019. Available at: https://www.nice.org.uk/guidance/ta561 [Accessed 11/05/2025].
28. Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis. 2020.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA partial review of TA663) [ID6291]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	CLL Support Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**CLL Support** - is the UK's only charity dedicated to supporting CLL patients. There are approx. 3,500 members of the charity and approx. 12,000 UK members of the on line support forum on Health Unlocked (c 50% of the 24,000 members) https://healthunlocked.com/cllsupport Our mission is to support and empower Chronic Lymphocytic Leukaemia (CLL) patients, and Small Lymphocytic Leukaemia (SLL) patients, their families and supporters through education and access to reliable, relevant and current information. We also represent CLL patients in discussions with government, pharmaceutical companies, other leukaemia charities and the National Institute for Care and Health Excellence (NICE).
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	**CLL Support has received funding from companies bringing the treatment to NICE and the comparator treatment. The most recent figures as follows** Abbvie:, £20,000 educational grant and £337.50 advisory fees Astra Zeneca: £15,000 educational grant and £900 advisory fees Johnson and Johnson: £5000 educational grant Beigene: £20,000 educational grand and £212.44 advisory fees Eli Lilly £3,960 advisory fees

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	An on line survey of UK patients and carers was compiled and analysed, led by Leukaemia Care. In addition patients were consulted on the Health Unlocked on line platform of CLL Support and 2024 survey of CLL patients and carers. https://cllsupport.org.uk/wp-content/uploads/2024/09/Survey-results-2024.pdf All gave permission for their experiences to be shared in this HTA.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL patients experience varying degrees of fatigue, swollen lymph nodes, weight-loss, anaemia, infections and night-sweats which can be very distressing. As the CLL progresses, then the symptoms become progressively more severe, with greater fatigue, anaemia leading to shortness of breath, sometimes excessive bruising and bleeding, and a much greater risk of infection. The majority of patients will start with a period of watch and wait or active monitoring as treatment is delayed whilst the patient's disease is in the early stages and with few symptoms. However, once the disease progresses and the patient's condition is compromised then patients will start treatment. Fatigue is overwhelming tiredness that doesn't improve with rest, impacting daily activities and mood. It can manifest as a lack of motivation, both physically and mentally. This fatigue can be persistent and pervasive, making it difficult to perform even simple tasks and affecting overall well-being. In addition, due to the physical symptoms that patients' have, their quality of life is reduced in many ways. Patients and carers suffer higher anxiety, even during the watch and wait period, almost living from one blood test or CT scan to the next with fears of progression, treatment failure and death. One patient survey found that 72% of patients expressed these fears and 96% stating that delaying disease progression was their priority with concerns that there will be a suitable treatment available for them when they relapse. Patients who are diagnosed at a younger age are even more likely to suffer from anxiety and depression as many have work and family responsibilities. Life insurance may be an issue. One patient said "***Diagnosed with CLL in my early 40s. I seem to respond well to treatments initially, then I have a relapse. My worry is where I go from my current treatment***". Older patients are more likely to isolate themselves in order to avoid infections and this can exacerbate the anxiety, loneliness and depression. Holidays, grandchildren and family get togethers are missed to avoid possible life threatening infection. On the Health Unlocked CLL Support platform patients often seek advice about visiting family and the anxiety they feel if they go or miss the event is very real. Some will wear face masks but still feel uncomfortable with normal family habits such as greeting hugs and kisses. This query is typical "***Our youngest grandchild has just had live vaccinations so obviously we are avoiding seeing him for a couple of weeks but what do we do about seeing the rest of the family who will be visiting him? I'm really not sure on this one, feeling nervous!"*** Patients' families, friends and caregivers are similarly affected with the same worries about their loved ones. As well as important emotional support and because CLL affects mainly an older age group, often with comorbidities, then as symptoms progress patients often require support with everyday activities such as shopping, cooking and cleaning and may also need support dealing with any side effects of the treatment they are taking. Patients often need help travelling to appointments and carers may be needed to be with the patient

	to listen to the doctor, which can be difficult when trying to understand a medical diagnosis. Patients express concerns about being a burden to their family members.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	CLL cannot currently be cured, and early treatment after diagnosis does not appear to improve survival so many patients undergo a period of watch and wait before their burden of symptoms means that treatment is required. Patients are very appreciative of the range of current non chemotherapy (CIT) treatments for CLL which have been very successful in providing long term remissions for many patients. The current range of treatments available, including V+O via the CDF, means that almost every patient has access to a treatment appropriate for their personal CLL, previous treatments and existing comorbidities. However, all patients and in particular young patients, suffer from treatment anxiety and worry about what effective treatment will be available to them when they need it. One patient said "***Diagnosed with CLL in my early 40s. I seem to respond well to treatments initially, then I have a relapse. My worry is where I go from my current treatment***". A patient's preferred treatment depends very much on their personal circumstances, both health and social but some of the things we are told that are considered are: Ability to adhere to treatment schedules Participating in normal activities including work and family life. Availability and affording travel and parking costs to attend appointments Anxiety about how well the treatment will work Their understanding of available treatment options Anxiety about disease progression and what might follow Ability to be able to manage potential side effects Degree of support and other resources available Many CLL/SLL patients have chosen Venetoclax +Obintuzumab as their first line treatment in preference to first-generation covalent BTK inhibitors (like ibrutinib or acalabrutinib) whilst it has been available via the CDF. Their reasons are generally a preference for a time limited treatment that is also proven to be very effective. Some patients have existing cardiovascular or bleeding comorbidities that may preclude the use of BTKi. V+O via the Cancer Drugs Fund has been a popular choice of first line treatment, in part because, if they achieve MRD negative status, they feel reassured it has been effective and are then hopeful of a long remission.

8. Is there an unmet need for patients with this condition?	Due to the heterogeneous nature of CLL there will always be an unmet need in some patients. Currently Venetoclax+Obintuzumab treatment has been available for via the **Cancer Drugs Fund (CDF)** as per a previous submission: TA663 and has met a significant unmet need for fit patients that do not have 17p or TP53 deletions who would otherwise have treatment options: ibrutinib + venetoclax (I+Ven), FCR or BCR. Almost all patients want to avoid Chemoimmunotherapy and the potential risk of AML or MDS in the future. First generation BTKi's are not suitable for all patients because of comorbidities, in particular pre existing cardiovascular ones or for patients taking anticoagulants. It is important that this access to Ven+O is now formally NICE approved and continues to be available following a review of the CDF data collection.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Many patients are choosing this Ven+O time limited combination treatment over other treatments. Sometimes this is because it is time limited and so toxicities and possible resistance are possibly reduced but patients also want to have treatment free periods to be able to get on with their lives. There are high rates of undetectable residual disease following Ven+O treatment which is hopefully a surrogate marker for long remissions, time to next treatment and survival and provides patients hope and reassurance. Ven+O has the advantage over Ibrutinib+Ven in that cardiac monitoring is not required. Time limited treatment also reduces the long term burden of frequent ongoing hospital appointments and requirement for transport (perhaps provided by family and carers). The results of a statistical analysis comparing Ven+O and Ibrutinib + Venetoclax showed the length of time patients survived without any disease progression was similar between patients treated with Ven+O and those treated with I+Ven. Likewise the overall length of time that patients lived after receiving treatment, was similar between those who received Ven+O and I+Ven. ***(REF: OPEN Health. Indirect Treatment Comparison (ITC) in Untreated CLL. 2024.)***

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients are regularly choosing the Ven+O combination over other treatment options despite the necessary hospital day case admissions for intravenous administration of Obintuzumab and the frequent monitoring for possible tumour lysis syndrome in the early few weeks of Venetoclax. This requires the patient and their carer to visit this setting 3-4 times in the first month, and once a month for the next 5 months. The infusion often induces a reaction and may take a long time to administer. However, after the first 6 months, obinutuzumab is no longer given, and so patients and carers no longer need to attend for infusions. Patients often report severe neutropenia and dose adjustments or GCSF are required to allow for recovery before further ramp up of the Venetoclax dose. Although these factors are seen as a disadvantage, patients are willing to accommodate this inconvenience because it is time limited and Ven+O is a very effective treatment leading to high rates of undetectable residual disease and hopefully long remissions and survival.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The population under consideration is appropriate.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It is not anticipated that would exclude from consideration any people protected by equality legislation,

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Time limited non chemotherapy treatment preferred by many patients • Effective treatment leading to long remissions in all groups of patients • Suitable for patients with cardiovascular and/or bleeding comorbidities • Tolerable safety profile with built in safeguards with the ramp up process and prophylactic antibiotics. • Patients understand the need for intense monitoring and infusions in the early weeks/months and are still choosing V+O

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA partial review of TA663) [ID6291]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care. Submission also submitted on behalf of Blood Cancer UK, Leukaemia UK and Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** Leukaemia Care is a UK leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected receives the best possible diagnosis, information, advice, treatment and support. Read more about our work, including the number of people supported, here: https://www.leukaemiacare.org.uk/about-us/our-impact-in-2024/. Blood Cancer UK: Blood Cancer UK is the UK's biggest blood cancer research charity. We fund world-class research and provide information, support and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has around 100 employees and is funded primarily through donations and legacies. Leukaemia UK: Leukaemia UK is a leading leukaemia research and advocacy charity, that believes research has the power to stop leukaemia devastating lives. We bring together the leukaemia community—patients, families, researchers, and advocates—to fund and drive the life-saving breakthroughs that matter most to those affected. We campaign for change, pushing for earlier diagnosis, better treatment options, improved care, and more investment in research to represent the nearly 60,000 people living with leukaemia in the UK and to make sure that the next person with leukaemia has the best possible experience and outcomes of diagnosis, treatment and care. Leukaemia UK receives income from a variety of sources (as detailed in the charity's 2023 Annual Report).

	Lymphoma Action: Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources; predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and there is also a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. This policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Leukaemia Care: AstraZeneca UK - £15,000 towards hospital hubs Janssen - £5,000 towards core services such as helpline Blood Cancer UK: AbbVie - £50,000 for the direct referral project, £472.50 speaker fees, £10,000 for health information, £135 patient experience insights AZ - £15,000 direct referral J&J - £91,290 for the Blood Cancer Action Plan, £180 for a CAR-T PAG stakeholder meeting , £240 for attendance to a Haem study day Pfizer - £2550 CEO consultancy fees, £30,000 for the CTSS expansion, £64.59 expenses to Pfizer office, £7,000 for the Blood Cancer Charter,

If so, please state the name of the company, amount, and purpose of funding.	Roche - £25,000 for the direct referral, £15,000 for the CNS programme of support Leukaemia UK: **Janssen-Cilag (**ibrutinib) - £9,500 funding from Janssen this year for HEU data project **Abbvie** (venetoclax) - £10k grant in 2024 for HEU data analysis Lymphoma Action: Abbvie: £40,000 towards information provision, helpline, workshops and preparing for treatment project AstraZeneca UK £15,000 towards preparing for treatment project Janssen-Cilag £5,000 towards Lymphoma Essentials course Pfizer £4,000 towards lymphoma information days Roche Products £40,000 towards information provision, peer support services, helpline and preparing for treatment project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**We have used information submitted to the previous technology appraisal conducted pre-CDF for this topic. This is supplemented with an on line survey of UK patients and carers was led by Leukaemia Care. In addition patients were consulted on the Health Unlocked on line platform of CLL Support and 2024 survey of CLL patients and carers. https://cllsupport.org.uk/wp-content/uploads/2024/09/Survey-results-2024.pdf** **All gave permission for their experiences to be shared in this HTA.**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia, with approximately 3,200 people diagnosed in England and Wales each year; however, it is still a rare cancer type. 85% of patients diagnosed aged 65 or older. CLL is also a heterogeneous condition, so the experience will be very different for each patient; therefore, a range of treatment options that fit individual needs as closely as possible is important. This remains true since this treatment was first examined. Common symptoms reported at diagnosis include fatigue (43% of those surveyed), swollen lymph nodes (32%) and fever or night sweats (27%). Patients with CLL also have a higher risk of infection, as their immune system is compromised by the disease. These frequent and persistent infections can impact hugely on quality of life, as well as being a leading cause of death for CLL patients. Additionally, current treatments can either cause side effects that last for a long time after treatment, or have to endure side effects for a long period of time whilst on a continuous therapy. Patients report that it is not just the severity of a side effect at the start of treatment that is concerning, it is also the time they must endure it for that is important. In addition to physical symptoms, being diagnosed with CLL has an emotional impact. 38% of CLL patients surveyed said they felt more anxious or depressed since diagnosis.This emotional impact is unsurprising given the course of the disease; CLL tends to respond less well to each line of therapy, with shorter subsequent remissions, leaving patients in fear of relapse. CLL patients would be reassured if there were treatments giving long and durable remissions from the start. As outlined above, living with CLL is difficult and does not affect a patient in isolation, but instead creates a “ripple effect” impacting on the whole family. Family, friends and colleagues of a patient may all be affected by the diagnosis. Family members/carers can be challenged with exhausting caretaking duties when someone they know is diagnosed with CLL. Even if CLL patients feel well and have few side effects day to day, patients report having to depend on their families more than they otherwise would and needing support unexpectedly. CLL patients are at increased risk of infection during treatment, due to a weakened immune system as side effect of the treatments. This presents a constant risk of hospitalisation, as the lack of immune system can lead to severe infections developing quickly.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Since the original appraisal for this treatment, BSH guidelines for the treatment of CLL patients have been updated in 2022. Whilst chemotherapy remains an option in this area, it is clear that VenO has become the preferred clinical option now, despite only a temporary approval via the CDF. FCR comes with many side effects due to its non-specific mechanism of action in the body. However, patients are keen to see treatments that work, but also favour those with better side effect profiles, seeing the two as a balancing act. The range of treatments available means that almost every patient has access to a treatment appropriate for their personal CLL, previous treatments and existing comorbidities. However, younger patients suffer from treatment anxiety and worry about what effective treatment will be available to them when they need it. Additionally, this group of patients under discussion here also have limited options, according to current guidelines, should VenO be no longer available. A patient's preferred treatment depends very much on their personal circumstances, both health and social but some of the things we are told that are considered are: Ability to adhere to treatment schedules Participating in normal activities including work and family life. Availability and affording travel and parking costs to attend appointments Anxiety about how well the treatment will work Their understanding of available treatment options Anxiety about disease progression and what might follow Ability to be able to manage potential side effects Degree of support and other resources available In one conducted in 2017 survey, although improved survival/response is the most popular feature of a potential new treatment (indicated as important by 76% of patients), improved quality of life and tolerable side effects are also indicated as important by the majority (chosen by 68% and 56% of patients respectively). The same result was seen in the most recent survey conducted, with quality of life being the 3rd most important factor for patients in choosing treatments. "There's no pain no gain… but there's a limit to the pain" – focus group participant

8. Is there an unmet need for patients with this condition?	This group of patients under discussion here, in whom chemotherapy is suitable, have been repeated left with few alternatives to chemotherapy or uncertain levels of access through the use of the CDF. Many patients feel they have been left the harsh side effects of an untargeted chemotherapy treatment, even if the worst side effects like secondary cancers are rare, whilst others are allowed to trial newer option specifically made for their cancer. Many of these patients will be living with CLL for a long time prior to initial treatment, so those that choose to follow news on treatment options whilst they are on active monitoring will see treatments becoming more and more available, yet be unable to access them at present. It is imperative that we allow these patients to trial newer and more innovative treatments if their doctors feel it is appropriate, not force them to wait until relapse. Patients are living longer with CLL and need as many options as possible.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	It is well recognised that enduring remission can be obtained and can be indicated by the speed and depth of MRD negativity. At the time of first appraisal, there was evidence from the CLL14 trial that patients were achieving this deep MRD negativity when treated with venetoclax and obinutuzumab, increasing the likelihood of enduring remission. This is a positive for patients; they are likely to have fewer symptoms in remission and then be more likely to be able to return to work, for example. We understand that further results in favour have been published since, and this has led to the change in BSH guidelines as described above. CLL patients recognise that MRD negative is a positive result in terms of the efficacy of treatment. Some would even suggest that they would consider it to be cured, if they were able to maintain the response. "Q: How do you define cure, in CLL? A: Oh gosh, MRD negative for a very long… you just never come out of MRD negative I suppose." – focus group patient The idea of representing a cure might not be corroborated by scientific evidence at present, but it does demonstrate patient desire to reach a state of remission that lasts as long as possible. Venetoclax and obinutuzumab is designed to be given for 12 months, followed by a treatment free period. One survey shows that 64% of CLL patients would consider this treatment-free period as a positive. Whilst CIT treatments also allow a treatment free period, venetoclax and obinutuzumab are more efficacious and have more tolerable side effects. In the most recent survey conducted of people who had already had venetoclax with obinutuzumab, 7 out of 8 reported only positive experiences of the treatment. The one person who was refractory to the treatment after a few months still agreed it was a useful treatment to have in the arsenal. Most of the patients reported having no other treatments mentioned to them as suitable at the time they were choosing VenO treatment. When asked how they would feel if VenO were to become unavailable, they said: “every patient should be able to try this treatment”

	"I think V and O is a good treatment and should not be taken away as other people on that regime have had good results"

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Disadvantages remain largely the same as when the treatment was first considered. Patients are aware of the risk of tumour lysis syndrome (TLS), as it is linked to the efficacy of the treatment. However, the dosing schedule in guideline has minimised the risk. Patients are happy with this TLS as a risk when balanced with the efficacy of the treatment. There is now significant experience of the use of venetoclax in haematology departments, being a standard of care in both CLL and AML patients, so side effects are well managed with protocols. There continues to be emerging evidence of clonal selection and relapse in people treated with venetoclax. However, this is not significant enough to warrant treatment removal in the absence of other treatment options, and the potential harm form chemotherapy options is not preferable.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All patients would benefit and need access to effective options. Therefore, we ask that NICE ensures there is equal access among patients who are newly diagnosed to access a targeted therapy, especially now it is the preferred option for clincians.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	none

Other issues

13. Are there any other issues that you would like the committee to consider?	none

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• CLL remains a disease that requires multiple treatment options, so clinicians and patients can tailor appropriately. Patients want treatments that work, but also disrupt their life as minimally as possible. • This treatment has been shown to be highly effective, particularly generating long term remission. • Patients who are currently suitable for chemotherapy would miss out on an effective treatment should access be revoked. VenO is already the preferred option for clinicians, according to updated guidelines, and patients are aware from each other the benefits that a targeted treatment could bring. • We are unaware of any clinical reason why permanent access to VenO should not also be extended to this group of patients. Therefore, there is an inequality between patients at present. • Side effects of VenO are very well managed given the wealth of experience with the drugs in the NHS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA partial review of TA663) [ID6291]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	**UK CLL Forum &** **British Society of Haematology**
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The **UK CLL Forum** is a charitable organisation for CLL in the UK. The aims of the CLL forum are to bridge the gap between the clinical and scientific aspects of the disease and the patients. It provides framework where the UK CLL community, can input into issues such as guidelines, clinical trials and translational science. UK CLL Forum does receive support from Pharmaceutical companies to carry out annual educational activities with specific focus in CLL. The **British Society of Haematology**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	**UK CLL Forum** The UK CLL forum has received funding from the manufacturers of the technology and the comparators as below. The purpose of this funding is to support the independent educational activities of the CLL forum. **Company** / **Amount** AstraZeneca — £12,000 AbbVie — £7,500 BeiGene — £12,000 Johnson & Johnson — £1,500

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	CLL is a cancer characterised by uncontrolled proliferation of lymphocytes within the bone marrow and/or lymph nodes. The aim of treatment is to induce remission by clearing disease within the bone marrow and nodes and improve obtaining the longest period of progression free survival (PFS) with the best quality of life. Increasing patient survival (OS) remains a desirable treatment goal, however the chronic nature of CLL and the good efficacy of treatments at relapse, makes impractical the assessment of survival based on the effect of a single technology. There is no cure currently for CLL and treatments have limited efficacy and associated toxicities. With the recent approval of fixed-duration treatment regimens in CLL, the treatment free period had become an increasingly valuable endpoint for CLL patients, particularly for the CLL patient community who value the absence of side effects that is characteristics of the interval between treatments.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Response in CLL is measured by the internationally standardised IWCLL criteria (International Workshop on Chronic Lymphocytic Leukaemia, Hallek et al, https://doi.org/10.1182/blood-2017-09-806398). Partial or complete responses are clinically acceptable for continuous therapy, provided they are accompanied with resolution of CLL-related symptoms. For fixed duration therapies depth of response is a relevant parameter, hence complete response by IWCLL criteria is desirable. For the present technology, measurable residual disease (MRD) is another relevant response parameter, MRD negative status at the end of fixed duration therapies has been demonstrated to be directly correlated to the PFS. MRD negativity is measured with the IWCLL criteria, being negative at a threshold of $1x\ 10^{-4}$ CLL cells/total WBC in peripheral bloods. MRD can be measured by flow cytometry or next-generation sequencing, being the former much more widely used in routine practice in the UK.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	In the setting of the current technology, the biggest unmet need continues to be the reduced availability of treatment options as compared to older patients with comorbidities. For this population the continuous therapy with BTK inhibitors is not available, making fixed duration venetoclax-based therapies the only alternative for this population Please note that the reference to FCR/BR suitability will be deliberately omitted from the responses in this submission, the stakeholders represented in this submission strongly support the abolition of the reference to chemoimmunotherapy (CIT) regimens to assess fitness/adequacy to treatments in CLL, due to the fact that that the use of CIT is no longer recommended in national and international guidelines. The treatment of CLL patients who fail all existing and available drug-classes remains the biggest unmet need. Despite the recent approval of novel agents for treatment of CLL, which are now readily available in the treatment pathway, there is still a significant subgroup of patients for whom treatment options are exhausted and who die of progressive CLL. These patients often carry aberrations of TP53 (TP53 mutation and/or 17p deletion) – TP53 status remain the strongest predictor of treatment response and PFS in CLL. Another relevant unmet need is the incorporation of MRD evaluation into the routine clinical practice. It has been now widely demonstrated in large randomised Phase 3 trials that MRD negativity predicts for longer PFS (CLL14, CLL13, GLOW, CAPTIVATE). MRD testing should be standardised for routine use in CLL treatment, results from the academic UK trial FLAIR have demonstrated improvement in overall survival with fixed duration Ibrutinib-Venetoclax therapy when administered using a tailored treatment duration based on MRD dynamics during treatment. Studies are ongoing by other international CLL groups that will likely corroborate FLAIR findings and consolidate MRD as a therapeutic tool in CLL.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment of CLL, according to the international (ESMO) guidelines, is divided into 3 therapeutic groups: Patients with TP53 aberrations, patients with mutated IGHV genes and patients with unmutated IGHV genes. Note that, as mentioned above, there is no reference to the fitness for chemoimmunotherapy (CIT) as a criterion for treatment selection. National BCSH guidelines are currently awaiting final publication and contemplate 2 treatment groups depending on the choice of therapy, whether that is fixed-duration venetoclax-based therapy or continuous BTK inhibitors. The recommendation acknowledges the efficacy of all available treatment options and the importance of shared decision-making when selecting the first line treatment regimen. Several treatment combinations are available for first line therapy based on three drug classes. B cell receptor pathway inhibitors (principally BTK inhibitors such as acalabrutinib and zanubrutinib), BCL2 inhibitors (principally Venetoclax) and anti-CD20 antibodies (Rituximab or Obinutuzumab) (TA359, TA429, TA487, TA561, TA663, TA 689). Expanding each of the subgroups the recommendations of the most recent BCSH guidelines are as follows: <u>Continuous therapy preferred</u> BTKi therapy is favoured for patients with **TP53 aberrations**. Among continuous treatment options, second generation cBTKi (acalabrutinib or zanubrutinib) are preferred to ibrutinib, which is no longer recommended. Idelalisib-rituximab remain an option but are less favoured due to higher risk of adverse events. Venetoclax single agent is also available for patients with TP53 aberration for whom BTKI are not an option.

	For patient with **intact TP53**, options are continuous acalabrutinib (TA689) and continuous zanubrutinib (TA931), only available to patients with age >65 years and/or comorbidities. No specific recommendation can be made with regards to choice between these two agents. Fixed duration therapy preferred Approved and recommended options for fixed-duration therapy are venetoclax-obinutuzumab (V+O, TA663) and venetoclax-ibrutinib (V+I, TA891), **irrespective of TP53 status**. Based on current evidence, no specific recommendation has been given for choice between V+O or V+I. Fixed-duration treatment options tend to be favoured for patients with mutated IGHV gene status, given the good outcomes of this patient population, who are most likely to benefit from the prolonged treatment free period. However, the later is not a formal recommendation due to the lack of randomised evidence to support it. The BCSH guidelines suggest the fitness for each of the treatment options to be evaluated individually, depending on comorbidities and potential contraindications for the use of each of the individual agents. Venetoclax fixed-duration alternatives are available across all age groups and degree of comorbidities, whereas BTKi are only available for patients above 65 years of age and with comorbidities. In addition, the use of V+I in older patients with comorbidities is cautioned due to concerns with cardiovascular safety. Its use should be carefully weighed against the individualised risk of cardiovascular complications. Patients with relapsed CLL are recommended to be treated as follows: • Targeted inhibitors (BTKi or BCL2i alone or in combination with rituximab) are the treatment of choice for relapsed CLL. • For patients relapsing after BTKi, offer venetoclax-based regimens, irrespective of *TP53* status

	• For patients relapsing following fixed-duration venetoclax-based therapy consider either a BTKi or venetoclax re-treatment depending on duration of PFS1 prior response, tolerance and patient preference. • For relapsed patients who are intolerant to ibrutinib, offer either venetoclax-based therapy or acalabrutinib/zanubrutinib depending on the reason for intolerance • Idelalisib-rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi and BCL2i-based treatment. • Pirtobrutinib is an option after two lines of treatment including BCL2 and BTKi, but it is currently available only through a named-patient scheme programme.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guideline for the treatment of chronic lymphocytic leukaemia**, 2025 ;** on **behalf of the Haemato-Oncology** Task Force of the British Society for Haematology**, in press BJHaem, this is an update on the published 2021 guidelines** Clinical Practice Guidelines – Chronic Lymphocytic Leukaemia (esmo.org) IwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL | Blood | American Society of Hematology (ashpublications.org)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience	The pathway of treatment is well defined, the new guidelines reflect the importance of patient choice in the selection of treatment, given excellent efficacy and minor differences in toxicity between the first line therapeutic options for CLL. The patient preference is becoming increasingly relevant and often a strong decision maker in the setting of first line therapy. The venetoclax fixed-duration alternatives require monitoring of TLS risk during the venetoclax ramp-up dose as per the drug SmPC (V+O and V+I options) and delivery of intravenous Obinutuzumab in the ambulatory setting

is from outside England.)	(only for V+O combination). The expert and the stakeholders acknowledge that there are some individual differences in infrastructure and support for the delivery of Obinutuzumab and the tumour lysis monitoring. This will depend on the hospital setting (academic / tertiary vs secondary care), staff availability and daycare/inpatient admission facilities. Hence, it must be acknowledged that these factors might influence the treatment of choice depending on the setting, creating discrepancies between NHS professionals with regards to treatment of choice.
9c. What impact would the technology have on the current pathway of care?	There will be no significant impact on the pathway of care if this technology remains available to the younger CLL patients as per the CLL13 trial results, given it is currently available through the CDF. On the contrary, if this technology ceased to be available, Ibrutinib-Venetoclax will be the only fixed duration alternative to this younger subgroup of patients, leaving a void in the therapeutic options. There are concerns with cardiovascular safety of the I+V combination, hence, it remains plausible that I+V is inadequate for a subset of patients with cardiovascular comorbidities, who would not qualify for continuous BTKi therapy and for whom Venetoclax-Obinutuzumab will be the ideal fixed-duration therapeutic choice.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, there are no changes foreseen with the way this technology will be used is remains available.
10a. How does healthcare resource use differ between the technology and current care?	Fixed duration Venetoclax with Obinutuzumab requires increased healthcare resources for administration compared to other fixed-duration options such as I+V. This is likely to be reflected accurately in the health economic model and will not differ from the healthcare resource use that is currently required for its delivery.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology will be exclusively used in secondary care under specialist care of clinical haematologists.
10c. What investment is needed to introduce the technology? (For	No additional investment is foreseen to continue using this technology as it is currently being used in the same setting under different funding arrangements.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The clinical benefit of Venetoclax with Obinutuzumab is clearly demonstrated by the results of randomised controlled trials (CLL13 for the specific population of this appraisal), showing a PFS of 82% at 4 years in comparison of 62% for the CIT arm (HR 0.47). The Venetoclax/Obinutuzumab combination provides a higher proportion of responses and MRD negativity when compared to the control arm and more importantly offers a significant treatment free period, as demonstrated by a prolonged time to next treatment. The main benefit already demonstrated is the significant improvement in progression free survival when compared to chemoimmunotherapy, leading to removal of CIT from the recommended options in the most recent guidelines, as stated above. There is no direct comparison of Venetoclax/Obinutuzumab with the other fixed-duration alternative (V+I). Evidence from the CAPTIVATE trial which shares a proportion of patients with characteristics equivalent to the CLL13 trial population, shows progression free survival of 67% at 5 years and time to new treatment of 75% at 5 years (See section 11b). Although the results are not directly comparable, mainly because CAPTIVATE population included patients with TP53 aberrations, the subgroup of patients in CAPTIVATE without TP53 abnormalities showed a PFS of 77% at 5 years, which compares more favourably to the population of CLL13 trial. Hence, it is reasonable to conclude that both venetoclax fixed-duration alternatives provide excellent efficacy in the first line treatment setting and that despite the lack of direct evidence comparing these two regimens, the clinical benefit is expected to be similar for younger patients with no comorbidities.
11a. Do you expect the technology to increase length of life more than current care?	Available treatment options for CLL have no significant prolongation of overall survival. This phenomenon is most likely related to efficacy of second line treatment options, hence, impact of technologies are best evaluated based on the progression free survival and time to next treatment.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Venetoclax-Obinutuzumab combination offers deep responses in CLL, including a high rate of MRD negativity as per the CLL13 (75.5%) and CLL14 (86%) studies. The depth of response achieved with venetoclax-based regimens in general guarantee a prolonged treatment-free period for CLL patients, which is likely to have a significant impact in health-related quality of life when compared to continuous treatment options.

	Time to next-treatment (TTNT) is a useful endpoint that provides insights into the treatment free period. TTNT has been reported for the Venetoclax/Obinutuzumab combination as 65% at 6 years (CLL14) and 90% at 4 years (CLL13). Moreover, similar TTNT is reported for the CLL13 patient population when compared to V+I combination (TTNT 75% at 5 years – CAPTIVATE trial), featuring a shorter treatment time (12m vs 15m for the V+I combination) and further contributing to the improved QoL of fixed duration therapy. Again, although TTNT are not directly comparable between CLL13 and CAPTIVATE data, these benefits are expected to be approximately similar. When comparing venetoclax/Obinutuzumab with V+I, there is an expected impact on quality of life in detriment of Ven+O during the initial phase of therapy (initial 2-3 months) with requires additional hospital visits and a higher side effect burden. This difference narrows after the first 2-3 months and is likely to be higher after the first 6 months of treatment when V+I combination is continued as opposed to Venetoclax alone. The quality of life is likely to be comparable during the treatment-free period that follows.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As mentioned in earlier sections, patients with mutated IGHV status are likely to derive the greatest benefit from fixed duration options, including Venetoclax with Obinutuzumab. This however, does not imply that patients with unmutated IGHV should not be offered this treatment combination, current evidence does not allow for a firm recommendation based on IGHV mutation status. There is no data for the Venetoclax/Obinutuzumab combination in the setting of TP53 abnormalities based on the CLL13 trial data, hence, there is uncertainty of its benefit when assessed against the comparator (V+I). However extrapolating the data from the population carrying TP53 aberrations within the CLL14 trial, there would be an expected reduction of efficacy for patients with TP53 aberration. The detrimental effect of TP53 aberration on the treatment outcomes of CLL13 patient population would have been theoretically proportional to that observed for CAPTIVATE, in which there is roughly a 20% reduction in the PFS rates at 5 years.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare	Use of current combination is already routine in the NHS and there will be no changes in its use based foreseen based on present appraisal.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	In comparison to V+I, the administration of the initial phase of Obinutuzumab, followed by the venetoclax dose escalation will somewhat increase the difficulty of delivery of Ven+O for both clinicians and patients. Similarly to point 11b, this differences will gradually diminish for the remainder of the treatment. Also, the frequency of visits during the first two months of Venetoclax/Obinutuzumab therapy as well as the need of intravenous administration might result in differences in patient acceptability of Ven+O vs regimens of purely oral therapy such as V+I.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The criteria to start therapy is based on the internationally accepted IWCLL criteria, stop of treatment is fixed based on the published schema of Venetoclax/Obinutuzumab with 12 months of therapy. Testing before starting therapy is not mandatory but recommended, including TP53 status [TP53 mutation and deletion (17p)] and IGHV mutation status.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted	There are no health-related benefits from this technology that would not be captured by the QALY.

life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The combination of Venetoclax and Obinutuzumab is the unique fixed-duration alternative that includes an anti-CD20 antibody. The later offers an alternative mechanism of action that has been demonstrated to be independent of most conventional cytogenetic and molecular abnormalities and has demonstrated to offer the higher rates of undetectable MRD. Moreover, venetoclax/obinutuzumab is the only combination available containing Obinutuzumab in the treatment pathway of CLL patients in the UK, hence, lack of availability of this combination for a subset of patients with CLL will result in inequalities as these patients will not have the possibility to benefit from the most efficacious anti-CD20 antibody available.
16a. Is the technology a 'step-change' in the management of the condition?	The use if Venetoclax-fixed duration therapy is currently well established as an option for untreated CLL patients and continues to represent a significant improvement in the therapy of CLL, due to the demonstration of improvement of clinical outcomes with venetoclax-based therapy when compared to CIT.
16b. Does the use of the technology address any particular unmet need of the patient population?	The main unmet need addressed by the current technology is the alternative fixed-duration therapy alternative for younger patients without comorbidities for whom BTKi remains unsuitable. As mentioned, it remains plausible that younger patients will not be suitable with treatment with V+I and as such will be left with no treatment alternatives apart from CIT (no longer recommended internationally).

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse events of the technology Are mainly confined to the initial weeks of therapy where the Obinutuzumab is given on its own, followed by the Venetoclax ramp-up dosing scheme. The main reported adverse events of the combination include the following, based on CLL13 trial: Neutropenia, Thrombocytopenia, Anaemia, Febrile neutropenia, infections and Obinutuzumab infusion reactions. Each of these variably affect quality of life depending on individual circumstances, however, it has been demonstrated that the burden of adverse events is confined to the treatment period and largely resolve once treatment is stopped. The rate of discontinuation of therapy within the CLL13 trial is low (6.1%), hence, the impact of management of the condition of the adverse events is expected to be low.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The trial population of CLL13 is representative of untreated CLL population in the UK and the use of the combination of drugs is used in routine practice following the schema of the CLL13 and CLL14 trial with no modifications.
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival, time-to-next treatment and rate of MRD negativity were all explored and reported in the CLL13 and CLL14 trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It has been demonstrated that MRD negative status is directly correlated with progression-free survival, however these are not reported as surrogates for PFS. Also, given the PFS is used as the primary endpoint of the trials, it does not represent a surrogate of overall survival, given the narrow differences observed in OS in the trial due to the efficacious second line therapy and the relative low number of progression events observed so far.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There are no additional adverse events reported in longer follow-up of the CLL13 and CLL14 trials. In fact, the CLL13 trial has been published with 2-3 years of delay compared to CLL14 and the profile of adverse events is comparable as demonstrated with a pooled analysis of trial results published in 2023 (Al-Sawaf O et al. Blood. 2023. 142 (Supplement 1): 4639)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE	The final analysis of the CAPTIVATE trial has been recently presented in international conferences. In brief, with median follow-up of 68-months there was a 5y PFS of 66% and OS of 97%. TTNT was 73% at 5-years.

technology appraisal guidance [TA891]?	For TP53 aberrant population the 5y PFS was 36% as opposed to 70% for nonTP53 aberrant. Rates of undetectable MRD were 69%, with ongoing increase in depth of response from cycle 7 onwards in at least a quarter of patients. Finally, there is evidence of good response rates for a minority of patients that have been treated in second line after V+I combination, with both BTKi and venetoclax-based regimens, albeit follow-up for these second line therapies is very short.
21. How do data on real-world experience compare with the trial data?	Aside from this, the population of these studies is largely representative of a first line treatment cohort and as such RWE efficacy data is expected to be similar to what has been published for the pivotal trials. The main difference expected for real-world evidence in comparison to trial data will be the rate of discontinuation, which is likely to be higher in the RWE scenario, particularly during the delivery of Obinutuzumab in the initial weeks of therapy.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The only potential equality issue for this technology is the difference in infrastructure between different NHS settings (tertiary centre vs district general setting). In particular, the delivery of the initial part of the treatment, requiring Obinutuzmab intravenous administration carries a higher risk of infusion reaction and the need of medical intervention. The specific set-up of the daycare unit in terms of proximity and opening times, as well as the ease of access to inpatient acute admission beds can be radically different between NHS trusts and has a direct impact on the potential use of this technology. Reduced availability of daycare and inpatient beds will clearly dissuade clinicians to use the current technology.
22b. Consider whether these issues are different from issues with current care and why.	These issues will not be different from routine care in NHS as the arise precisely form the experience gather with the use of Venetoclax/Obinutuzumab through the CDF.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Venetoclax/Obinutuzumab, currently available via CDF, will continue to represent an excellent treatment option for patients with younger age and no comorbidities. In particular for those who are not good candidates for V+I, due cardiovascular or other safety considerations. Moreover, lack of availability of this combination will leave patients who are no good candidates for BTKi treatment with a void of therapeutic options in first line therapy. • Venetoclax/Obinutuzumab is a highly efficacious regimen with demonstrated improvement in clinical outcomes when compared to CIT. The later is no longer recommended as treatment option for first line CLL and should not be used as a comparator to assess cost-effectiveness of Venetoclax/Obinutuzumab. (SEE ATTACHED LETTER) • With the caveat of no direct comparison, it is expected that efficacy of Venetoclax/Obinutuzumab is similar to that observed for Ibrutinib + Venetoclax combination in the setting of younger CLL patients with TP53 intact disease. • Venetoclax/Obinutuzumab use could vary within the NHS based on the local resources available to deliver the initial phases of treatment that involve intravenous administration of Obinutuzumab. • Availability of Venetoclax/Obinutuzumab as an option for fixed-duration therapy is desirable for CLL the patient population. In general fixed duration alternatives offer a treatment-free period that is likely to positively impact the health-related quality of life and health-care associated costs when compared to continuous therapy.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

Nottingham, UK, July 2025

To:

National Institute for Health and Care Excellence

Health Technology Evaluation Team (TAT Team 4)

Ref: **Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (Managed access partial review of TA663) [ID6291]**

Dear Colleagues:

We write this letter to complement our stakeholder submission for the technology appraisal referenced above.

