

Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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 AstraZeneca UK Ltd:**
 - a. Full submission
 - b. Managed access proposal
 - c. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. Joint Submission: LC, BCUK, LUK, CLL, & LA
 - b. Joint submission: UKCLLF & BSH*
- 4. Expert personal perspectives from:**
 - a. Dr Nicolas Martinez-Calle, consultant haematologist – clinical expert, nominated by AstraZeneca UK
 - b. Dr Helen Marr, consultant haematologist – clinical expert, nominated by UK CLL Forum (see item 3b*)
 - c. Mr Hugh Pender – patient expert, nominated by Leukaemia UK
 - d. Ms Jackie Martin – patient expert, nominated by CLL Support
- 5. SACT report**
- 6. External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science
 - a. EAG addendum
- 7. External Assessment Report – factual accuracy check**
- 8. Managed access feasibility assessment**

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

Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia

ID6232

Company evidence submission

September 2025

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Abbreviations

Abbreviation	Definition
2L	Second line
A	Acalabrutinib
ACD	Appraisal Consultation Document
AE	Adverse event
AIC	Akaike information criterion
ANC	Absolute neutrophil count
AO	Acalabrutinib with obinutuzumab
AV	Acalabrutinib with venetoclax
AVO	Acalabrutinib with venetoclax and obinutuzumab
BCL2	B-cell lymphoma 2
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BR	Bendamustine with rituximab
BSA	Body surface area
BSH	British Society for Haematology
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CC	Complication and Comorbidity
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CLL	Chronic lymphocytic leukaemia
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CR	Complete response
CRi	Complete response with incomplete marrow recovery
CSR	Clinical study report
CT	Computed tomography
CX	Cycle X
DCO	Data cut-off
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DX	Day X
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
PS	Performance Status
eCRF	Electronic case report form

EDC	Electronic data capture
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic Medicines Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
FCR	Fludarabine with cyclophosphamide and rituximab
FIS	Fatigue impact score
FSS	Fatigue symptom score
GFS	Global fatigue scale
GP	General practitioner
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgHV	Immunoglobulin heavy-chain variable region
IL27	Item Library 27
Incr	Incremental
INHB	Incremental net health benefit
IPD	Individual patient data
IQR	Interquartile range
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVO	Ibrutinib with venetoclax and obinutuzumab
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
Max	Maximum
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
Min	Minimum
MMRM	Mixed-model repeated measures
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NHB	Net health benefit

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nPR	Nodular partial response
NR	Not reported
OC1b	Obinutuzumab with chlorambucil
ORR	Overall response rate
OS	Overall survival
P25	25th percentile
P75	75th percentile
PAS	Patient access scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PO	Oral administration
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial
RDI	Relative dose intensity
REML	Restricted maximum likelihood
RMST	Restricted mean survival time
SAE	Serious adverse event
SC	Steering committee
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STC	Simulated treatment comparison
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
TLS	Tumour lysis syndrome
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTP	Time to progression
UK	United Kingdom
uMRD	Undetectable minimal residual disease

US	United States
V	Venetoclax
VAS	Visual analogue scale
VenI	Venetoclax with ibrutinib
VenO	Venetoclax with obinutuzumab
WHO	World Health Organization
WTP	Willingness-to-pay

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

1.1 Decision problem

The marketing authorisation extension for acalabrutinib relevant to this submission is: acalabrutinib in combination with venetoclax, with or without obinutuzumab, is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).¹

AstraZeneca is seeking reimbursement in this new indication for acalabrutinib plus venetoclax (AV) only. This is based on the feasibility of demonstrating cost-effectiveness as well as feedback from UK clinical experts who indicated that treatment with AV would be preferred over acalabrutinib with venetoclax and obinutuzumab (AVO) in the majority of patients, as the efficacy benefit associated with the addition of obinutuzumab does not outweigh the associated adverse event (AE) burden. AVO is therefore not considered for reimbursement in this submission and is not discussed further.

The target population for AV in this submission focuses on part of the technology's marketing authorisation extension and comprises adults with untreated CLL *without a 17p deletion (del[17p]) or TP53 mutations*. This aligns with the population included in the pivotal clinical trial for AV in this indication (the AMPLIFY trial; NCT03836261).^{2,3} Hereafter, the target population is referred to as patients with untreated *non-high risk* CLL.

An overview of the decision problem addressed in this submission is presented 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 CLL.	Adult patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation.	The target population in this submission is adult patients with untreated CLL <i>without a del(17p) or TP53 mutation</i> . This aligns with the population included in the pivotal clinical trial for AV in this indication (the AMPLIFY trial) and is referred to in this submission as untreated <i>non-high risk</i> CLL. ^{2,3}
Intervention	Acalabrutinib and venetoclax with/without obinutuzumab	AV	The AMPLIFY trial provides efficacy and safety data for AV and AVO in patients with untreated non-high risk CLL. ³ However, AstraZeneca is seeking reimbursement in this new indication for AV only. This is based on the feasibility of demonstrating cost-effectiveness. Additionally, UK clinical experts indicated that treatment with AV would be preferred over AVO in the majority of patients as the efficacy benefit associated with the addition of obinutuzumab does not outweigh the associated AE burden.
Comparator(s)	1. For adults with untreated CLL where mutation is not specified: - Venetoclax with ibrutinib (VenI) (TA891)⁴ - Obinutuzumab with chlorambucil (OC Ib; for adults who have comorbidities that make full-dose fludarabine-based therapy unsuitable, and only if bendamustine-based therapy is not suitable) (TA343)⁵ - Bendamustine (for whom fludarabine combination chemotherapy is not	For adult patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation: - VenI - VenO	As outlined above, the target population for AV in this submission is patients with untreated CLL without a del(17p) or <i>TP53</i> mutation. As such, only treatments included under subheading 2 in the NICE final scope represent possible relevant comparators to AV. In addition, based on treatment guidelines and feedback from UK clinical experts, VenI is used in patients without a del(17p) or <i>TP53</i> mutation and is therefore also a relevant comparator to AV in this submission. ¹⁵

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	appropriate) (TA216)⁶ - Fludarabine with cyclophosphamide and rituximab (FCR) (TA174)⁷ - Bendamustine with rituximab (BR) - Acalabrutinib with obinutuzumab (AO) 2. For adults with untreated CLL without a 17p deletion or TP53 mutation only: - Zanubrutinib (for whom FCR or BR is unsuitable) (TA931)⁸ - Acalabrutinib (if FCR or BR is unsuitable) (TA689)⁹ - Venetoclax with obinutuzumab (VenO; if FCR or BR is unsuitable) (TA663)¹⁰ - VenO (if FCR or BR is suitable) (ID6291);¹¹ subject to NICE evaluation 3. For adults with untreated CLL with a 17p deletion or TP53 mutation only: - Zanubrutinib (TA931)⁸ - Acalabrutinib (TA689)⁹ - VenO (TA663)¹⁰ - Idelalisib with rituximab (TA359)¹² - Venetoclax (if a B-cell receptor pathway inhibitor is unsuitable) (TA796)¹³ - Ibrutinib (if chemoimmunotherapy is unsuitable) (TA429)¹⁴		Discussion of treatments included within the NICE final scope that are not considered comparators is provided below: Treat-to-progression therapies The NICE final scope does not reflect the importance of different dosing regimens, namely fixed-duration or treat-to-progression. In non-high risk CLL, fixed-duration therapies are generally used in younger, fitter patients, whereas treat-to-progression therapies are favoured in older, less-fit patients. This was confirmed by UK clinical experts interviewed by AstraZeneca, highlighted in the NICE evaluation of zanubrutinib in CLL (TA931), and is expected to be reflected in the upcoming update to the British Society for Haematology (BSH) CLL treatment guidelines.^{8, 15} Feedback from UK clinical experts interviewed between April and July 2025 indicated that the introduction of AV, which is a fixed-duration therapy, is not expected to affect treatment choice in patients for whom treat-to-progression therapies (i.e., acalabrutinib monotherapy [TA689] and zanubrutinib monotherapy [TA931]) are deemed more suitable.^{8, 9, 15} As outlined and accepted by the Committee in TA931, the decision of whether to use a treat-to-progression or fixed-duration therapy will be unchanged by the introduction of a new therapy, such as AV.⁸

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			As such, the treat-to-progression therapies included in the NICE final scope under subheading 2 (i.e., acalabrutinib monotherapy and zanubrutinib monotherapy) are not relevant comparators to AV in this indication. Treatments not used in clinical practice In addition to the treat-to-progression therapies listed above, the following therapies should not be included as comparators within any subgroups, for the reasons detailed below: • OClb is rarely used in UK clinical practice since the introduction of targeted therapies (i.e., acalabrutinib monotherapy, zanubrutinib monotherapy, Venl and VenO). This was confirmed by UK clinical experts.¹⁵ • For the same reason, bendamustine monotherapy is not used in UK clinical practice for untreated CLL. Bendamustine monotherapy was also not considered a relevant comparator in the recent NICE evaluations of CLL therapies in FCR/BR unsuitable patients (e.g., VenO, Venl and zanubrutinib monotherapy).^{4, 8, 10} • Whilst FCR/BR represent treatment options for patients without a del(17p) or TP53 mutation, feedback from UK clinical experts indicated that FCR/BR are rarely used in UK clinical practice.¹⁵ In addition, this feedback highlighted that FCR/BR are expected to be

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			excluded from the upcoming update to the BSH CLL treatment guidelines.¹⁵ Finally, AO has not been evaluated or recommended by NICE in this indication and so is not available or used in National Health Service (NHS) clinical practice. In summary, the relevant comparators to AV in this submission are VenO and VenI.
Outcomes	The outcome measures to be considered include: - Overall survival (OS) - Progression-free survival (PFS) - Minimal residual disease (MRD) levels - Event-free survival (EFS) - Overall response rate (ORR) and complete response (CR) rate - Time to treatment failure - Duration of response (DOR) - Time to next treatment (TTNT) - AEs of treatment - Infection free survival - Health-related quality of life (HRQoL)	The outcome measures included in this submission are: - OS - PFS - MRD levels - EFS - ORR and CR rate - Time to treatment failure - DOR - TTNT - AEs of treatment - HRQoL	Infection-free survival is not a standard outcome measure in CLL and was not collected in the AMPLIFY trial. In addition, data on infection-free survival are unlikely to be publicly available for the relevant comparators. As such, infection-free survival outcomes specifically have not been included in this submission. Data on infections as AEs have been collected as part of the safety outcomes. Time to treatment failure was also not collected as part of the AMPLIFY trial, and as such, is not presented in this submission.
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. - The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies	As per the NICE final scope.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	being compared. - Costs will be considered from an NHS and Personal Social Services (PSS) perspective. - The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. - The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If evidence allows the following subgroups will be considered: - People with and without a 17p deletion or TP53 mutation - According to immunoglobulin heavy chain variable region gene (<i>IgHV</i>) mutation status (mutated or unmutated) - People with complex or high-complex karyotype (those with more than 3 or more than 5 chromosomal aberrations respectively)	No economic subgroup analyses have been conducted for this submission. Clinical effectiveness data by <i>IgHV</i> mutational status (mutated or unmutated) and complex karyotype status are presented where available.	As the target population for AV is adults with untreated CLL without a del(17p) or <i>TP53</i> mutation, the presence or absence of a del(17p) or <i>TP53</i> mutation is not a relevant subgroup to this submission. Clinical effectiveness subgroup analyses by <i>IgHV</i> mutation and complex karyotype, status from AMPLIFY are presented in Section 2.8 for PFS and Appendix C for OS. Economic subgroup analyses in these subgroups have not been conducted due to the lack of comparator data by <i>IgHV</i> mutation or complex karyotype status.

Abbreviations: AE: adverse event; AO: acalabrutinib with obinutuzumab; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; CR: complete response; DOR: duration of response; EFS: event-free survival; FCR: fludarabine with cyclophosphamide and rituximab; HRQoL: health-related quality of life; *IgHV*: immunoglobulin heavy chain variable region gene; MRD: minimal residual disease; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OClb: obinutuzumab with chlorambucil; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment; UK: United Kingdom; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

1.1 Description of the technology being evaluated

A summary of the technology being appraised in this submission is provided in Table 2. The summary of product characteristics (SmPC) can be found in Appendix A.¹

Table 2: Technology being evaluated

UK approved name and brand name	Acalabrutinib (Calquence®) with venetoclax (Venclyxto®), which is referred to in this submission as AV.
Mechanism of action	Acalabrutinib is a second generation, highly selective, covalent bruton tyrosine kinase inhibitor (BTKi). BTK is an important component of the signalling pathway which promotes the survival and proliferation of B-lymphocytes. It is normally upregulated in CLL cells and has been implicated in CLL tumour formation.¹⁶ Acalabrutinib binds to the Cys481 residue of BTK, effectively blocking the survival and proliferation of CLL cells, thus limiting cancer progression.^{17, 18} Venetoclax is a BH3-mimetic BCL2 inhibitor. BCL2, which is a protein involved in blocking cell death (apoptosis), is inhibited by the binding of BH3.¹⁹ By mimicking the structure of BH3, venetoclax can bind to BCL2 and block its anti-apoptotic activity, thus promoting cell death in apoptotic-resistant CLL cells.²⁰ As AV is a combination of acalabrutinib and venetoclax, it acts through two distinctive and complementary mechanisms, therefore targeting both dividing and resting CLL cells. This is achieved by simultaneously blocking CLL proliferation through acalabrutinib-induced BTK inhibition and promoting cell death through venetoclax-induced BCL2 inhibition. Furthermore, this combination of drug classes has been shown to act synergistically, as acalabrutinib increases the susceptibility of CLL cells to death through venetoclax-induced BCL-2 inhibition. This synergy subsequently allows AV to eradicate as many CLL cells as possible, to achieve the deepest possible response.^{21, 22}
Indications and any restriction(s) as described in the SmPC	Acalabrutinib holds an existing marketing authorisation in the following indications:¹ • As monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL. • As monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy. Venetoclax holds an existing marketing authorisation in the following indications:²³ • In combination with obinutuzumab or ibrutinib for the treatment of adult patients with previously untreated CLL. • In combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy. • As monotherapy for the treatment of CLL: ○ In the presence of 17p deletion or <i>TP53</i> mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor. ○ In the absence of 17p deletion or <i>TP53</i> mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. • In combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy.

Marketing authorisation/CE mark status	The marketing authorisation extension for acalabrutinib relevant to this submission is as follows: Acalabrutinib in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).¹ A marketing authorisation extension application for the above update was submitted to the European Medicines Agency (EMA) in October 2024. On 25th April 2025, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion of the marketing authorisation extension for acalabrutinib in this indication,²⁴ and European Union (EU) regulatory approval was granted as of 6th June 2025.²⁵ Submission to the Medicines and Healthcare products Regulatory Agency (MHRA) was made [REDACTED], and UK regulatory approval was granted on 27th August 2025.
Method of administration and dosage	Acalabrutinib is available as 100 mg film-coated tablets. The expected recommended dose for acalabrutinib in the indication relevant to this submission is 100 mg taken orally twice daily. Patients are expected to receive treatment in 28-day treatment cycles for a total of 14 cycles.¹ Venetoclax is available as 10 mg, 50 mg and 100 mg film-coated tablets.²³ For the indication of relevance to this submission, patients are expected to receive treatment in 28-day treatment cycles.¹ The expected recommended dose for venetoclax is 20 mg taken orally once daily starting on Day 1 of Cycle 3, with a 5-week ramp-up to reach a target dose of 400 mg by Day 1 of Cycle 4.¹
Additional tests or investigations	Testing for <i>TP53</i> aberrations (including del[17p] and <i>TP53</i> mutations) prior to each line of treatment for patients with CLL is already recommended by the BSH and conducted in UK clinical practice.²⁶ As such, the prescribing of AV in this indication will not require any <i>additional</i> tests or investigations to be conducted.
List price and average cost of a course of treatment	The list price of acalabrutinib is as follows:²⁷ 60-tablet pack (100 mg): £5,059.00 The list price of venetoclax is as follows:²⁸ 14-tablet pack (10 mg): £59.87 7-tablet pack (50 mg): £149.67 7-tablet pack (100 mg): £299.34 14-tablet pack (100 mg): £598.68 112-tablet pack (100 mg): £4,789.47
Patient access scheme (PAS; if applicable)	This submission includes the existing confidential simple PAS for acalabrutinib, representing a discount to the list price of [REDACTED]. The resulting price of a 60-tablet pack (100 mg) of acalabrutinib with PAS is [REDACTED]

Abbreviations: AV: acalabrutinib with venetoclax; BCL2: B-cell lymphoma 2; BSH: British Society of Haematology; BTKi: bruton tyrosine kinase inhibitor; CHMP: Committee for Medicinal Products for Human Use; CLL: chronic lymphocytic leukaemia; EMA: European Medicines Agency; EU: European Union; MHRA: Medicines and Healthcare products Regulatory Agency; PAS: patient access scheme; SmPC: summary of product characteristics; UK: United Kingdom.

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

CLL is a slow progressing, highly heterogeneous form of leukaemia, with a disease burden that can greatly impair patients' physical, mental and emotional well-being.

- CLL is a chronic form of leukaemia, characterised by the clonal proliferation and accumulation of mature B-lymphocytes in the blood, bone marrow, lymph nodes and spleen.²⁹ Approximately 4,500 new cases of CLL are diagnosed each year in the UK, making it one of the most common types of leukaemia in the UK.³⁰
- The disease course for CLL is highly heterogeneous, with several molecular and genetic factors, such as aberrations in the *TP53* gene, contributing to poor disease prognosis.³¹ The clinical manifestations of CLL greatly compromise patients' HRQoL, with several studies reporting a reduced HRQoL for patients with CLL versus healthy controls.^{32, 33}

Treatment choice for patients with untreated non-high risk CLL is informed by a broad concept of patient fitness, within which patient suitability for fixed-duration or treat-to-progression therapies is an important determining factor.