The executive committee members of the CLL Forum have worked in close relationship with thew British Society of Haematology to produce and updated version of the guidelines for treatment of CLL, which are due to be published in the next 1-2 months.

The updated guidelines bring a significant change in the paradigm of CLL therapy, eliminating the recommendation of treatment with chemoimmutoherapy (namely FCR, BR or R-Chlorambucil) for CLL, given the compelling and unquestionable evidence of superiority of novel targeted agents such as BTK inhibitors and BCL2 inhibitors in extending progression-free survival in CLL patients when compared directly to chemoimmunotherapy (CIT).

With the above to mind, we have seen with concern that the most recent draft scope for the ID6291 technology appraisal continues to feature FCR and BR regimes as comparators for the combination of Venetoclax-Obinutuzumab (VenO).

Whilst we appreciate that FCR/BR have been the comparators in the randomised controlled trial that provided the original recommendation for the VenO combination, we strongly believe as a scientific community, that the use of these two CIT regimens goes against the current recommendations and their use as a comparators poses a risk to the availability of the effective VenO combination for the CLL patient community.

We also believe that there are sufficient grounds with age and comorbidity scoring to effectively differentiate the population of this ID6291 appraisal from that of TA663.

We, therefore, suggest that FCR/BR are not used as comparators to definitively evaluate the cost effectiveness of VenO and that the terminology of the final recommendation, if positive, should avoid mentioning chemotherapy regimens that are not currently recommended in routine practice as criterion to define eligibility for VenO combination.

We acknowledge the unprecedented circumstance of evaluating a technology for whom the comparator(s) have seized to be standard of care, but we strongly believe that the efficacy of VenO should be benchmarked against the current standards of treatment that include novel agents, principally the combination of BTK and BCL2 inhibitors, as has been appropriately included already in the draft scoping.

We also suggest that additional criteria are included within the recommendation, which we believe are sufficient to allow clinicians to accurately identify the population of patients that would be suitable for VenO, based on age and/or comorbidities.

As stakeholders, we bring this to your attention separately to highlight its importance, even though our submission is already reflecting all the above points.

Yours Sincerely

[redacted]

[redacted]

[redacted], UK CLL Forum

[redacted], Nottingham University Hospitals, NHS Trust

UNIVERSITY OF BIRMINGHAM

External Assessment Group (EAG) Report

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR or BR are suitable (MA part review of TA663) [ID6291]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Mandy Maredza, Research Fellow II, University of Birmingham Jill Colquitt, Clinical Effectiveness Reviewer, Effective Evidence Mubarak Patel, Research Fellow II, University of Birmingham Naila Dracup, Information Specialist, University of Birmingham Mary Jordan, Clinical Effectiveness Reviewer, Effective Evidence Scott Marshall, Haematology Consultant, QE Hospital Gateshead Daniel Gallacher, Senior Research Fellow, University of Birmingham
Correspondence to	Dr Daniel Gallacher, d.c.gallacher@bham.ac.uk
Date completed	Date completed (25/09/2025)

Source of funding

This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR176615.

Declared competing interests of the authors

SM has served on advisory boards for AbbVie and AstraZeneca in the last 12 months. SM has received speaker fees and sponsored conference attendance from AbbVie.

RJ has served on advisory boards and received speaker fees from AbbVie and AstraZeneca. RJ received sponsored conference attendance from Roche.

Acknowledgements

The EAG are grateful to Dr Rosalynd Johnston (Consultant Haematologist, University Hospitals Sussex) for providing expert clinical advice, and to Prof Aileen Clarke who provided quality assurance for this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

M Maredza, J Colquitt, M Patel, N Dracup, M Jordan, S Marshall, D Gallacher. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR or BR are suitable (MA part review of TA663) [ID6291]: A Single Technology Appraisal. Centre for Evidence and Implementation Science, 2025.

Contributions of authors

Daniel Gallacher led the project and conducted the review of the statistical analysis.
Jill Colquitt, Mubarak Patel and Mary Jordan conducted the review of the clinical evidence.
Mandy Maredza conducted the review of the cost-effectiveness evidence.
Naila Dracup conducted the review of the literature search.
Scott Marshall provided expert clinical advice and reviewed the final version of this report.

Copyright statement

Table of Contents

Table of Tables

Table of Figures

Table of Abbreviations

AEPI	adverse events of particular interest
BCL2	B cell leukaemia/lymphoma 2
BR	bendamustine and rituximab
BNF	British National Formulary
BSH	British Society of Haematology
CDF	Cancer Drugs Fund
CI	confidence interval
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukaemia
CLL-IPI	International Prognostic Index for Chronic Lymphocytic Leukemia
cPAS	Confidential patient access scheme
CR	complete remission
CTC	common toxicity criteria
CV	cardiovascular
DSA	deterministic sensitivity analysis
DSMB	data safety monitoring board
EAG	external assessment group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FCR	fludarabine, cyclophosphamide and rituximab
FISH	fluorescent in-situ hybridisation
HCRU	healthcare resource utilisation
HR	hazard ratio
HRQoL	health-related quality of life
I+Ven	ibrutinib + venetoclax
I+Ven+O	ibrutinib + venetoclax + obinutuzumab
ICER	incremental cost-effectiveness ratio
Ig	immunoglobulin
IGHV	immunoglobulin heavy-chain variable region gene
IPD	individual patient data
IQR	interquartile range
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MAIC	matching-adjusted indirect comparison

MRD	minimal residual disease
ORR	overall response rate
OS	overall survival
PD	progressed disease
PDS	personal demographics service
PF	progression-free
PFS	progression-free survival
PH	proportional hazards
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
PV	prognostic variable
QALY	quality-adjusted life year
QoL	quality of life
SACT	systemic anti-cancer therapy
SAE	serious adverse event
SCIT	standardised chemoimmunotherapy
SLR	systematic literature review
STC	simulated treatment comparison
TEAE	treatment-emergent adverse event
TEM	treatment effect modifier
TLS	tumour lysis syndrome
TTNT	time to next treatment
uMRD	undetectable MRD
Ven+O	venetoclax + obinutuzumab
Ven+R	venetoclax + rituximab

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

The key issues identified by the EAG are listed in Table 1.

Table 1: Summary of key issues

ID6291	Summary of issue	Impact on results	Report sections
1	Choice of population to inform baseline overall survival for venetoclax+obinutuzumab (Ven+O)	Small	4.2.5.1
2	Approach to obtaining extrapolations for venetoclax+ibrutinib (I+Ven) – MAIC or equal efficacy	Small	4.2.5.1, 4.2.5.2 (and 3.5)
3	Time to next treatment for Ven+O and I+Ven	Small	4.2.5.4
4	Source of data to model adverse events related to Ven+O	Small	4.2.6.4

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The population to inform overall survival extrapolation for Ven+O

- Whether to apply hazard ratios from the MAIC, or assume equal efficacy to obtain extrapolations for I+Ven

- Whether to model time to next treatment for Ven+O and I+Ven using CLL13 data or the company algorithm.

- Whether to use most recently available information for inform on adverse event frequency used in the economic model.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Having superior time in progression-free health state, and lower mortality rate, according to company analyses.
- Having a different side effect profile to I+Ven

Overall, the technology is modelled to affect costs by:

- Having a different acquisition cost and different administration cost to I+Ven
- Having a different side effect profile to I+Ven

The modelling assumptions that have the greatest effect on the ICER are:

- Whether to assume that Ven+O offers PFS and OS benefit over I+Ven or assume equal efficacy.

1.3 EAG's key issues

Issue 1: Choice of population to inform baseline overall survival for Ven+O

Report section	4.2.5.1
Description of issue and why the EAG has identified it as important	The company extrapolates efficacy data from CLL13 which has been weighted to match the baseline characteristics of the CAPTIVATE trial. Survival extrapolations are effectively identical to background mortality. This approach does not utilise the SACT data which suggests mortality rates are slightly higher than those observed in the trial. It is uncertain whether longer OS follow-up from CLL13 or SACT could show greater deviation from general population mortality rates.
What alternative approach has the EAG suggested?	The EAG has digitised the SACT dataset for OS of Ven+O and extrapolates this using parametric survival models.
What is the expected effect on the cost-effectiveness estimates?	This has a small impact on the cost-effectiveness, especially if equal efficacy is assumed.
Could any additional evidence or analyses be provided to resolve this key issue?	Longer follow-up of the SACT population would provide greater certainty about the long-term efficacy of Ven+O.

Issue 2: Approach to obtaining extrapolations for venetoclax+ibrutinib – MAIC or equal efficacy

Report section	4.2.5.1, 4.2.5.2 (and 3.5)
Description of issue and why the EAG has identified it as important	The company utilises relative efficacy estimates from its preferred MAIC analysis, [redacted] These are applied to the extrapolations for Ven+O, to obtain predictions for I+Ven. The EAG considers the estimates coming from the MAIC analyses to be at high risk of bias and highly uncertain. They are also inconsistent with results from a published NMA which included Ven+O and I+Ven, but are for a different population. The EAG concludes the evidence provided does not support a difference in efficacy between Ven+O and I+Ven.
What alternative approach has the EAG suggested?	If further MAIC analyses are not undertaken focusing on the non-complex karyotype population of CLL13, which could be compared to the equivalent population of CAPTIVATE but requiring a generalisibity assumption of baseline characteristics of the wider CAPTIVATE trial to the non-complex karyotype, then the EAG preference is to assume equal efficacy for PFS and OS of Ven+O and I+Ven.
What is the expected effect on the cost-effectiveness estimates?	Small
Could any additional evidence or analyses be provided to resolve this key issue?	A head-to-head trial of these regimens would provide unbiased estimates of real-world efficacy. Access to SACT data for I+Ven would also be helpful to inform whether the assumption of equal efficacy is reasonable.

Issue 3: Time to next treatment (TTNT) for Ven+O and I+Ven

Report section	4.2.5.4
Description of issue and why the EAG has identified it as important	For Ven+O and I+Ven, the company attempts to estimate TTNT using the proportion of people entering post-progression survival. However this approach appears flawed, with subsequent treatment costs incurred when no people are in the post-progression health state.
What alternative approach has the EAG suggested?	The EAG extrapolates TTNT data from CLL13 for Ven+O, constraining it such that it does not fall below PFS. The EAG assumes the same TTNT extrapolation would also apply for I+Ven, i.e. equal TTNT for Ven+O and I+Ven.
What is the expected effect on the cost-effectiveness estimates?	Small
Could any additional evidence or analyses be provided to resolve this key issue?	Detail on TTNT for I+Ven, and longer follow-up of this outcome from CLL13 would allow for more accurate extrapolation and comparison of this outcome between Ven+O and I+Ven.

Issue 4: Source of data to model adverse events related to Ven+O

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The EAG is unable to align the inputs used by the company for the adverse events of Ven+O with any publications related to the CLL13 trial. The values used by the company appear to infer a lower rate of adverse events than reported by more recent data-cuts of CLL13.
What alternative approach has the EAG suggested?	The EAG uses adverse event frequencies as reported by a more recent publication of follow-up from CLL13.
What is the expected effect on the cost-effectiveness estimates?	This absolute effect is small, but when equal efficacy is assumed for PFS and OS, adverse events are the only thing that drives a QALY difference between Ven+O and I+Ven.
Could any additional evidence or analyses be provided to resolve this key issue?	Updated follow-up from CLL13 and CAPTIVATE, or from real-world studies of Ven+O and I+Ven could be used as alternative sources to inform adverse event frequency.

1.4 Secondary issues identified by the EAG

Issue 5: Source of information for age and sex of the starting population in the economic model

Report section	4.2.3
Description of issue and why the EAG has identified it as important	The company uses CLL13 as the source of information for age and sex distribution parameters in their economic model. The EAG considers that information from the SACT report should be utilised as it is more representative of the UK population.
What alternative approach has the EAG suggested?	The EAG preference is to use information from the SACT report to provide age and sex parameters. This is also consistent with the EAG's preferred source for overall survival data. The EAG uses the median age of the SACT population, as the mean was not reported.
What is the expected effect on the cost-effectiveness estimates?	Small, as these characteristics are similar across the SACT and CLL13 populations
Could any additional evidence or analyses be provided to resolve this issue?	Obtaining the mean age for a more recent sample for people who received Ven+O or I+Ven and are recorded in SACT would reduce the uncertainty in this parameter

Issue 6: Whether it is appropriate to apply a standardised mortality ratio for long-term mortality

Report section	4.2.5.1
Description of issue and why the EAG has identified it as important	There remains uncertainty about the long-term mortality rate for people with CLL undergoing first-line treatment, as the treatment pathway has evolved rapidly in recent years. Both EAG and company approaches rely heavily on general population mortality to obtain plausible extrapolations for overall survival. The company acknowledge that they anticipate some increased mortality and added the option to apply a SMR, so that the extrapolations converge to a mortality rate that is higher than general population mortality. The company's scenario is based on clinical opinion and not supported by data.
What alternative approach has the EAG suggested?	The EAG has not explored the effect of applying a SMR in its base case as equal efficacy is assumed. However, the hazard rate of the EAG's extrapolation of SACT data converges with background mortality much later than the company's preferred extrapolation.
What is the expected effect on the cost-effectiveness estimates?	Small, especially if equal efficacy is assumed.
Could any additional evidence or analyses be provided to resolve this issue?	The company could explore using relative survival models (or additive models) which capture excess mortality, accounting for general population mortality. However, longer follow-up may be required for these models to be used. Longer follow-up could allow the calculation of an appropriate SMR, or produce extrapolations which do not require a SMR.

1.5 Company's modelling errors identified by the EAG

The EAG noted the company's modelling of TTNT assumed all people received three subsequent treatments, however the EAG used an alternative approach.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of EAG's preferred assumptions and ICER for Ven+O vs. I+Ven

Scenario	Incremental cost	Incremental QALYs	ICER (change from company's base case)
Company's deterministic base case [CS V1.0]	[redacted]	0.37	[redacted]
Key Issue 1 and 2: OS exponential extrapolation for Ven+O based on SACT data and equal efficacy is assumed between Ven+O and I+Ven	[redacted]	0.12	[redacted]
Key Issue 2: Equal PFS for Ven+O and I+Ven based on CLL13 data whilst maintaining the company's choice of extrapolation (Weibull)	[redacted]	0.25	[redacted]
Key Issue 3: Gompertz extrapolation for TTNT constrained to not fall below PFS and set equal for both arms	[redacted]	0.37	[redacted]
Key Issue 4: Adverse events for Ven+O based on CLL13 trial published data (Jan 2023 data cut) for grade 3 or 4 AEs	[redacted]	0.37	[redacted]
Additional EAG preferred assumptions:			
Issue 5: Baseline starting age of [redacted] years based on SACT data	[redacted]	0.37	[redacted]
Issue 5: Proportion males of [redacted]% based on SACT data	[redacted]	0.39	[redacted]
EAG's preferred base-case - deterministic (combining all the above scenarios)	[redacted]	0*	[redacted]
EAG's preferred base-case - probabilistic (combining all the above scenarios)	[redacted]	0	[redacted]

*To two decimal places, the QALYs are identical, however the absolute (unrounded figure) of incremental QALYs is 0.0035 QALYs in favour of I+Ven which results in a deterministic ICER of [redacted]. The ICER can be interpreted as: for every additional QALY gained by using I+Ven compared to Ven+O, it costs [redacted].

1.7 Outline of confidential comparator or subsequent treatment prices

Confidential competitor discounts (cPAS) were provided to the EAG for ibrutinib, obinutuzumab, acalabrutinib and zanubrutinib. Confidential MPSC prices were provided for rituximab. These prices are not used in this EAG report, but are used in the EAG cPAS appendix. Additional detail of this information can be found in section 5.4.

2 Background

This report critiques the company submission for venetoclax with obinutuzumab (Ven+O) for untreated chronic lymphocytic leukaemia (CLL) when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable.

2.1 Critique of the company's description of underlying health problem

The company discusses the disease pathophysiology and risk factors for CLL, symptoms of CLL and burden of CLL in CS sections 1.3.1 to 1.3.3. The EAG notes that many of the references cited by the company are secondary sources of evidence, such as overviews or websites. CLL is described as the most common lymphoproliferative disease in Western countries, representing 25 – 30% of leukaemia cases.[1] The EAG notes that the reference used by the company (Ghia *et al*., 2007)[1] was actually a secondary reference taken from Rozman and Montserrat, (1995). However, the 25 – 30% figure was not actually stated in Rozman and Montserrat, (1995). In the UK, the mean reported yearly incidence between 2017 and 2019 was 3,952, which equates to 6.0 cases per 100,000, as reported by Cancer Research UK.[2] The company does not characterise CLL as rare or indicate its proportion among all cancers, but the figures confirm that it remains an uncommon malignancy in the general population while being the predominant form of adult leukaemia, which is most common in older adult males (aged ≥75 years).[2, 3]

Disease pathophysiology and risk factors

The company describes CLL as a blood cancer of mature $CD5^+$ B cells with proliferation supported by microenvironmental interactions and B-cell receptor (BCR) signalling pathways such as NF-kB, ERK/MAPK, JNK and mTOR.[4, 5] The pathways promote survival, proliferation, disease progression and drug resistance.[4-6] The company states that enhanced BCR signalling is a key feature of CLL. This is because it regulates cell apoptosis, via the NF-kB signalling pathway, and promotes the differentiation and proliferation of B cells.[7] The company further cites that ~80% of CLL patients carry chromosomal deletions and that some of these mutations are

associated with worse prognoses.[8] The prevalence of TP53 mutations is cited as ~10% in untreated patients.[8]

In addition to male sex, age and genetic factors were associated with increased risk of CLL.[9] Furthermore, obesity, smoking and agricultural chemical exposure are suggested as risk factors.[2, 9] However, the EAG notes that these associations are taken from secondary sources.

Symptoms of CLL

According to the CS, most patients are asymptomatic at diagnosis, with symptoms typically emerging as the disease advances. Diagnosis occurs with a routine blood test, or a patient may present with non-specific symptoms such as fatigue, weight loss, night sweats, fever or swollen lymph nodes.[10, 11] The 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) diagnostic threshold for CLL is ≥5 × 10^9/L B lymphocytes sustained for three months, confirmed by flow cytometry.[12] When the disease progresses to an advanced stage, patients may experience a range of symptoms including extreme weakness and shortness of breath (due to anaemia), increased number of infections (due to neutropenia) and excessive bruising or bleeding (due to thrombocytopenia), which is consistent with guideline descriptions.[10] These symptoms are caused by excessive proliferation and survival of CLL cells, which causes overcrowding of healthy blood cells. This then impairs development and growth in the bone marrow thus impeding their functions.[12, 13]

The CS also describes the recommended diagnostic and baseline work-up, including fluorescent in-situ hybridisation (FISH) for cytogenetics and mutational testing for TP53 and IGHV status, to determine circulating antibody levels fighting infection, and the Direct Coombs test, which measures if CLL cells are producing antibodies that target and damage erythrocytes.[12] While this may reflect best practice, the company does not acknowledge variability in access across NHS centres. The EAG clinical experts confirmed that IGHV testing is possible but not universally available in all UK regions and can have long turnaround times of between 6 and 12 weeks. Nevertheless, the EAG clinical experts noted that whilst this testing is not mandatory, it makes significant differences to treatment plans. The submission also does not quantify the frequency of specific symptoms at diagnosis or during disease progression, which would help contextualise patient experience and disease burden.

CLL severity is determined in accordance with the Rai and Binet staging systems, these are described in CS Table 3.

Disease burden

The company describes CLL as having a 'substantial detrimental impact' on patients' health related quality of life (HRQoL). The company provides references suggesting that this burden is due to the high symptom burden, treatment-associated toxicity and the emotional impact of living with an incurable illness.[10, 14-17]

The CS explains how in the early stages of CLL, patients may be asymptomatic but can then eventually begin to experience fatigue, weight loss, chills, fever, night sweats and swollen lymph nodes.[10] However, as CLL progresses, patients are prone to experiencing more burdensome symptoms, these may include, greater fatigue, weakness, shortness of breath due to anaemia, excessive bruising and bleeding due thrombocytopenia and greater risk of infection due to neutropenia.[10] The company cites a systematic review that reported patients with CLL had significantly worse HRQoL than the general population in terms of fatigue, anxiety, physical functioning, social functioning, sleep disturbance and pain interference.[16] The company also suggested that "*patients with CLL have significantly reduced emotional wellbeing than the general population ($p < 0.001$), and patients with other cancers ($p < 0.001$)*."[14] However, the EAG notes that the reference cited by the company was a qualitative study in patients with CLL, and that the finding that emotional wellbeing was reduced in CLL patients compared to other types of cancer came from a different source. The company also describes the CLL burden on employment. In a HRQoL study, Shanafelt *et al*. (2007), found that 11.8% of patients reported being medically disabled when describing their employment status, with 78.3% of patients attributing their disability to CLL.[14] However, fitness of the patients was not described, therefore the relevance to the population in the current appraisal is unclear.

A systematic review of the economic burden of CLL by Waweru *et al*. 2020,[16] reported that "*healthcare costs are primarily driven by treatment and hospitalisation-related costs, AE management, and disease progression*." In addition to economic burdens of CLL treatment, CLL patients with other ailments such as cytopenia will require additional treatment, thus increasing *healthcare* resources.

2.2 Critique of the company's overview of current service provision

2.2.1 Current treatment pathway

The current treatment pathway is described in full in CS section 1.3.5 and CS Fig. 1. Clinical advisors to the EAG broadly agree with the treatment pathway as described.

CLL is considered incurable, therefore the overall aim is to achieve long lasting remission whilst minimising side effects and toxicities from treatment. Treatment of early stage CLL follows a strategy of 'active monitoring', with treatment started in patients who meet the iwCLL[12] criteria for progressive or symptomatic disease.

Treatment strategies vary according to prognostic and predictive factors, including genetic abnormalities, patients' fitness or comorbidities, concomitant medication, and prior treatment. Comorbidities are common among CLL patients and British Society of Haematology (BSH) (2018)[18] guidelines confirm there is no agreement on the use of a specific formal co-morbidity assessment tool to determine fitness of patients for chemotherapy.[19] The EAG notes that the criteria previously used have been as simplistic as aged <65 years with no significant comorbidities as per TA689.[20]

The company presents evidence from an advisory board of UK clinicians, that 'end-of-bed' assessments of patient fitness are used to inform selection of 1L therapy. Clinical experts advised the EAG that in practice, clinicians would consider if they were prepared to give patients toxic chemotherapy, but now that newer drugs are significantly better, standardised chemoimmunotherapy (SCIT) is rarely used so defining fitness by this criterion is rarely required.

Treatment guidelines in the UK and Europe are dictated by BSH guidelines (2022)[19] ([redacted]), and the European Society for Medical Oncology (ESMO) guidelines (2024).[21] These are heavily referenced throughout CS sections 1.3.5 and 1.3.6, as are the anticipated contents of the [redacted]. The EAG has verified current guidelines[19, 21] and are satisfied these are accurately depicted in the CS. A clinical advisor for the EAG confirmed [redacted]

[redacted].

BSH guidelines (2022)[19] recommend that fit patients with untreated CLL and no del(17p)/ *TP53* mutation, receive 1L treatment with targeted therapies, including Ven+O (where accessible via the CDF) or other funding streams. The company state that since the approval of Ven+O for this population, SCIT treatment has declined considerably and is avoided by clinicians (CS section 1.3.5.1). Additionally, the [redacted] ESMO guidelines[21] [redacted] that time-limited SCIT treatment, such as FCR, should only be considered in certain patients and only if targeted therapies are not reimbursed.

The company also presents feedback from clinical engagement, including an advisory board of UK-based consultants they conferred with, to support their position that FCR and BR are no longer routinely used in clinical practice. The company did not provide the source material referenced as their clinical engagement for the EAG to verify. However, clinical advisors to the EAG were aligned in their assessment of the current treatment landscape, confirming that SCIT is now rarely used in UK clinical practice.

Response to treatment is usually assessed at least two months after therapy is completed, consisting of complete and differential blood counts, physical examination, and evaluation of bone marrow in cases with cytopenia. The extent of response is defined using parameters relating to lymphoid tumour load and constitutional symptoms, and the haematopoietic system.[12]

The company stated that extent of remission is also measured as the presence of minimal residual disease (MRD) or undetectable MRD (uMRD), categorised clinically as <1 CLL cell per 10,000 (10^4) leukocytes in peripheral blood (PB) or bone marrow (BM). CS section 1.3.5 provides satisfactory evidence from CLL8 and CLL10 that achieving uMRD is associated with longer remission periods and survival.[22, 23] However, the most recent review of MRD-driven treatments, used by the company to

corroborate that uMRD of < 10^4 in PB at the end of treatment (EOT) is indicative of treatment efficacy.[24] This review also discussed heterogeneity of responses across subgroups in later updates of GLOW and CAPTIVATE trials. This was not reported by the company. uMRD rates in both trials were higher in unmutated immunoglobulin heavy-chain variable region gene (IGHV) groups compared to mutated IGHV groups, although this did not translate into improved progression free survival (PFS) outcomes. In contrast, PFS rates were unaffected by EOT MRD status in mutated IGHV subgroups.[24]

The company also states that MRD is primarily used as an endpoint in clinical trials, although its importance in clinical practice is increasing. The EAG notes the iwCLL currently considers measurement of MRD desirable in clinical trials but not generally indicated for clinical practice.[12]

The EAG clinical experts explained the significance of MRD and confirmed the current position on its use in UK clinical practice:

a. MRD has been shown to be a surrogate marker of PFS to demonstrate improved outcomes with treatments, although EAG clinical experts note that excellent PFS can occur in the context of ongoing detectable MRD. Higher rates of MRD negativity predict better outcomes in PFS but do not predict overall survival (OS), because OS is also determined by success and outcomes of second and subsequent lines of therapy.

b. MRD negativity is a very good predictor of PFS when taken in populations as a whole, and useful to analyse data from trials, but is much less dependable when making individual patient assessments.

c. MRD has the strongest prediction in IgVH unmutated disease which accounts for 60-70% of CLL disease. It is much less useful for IgVH mutated disease where long PFS/ OS is seen in those with both MRD negativity and positivity, highlighting the importance of the biological behaviour of CLL in outcomes.

d. MRD monitoring and use in disease prediction is not currently recommended in routine NHS practice because at present there is not

the infrastructure for delivering MRD testing in all patients and MRD is not paid within standard commissioning.

e. There is much debate around the depth and quality of MRD testing. There are two main methods: Flow cytometry and PCR testing, where PCR testing has greater sensitivity (down to 1 in 1,000,000 cells) compared to flow cytometry (1 in 10,000 cells).

f. Although MRD can be useful in many factors of patient management, it is still not a reliable predictor of disease behaviour over time, because a single MRD timepoint measurement gives a single snapshot of disease load. A patient who has achieved MRD negativity is unlikely to relapse within 2-3 years, however, disease behaviour becomes the dominant prognostic factor beyond this point.

Time to relapse is dependent on several aspects, including prognostic factors, previous treatment and genotype.[25, 26] In the event of relapse, re-initiation of treatment is required, and may occur multiple times throughout a patient's lifetime.[19] The company state that duration of remission (DOR) after 1L therapy may influence choice of 2L therapy, and that according to the clinicians they interviewed, if long remission was seen with fixed-duration 1L therapy, they might then consider another fixed-duration treatment at 2L. Clinical experts for the EAG agreed, giving the example that if 1L Ven+O gave a PFS of >3 years then they would consider the use of Ven+R for 2L, but if <3 years then they would prefer BTKi in the hope that longer disease control would be achieved with a different drug mechanism.

The EAG and clinical experts agree that CS Figure 1 displays the current treatment pathway, as outlined in previous NICE technology appraisals, which best represents current UK clinical practice and acknowledge that I+Ven and Ven+O (including the population in the CDF) are the only treatments recommended in all sub-populations of previously untreated CLL.

2.2.2 Limitations in current treatment pathway

The company presents I+Ven as the only relevant 1L treatment comparator to Ven+O, for fit patients with untreated CLL and no del(17p)/ *TP53* mutation. CS

section 1.3.6 discusses the limitations of its use based on trial evidence of AEs[27-29] and guidance from the British National Formulary (BNF)[30] and Medicines and Healthcare products Regulatory Agency (MHRA).[31]

The AE profile of I+Ven, namely cytopenia, bruising, arthralgia, nausea/vomiting and diarrhoea, are well supported by the literature, as is the association with cardiovascular (CV) side effects across all BTKi-based therapies. Whilst figures for the fixed-duration cohort of I+Ven in the CAPTIVATE trial were correctly reported for AEs of any grade in CS section 1.3.6, the EAG reports for context that 2/98 patients (2%) not using concomitant anticoagulants experienced bleeding events of grade 3/4 and 2/159 patients (1%) experienced atrial fibrillation of grade >3.[27]

Good practice is appropriately cited advising healthcare professionals to evaluate patients' cardiac history and function before initiating therapy, and consider alternatives in those at higher risk if available.[32] However, the EAG highlights the population to which this guidance refers (i.e. those at increased risk of CV events) who are older patients, patients with cardiac comorbidities or those with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, as per the BNF guidelines.[30] Ven+O is already approved in this population,[33] whilst this appraisal addresses the fit patient population.

The company references TA663[33] where clinical and patient experts advised that CV comorbidities can prevent patients from taking ibrutinib-based therapies. The EAG notes the only specified contraindications to BTKi initiation are recurrent decompensated cardiac failure secondary to AF and anticoagulation due to history of a life-threatening bleed or uncontrolled bleeding.[34]

In addition to CV assessments prior to BTKi treatment, monitoring CV cardiac function during treatment and follow-up is advised due to the incidence of new onset CV events observed in studies of BTKis,[32] and guidance provided on treatment interruptions and discontinuation.[31, 34] The company suggests this is likely to increase resource use through outpatient monitoring but do not provide any qualifying evidence for this.

The company concludes there is a significant need for tolerable and effective alternative treatment options for fit patients with untreated CLL and no del(17p)/ *TP53* mutation, to facilitate individualised treatment based on underlying comorbidities, offer patient choice, and expand access to Ven+O for patients who are not suitable for I+Ven.

Clinical advisors for the EAG agree on the importance of treatment choice, as although rates of cardiac side-effects are lower in fixed-term I+Ven treatment compared to continuous use, the option of choosing Ven+O over I+Ven is an important therapeutic option for those at high risk of experiencing side-effects. Similarly, ibrutinib is not recommended with warfarin use because of the increased risk of bleeding and higher rates of intracranial bleeds in clinical studies, so these patients require access to an effective treatment option.

No evidence is presented by the company on the proportion of fit patients with untreated CLL and no del(17p)/ *TP53* mutation in the UK who are not suitable for treatment with I+Ven to allow objective comment from the EAG on the significance of Ven+O reimbursement within this population.

2.2.3 Positioning of Ven+O

The company states that under current guidelines, 1L Ven+O treatment represents the only opportunity to use obinutuzumab for fit patients with untreated CLL and no del(17p)/ *TP53* mutation,[19] and provides an effective and tolerable treatment option. Without Ven+O for 1L treatment, obinutuzumab would not be available for this population at any stage.

Clinical advisors to the EAG value Ven+O as a treatment option for CLL patients and emphasise that it is vitally important to have a choice of treatments available in this population.

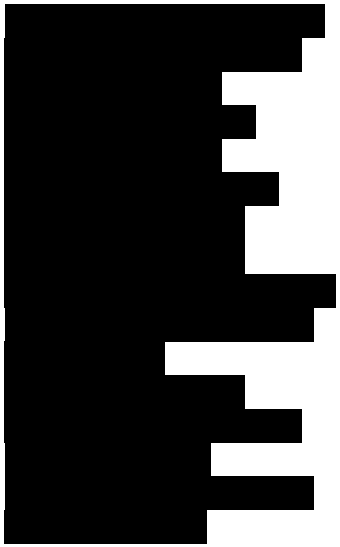
2.3 Critique of the company's definition of decision problem

The decision problem in the company's submission has some differences to the final NICE scope. The population in the company's decision is described differently to the

NICE scope, however the population remains the same (Table 3). Only one comparator, ibrutinib with venetoclax (I+Ven), is considered by the company. The EAG considers that the exclusion of the other comparators is appropriate.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation and for whom FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) is suitable	Fit patients with untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation	This wording reflects the evolution in the treatment pathway for patients with untreated CLL, though does not impact the patient cohort being appraised, as this is the same cohort previously considered suitable for FCR/BR.	The EAG clinical experts considered it appropriate to use the term 'fit patients' rather than 'unsuitable for FCR/BR', as FCR/BR are no longer recommended treatments for untreated CLL. The population addressed by the company remains in line with the NICE scope. The EAG clinical experts considered that the key trial is representative of the population in England and Wales needing treatment.
Intervention	Venetoclax with obinutuzumab	Venetoclax with obinutuzumab (Ven+O)	Not applicable	The intervention matches the scope. Ven+O is indicated for the treatment of adult patients with previously untreated CLL.
Comparator(s)	• Bendamustine plus rituximab (BR)	Ibrutinib with venetoclax (I+Ven)	As detailed in CS section 1.1 and CS section 1.3.5.1, use of FCR and BR as 1L treatment for	The EAG clinical experts agreed with the exclusion of FCR and BR and with

	• Fludarabine with cyclophosphamide and rituximab (FCR) • Ibrutinib plus venetoclax Acalabrutinib with venetoclax with or without obinutuzumab (subject to ongoing NICE evaluation)		CLL in the UK is rare and has declined over time.[35]  Acalabrutinib with venetoclax with or without obinutuzumab is not considered a relevant comparator as it is not established practice in the NHS due to its ongoing NICE appraisal.	the company's justification for this. The NICE appraisal of acalabrutinib with venetoclax with or without obinutuzumab is ongoing (expected publication date 22 April 2026).[37] The EAG agrees that the only relevant comparator in this appraisal is I+Ven.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	Primary endpoints: • Progression-free survival (PFS) • Undetectable minimal residual disease (uMRD) in peripheral blood	Not applicable	The company submission considers the outcomes listed on the NICE scope. In addition, uMRD outcomes are reported as surrogate endpoints for PFS. The EAG clinical experts considered uMRD

		Secondary endpoints: • uMRD in bone marrow • Overall survival • Response rate • Adverse events (AEs) Health-related quality of life		useful as PFS and overall survival need longer follow-up to assess. However, it is not currently recommended in routine NHS practice (see section 2.2.1)
Economic analysis	As per the NICE reference case	As per the NICE reference case	Not applicable	Not applicable.
Subgroups	None specified	Not applicable	Not applicable	Not applicable
Special considerations including issues related to equity or equality	None specified	Not applicable	Not applicable	Not applicable

3 Clinical effectiveness

This section presents a summary and critique of the clinical effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 and 3.3 provide a critique of the included studies and clinical effectiveness analyses. Sections 3.4 and 3.5 critique any indirect comparisons presented by the company. Section 3.6 covers additional work done by the EAG.