- Historically, treatment choice for patients with untreated non-high risk CLL was determined by their ability to tolerate FCR/BR treatment. However, with the introduction of newer and better tolerated targeted therapies, FCR/BR are no longer routinely used and, as a result, suitability for FCR/BR is no longer as relevant for classifying patients in UK clinical practice.¹⁵ Instead, treatment options are informed by a broader concept of patient fitness, determined by several factors such as age and relevant comorbidities.¹⁵
- Currently available therapies for patients with untreated non-high risk CLL are categorised according to their dosing regimen into fixed-duration and treat-to-progression therapies and suitability for either regimen is an additional key driver of treatment choice.¹⁵
- UK clinical experts have indicated that fixed-duration therapies are generally considered more suitable for younger, fitter patients, whereas treat-to-progression therapies are more commonly used in older, less-fit patients.^{8, 15}

The comparators to AV in this submission are VenI and VenO.

- Current fixed-duration therapies recommended for reimbursement by NICE in untreated non-high risk CLL include VenO (TA663),¹⁰ VenI (TA891),⁴ OC1b (TA343),⁵ FCR (TA174)⁷ and BR (TA216).⁶
 - Given the recent availability of better tolerated, targeted fixed-duration therapies (i.e., VenI and VenO), the use of chemoimmunotherapy (OC1b and FCR/BR) is no longer considered standard clinical practice.¹⁵ Indeed, UK clinical experts anticipate chemoimmunotherapy to be removed from the upcoming update to the BSH CLL treatment guidelines.^{15, 34}
- NICE-recommended treat-to-progression therapies for untreated CLL include acalabrutinib monotherapy (TA689) and zanubrutinib monotherapy (TA931).^{8, 9}
 - Since fixed-duration and treat-to-progression therapies are generally used in separate patient populations, the introduction of AV is not expected to affect treatment choice in patients for whom treat-to-progression therapies are deemed more suitable.¹⁵ This was similarly outlined and accepted by the Committee in the NICE evaluation of zanubrutinib monotherapy in CLL (TA931).⁸
- As a result, the only relevant comparator therapies to AV in this submission are VenI and

VenO.

There is an unmet need for an effective, convenient and well-tolerated fixed-duration treatment option for patients with untreated non-high risk CLL.

- The current mainstay fixed-duration therapies for untreated non-high risk CLL (i.e., VenO and VenI) are poorly tolerated by some patients.^{35, 36}
 - Ibrutinib, a first-generation BTKi, is associated with challenging AEs, notably cardiac events, that occur more frequently than with second-generation BTKi therapies.^{36, 37} VenI treatment is therefore typically unsuitable for patients with cardiac comorbidities.¹⁵
 - Similarly, UK clinical experts noted that obinutuzumab is associated with tolerability issues, mainly infection risk, as well as infusion-related reactions, as it is administered via intravenous (IV) injection.¹⁵

AV represents a valuable treatment option, offering an effective, convenient and well-tolerated alternative to VenI and VenO for patients with untreated non-high risk CLL.

- As a second-generation, highly-selective BTKi, acalabrutinib has a more favourable tolerability profile compared with ibrutinib,^{38, 39} and UK clinical experts indicated that AV is expected to have an improved tolerability profile compared with both VenI and VenO.¹⁵
- As an all-oral fixed-duration combination therapy, AV reduces the administration burden on the NHS and on patients compared with IV-oral combination therapies such as VenO, and minimises the potential risk of infusion-related reactions.⁴⁰

1.2.1 Disease overview

CLL is one of the most common types of leukaemia diagnosed in adults in the UK, accounting for 38% of all leukaemia cases.⁴¹ It is a slow-progressing cancer that is characterised by the abnormal clonal proliferation and accumulation of mature and typically CD5-positive B-lymphocytes within the hematopoietic system (i.e., the blood, bone marrow, lymph nodes and spleen).²⁹

Clinical presentation, diagnosis and staging

Most patients with CLL (~70–80%) do not exhibit any symptoms at presentation, with CLL often diagnosed incidentally during routine blood tests.^{42, 43} Clinical guidelines published by the International Workshop on CLL (iwCLL), the BSH and the European Society for Medical Oncology (ESMO) indicate that a diagnosis of CLL should be based on a concentration of $\geq 5 \times 10^9/L$ monoclonal B-lymphocytes in the peripheral blood sustained for a period of at least three months.^{26, 31, 44} To confirm B-lymphocyte monoclonality, flow cytometry can be used to demonstrate the lack of heterogeneity in B-lymphocyte origin.³¹

There are two systems typically used for CLL disease staging in clinical practice: the Binet system, mostly used in the UK and Europe, and the Rai classification system, mostly used in the US.⁴⁵ The Binet system uses an ordinal scale to classify CLL stage as either being Stage A, Stage B or Stage C, depending on the presence of anaemia or thrombocytopenia and the degree of lymphatic tissue involvement.⁴⁶ The Rai staging system classifies CLL as being low-risk (Stage 0), intermediate-risk (Stage I and II) or high-risk (Stage III and IV). Low-risk disease is defined as the presence of lymphocytosis (i.e., an increase in the concentration of lymphocytes) in the peripheral blood or the bone marrow, while intermediate-risk disease is defined as the presence of peripheral blood lymphocytosis, enlarged lymph nodes, hepatomegaly (i.e., enlarged liver) or

splenomegaly (i.e., enlarged spleen). High-risk disease is characterised by the presence of disease-related anaemia or thrombocytopenia.⁴⁷

Molecular and genetic prognostic factors

In CLL, several genetic mutations, alterations and biomarkers are known to impact disease prognosis. These cytogenetic factors, in part, drive the highly heterogeneous disease course of CLL. For example, patients with aberrations to the *TP53* gene are known to have a poor disease prognosis, in particular shorter survival, when compared with patients without.²⁹ Aberrations to the *TP53* gene, which encodes a protein that suppresses tumour formation, comprise the deletion of chromosome 17p (del[17p]) or mutations to the gene, and their presence is used to define high-risk CLL.²⁹ Patients carrying either of these aberrations have been shown to have shorter survival than patients who do not.⁴⁸ As noted in Section 1.1, the patient population of interest in this submission is the non-high risk population of patients with untreated CLL who do not carry these genetic alterations.

Other disease prognostic factors include del(11q), unmutated *IgHV*, a complex or high-complex karyotype (defined as those with three or more, or five or more chromosomal mutations, respectively) and increased beta-2 microglobulin concentration, all of which are associated with poor disease prognosis and shorter patient survival.^{15, 34}

Epidemiology

In the UK, CLL accounts for one in four cases of all leukaemia diagnoses,⁴⁹ making it the most common leukaemia in adults.⁴¹ Data from Cancer Research UK indicate that, on average, there are close to 4,500 new cases of CLL diagnosed each year in the UK, with the median age at diagnosis reported to be 71.8 years.^{30, 50} CLL is more common in males than females, and in individuals aged 75 and above, with 4 in 10 new cases belonging to this age group.³⁰

CLL generally progresses slowly and can be controlled with treatment; the five-year relative survival rate from diagnosis ranges from 95% for patients under 60 years, to 69% for those above 80 years.⁵¹

1.2.2 Disease burden

Clinical burden

Due to its slow-progressing nature, most patients with CLL do not show any symptoms at the time of diagnosis.⁴² In active disease, patients may experience typical 'B symptoms', which include unintentional weight loss, fever and night sweats.³¹ Additionally, patients may develop anaemia or thrombocytopenia driven by progressive marrow failure, as well as splenomegaly and lymphadenopathy (i.e., enlarged lymph nodes).³¹

Patients with active CLL may also experience significant fatigue, making them unable to work or perform usual activities.³¹ As a result of impaired B-cell function, CLL can also leave patients more susceptible to infections, with infection in CLL being associated with a high mortality rate.⁵² In the NICE evaluation for VenO in untreated CLL (TA663), patient advocacy groups noted that the most common CLL symptoms reported at diagnosis are fatigue (43%), swollen lymph nodes (32%) and fever or night sweats (27%).¹⁰ In addition, they highlighted the high infection risk associated with CLL, which can greatly compromise patient HRQoL and is the leading cause of death for CLL patients.¹⁰

As highlighted by UK clinical experts interviewed by AstraZeneca, current fixed-duration therapies for CLL, VenO and VenI, are associated with challenging toxicity profiles, which may lead to treatment discontinuation.¹⁵ For example, a key tolerability concern related to ibrutinib treatment is cardiac events. In the phase III GLOW trial, which assessed the efficacy and safety of VenI in older patients with untreated CLL, 8/106 patients (7.5%) in the VenI arm experienced grade ≥ 3 hypertension events. Additionally, 7/106 (6.6%) patients in the VenI arm experienced grade ≥ 3 atrial fibrillation events, likely attributable to ibrutinib treatment. In the OC1b arm, the corresponding rates of grade ≥ 3 hypertension events and grade ≥ 3 atrial fibrillation events were 1.9% and 0%, respectively.³⁷ Cardiac events were the leading cause of treatment-emergent death in patients receiving VenI in the trial, with four out of seven treatment-emergent deaths in the VenI arm being attributable to cardiac or sudden events.³⁷ In a separate analysis of 308 CLL patients across several clinical trials that included treatment with ibrutinib, over half of ibrutinib discontinuations were attributed to treatment-related AEs.⁵³ Moreover, in a real-world analysis of patients with CLL who discontinued ibrutinib, compared with those who did not, the rate of AEs was higher in the former group, with treatment-emergent cardiac events being one of the most common AEs.⁵⁴ Taken together, these studies highlight the cardiac-related tolerability concerns associated with ibrutinib.

Obinutuzumab is similarly associated with tolerability concerns due to its IV administration route, which puts patients at risk of infusion-related reactions, as well as infections. In the CLL14 trial, the key clinical trial that assessed the safety and efficacy of VenO in patients with untreated CLL, 95/212 patients (44.8%) experienced infusion-related reactions in the VenO arm.⁵⁵ Similarly, in patients receiving VenO in the CLL13 trial, which compared the safety and efficacy of several venetoclax-based combination therapies, grade 1/2 infusion-related reactions were reported in 91/228 patients (39.9%), while grade 3 infusion-related reactions were reported in 26/228 patients (11.4%).⁵⁶ Furthermore, in the CLL11 clinical trial, which compared the safety and efficacy of OC1b, chlorambucil with rituximab, and chlorambucil monotherapy in patients with untreated CLL, 121/336 patients (36%) in the OC1b arm had to interrupt or delay treatment due to infusion-related reactions, while 26/336 patients (8%) had to be hospitalised.⁵⁷ As a result, infusion-related reactions associated with obinutuzumab exacerbate the disease burden for patients and the resource burden for the NHS. UK clinical experts also noted that infection risk is another key consideration related to obinutuzumab treatment in patients with CLL.¹⁵ Infection was the leading cause of death in the CLL14 trial in patients receiving VenO, with eight out of 16 deaths being due to infection.⁵⁵

In addition to the AEs associated with treatment, patients receiving VenO experience an additional burden associated with treatment administration, as the IV administration of obinutuzumab necessitates regular hospital visits. CLL charity trustees and patients participating in an advisory board conducted as part of the NICE evaluation for VenI in 2022 (TA891) noted that “it’s inconvenient to go to hospital, to drive there and pay for parking... not having these trips to hospital is just easier on the mind”.⁴ Similarly, UK clinical experts highlighted the importance of an all-oral regimen to patients with CLL to help with the convenience of treatment administration.¹⁵

Impact on quality of life

Despite the slow-progressing nature of CLL, the disease greatly compromises patients’ HRQoL, affecting their physical, mental and emotional well-being. In one study, which used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) to assess HRQoL, patients with CLL had lower scores across all domains

compared with healthy controls.³² Patients typically reported that symptoms including fatigue, nausea, vomiting, constipation and dyspnoea had a sizeable effect on their HRQoL.³² A separate study, which used a modified version of the EuroQoL five dimensions (EQ-5D) scale, reported a similar deterioration in HRQoL in patients with CLL compared with healthy controls.³³ The compounding impact of disease-related symptoms, the AEs of treatment and the comorbidities patients often suffer from, means CLL can also have a greater impact on HRQoL when compared with other cancers. In a study comparing patients with CLL to those with other cancers, CLL was associated with significantly worse emotional well-being ($p < 0.001$), as measured by the Functional Assessment of Cancer Therapy – General (FACT-G) scale.⁵⁸

Several studies have also highlighted the anxiety that patients with CLL experience, primarily due to the incurable, relapsing-remitting nature of the disease.³³ Of note, one study which mostly included untreated patients, likely indicative of absent disease progression, reported a significantly lower emotional well-being FACT-G score for patients with CLL, compared with healthy controls.⁵⁹ This suggests that even in patients without active disease, CLL can greatly impact HRQoL through a deterioration in emotional well-being, especially as many patients without active disease are on 'Watch and Wait' (i.e., not receiving treatment until disease progression; see Section 1.2.3). It is estimated that there are currently 13,300 patients with CLL in the UK who are on 'Watch and Wait'.⁶⁰ Among these patients, one in two reported experiencing anxiety, while one in ten reported a constant feeling of depression.⁶⁰ Furthermore, during the NICE Appraisal Committee Meeting for TA429 (ibrutinib monotherapy for previously treated and untreated CLL with a del[17p] or TP53 mutation), patient experts described how uncertainty associated with living with CLL greatly affects patients' quality of life, as they become isolated from family and friends to protect themselves from infection.¹⁴ This prevents patients from living a normal life, reduces their contribution to society and may even shorten their life expectancy.¹⁴

Economic burden

CLL is associated with a significant economic burden both directly, for example through the cost of treatment and hospitalisations, and indirectly, through the loss of output and productivity. In a UK retrospective chart review, the main cost drivers in CLL care were reported to be hospitalisations, with 40% of patients hospitalised during the follow-up period, followed by outpatient care.⁶¹ As described above, current CLL therapies are associated with a number of tolerability concerns, which are consequently associated with a high cost due to the need for AE management. A 2025 study of hospital records reported that 22% of expenditure incurred by CLL patients was related to AEs.⁶² In particular, infusion-related reactions were reported to be the most costly AEs, highlighting the unmet need for therapies with safer, less resource-intensive administration routes.⁶³ Additionally, even the cost of administering treatments by infusion requires substantial resource, contributing to the significant capacity challenges already being faced by the NHS. Upon relapse, the economic burden of CLL further increases, primarily driven by greater HCRU, including inpatient and outpatient hospital visits.^{64, 65}

Given the older age of the patient population with CLL, a substantial caregiver burden is also imposed. Patients may rely heavily on friends and family to support with medical care for CLL as well as their various comorbidities, for example, by taking time off work to attend outpatient appointments.^{66, 67} In addition, although the median age at CLL diagnosis is over 70 years, a proportion of patients with CLL are younger, working-age individuals, with over 700 individuals between the ages of 25–59 years being diagnosed with CLL each year.⁶⁸ CLL may impact these patients' abilities to work, contributing to the indirect economic burden of the disease. One patient with CLL from a 2022 advisory board conducted as part of the NICE evaluation for Venl

(TA891) stated that “I felt so tired all the time – all my energy was going into work. I had to have some energy for my family, so I stopped working”.⁴ Finally, as a result of the ageing UK population,⁶⁹ the prevalence of CLL is likely to increase, further compounding the economic burden associated with the disease.

1.2.3 Clinical pathway of care

Most patients with CLL are initially diagnosed with asymptomatic, early-stage disease (Rai 0/1, Binet A), and approximately one-third of these do not experience disease progression.⁴² In UK clinical practice, early-stage CLL is actively monitored without therapy (i.e., ‘Watch and Wait’) until evidence of progression.^{31, 70} The findings from multiple studies support the iwCLL’s recommendations for ‘Watch and Wait’, indicating that treatment in patients with early-stage disease yields no survival benefit.⁷¹⁻⁷³ As such, the majority of these patients may never require treatment during their lifetime.⁷⁴

However, CLL remains an incurable disease; for patients who develop symptoms and therefore require treatment, the goal of treatment is to improve OS and achieve deep remission through sustained periods of PFS, without impairing HRQoL.²⁹

Treatment choice for patients with untreated non-high risk CLL

Since AstraZeneca are only seeking reimbursement for AV in patients with untreated non-high risk CLL (i.e., no del[17p] or *TP53* mutation), treatment recommendations for high-risk patients have not been considered further.

Historically, chemoimmunotherapy with FCR/BR was the standard first-line treatment for untreated non-high risk CLL, with alternative treatment options typically reserved for patients for whom FCR/BR was considered unsuitable. Specifically, elderly patients or younger patients with comorbidities were often considered unfit for FCR/BR as they are more likely to experience toxicity with these intensive regimens.⁷⁰ As such, in previous NICE evaluations for new treatments in untreated CLL, FCR/BR-suitability was used to segment patient populations and classify patient ‘fitness’.^{4, 5, 10, 14}

However, with the introduction of newer and better tolerated targeted therapies suitable for a broad range of patient profiles, the use of FCR/BR is now limited, as confirmed by UK clinical expert feedback collected by AstraZeneca.¹⁵ As a result, the previously used FCR/BR-suitability classification is no longer as relevant in UK clinical practice.¹⁵ Instead, treatment options for patients with untreated non-high risk CLL are now informed by a broader concept of fitness. Although there are no well-established criteria for assessing patient fitness, UK clinical experts indicated that they would commonly consider factors of factors, such as age, comorbidities (e.g., using the Cumulative Illness Rating Scale [CIRS] score)¹⁵ and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score.⁹