3.1 Critique of the methods of review

A systematic literature review (SLR) was conducted by the company and presented in Appendix B. The scope was wider than the current decision problem and included populations and interventions beyond the scope of this appraisal.

3.1.1 Search strategies

Searches were originally undertaken in December 2018 and updated five times; the most recent update was carried out in February 2025. The company reported the latest full search strategy only in the company submission (CS Appendix B) and the overall sets of results for each database update search (CS Appendix B Table 1). The company confirmed in the clarification response that the search strategy had not changed from the original search and provided the original search strategy (CS Clarification response A1). An appropriate range of bibliographic databases, recent conference proceedings and reference lists of systematic reviews and meta-analyses retrieved from the database searches were searched. Clinical trials registries were not reported to have been searched, which could introduce publication bias as not all trials are published.[38] The database search strategies combined indexing and free text terms for previously untreated chronic lymphatic leukaemia and randomised and non-randomised controlled studies (CS Appendix B Table 2, Clarification response Table 2). The CS Appendix B 'Date of Searches' section reports that 'Additional search updates conducted on 05 December 2022, 12 February 2024, and 06 February 2025 summarised evidence from randomised controlled trials only'. The Inclusion

Criteria (CS Appendix B, Table 4) lists 'observational studies' within the inclusion criteria; therefore, it is not clear if or why the company excluded non-randomised studies for data extraction. The company's response to Clarification A.1 is also unclear. Please refer to Section 3.1. Publication date limits were used in the update search strategies to exclude results published before the date of the previous search. This is not best practice and risks missing relevant results, as publications are not added to Embase/Medline immediately after publication. The EAG would recommend using the more appropriate date fields 'date created' or 'date delivered' to ensure that the searches are more comprehensive.[39] Language filters were not applied to the search strategy; however, the company report that they only considered studies published in English language for inclusion, which would introduce language bias (CS Appendix B Search terms). The free text searches of the Medline and Embase searches only searched within the title or abstract fields in the free text searches. Searching the keyword fields in addition to these would increase the sensitivity.

3.1.2 SLR Methods

A summary of the EAG's assessment of the SLR is presented in Table 4. The methods of the review were generally appropriate, although the risk of bias assessments were conducted by a single reviewer, which is not best practice.

The eligibility criteria for the SLR were broad and generally appropriate. However, there were concerns over the company's decision to only present and synthesise RCT data and ultimately exclude 275 non-RCT studies despite being eligible. The EAG considers this to be a limitation, particularly as additional non-RCTs of the NICE scoped comparator I+Ven could have been considered to strengthen the MAIC. Nevertheless, a key concern is the handling of the CAPTIVATE study, which was identified and presented among the 46 RCTs in the SLR, but was in fact a phase 2, open label, single arm trial. Additionally, CAPTIVATE was selected to inform the MAIC without undergoing any structured quality appraisal. The EAG notes this reflects a

lack of systematic and transparent use of non-RCT evidence and undermines the robustness of the comparative analysis. The EAG also notes that only 42 of the 46 included studies listed by the company in the SLR underwent a risk of bias assessment.

The company presented data of the “46 RCTs” which included survival and response outcomes (Tables 7, 8 and 9 of CS Appendix B). These data were not discussed further in the CS or in the Appendix.

In conclusion, while the company’s SLR followed broadly appropriate methods for identifying RCTs, its handling of non-RCT evidence was inconsistent and not systematic. The inclusion of CAPTIVATE, despite stated non-eligibility of data extraction for non-RCTs, raises concerns about selective inclusion, while relevant non-RCT evidence for I+Ven may have been excluded, limiting the strength of indirect comparison. The EAG therefore undertook additional screening to identify any potentially relevant I+Ven studies that may have been missed by the company’s approach (section 3.6.1) These issues reduce confidence in the completeness and transparency of the company's evidence base.

Table 4: Summary of SLR methods and EAG assessment of robustness

Systematic review step	**EAG assessment of robustness of methods**
Searches CS Appendix B	Searches of several suitable databases and grey literature is reported. The grey literature searches were provided in the clarification responses. Appropriate search terms are used. Clinical trial registries were not searched, and inbuilt publication date limits were used.
Inclusion criteria CS Appendix B, Table 4	The inclusion criteria were broadly appropriate and structured using the PICOS framework. The population of interest was adults (≥ 18 years) with previously untreated CLL/SLL, with or without del(17p)/TP53 mutation, and including both fit and unfit participants. This scope is wider than the decision problem, which focuses on fit patients without del(17p)/TP53

	mutation, and therefore includes studies with populations beyond the scope of the current appraisal. Intervention and comparator inclusion criteria encompassed a wide range of therapies which extended beyond the NICE scope and decision problem, reflecting the global SLR approach. Eligible efficacy outcomes were appropriate (e.g., PFS, OS, MRD) as were safety outcomes (e.g., adverse events, haematological and non-haematological). Only English language publications were considered, which may have excluded potentially relevant evidence from non-English publications. Although non-RCTs and observational studies were initially eligible, these were excluded from the data synthesis and no details were provided in the CS. The EAG considers that non-RCTs of the NICE scoped comparator, I+Ven, should have been considered for use in the MAIC, see section 3.6.1.
Screening CS Appendix B	The screening process was appropriate and in line with best practice for systematic reviews. Following deduplication, titles and abstracts were screened independently by two reviewers against the pre-specified inclusion criteria. Studies passing this stage underwent full text screening, again by two independent reviewers. Any disagreements at either stage were resolved through discussion or via a third independent reviewer.
Selection of included studies CS Appendix B	The EAG has concerns with study selection. Results were appropriately documented using a PRISMA diagram (CS Appendix Figure 1). From an initial 8,276 records, 404 papers met the inclusion criteria, comprising 129 reports of 46 RCTs and 275 non-RCT or observational studies. The PRISMA diagram and narrative suggests that 162 records were identified from conference proceedings and citation searching, and that all 162 were assessed for eligibility and were subsequently included, which seems unlikely to the EAG. Although both RCT and non-RCT evidence met the inclusion criteria, the clinical evidence synthesis presented by the company included only RCT data. While this focus on RCTs prioritises high-quality evidence, the rationale for excluding non-RCT evidence from any contextual discussion was not clearly provided. This may limit the completeness of the SLR, particularly for the NICE scoped comparator, I+Ven,

	and the EAG considers that non-RCT evidence should have been considered in the MAIC, for safety outcomes, or longer-term follow-up data from real world sources. In response to clarification A1 regarding literature searches, the company explained that non-randomised studies were not considered eligible for data extraction in the second, third, fourth and fifth updates of the SLR, because a critical mass of clinical evidence was reached. However, this explanation is not entirely clear. CAPTIVATE was a single arm study selected for use in the MAIC. It was published in 2022, meaning it could only have been identified in the third update onwards, at a time when non-RCT evidence were ostensibly excluded from consideration. The inclusion of CAPTIVATE in the MAIC therefore appears inconsistent with the company's stated approach, which the EAG notes could represent potential selective use of non-RCT evidence. The company provided a list of excluded studies at full text screening in CS Appendix Table 12, but a list of the 275 eligible observational studies and non-RCTs was not initially provided. This was provided in response to Clarification A5.
Data extraction CS Appendix B	Data extraction methods were largely appropriate, using a pre-specified protocol to capture a variety of relevant data and information. Extraction was conducted by a single reviewer and checked by a second reviewer.
Tools for quality assessment CS Appendix B	The risk of bias assessment for the eligible RCTs was conducted using the Centre for Reviews and Dissemination (CRD) checklist, which is an appropriate tool consistent with NICE methods. Assessments were performed at trial level. Conference abstracts were not assessed due to insufficient reporting detail. Many domains were rated as 'unclear (N/R)', often due to reporting gaps in primary publications, and it is unclear whether trial authors were contacted to resolve these uncertainties. Risk of bias assessments were conducted by a single reviewer, which is not best practice. The EAG notes that only 42 of the 46 included studies were quality assessed. The company did not quality assess non-RCTs, therefore the CAPTIVATE trial, which was ultimately used to inform the MAIC, was not assessed

Evidence synthesis CS Appendix B	Clinical outcomes including survival and response outcomes, were presented for the 46 included studies in Tables 7, 8 and 9 of CS Appendix B. No discussion of these results was provided by the company. Safety data and outcomes were not provided or discussed. Finally, MRD as an outcome was not presented or discussed by the company in the SLR (other than for the selected comparator trial, CAPTIVATE).

3.2 Critique of the methods of the trials of the technology of interest

The company derives evidence for the clinical efficacy of Ven+O from the phase 3 clinical trial CLL13 (NCT02950051)[40, 41] and the Systemic Anti-Cancer Therapy (SACT) dataset.[42] The studies are summarised in Table 5.

Table 5: Clinical effectiveness studies of technology of interest

	CLL13 (NCT02950051)	**SACT database**
Role in this evaluation	Only the Ven+O treatment arm from CLL13 is used in the evaluation, essentially treating it as a single arm trial.	Used by the EAG for information on overall survival, and patient baseline characteristics
Study type	Phase III prospective, multicentre, open-label, randomised trial to evaluate superiority in the co-primary endpoints (MRD negativity rate in peripheral blood at month 15 [Ven+O vs SCIT] and PFS).	Retrospective observational cohort study based on routinely collected registry data.
Patient group	Fit patients with previously untreated CLL without del17p or *TP53* mutation (fit patients defined by a CIRS score ≤6 and a normal creatinine clearance ≥70ml/min).	Patients in England with CLL without del17p or *TP53* mutation receiving first-line systemic anti-cancer therapy recorded in the SACT database.
Subgroups	Age (≤ 65 and > 65) Binet stage at screening Cytogenetic subgroup	None

	CLL13 (NCT02950051)	SACT database
	IGHV mutation status CLL-IPI risk group Complex karyotype	
Inclusion criteria[a]	1. Documented CLL requiring treatment according to iwCLL criteria. 2. GFR ≥70ml/min directly measured with 24hr urine collection, calculated according to the modified formula of Cockcroft and Gault. 3. Eastern Cooperative Oncology Group Performance Status (ECOG) performance status 0-2.	Diagnosis of CLL and receipt of first line systemic therapy during the extraction period.
Exclusion criteria[a]	1. Any prior CLL-specific therapies. *Prior treatment with rituximab even for other indications than CLL is not permitted.* 2. Transformation of CLL (Richter's transformation). 3. Decompensated haemolysis, defined as ongoing haemoglobin drop in spite of prednisolone or intravenous immunoglobulins (IVIG) being administered for haemolysis. 4. Detected del17p or *TP53* mutation. 5. Patients with a history of PML. 6. Any comorbidity or organ system impairment rated with a single CIRS score of 4 or total CIRS score of more than 6.	Patients not recorded as receiving systemic therapy during the extraction period.
Intervention	Ven+O (n=229) • Obinutuzumab IV infusion:	Ven+O (n=513) Obinutuzumab IV infusion on days 1±2, 8 and 15 of cycle

	CLL13 (NCT02950051)	SACT database
	Cycle 1 100mg on day 1, 900mg on day 2, 1000mg on days 8 and 15 Cycles 2-6 1000mg on day 1 • Venetoclax oral tablets: Daily over 12 cycles with a slow dose escalation of ven started on day 22 of cycle one. Cycle 1 Days 22-28: ven 20 mg (2x10 mg tablets) Cycle 2 Days 1-7: ven 50 mg (1x50 mg), days 8-14: ven 100 mg (1x100 mg), days 15-21: ven 200 mg (2x100 mg), days 22-28: ven 400 mg (4x100 mg) Cycles 3-12 Days 1-28: ven 400 mg (4x100 mg tablets) I+Ven+O and Ven+R (Neither treatment arm considered in this submission)	1, and then on day 1 of cycles 2 through 6. Venetoclax dose titration was given on day 22 of cycle 1 and to be completed on cycle 2 day 28. Maximum treatment duration of venetoclax was day 28 of the 12th cycle. Specific doses were not mentioned.
Comparator	SCIT (n=229): • FCR (age < 65 years) 6 x 28 day cycles of FCR • Fludarabine IV 25 mg/m^2 on days 1-3 (cycle 1-6). • Cyclophosphamide IV 250 mg/m^{2}on days 1-3 (cycle 1-6). • Rituximab IV 375 mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2-6, before the application of chemotherapy at a dosage, with premedication according to clinical practice of the participating sites. • BR (age > 65 years) 6 x 28 days cycles of BR. • Bendamustine IV 90 mg/m^2 on days 1 and 2 (cycle 1-6).	

	CLL13 (NCT02950051)	SACT database
	• Rituximab IV 375 mg/m^2 in cycle 1 and at 500 mg/m^2 in cycles 2-6 before the application of chemotherapy, with premedication according to the clinical practice of the participating sites.	
Outcomes	Primary endpoints: • Progression-free survival (PFS) • Undetectable minimal residual disease (uMRD) in peripheral blood Secondary endpoints: • uMRD in bone marrow • Overall survival • Response rate • Adverse events (AEs) • Health-related quality of life	Overall survival
Study dates	Between 13 December 2016 and 13 October 13 2019	Between 10 November 2020 to 31 October 2022
Median follow-up	January 2023 data cut,[40] median 50.7 months follow-up (patient level data) February 2024 data cut,[43] median 63.8 months follow-up (PFS) February 2021 data cut;[41] median follow-up 38.8 months (MRD negativity).	31 October 2022 Vital status traced on 13 February 2023 Median follow-up in SACT was 10.2 months (310 days), with a maximum of 23 months.
Location	159 sites in ten countries in Europe and the Middle East (Austria, Belgium, Denmark, Germany, Finland, Ireland, Israel, Netherlands, Sweden and Switzerland)[40]	NHS hospitals in England submitting data to the SACT registry.

Source: adapted from CS Table 5, Eichhorst et al. 2023,[41] Fürstenau et al. 2024,[40] CLL13 trial protocol.[44] SACT report[42] [a] The full list of key inclusion/exclusion is reported in CS Table 7. MRD, minimal residual disease CIRS, cumulative illness rating scale; PML, progressive multifocal leukoencephalopathy; CLL, chronic lymphocytic leukemia.

3.2.1 Overview of CLL13

CLL13 was a phase 3, multicentre, randomised, prospective open-label trial evaluating the safety and efficacy of Ven+O, I+Ven+O and venetoclax+rituximab (Ven+R) compared with SCIT (FCR and BR) in fit patients with previously untreated CLL without del17p or *TP53* mutation. Fit patients were defined as patients with a CIRS score ≤6 and a normal creatinine clearance (≥70ml/min); see below for comment on this. The trial was conducted across 159 sites in ten countries in Europe and the Middle East, with 926 patients randomised 1:1:1:1 across the 4 treatment arms. Randomisation was stratified according to age (≤ 65 vs > 65), Binet stage at screening (A, B or C), and geographic region.

Clinical effectiveness results of the SCIT, I+Ven+O and Ven+R treatment arms are reported in the CS, but the company notes they are not currently relevant comparators for this indication in the UK. In the EAG report, the SCIT arm results are reported alongside the Ven+O arm for transparency only and are not considered a relevant comparator by the company, the EAG or their respective clinical experts.

Clinical experts for the EAG reinforced that SCIT should no longer be used in practice due to its clinical inferiority, and that [redacted] with the caveat that European guidelines may still differ as they cover other countries which are limited to the treatments they have available.

Experts expressed no concerns with the trial inclusion/exclusion criteria and considered that the use of the term ‘fit’ as alternative to ‘unsuitable for FCR/BR’ was reasonable, with the latter being considered as historical terminology. However, ‘fit’ is difficult to define in clinical practice. Clinical experts explained that clinicians would consider if they were prepared to give toxic chemotherapy, but don’t necessarily utilise a formal assessment criteria.

They highlighted that whilst CIRS is reasonable for use in trials, it requires extra documentation so is not often done in clinical practice.

Outcomes presented by the company align with those in the NICE scope (CS Table 1) and include additional measures of undetectable minimal residual disease (uMRD). Primary endpoints are progression free survival (PFS) and uMRD in peripheral blood (PB), with secondary endpoints as uMRD in bone marrow (BM), overall survival (OS), response rate, adverse events (AEs), and health related quality of life (HRQoL). EAG clinical experts advised that MRD monitoring and its use in disease prediction is not currently recommended in routine NHS practice because the UK does not have the infrastructure for delivering MRD testing in all patients and MRD tests are not paid for within standard commissioning. There is also much debate around the depth and quality of MRD testing and its value within clinical practice (see detailed discussion in EAG section 2.2.1).

The planned treatment duration was six cycles in the SCIT group and 12 cycles in the Ven+O group, with all treatments administered in 28-day cycles. In the SCIT group, patients aged ≤65 years received FCR and those > 65 years received BR.

3.2.1.1 Data cuts in CLL13

Three data cuts for CLL13 have been published. These are summarised in Table 6. Analysis of the co-primary endpoint of uMRD was conducted at the February 2021 data cut (median 38.8 months follow-up). Individual patient data is available for the January 2023 data cut (interim analysis) with 50.7 months median follow-up. Longer follow-up (median 63.8 months) of OS, PFS, TTNT and some safety data is available in a recent conference proceeding.[43]

Table 6: Data cuts in CLL13

Data cut	Median follow-up	Latest outcomes available	Source
February 2021	38.8 months	uMRD at month 15.	Eichhorst 2023[41]
January 2023 (interim analysis)	50.7 months	IPD for MAIC: OS, PFS, CR, ORR. Subsequent treatments. Adverse events.	Fürstenau 2024[40] CLL13 Priority 1 analyses[45]
February 2024 (final analysis)	63.8 months	OS, PFS, TTNT. Some safety data.	Fürstenau 2025[43] (conference proceeding).

3.2.1.2 Baseline characteristics of CLL13

Differences in patient disposition (Table 7) in CLL13 were notable between treatment arms, with less people who were randomised to the SCIT arm receiving treatment than in the Ven+O arm (216 vs 228), mainly because they withdrew consent. Similarly, more patients in the SCIT arm discontinued study treatment early due to adverse events (32 vs 9), and more were lost to follow-up (41 vs 14).

Baseline characteristics of patients in the Ven+O and SCIT treatment arms of the CLL13 trial appear similar (Table 8). The median age of patients was 62 and 61 years, respectively, with females representing 25.3% of Ven+O patients and 28.8% of SCIT patients. Similar measures of fitness were displayed across treatment arms, with mean CIRS score for both Ven+O and SCIT patients being 2.3, and similar proportions of patients in each CLL-IPI risk group.

Binet staging of CLL severity showed similar proportions in stages A, B and C across the Ven+O arm, 25.3%, 39.7% and 34.9%, respectively, and 27.5%, 36.7% and 35.8% in the SCIT treatment arm. The EAG notes that slightly different data were reported for Binet stage between the two main trial publications;[40, 41] the reason for this is unclear, but the differences are only minor (Table 8). The presence of bulky disease (lymph nodes ≥ 5 cm), and genetic abnormalities, pertinent to CLL prognosis, were also broadly similar across trial arms. Clinical experts for the EAG considered that overall, the differences in baseline characteristics are not important.

96% of patients randomised within the whole trial were treated at European centres (10 and 8 patients in the SCIT and VEN+O arms, respectively, were recruited from Southern Ireland; none were from the UK,[40] Clarification A9) and as such the EAG considers the trial generalisable to UK clinical practice. In addition, the EAG clinical experts considered that the baseline characteristics were representative of patients seen in UK clinical practice.

Table 7: Patient disposition from two relevant arms of CLL13

	Ven+O	**SCIT**
Randomised	229	229
Received study treatment	228	216
Did not receive study treatment	1	13
Withdrew consent	0	11
Other reasons	0	2
Died before receiving study treatment	1	0
Discontinuations		
Discontinued study treatment per protocol	214	176
Discontinued study treatment early	14	40
Progressive disease	3	2

	Ven+O	SCIT
Death	1	0
Adverse event	9	32
Non-compliance	1	2
Other reasons	0	4
Lost to follow up		
Total	14	41
Death	11	17
Patient withdrawal	3	17
Non-compliance	0	2
Other reasons	0	5
In follow-up as of January 2023 data cut	215	188
Source: adapted from CS Table 11.		

Table 8: Baseline characteristics from two relevant arms of CLL13

Characteristic	**Ven+O (N = 229)**	**SCIT (N = 229)**
Median age (range)	62 (31–83)	61 (29–84)
Mean (SD)	60.9 (10.0)[a]	60.5 (10.4)[a]
≤ 65 years, N (%)	147 (64.2)	150 (65.5)
> 65 years, N (%)	82 (35.8)	79 (34.5)
Sex		
Male, N (%)	171 (74.7)	163 (71.2)
ECOG PS score of 0, N (%)	165 (72.1)	164 (71.6)
Time between first diagnosis and randomisation, months Median (IQR)	27.7 (8.3-62.0)	26.7 (9.2-59.1)
CIRS score, Median (IQR)	2 (1-4)[a]	2 (0.5-4)[a]
CIRS score, Mean (SD)	2.3 (1.9)	2.3 (1.9)

Characteristic	**Ven+O (N = 229)**	**SCIT (N = 229)**
CIRS score, N (%)		
≤ 1	90 (39.3)	93 (40.6)
> 1	139 (60.7)	136 (59.4)
Tumour lysis syndrome risk category, n/N (%)		
Low	31/211 (14.7)	31/214 (14.5)
Intermediate	127/211 (60.2)	132/214 (61.7)
High	53/211 (25.1)	51/214 (23.8)
Binet stage, N (%)		
Stage A	58 (25.3)[a] / 60 (26.2)[b]	63 (27.5)[a] / 61 (26.6)[b]
Stage B	91 (39.7)[a] / 90 (39.3)[b]	84 (36.7)[a] / 85 (37.1)[b]
Stage C	80 (34.9)[a] / 79 (34.5)[b]	82 (35.8)[a] / 83 (36.2)[b]
Rai stage n/N (%)		
0	13/228 (5.7)	7/227 (3.1)
I or II	122/228 (53.5)	113/227 (49.8)
III or IV	93/228 (40.8)	107/227 (47.1)
Creatinine clearance (Cockroft-Gault) (ml/min)		
Median (IQR)	86.3 (72.6-108.6)	86.3 (73.4-104.6)
Range	41.5-180.2[b]	39.5-223.6[b]
Missing information, N (%)	1 (0.4)	0 (0.0)
Cytogenetic subgroup by hierarchical order, N (%)		
Del17p	0 (0.0)	0 (0.0)
Del11q	44 (19.2)	41 (17.9)
Trisomy 12	47 (20.5)	34 (14.8)
No abnormalities	44 (19.2)	53 (23.1)

Characteristic	**Ven+O (N = 229)**	**SCIT (N = 229)**
Del13q	94 (41.0)	101 (44.1)
IGHV mutational status, N (%)		
Unmutated	130 (57.0)	131 (57.2)
Mutated	89 (39.0)	95 (41.5)
Not evaluable	9 (3.9)	3 (1.3)
Missing information	1 (0.4)	0 (0.0)
$Beta_2$-microglobulin		
Median (range) (IQR)	4.0 (2.0-16.2)[b] (3.2-5.2)[a]	4.2 (1.4-15.5)[b] (3.3-5.0)[a]
>3.5 mg/litre, n/N (%)	136/227 (59.9)	155/228 (68.0)
CLL-IPI risk group, N (%)		
Low	32/217[b] (14.7)	36/225[b] (16.0)
Intermediate	76/217[b] (35.0)	67/225[b] (29.8)
High	109/217[b] (50.2)	122/225[b] (54.2)
Very High	0 (0.0)	0 (0.0)
Missing information	12 (5.2)[a]	4 (1.7)[a]
Complex karyotype, N (%)		
< 3 aberrations	182/218[b] (83.5)	177/223[b] (79.4)
≥ 3 and < 5 aberrations	25/218[b] (11.5)	30/223[b] (13.5)
≥ 5 aberrations	11/218[b] (5.0)	16/223[b] (7.2)
Missing information	11 (4.8)[a]	6 (2.6)[a]
Bulky disease, N (%)		
All measurable lymph nodes with the largest diameter < 5 cm	156 (70.9)	153 (68.9)
Any measurable lymph node with the largest diameter ≥ 5 cm & < 10 cm	48 (21.8)	50 (22.5)

Characteristic	Ven+O (N = 229)	SCIT (N = 229)
Any measurable lymph node with the largest diameter ≥ 10 cm by CT/MRI scan	16 (7.3)	19 (8.6)
Missing information	9 (3.9)	7 (3.1)
Source: adapted from CS Table 12. [a]Fürstenau et al. 2024.[40] [b]Eichhorst et al. 2023.[41] CIRS, cumulative illness rating scale; CLL-IPI, International Prognostic Index for Chronic Lymphocytic Leukaemia; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain gene; PS, Performance Status		

3.2.1.3 Quality assessment of CLL13

Quality assessment of CLL13 is presented in CS section 2.5, using questions recommended by the Centre for Reviews and Dissemination. A comparison of the company's and EAG's assessment is presented in Appendix 7.1. The EAG agrees with most of the company's judgements but notes that the company has confused concealment of treatment allocation with masking of care providers, participants and outcome assessors, and considers that concealment of treatment allocation was adequate in the trial. CLL13 is an open label study with no blinding of outcome assessors; the company states that 'blinding of investigators and patients would not have been possible due to differences in the nature and schedules of treatments'. The EAG notes that there is a potential risk of bias from differences in care or exposure to other factors, and from differences in how outcomes are determined. In open label studies, measures of response and progression can be assessed by a blinded independent committee. Masking is less of an issue for objective measures such as overall survival. Overall, the EAG considers CLL13 to have a low risk of bias within the limits of its open label design.

However, the EAG notes that for the purposes of this appraisal, CLL13 is essentially a single-arm study as the trial comparators are not relevant.

3.2.2 SACT dataset

The data for this analysis were drawn from the National Disease Registration Service (NDRS) through linkage of the NHS England Blueteq® prior approval system and the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

Ven+O was made available through the Cancer Drugs Fund (CDF) following NICE guidance (TA663), which recommended managed access because of uncertainty in OS estimates at the time of appraisal. During this period, real-world evidence was collected using SACT to capture treatment activity and outcomes, with Blueteq used to confirm eligibility criteria and ensure patients met the conditions of the Data Collection Agreement.
Eligible patients were identified from Blueteq applications for Ven+O during the CDF access window from 10 November 2020 to 31 October 2022. NHS numbers were used to link applications to SACT records, which provided treatment dates, regimen details, and subsequent treatment history.

Exclusions were applied to remove duplicate applications, patients who died prior to treatment initiation, and patients who did not commence therapy. In total, 542, Blueteq applications were submitted, which corresponds to 513 unique patients. After exclusions, 483 patients were confirmed as having started treatment and were included in the final SACT analysis cohort, representing 96% of expected records. Patients were followed up in SACT until 31 October 2022, with vital status traced through the Personal Demographics Service on 13 February 2023. The median follow-up in SACT was 10.2 months (310 days), with a maximum of 23 months.

The outcomes of interest for this dataset were treatment duration, defined as the time from initiation to cessation of Ven+O, and OS, defined from treatment initiation to death from any cause or censoring. In addition, treatment outcomes were assessed through SACT outcome summaries, which provided reasons for stopping therapy, including completion as prescribed, discontinuation due to toxicity, progression, patient choice of death.

The baseline characteristics of the 483 patients included in the analysis are in Table 9. The median age at treatment initiation was 61 years, and 67% of the cohort were male. Most patients were between 50 years and 79 years, and the majority had a performance status of 0 or 1 at treatment start. According to Blueteq, 70% of patients were considered suitable for FCR and 30% were suitable for BR as comparator regimens.

Table 9: SACT dataset patient characteristics (n = 483)

Characteristic	**N (%)**
Male	324 (67)
Median age, years	Males: 61.5 Females: 61
60 – 69 years	200 (41)
70 – 79 years	86 (18)
80+ years	4 (1)
Performance status 0	209 (43)
Performance status 1	131 (27)
Performance status 2	11 (2)
Missing performance status	132 (27)
Suitable for FCR	339 (70)
Suitable for BR	144 (30)
Source: SACT Report[42]	

Treatment was administered in accordance with the licensed schedule. Obinutuzumab was given intravenously on days 1 (±2), 8 and 15 of cycle 1, with venetoclax dose titration commencing on cycle 1, day 22 and continuing until cycle 2, day 28. Venetoclax was then administered orally in 28 day cycles for a maximum of twelve cycles (approximately 45 weeks), while

obinutuzumab was limited to six cycles. Treatment discontinuation could occur earlier in the event of unacceptable toxicity, disease progression, patient choice, or death.

Treatment start dates were defined as the earliest date recorded in SACT across regimen start, cycle start, or administration fields. The last treatment data was similarly derived, with a prescription length of 28 days added to capture the expected interval to the next cycle.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Clinical Outcomes from CLL13

This section summarises and critiques the results from CLL13. Note, the outcomes do not all use the same data-cut. The EAG has indicated which data-cut has been used for each outcome.

3.3.1.1 Progression-free survival

The first co-primary outcome from CLL13 presented in the CS was PFS. Results presented in the CS were from the February 2024 data cut with a median follow-up of 63.8 months. The Ven+O arm is demonstrated as superior PFS to SCIT (log-rank p value <0.001). A hazard ratio was not reported as the proportional hazards (PH) assumption was not met,[43] though the statistical analysis plan (SAP) presented to the EAG (v6.0) does not describe this requirement.[46] A comparison of the reported hazard ratios undertaken by the EAG suggests that the hazard ratio of Ven+O vs SCIT is in the region of 0.55. However, the violation of the PH assumption means this may be an unreliable estimate of relative effect, and should be interpreted alongside the observation that the Kaplan-Meier curves for Ven+O and SCIT begin to converge, with their difference clearly reducing over time (Figure 4 of CS).

3.3.1.2 Minimal residual disease

The other co-primary endpoint of CLL13 related to MRD negativity at 15 months.

MRD results are presented using the February 2021 data-cut. The EAG understands that this is because the primary and secondary MRD outcomes were based on using 15 months of follow-up, and so these would be unaffected by longer follow-up.

The EAG considers that extended monitoring of MRD would have been helpful to inform assumptions around long-term efficacy.

The EAG notes that at the 15-month assessment, people given SCIT finished treatment 6 months earlier than Ven+O, and so people randomised to SCIT had a longer period without active treatment. However, the benefit observed at month 15 was consistent with benefit at months 9 and 12.

Table 10: Outcomes relating to MRD from CLL13

Outcome	Ven+O	SCIT	Difference
uMRD negativity rate in peripheral blood at month 15	86.5% (97.5% CI, 80.6 to 91.1)	52.0% (97.5% CI, 44.4 to 59.5)	P<0.001
uMRD negativity rate in bone marrow blood at final staging	72.5%	37.1%	NR

uMRD: undetectable minimal residual disease

3.3.1.3 Overall survival

Overall survival was a secondary endpoint, and was presented using data from the February 2024 data-cut. No significant difference was observed between the treatments in CLL13 despite up to 7 years of follow-up (CS Figure 8).

The company has not reported the hazard ratio for Ven+O relative to SCIT, but the EAG notes this is reported in the original source. The hazard ratio is 0.76 (97.5% CI: 0.36, 1.63; p=0.42).[43]

3.3.1.4 Time to next CLL treatment (TTNT)

Using the February 2024 data-cut, Ven+O showed a statistically significant longer TTNT than SCIT (HR 0.43 [97.5% CI: 0.27; 0.68], log-rank p<0.001). This effect appears slightly larger than the benefit for PFS (CS Figure 9), which may be explained by the toxicity associated with SCIT. The company's source of information is consistent with this, where SCIT had 18.5% of people with early discontinuations vs 6.1% for Ven+O. Discontinuation attributable to AEs was [redacted]% and [redacted]% for SCIT and Ven+O in the 2023 data-cut, respectively.[45] The EAG notes a recent abstract using a February 2024 data-cut reported that [redacted]% discontinued Ven+O due to AEs and it is unclear how this proportion could have decreased over time.[43] The CS reports subsequent therapy for CLL by combining all arms (CS section 2.6). Therefore, the EAG asked for clarification on the precise subsequent therapy for Ven+O and SCIT treatment arms (Clarification A16). The company responded by highlighting Figure 5 of Fürstenau 2024.[40] Eighteen people received subsequent therapy for CLL at the January 2023 data cut (excluding five people with subsequent treatment due to Richter's transformation), of which nine received BTKi-based treatment, six received BTKi + venetoclax, two received SCIT, and one received venetoclax-based treatment. More detailed information on the number of treatments was provided in a separate document following clarification question A16, revealing [redacted] subsequent treatments were received by these 18 people.[47] The most commonly received treatments were BTKi monotherapy ([redacted]%) and venetoclax related regimens ([redacted]%). No information on subsequent treatments was provided from more recent data-cuts.

3.3.1.5 Complete Response

Planned secondary outcomes included the complete (CR) and partial response (PR) rate at 15 months, and the duration of response beyond this. Only information relating to the response rates at 15 months were provided in the company submission. The CR for Ven+O was 56.8% compared with 31.0% for SCIT (CS Figure 10). When combining PR or CR, this difference is reduced between Ven+O (96.1%) and SCIT (80.8%), but is still indicative of a higher response rate for Ven+O.

3.3.1.6 Patient Reported Outcomes

Patient reported quality of life was measured in CLL13 using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the CLL specific module, EORTC QLQ-CLL16, evaluating disease and treatment-related symptoms, and changes in role functioning and global health status.[44] Only change in global health status from the QLQ-C30 is reported in the CS (CS section 2.6.2.8) and no data are provided in the Priority 1 analyses document provided by the company.[45] However, the CS cites a poster publication that provides some limited additional information (Fürstenau 2024[48]) on QLQ-C30 and QLQ-CLL16. The EAG was not able to identify how time on treatment, or subsequent treatments were considered in this analysis, hence it is unclear how these factors may influence the results.

Questionnaire return rates were relatively low; rates at months 48 and 60 were just 30% and 12%, respectively, so these timepoints were not used to track changes of QoL from baseline. Other rates ranged from 76% at baseline to 34% at month 24. These rates make it unclear whether the resulting data are representing the full range of patient experiences, and is at risk of bias.

Change in global health status is presented in CS Figure 11. In the Ven+O arm, improvements from baseline became greater than the minimal important difference (MID) at month 9, whereas in the SCIT arm this didn't occur until

month 24 however it remains just below the MID from month 9. Some fluctuation in mean change can be seen in CS Figure 11, but measures of variance at each timepoint were not provided.

Figures from (Fürstenau 2024[48]) show that the MID from baseline was not reached for either Ven+O or SCIT for physical functioning, role functioning, social functioning, fatigue/physical condition or symptom burden subscales (other than at month 15 for Ven+O), although numerical improvements tended to occur earlier with Ven+O. No testing for a statistical difference between the treatment groups was presented, and a SAP for secondary outcomes was not provided so it is unclear whether this was planned. Improvements in fatigue occurred and followed a similar pattern between interventions. Time until first deterioration of diarrhoea was significantly longer with SCIT than with Ven+O (HR 0.65, p=0.007), i.e. Ven+O patients experienced diarrhoea earlier, but there was no statistically significant difference between interventions for time until first deterioration of nausea/vomiting (HR 0.92, p=0.58).

3.3.1.7 Subgroup Analyses

The company reports the existence of, but does not present output for, subgroup analyses for the following pre-specified subgroups:

- age (≤ 65 years vs > 65 years)
- Binet stage
- cytogenetic subgroup
- IGHV mutation status
- CLL-IPI risk group
- complex karyotype

These are identical to the subgroups listed in the SAP, where they are described as exploratory analyses.

The most recent subgroup analyses identified by the EAG were where the populations for Ven+O and Ven+O+I were pooled and compared with CIT, using the January 2023 data-cut.[40] Given that Ven+O+I had a stronger PFS benefit than Ven+O, this pooling introduces bias if we assume the effect sizes are equivalent for Ven+O vs CIT. All subgroups had a point estimate suggesting a benefit of Ven+O/Ven+O+I, with almost all 95% confidence intervals for the hazard ratio not including the point of no difference.

Subgroup results comparing PFS outcomes for Ven+O vs SCIT were reported by Eichorst et al.[41] which used the January 2022 data-cut. These analyses also had all point estimates below 1, though more confidence intervals crossed one as there were fewer people included in the analysis and the shorter follow-up meant fewer events.