Currently available targeted therapies for untreated non-high risk CLL in the UK can be categorised according to their dosing regimen, namely treat-to-progression or fixed-duration therapies. These two types of regimens are typically used in separate patient populations. Fixed-duration therapies are generally considered more suitable for younger, fitter patients, whereas treat-to-progression therapies are preferred for less fit patients or patients with *TP53* aberrations (high-risk disease), in order to maximise their treatment response.⁷⁰ This was confirmed by UK clinical experts, and highlighted in the NICE evaluation of zanubrutinib monotherapy in CLL (TA931).^{8, 15} As such, the suitability for fixed-duration versus treat-to-progression therapies plays

an important role in determining treatment options for patients with untreated non-high risk CLL.¹⁵ Based on this, the upcoming updates to the BSH CLL treatment guidelines are expected to split the treatment pathway according to suitability for fixed-duration versus treat-to-progression regimens.^{15, 34}

In line with this, the treatment pathway informing this submission focuses on the suitability of fixed-duration versus treat-to-progression therapies for patients with untreated non-high risk CLL. This was confirmed to be reflective of UK clinical practice by clinical experts interviewed by AstraZeneca.¹⁵

Fixed-duration therapies

Current fixed-duration therapies recommended for reimbursement by NICE for untreated non-high risk CLL include VenO (TA663),¹⁰ VenI (TA891),⁴ OC1b (TA343),⁵ FCR (TA174)⁷ and BR (TA216).⁶ However, given the availability of better tolerated and targeted fixed-duration therapies (i.e., VenO and VenI), recent CLL treatment guidelines from ESMO and the BSH indicate that OC1b is no longer recommended for the treatment of CLL, while FCR/BR use is only recommended in specific patient subpopulations.^{70, 75} It is also anticipated that FCR/BR will be excluded from the upcoming update to the BSH CLL treatment guidelines.¹⁵ Furthermore, UK clinical experts interviewed between April and July 2025 stated that they no longer use FCR/BR, which further highlights that the use of chemoimmunotherapy is no longer routine in UK clinical practice.¹⁵ As such, OC1b and FCR/BR are not considered relevant comparators to AV in this submission. This evolution in the treatment landscape reiterates that the classification of patients according to suitability for FCR/BR is no longer as relevant in informing treatment choice for patients with untreated non-high risk CLL.

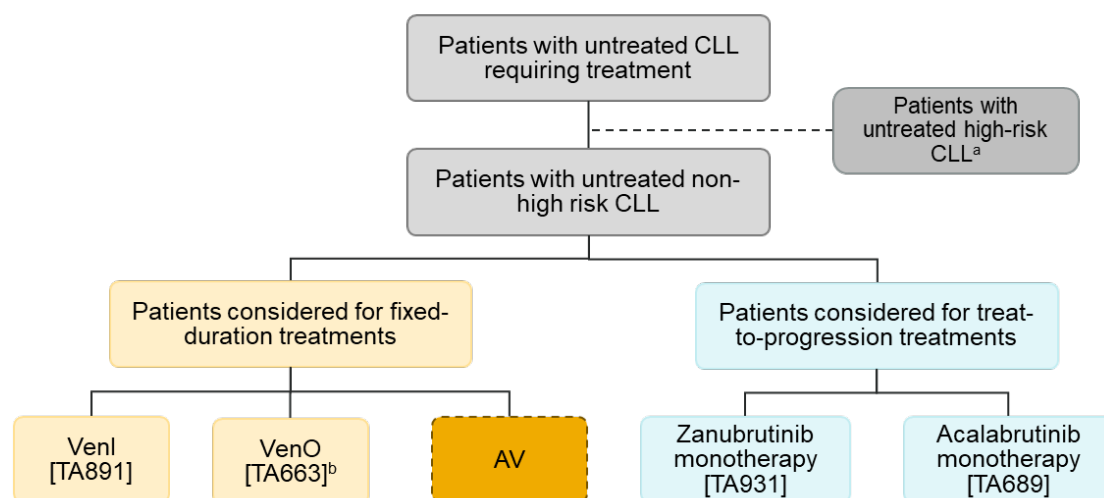
Treat-to-progression therapies

NICE-recommended treat-to-progression therapies for untreated non-high risk CLL include acalabrutinib monotherapy (TA689) and zanubrutinib monotherapy (TA931), which are recommended for use in patients with non-high risk CLL deemed unsuitable for FCR/BR, as well as patients with high-risk CLL.^{8, 9} Whilst the FCR/BR suitability classification is no longer as relevant in UK clinical practice, it is indicative of treat-to-progression regimens being more suitable for older, less fit patients, as previously highlighted. This was also confirmed by UK clinical experts consulted by AstraZeneca and during the NICE evaluation of zanubrutinib monotherapy in CLL (TA931).⁸

AV is a fixed-duration treatment for untreated non-high risk CLL patients. Given that the suitability for fixed-duration versus treat-to-progression therapies is a key decision point, feedback from UK clinical experts interviewed by AstraZeneca indicated that the introduction of AV is unlikely to influence treatment options for patients deemed more suitable for treat-to-progression therapies.¹⁵ Furthermore, in the NICE evaluation of zanubrutinib monotherapy in CLL (TA931), the Committee accepted that the decision of whether to use a treat-to-progression or fixed-duration therapy is unchanged by the introduction of a new therapy.⁸ Therefore, as treat-to-progression therapies, acalabrutinib monotherapy and zanubrutinib monotherapy are not considered relevant comparators to AV in this submission.

The current treatment pathway and proposed positioning of AV for patients with untreated non-high risk CLL in UK clinical practice is shown in Figure 1, and is based on UK clinical expert feedback, BSH guidelines and NICE recommended therapies.^{4, 10, 70}

Figure 1: The current treatment pathway and proposed positioning of AV for patients with previously untreated non-high risk CLL in the UK



^aAstraZeneca are not submitting for reimbursement in the high-risk population (i.e., patients with mutated *TP53* or del[13p]), therefore the treatment pathway for patients with high-risk CLL has not been described in the diagram above.

^bVenO is only available via routine commissioning for patients who are unsuitable for FCR/BR and is currently undergoing review for CDF exit in the FCR/BR suitable population.

Abbreviations: AV: acalabrutinib with venetoclax; BR: bendamustine with rituximab; CDF: Cancer Drug Fund; CLL: chronic lymphocytic leukaemia; FCR: fludarabine with cyclophosphamide and rituximab; UK: United Kingdom; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

1.2.4 Unmet need and proposed positioning of AV

The proposed positioning of AV in the current treatment pathway for patients with untreated non-high risk CLL in UK clinical practice is shown in Figure 1. The comparators considered relevant to this submission are VenI and VenO.

The use of chemoimmunotherapy for patients with untreated non-high risk CLL has seen a decline following the introduction of newer and better tolerated targeted therapies,⁷⁶ which have been shown to be effective in terms of PFS and OS in patients with untreated CLL.^{35, 55} However, the availability of targeted fixed-duration therapy options in the UK is limited, despite treatment choice being valued by patients.⁴ Currently available targeted fixed-duration therapies, VenO and VenI,^{4, 10} are also associated with challenging toxicities, notably cardiac AEs in the case of ibrutinib and infection risk in the case of obinutuzumab.¹⁵

As described in Section 1.2.2, VenI is associated with AEs such as cardiac events, haematological toxicities and bleeding, which may be partially a result of the off-target effects of ibrutinib that lead to the inhibition of various enzymes other than BTKs.³⁶ Consequently, real-world and clinical trial evidence indicates that ibrutinib has a high discontinuation rate in patients with CLL due to treatment-related AEs, and UK clinical experts indicated that ibrutinib is often not offered to patients with a history of cardiac comorbidities.^{15, 77, 78} In contrast, acalabrutinib is a second-generation, highly selective BTKi, which has demonstrated limited off-target activity compared to first-generation BTKis such as ibrutinib.⁷⁹ This means that acalabrutinib is more specific in its binding, which may help circumvent the high incidence of AEs related to the off-target binding of ibrutinib. Indeed, the findings of several studies have suggested that acalabrutinib has a more favourable AE profile than ibrutinib.^{36, 38, 39} In a phase III trial that included patients with previously treated CLL receiving either acalabrutinib or ibrutinib, the

proportion of patients who experienced atrial fibrillation was statistically significantly higher for ibrutinib compared with acalabrutinib (16.0% versus 9.4%; $p=0.020$).⁸⁰ Furthermore, feedback from UK clinical experts indicates that AV is associated with an improved tolerability profile compared with VenI and VenO.¹⁵

Obinutuzumab is similarly associated with tolerability concerns, in part due to its IV administration route, which puts patients at risk of infection as well as infusion-related reactions. UK clinical experts indicated that infection risk is a key consideration related to obinutuzumab treatment in patients with CLL.¹⁵ In addition to the AE burden associated with treatment, obinutuzumab is also associated with the burden of IV administration.⁵⁵ As an all-oral combination therapy, patients can take AV at home without the need to visit the hospital, or the requirement for nursing resources for administration. As such, unlike obinutuzumab, AV would ease capacity constraints on daycare units in the NHS, is more comfortable for patients to take themselves at home, and is not associated with a risk of infusion-related reactions or bloodstream infection.^{15, 81}

In the context of the current treatment pathway, AV therefore represents a valuable treatment option as it offers an effective, all-oral and well-tolerated fixed-duration treatment alternative to VenI and VenO for patients with previously untreated non-high risk CLL.