			CIT			GV/GIV							
Category	Subgroup	Total n	n	Events	PFS rate month 48 (%)	n	Events	PFS rate month 48 (%)	P-Value (Schoenfeld residuals)	Hazard ratio	95% Wald CI	P-Value (2-sided)	GV/GIV better / CIT better
All		**926**	**229**	**90**	**62.0**	**460**	**92**	**83.6**					
Binet stage at screening	A	246	61	22	67.0	123	18	88.7	0.29	0.30	0.16-0.56	0.00019	
	B	349	85	32	62.5	174	40	80.9	0.14	0.46	0.29-0.73	0.0011	
	C	331	83	36	57.9	163	34	83.2	0.28	0.37	0.23-0.58	< 0.0001	
Age groups (years)	≤ 65	597	150	47	69.8	295	64	83.4	0.39	0.52	0.35-0.76	0.00063	
	> 65	329	79	43	48.9	165	28	84.2	0.91	0.24	0.15-0.38	< 0.0001	
Complex karyotype	NCKT	742	177	65	67.3	378	71	84.5	0.80	0.41	0.29-0.58	< 0.0001	
	CKT	153	46	24	38.8	63	17	75.3	0.24	0.33	0.18-0.61	0.00047	
Cytogenetic subgroups as per hierarchy	del(11q)	162	41	27	34.4	76	18	78.9	0.34	0.22	0.12-0.40	< 0.0001	
	Trisomy 12	150	34	16	61.1	82	24	79.2	0.34	0.53	0.28-1.00	0.049	
	No abnormalities	201	53	14	71.5	103	26	74.8	0.83	0.71	0.37-1.37	0.31	
	del(13q)	413	101	33	69.6	199	24	92.1	0.31	0.30	0.18-0.50	< 0.0001	
Serum β_2-microglobulin (mg/L)	≤ 3.5	333	73	21	70.2	174	26	89.0	0.28	0.40	0.22-0.71	0.0019	
	> 3.5	587	155	69	57.9	282	64	80.5	0.46	0.39	0.28-0.55	<0.0001	
***IGHV* mutational status**	Unmutated	518	131	70	46.4	253	75	76.2	0.39	0.36	0.26-0.50	< 0.0001	
	Mutated	380	95	17	84.9	190	16	93.1	0.93	0.42	0.21-0.84	0.013	

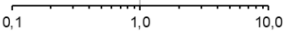


Figure 1: Forest plot of PFS subgroups from CLL13 (Taken from Fürstenau et al., 2024)[40]

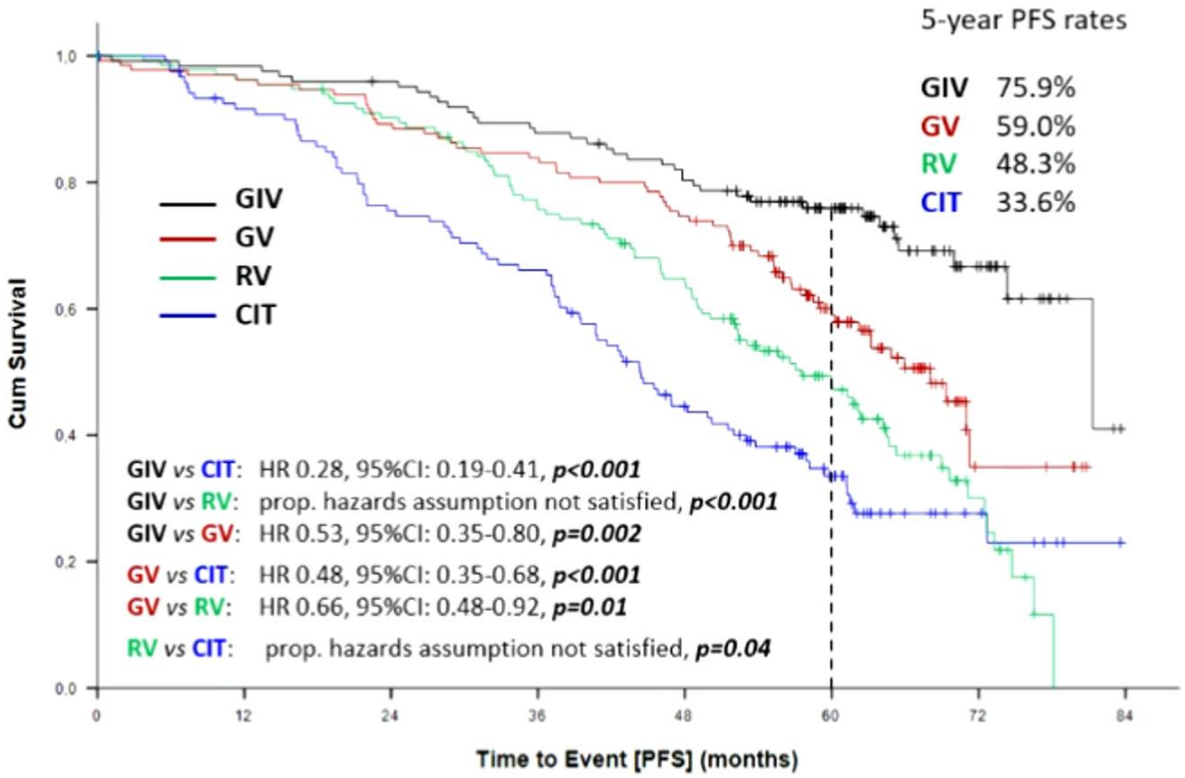
The EAG notes that subgroup analyses by IGHV status for PFS were presented in the presentation of the most recent data cut of CLL13.[43]

In this more recent data-cut, IGHV status appears to have a larger influence on the baseline PFS rate, and the relative treatment effect. For people with unmutated IGHV, the probability of remaining progression-free at 5 years were 33.6% and 59.0%, with a hazard ratio of 0.48 (95% CI: 0.35, 0.68; p<0.001) (CIT: Chemoimmunotherapy, GIV: Obinutuzumab+ibrutinib+venetoclax, GV: Obinutuzumab+venetoclax, RV: Rituximab+venetoclax

Figure 2). Whilst for people with mutated IGHV, the probability of remaining free of PFS at 5 years were 75.3% and 82.9%, with a hazard ratio of 0.79 (95% CI: 0.43, 1.46; p=0.45) (CIT: Chemoimmunotherapy, GIV: Obinutuzumab+ibrutinib+venetoclax, GV: Obinutuzumab+venetoclax, RV: Rituximab+venetoclax

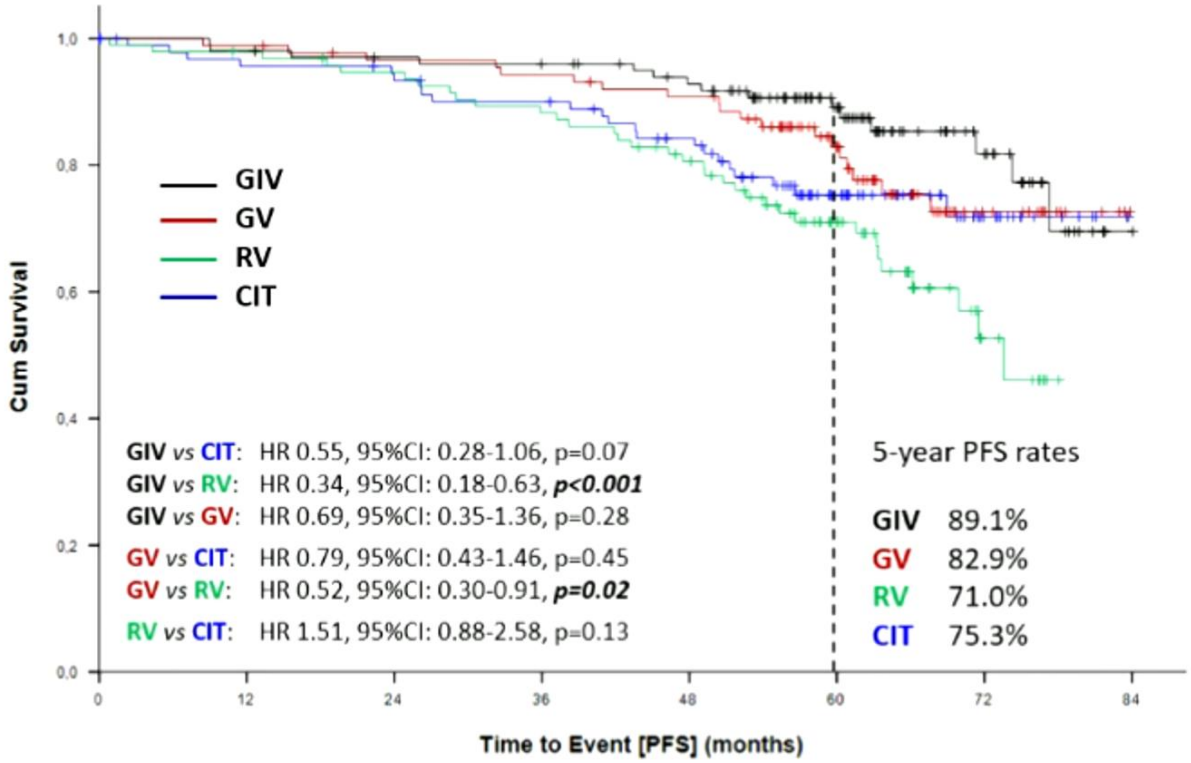
Figure 3).

A similar pattern was observed for OS and TTNT, however hazard ratios were not estimated for these outcomes/subgroups. The EAG considers that Ven+O may be more clinically and cost-effective relative to SCIT in the IGHV unmutated subgroup, however formal testing for this hypothesis was not considered in the trial design, and so this conclusion remains uncertain.



CIT: Chemoimmunotherapy, GIV: Obinutuzumab+ibrutinib+venetoclax, GV: Obinutuzumab+venetoclax, RV: Rituximab+venetoclax

Figure 2: PFS from CLL13 for people with unmutated IGHV (taken from Fürstenau et al. 2025[43])



CIT: Chemoimmunotherapy, GIV: Obinutuzumab+ibrutinib+venetoclax, GV: Obinutuzumab+venetoclax, RV: Rituximab+venetoclax

Figure 3: PFS from CLL13 for people with mutated IGHV (taken from Fürstenau et al. 2025[43])

3.3.1.8 Adverse events

Adverse events are reported for the safety population, which is all patients who received at least one dose of study treatment. The presentation of adverse events (AEs) in the CS is limited to treatment-emergent serious adverse events (SAEs) grade ≥3 (CS Table 27), and adverse events of particular interest (AEPI) of any grade (CS Table 28). However, AEs of any grade and SAEs are available in CLL13 Priority 1 analyses[45] and were provided again by the company in response to Clarification A13. Grade 3/4 AEs are available in the trial publications,[40, 41] but these and overall AEs were not provided by the company in response to Clarification A13. The differences between the definitions of SAEs grade ≥3, SAEs and grade 3/4 AEs are not

clearly described in the CS, but there appears to be some overlap between the three categories. The EAG discusses which is considered most appropriate for use in the economic model in section 4.2.6.4.

The EAG also notes that adverse events were not defined as related or not related to treatment.

Treatment-emergent SAEs grade ≥3

Treatment-emergent SAEs of grade ≥3 (CS Table 27) are summarised in Table 11 below. These were slightly less frequent with Ven+O than with SCIT ([redacted]) vs ([redacted]). The most common treatment-emergent SAEs grade ≥ 3 in the Ven+O arm were infusion-related reactions ([redacted]), pneumonia ([redacted]), tumour lysis syndrome ([redacted]) and thrombocytopenia ([redacted]). These events (among others, see section 4.2.6.4) were used in the company's economic model.

SAEs

SAEs of any grade are presented in CLL13 Priority 1 analyses[45] for FCR and BR separately, rather than as a combined SCIT arm. SAEs occurred in [redacted] of Ven+O participants, with the most common SAEs being infusion-related reaction ([redacted]), pneumonia ([redacted]), COVID-19 ([redacted]) and tumour lysis syndrome ([redacted]).

Adverse events grade ≥3

The most common grade ≥3 adverse events with Ven+O, as reported in the trial publication,[40] were neutropenia (56%), thrombocytopenia (18%), and infusion-related reaction (11%). The presentation for the February 2025 data cut reports incidence rates for grade 3-5 infections of 14/1000 patient months for Ven+O and 33/1000 patient months for SCIT, and for grade 3-5 cardiac disorders of 7/1000 patient months for Ven+O and 12/1000 patient months for SCIT.[43]

AEPI

According to the trial protocol, AEPI are adverse events associated with the disease itself i.e. immunodeficiency, infections and autoimmune disorders.[44] AEPI are summarised in Table 12. The proportion of patients experiencing an AEPI was [redacted] between Ven+O and SCIT ([redacted]). The most common AEPIs in the Ven+O arm were nasopharyngitis ([redacted]), COVID-19 ([redacted]), upper respiratory tract infection ([redacted]) and neutrophil count decreased ([redacted]).

Adverse events leading to discontinuation

Adverse events leading to discontinuation of the study drug occurred in [redacted] of the Ven+O arm and [redacted] of the SCIT arm at the January 2023 data cut; details of the events were not provided.[45] However, in the presentation for the February 2024 data cut these values are 3.9% and 14.8%, respectively.[43] It is unclear how the value in the Ven+O arm could be [redacted] with longer follow-up.

Adverse events (any grade)

The most common adverse events of any grade with Ven+O were infusion related reaction ([redacted]) neutropenia ([redacted]), diarrhoea ([redacted]), fatigue ([redacted]) nausea ([redacted]) and nasopharyngitis ([redacted]) (not tabulated here).[45]

Table 11: Treatment-emergent SAEs with maximum grade ≥3[a] and incidence ≥1% in any arm

	Ven+O N = 228	SCIT N = 216
Patients with ≥ 1 TESAE, N (%)	[redacted]	[redacted]
Blood and lymphatic system disorders		
Anaemia[b]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Neutropenia[b]	[redacted]	[redacted]
Thrombocytopenia[b]	[redacted]	[redacted]
General disorders and administration site conditions		
Pyrexia	[redacted]	[redacted]
Infections and infestations		
Febrile infection	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Pneumonia[b]	[redacted]	[redacted]
Injury, poisoning and procedural complications		
Infusion related reaction[b]	[redacted]	[redacted]
Metabolism and nutrition disorders		
Tumour lysis syndrome[b]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Basal cell carcinoma	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]
Richter's syndrome	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]

Source: adapted from CS Table 27. [a]The company does not clearly explain 'with maximum grade ≥3'. [b]AEs used in the economic model (among others, see section 4.2.6.4). CTC, common toxicity criteria; SCIT, standardised chemoimmunotherapy; TESAE, treatment-

	Ven+O N = 228	SCIT N = 216
emergent serious adverse event. The company notes that the percentages have been calculated using the total N number as the denominator.		

Table 12: Adverse events of particular interest of any grade with incidence ≥5% in the Ven+O arm

	Ven+O N = 228	SCIT N = 216
Patients with ≥ 1 AEPI, N (%)	[redacted]	[redacted]
General disorders and administration site conditions		
Influenza like illness	[redacted]	[redacted]
Infections and infestations		
Bronchitis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Investigations		
Neutrophil count decreased	[redacted]	[redacted]
Source: adapted from CS Table 28. The company notes that percentages have been calculated using the total N number as the denominator AEPI, adverse event of particular interest; CTC common toxicity criteria; SCIT, standardised chemoimmunotherapy		

In summary, the EAG has concerns with the clarity of the definitions of

grade ≥3 adverse events/SAEs reported in the CS. However, grade ≥3 adverse events are available from the trial publications. The most common grade ≥3 adverse events with Ven+O were neutropenia (56%), thrombocytopenia (18%), and infusion-related reaction (11%).

3.3.2 Results from SACT

At the time of the data cut-off (31 October 2022), 200 patients (41%) were still receiving treatment, while 283 (59%) had ended treatment. The most common outcome among those who stopped therapy was completion as prescribed, recorded in 70% of cases. An additional 12% were assumed to have completed treatment based on absence of records for at least three months. Discontinuation due to toxicity occurred in 5% of patients, while 3% chose to strop treatment. Small proportions of patients discontinued due to progression (2%), comorbidities (1%), or palliative benefit (2%). Deaths occurred both on treatment (1%) and not on treatment (4%). A very small number stopped due to COVID-19 (< 1%). Table 13 shows a breakdown for patients who ended therapy.

Table 13: Treatment outcomes for patients who ended Ven+O therapy in SACT (n=283)

Outcome	**N (%)**
Completed as prescribed	199 (70)
No treatment in ≥ 3 months (assumed completed)	33 (12)
Stopped due to acute toxicity	13 (5)
Stopped by patient choice	9 (3)
Death not on treatment	11 (4)
Palliative benefit	6 (2)
Disease progression	5 (2)
Death on treatment	4 (1)
Other comorbidity	2 (1)
COVID-19	1 (< 1)
Source: SACT report[42]	

Kaplan-Meier estimate of median treatment duration was 11.1 months (337 days, 95% CI: 11.1 to 11.3). At six months, 93% of patients remained on

therapy, while by twelve months only 21% continued treatment, reflecting the maximum one-year duration specified in the managed access agreement. The EAG clinical experts note that 21% of patients continuing treatment is high, as very few patients continue over 12 months. Therefore, this figure could include patients who had a pause in treatment.

For OS, vital status was traced on 13 February 2023, giving a median follow-up of 15.3 months (465 days). Of the 483 patients, 18 deaths were observed, and 465 patients were censored as alive at follow-up. Median OS was not reached. Survival was very high throughout follow-up, with 99% of patients alive at 6 months, 97% at 12 months, 96% at 18 months, and 94% at 24 months (Table 14). A sensitivity analysis restricted to patients with at least six months of follow-up (n = 431) showed identical conclusions, with survival estimates closely aligned to those of the full cohort.

Table 14: Overall survival estimates from SACT report for Ven+O (n=483)

Time point	**OS % (95% CI)**
6 months	99 (97 to 99)
12 months	97 (94 to 98)
18 months	96 (93 to 98)
24 months	94 (90 to 96)
Source: SACT report[42]	

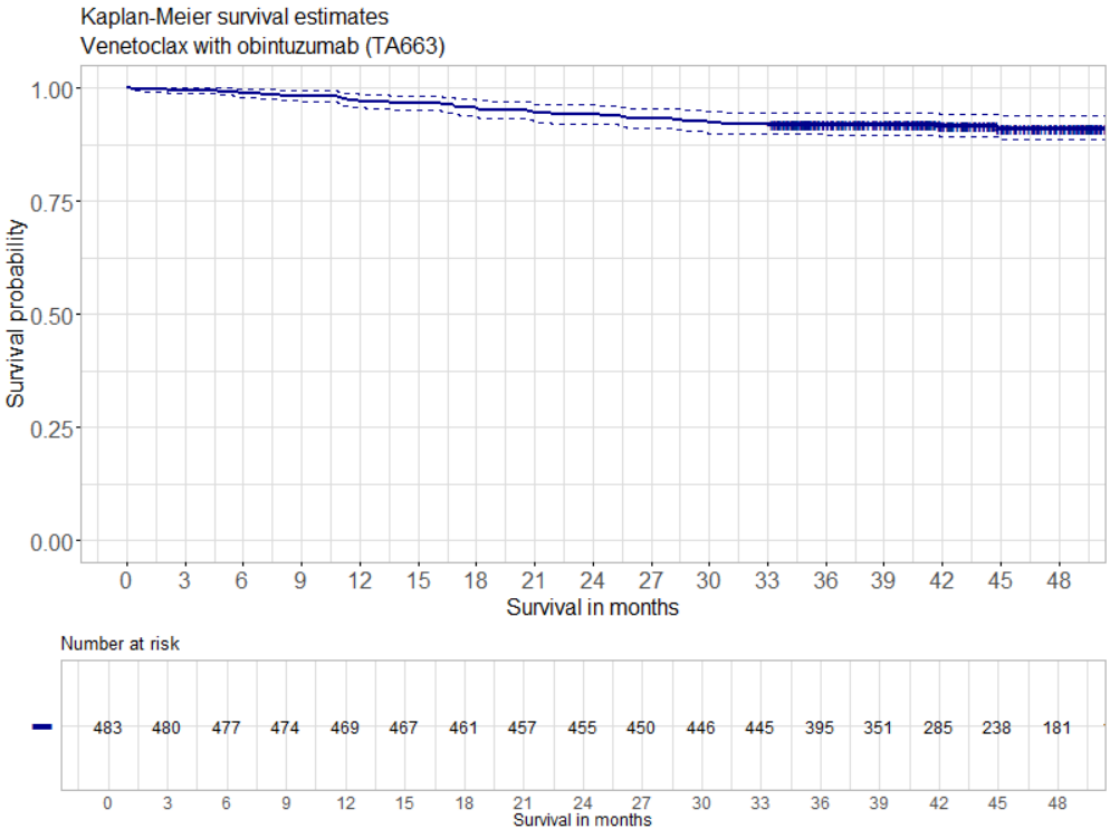


Figure 4: Overall survival for Ven+O (taken from SACT report addendum Figure 1)

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

3.4.1 Identification of studies included in the indirect treatment comparison

CS section 2.10.1.1 reports conducting an SLR to identify relevant clinical evidence for I+Ven, the key comparator of interest (see section 3.1 for the EAG critique of the SLR). The company states that 11 records remained after

exclusion based on trial design and investigations being investigated. Details of the 11 studies were requested by the EAG at the clarification meeting, but the question was not included in the formal list of clarifications and details were not provided by the company. The company names two trials of I+Ven that were identified but excluded, GLOW and FLAIR. The EAG agrees with the company's reasons for exclusion of these studies. Only one study of I+Ven, CAPTIVATE, was eligible for inclusion. The EAG agrees that no other studies of I+Ven are eligible (see sections 3.6.1 and 3.6.2).

3.4.2 Overview of CAPTIVATE

CAPTIVATE (NCT02910583)[27, 49] was included by the company as the only available evidence of I+Ven for fit patients with untreated CLL and no del(17p)/TP53 mutation (although 17% of people did have del17p/TP53 mutation).

CAPTIVATE was the key trial for the 'FCR-suitable' population in NICE TA891. It is an international open-label non-randomised phase 2 study in people with untreated CLL and small lymphocytic lymphoma (SLL) aged ≤70 years. In CS section 2.10.1.2 it is incorrectly described as 'randomised' (*'CAPTIVATE was a phase 2, multicentre, randomised, two-cohort, prospective clinical trial'*), but is correctly described elsewhere in the CS. Two cohorts were assessed in the trial: MRD-guided treatment and fixed-duration treatment; the EAG agrees that the latter cohort is the one relevant to this appraisal and best reflects UK practice. The MRD-guided cohort is not discussed in this report. Participants in the fixed-duration treatment cohort received all-oral treatment with three 28-day cycles of single-agent ibrutinib 420 mg once daily, followed by twelve 28-day cycles of I+Ven, with a target dose of venetoclax of 400 mg once daily after a standard ramp-up of 5 weeks. After completion of treatment, patients with subsequent confirmed progressive disease could be treated with single-agent ibrutinib, and those with progressive disease more than 2 years after I+Ven could be retreated with I+Ven. The EAG notes that re-treatment with I+Ven is not available on the NHS. The primary outcome was complete

response rate. Secondary endpoints included uMRD rates in PB and BM (proportion of patients with <1 CLL cell per 10 000 leukocytes), PFS and OS, among others.

The company does not conduct a quality assessment of CAPTIVATE. To avoid duplication of effort, the EAG considered the views of the EAG for TA891. The following points were noted:[35]

- The cohort included a representative sample from a relevant population with participants at a similar point in severity of disease.
- The study involved a clearly defined intervention undertaken by appropriate staff and in an appropriate setting.
- Data were collected prospectively, and appropriate outcomes and measures were used.
- Information on participant flow was fully reported and all participants were accounted for.
- Prognostic factors such as relevant cytogenetic factors were identified.
- The EAG for TA891 considered that, overall, the cohort was acceptable quality but subject to the bias inherent in studies of this design. The current EAG agrees with this judgement.

3.4.3 Comparison of CAPTIVATE and CLL13

The company conducted a heterogeneity assessment of CLL13 and CAPTIVATE to determine the feasibility of a MAIC in CS section 2.10.1.3, presenting an overview of the main study characteristics CS Table 17 together with a discussion of the issues.

3.4.3.1 Study design

CAPTIVATE is a phase 2 single arm non-randomised study, whereas CLL13 is a phase 3 RCT. The EAG is not concerned by this difference, given that only a single arm of CLL13 was used in the MAIC, and CAPTIVATE was considered

to be of acceptable quality. However, it prevents a connected network being formed for an indirect treatment comparison.

3.4.3.2 Population

The company notes three key differences in the populations of CLL13 and CAPTIVATE: the inclusion of small lymphocytic lymphoma (SLL), del(17p) or TP53 mutations, and age. The EAG clinical expert agrees that CLL and SLL are considered the same disease and respond equally well to treatments. In CAPTIVATE, 17% of patients had del(17p) or TP53 mutation, whereas these were excluded from CLL13. The company states that despite this, clinical experts considered CAPTIVATE to be sufficiently representative of the UK patient population. The EAG clinical expert notes that TP53 disruption remains the most significant prognostic marker of CLL behaviour, and that it is recommended that all patients who need treatment for CLL undergo testing for del(17p) or TP53 mutations as treatment options differ. They considered the number with this in CAPTIVATE as small, and noted that the exclusion of TP53 disrupted disease in CLL13 makes the study population typical for about 80-85% of fit CLL patients treated in UK. The EAG was concerned by the difference in inclusion of del(17p) or TP53 mutations between CLL13 and CAPTIVATE, which is discussed in more detail. CAPTIVATE excluded people aged over 70 years, whereas CLL13 did not have that criterion. The company therefore restricted the CLL13 population to those aged ≤70 years for the MAIC. This reduced the population of the Ven+O arm of CLL13 from 229 to [redacted].

In addition, the EAG notes that CAPTIVATE did not specify a minimum score on the CIRS scale, and that the creatine clearance requirements differed between the studies (CLL13: ≥70 ml per minute, CAPTIVATE: ≥60 mL/min, CS Table 17). The company states that in line with clinical feedback, it was assumed the age-restricted CLL13 and CAPTIVATE populations had comparable fitness. The EAG clinical experts agreed with this.

Baseline characteristics in the age-restricted CLL13 and CAPTIVATE populations is presented in Table 15. The company highlighted a number of imbalances in addition to those in del(17p) or TP53 mutation noted above, as determined by ≥10% difference. These were Rai stage, anaemia at baseline, deletion in 13q and complex karyotype. The EAG clinical experts considered that the differences in Rai stage and anaemia at baseline suggest that the CAPTIVATE population had less advanced disease than CLL13, which could lead to poorer outcomes in CLL13. Conversely, other imbalances such as del(17p) or *TP53* mutations or complex karyotype could lead to poorer outcomes in CAPTIVATE. Complex karyotype which often co-exists with deletion 17p and/ or mutations in p53 and therefore those patients are under-represented in CLL13. 13q deletion is associated with better prognosis, but one expert stated that the effect is mild and overcome if other cytogenic markers are present. They also noted that the CS reported the number of people with ≥3 complex karyotype abnormalities (predicting poorer outcome), but explained there is debate over the number needed to identify more aggressive disease. An EAG expert noted that data were missing for 16% of CAPTIVATE, and overall was not concerned by the difference. The company also points out slight differences in gender ([redacted]%), ECOG PS ([redacted]%), bulky disease ([redacted]%), and *IGHV* mutation status ([redacted]%). Overall, the EAG considers that differences exist between the populations, but it is not possible to determine the direction or magnitude of any bias from a naïve comparison.

3.4.3.3 Outcomes

The CS reports that median follow-up in CAPTIVATE is 61 months for the data used in the MAIC, however in the cited reference[50] it is reported as 68.9 months (range, 0.8–83.9) and was 61.2 months in an earlier publication.[49] Follow-up in CLL13 for the data-cut of the IPD data used in the MAIC was shorter, at 50.7 months. The HR should not be affected by the differing follow-up, although it is possible that independent survival models could be biased

by capturing a trend that would emerge in the other arm if longer follow-up was available. PFS was investigator-assessed in both studies.

In summary, the EAG agrees that an indirect comparison between CLL13 and CAPTIVATE was feasible.

Table 15: Baseline characteristics in the age-restricted (≤70 years) CLL13 subgroup and the CAPTIVATE ITT population

Baseline characteristics	**CLL 13 Ven+O (≤70 years)** [redacted]	**CAPTIVATE (≤70 years) N=159**
Median age (years) (range)	[redacted]	60 (33-71)
≥ 65 years, N (%)	[redacted]	45 (28)
Male gender, N (%)	[redacted]	106 (67)
Race, N (%)		
White	[redacted]	147 (92.5)
Non-White	[redacted]	12 (7.5)
ECOG PS, N (%)		
0	[redacted]	110 (69)
1	[redacted]	49 (31)
2	[redacted]	0 (0)
IGHV mutation status, N (%)		
Unmutated	[redacted]	89 (56)
Mutated	[redacted]	66 (42)
Not evaluated	[redacted]	0 (0)
Missing	[redacted]	4 (3)
Rai		
0/I/II	[redacted]	113 (71)[a]
III/IV	[redacted]	44 (28)[a]
Missing	[redacted]	2 (1)
Cytopenia at baseline		
Anaemia at baseline (Hb ≤ 11 g/dL)	[redacted]	37 (23)[a]
Thrombocytopenia at baseline (PLC ≤ 100 x 10^9 /L)	[redacted]	21 (13)

Neutropenia at baseline (ANC ≤ 1.5 x 10^9 /L)	[redacted]	13 (8)
Bulky disease		
< 5 cm	[redacted]	111 (70)
≥ 5 cm	[redacted]	48 (30)
≥ 10 cm	[redacted]	5 (3)
Unknown/Missing	[redacted]	0 (0)
Cytogenetic subgroup (per Dohner hierarchy)		
Deletion 17p	[redacted]	20 (13)[a]
Deletion 11q	[redacted]	28 (18)
Trisomy 12	[redacted]	23 (14)
No abnormalities	[redacted]	33 (21)
Deletion in 13q	[redacted]	54 (34)[a]
Unknown	[redacted]	1 (1)
Complex karyotype		
Yes (≥ 3 abnormalities)	[redacted]	31 (19)
No	[redacted]	102 (64)[a]
Unknown	[redacted]	26 (16)[a]

Source: adapted from CS Table 18. Numbers may not sum to 100% due to rounding.
[a]considered by the company to be different across the CLL13 and CAPTIVATE trials, classified by ≥10% difference. ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat.

3.4.3.4 Results

Results from the CAPTIVATE trial are presented in Table 16. These results were taken from two different sources, respectively.[27, 49] Tam *et al*. (2022) was a full text paper with a shorter median follow-up of 27.9 months. Wierda *et al*. (2025) was a conference abstract with a median 61.2 month follow-up focusing on progression free survival (PFS) and overall survival (OS) outcomes. The 5-year overall survival was high at 96% (95% CI: 91 to 98), whilst the PFS was considerably lower at 67% (95% CI: 59 to 74). Similarly, ORR was reported at 96%, whilst CR was lower at 56%.

Table 16: Results from CAPTIVATE study for I+Ven

Outcome	**N**	**% (95% CI)**

5-year PFS	159	67 (59 to 74)
5-year OS	159	96 (91 to 98)
5 year (61.2 median month follow-up) PFS in subgroups with genomic risk factors[a]		
With del(17p)/mutated *TP53*	27	41 (21 to 59)
With complex karyotype	31	57 (37 to 72)
With del(11q)	11	64 (30 to 85)
With unmutated IGHV	40	68 (50 to 80)
5 year (61.2 month follow-up). PFS in subgroups without genomic risk factors		
Without del(17p)/mutated *TP53*	129	73 (64 to 80)
Without complex karyotype	102	72 (61 to 80)
Without unmutated IGHV	44	85 (69 to 93)
27.9 median follow-up. Complete response rates in subgroups[b]		
without del(17p)/mutated TP53	129	55 (47 to 64)
with del(17p)/mutated TP53	27	56 (37 to 74)
ORR in subgroups		
without del(17p)	136	96 (92 to 99)
with del(17p)/mutated TP53	27	96 (89 to 100)
Data sourced from [a]Wierda *et al*. (2024)[49] and [b]Tam *et al*. (2022).[27] Abbreviations: CI = confidence intervals; CR = complete response; IGHV = immunoglobulin heavy-chain variable; ORR = overall response rate; OS = overall survival; PFS = progression free survival		

3.4.3.5 Adverse events

Grade 3/4 adverse events for CAPTIVATE were reported in Tam *et al*. (2022) and TA891, and are presented in Table 17 together with those from CLL13.

Table 17: Grade 3-4 adverse events in CLL13 and CAPTIVATE >5% in either study

Adverse event	**CLL13**	**CAPTIVATE**	**CAPTIVATE source**
	Ven+O	**I+Ven**	**Specific population in TA891 (Clarification Response B8)**

Neutropenia	45.2%[b] 55.7%[c,d]	32.7%	CAPTIVATE (full population) TA891 Appendix F
Thrombocytopenia	14.9%[b] 18.4%[c,e]	Not reported	-
Infusion related reaction	11.4%	Not reported	-
All infections	13.2%[b]	8.2%	CAPTIVATE (full population) TA891 Appendix F
Pneumonia	5.3%[b] 4.8%[c]	Not reported	-
Hypertension	1.8%	5.7%	CAPTIVATE (FCR-suitable population), TA891 Table 48
Clinical tumour lysis syndrome	1.7%[b,f]	Not reported	-

[b]Eichhorst 2023 [c] Furstenau 2024.
[d]Values reported combine neutropenia and/or neutrophil count decreased which could explain differences with values in Eichhorst et al. 2023 where neutropenia and neutrophil count decreased are reported separately. [e]Values reported combine thrombocytopenia and/or platelet count decreased which could explain differences with values in Eichhorst et al. 2023 where the 2 are reported separately. [f]This does not include laboratory-confirmed TLS and not specified TLS.

In summary, neutropenia was higher with Ven+O than with I+Ven. Adverse events that occurred in CLL13 but were not reported in CAPTIVATE included thrombocytopenia, infusion related reaction and pneumonia. Conversely, hypertension appeared to be slightly lower with Ven+O than with I+Ven.

3.5 Critique of the indirect comparison or multiple treatment comparison

The most relevant comparator for this indication is I+Ven, however the pivotal study for this combination is the single arm CAPTIVATE trial. No connected network or anchored comparison was possible, and the company performed an unanchored MAIC to compare the Ven+O arm from CLL13 to the venetoclax+ibrutinib CAPTIVATE population.

The company used patient level data for the January 2023 data-cut of CLL13, in the indirect comparison and this was compared to CAPTIVATE using follow-up data reported by Wierda et al.[49] Patient level data were not available for CAPTIVATE.

The company highlights three differences between the trial populations. First, patients with SLL were excluded from CLL13, but make up 13% of the population of CAPTIVATE. The company assume that treatment effect was same for patients, regardless of whether they have CLL or SLL.

Secondly, CAPTIVATE did not include people aged > 70 years old, whilst their recruitment was permitted in CLL13. To overcome this, the company excluded CLL13 patient aged >70 years from the MAIC analysis. The EAG considers this an appropriate adjustment.

Thirdly, CLL13 did not include people with del(17p) or TP53 mutation, whilst these made up 17% of the CAPTIVATE population. The company assumes that within the CAPTIVATE population, outcomes for people with the deletion/mutation are equal to those for people without the deletion/mutation. The EAG considers this a source of bias, as presence of the deletion/mutation is associated with worse outcomes. For example, within CAPTIVATE, 36-month PFS was 81% for people with the deletion/mutation, compared with 91% for those without it.[51]

The EAG notes that PFS and OS outcomes from CAPTIVATE were reported for the subgroup of people without any of del(17p), TP53 mutation of complex karyotype, and that the company could have used these in their MAIC analysis (Figure 5, Figure 6).[49] This would rely on assuming that the baseline characteristics included in the MAIC for the whole CAPTIVATE population are equivalent for the subpopulation, whereas this subgroup may have had different baseline characteristics. However, on balance the EAG considers this approach would likely be less biased than the current analyses provided by the company. The EAG notes that in this subpopulation from CAPTIVATE no OS events occur (Figure 6), but is unsure whether this is the case for CLL13.