1.3 Equality considerations

No equality issues have been identified as part of this submission.

2 Clinical effectiveness

A systematic literature review (SLR) identified one phase III, RCT for AV in patients with untreated non-high risk CLL (the AMPLIFY trial; NCT03836261).^{2, 3}

- AMPLIFY is an ongoing, phase III, randomised, multicentre, open-label study designed to compare the efficacy and safety of AV, with or without obinutuzumab, to investigator's choice of chemoimmunotherapy (FCR or BR) in patients with untreated CLL without a del(17p) or TP53 mutation.^{2, 3}
 - The primary endpoint in the AMPLIFY trial is PFS for AV versus FCR/BR as assessed by an Independent Review Committee (IRC). The key secondary endpoints in the AMPLIFY trial are OS and MRD negativity rate.
 - Results presented in this submission are from the interim analysis (data cut-off date [DCO]: 30th April 2024), where patients had a median follow-up of 40.8 months.^{2, 3}
- Baseline demographic and disease characteristics in the AMPLIFY trial were reflective of the characteristics of patients in the UK for whom fixed-duration therapies are considered most suitable.¹⁵

The AMPLIFY trial met its primary objective, demonstrating that treatment with AV was associated with a statistically significant and clinically meaningful improvement in IRC-assessed PFS versus FCR/BR.

- At a median follow-up of 40.8 months, 89 (30.6%) IRC-assessed PFS events were reported for AV and 95 (32.8%) for FCR/BR (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.49, 0.87; p-value: 0.004 [p-value boundary: 0.0469]).
- An improvement in IRC-assessed PFS in favour of treatment with AV compared to treatment with FCR/BR was also observed across almost all clinically relevant pre-specified subgroups.

AMPLIFY demonstrated that treatment with AV was associated with a statistically significant improvement in OS versus FCR/BR.

- The OS HR for AV versus FCR/BR was 0.33 (95% CI: 0.18, 0.56; nominal p-value: <0.001), representing a 67% reduction in the risk of death at a median follow-up of 40.8 months for patients who received AV versus FCR/BR.

Treatment with AV was associated with no clinically meaningful deterioration in patient reported outcomes (PROs), as measured by EQ-5D, EORTC QLQ-C30 and FACIT-Fatigue.

- At 3 years post-treatment follow-up, patients in both the AV and FCR/BR arms experienced an improvement in HRQoL versus baseline as measured by EQ-5D, EORTC QLQ-C30 and FACIT-Fatigue.
- Improvements in HRQoL during and after treatment were generally greater in the AV arm versus the FCR/BR arm, owing to fewer AEs and lower long-term toxicity.

Overall, results of the AMPLIFY trial demonstrated that compared with FCR/BR, treatment with AV led to a statistically significant improvement in PFS and OS in patients with untreated non-high risk CLL, without compromising HRQoL

- Full details of the comparative efficacy of AV versus VenI and VenO are presented in Section 2.10.
- Full details of the safety outcomes from the AMPLIFY trial are presented in Section 1.1.

2.1 Identification and selection of relevant studies

An SLR was performed on 11th October 2024 and subsequently updated on June 2025, to identify all relevant clinical evidence from clinical trials on the efficacy and safety of acalabrutinib in untreated CLL.

Overall, the original and updated SLRs identified a total of 161 relevant publications reporting on 53 unique studies. Of these, two studies were identified for AV (AMPLIFY, Swaminathan *et al.* [2024]),^{3, 82} six for VenI (CAPTIVATE MRD, CAPTIVATE FD, ERADIC, FLAIR, GLOW, Jain *et al.* [2019])^{37, 83-87} and five for VenO (CLL13, CLL14, CRISTALLO, Flinn *et al.* [2019], Roeker *et al.* [2024]).^{55, 88-91}

Full details of the SLR search strategy, study selection process and results can be found in Appendix B.

2.2 List of relevant clinical effectiveness evidence

As described in Section 2.1, two studies assessing the safety and efficacy of AV were identified: the AMPLIFY trial and Swaminathan *et al.* (2024).^{3, 82}

AMPLIFY was the only phase III RCT identified by the SLR that provided clinical evidence of the efficacy and safety of AV as a treatment in the patient population of relevance for this submission. A summary of the AMPLIFY trial is presented in Table 3.

Swaminathan *et al.* (2024) was a phase II, randomised clinical trial comparing the safety and efficacy of AV versus AVO in patients with treated or untreated high-risk CLL, as defined by the presence of any one of the following criteria: age >65 years, unmutated *IgHV*, *TP53* abnormalities, or del(11q).⁸² The primary efficacy endpoint in the Swaminathan *et al.* (2024) study was undetectable minimal residual disease (uMRD). As the Swaminathan *et al.* (2024) study did not report PFS and OS, and the patient population was not limited to the patient population of relevance to this submission (i.e., patients with untreated CLL without del[17p] or *TP53* mutations), with no relevant subgroup analyses being performed, AMPLIFY was considered the pivotal trial for this submission and Swaminathan *et al.* (2024) has not been considered further.

Table 3: Clinical effectiveness evidence – AMPLIFY

Study	AMPLIFY (NCT03836261)
Study design	Phase III, randomised, multicentre, open-label study
Population	Patients with untreated CLL without a del(17p) or <i>TP53</i> mutation
Intervention(s)	AV/AVO
Comparator(s)	FCR/BR
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Reported outcomes specified in the decision problem^a	• IRC-assessed PFS • MRD negativity rate • OS

Study	AMPLIFY (NCT03836261)
	• HRQoL • AEs
All other outcomes	• Investigator-assessed PFS^b • IRC- and investigator-assessed EFS, ORR, DOR, TTNT^b • Plasma concentrations of acalabrutinib and venetoclax^c • Hospitalisations/resource use^c

^aOutcomes marked in bold are included in the economic model.

^bResults for these endpoints are presented in Appendix J.

^cResults for these endpoints are not presented in this submission but can be found in the AMPLIFY CSR.²

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; DOR: duration of response; EFS: event-free survival; FCR: fludarabine with cyclophosphamide and rituximab; HRQoL: health-related quality of life; IRC: Independent Review Committee; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial overview

Trial design

AMPLIFY (NCT03836261) is an ongoing, phase III, randomised, multicentre, open-label study designed to compare the efficacy and safety of AV, with or without obinutuzumab, to investigator's choice of chemoimmunotherapy (FCR or BR) in patients with untreated CLL without a del(17p) or *TP53* mutation.^{2, 3}

Patients who fulfilled the eligibility criteria of the trial (see Table 4) were centrally randomised in a 1:1:1 ratio through a block stratified randomisation procedure to each study treatment arm (A, B and C) using an interactive voice/web response system (see Figure 2). The following stratification factors were used: age (>65 or ≤65), *IgHV* mutational status (mutated versus unmutated), Rai stage (high risk [≥3] versus non-high risk [<3]), and geographic region (North America versus Europe versus Other).^{2, 3}

Patients in Arm A received AV, patients in Arm B received AVO, and patients in Arm C received investigator's choice of chemoimmunotherapy which consisted of FCR or BR. For Arm C, approximately 50% of patients were planned to be treated with FCR and 50% treated with BR per investigator's choice.^{2, 3}

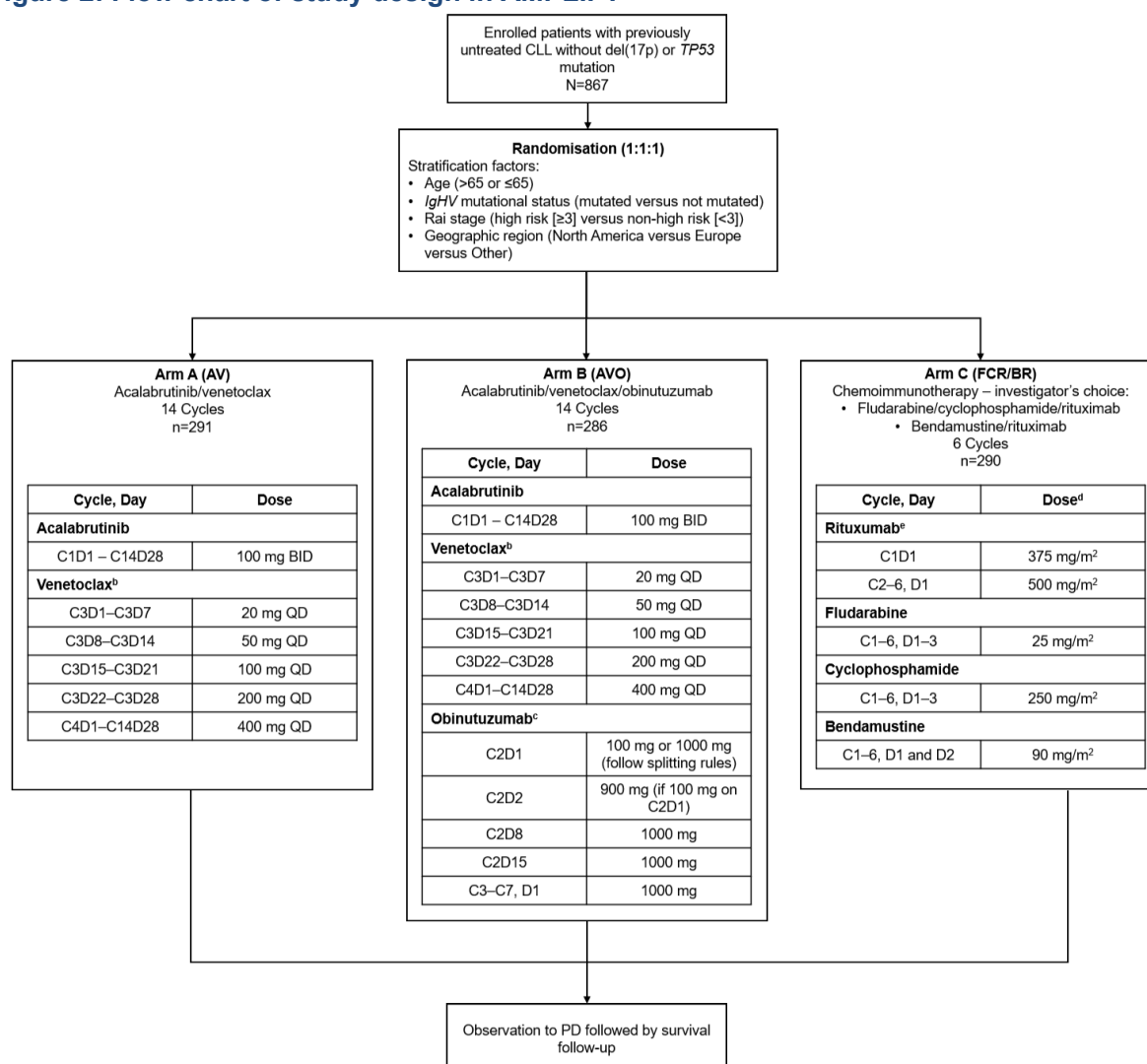
All treatment regimens received in the AMPLIFY trial were administered in 28-day cycles. Refer to Figure 2 for an overview of the AMPLIFY trial design and Figure 3 for an overview of the treatment regimens.^{2, 3}

Patients in the AV arm received oral acalabrutinib 100 mg twice daily from Day 1 of Cycle 1 until Day 28 of Cycle 14, and oral venetoclax once daily starting at 20 mg on Day 1 of Cycle 3, with a 5-week ramp-up to reach a target dose of 400 mg by Day 1 of Cycle 4. Venetoclax treatment was continued at 400 mg once daily until Day 28 of Cycle 14.^{2, 3}

Patients in the AVO arm received the same doses of acalabrutinib and venetoclax as described for the AV arm plus 1,000 mg IV obinutuzumab on Days 1, 2, 8 and 15 of Cycle 2, then on Day 1 of Cycles 3 to 7.^{2, 3}

Patients who received FCR in Arm C received fludarabine 25 mg/m² IV and cyclophosphamide 250 mg/m² IV from Days 1–3 of Cycles 1–6 in addition to 375 mg/m² IV rituximab on Day 1 of Cycle 1, which was increased to 500 mg/m² on Day 1 of Cycles 2 through 6. Patients who received BR in Arm C received bendamustine 90 mg/m² IV on Days 1 and 2 of Cycles 1 to 6 in addition to the same rituximab treatment regimen as patients who received FCR.^{2, 3}

Figure 2: Flow chart of study design in AMPLIFY^a



^aAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. Reference to AVO is only included where necessary to accurately describe the methodology of the AMPLIFY trial.

^bThe 20-mg and 50-mg doses of venetoclax were administered in the hospital for patients who were at high risk of tumour lysis syndrome (TLS), or if they were indicated to hospitalise, and thereafter at home daily for 7 days. The dose then increased every seven days to the target dose of 400 mg, and venetoclax was administered at home unless a patient was indicated to hospitalise.

^cOnly the first dose (1,000 mg) of obinutuzumab administration was allowed to be split over two days.

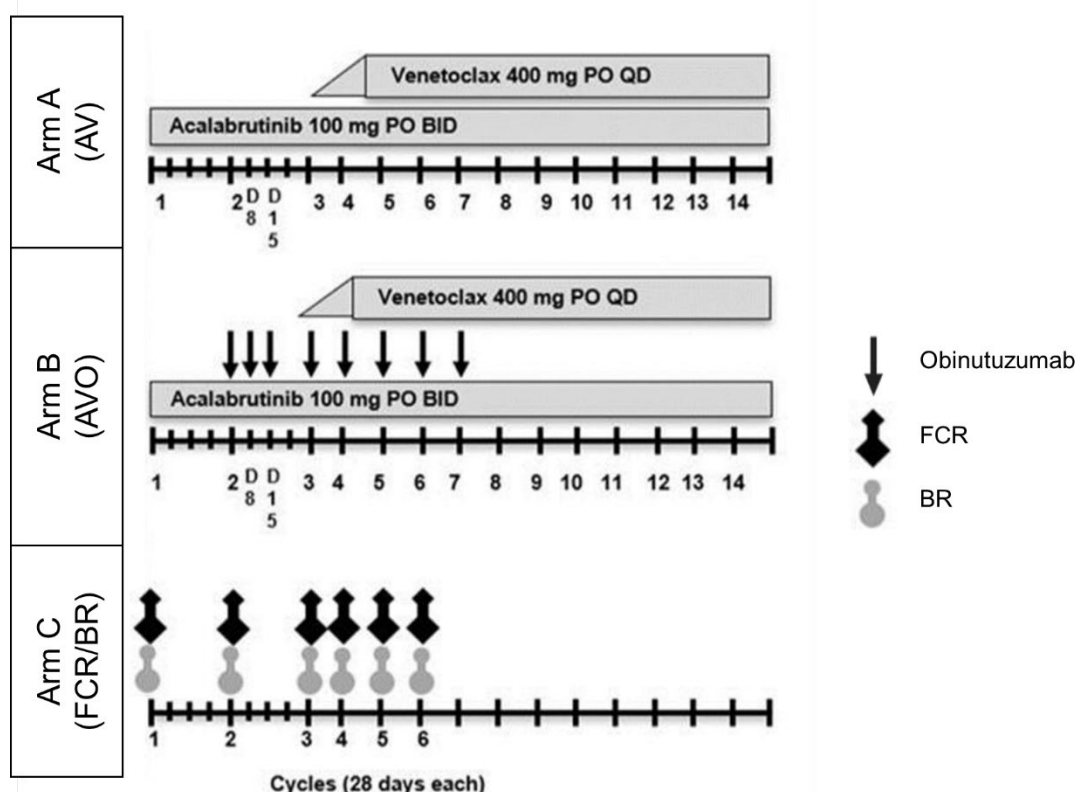
^dPatients either received FCR or BR.

^eThe first dose could have been given over two days at investigator discretion per standard of care.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BID: twice daily; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; CX: Cycle X; DX: Day X; FCR: fludarabine with cyclophosphamide and rituximab; IgHV: immunoglobulin heavy-chain variable region gene;

PD: progressed disease; QD: once daily; TLS: tumour lysis syndrome.
Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Figure 1).²

Figure 3: Treatment regimens for AV, AVO and FCR/BR in AMPLIFY^a



^aAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. Reference to AVO is only included where necessary to accurately describe the methodology of the AMPLIFY trial.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BID: twice daily; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; PO: orally; QD: once daily.

Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Figure 2).²

Follow-up visits

A safety follow-up visit was required 30 (+7) days after treatment discontinuation within the trial, to monitor for resolution or progression of AEs and to document the occurrence of any new events. The safety follow-up visit was not required if the patient permanently discontinued treatment due to withdrawal of consent, loss to follow-up, or death.⁹²

If disease progression had not occurred at the time of the 30-day safety follow-up visit, post-treatment disease follow-up visits occurred until disease progression, regardless of whether the patient received a new anti-cancer therapy. During this period, patients were followed for disease progression via computed tomography (CT) or magnetic resonance imaging (MRI) scans, complete blood counts, physical examinations, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Post-treatment follow-up was performed every 12 weeks for approximately three years (144 weeks), then every 24 weeks thereafter until disease progression, death, withdrawal of consent by patient, loss to follow-up, or study termination by sponsor, whichever occurred first.⁹² Patients who progressed (and had not withdrawn consent) were contacted approximately every year by clinic visit or telephone, to assess survival and subsequent anti-cancer therapy until death, withdrawal of consent, loss to follow-up, or study termination by sponsor, whichever occurred first.⁹²

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2.3.2 Trial methodology

The AMPLIFY trial methodology is summarised in Table 4 and outcome measures and definitions are summarised in Table 5.