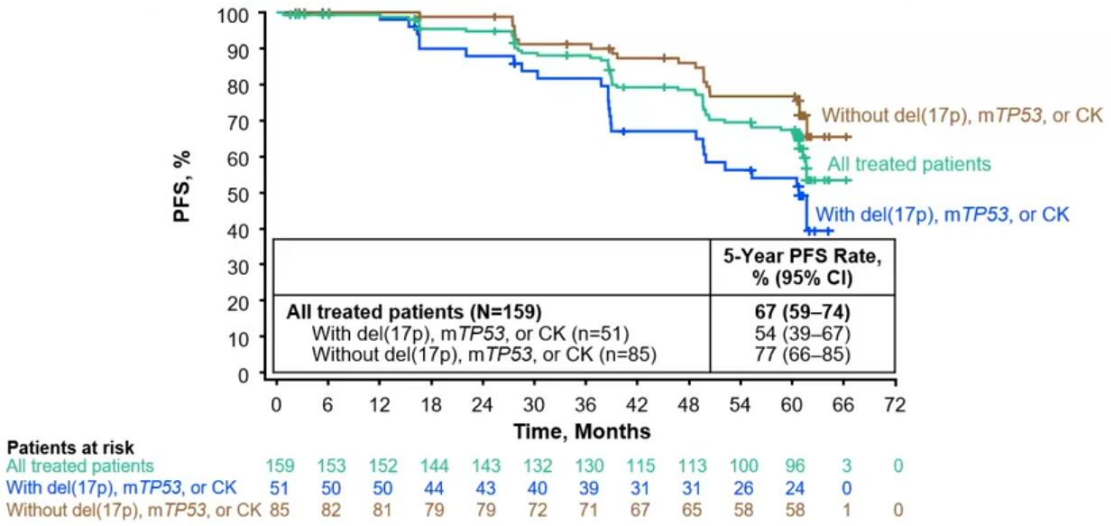


Figure 5: PFS follow-up from CAPTIVATE[49]

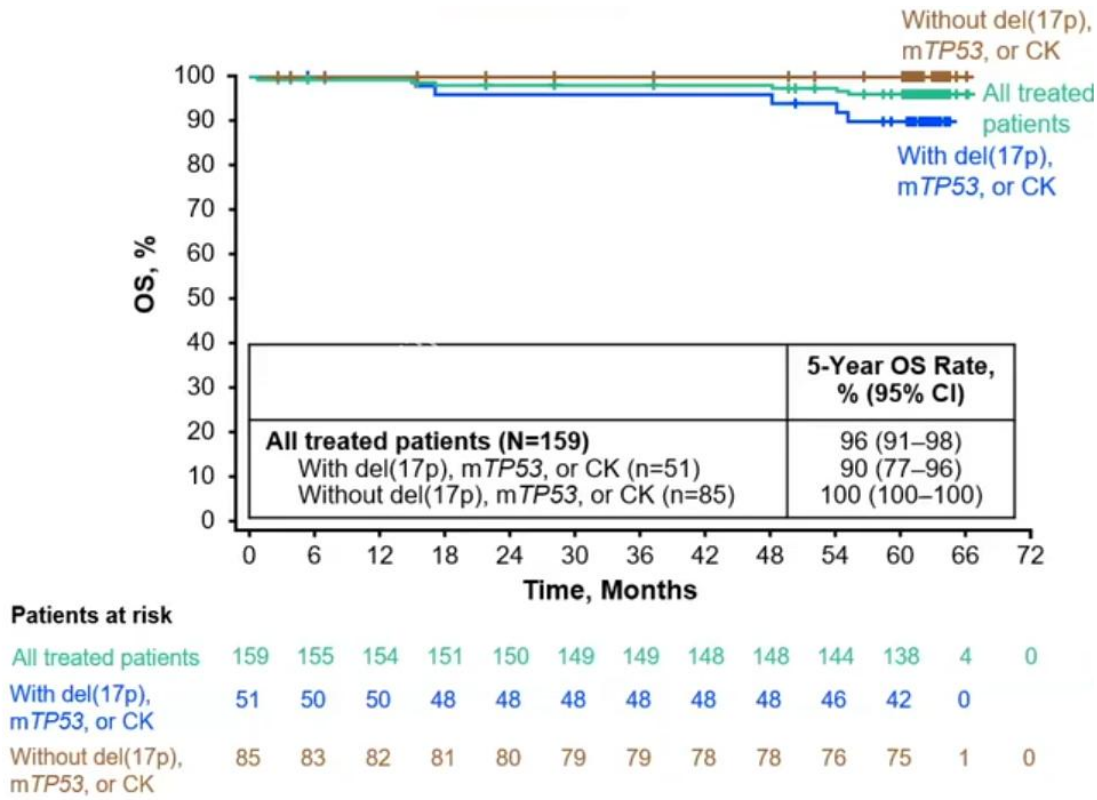


Figure 6: OS follow-up from CAPTIVATE[49]

3.5.1 MAIC methods

The company calculated propensity scores using logistic regression and the method of moments, which matched the selected covariates for the population of CLL13 to those of CAPTIVATE. The resulting weights were reweighted based on the original sample size in CLL13. The company submission at one point describes propensity score matching on a 1:1 ratio, however the EAG considers this does not align with the majority of the text which refers to weighting rather than matching. The EAG notes that patient level data from CAPTIVATE would be required to undertake 1:1 matching.

For a MAIC to provide unbiased estimates of relative effect, it requires that all treatment effect modifiers and prognostic factors are matched and balanced

across the two datasets. The company identified these factors through a literature search, data analyses from CLL13 and expert elicitation.

The company literature search suggested ten important factors which were:

- Unmutated/mutated immunoglobulin heavy chain gene (*IGHV*)
- Del17p or *TP53* mutation
- β_2-macroglobulin
- Rai/Binet stage
- Age
- Sex
- ECOG performance status (PS)
- Fitness
- CIRS
- Creatine clearance

For the analyses of CLL13 data, the company analysed PFS and OS data using Cox proportional hazards models. The influence of candidate factors was included through either covariates or treatment interaction terms in a series of univariate analyses. Patients ≤ 70 from the I+Ven and SCIT arms of CLL13 were included in these analyses. The threshold used by the company to be flagged as a potential factor was $p \leq 0.25$. The following covariates were identified by at least one analysis as being influential:

- Age > 60 years
- ECOG ≥ 1
- Rai stage = missing
- Bulky Disease ≥ 5cm
- Bulky Disease ≥ 10cm
- Anaemia
- Thrombocytopenia
- IGHV mutation

- FISH Del11q
- FISH Trisomy 12
- FISH Del13q
- Complex karyotype (yes vs no)

The selection of final covariates for the MAIC was made based on the covariates reported by both CLL13 and CAPTIVATE. This produced the following set of factors, the first four of which were deemed of primary importance:

- IGHV mutation status (mutated vs unmutated)
- Bulky disease (≥ 5cm, ≥ 10cm vs no)
- FISH (Del11q, Trisomy12, Del13q vs normal)
- Complex karyotype (yes vs no)
- Age (>60 years vs ≤ 60)
- ECOG PS (≥ 1 vs 0)
- Rai staging (≥ 3 vs <3)

Compiling these sources, the company decided to match on the following set of characteristics, with additional covariates included in four further sensitivity analyses:

- IGHV mutation status (mutated vs unmutated)
- Bulky disease (≥ 5cm, ≥ 10cm vs no)
- FISH (Del11q, Trisomy12, Del13q vs normal)
- Complex karyotype (yes vs no)

Of the candidate MAIC analyses, the EAG preference is to use the one titled “fully adjusted analysis”, as it includes the largest number of prognostic and effect modifying factors, and the effective sample size (ESS) remains sufficient to produce reliable estimates of relative efficacy.

3.5.2 MAIC results

In Table 18, the EAG summarises the covariates, ESS and output from each MAIC conducted by the company. The EAG was satisfied with the distribution of weights in all the MAIC analyses, with no individuals having a concerning degree of influence on the analyses.

Across the analyses, [redacted] The estimates for OS [redacted]. All MAICs suggested that for CRR, [redacted]. The final outcome presented was ORR, where all MAICs suggested a [redacted]. The EAG considers all analyses to be at significant risk of bias, favouring Ven+O, due to the inclusion of people with del(17p) or TP53 mutation in the CAPTIVATE trial.

Table 18: Overview of MAIC outputs from analyses undertaken by the company

	PFS HR (95%CI)	OS HR (95% CI)	CRR OR (95% CI)	ORR OR (95% CI)
Unweighted comparison (no matching)	[redacted]	[redacted]	[redacted]	[redacted]
1) Company preferred – IGHV, FISH, Bulky Disease, Complex karyotype [ESS=158.01]	[redacted]	[redacted]	[redacted]	[redacted]
2) Extended variables – (1) plus Age, ECOG, Rai [ESS=135.43]	[redacted]	[redacted]	[redacted]	[redacted]

3) Data driven – (2) plus Anaemia, Thrombocytopenia [ESS=128.99]	[redacted]	[redacted]	[redacted]	[redacted]
4) Fully adjusted – (3) plus Sex, Neutropenia [ESS=122.17]	[redacted]	[redacted]	[redacted]	[redacted]

CRR: complete response rate; ESS: effective sample size; ORR: overall response rate; OS: overall survival; PFS: progression-free survival;

In

Figure 7 the EAG presents the Kaplan-Meier plot for OS for the company's preferred MAIC. Despite an estimated hazard ratio of [redacted]

[redacted]

Figure 7: Kaplan Meier plot for OS from company preferred MAIC (taken from Figure 17 of company submission)

The EAG recommend that the company implement MAIC analyses which exclude people with del(17p)/TP53 mutation or complex karyotype from the CAPTIVATE data. This would enable a less biased comparison with the subgroup from the CLL13 study to obtain more reliable estimates of relative efficacy between Ven+O and I+Ven. The EAG considers this would be feasible as 83.5% of the Ven+O arm of CLL13 had less than 3 complex karyotype aberrations, and could be included in the MAIC, though some of these may be aged over 70, the exclusion of which may slightly further reduce the starting sample size from CLL13.

The EAG identified a recently published network meta-analysis which compared first line treatments for CLL.[52] This study was not restricted to patients who were fit or eligible for FCR/BR, hence could include a wider range of trials, allowing a connected network to be assessed but at the risk of introducing bias. Wen et al. reports a PFS hazard ratio of 0.53 (95% CI: 0.32, 0.87) suggesting I+Ven has a lower rate of disease progression than Ven+O, which is [redacted] presented by the company. The results of this NMA are not based on the same population as the MAIC, but it is unclear whether this [redacted].

Based on the currently provided results, the EAG does not consider there is sufficient evidence to support that Ven+O offers any significant benefit in efficacy over I+Ven. The current MAICs are subject to bias in favour of Ven+O, but analyses with likely reduced bias could be performed. However, any estimated difference of treatment effect is likely to be small due to the limited number of observed events, particularly for OS.

3.6 Additional work on clinical effectiveness done by the EAG

3.6.1 Screening of included and excluded studies

A total of 275 eligible non-RCTs or observational studies were identified by the company but were excluded from the data synthesis. A list of these studies was requested by the EAG (Clarification A5) and titles were screened for eligibility by one reviewer. Seven full texts were selected for further examination by two independent reviewers, but none were considered useful for the MAIC.

The EAG checked the list of 129 included publications of RCTs (relating to 46 included RCTs) for studies potentially relevant to the MAIC. The EAG agrees that CAPTIVATE is the only relevant study. The EAG also checked the 286 publications excluded at full text and confirmed none were wrongly excluded.

3.6.2 EAG targeted searches

The EAG conducted targeted searches for single arm and real-world evidence studies of I+Ven to identify non-randomised studies that may have been excluded by the company. Studies published in 2024 or later (n=81) were screened by the EAG. No phase 2 studies or real-world evidence studies of I+Ven were identified. No additional studies of CAPTIVATE with longer follow-up were identified. The search strategy of the targeted searches carried out by the EAG can be found in Appendix 7.1.2

3.7 Conclusions of the clinical effectiveness section

CLL13 showed that Ven+O is superior treatment to SCIT, offering better disease control and less severe side effect profile. The company relies on an

unanchored MAIC to assess the relative efficacy of Ven+O and I+Ven, as a connected network was not available. This comparison is subject to bias, and the outcomes remain highly uncertain. The EAG considers that there is insufficient evidence to justify the conclusion that there is a difference in efficacy between Ven+O and I+Ven, though there is some variation in their safety profile. SACT data for Ven+O suggests real-world outcomes are slightly inferior than those observed in CLL13.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

4.1.1 Search strategy

Searches were originally undertaken in December 2018, with five additional updates. The most recent updates were undertaken in February 2025. A single database search was carried out across Medline, Embase and Econlit to search for the condition and treatment setting and cost-effectiveness or healthcare cost and resource use or health related quality of life (HRQoL) and utilities studies. The database searches included broad and comprehensive database specific and free text terms. An appropriate selection of sources was searched, including bibliographic databases, HTA agencies' websites and recent conference proceedings. Given that the CRD database is no longer being updated; the EAG would recommend searching the International HTA Database (INAHTA) in addition to the manual searches of HTA agencies to ensure comprehensiveness. The update searches of Medline, Embase and EconLit were limited by publication date. The EAG would recommend using the more appropriate date limits 'date created' or 'date delivered' to ensure a more comprehensive search. An additional limitation of the database searches is not searching within the keyword fields for free text searches (CS Appendix E.1.3 Table 13).

4.2 Critique of the submitted economic evaluation

The eligibility criteria were suitable for the SLR performed. The EAG considers the company's submitted economic evaluation evidence comprehensive.

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference checklist is presented in Table 19.

Table 19: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and Personal Social Services	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes - 39.1 years
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	No. EQ-5D data was not collected in the CLL13 trial. Utility values not directly elicited but based on Hancock et al. 2002[53] as used in TA174 where the QoL instruments used were the EORTC QLQ-C30 and FACT-G (rather than the EQ-5D instrument)
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Longitudinal analysis of 81 patients with CLL
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No value set used but population based on a UK patient population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of	Yes

	the people having the health benefit, except in specific circumstances	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

4.2.2 Model structure

The company constructed a de novo cost-utility model using partitioned survival with a four-weekly cycle length (28 days) and a lifetime horizon of 39.1 years. The 28-day cycle length is consistent with the dosing schedules of Ven+O and I+Ven. The model defines three health states: progression free (PF), progressed disease (PD) and death (absorbing health state) (Figure 8). All patients entered the model in the PF state and remained there until disease progression or death.

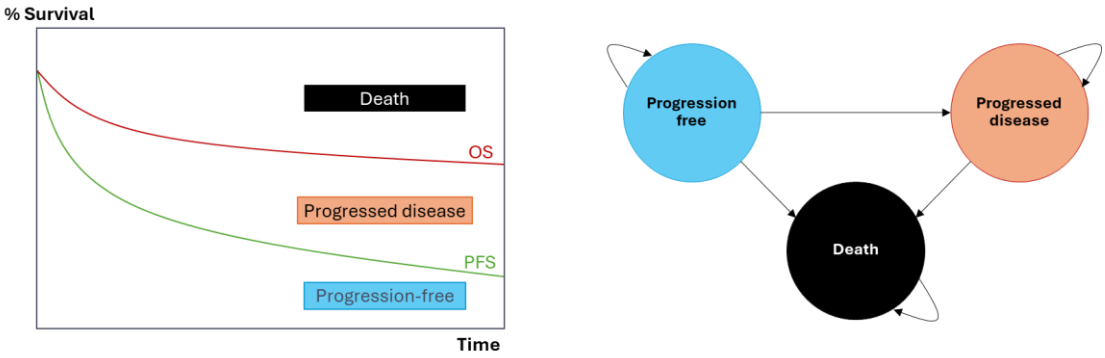


Figure 8: Health state structure used in company's economic model
Source: CS (Figure 19)

The partitioned survival method uses the “area under the curve” approach, where the number of patients in each health state at a given time point is

taken directly from survival curves fitted to the clinical data. The proportion of patients who have not progressed or died are determined by the PFS curves whilst the OS curves indicate the proportion of patients who are alive at a given time point. The difference between the proportion of living patients (OS health state) and the proportion of patients who were both living and pre-progression (PFS health state) informs the proportion of patients that are alive post-progression. The OS and PFS curves were determined by fitting parametric models to the data from the CLL13 trial adjusted to the CAPTIVATE dataset[27] through the MAIC analysis. For the base case analysis, the company assumes that the proportional hazards assumption holds and extrapolates long term outcomes (OS and PFS) for the I+Ven arm by applying MAIC-adjusted HRs to the adjusted Ven+O data. A detailed description and critique of the company's approach is provided in section 4.2.5.

Time on treatment for the Ven+O arm is modelled based on observed treatment data in CLL13 trial. For the I+Ven arm, time on treatment is modelled based on outcomes from the CAPTIVATE trial which reported that 92% of patients completed the full 15 cycles of treatment as per I+Ven's dosing regimen. The company makes some simplifying assumptions to arrive at the 92% completion rate by cycle 15. The EAG considers the approach acceptable based on clinical expert input.

4.2.2.1 Perspective and discounting

The analysis follows the NICE reference case, with benefits assessed from a patient perspective and costs from the NHS and Personal Social Services (PSS) perspective. In the base case, both costs and benefits are discounted at an annual rate of 3.5%, in line with NICE guidance.

4.2.3 Population

The population considered in the model is specifically “fit patients with untreated chronic lymphocytic leukaemia where there is no 17p deletion or TP53 mutation”. Whilst the wording differs from that specified in the NICE final scope where suitability for FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) is used instead of ‘fit’, the EAG’s clinical experts agree that this terminology reflects the evolution in the current treatment pathway. Thus, the EAG considers that the patient population considered in the CS aligns with the patient population specified in NICE final scope. See Table 3 (decision problem) for further discussion.

As described in section 3.2.1, the submission mainly relies on the CLL13 trial - a phase 3, multicentre, randomised, prospective open-label trial evaluating the safety and efficacy of venetoclax regimens Ven+O, I+Ven+O and Ven+R compared with SCIT (FCR and BR) in fit patients with previously untreated CLL without del17p or TP53 mutation.[40] The Ven+O arm of this trial is considered relevant for this appraisal. The data for the Ven+O arm (N=229, unweighted; N=158, weighted sample size in MAIC analysis) provided information on the use of, and clinical efficacy, safety, and time on treatment of Ven+O in fit patients with previously untreated CLL where there is no 17p deletion or TP53 mutation. A detailed discussion is provided in section 4.2.5.

- For the purposes of this appraisal, the EAG considers this a single arm trial as none of the comparators in the CLL13 trial are relevant comparators for this appraisal.

For the I+Ven arm, the CS submission relies on the fixed-duration treatment cohort of the CAPTIVATE trial; an international open-label non-randomised phase 2 study in people with untreated CLL and small lymphocytic lymphoma (SLL) aged ≤70 years (NCT02910583).[49, 50]

- The EAG agrees with the selection of this cohort as it best reflects current UK clinical practice.

A detailed EAG critique of these trials is provided in sections 3.2.1 and 3.4.

Baseline patient parameters for the modelled populations were derived from CLL13 trial (mean age, proportion of males) and from CLL14 trial (mean body-weight and mean body height). During clarification, the EAG questioned the use of CLL14 data and the company confirmed that they do not have unrestricted access to patient characteristics or outcomes but such values from CLL14 were considered an appropriate proxy (Clarification Response B4).

- The CLL 14 population is characterised by the company as unfit population (table 4 CS). It is possible that baseline body-surface areas (calculated from mean body weight and height) could be different between the CLL13 and CLL14 populations. However, the EAG agrees with the company that this is unlikely to have a significant impact on the cost-effectiveness results based on additional scenario analyses presented by the company in response to clarification question B4. The scenario analyses are discussed further in section 5.1.2.

SACT dataset

The SACT cohort data was available to the company as an additional real-world evidence base to establish efficacy of Ven+O in the population under consideration for this appraisal within NHS clinical practice. However, this data was not used to inform the cost-effectiveness assessment of Ven+O and the company stated, in response to clarification question B6, that it was not possible to include RWE inputs, specifically survival inputs into the model as they did not have access to IPD and the SACT report did not include PFS outcomes. The EAG briefly summarises the SACT cohort population data (further details are in section 3.2.2) and comments on the appropriateness of

the company's approach to not include SACT cohort demographics and any survival data as RWE inputs into the economic model.

NHS England evaluated the real-world treatment effectiveness of venetoclax with obinutuzumab in the CDF population during the managed access period. Data on patients who received treatment with Ven+O (and suit the eligibility criteria) were analysed for the period 10 Nov 2020 – 31 October 2022. The data included the baseline characteristics of the cohort, median treatment duration (and reasons for stopping treatment) and overall survival. An in-depth summary of the SACT dataset is provided in section 3.3.2. The median age of the SACT cohort was reported as 61 years which closely matches the median age for the CLL13 Ven+O population of 62 years (Range: 31-83). For the economic model, a mean age of 60.9 years, rather than the median ages are used and this figure likely reflects the mean ages observed in UK clinical practice as confirmed by the EAG's clinical experts.

- The age at start of treatment used in the company's economic model resembles the population that is currently treated with Ven+O based on SACT CDF results and EAG clinical experts' opinions.

There were noticeable differences in the gender distribution between the SACT cohort and CLL13 trial population. The proportion of males in CLL13 and used in the economic model was 74.7%, whereas 67% of the SACT cohort were males.

- The gender distribution of the modelled population should closely match that of the SACT cohort for the cost-effectiveness results to be generalizable to NHS patients and this does not appear to be the case in the company's base case analysis

Modelled population: Summary of EAG comments and relevance of SACT cohort data

The EAG agrees with the company that an ITC using SACT cohort data is constrained by the absence of individual patient data (IPD) for the SACT cohort and by the lack of progression-free survival (PFS) outcomes. However, the EAG considers that use of SACT data, where feasible, would help to maximise the use of real-world evidence. This is particularly valuable where baseline characteristics are representative of the patient population currently receiving Ven+O and overall survival (OS) outcomes are reflective of efficacy observed in current clinical practice.

4.2.4 Interventions and comparators

The description of comparators in the NICE scope is as follows: Bendamustine plus rituximab (BR); Fludarabine with cyclophosphamide and rituximab (FCR); Ibrutinib plus venetoclax and acalabrutinib with venetoclax with or without obinutuzumab (subject to ongoing NICE evaluation). The company's base case compares Ven+O with I+Ven, partly reflecting the description of comparators in the NICE scope but aligning with the comparator for the proposed population in the CS.

- The EAG clinical experts agree with the company that I+Ven is currently the only relevant comparator for this appraisal (see description of decision problem).

4.2.5 Treatment effectiveness and extrapolation

The company used standard parametric survival models and hazard ratios to extrapolate and obtain predictions for the future efficacy of Ven+O and I+Ven. Each time-to-event outcome is summarised and critically appraised in the following sections.

4.2.5.1 Overall survival

For Ven+O, the company extrapolates their OS data from CLL13 that uses their preferred set of MAIC weights to match to the CAPTIVATE population characteristics (see section 3.5.2).

The company fit a standard set of parametric models, and select a preferred model using a combination of information criterion, visual fit, and plausibility of extrapolations. The company states that the goodness of fit statistics suggest all models are plausible. The company's preferred model was the log-logistic. The rationale for this choice appears based on a comparison of 10-year predictions before any adjustment for background mortality is applied, which the EAG considers invalid and not representative of what is modelled within the economic model.

For both arms, the hazard rate for OS is constrained such that it does not fall below the hazard rate for the age- and sex-matched general population. The EAG notes that for the company's preferred extrapolation of Ven+O, this occurs in the very first cycle of the model (i.e. the extrapolated hazard rate is immediately below general population mortality within the observed period). The EAG considers this implausible in real-world practice, despite being observed in CLL13, as it is possible that a small number of patients have disease that is fast moving and does not respond well to treatment, meaning they will experience a higher mortality rate than the general population. The company states that through clinical validation "it was established that CLL patients would have slightly worse survival compared to the general population due to potential secondary illnesses such as Richter's transformation, secondary malignancy, and infection", which was echoed by the EAG's clinical experts. The EAG notes that there are short periods where the hazard rate is slightly above general population mortality, however the majority of the extrapolation is directly informed by general population mortality, which appears inconsistent with the company's preferred model.

In a scenario analysis presented at clarification stage, the company show the impact of applying a 1.05 standardised mortality ratio to general population mortality to constrain the overall survival extrapolation. This may increase plausibility, but this estimate is based on expert opinion and not supported by data.

As an alternative approach, the EAG digitally recreated the SACT dataset (13 August 2025 data-cut), and fitted standard parametric survival models to this data. The candidate models are shown in Figure 9, without background mortality applied. It is clear that the extrapolations of SACT data still rely heavily on background mortality to obtain a plausible extrapolation.

In Table 20 the EAG provides additional detail to support a comparison, including goodness of fit statistics, 10 year survival predictions, and information on when general population mortality comes into effect. Comparing AIC, the EAG considers the models show no clear difference, aside from the generalised gamma which has the worst fit. For BIC, the exponential model has the best statistical fit. An examination of the cumulative hazard plot (

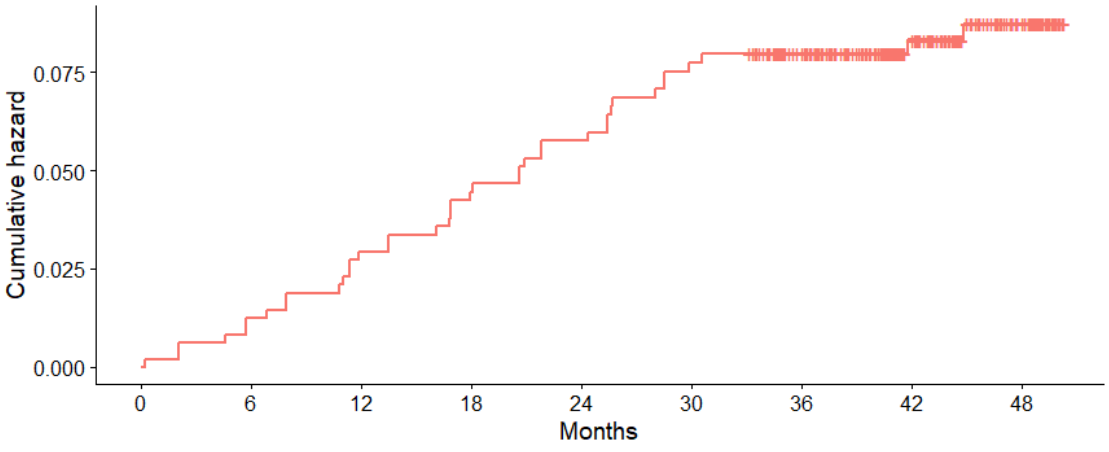


Figure 10) suggests a constant hazard rate (straight line) prior to people being censored. Hence the EAG selects the exponential scenario, however notes a high level of agreement between the candidate models when comparing their

predictions of 10-year survival, and considers the choice of model has only a small impact on the modelling outcomes.

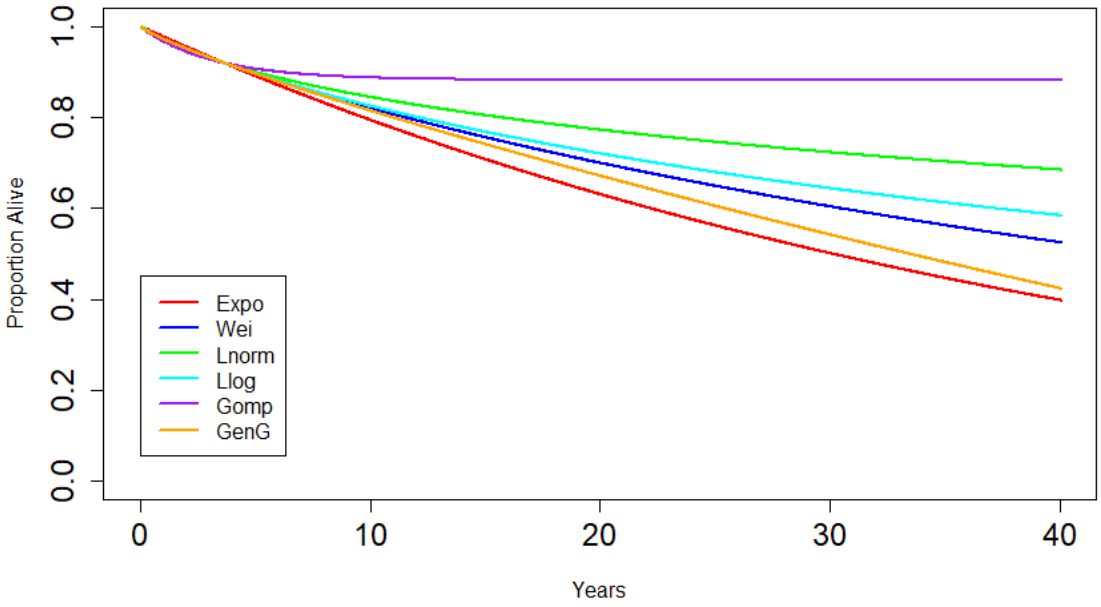


Figure 9: Extrapolations of SACT OS data for Ven+O, without adjustment for background mortality.

Table 20: Comparison of survival extrapolations fitted to SACT OS data for Ven+O

Parametric Model	AIC	BIC	Years when background mortality is applied	Proportion alive when background mortality is applied	10 year survival
Exponential	834.3	838.5	12.2	75.5%	79.3%
Weibull	835.2	843.6	9.2	83.1%	81.9%
Log-normal	833.9	842.3	6.3	88.3%	83.1%
Log-logistic	834.9	843.3	8.1	85.0%	82.2%

Gompertz	832.2	840.5	4.1	91.3%	83.8%

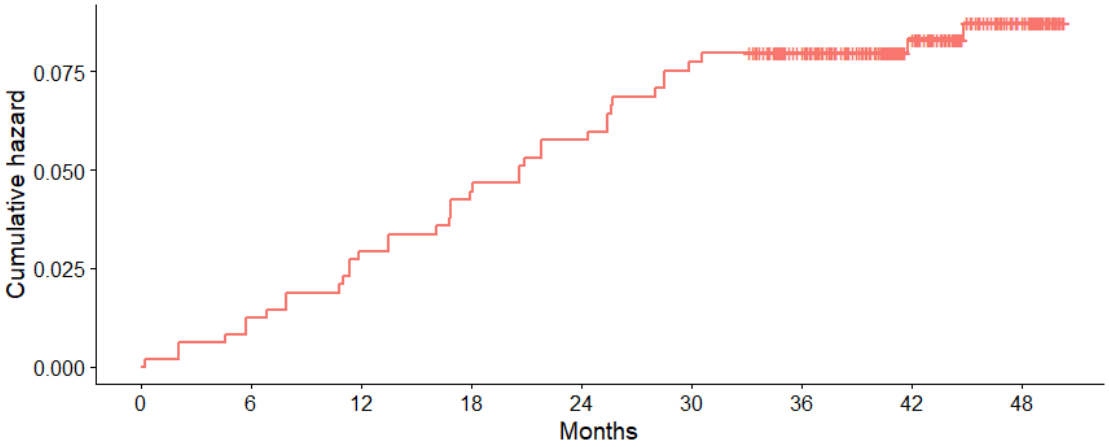


Figure 10: Cumulative hazard plot for Ven+O SACT OS follow-up.

For I+Ven, for the company base case analysis, the inverse of the MAIC hazard ratio is applied to the extrapolation for Ven+O ([redacted]).

The company implement this approach as they consider that the proportional hazards (PH) assumption is not violated, and this approach reduces the estimated degrees of freedom.

The EAG accepts that the PH assumption appears to hold, however the data is very immature for this outcome, and it is unclear whether this assumption would hold into the future. The EAG is unsure what is meant by "estimated degrees of freedom" but notes that the degrees of freedom usually want to be maximised. If the company wanted to maximise the degrees of freedom, then a single model could be fitted simultaneously to the Ven+O and I+Ven data, which would preserve the proportionality assumption whilst maximising the information used in the modelling.

The company presents a scenario analysis where equal efficacy is assumed between Ven+O and I+Ven. This approach is preferred by the EAG, as the MAIC analyses undertaken by the company do not support a consistent or clear benefit of Ven+O. The EAG explores the impact of applying the inverse

of the hazard ratio from the EAG's preferred MAIC analysis ([redacted]) in a scenario analysis (i.e. [redacted]).

The EAG does not explore the impact of applying a SMR given that it considers the assumption of equal efficacy to be reasonable, hence any further adjustments on mortality would not have any effect on the ICER. However, the EAG considers addition of an increased SMR to reflect the experience of the CLL population better may improve the accuracy of the extrapolations and should not be ruled out.

4.2.5.2 Progression free survival

For PFS, the company implement a similar methodology as for OS. For Ven+O, parametric extrapolations were obtained from the company's preferred MAIC weighted data from CLL13. A comparison of the goodness of fit statistics suggested that aside from the exponential and log-normal models, all other candidate models were plausible. The company ultimately select the Weibull model as it is the model which produces predictions of 10-year PFS most in line with the estimates of the clinical experts (20-30%), though the EAG notes this decision again appears based on models prior to any adjustment for background mortality. The Weibull model prediction of 10-year PFS before adjustment is ~[redacted]%, however after adjustment it is ~[redacted]%.

The EAG notes that for the first five cycles of the model, the PFS is dictated by background mortality, before the increasing hazard rate of the Weibull models rises above background mortality.

As no alternative data source is available for PFS, the EAG maintains using the same CLL13 MAIC weighted dataset, and is content with the Weibull extrapolation. The MAIC weighted PFS data showed minimal difference to the original CLL13 data when comparing their Kaplan-Meier functions (CS Figure 16), and all MAIC analyses showed similar estimates of relative effect, and the

EAG is content with this choice, however ideally PFS outcomes from SACT would be available for consistency with the EAGs preferred approach for OS.

For I+Ven, the company apply the inverse hazard ratio from their preferred MAIC analysis ([redacted]). The EAG is concerned at the potential bias of this estimate coming from the presence of people with del(17p)/TP53 mutation in the CAPTIVATE population, who are included in the MAIC. Hence, the EAG prefers to assume equal efficacy (i.e. hazard ratio =1) for PFS between Ven+O and I+Ven for the EAG base case. The EAG applies the hazard ratio from the EAG preferred MAIC in a scenario analysis.

The EAG has some concern over the increasing hazard rate observed for PFS in CLL13 (CS Figure 25), and considers that it is plausible a similar trend could be observed for OS if longer follow-up were available where the hazard rate could increase higher than background mortality, which is not reflected in current modelling. However, as this would likely apply similarly for both Ven+O and I+Ven, the EAG does not consider this a source of bias.

4.2.5.3 Time on treatment

The company used observed data from CLL13 in the form of the Kaplan-Meier estimator to model time on treatment for Ven+O. These estimates are capped by overall survival and progression-free survival, so they cannot exceed the proportion of people estimated alive or progression-free.

The company also limits TOT for Ven+O to not exceed 12 months, though the EAG notes a small number of people received one additional cycle of treatment beyond this in CLL13 ([redacted]%).

The EAG notes that information on TOT is available for Ven+O in the SACT report (Figure 11; n=483). This plot shows that a slightly larger group of people receive treatment beyond 12 months. Following consultation with the

EAG clinical experts, the most likely reason for this is dose pausing, with the treatment period extending beyond 12 months but people not receiving any additional Ven+O treatment. Hence, the EAG utilise the CLL13 data for the EAG base case, and explore the impact of using the SACT data without capping the number of cycles in a scenario analysis.

The choice of source for TOT only has a small influence on the cost-effectiveness analysis, as the SACT data-set has a lower TOT than CLL13 for the first 12 months, which somewhat balances out the higher TOT beyond 12 months. E.g. a comparison of CLL13 vs SACT at 6 months: ~[redacted]% vs ~93.5%, but at 12 months: ~[redacted]% vs ~19.2%.

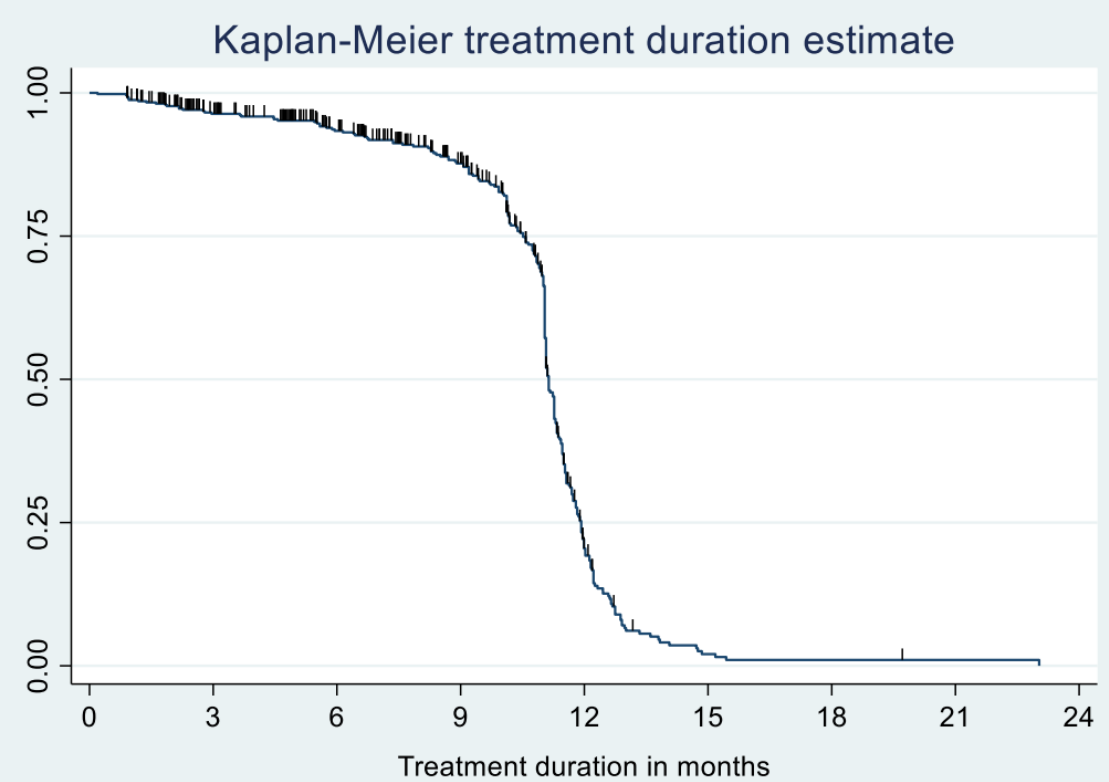


Figure 11: TOT for Ven+O from NHS England SACT report

The SACT report also conducted a sensitivity analysis focusing on people who had at least 6 months follow-up at the point of the data-cut (October 2022; n=376), however TOT was almost identical to the original analysis.

For I+Ven, the company use information reported by CAPTIVATE. The company note that the standard dosing regimen for I+Ven is three cycles longer than for Ven+O, and so they did not apply a relative effect (e.g. hazard ratio) to the modelling for Ven+O as was done for PFS and OS.

The company identified that it was reported for CAPTIVATE that 92.5% of 159 people completed 15 cycles of I+Ven, with 153 completing the ibrutinib lead-in phase. The company use this information and model that 100% of people (capped by mortality) receive 3 cycles of ibrutinib, with 96.2% beginning the combination I+Ven. For the remaining period of the 15 cycles, the company assume a linear decreasing trend from 96.2% to 92.5%. The EAG considers this approach reasonable and maintains it for the EAG base-case.

4.2.5.4 Time to next treatment

In the company base case, the company captures time on subsequent treatment based on entry into the progressed-disease health state. The company did have access to TTNT data from CLL13 for Ven+O, but no equivalent information was available for I+Ven. Hence, the company used an alternative approach that could be applied equally to both initial regimens.

The company's approach is based on the following formula:

$$\Delta ST_t = (PD_t - PD_{t-1}) + (Death_t - Death_{t-1})$$

The company state that deaths are included in the calculation to include counting people who move straight to the death health state from progression-free, ensuring that they incur subsequent treatment costs. The company assumes that all people will receive all subsequent therapies (acalabrutinib, zanubrutinib and Ven+R). The EAG does not agree with this approach. For example, within the model people move from pre-progression health state to death within the first few model cycles, and there is no occupancy of the post-

progression health state, yet subsequent treatment costs are applied in the model for these people based on receiving three subsequent treatments.

Hence the EAG explored an alternative approach using the limited information available. The economic model allowed an alternative approach to be taken for Ven+O, where the observed TTNT data from CLL13 could be extrapolated. No information was included in the company submission related to these extrapolations, and so the EAG could only consider clinical plausibility and visual fit. The EAG anticipates that PFS and TTNT would follow a similar trend as they are clinically linked (Figure 12). Of the candidate models for TTNT, only the Gompertz model vaguely resembled the PFS Weibull extrapolation. The problem with the Gompertz is that it crossed the PFS extrapolation at 11.8 years (when ~[redacted]% of people remain progression-free), which the EAG considers implausible. Hence the EAG approach uses the Gompertz extrapolation but constrains it such that the TTNT extrapolation cannot fall below PFS. This approach results in modelling that [redacted]% of people receive all three subsequent therapies, rather than 100% assumed by the company.

Figure 12: Comparison of PFS, OS and TTNT from CLL13 for Ven+O

4.2.6 Health-related quality of life

HRQoL was sourced from Hancock et al. publication (used in TA174) via a SLR as although quality of life was measured in the CLL13 trial, response rates were poor and no EQ-5D data were collected (see section 3.3.1.6).

4.2.6.1 Health-related quality of life data identified in the review

The company's SLR identified a total of 32 studies of which 26 studies reporting on HRQoL or utilities associated with patients with CLL in the 1L treatment setting were presented (Appendix F). The CS also provided a detailed summary of source of utilities data from the 65 economic evaluation studies that were identified through the SLR (CS Appendix E). In summary, utilities data used in the economic evaluation studies were primarily derived from the published literature. The studies by Kosmas et al.,[54] Beusterien et al.[55] and Tolley et al.[56] were the most cited sources of health state utilities in the economic evaluations and are briefly described below as they appeared relevant to this submission.

Komsas et al. elicited societal utility values for states related to chronic lymphocytic leukaemia (CLL).[54] These states were progression free survival (PFS) on initial intravenous (IV) therapy; PFS on initial oral therapy; PFS on initial therapy with increased hospital visits; PFS without therapy; progression after 1st line therapy; PFS on 2nd line therapy; PFS without 2nd line therapy (post 2nd line treatment, but not currently receiving therapy); further progression (disease progression after 2 lines of treatment); and relapsed lines of treatment (≥3 lines of treatment). The utilities for the different health states were: PFS without therapy (mean utility=0.82); PFS on initial oral therapy (0.71); PFS on initial IV therapy (0.67), PFS on initial therapy with

increased hospital visits (0.55). Mean utility for disease progression after 1st line therapy was 0.66 and for PFS without 2nd line therapy was 0.71; further progression (0.59), PFS on 2nd line therapy (0.55), and relapsed lines of treatment (0.42). Similarly, Tolley et al.[56] conducted a societal utility-elicitation study using the time trade-off (TTO) method to obtain societal preferences in the UK for "progression-free" and "progressive" states of late-stage CLL, refractory to current first and second line regimens. The primary disease state mean TTO utility scores were: baseline: 0.549; PFS response: 0.671; PFS non-response: 0.394; and progression: 0.214. Beusterien et al.[55] measured preferences for health states associated with CLL treatment based on a cross-sectional study of 89 members of the general public in the UK using the standard gamble method. The health states and the associated utilities were: complete response (CR) (mean utility:0.91), partial response (PR), 0.84; no change (NC), 0.78; and progressive disease (PD), 0.68. There are differences in the descriptions of health state utilities across the studies. Most importantly, the study by Tolley et al.[56] elicited health state utility values for a patient population refractory to first line treatment unlike the current submission where the population under consideration is 1L CLL. The societal studies are also not based on a description of ‘fit’ patients and this population could have different utility values to those from the general CLL population.

The company also presented utility data (where applicable) from the 26 studies included in their review of HRQoL (Table 40, Appendix F). The company comments that there was some variation in comparable health-state utilities with Holtzer-Goor reporting utility values of 0.88 for “watch and wait” and 0.81 during treatment[57] compared to Shingler reporting utility values of 0.82 for PFS without therapy and 0.67-0.71 while on treatment.[58] The company further states that the target countries were different and that the utility values for both studies were used only once in 41 identified economic evaluations. There is a factual inaccuracy in the latter part of that statement as the utility values reported by Shingler, Kosmas et al. (in a poster) are the same values used in at least 10 of the identified economic evaluations and

reported by Kosmas, Shingler et al. in the full-text article in 2015.[54] That text was described earlier in this section.

EAG Comments

Though there are several utility-elicitation studies that have been conducted targeting the CLL population and used in many published economic evaluations of CLL, these have not been specifically targeted at the 'fit' population. The EAG therefore considers the company's decision to not use the utility estimates described above reasonable.

4.2.6.2 HRQoL data identified through NICE technology appraisals

The CS states that, as utility analyses could not be performed using the CLL13 trial data (no EQ-5D data were collected), the company instead sourced utility values from previous NICE technology appraisals. The CS provides a summary of the relevant NICE technology appraisals, which is reproduced in the table below.

Table 21:Summary of utility values from previous NICE technology appraisals

NICE TA	Population considered	Progression status	Utility value	Source
TA891	Untreated CLL in adults	Progression free first-line (PF1L)	0.86 (FCR-suitable)	GLOW trial adjusted to FCR-suitable population[35]
		Progression free second line (PF2L)	0.63 (FCR-suitable)	TA689[20] (derived from Holzner et al., 2004)[59]
		Post-progression (PP)	0.63 (FCR-suitable)	TA689[20] (derived from Holzner et al., 2004)[59]
TA343	Adults with untreated chronic lymphocytic leukaemia who have	Progression free on oral treatment	0.71	Utility elicitation study of general UK public[54]

	comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable	Progression free on IV treatment	0.67	
		Progression free on initial therapy with increased hospital visits	0.55	
		Progression free after initial treatment completed	0.82	
		Progressed disease	0.60	
TA561	Chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy	Progression free	0.748	TA487 (later updated to TA796)[60] & TA359[61]
		Progressed disease	0.60	
TA487/ TA796	Patients with CLL with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or Patients without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.	Progression free	0.748	As per ERG and NICE committee recommendation
		Progressed disease	0.60	
TA359	Untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation, or for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.	Progression free (comparator)	0.75	Study 116 EQ-5D data
		Intervention treatment utility effect	0.07	
		Progression free off treatment	0.80	TA193[62]
		Progressed disease	0.60	

TA193	Relapsed or refractory CLL excluding patients that are refractory to fludarabine or have been previously treated with rituximab	Progression free	0.80	Hancock et al., 2002[53]
		Progressed disease	0.60	
TA174	First line treatment of CLL where FCR is considered appropriate	Progression free	0.80	Hancock et al., 2002[53]
		Progressed disease	0.60	

4.2.6.3 Health-state utility values

The utility values from TA174 were used to inform the health states in the model for Ven+O and I+Ven.[63] Deterministic sensitivity analysis was conducted to explore impact on cost-effectiveness of varying the progression-free (1L) and post-progression utilities (1L) by ±20%. The source of utilities in TA174 was Hancock et al.[53] The Hancock publication estimated the utility values based on QoL data collected by Holzner et al. through a longitudinal study that investigated the long-term quality of life of patients with chronic lymphocytic leukaemia. The QoL instruments used were the EORTC QLQ-C30 and FACT-G (rather than the EQ-5D instrument). Hancock et al. state that although the main purpose of the research in Holzner et al.[59] was to assess the correlation between the 2 instruments, “the data can be used to give a general indication of reasonable utility values for CLL.

EAG Comments

Whilst the utility data from Hancock et al. does not seem to be specifically targeted at the untreated CLL ‘fit’ population and could not be directly elicited due to the data instruments used, these utility estimates have been considered appropriate in related appraisals.[63] In addition, the utility values are comparable to those used in TA359 (based on study 116 EQ-5D) data. The EAG accepts the company’s choice of utility data.

4.2.6.4 Adverse events applied in economic model and associated disutilities

Ven+O

Section 3.3.1.8 presents a detailed critique of adverse events data presented in the CS. Of relevance to the cost-effectiveness section is the apparent mismatch between the data used in economic model for Ven+O (reported in Table 36 CS) versus the main trial publication findings reported in Eichhorst et al. 2023[41] and Furstenau 2024.[40] AE rates in the latter appear [redacted] than values used in the company's economic model (see Table 22). In addition, the AE data from Eichhorst et al. 2023[41] and Furstenau 2024[40] is broadly similar, with a few discrepances that are likely attributable to the data cut-offs and method of reporting as noted under Table 22. Whilst the EAG acknowledges that the different data cuts between Eichhorst et al. 2023[41] and CLL 13 priority analyses could partially explain some of the differences, it is not clear why there are any differences with data from Furstenau 2024[40], which appears to use the same data-cut as company's priority analyses (Jan 2023). A plausible explanation is that the company has included grade 3 or 4 serious adverse events (SAEs). However, this is not made very clear in the CS. Even if this were the case, the data from TA891 for I+Ven appears to be for grade 3 or 4 AEs not SAEs (with the exception of pneumonia), so using values from the company's priority analyses would be inconsistent with what's used for I+Ven. The EAG's clinical experts' opinions were that the published estimates for Ven+O appear clinically more plausible especially when considered alongside the rates for I+Ven included in the model.

Table 22: Incidence of adverse events of grade 3 or 4 for Ven+O by data source

Adverse Event	CS (CLL13 Priority Analyses) [a]	Eichhorst 2023 [b]	Furstenau 2024 [c]
Anaemia	[redacted]	4.8%	4.8%
Diarrhoea	[redacted]	1.8%	1.8%
Infections (UTI)	[redacted]	1.3%	0.9%
Infusion related reaction	[redacted]	11.4%	11.4%
Neutropenia	[redacted]	45.2%	55.7%[d]
Pneumonia	[redacted]	5.3%	4.8%
Thrombocytopenia	[redacted]	14.9%	18.4%[e]
Atrial fibrillation	[redacted]	0.0%	0.0%
Cardiac failure	[redacted]	N/R	0.4%
Hypertension	[redacted]	1.8%	1.8%
Hyponatraemia	[redacted]	N/R	0.4%
Tumour lysis syndrome	[redacted]	8.3%	8.8%

[a] Values included in economic model (Jan 2023 data cut-off); [b] based on 2022 data cut-off; [c] Based on Jan 2023 data cut-off; [d] Values reported combine neutropenia and/or neutrophil count decreased which could explain differences with values in Eichhorst et al. 2023 where neutropenia and neutrophil count decreased are reported separately. [e] Values reported combine thrombocytopaenia and/or platelet count decreased which could explain differences with values in Eichhorst et al. 2023 where the 2 are reported separately.

I+Ven

Whilst the AE data for Ven+O is derived exclusively from a 'fit' population, with previously untreated CLL and no 17p del, this is not the case for I+Ven. The population upon which incidence data for I+Ven is derived is a mix of (fit and unfit population) i.e., FCR-suitable and FCR unsuitable population. In the CS (section 3.3.3), the company states that data for I+Ven was derived from TA891 (where available). The company further states that due to limited availability of AE incidence data for I+Ven, simplifying assumptions had to be made. Of note was the assumption that CAPTIVATE and GLOW study populations would exhibit similar adverse event profiles. During clarification (CQ B8), the EAG requested that the company provide further details highlighting which population from TA891 was used to derive incidence data

for each of the AEs that were included in the model for I+Ven i.e., CAPTIVATE (FCR-suitable population) vs. CAPTIVATE (full population) vs. GLOW. The company's clarification response is incorporated into Table 23 shows that only hypertension and atrial fibrillation were based on the FCR-suitable population of CAPTIVATE trial (although this also included 17% patients with 17p del). Notably, the CS stated that GLOW trial was excluded as a relevant study in the company's SLR as it was not conducted in the population of interest i.e., did not include 'fit' patients. Specifically, the patients in the GLOW trial had comorbidities and would not have been suitable for FCR. However, despite this, the EAG's clinical experts' opinion was that the incidence of AEs reported for CAPTIVATE (full trial population) is reflective of the population under consideration in this appraisal i.e., fit patients. One expert further commented that TP53 disruption has no effect on adverse event profile when CLL is treated and patients have similar adverse event profiles with treatments whether they have TP53 disrupted CLL or TP53 intact CLL. With regards to the GLOW study population the EAG clinical expert opinion was that they would expect worse adverse events in the older GLOW population.

Table 23: Incidence of adverse events of grade 3 or 4 for Ven+O and I+Ven

AE	Ven+O	I+Ven	
			Specific population in TA891 (Clarification Response B8)
Anaemia	[redacted]	0.0%	Assumed zero – no reliable input found for grade ≥3 adverse event
Diarrhoea	[redacted]	3.1%	CAPTIVATE (full population) Input sourced from TA891 Appendix F
Infections (UTI)	[redacted]	8.2%[a]	CAPTIVATE (full population) Input sourced from TA891 Appendix F
Infusion related reaction	[redacted]	0.0%	Assumed zero – no reliable input found for grade ≥3 adverse event

Neutropenia	[redacted]	32.7%	CAPTIVATE (full population) Input sourced from TA891 Appendix F
Pneumonia	[redacted]	2.0%[b]	CAPTIVATE (full population) Input sourced from Tam et al. 2022 Supplementary Appendix Table 4
Thrombocytopenia	[redacted]	5.7%	GLOW (FCR-unsuitable population) Input sourced from TA891 Table 49
Atrial fibrillation	[redacted]	1.3%	CAPTIVATE (FCR-suitable population) Input sourced from TA891 Table 48
Cardiac failure	[redacted]	3.8%	GLOW (FCR-unsuitable population) Input sourced from TA891 Table 49
Hypertension	[redacted]	5.7%	CAPTIVATE (FCR-suitable population) Input sourced from TA891 Table 48
Hyponatraemia	[redacted]	5.7%	GLOW (FCR-unsuitable population) Input sourced from TA891 Table 49
Tumour lysis syndrome	[redacted]	0.0%	Assumed zero – not reported as an adverse event in TA891 or Tam et al. publication

[a] Value presented for I+Ven is for all grade 3 or 4 infections and not just UTI. The corresponding value for Ven+O would be 13.2% as reported in Eichhorst 2023[41] [b]Value reported is for SAE
TESAE incidence for Ven+O sourced from CLL13. AE incidence for I+Ven sourced from TA891.
AE, adverse event; TESAE, treatment-emergent serious adverse event; UTI, urinary tract infection

EAG Comments:

As outlined in Section 3.3.1.8, the distinctions between the definitions of SAEs (serious adverse events) grade ≥3, SAEs, and grade 3/4 AEs (adverse events) are not clearly described in the company submission (CS), making it difficult to assess the estimates used in the economic model. Based on feedback from clinical experts consulted by the EAG, the publication by Furstenau et al. (2024)[40] is considered the most appropriate data source for these estimates, subject to two minor modifications:

- **Infections**: To ensure consistency with the infection rate used for ibrutinib plus venetoclax (I+Ven)—which includes all grade 3 or 4 infections—the EAG has adopted a rate of 13.2% from Eichhorst et al. (2023).[41] This figure represents the incidence of all grade 3/4 infections, not limited to urinary tract infections (UTIs).
- **Tumour Lysis Syndrome (TLS)**: The EAG retained the company's original values for TLS. Clinical expert feedback indicated that clinical (symptomatic) TLS is rare when appropriate monitoring and early intervention follow the detection of biochemical TLS. The value reported in Furstenau et al. (2024)[40] includes both laboratory-confirmed and clinical TLS.

For I+Ven, the EAG retains the adverse event values used by the company, with the exception of pneumonia. In this case, the incidence is assumed to be zero, as the value sourced from TA891 reflects serious adverse events (SAEs) rather than specifically grade 3 or 4 adverse events (AEs).

AE disutilities

The impact of AEs is captured in the model by taking the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates and the mean utility decrements associated with these AEs and the duration of AEs. It was assumed that all AEs occur within the first cycle only. Adverse event disutilities and duration of AEs were sourced from TA746: “Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer”.[64] The EAG’s clinical expert’s opinion was that duration of AEs whilst, rarely reported, is likely to be very different for CLL compared to gastro-oesophageal junction cancer. They stated that duration of infections, for example, is likely to be higher than the figures reported in CS (table 39)

IV disutilities

To fairly account for the impact of IV treatment on patients' quality of life in the cost-effectiveness model, a disutility of -0.04 per IV administration is applied during each treatment cycle. The disutility is scaled by the number of IV doses per cycle, ensuring that more burdensome IV schedules result in a greater negative impact on quality of life in the model. The EAG finds this approach reasonable.

4.2.7 Resources and costs

The CS provides a detailed report of the costing approach, including the assumptions and sources used to measure and value resource use for Ven+O and I+Ven. The following cost categories were included in the model:

- Drug acquisition and administration costs applied for the duration of treatment
- Health-state unit costs and resource use, irrespective of treatment arm
- The cost of AEs applied as a one-off cost in the first cycle
- End of life costs applied as a one-off cost to patients leaving the PD health state

EAG Comments

- The cost categories included are sufficient to capture the costs associated with treatment for both Ven+O and I+Ven.
- The EAG's clinical advisor commented that AEs are observed within the first 12 months, e.g., infections and whilst the company's approach follows previous technology appraisals, applying AE costs within the first cycle is unlikely to capture the 'true' costs of treating adverse events.

4.2.7.1 Intervention and comparator costs

Drug acquisition costs

The drug acquisition costs for both treatments were based on the dosing regimens detailed in Table 24 below. Dosing schedule for Ven+O and I+Ven followed that of the respective trials (CLL13; CAPTIVATE) and the summaries of product characteristics (SmPCs).[27, 31, 40, 41, 65] Unit costs were sourced from the British National Formulary (BNF).[66]

A patient access scheme (PAS), comprising a discount of [redacted]% was applied to the list price for venetoclax. Assuming 100% treatment compliance and accounting for this PAS, the cost of Ven+O for the entire treatment duration is £[redacted]. Drug acquisition costs for Ven+O and I+Ven do not consider the confidential commercial discounts available for obinutuzumab and ibrutinib but incorporate list prices (see Table 25).

Table 24: Dosing schedule for intervention and comparator drugs

Ven+O	Ven+O treatment consisted of 12 cycles, each with a duration of 28 days. During the first cycle obinutuzumab was administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of cycles 2-6. • Obinutuzumab IV infusion: Cycle 1 Day 1: obinutuzumab 100 mg Day 1 (or 2): obinutuzumab 900 mg Day 8: obinutuzumab 1000 mg Day 15: obinutuzumab 1000 mg Cycles 2-6 Day 1: obinutuzumab 1000 mg • Venetoclax was administered daily with a slow dose escalation of venetoclax started on day 22 of cycle one. Cycle 1 Days 22-28: venetoclax 20 mg (2 tablets at 10 mg) Cycle 2 Days 1-7: venetoclax 50 mg (1 tablet at 50 mg) Days 8-14: venetoclax 100 mg (1 tablet at 100 mg) Days 15-21: venetoclax 200 mg (2 tablets at 100 mg) Days 22-28: venetoclax 400 mg (4 tablets at 100 mg) Cycles 3-12 Days 1-28: venetoclax 400 mg (4 tablets at 100 mg)
I+Ven	Dosing schedule followed that in GLOW and CAPTIVATE trials i.e., • Ibrutinib monotherapy (420 mg/day orally) as a lead-in treatment for three cycles. • A dose ramp-up for venetoclax initiated (from 20 mg/day to 400 mg/day orally over 5 weeks) from Cycle 4. • Treatment with venetoclax (400 mg/day orally) in combination with ibrutinib (420 mg/day orally) for 12 cycles, until Cycle 15

Table 25: Acquisition costs (list prices) of the intervention and comparator technologies

	Drug	Dose per tablet or vial	Units per package	Cost per package	Price per mg
Ven+O		10 mg	14	£59.87	£0.43

	Venetoclax, Tablet	50 mg	7	£149.67	£0.43
		100 mg	112	£4,789.47	£0.43
	Obinutuzumab, IV	1000mg	1	£3,312.00	£3.31
I+Ven	Venetoclax, Tablet	10 mg	14	£59.87	£0.43
		50 mg	7	£149.67	£0.43
		100 mg	112	£4,789.47	£0.43
	Ibrutinib, Tablet, mg	140 mg	28	£1,430.80	£0.37
		280 mg	28	£2,861.60	£0.37
		420 mg	28	£4,292.40	£0.37
		560 mg	28	£5,723.20	£0.37

Relative dose intensity was assumed to be [redacted]% for venetoclax for both Ven+O and I+Ven whilst a dose intensity of [redacted]% is applied for obinutuzumab based on CLL13 trial data. RDI for ibrutinib was estimated to be 94.5%, based on data from RESONATE-2 for ibrutinib monotherapy as reported in TA891. As RDI data for CAPTIVATE was redacted, the EAG accepts this is a reasonable estimate; as highlighted in the CS, the figure is consistent with 5.7% of patients with dose reductions due to TEAEs observed in CAPTIVATE.

4.2.7.2 Drug administration and monitoring costs

Drug administration costs included in the analysis are presented in Table 26 and were sourced from the NHS reference costs 2023-24. No administration costs were included in analysis for drugs that are administered orally, in line with previous NICE technology appraisals.[20, 33, 64]

Table 26: Drug administration costs

Administration route	Cost	Source
IV	£430.24	NHS reference costs code (2023-2024): SB15Z
Rapid IV	£403.52	NHS reference costs code (2023-2024): SB12Z + £9.35 dispensing fee

4.2.7.3 Subsequent treatment use

Subsequent treatments were included in the model as an average one-off cost to patients entering the progressed disease heath state, taking into account the mean duration of treatment, the timing at which patients switch to the next treatment line, the treatment regimens received and proportion of patients receiving subsequent treatment. For the latter, the company assumes the proportion of subsequent treatments is equal between arms and justified this on the basis that all patients will eventually receive all relevant subsequent treatments. The company further states that the clinical experts consulted stated that the choice of 2L treatment is based on duration of response to 1L treatment rather than the 1L treatment itself. The company's method of estimating TTNT and the EAG's critique are summarised in detail above (section 4.2.5.4).

The choice of subsequent treatments and the proportions of patients assumed to receive each subsequent treatment in the model are based on clinical experts' opinion and not CLL13 or CAPTIVATE trial data (Table 27 and Table 28 below). In response to clarification question A16, the company provided more granular data on subsequent treatments for the CLL13 Jan 2023 data cut. The EAG notes that whilst the CS assumes that no patients on Ven+O subsequently receive ibrutinib, [redacted]) i.e., [redacted]% of patients who received subsequent treatments by the data cut off received ibrutinib monotherapy in the Ven+O arm. Other noteworthy differences are that [redacted]

patients ([redacted]%) received allogeneic stem cell transplant and [redacted]%) of patients received Venetoclax single agent as subsequent therapy.

Table 27: Proportion of patients on subsequent treatments following Ven+O and I+Ven

Treatment arm	Acalabrutinib	Ibrutinib	Zanubrutinib	Ven+R
Ven+O	38.54%	0.00%	36.46%	25.00%
I+Ven	38.54%	0.00%	36.46%	25.00%

Estimates based on company's clinical experts' input

Table 28: Mean time on subsequent treatments

Subsequent Treatment	Mean time on subsequent treatment (months)	Total number of cycles
Acalabrutinib	39	42
Zanubrutinib	46.8	51
Ven+R	24.4	27

Estimates based on company's clinical experts' input

EAG Comments

Regarding subsequent treatments received, the EAG's clinical expert commented that both the response to 1L therapy and the choice of 1L therapy drive the choice of 2L treatment. They stated that the new guidelines will say:

[redacted] They also

commented that: (i) in the updated CAPTIVATE data, patients were retreated with I+Ven or single agent ibrutinib but in clinical practice, I+Ven retreatment would not be funded in the NHS and patients would be much more likely to receive a second generation BTKi; (ii) there is emerging data on retreatment with venetoclax, in the form of Ven+R which would be funded in the NHS. Taking the clinical experts' comments into account, the EAG concludes that the subsequent treatments proposed and the proportional usage applied in the company's economic model seem reasonable and align with what is expected in NHS clinical practice.

4.2.7.4 Health state unit costs and resource use

The cost per cycle included disease-related management costs in the progression-free and progressed disease states which were calculated by multiplying the resource use per cycle (Table 29) by the unit cost of each resource item (Table 30). The resource use estimates sourced from TA891 were considered suitable by the EAG's clinical experts.

Table 29: Progression free and post-progression resource use frequency

Resource use	Annual pre-progression frequency	Annual post-progression frequency	Per cycle pre-progression frequency	Per cycle post-progression frequency
Full blood count	5.0	7.0	0.39	0.53
Chest X-ray	1.0	1.0	0.07	0.07
Bone marrow exam	0.0	1.0	0.00	0.07
LDH	2.0	3.0	0.16	0.23
Haematologist visit	4.0	5.0	0.30	0.39
CT scan	0.2	2.0	0.02	0.16

Biochemistry test: renal - Urea and electrolytes test (UE test)	4.0	7.0	0.30	0.53
Biochemistry test: liver function test	4.0	7.0	0.30	0.53
Immunoglobulins Blood Test	1.0	1.0	0.07	0.07
Inpatient non-surgical/medical visit	1.0	2.0	0.07	0.16
Full blood transfusion	0.0	1.0	0.39	0.07

Source: NICE TA891
CT, computerised tomography; ECG, electrocardiogram; LDH, lactate dehydrogenase; UE, urea and electrolytes

The most recent National Schedule of NHS Costs (2023-2024) is used to inform the routine care and monitoring costs detailed in Table 30.[67]

Table 30: Routine care and monitoring costs used in the model

Resource use	Cost	Source – NHS reference costs (2023-2024)
Full blood count	£3.10	NHS reference costs code: DAPS05
Chest X-ray	£50.06	NHS reference costs code: RD97Z
Bone marrow exam	£740.05	NHS reference costs code: SA33Z
LDH	£1.53	NHS reference costs code: DAPS04
Haematologist visit	£184.09	NHS reference costs code: Outpatient Attendances Data: 303- Clinical haematology
CT scan	£113.66	NHS reference costs code: Weighted average of RD20A (£113) and RD21A (£116)
Biochemistry test: renal - Urea and electrolytes test (UE test)	£1.53	NHS reference costs code: DAPS04
Biochemistry test: Liver function test	£1.53	NHS reference costs code: DAPS04
Immunoglobulins Blood Test	£3.10	NHS reference costs code: DAPS05
Inpatient non-surgical/medical visit	£561.72	NHS reference costs code: Weighted average of day case, Chronic Lymphocytic Leukaemia, including Related Disorders, SA32A (£408),

		SA32B (£438), SA32C (£459) and SA32D (£403) = £418.72 PSSRU 2021: Medical consultant hour + qualification costs = £143
Full blood transfusion	£398.79	NHS reference costs code: SA44A

Source: CS Table 46
CT, computerised tomography; ECG, electrocardiogram; LDH, lactate dehydrogenase; PSSRU, Personal Social Services Research Unit; UE, urea and electrolytes

4.2.7.5 TLS management and monitoring costs

TLS Costing and monitoring – summary of methods

- Patients are assigned to TLS risk categories (low / medium / high) after debulking using published proportions (Fürstenau et al. 2021[68] and Tam et al. 2022[27]). Proportions with "missing" TLS risk are removed by normalisation (Table 31).
- 25% of patients initially classified as medium risk are "up-shifted" into the high-risk category (i.e., 25% of the medium group are re-allocated to high) based on clinical expert input provided to the company.
- Each TLS risk category has a defined prophylaxis package (hydration, lab testing, rasburicase use if indicated; inpatient care for high risk). Unit costs and resource use were sourced from NHS references and list prices.
- The model computes a weighted TLS prophylaxis cost across risks for Ven+O, I+Ven, Ven+R by applying the adjusted patient-risk distribution to the per-risk resource costs. Ven+R is given as subsequent treatment in both treatment arms.
    - Results are shown in Table 32 indicating the following TLS prophylaxis costs across TLS risk groups: Ven+O ;£1,458.68, I+Ven; £1,523.47, Ven+R; £1,775.69).
- A **one-off TLS monitoring cost** is applied in model cycle-1 for each arm. This equals:

- (Prophylaxis cost across risks for the intervention arm (Ven+O/I+Ven)× proportion of patients monitored)
  PLUS
- (Prophylaxis cost across risks for Ven+R × proportion of patients monitored × proportion expected to receive Ven+R as subsequent therapy).

- Parameters used:
  - Proportion of patients monitored = 25.12%**.**
  - Proportion receiving Ven+R as subsequent therapy = 25%**.**
- Applying the above gives monitoring costs: Ven+O £477.93 and I+Ven £494.20 (Table 33).
- Because Ven+O has a larger share of patients in the low tumour burden category, its TLS costs are lower than for I+Ven.
- The EAG found the overall approach to costing TLS management and monitoring reasonable.

Table 31: Proportions of patients in each TLS risk category after debulking

	TLS risk			
	Low tumour burden	Medium tumour burden	High tumour burden	Missing
Sourced from published literature				
Ven+O	61.0%	21.0%	7.0%	11.0%
I+Ven	29.0%	67.0%	1.0%	4.0%
Normalised to account for patients with missing TLS risk				
Ven+O	68.5%	23.6%	7.9%	-
I+Ven	29.9%	69.1%	1.0%	-
Adjusted to account for 25% of patients with medium tumour burden being treated as high risk				

Ven+O	68.5%	17.7%	13.8%	-
I+Ven	29.9%	51.8%	18.3%	-

**Proportions based on Fürstenau et al. 2021[68] and Tam et al. 2022[27]

Table 32: Total costs of TLS prophylaxis by tumour burden risk for Ven+O,I+Ven and Ven+R

	Costs by TLS Risk			
Treatment	**Low tumor burden**	**Medium tumor burden**	**High tumor burden**	**All risks**
Ven+O	£871.43	£226.94	£360.30	£1,458.68
I+Ven	£380.12	£664.34	£479.02	£1,523.47
Ven+R	£289.53	£514.23	£971.93	£1,775.69
All	£1,271.43	£1,282.40	£2,617.72	£5,171.56

Table 33: One-off monitoring costs for TLS

Treatment arm	**Cost (£)**
Ven+O	£477.90
I+Ven	£494.20

4.2.7.6 Terminal care costs

In line with previous technology appraisals, costs associated with terminal care were sourced from Round et al. and inflated to 2024 values.[69] A one-off terminal care cost of £9,007.92 is applied upon entry into the death health state.

4.2.7.7 Miscellaneous costs

Based on clinical expert opinion and published good practice guidelines, patients receiving I+Ven are expected to undergo cardiac monitoring due to the cardiotoxicities associated with ibrutinib.[32] It is assumed that patients receiving I+Ven require five electrocardiograms (ECGs) in the first treatment year due to ibrutinib cardiotoxicity risks, at a cost of £176.40 each (total applied in the first model cycle). No cardiac monitoring is required for Ven+O. The EAG's clinical experts confirmed that this is current clinical practice for I+Ven and the assumption is maintained in the EAG's base case.

4.2.7.8 Confidential comparator and subsequent treatment prices

All the analyses in this EAG report (reported in section 5) will use the list prices of comparator and subsequent treatments. Details on confidential comparator and subsequent treatment prices are provided in section 5.4.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 briefly discusses severity weighting; the company has not presented a case for severity weighting for this appraisal.

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

The discounted life years gained (LYG) and quality adjusted life years (QALYs), total and incremental costs, between Ven+O and I+Ven are presented in Table 34 and Table 36 for deterministic and probabilistic analyses respectively. The results presented are for the company's base case in original CS (there were no amendments post clarification). All results are presented without a severity modifier as the company stated that Ven+O is not anticipated to qualify for a severity modifier (see section 5.3.1)

Table 34: Company's deterministic base case cost-effectiveness results (no severity modifier)

	Total			Incremental			
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**
Ven+O	[redacted]	22.35	9.85	[redacted]	0.83	0.37	[redacted]
I+Ven	[redacted]	21.51	9.48	-	-	-	-

Table 35 shows a summary of net monetary benefit (NMB) and net health benefit (NHB) outcomes in the company's base case.

Table 35: Incremental net benefit results in the company's base case analysis

Incremental net monetary benefit (NMB)		Incremental net health benefit (NHB)	
£20,000 threshold	£30,000 threshold	£20,000 threshold	£30,000 threshold
[redacted]	[redacted]	[redacted]	[redacted]

A probabilistic sensitivity analysis (PSA) was conducted to assess model uncertainty. The PSA was conducted over 1,000 iterations in line with NICE guidance to ensure convergence. Parameter distributions followed Briggs et al. (2006),[70] with Dirichlet distributions applied to correlated parameters. Variance was derived from available standard errors (SEs), or assumed at 20% where unavailable. Results are presented as cost-effectiveness acceptability curves (Figure 14), incremental cost-effectiveness scatter plots (Figure 13), and mean probabilistic outcomes (costs, QALYs, ICER) for Ven+O versus I+Ven (Table 36).

Table 36: Company's probabilistic base case cost-effectiveness results (no severity modifier)

Technologies	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Ven+O	[redacted]	8.32	[redacted]	0.42	[redacted]
I+Ven	[redacted]	7.90	-	-	-

Figure 13: Cost-effectiveness scatterplot for Ven+O versus I+Ven

Source: CS (Figure 27)

Analysis performed using venetoclax PAS price and other therapies at list price
ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years; WTP, willingness to pay

Figure 14: Cost-effectiveness acceptability curve for Ven+O versus I+Ven
Source: CS (Figure 28)

The probability of cost-effectiveness of Ven+O versus I+Ven, at £30,000 WTP threshold was [redacted] under the company's base case assumptions.

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Deterministic sensitivity analysis

The company presented deterministic sensitivity analysis (DSA) results in section 3.9.2 of the CS. The DSA varied parameters one at a time to assess their impact on incremental costs, QALYs, and the ICER. Bounds were based on SEs from input estimates or assumed at 10% where unavailable. Parameters included are listed in Appendix L (CS).

Figure 15: DSA tornado plot for Ven+O versus I+Ven

Source: Figure 29 (CS)

Figure 15 shows the results for 10 parameters with the most influence on ICER; with baseline starting age in model and time horizon having the most impact.

The company presented the following scenario analyses:

- Cost-comparison analysis – assuming equal efficacy between Ven+O and I+Ven. In the cost-comparison scenario, Ven+O incurs lower total costs (£[redacted]) compared with I+Ven (£[redacted]) and

results in a cost saving of £[redacted] when the venetoclax PAS is considered (Table 37). The company's CCA is appropriate. However, the error in implementing TTNT is also carried forward in this analysis; the EAG was unable to correct this error. Since this affects each arm equally in the CCA, no bias is incurred.

Table 37: Summary of cost-comparison analysis scenario

Outcome	Ven+O	I+Ven	Incremental
Acquisition (1L) costs	[redacted]	[redacted]	[redacted]
Administration (1L) costs	[redacted]	[redacted]	[redacted]
TLS Prophylaxis costs	[redacted]	[redacted]	[redacted]
TRAE costs	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition costs	[redacted]	[redacted]	[redacted]
Subsequent treatment administration costs	[redacted]	[redacted]	[redacted]
Disease management (PFS) costs	[redacted]	[redacted]	[redacted]
Disease management (PP) costs	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

- Applying a standardised mortality ratio (SMR) to general population mortality hazard such that patients with CLL have a 5% higher risk of death compared with the general population at each cycle accounting for age and sex (analysis was presented in response to Clarification question B5). The scenario analysis results followed the same pattern as base case cost-effectiveness results that Ven+O was more effective and less costly than I+Ven under the company's base case assumptions (See Table 38)

Table 38: Applying a SMR to general population mortality hazard based on outputs from clinical engagement (PSM)

Technologies	Total			Incremental			
	Costs (£)	LYs	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)
Ven+O	[redacted]	22.02	9.77	[redacted]	0.71	0.34	[redacted]
I+Ven	[redacted]	21.31	9.43	-	-	-	-

Source: Table 36 Clarification Responses v1.0

ICER, incremental cost-effectiveness ratio; LYG, life years; PSM, partitioned survival model; QALY, quality-adjusted life year; SMR, standardised mortality ratio

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The EAG conducted an extensive review of the model submitted by the company. The model appears to reflect the assumptions made by the company and contained clinical aspects necessary to address the decision problem, aside from the modelling of TTNT where the EAG used an alternate approach(section 4.2.5.4). The EAG sought clinical validation of (i) the model assumptions (both EAG and company's) and (ii) model's output ((LYG, QALYs) and relevant economic outcomes (e.g., treatment costs)).

5.2.2 EAG's exploratory analyses using company's base case

Based on our critique of the company's economic model, the EAG made changes to the company's model to explore the impact of individual changes

to the company's base case results. The suggested changes along with the EAG's justifications are presented below:

Baseline characteristics of modelled population

- Using baseline characteristics (age, proportion males) from the SACT data in the economic model

The EAG believes using SACT data maximises use of the real-world evidence and ensures the baseline characteristics of the modelled population is more representative of patients seen in NHS clinical practice

Differing choice of OS data source and preferred extrapolation

- OS extrapolation for Ven+O based on SACT data and equal efficacy is assumed between Ven+O and I+Ven

The EAG explores the above scenario as the MAIC analyses undertaken by the company do not support a consistent or clear benefit of Ven+O. Furthermore, both the EAG and company experts noted that outcomes for Ven+O and I+Ven are likely comparable. Using SACT data also maximises use of the real-world evidence of efficacy of Ven+O as observed in NHS clinical practice.

Assuming equal PFS for Ven+O and I+Ven based on CLL13 data whilst maintaining the company's choice of extrapolation (Weibull)

Similar to comment above, the MAIC analyses undertaken by the company do not support a consistent or clear benefit of Ven+O. Furthermore, both the EAG and company experts noted that outcomes for Ven+O and I+Ven are likely comparable.

Differing choice of extrapolation for TTNT

In this exploratory analysis, the EAG uses the observed data from the CLL13 trial to extrapolate TTNT for Ven+O. The Gompertz extrapolation is selected and constrained to not fall below PFS and is set equal for both arms. A detailed discussion in provided in section 4.2.5.4.

Different source of data to model Ven+O grade ≥3 adverse events

The EAG noted the discrepancy between the company's modelled estimates for grade ≥3 AEs for Ven+O and the published estimates from CLL13 trial publications[40, 41] and explores a scenario analysis where the estimates by Furstenau et al are used.[40] The EAG clinical experts preferred the published estimates as they considered these plausible and reflective of what would be observed in clinical practice. Detailed discussion is provided in section 4.2.6.4

Table 39: Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Baseline starting age of 60.90 years based on CLL13 trial data	Baseline starting age of [redacted] years based on median age of SACT population	Reflects demographic characteristics in NHS clinical practice	4.2.3
2	Proportion males of 74.7% based on CLL13 trial data	Proportion males of [redacted]% based on SACT population	Reflects demographic characteristics in NHS clinical practice	4.2.3
3	Log-logistic extrapolation of OS for Ven+O using CLL13 data. For I+Ven, the inverse of the MAIC hazard ratio of [redacted] is applied to the log-logistic extrapolation for Ven+O	OS exponential extrapolation for Ven+O based on SACT data and equal efficacy is assumed between Ven+O and I+Ven	MAIC analyses shows no clear/consistent benefit; Company and EAG experts consider outcomes likely comparable	4.2.5.1
4	For I+Ven PFS, the inverse of the MAIC hazard ratio of [redacted]	Equal PFS for Ven+O and I+Ven based on CLL13	MAIC analyses shows no clear/consistent	4.2.5.2

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
	is applied to the Weibull extrapolation for Ven+O	data whilst maintaining the company's choice of extrapolation (Weibull)	benefit; Company and EAG experts consider outcomes likely comparable	
5	For I+ Ven: Model tracks net change in progressed disease and death states per cycle to estimate TTNT	Gompertz extrapolation for TTNT constrained to not fall below PFS and set equal for both arms	Company approach appears to overestimate patients receiving subsequent treatment	4.2.5.4
6	Adverse events for Ven+O based on company's CLL13 Priority Analyses (Jan 2023 data cut) for grade 3 or 4 AEs	Adverse events for Ven+O based on CLL13 trial published data (Jan 2023 data cut) for grade 3 or 4 AEs	EAG clinical experts considered the estimates in the publication more plausible	4.2.6.4

Table 40 reports the impact of EAG scenario analyses on incremental costs, QALYs, and ICER relative to the company's base case.

Table 40: Results of EAG's exploratory analyses using company's base case

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs (no severity weighting)	ICER £/QALY (no severity weighting)
1	Baseline starting age of 61 years based on SACT data	[redacted]	0.37	[redacted]
2	Proportion males of [redacted]% based on SACT data	[redacted]	0.39	[redacted]
3	OS exponential extrapolation for Ven+O based on SACT data and equal efficacy is assumed between Ven+O and I+Ven	[redacted]	0.12	[redacted]

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs (no severity weighting)	ICER £/QALY (no severity weighting)
4	Equal PFS for Ven+O and I+Ven based on CLL13 data whilst maintaining the company's choice of extrapolation (Weibull)	[redacted]	0.25	[redacted]
5	Gompertz extrapolation for TTNT constrained to not fall below PFS and set equal for both arms	[redacted]	0.37	[redacted]
6	Adverse events for Ven+O based on CLL13 trial published data (Jan 2023 data cut) for grade 3 or 4 AEs	[redacted]	0.37	[redacted]

5.2.3 EAG's preferred assumptions

Based on all considerations in Section 4 of this report, the EAG defined a new base case. The adjustments made to the company model are described below and impact on QALYs and incremental costs summarised in Table 41.

Table 41: Results using EAG's preferred model assumptions without severity weighting

Preferred assumption	Exploratory analysis number	Total costs		Total QALYs		Incremental costs (£)	Incremental QALYs No severity weighting	Cumulative ICER £/QALY No severity weighting
		Ven+O	I+Ven	Ven+O	I+Ven			
Company's base case [CS V1.0]	Not applicable	[redacted]	[redacted]	9.85	9.48	[redacted]	0.37	[redacted]
Baseline starting age of [redacted] years based on SACT data	1	[redacted]	[redacted]	9.87	9.50	[redacted]	0.37	[redacted]
Proportion males of [redacted]% based on SACT data	2	[redacted]	[redacted]	9.88	9.49	[redacted]	0.39	[redacted]
OS exponential extrapolation for Ven+O based on SACT data and equal efficacy is assumed between Ven+O and I+Ven	3	[redacted]	[redacted]	9.19	9.07	[redacted]	0.12	[redacted]
Equal PFS for Ven+O and I+Ven based on CLL13 data whilst maintaining the company's choice of extrapolation (Weibull)	4	[redacted]	[redacted]	9.85	9.60	[redacted]	0.25	[redacted]
Gompertz extrapolation for TTNT constrained to not fall below PFS and set equal for both arms	5	[redacted]	[redacted]	9.85	9.48	[redacted]	0.37	[redacted]

Preferred assumption	Exploratory analysis number	Total costs		Total QALYs		Incremental costs (£)	Incremental QALYs No severity weighting	Cumulative ICER £/QALY No severity weighting
		Ven+O	I+Ven	Ven+O	I+Ven			
Adverse events for Ven+O predominantly based on CLL13 trial published data (Jan 2023 data cut) for grade 3 or 4 AEs except for infections and TLS which are based on Eichhorst et al (2023[41] and company analyses respectively	6	[redacted]	[redacted]	9.84	9.48	[redacted]	0.37	[redacted]
EAG's base case**	-	[redacted]	[redacted]	9.22	9.22	[redacted]	0[a]	[redacted]

No severity modifier is applied in both the EAG and company base case. [a]There is a very slight QALY decrement for Ven+O of -0.0035 QALYs in the EAG's base case.

5.2.3.1 EAG deterministic base case results

Table 42 below shows that Ven+O incurs lower total costs (£[redacted]) compared with I+Ven (£[redacted]) and results in a cost saving of [redacted] when the venetoclax PAS is considered.

The EAG assumes equal efficacy (PFS, OS) between Ven+O and I+Ven, which shifts the base case analysis from cost-effectiveness to a predominantly cost-comparison. Since both treatments are considered equally effective, the cheaper option (Ven+O) is preferred. The EAG references the company's cost-comparison scenario, as it aligns with this assumption and supports the base case conclusion. For completion, the EAG shows the QALY breakdown in Table 43 which shows that the slight QALY decrement for Ven+O arises from the treatment related adverse events disutilities and IV treatment disutility (1L). The latter only applied to obinutuzumab at 1L.

Table 42: EAG base case deterministic cost-effectiveness results (no severity modifier)

	Total			Incremental			
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**
Ven+O	[redacted]	20.55	9.215	[redacted]	0	0	[redacted]*
I+Ven	[redacted]	20.55	9.219	-	-	-	-
Note: The absolute (unrounded figure) of incremental QALYs is 0.0035 QALYs in favour of I+Ven which results in an ICER of [redacted]. The ICER can be interpreted as: for every additional QALY gained by using I+Ven compared to Ven+O, it costs [redacted]. EAG thus interprets the ICER (for Ven+O) as cost-saving as incremental QALYs as incremental QALYS are rather small ≈ zero.							

Table 43: QALY breakdown in EAG base case

Outcome (per patient)	Ven+O	I+Ven	Incremental
Progression free survival	4.8821	4.8821	0.0000
Post-progression	4.3416	4.3416	0.0000

Outcome (per patient)	Ven+O	I+Ven	Incremental
Treatment related adverse events	-0.0073	-0.0047	-0.0026
IV treatment disutility(1L)	-0.0009	0.0000	-0.0009
Total	**9.2154**	**9.2189**	**-0.0035**

The company presents a breakdown of costs associated with Ven+O versus I+Ven in its cost-comparison scenario analysis. Since the EAG's base case analysis assumes equal efficacy (OS and PFS), we compare the differences in costs across cost categories between the company and EAG's analysis:

- Acquisition costs are the main driver of cost-differences between Ven+O and I+Ven but are slightly lower in EAG base case
- Treatment-related adverse event (TRAE) costs differ notably: Company CCA shows TRAE for Ven+O less than I+Ven with an incremental cost of [redacted], while EAG base case shows TRAE costs are higher for Ven+O vs. I+Ven i.e., incremental cost of [redacted]. The discrepancy arises from the differences in the AE rates applied by the EAG in the economic model which were based on CLL13 trial data publications and are higher than the estimates used by the company (see section 4.2.6.4).
- Disease management and terminal care costs are lower in the EAG base case compared with company CCA (e.g., post-progression costs: [redacted] vs £[redacted]; Terminal care: £[redacted] vs £[redacted]).

Table 44: Summary of cost-breakdown, EAG base case analysis

Outcome	Ven+O	I+Ven	Incremental
Treatment Acquisition (1L) costs	[redacted]	[redacted]	[redacted]
Administration (1L) costs	[redacted]	[redacted]	[redacted]
One-off monitoring	[redacted]	[redacted]	[redacted]

TRAE costs	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition costs	[redacted]	[redacted]	[redacted]
Subsequent treatment administration costs	[redacted]	[redacted]	[redacted]
Disease management (PFS) costs	[redacted]	[redacted]	[redacted]
Disease management (PP) costs	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

5.2.3.2 EAG Probabilistic base case cost-effectiveness results

The EAG's base case was subjected to a probabilistic sensitivity analysis using 1,000 iterations consistent with the company's approach. The probabilistic incremental costs were [redacted] and incremental QALYs were -0.0035. The resulting ICER [redacted] is best interpreted in terms of Ven+I and indicates that : for every additional QALY gained by using I+Ven compared to Ven+O, it costs [redacted]. As such, Ven+I has a [redacted] probability of cost-effectiveness when compared to Ven+O. As the incremental QALY decrement for Ven+O is rather small ≈ zero, it is more appropriate to consider that QALY gains are similar between Ven+O and I+Ven (see

Figure 16) and interpret the ICER for Ven+O as indicating that Ven+O is [redacted].

Figure 16: EAG probabilistic incremental scatterplot

5.2.4 Scenario analyses using EAG's preferred assumptions

Table 45 outlines the additional scenario analyses that the EAG has done using the EAG's preferred base case. Most of the scenario analyses test the impact of company's preferred assumption on EAG's base case.

Table 45: Summary of EAG's scenario analyses on EAG's base case

Scenario analysis number	EAG's base-case assumption	EAG's scenario
1	Starting age = [redacted] years	Starting age = 60.9 years
2	Proportion males = [redacted]%	Proportion males = 74.7%
3	Survival estimates: OS: I+Ven OS set equal to Ven+O OS PFS: I+Ven PFS set equal to Ven+O PFS Gompertz extrapolation for TTNT constrained to not fall below PFS and set equal for both arms	Survival estimates: PFS hazard ratio of [redacted] based on EAG's preferred MAIC analysis is modelled on EAG base case assumptions for OS and TTNT
4	Survival estimates: OS: I+Ven OS set equal to Ven+O OS PFS: I+Ven PFS set equal to Ven+O PFS Gompertz extrapolation for TTNT constrained to not fall below PFS and set equal for both arms	Survival estimates: OS hazard ratio of [redacted] based on company's preferred MAIC is modelled on EAG base case assumptions for PFS and TTNT
5	Adverse events for Ven+O based on CLL13 trial published data (Jan 2023 data cut) for grade 3 or 4 AEs	Adverse events for Ven+O based on company's CLL13 priority analyses
6	Time on treatment for Ven+O based on CLL13 data as applied in company's base case	Time on treatment for Ven+O based on SACT data

The deterministic results of the additional scenario analyses (on EAG's base case) are presented in Table 46. No QALY weighting is applied as discussed in section 5.3.1.

Table 46: Scenario analyses deterministic cost-effectiveness results on EAG base case

Scenario analysis number	Scenario Applied to EAG Base Case	Total costs		Total QALYs		Incremental costs (£)	Incremental QALYs No severity weighting	ICER £/QALY No severity weighting
		Ven+O	I+Ven	Ven+O	I+Ven			
Not applicable	EAG's base case	[redacted]	[redacted]	9.22	9.22	[redacted]	0[a]	[redacted]
1	Baseline starting age of 60.9 years based on CLL13 data	[redacted]	[redacted]	9.20	9.20	[redacted]	0	[redacted]
2	Proportion males of 74.7% based on CLL13 data	[redacted]	[redacted]	9.204	9.207	[redacted]	0[a]	[redacted]
3	PFS hazard ratio of [redacted] based on EAG's preferred MAIC is modelled on EAG base case assumptions for OS and TTNT	[redacted]	[redacted]	9.22	9.10	[redacted]	0.12	[redacted]
4	OS hazard ratio of [redacted] based on company's preferred MAIC is modelled on EAG base case assumptions for PFS and TTNT	[redacted]	[redacted]	9.22	9.32	[redacted]	-0.11	ICER for I+Ven = [redacted][b]

Scenario analysis number	Scenario Applied to EAG Base Case	Total costs		Total QALYs		Incremental costs (£)	Incremental QALYs No severity weighting	ICER £/QALY No severity weighting
		Ven+O	I+Ven	Ven+O	I+Ven			
5	Adverse events for Ven+O based on CLL13 trial published data (Jan 2023 data cut) for grade 3 or 4 AEs	[redacted]	[redacted]	9.22	9.22	[redacted]	0[c]	[redacted][c]
6	Time on treatment for Ven+O based on SACT data	[redacted]	[redacted]	9.22	9.22	[redacted]	0[a]	[redacted]

[a]There is a 0.003 QALY increment in favour of I+Ven (rounded off figure = zero).
[b] The ICER of £[redacted] per QALY is much easier to interpret for I+Ven i.e., for every additional QALY gained by using I+Ven (under this scenario) compared to Ven+O, it costs £[redacted].
[c]There is a 0.0029 QALY increment in favour of Ven+O (rounded off figure = zero).

5.3 Decision modifiers

5.3.1 QALY weighting for severity

In its submission, the company did not provide evidence to support the application of a QALY weighting for this appraisal. A QALY weight is an additional weight applied to QALY gains in severe diseases. Whether QALY weighting applies depends on both the absolute and proportional QALY shortfalls.

Absolute shortfall: the number of future QALYs lost by people living with the disease on current standard of care.

Proportional shortfall: the proportion of future QALYs lost by people living with the disease on current standard of care.

For example, if the proportional QALY shortfall is ≥0.95, or if the absolute QALY shortfall is ≥18, the incremental QALYs are multiplied by a weighting of 1.7 (see Table 47).

Table 47: Severity Modifier Weight Definitions

QALY weight	Proportional shortfall	Absolute shortfall
x1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

The company did not provide any QALY shortfall analysis in its submission (Document B) for the EAG to verify but stated that it did not believe the appraisal qualified for a severity weighting. The EAG agrees with the company's position that QALY weighting does not apply for this appraisal. The QALY shortfall calculator by Schneider et al. was used to derive the shortfall values presented in Table 48 (https://shiny.york.ac.uk/shortfall/).

Table 48: Parameters used to calculate QALY shortfalls, EAG Base Case

Parameter	Value
Starting age (years)	61

Percentage female	33
Discount rate	3.5
QALYs without disease	11.99
QALYs with disease (current standard of care)	9.22
Absolute QALY shortfall	2.77
Proportional QALY shortfall	0.231
QALY weight	**1**

5.3.2 Uncaptured benefits

The company highlights two benefits of Ven+O not fully captured in QALY estimates. First, it enables patient access to obinutuzumab, which would otherwise be unavailable later in the treatment pathway. Clinical experts support this as a meaningful advantage. Second, the company argues that broader system benefits (e.g., reduced cardiac monitoring demands) are not fully reflected. However, the EAG considers the reduced healthcare resource use to be adequately captured in the appraisal.

5.3.3 Health inequalities

The company states that this appraisal is not expected to exclude or disadvantage any groups protected under equality legislation, nor to have a different or adverse impact on people with particular disabilities compared with the wider population.

5.4 Confidential comparator and subsequent treatment prices

All analyses presented in section 5 only consider the venetoclax PAS. However, there are other confidential discounts that are relevant for this appraisal for the comparator treatment (ibrutinib) as well as subsequent treatments: acalabrutinib, zanubrutinib. There are also medicines procurement

supply chain (MPSC) prices for rituximab. In addition, there is a confidential discount for obinutuzumab which is part of the intervention technology. A separate confidential appendix (accompanying the EAG report) will be submitted, replicating the: EAG's exploratory analyses (on company's base case); EAG's base case analysis; EAG scenario analyses (on EAG base case); company's base analysis. The analyses in the confidential appendix will use all confidential comparator and subsequent treatment price discounts relevant to this appraisal.

Table 49: Pharmaceutical products and sources for the EAG cPAS appendix

Drug	Form	Dose per unit/strength	Source for main report	Source for cPAS appendix
Venetoclax	Oral tablet	10mg	BNF	PAS
Venetoclax	Oral tablet	50mg	BNF	PAS
Venetoclax	Oral tablet	100mg	BNF	PAS
Obinutuzumab	Intravenous infusion vial	1000mg / 40ml	BNF	PAS
Ibrutinib	Oral tablet	420mg	BNF	PAS
Acalabrutinib	Oral tablet	100mg	BNF	PAS
Zanubrutinib	Oral tablet	80mg	BNF	PAS
Rituximab	Solution for infusion vial	500mg / 50ml	BNF	MPSC
Rituximab	Solution for injection vial	1400mg / 11.7ml	BNF	MPSC

5.5 Conclusions of the cost-effectiveness section

The company's model is broadly logical, with the main exception being the handling of time to next treatment (TTNT). The model appears to incorrectly assume that subsequent treatment costs are incurred even without progression-state occupancy.

The systematic literature review appears comprehensive. However, the EAG identified the following concerns with the cost-effectiveness analysis (outlined in Section 1.1), though all are judged to have minimal impact on the ICER:

- Choice of population for overall survival extrapolation for Ven+O
- Use of hazard ratios from the MAIC vs. assuming equal efficacy to obtain extrapolations for I+Ven
- Approach to modelling TTNT for both treatments
- Choice of data to estimate grade 3 or 4 adverse events for Ven+O in the economic model
- Source of information for starting age and sex distribution of the population in the economic model

Whilst not explored in any of the EAG's analyses, there is remaining uncertainty in utility estimates used in the economic model. Utility estimates were not derived from EQ-5D data and not based on the target population (i.e., fit, untreated CLL patients without 17p deletion/TP53 mutation). The EAG was unable to source alternative data sources and cannot comment on the direction of likely bias introduced by current utility estimates applied in the model.

The EAG's base case assumes equal efficacy (OS, PFS) between treatments, defaulting the analysis to a cost-comparison, where Ven+O remains [redacted].

The company also supports a cost-comparison approach over a full cost-utility analysis. The EAG agrees this is reasonable, given clinical feedback and exploratory analyses suggest similar survival and potentially, quality of life between treatments - and that Ven+O is unlikely to be [redacted] than I+Ven.

6. References

1. Ghia P, Ferreri AJ, Caligaris-Cappio F. Chronic lymphocytic leukemia. *Critical reviews in oncology/hematology* 2007;**64**(3):234-46. https://doi.org/10.1016/j.critrevonc.2007.04.008
2. Cancer Research UK. *Risks and causes of chronic lymphocytic leukaemia (CLL)*. 2024. URL: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/risks-causes (Accessed 10th October 2025).
3. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. *American Journal of Hematology* 2017;**92**(9):946-65. https://doi.org/10.1002/ajh.24826
4. Kikushige Y. Pathogenesis of chronic lymphocytic leukemia and the development of novel therapeutic strategies. *J Clin Exp Hematop* 2020;**60**(4):146-58. http://dx.doi.org/10.3960/jslrt.20036

5. Ten Hacken E, Burger JA. Microenvironment interactions and B-cell receptor signaling in Chronic Lymphocytic Leukemia: Implications for disease pathogenesis and treatment. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 2016;**1863**(3):401-13. http://dx.doi.org/10.1016/j.bbamcr.2015.07.009
6. van Attekum MH, Eldering E, Kater AP. Chronic lymphocytic leukemia cells are active participants in microenvironmental cross-talk. *haematologica* 2017;**102**(9):1469. http://dx.doi.org/10.3324/haematol.2016.142679
7. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. *Blood* 2012;**120**(6):1175-84. http://dx.doi.org/10.1182/blood-2012-02-362624
8. Gaidano G, Rossi D. The mutational landscape of chronic lymphocytic leukemia and its impact on prognosis and treatment. *Hematology 2014, the American Society of Hematology Education Program Book* 2017;**2017**(1):329-37. http://dx.doi.org/10.1182/asheducation-2017.1.329
9. Wu S-J, Huang S-Y, Lin C-T, Lin Y-J, Chang C-J, Tien H-F. The incidence of chronic lymphocytic leukemia in Taiwan, 1986-2005: a distinct increasing trend with birth-cohort effect. *Blood, The Journal of the American Society of Hematology* 2010;**116**(22):4430-5. http://dx.doi.org/10.1182/blood-2010-05-285221
10. American Cancer Society. *Signs and symptoms of chronic lymphocytic leukemia*. 2018. URL: https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html (Accessed 30/01/2024).
11. Muchtar E, Kay NE, Parikh SA. Early intervention in asymptomatic chronic lymphocytic leukemia. *Clin Adv Hematol Oncol* 2021;**19**(2):92-103. https://www.ncbi.nlm.nih.gov/pubmed/33596191
12. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H*, et al.* iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 2018;**131**(25):2745-60. http://dx.doi.org/10.1182/blood-2017-09-806398
13. Devi A, Thielemans L, Ladikou EE, Nandra TK, Chevassut T. Lymphocytosis and chronic lymphocytic leukaemia: investigation and management. *Clinical Medicine* 2022;**22**(3):225-9. http://dx.doi.org/10.7861/clinmed.2022-0150
14. Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE*, et al.* Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol* 2007;**139**(2):255-64. http://dx.doi.org/10.1111/j.1365-2141.2007.06791.x
15. Price M, Ravelo A, Sae-Hau M, Torney PA, Gonzalez V, Weiss ES*, et al.* Patient-reported disease burden in chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and follicular lymphoma: Results from a national patient advocacy survey. *Journal of Clinical Oncology* 2019;**37**(15_suppl):e18198-e. http://dx.doi.org/10.1200/JCO.2019.37.15_suppl.e18198

16. Waweru C, Kaur S, Sharma S, Mishra N. Health-related quality of life and economic burden of chronic lymphocytic leukemia in the era of novel targeted agents. *Current Medical Research and Opinion* 2020;**36**(9):1481-95. http://dx.doi.org/10.1080/03007995.2020.1784120
17. Lien PW, Jawaid D, Emechebe N, Manzoor B, Glenn B, Marx S*, et al.* EE124 Real-World Mental Health Burden in Patients With Chronic Lymphocytic Leukemia. *Value in Health* 2024;**27**(6):S80. http://dx.doi.org/10.1016/j.jval.2024.03.423
18. Schuh AH, Parry-Jones N, Appleby N, Bloor A, Dearden CE, Fegan C*, et al.* Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. *British journal of haematology* 2018;**182**(3):344-59. http://dx.doi.org/10.1111/bjh.15460
19. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H*, et al.* Guideline for the treatment of chronic lymphocytic leukaemia. *Br J Haematol* 2022;**197**(5):544-57. https://doi.org/10.1111/bjh.18075
20. NICE. *Acalabrutinib for treating chronic lymphocytic leukaemia [TA689]*. National Institute for Health and Care Excellence; 2021. URL: https://www.nice.org.uk/guidance/ta689/chapter/1-Recommendations (Accessed 06/02/2024).
21. Eichhorst B, Ghia P, Niemann C, Kater A, Gregor M, Hallek M*, et al.* ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. *Annals of Oncology* 2024;**35**(9):762-8. http://dx.doi.org/10.1016/j.annonc.2024.06.016
22. Kovacs G, Robrecht S, Fink AM, Bahlo J, Cramer P, von Tresckow J*, et al.* Minimal Residual Disease Assessment Improves Prediction of Outcome in Patients With Chronic Lymphocytic Leukemia (CLL) Who Achieve Partial Response: Comprehensive Analysis of Two Phase III Studies of the German CLL Study Group. *J Clin Oncol* 2016;**34**(31):3758-65. http://dx.doi.org/10.1200/jco.2016.67.1305
23. Böttcher S, Ritgen M, Fischer K, Stilgenbauer S, Busch RM, Fingerle-Rowson G*, et al.* Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J Clin Oncol* 2012;**30**(9):980-8. http://dx.doi.org/10.1200/jco.2011.36.9348
24. Davids MS, Lin KH, Mohamed AI, Munir T, Eyre TA. Measurable residual disease-driven treatment in first-line chronic lymphocytic leukaemia. *Br J Haematol* 2025;**206**(1):33-43. http://dx.doi.org/10.1111/bjh.19902
25. Bennett R, Seymour JF. Update on the management of relapsed/refractory chronic lymphocytic leukemia. *Blood Cancer J* 2024;**14**(1):33. http://dx.doi.org/10.1038/s41408-024-01001-1
26. Odetola O, Ma S. Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL). *Current Hematologic Malignancy Reports* 2023;**18**(5):130-43. http://dx.doi.org/10.1007/s11899-023-00700-z
27. Tam CS, Allan JN, Siddiqi T, Kipps TJ, Jacobs R, Opat S*, et al.* Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary

analysis of the CAPTIVATE FD cohort. *Blood, The Journal of the American Society of Hematology* 2022;**139**(22):3278-89. http://dx.doi.org/10.1182/blood.2021014488
28. Kater AP, Owen C, Moreno C, Follows G, Munir T, Levin M-D*, et al.* Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM evidence* 2022;**1**(7):EVIDoa2200006. http://dx.doi.org/10.1056/EVIDoa2200006
29. Jain N, Keating M, Thompson P, Ferrajoli A, Burger J, Borthakur G*, et al.* Ibrutinib and venetoclax for first-line treatment of CLL. *New England Journal of Medicine* 2019;**380**(22):2095-103.
30. BNF. *Ibrutinib [Specialist drug] - Medicinal Forms*. British National Formulary; 2024. URL: https://bnf.nice.org.uk/drugs/ibrutinib-specialist-drug/medicinal-forms/ (Accessed 3rd September 2025).
31. MHRA. *Imbruvica 280 mg film-coated tablets - Summary of Product Characteristics*. Medicines and Healthcare products Regulatory Agency; 2024. URL: https://mhraproducts4853.blob.core.windows.net/docs/efbf3894089ca5d85fafca6de6b186e0109b9176 (Accessed 17th September 2025).
32. Tang CPS, Lip GY, McCormack T, Lyon AR, Hillmen P, Iyengar S*, et al.* Management of cardiovascular complications of Bruton tyrosine kinase inhibitors. *British journal of haematology* 2022;**196**(1):70-8. http://dx.doi.org/10.1111/bjh.17788
33. NICE. *Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [TA663]*. National Institute for Health and Care Excellence; 2020. URL: https://www.nice.org.uk/guidance/ta663/chapter/3-Committee-discussion (Accessed 05/02/2024).
34. Quartermaine C, Ghazi SM, Yasin A, Awan FT, Fradley M, Wiczer T*, et al.* Cardiovascular Toxicities of BTK Inhibitors in Chronic Lymphocytic Leukemia: JACC: CardioOncology State-of-the-Art Review. *JACC: CardioOncology* 2023;**5**(5):570-90. https://doi.org/10.1016/j.jaccao.2023.09.002
35. NICE. *Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [TA891]*. National Institute for Health and Care Excellence; 2023. URL: https://www.nice.org.uk/guidance/ta891/chapter/1-Recommendations (Accessed 10/07/2025).
36. British Society for Haematology. Guideline for the treatment of chronic lymphocytic leukaemia [in review, expected 2025]. In; 2025.
37. NICE. *Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]*. National Institute for Health and Care Excellence; [expected 2026]. URL: https://www.nice.org.uk/guidance/indevelopment/gid-ta11230.
38. Greiner B, Corcoran A, Wheeler D. Clinical trial registry searches are under-utilized in systematic reviews from critical care journals: A bibliometric analysis. *Journal of Critical Care* 2021;**63**:175-8. https://doi.org/10.1016/j.jcrc.2020.09.010

39. Source Health Economics. *Improving your search strategy: date limit filters (2/2)*. 2021. URL: https://source-he.com/improving-your-search-strategy-date-limit-filters-2-2/ (Accessed 05th September 2025).
40. Fürstenau M, Kater AP, Robrecht S, von Tresckow J, Zhang C, Gregor M*, et al.* First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology* 2024;**25**(6):744-59. http://dx.doi.org/10.1016/S1470-2045(24)00196-7
41. Eichhorst B, Niemann Carsten U, Kater Arnon P, Fürstenau M, von Tresckow J, Zhang C*, et al.* First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. *New England Journal of Medicine* 2023;**388**(19):1739-54. http://dx.doi.org/10.1056/NEJMoa2213093
42. National Disease Registration Service. *Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia in people without del(17p)/TP53 mutation and for whom FCR and BR are suitable – data review*. Leeds; 2023.
43. Fürstenau M, Robrecht S, Tresckow Jv, Zhang C, Gregor M, Thornton P*, et al. THE TRIPLE COMBINATION OF VENETOCLAX-IBRUTINIB-OBINUTUZUMAB PROLONGS PROGRESSION-FREE SURVIVAL COMPARED TO VENETOCLAX-CD20-ANTIBODY COMBINATIONS AND CHEMOIMMUNOTHERAPY IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA: FINAL ANALYSIS FROM THE PHASE 3 GAIA/CLL13 TRIAL*. European Hematology Association; 2025. URL: https://library.ehaweb.org/eha/2025/eha2025-congress/4159268/moritz.frstenau.the.triple.combination.of.venetoclax-ibrutinib-obinutuzumab (Accessed 2nd October 2025).
44. University of Cologne. Trial Protocol: A Phase 3 Multicenter, Randomized, Prospective, Open-Label Trial of Standard Chemoimmunotherapy (FCR/BR) Versus Rituximab Plus Venetoclax (RVE) Versus Obinutuzumab (GA101) Plus Venetoclax (GVe) Versus Obinutuzumab (GA101) Plus Ibrutinib Plus Venetoclax (GIVe) in Fit Patients With Previously Untreated Chronic Lymphocytic Leukaemia (CLL) Without Del(17p) or TP53 Mutation. 2021.
45. Deutsche Studiengruppe. CLL13 (GAIA) Priority 1 analyses for AbbVie (Jan 2023 data cut-off) v1.0. 2023.
46. Deutsche Studiengruppe. CLL13 STATISTICAL ANALYSIS PLAN – PRIMARY ENDPOINTS ANALYSIS. 2021.
47. Deutsche Studiengruppe. CLL13 (GAIA) - Further Analyses for AbbVie NICE Submission - Subsequent Treatments. In; 2025.
48. Fürstenau M, Rotbain EC, Eurelings L, Robrecht S, von Tresckow J, Giza A*, et al.* Patient-Reported Quality of Life Outcomes with Venetoclax-Based First-Line Combinations in CLL: An Analysis from the Phase 3 GAIA/CLL13 Trial. *66th ASH annual meeting, 2024, San Diego, Publication Number: 3238* 2024;**144**(Supplement 1):3238-. http://dx.doi.org/10.1182/blood-2024-198917

49. Wierda WG, Jacobs R, Barr PM, Allan JN, Siddiqi T, Tedeschi A*, et al.* Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Up to 5.5 years of follow-up in the phase 2 CAPTIVATE study. *Journal of Clinical Oncology* 2024;**42**(16_suppl):7009-. http://dx.doi.org/10.1200/JCO.2024.42.16_suppl.7009
50. Wierda W, Barr P, Allan J, Siddiqi T, Tedeschi A, Kipps T*, et al. FINAL ANALYSIS OF FIXED-DURATION IBRUTINIB + VENETOCLAX FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL) IN THE PHASE 2 CAPTIVATE STUDY*. 2025. URL: https://library.ehaweb.org/eha/2025/eha2025-congress/4159233/paolo.ghia.final.analysis.of.fixed-duration.ibrutinib.2B.venetoclax.for.chronic.html?f (Accessed 17th September 2025).
51. Allan JN, Flinn IW, Siddiqi T, Ghia P, Tam CS, Kipps TJ*, et al.* Outcomes in Patients with High-Risk Features after Fixed-Duration Ibrutinib plus Venetoclax: Phase II CAPTIVATE Study in First-Line Chronic Lymphocytic Leukemia. *Clin Cancer Res* 2023;**29**(14):2593-601. http://dx.doi.org/10.1158/1078-0432.Ccr-22-2779
52. Wen T, Sun G, Jiang W, Steiner K, Bridge S, Liu P. Comparing the efficacy and safety of first-line treatments for chronic lymphocytic leukemia: a network meta-analysis. *J Natl Cancer Inst* 2025;**117**(2):322-34. http://dx.doi.org/10.1093/jnci/djae245
53. Hancock S, Wake B, Hyde C. *Fludarabine as first line therapy for chronic lymphocytic leukaemia. A West Midlands Health Technology Assessment Collaboration report* Department of Public Health and Epidemiology, Univeristy of Birmingham 2002. URL: https://www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2002/Fludarabine.pdf (Accessed 22nd September 2025).
54. Kosmas CE, Shingler SL, Samanta K, Wiesner C, Moss PA, Becker U*, et al.* Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. *Leukemia & lymphoma* 2015;**56**(5):1320-6. http://dx.doi.org/10.3109/10428194.2014.961012
55. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A*, et al.* Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes* 2010;**8**:50. http://dx.doi.org/10.1186/1477-7525-8-50
56. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *The European Journal of Health Economics* 2013;**14**(5):749-59. http://dx.doi.org/10.1007/s10198-012-0419-2
57. Holtzer-Goor K, Schaafsma M, Joosten P, Posthuma E, Wittebol S, Huijgens P*, et al.* Quality of life of patients with chronic lymphocytic leukaemia in the Netherlands: results of a longitudinal multicentre study. *Quality of Life*

Research 2015;**24**(12):2895-906. http://dx.doi.org/10.1007/s11136-015-1039-y
58. Shingler S, Kosmas C, Samanta K, Wiesner C, Lloyd A. Health state utilities for chronic lymphocytic leukemia. *Value in Health* 2014;**17**(3):A92.
59. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur J Haematol* 2004;**72**(6):381-9. http://dx.doi.org/10.1111/j.1600-0609.2004.00233.x
60. NICE. *Venetoclax for treating chronic lymphocytic leukaemia [TA796]*. National Institute for Health and Care Excellence; 2022. URL: https://www.nice.org.uk/guidance/ta796 (Accessed 11th September 2025).
61. NICE. *Idelalisib for treating chronic lymphocytic leukaemia*. National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ta359 (Accessed 3rd September 2025).
62. NICE. *Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia [TA193]*. National Institute for Health and Care Excellence; 2010. URL: https://www.nice.org.uk/guidance/ta193 (Accessed 16th September 2025).
63. NICE. *Rituximab for the first-line treatment of chronic lymphocytic leukaemia [TA174]*. National Institute for Health and Care Excellence; 2009. URL: https://www.nice.org.uk/guidance/ta174/chapter/1-Recommendations (Accessed 06/02/2024).
64. NICE. *Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer [TA746]*. National Institute for Health and Care Excellence; 2021. URL: https://www.nice.org.uk/guidance/ta746 (Accessed 13th September 2025).
65. MHRA. Venclyxto 10 mg film-coated tablets - Summary of Product Characteristics. 2025. https://mhraproducts4853.blob.core.windows.net/docs/7684ff182c62a99c80faac1ef82cfff0a11c988e (Accessed 3rd September 2025).
66. BNF. British National Formulary; 2025. URL: https://bnf.nice.org.uk/ (Accessed 15th September 2025).
67. NHS England. National Cost Collection Data 2023/24: National Schedule of NHS costs. 2025. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (Accessed 15th September 2025).
68. Fürstenau M, Robrecht S, Zhang C, Von Tresckow J, Niemann CU, Kater AP*, et al.* Comparison of Tumor Lysis Syndrome (TLS) Risk Reduction and Incidence in Different Venetoclax-Based Combinations within the Randomized Phase 3 GAIA (CLL13) Trial. *Blood* 2021;**138**(Supplement 1):2639. https://doi.org/10.1182/blood-2021-147790
69. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med* 2015;**29**(10):899-907. http://dx.doi.org/10.1177/0269216315595203
70. Briggs. A SM, Claxton. K,. *Decision Modelling for Health Economic Evaluation*: University of Oxford; 2006.

7. Appendices

7.1. Quality assessment of CLL13

Table 50 Comparison of company and EAG quality assessment of CLL13

-	Company assessment	EAG assessment
Was randomisation carried out appropriately?	Yes – patients were randomised 1:1:1:1 by an interactive voice and web response system (IXRS), across four treatment groups. Randomisation was stratified according to trial group, age (≤ 65 or > 65 years), and Binet stage before initiation of therapy (A, B, C) and region.	Yes - as described by company.
Was the concealment of treatment allocation adequate?	No – as is common practice in oncology trials, the study was open label as a safety measure so that prompt and accurate assessment of the unique toxicities associated with study treatments could be conducted. Investigators and patients were not masked to treatment assignments, and neither was an independent data and safety monitoring lead, nor the DSMB.	Yes – use of the IXRS. In their assessment, the company has confused concealment of treatment allocation with masking of care providers, participants and outcome assessors.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – baseline characteristics were well balanced between the treatment groups (CS Table 12).	Yes
Were the care providers, participants and outcome assessors blind to	No – the study was open label as a safety measure, which is typical for clinical trials in oncology. Blinding of investigators and patients would not have been possible due to differences	No – open label study, and no blinding of outcome assessors.

treatment allocation?	in the nature and schedules of treatments (CS Table 6).	
Were there any unexpected imbalances in dropouts between groups?	No – a similar number of patients discontinued in each treatment arm (CS Table 11).	No – as expected due to the safety profile, more people in the SCIT arm discontinued treatment early due to adverse events. Also, more people in the SCIT arm did not receive study treatment as they withdrew consent.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all trial outcomes are reported within the CSRs provided.	Partial – Overall response rate is a secondary outcome specified in the protocol, but it is not reported in the CS or the analyses document(CS ref 13), Complete and partial responses are reported however. A full CSR was not provided (clarification)
Did the analysis include an intention-to-treat analysis (ITT)? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – this was appropriate. The ITT population was used for evaluation of all efficacy endpoints. Where responses were not assessable, patients were counted as missing (CS Table 9).	Yes – ITT analysis undertaken and methods to account for missing data were appropriate.

7.2 EAG additional searches

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (MA partial review of TA663) [ID6291]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 6 October 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 MAIC scenarios

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Key Issue 2 discusses the limitations of the company's approach to the MAIC and the consideration of an alternative approach. However, the limitations of the alternative approach are not fully described, and judgements are made about the direction of bias of the alternative approach without adequate justification. The main limitation of the EAG's suggested approach is the unavailability of baseline characteristics by subgroup from CAPTIVATE; the EAG statements infer that this analysis can be done when in fact this is technically and	Proposed amendments are: **MAIC:** Page 14: '*If further MAIC analyses are not undertaken focusing on the non-complex karyotype population of CLL13, which could be compared to the equivalent population of CAPTIVATE* ***though noting that baseline characteristics are not available for this population****, then the EAG preference is to assume equal efficacy for PFS and OS of Ven+O and I+Ven*.' Page 77: '*However, on balance the EAG considers* ***the direction of bias*** *of this approach* ***to be uncertain compared*** *to* ~~***would likely be less biased than***~~ *the current analyses provided by the company*.' Page 82: '*The EAG recommend that the company implement MAIC*	To avoid potential misinterpretation, given that the main limitation of the EAG's suggested approach is the unavailability of baseline characteristics by subgroup from CAPTIVATE. The reference to the published NMA suggests that the NMA could be applicable to the decision problem, however, it is in the entirety of the front line CLL population and includes I+Ven treatment based on achieving MRD guided treatment duration (unlicensed dosage of up to 6 years of I+Ven) and not the reimbursed (and licensed) fixed treatment duration in the UK.	Page 14 (a): the EAG has added text to clarify the necessary assumption to enable a MAIC to be performed. Page 77: Not a factual error. Page 82: Not a factual error. Page 14 (b): Not a factual error. Page 83: Not a factual error.

scientifically not feasible due to a lack of baseline characteristics for the population without del17p/TP53/CK in CAPTIVATE.	*analyses which exclude people with del(17p)/TP53 mutation or complex karyotype from the CAPTIVATE data**, although this is technically not possible as baseline characteristics for I+Ven in this subgroup are not available**. This would enable a**n alternatively** ~~less~~ biased comparison with the subgroup from the CLL13 study to obtain ~~more reliable~~ **further** estimates of relative efficacy between Ven+O and I+Ven*.' **Published NMA:** Page 14: '*The EAG considers the estimates coming from the MAIC analyses to be at high risk of bias and highly uncertain. **~~They are also inconsistent with results from a published NMA which included Ven+O and I+Ven, but are for different population~~.** The EAG concludes the evidence provided does*		

	not support a difference in efficacy between Ven+O and I+Ven.' Page 83: '*The results of this NMA are not based on the same population as the MAIC* ***and therefore, cannot be used in the context of this decision problem.***~~*, but it is unclear whether this*~~ [redacted]		

Issue 2 Use of SACT to inform Ven+O survival outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG highlight their preference to use data from SACT to inform both patient characteristics and survival outcomes (for which only OS is available) for Ven+O, but do not highlight the limitations of this approach: 1. That the EAG and AbbVie only have access to summary data from SACT as opposed to the CLL13 individual patient data used by AbbVie to undertake the comparative analysis 2. That the EAG analysis comparing SACT outcomes for Ven+O with I+Ven does not account for differences in population characteristics (i.e. it is a naïve comparison).	It is proposed that the following amendments are made: Page 13: '*The company extrapolates efficacy data from CLL13**, the primary evidence source required as per exit of the managed access agreement,** which has been weighted to match the baseline characteristics of the CAPTIVATE trial*. Page 13: '*This approach does not utilise the **secondary data source of real-world evidence,** SACT data**,** which suggests mortality rates are slightly higher than those observed in the trial*.' Page 84: '*SACT data for Ven+O suggests real-world outcomes ~~are~~ **may be** slightly inferior than those observed in CLL13, **although any use of the SACT data for informing treatment effects has the limitation that population***	Omission of important contextual information, without which could lead to misinterpretation: the proposed amendments will aid in providing clarity and transparency in the interpretation of the SACT data, and highlight the conditions of the managed access agreement and the marketing authorisation Note that CLL13 was deemed generalisable to UK clinical practice by clinicians as noted by the company in the CS and as confirmed by the clinical advisors to the EAG.	Page 13 (a): not a factual error Page 13 (b): not a factual error Page 84: not a factual error Page 91: not a factual error Page 98: The EAG has removed this sentence

Whilst AbbVie is not expecting vast differences in outcomes, between SACT and CLL13, it is inaccurate to mischaracterise the SACT data as being more appropriate for informing survival for Ven+O without acknowledging that adjustments have not been made 3. SACT included some apparent VenO dosing beyond the fixed treatment duration of 12 cycles, which is not within the UK marketing authorisation, as per the EAG report on page 66, this is likely to be due to a pause in treatment. 4. Taking OS and PFS from two different sources (SACT and CLL13 respectively) is highly problematic; PFS	***characteristics have not been aligned with comparator evidence sources*****'** Page 91: '*The gender distribution of the modelled population should closely match that of the SACT cohort for the cost-effectiveness results to be generalizable to NHS patients. and this does not appear to be the case in the company's base case analysis~~,~~* ***although the company have used CLL13 which they consider generalisable to the UK population.***' Page 98: '*The EAG prefers to use estimates from the SACT data, ~~which better reflect UK use of Ven+O~~, without capping treatment costs at 12 months.* ***However, it should be noted that any use of Ven+O beyond 12 cycles is not within the marketing authorisation.***'		

and OS are inherently linked.			

Issue 3 Modelling of time to next treatment (TTNT)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 100-101: Based off section 3.5.1 of the CS, AbbVie noted that 'The change in deaths is added because any patient who progresses to PD and then dies in the same cycle would never contribute to a net rise in the PD count. By adding deaths back in, it captures those who transition from PD to death and avoids underestimating how many actually entered the PD state (i.e. it applies costs to those entering PD as a one-off cost).' This means that the model captures those who move through the PD state into	It is proposed that the following amendments are made: Page 100-101: '*The company state that ~~deaths are included in the calculation to avoid counting people who move straight to the death health state from progression-free, and so would not incur subsequent treatment costs~~* ***the change in deaths is added in the calculation because any patient who progresses to PD and then dies in the same cycle would never contribute to a net rise in the PD count, so, by adding deaths back in, it captures those who transition from PD to death and avoids underestimating how many actually entered the PD state. Therefore, when there are no patients in the PD state but are***	To ensure clarity on interpretation of AbbVie's modelling approach for TTNT and to avoid incorrectly labelling it as 'inconsistent with desired logic'. The EAG's suggested fix does not avoid the same issue it raises (costs accruing without PD occupancy).	The EAG has amended this text to better reflect the company's approach and rationale. Concerns with the company's approach remain, which are addressed by the EAG approach, which remains unchanged.

the death state within the same cycle and ensures they accrue a subsequent treatment cost to avoid underestimating the number in the PD state. However, the EAG reports that '*The company state that deaths are included in the calculation to avoid counting people who move straight to the death health state from progression-free, and so would not incur subsequent treatment costs. The EAG agrees with this principle, however when examining how this is implemented within the economic model, the EAG can see that all people in the model incur subsequent treatment costs, which is inconsistent with desired logic. For example, for the first few model cycles, there is no occupancy of the post-progression*	***patients in the dead state, patients who would have passed through PD in the same cycle they died in, and subsequent treatment costs are accounted for.*** ~~*The EAG agrees with this principle, however when examining how this is implemented within the economic model, the EAG can see that all people in the model incur subsequent treatment costs, which is inconsistent with desired logic. For example, for the first few model cycles, there is no occupancy of the post-progression health state, yet subsequent treatment costs are applied in the model for these cycles.*~~'		

health state, yet subsequent treatment costs are applied in the model for these cycles.' To clarify, AbbVie are showing that patients passing through the PD state into death would incur subsequent treatment costs, even if only for a short duration within the 28-day cycle length. The EAG attempt's to 'rectify' this by applying subsequent treatment costs based on the Ven+O TTNT curve for both Ven+O and I+Ven. However, this also results in 0 patients in PD while subsequent treatment costs still accrue. It also assumes that patients in PFS cannot be on subsequent treatment, whereas in practice, patients in PFS may also transition to subsequent treatments before			

progression. Therefore, the EAG's correction does not resolve the issue and is not necessarily more appropriate than AbbVie's approach. Furthermore, note that the terms progressed disease (PD) and post-progression survival (PPS) can be used interchangeably.			
On page 129, the EAG report states: *"The EAG noted the company's modelling of TTNT was incorrect, however it was not able to amend the company's approach."* This is misleading. The company did not model TTNT for I+Ven because no TTNT data were available in the population to match CLL13 (fit patients without 17pdel/TP53); instead, it used a progression-based	It is proposed that the following amendments are made: Page 129: '*The EAG noted that the* ***company used a progression-based method to allocate subsequent treatment costs rather than modelling TTNT directly. The EAG explored an alternative assumption by applying Ven+O TTNT to I+Ven but recognised that this may not fully reflect differences in treatment duration between regimens***.'	As stated previously, the word "incorrect" implies a modelling error; in fact, the company adopted a pragmatic approach given the lack of TTNT data for I+Ven in the relevant population. The EAG was able to test an alternative (using Ven+O TTNT), but this should not be presented as the sole "correct" method. Neutral, accurate wording avoids prejudicing the reader against the	The sentence has been deleted and the following amendment made to the preceding paragraph: "The model appears to reflect the assumptions made by the company and contained clinical aspects necessary to address the decision problem, aside from the modelling of TTNT where the EAG preferred to use an alternative approach (section **Error! Reference source not found.**)."

method , whereby subsequent treatment costs are triggered at the point of progression rather than relying on TTNT curves. This ensures that patients who progress (including those who move quickly into PD into death) are consistently allocated subsequent treatment costs across regimens. The EAG did test an alternative by applying Ven+O TTNT to I+Ven, but this is not necessarily the '*correct'* approach given the different treatment durations (12 vs 15 cycles).		company's approach and clarifies that both methods have limitations.	
There is a contradiction between pages 17 and 129, which could be the result of a typo: Page 17 suggests the EAG could amend the company's modelling of TTNT, while page 129 suggests the EAG was not	It is proposed that the following amendments are made: Page 17: *The EAG noted 'the company's modelling of TTNT ~~was incorrect~~* ***used an alternative method to the EAG****, however* ***it was able to amend*** *~~could rectify~~ the company's approach*.'	To provide clarity on EAG amendments	Page 17: The EAG has amended this text for clarity Page 129: Amended as described above.

able to amend the company's approach. Furthermore, the use of the word '*rectify*' suggests the company approach is an error rather than it being an alternate way of accounting for TTNT (see specific response on this issue above).	Page 129: *The EAG noted the company's modelling of TTNT ~~was incorrect~~* ***used an alternative method to the EAG****, however it was ~~not~~ able to amend the company's approach*.' .		

Issue 4 Errors in the reporting of model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93: The EAG states that the hazard rate for the log-logistic (preferred model) OS for Ven+O falls below that for the general population. Whilst this is true, this is simply based off the CLL13 trial data which displays the strong OS benefit that Ven+O has. It would be	It is proposed that the following amendments are made: Page 93: '*The EAG considers this implausible, as it is possible that a small number of patients have disease that is fast moving and does not respond well to treatment, meaning they will experience a higher mortality rate than the general population.* ***However, it is acknowledged that the CLL13 trial data has high OS***	To ensure company modelling approach and its rationale (i.e. high survival outcomes are capped by general population mortality) is fairly explained.	Not a factual error, however the EAG has added text to improve clarity.

inappropriate to artificially amend the data as bias and assumptions would be introduced, and therefore a cap has been applied in the company base case model to ensure CLL13 OS is not above that of the general population.	***and a general population mortality cap has been applied to correct for this.***'		
Page 18: The incremental cost under Key Issue 3 is noted as incurring £[redacted] incremental costs. We believe that this is incorrect. These analyses are presented on Page 133 as exploratory analysis 5 and are associated with -£[redacted] incremental costs.	It is proposed that the following amendments are made to update the table with the correct reporting of model outputs: Page 18: '£[redacted] - £[redacted]'	To correct reporting of incremental costs	The EAG apologies for the error. Total costs were reported instead of incremental costs. This has been amended and the correct figure of [redacted] shown
Page 18: Table 2 footer states '*These analyses produce a negative ICER in the southwest quadrant with a magnitude in excess of £1,000,000/QALY*' however as per Table 42,	It is proposed that the following amendments are made to align with the footer under Table 42: Page 18: '*Note: The absolute (unrounded figure) of incremental QALYs is 0.0035 QALYs in favour of I+Ven which results in an ICER of*	To correct reporting of ICERs and interpretation	Table 2 footnote has been amended as follows: "To two decimal places, the QALYs are identical, however the absolute (unrounded figure) of incremental QALYs is 0.0035 QALYs in favour of

the company believes this should be updated as this is incorrect	[redacted]. *The ICER can be interpreted as: for every additional QALY gained by using I+Ven compared to Ven+O, it costs* [redacted]*'* It is also proposed to add that **the higher the ICER, the more cost-effective**, to aid with interpretation.		I+Ven which results in an ICER of [redacted]. The ICER can be interpreted as: for every additional QALY gained by using I+Ven compared to Ven+O, it costs [redacted]."
Page 132-136: Incorrect reporting of incremental costs. In Table 40 the results for scenario 6 are reported as being associated with -£[redacted] incremental costs. This same scenario in Table 41 is noted as being associated with -£[redacted] incremental costs. We believe that -£[redacted] is the correct value, but please check model outputs and update them throughout. The incorrect figure is also reported in Table 2 for Key Issue 4.	It is proposed that the following amendments are made: Page 133: ~~-£[redacted]~~ **-£[redacted]** Page 18: ~~-£[redacted]~~ **-£[redacted]**	To correct reporting of model outputs	The EAG has amended this error. The correct incremental costs of [redacted] are now reported in Table 2 (for key issue 4) and Table 40 (scenario 6)

Issue 5 General factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53: This sentence should be taken out, the 6 months of treatment with SCIT is per the dosing and therefore, this cannot be biased	It is proposed that the following amendments are made: Page 53: '~~*The EAG considers there is some potential for bias in the 15-month assessment, given that SCIT treatment finished 6 months earlier than Ven+O, and so people randomised to SCIT had a longer period without active treatment*~~.'	The proposed amendment would reduce the scepticism of the MRD outcome, which is based on the dosage of the relevant interventions, and the EAG suggest that they are satisfied based on earlier MRD time assessments of 9, 12, and 15 months	The EAG acknowledges the company's clarification that the difference in treatment duration between Ven+O and SCIT reflects the intended dosing regimens. However, the EAG considers that this timing difference is relevant when interpreting the 15 month MRD assessment, as patients in the SCIT arm had completed treatment several months earlier than those in the Ven+O arm. Therefore, the EAG does not consider this to be a factual error, but acknowledges that this relates to interpretation rather than to bias in trial conduct. The EAG has amended the sentence to be as followed "*The EAG* ***notes that at*** ~~*considers*~~

			*~~there is some potential for bias in~~ the 15-month assessment, **people** given th~~**eat**~~ SCIT treatment finished 6 months earlier than Ven+O, and so people randomised to SCIT had a longer period without active treatment*."
Page 54: Priority 1 analyses and Furstenau 2024 supplementary materials both include the 5.7% discontinuation rate for VenO.[2,3] The Furstenau 2025 abstract shows this value has decreased,[5] but as this is purely a summary slide, details of calculations or rationale for this are unclear.	It is proposed that the following amendments are made: Page 54: '*Discontinuation attributable to AEs was 14.8% and 3.9% for SCIT and Ven+O, respectively, **though note this was taken from the Furstenau 2025 abstract summary slides, so it is unclear exactly what subset of patients this is taken from***.[43]'	The proposed amendment would add clarity as this could be perceived as unclear	This is not a factual error, but for clarity the EAG have made the following changes: "Discontinuation attributable to AEs was [redacted] and [redacted] for SCIT and Ven+O, respectively.[45] The EAG notes ~~an inconsistency in the these values, as a document of priority analyses provided by the company~~ a **recent abstract using the** ~~January 2023~~ **February 2024** data cut reports that **3.9**% discontinued Ven+O due to AEs and **it i**s unclear how this proportion could have decreased over time**."**

Page 71: The statement appears to confuse the data availabilities for CAPTIVATE;[6] 61-month median follow-up data for CAPTIVATE was used for the MAIC as that was the latest data cut for which Baseline characteristics were available. 68.9-month median-follow up data for the CAPTIVATE final analysis is available in abstract form, however Baseline characteristics were not available for this so this data could not be used in the MAIC	It is proposed that the following amendments are made: Page 71: '*The CS reports that median follow-up in CAPTIVATE is 61 months* ***for the data used within the ITC, which has baseline characteristics****, however in the cited reference* ***relating to the final analysis, which does not report baseline characteristics,****[50] it is reported as 68.9 months (range, 0.8–83.9) and was 61.2 months in an earlier publication*.[49]'	This is potentially misleading – the proposed amendment adds clarity to the data used within the MAIC and the data available for CAPTIVATE	This is not a factual error.
Page 156: Missing section 7.2	7.2 EAG additional searches does not include any further text – please can the EAG clarify if this section is incorrectly included or if there should be text within this section	Missing section	Added. The additional searches are reported in the Appendix 7.2.

Issue 6 Typographical and formatting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: '*but are for different population*'	Update to 'but are for **a** different population'	Typographical error	Amended
Page 19: '*acalbrutinib*'	Update to 'acal**a**brutinib'	Typographical error	Amended
Page 19: '*These prices are not used in this EAG report, but are used in the EAG confidential cPAS appendix.*' – cPAS stands for confidential PAS	Update to 'These prices are not used in this EAG report, but are used in the EAG ~~confidential~~ cPAS appendix.'	Typographical error	Amended
Page 20: '*cancer*'	Update to 'cancer**s**'	Typographical error	Amended
Page 24: '*…but is much less dependable when making individual patient assessment.*'	Update to '…but is much less dependable when making individual patient assessment**s**.'	Typographical error	Amended
Page 25: '*MRD has strongest prediction in IgVH unmutated disease which accounts for 60-70% of CLL disease. It is much less useful for IgVH mutated disease*' this includes three typographical errors	Update to 'MRD has **the** strongest prediction in ~~IgVH~~ IGHV unmutated disease which accounts for 60-70% of CLL disease. It is much less useful for ~~IgVH~~ IGHV mutated disease' to correct grammar and update to the appropriate acronym for immunoglobulin heavy-chain variable	Typographical errors	Amended

Page 30: '*Ven-O is indicated for the treatment of adult patients with previously untreated CLL*'	Update to 'Ven+O…..'	Typographical error	Amended
Page 32: '*clinical-effectiveness*'	Update to clinical effectiveness	Typographical error	Amended
Page 38: Table 5: '*(Fit patients defined…*' Table 5: includes '*Age, sex, performance status*' but SACT does not report outcomes by these subgroups Table 5: notes '*Obinutuzumab IV infusion: 12 x 28 day cycles*' which is incorrect as Obinutuzumab is not given post-cycle 6	Update to '(fit patients defined…' Please remove 'Age, sex, performance status' Update to 'Obinutuzumab IV infusion: ~~12 x 28 day cycles~~'	Typographical errors and inaccuracies	Amended
Page 45: '*practise*'	Update to practice	Typographical error	Amended
Page 46: Standard deviation of mean age for Ven+O is missing a decimal place	Mean (SD) should read '60.9 (10.0)[a]'	Typographical error	Amended
Page 48: Table 8: Missing ECOG abbreviation in table footer	Add 'ECOG, Eastern Cooperative Oncology Group;' after 'CLL-IPI,	Missed abbreviation	Amended

	International Prognostic Index for Chronic Lymphocytic Leukaemia;'		
Page 54: '*This effect appears slightly larger than the benefit for PFS (CS Figure 9), which may be explained by the toxicity associated with CIT.*'	Update to '…**S**CIT'	Typographical error	Amended
Page 54: Incorrect figure referenced in discussion of Clarification A16	Update to 'Figure 5 of Furstenau 2024.'	Typographical error	Amended
Page 55: '*…but is still indicative a higher response rate for Ven+O.*'	Update to '…but is still indicative **of** a higher response rate for Ven+O.'	Typographical error	Amended
Page 55: Questionnaire return rate at month 60 erroneously reported as 22%	Update to 12%	Typographical error	Amended
Page 58: Incorrect reference to PFS twice; '*… the probability of remaining free of PFS at…*'	Update to '… the probability of remaining progression-free at…'	Typographical error/ miscommunication	Amended
Page 61 & 62: Incorrect reference to Furstenau publication year	Update February 2024 to February 2025	Typographical error	This is not an error, as the EAG is referring to the data cut off which is February 2024 and not the publication here.

Page 61: Superfluous crosslink: 4.2.6.3	Remove 4.2.6.3 at end of first paragraph	Typographical error	Amended
Page 64: Table 12: Superfluous percentage symbol in row 2, column 2 '*(87.5%)*'	Remove %	Typographical error	Amended
Page 64: Table 12: AE of nasopharyngitis in SCIT arm reported as [redacted]	Update to [redacted]	Typographical error	The data in EAG Table 12 is from CS Table 28, where nasopharyngitis is incorrectly reported as [redacted] The EAG agrees the correct percentage is [redacted]
Page 66: Remove the repetition of the word '*could*' from '*Therefore, this could figure could…*"	Update to: 'Therefore, this ~~could~~ figure could include patients who had a pause in treatment.'	Missed redactions	Amended
Page 68: Incorrect I+Ven acronym '*The EAG notes that re-treatment with Ven-I is not available on the NHS*'	Update to 'I+Ven'	Typographical error	Amended
Page 70: the final line of the first paragraph of 3.4.3.2 suggests that the restriction of the CLL13 population to those aged ≤70 reduced the	Update final sentence of the first paragraph of 3.4.3.2 to read: This reduced the population of the Ven+O arm of CLL13 from 229 to [redacted].	Clarification	Not a factual error, but amended to include the suggested sentence for clarity.

population of CLL13 from 229 to [redacted]. AbbVie proposes indicating that this reduced the population of the Ven+O arm of CLL13 specifically.			
Page 72: Thrombocytopenia at baseline (PLC ≤ 100 x 10^9 /L) in CLL 13 Ven+O (≤70 years) missing space between 32 and (17.0)	Update to '32 (17.0)'	Typographical error	Amended
Page 74: Table 16: Response rates in subgroups at 27.9 median follow-up reported incorrectly for patients without del(17p)/mutated TP53	Update N to 136, and % (95% CI) to 56 (48 to 64)	Typographical error	This is not a factual error, the data presented is from Figure B of Tam 2022. For clarity the subheading in the table has been edited to "*27.9 median follow-up. **Complete** response rates in subgroups*[b]"
Page 74: Table 16: Footer includes mis-spelling of author name	Update 'Werida' to 'Wierda'	Typographical error	Amended
Page 74: Table 17: AEs should be grade 3-4 not ≥3 – this is misleading as implies grade 5 could be included	Update 'Grade ≥3 adverse events…' to 'Grade 3-4 adverse events'	Typographical error	This is not a factual error as adverse events are presented as ≥3 in the CAPTIVATE trial. Nevertheless, this has been

			amended to be in line with Eichhorst 2023.
Page 74: Table 17: CLL13 misspelt in header row	Update 'CLL113' to 'CLL13'	Typographical error	Amended
Page 75: Table 17: Ven+O thrombocytopenia value from Furstenau reported as 18.4%, should be 18.5%	Update to '18.5%'	Typographical error	Not an error, 18.4% is the correct figure as reported in Furstenau 2024.
Page 75: thrombocytopenia misspelt in Table 17 footer	Update to 'thrombocytopenia'	Typographical error	Amended
Page 76: inconsistency in reporting (venetoclax+ibrutinib)	Update to 'I+Ven'	Typographical error	Amended
Page 76: Reference to an anchored MAIC is incorrect	Update to 'unanchored MAIC'	Typographical error	Amended
Page 76: Reference should be 49 not 50, as AbbVie used the 61-month median follow-up data not the final analysis from CAPTIVATE due to available baseline characteristics	Update to '…in the indirect comparison and this was compared to CAPTIVATE using follow-up data reported by Wierda et al.~~50~~ **49**'	Typographical error	Amended
Page 80: ESS abbreviation not explained at first mention	Update to 'effective sample size (ESS)' Remove explanation of abbreviation	Typographical error	Amended

	from first line of 3.5.2, and replace with ESS		
Page 81: Table number missing from first sentence of section 3.5.2.	Update to 'In Table 18, the EAG…'	Typographical error	Amended
Page 91: '*which closely matches the median age for the CLL13 cohort population of 62 years (Range: 31-83)*'	AbbVie proposes that this be corrected to 'which closely matches the median age for the CLL13 Ven+O cohort population of 62 years (Range: 31-83)'	Typographical error – the median age and range is specific patients in the Ven+O arm of the CLL13 trial and not the whole patient population	Ven+O has been added to the sentence
Page 107: '*and method of reporting as noted under Table(notes)*'	AbbVie proposes that this be corrected to 'and method of reporting as noted under Table 22'	Typographical error	Amended
Page 109: '*The company's clarification response is incorporated into Table above*'	AbbVie proposes that this be corrected to 'The company's clarification response is incorporated into Table 23 below'	Typographical error	Amended
Page 112: '*TA476*'	AbbVie believes this should be TA746	Typographical error	Amended
Page 132: '*The Table reports the impact of EAG scenario analyses on incremental costs, QALYs, and ICER relative to the company's base case.*'	AbbVie proposes that this be corrected to 'Table 40 reports the impact of EAG scenario analyses on incremental costs, QALYs, and ICER relative to the company's base case.'	Typographical error	Amended

Page 139: '*and intrepret the ICER for Ven+O*'	AbbVie proposes that this be corrected to 'and interpret the ICER for Ven+O'	Typographical error	Amended
Page 140: Table number missing from first sentence of 5.2.4.	Update to 'Table 45 outlines the additional scenario analyses that the EAG has done using the EAG's preferred base case'	Typographical error	Amended

Issue 7 Incorrect confidentiality markings

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Page 50	Missing CIC marking on reporting of SACT data	Exclusions were applied to remove duplicate applications, patients who died prior to treatment initiation, and patients who did not commence therapy. In total, [redacted] Blueteq applications were submitted, which corresponds to [redacted] unique patients. After exclusions, [redacted] patients were confirmed as having started treatment and were included in the final SACT analysis cohort, representing 96% of expected records. Patients were followed up in SACT until 31 October 2022,	Not an error – the EAG has confirmation from NICE that SACT information should be in the public domain and not redacted.

		with vital status traced through the Personal Demographics Service on 13 February 2023. The median follow-up in SACT was [redacted]	
Page 51	Demographic data from SACT should be marked as confidential in the main body, as it is in the subsequent table	The baseline characteristics of the [redacted] patients included in the analysis are in Table 9. The median age at treatment initiation was [redacted] years, and [redacted] of the cohort were male. [redacted] patients were between [redacted] years and [redacted] years, and [redacted] had a performance status of [redacted] at treatment start. According to Blueteq, [redacted] of patients were considered suitable for FCR and [redacted] were suitable for BR as comparator regimens.	Not an error.

Page 42	Reference to the content of the as yet unpublished BSH guidelines should be marked as confidential	Clinical experts for the EAG reinforced that SCIT should no longer be used in practice due to its clinical inferiority, and that [redacted] with the caveat that European guidelines may still differ as they cover other countries which are limited to the treatments, they have available.	Marking has been added.
Page 65 and 66	Missing CIC marking on reporting of SACT data	Kaplan-Meier estimate of median treatment duration was [redacted] months ([redacted] days, 95% CI: [redacted] to [redacted]). At six months, [redacted] of patients remained on therapy, while by twelve months only [redacted] continued treatment, reflecting the maximum one-year duration specified in the managed access agreement. The EAG clinical experts note that [redacted] of patients continuing treatment is high, as very few patients continue over 12 months. Therefore, this ~~could~~	Not an error.

		figure could include patients who had a pause in treatment. For OS, vital status was traced on 13 February 2023, giving a median follow-up of [redacted] months ([redacted] days). Of the [redacted] patients, [redacted] deaths were observed, and [redacted] patients were censored as alive at follow-up. Median OS was not reached. Survival was very high throughout follow-up, with [redacted] of patients alive at 6 months, [redacted] at 12 months, [redacted] at 18 months, and [redacted] at 24 months (Table 14). A sensitivity analysis restricted to patients with at least six months of follow-up (n = [redacted]) showed identical conclusions, with survival estimates closely aligned to those of the full cohort.	
Page 66	Missing CIC marking on reporting of SACT data	(Table 14; n=[redacted]) [redacted]	Not an error.

		[redacted]	
Page 95-96	Figure 9-10 and Table 20 should be marked as confidential	Figure 9-10 and Table 20 should be marked as confidential	Not an error.
Pages 98, 100	The cohort size from the SACT report should be redacted as this information is not published. Similarly, TOT data should be redacted	(Figure 11; n=[redacted]) (October 2022; n=[redacted]) [redacted] [redacted]	Not an error.
Page 132: Table 40	The baseline age from the SACT report should be redacted as this information is not published	Baseline starting age of [redacted] years based on SACT data	Not an error.
Page 144/145: Table 48	The baseline age and gender distribution are taken from the SACT report should be redacted as this information is not published	[redacted] [redacted]	Not an error.

References

1. László T, Kotmayer L, Fésüs V, et al. Low-burden TP53 mutations represent frequent genetic events in CLL with an increased risk for treatment initiation. The Journal of Pathology: Clinical Research. 2024;10(1):e351.
2. Deutsche Studiengruppe. CLL13 (GAIA) Priority 1 analyses for AbbVie (Jan 2023 data cut-off) v1.0. 2023.

3. Fürstenau M, Kater AP, Robrecht S, et al. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2024;25(6):744-59.
4. Eichhorst B, Niemann Carsten U, Kater Arnon P, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2023;388(19):1739-54.
5. Fürstenau M, Robrecht S, Tresckow Jv, et al. THE TRIPLE COMBINATION OF VENETOCLAX-IBRUTINIB-OBINUTUZUMAB PROLONGS PROGRESSION-FREE SURVIVAL COMPARED TO VENETOCLAX-CD20-ANTIBODY COMBINATIONS AND CHEMOIMMUNOTHERAPY IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA: FINAL ANALYSIS FROM THE PHASE 3 GAIA/CLL13 TRIAL. 2025. Available at: https://library.ehaweb.org/eha/2025/eha2025-congress/4159268/moritz.frstenau.the.triple.combination.of.venetoclax-ibrutinib-obinutuzumab [Accessed 05/06/2025].
6. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood, The Journal of the American Society of Hematology. 2022;139(22):3278-89.
7. Wierda W, Barr P, Allan J, et al. FINAL ANALYSIS OF FIXED-DURATION IBRUTINIB + VENETOCLAX FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL) IN THE PHASE 2 CAPTIVATE STUDY. 2025; Updated 09/07/2025. Available from: https://library.ehaweb.org/eha/2025/eha2025-congress/4159233/paolo.ghia.final.analysis.of.fixed-duration.ibrutinib.2B.venetoclax.for.chronic.html?f= [accessed 17th September 2025].