Table 4: Summary of trial methodology in AMPLIFY

Trial name	AMPLIFY (NCT03836261)
Location	Multiple locations, including the UK
Trial design	Phase III, randomised, multicentre, open-label study
Eligibility criteria for patients	Patients were deemed eligible for inclusion in the AMPLIFY trial if they met the following eligibility criteria: • Men and women ≥ 18 years of age • ECOG PS of 0–2 • Diagnosis of CLL that met published diagnostic criteria³¹ • Active disease per iwCLL 2018 criteria that required treatment³¹ • Not received any prior CLL-specific treatment • Did not have a del(17p) or <i>TP53</i> mutation The full eligibility criteria for the AMPLIFY trial can be found in the CSR, Section 9.3.² The full eligibility criteria for the AMPLIFY trial can be found in the clinical study report (CSR), Section 9.3.²
Intervention^a	• AV: Acalabrutinib 100 mg orally twice daily from Day 1 of Cycle 1 through Day 28 of Cycle 14 plus oral venetoclax once daily starting at 20 mg on Day 1 of Cycle 3, with a 5-week ramp-up to reach 400 mg by Day 1 of Cycle 4. Venetoclax treatment was continued at 400 mg once daily until Day 28 of Cycle 14 • AVO: Same dosing regimen as the AV arm with the addition of obinutuzumab 1,000 mg IV on Days 1, 2, 8, and 15 of Cycle 2, then on Day 1 of Cycles 3 to 7^a
Comparator	• FCR: Fludarabine 25 mg/m² IV and cyclophosphamide 250 mg/m² IV from Days 1–3 of Cycles 1–6 in addition to rituximab 375 mg/m² IV on Day 1 of Cycle 1, which was increased to 500 mg/m² on Day 1 of Cycles 2 through 6 • BR: Bendamustine 90 mg/m² IV on Days 1 and 2 of Cycles 1 to 6 in addition to the same rituximab treatment regimen as patients who received FCR
Method of study drug administration	• Acalabrutinib: oral • Venetoclax: oral • Obinutuzumab: IV • FCR: IV • BR: IV
Permitted and disallowed concomitant medication	The following concomitant medications were permitted: • Standard supportive care medications, which included premedication to decrease the risk of TLS, infusion-related reactions, infections, and other risks or toxicities • Haematopoietic growth factors (e.g., granulocyte-colony stimulating factor) • Transfusions of packed red blood cells or platelets at the discretion of the investigator • In accordance with prescribing information or institutional standards, infection prophylaxis where indicated. Additional prophylaxis was also allowed at the discretion of the investigator, particularly for patients who

	developed severe neutropenia The following concomitant medications were prohibited: - Any chemotherapy, anti-cancer immunotherapy, experimental therapy including targeted small molecule agents, or radiotherapy for treating CLL - Steroid therapy for antineoplastic intent, with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids (dose equivalents of ≥ 20 mg prednisolone) - Warfarin or equivalent vitamin K antagonists - Immunisation with a live vaccine within 28 days before study treatment and during study treatment
Primary outcome(s)^b	IRC-assessed PFS for AV versus FCR/BR
Secondary endpoints^b	- IRC-assessed PFS for AVO versus FCR/BR^{a, c} - MRD negativity rate - OS - Investigator-assessed PFS - IRC- and investigator-assessed EFS, ORR, DOR, TTNT
Other/exploratory endpoints	- AEs - HRQoL - EORTC QLQ-C30 - EQ-5D - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue - Item Library 27 (IL27)^c - Patient Global Impression of Change (PGIC)^c - Patient Global Impression of Severity (PGIS)^c - Plasma concentrations of acalabrutinib and venetoclax^c - Hospitalisations/resource use^c
Pre-planned subgroup analyses	Subgroup analyses of IRC-assessed PFS (primary endpoint) and OS (key secondary endpoint) for AV versus FCR/BR were performed to assess the consistency of the results across clinically relevant patient subgroups. The following subgroups were of primary interest, based on predicted prognostic factors and baseline stratification: - Randomisation stratification factors per electronic data capture (EDC)/lab data recording: - Age <i>IgHV</i> mutational status - Rai stage - Geographic region - Sex - Race - Ethnicity - ECOG PS - Complex karyotype - CD38 expression - ZAP-70 expression - Del(11q)
Duration of study and follow-up	- The end of study is defined as approximately five years after the last patient is randomised in the study (unless all patients have died). - Results presented within this submission are from the interim analysis (DCO date: 30th April 2024), where patients had a median follow-up of

40.8 months.^{2, 3}

^aAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. Reference to AVO is only included where necessary to accurately describe the methodology of the AMPLIFY trial.

^bAll endpoints were for AV versus FCR/BR and AVO versus FCR/BR, unless otherwise specified.

^cResults for these endpoints are not presented in this submission but can be found in the AMPLIFY CSR.²

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; DCO: data cut-off; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; EDC: electronic data capture; EFS: event-free survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: EuroQoL 5-Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; FCR: fludarabine with cyclophosphamide and rituximab; HRQoL: health-related quality of life; *IgHV*: immunoglobulin heavy-chain variable region gene; IL27: Item Library 27; IRC: Independent Review Committee; IV: intravenous; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; TTNT: time to next treatment.

Table 5: Outcome measures and definitions used in AMPLIFY^a

Outcome	
PFS^b	- PFS was defined as the time from the date of randomisation until disease progression (assessed per iwCLL 2018 criteria)³¹ or death from any cause, whichever occurred first. PFS was calculated as: <i>Date of first disease progression or death (censoring date for censored subjects) – randomisation date + 1</i> - An “adequate” response assessment was defined for IRC-assessed PFS as any assessment (regardless of visit name, whether scheduled or unscheduled) where the patient had a physical exam, with labs (labs may be within a window if not on the exact date of the physical exam) or a CT scan. - A “valid” response assessment was defined for investigator-assessed PFS as CR, complete response with incomplete marrow recovery (CRi), partial response (PR), nodular partial response (nPR), stable disease (SD) and progressed disease (PD). - For the primary endpoint, PFS was assessed in a blinded manner by an IRC composed of radiologists and oncologists, board-certified or equivalent, with experience in CLL.⁹² - For the secondary endpoint, PFS was determined by investigator assessment.
OS	- OS was defined as the time from date of randomisation to date of death due to any cause. - OS was calculated as: <i>Death date (or censoring date) – randomisation date + 1</i>
MRD negativity	MRD negativity rate was defined as the proportion of patients having blood/bone marrow with less than one CLL cell per 10,000 leukocytes (white blood cells).
EFS	- EFS was defined as the time from date of randomisation to the date of first disease progression, death due to any cause, or initiation of subsequent anti-CLL therapy, as determined by IRC and investigator assessment. - EFS was calculated as: <i>Date of first event (censoring date for censored subjects) – randomisation date + 1</i>
ORR^b	ORR was defined as the proportion of patients achieving a best overall response of CR, CRi, nPR or PD, as per IRC and investigator assessment. Best overall response was determined by IRC and investigator assessment, at or before the initiation of subsequent anti-CLL therapy or disease progression, whichever came first.
DOR^b	DOR was defined as the time from the date of first CR, CRi, nPR or PR to the

Outcome	
	date of first disease progression (determined by IRC and investigator assessment) or death due to any cause. DOR was calculated as: $\text{Date of event or censoring} - \text{date of first CR, CRi, nPR or PR} + 1$
TTNT	- TTNT was defined as the time from the date of randomisation to date of institution of non-protocol specified anti-CLL therapy or death due to any cause. - TTNT was calculated as: $\text{Earlier of the start date of non-protocol specified anti-CLL therapy or date of death (date of last visit for censored subjects)} - \text{date of randomisation} + 1$
Safety and tolerability	Analyses included treatment exposure and dose interruptions, AEs, AEs of special interest, serious adverse events (SAEs), discontinuation of investigational product due to AE(s), deaths, laboratory data, and vital signs.

^aDefinitions for outcomes not presented in this submission can be found in the AMPLIFY CSR.²

^bResponse assessed by the IRC/investigators according to the iwCLL 2018 criteria.³¹

Abbreviations: AE: adverse event; CLL: chronic lymphocytic leukaemia; CR: complete response; CRi: complete response with incomplete marrow recovery; DOR: duration of response; EFS: event-free survival; IRC: Independent Review Committee; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; MRD: minimal residual disease; nPR: nodular partial response; ORR: overall response rate; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PR: partial response; SAE: serious adverse event; SD: stable disease; TTNT: time to next treatment.

2.3.3 Baseline characteristics

Baseline patient demographic and disease characteristics were well-balanced across all treatment arms of the AMPLIFY trial (AV and FCR/BR: Table 6, Table 7; AVO: Appendix J). Feedback from UK clinical experts indicated that baseline characteristics in the AMPLIFY trial were reflective of the characteristics of patients in the UK for whom fixed-duration therapies are considered most suitable.¹⁵ Of note, patients for whom fixed-duration therapies are considered most suitable are typically younger and fitter compared with patients considered more suitable for treat-to-progression therapies.¹⁵

Patient demographic characteristics

Baseline patient characteristics for the AV and FCR/BR arms in the AMPLIFY trial are presented in Table 6.

In the AV arm, the majority of patients randomised were male (61.2%) and white (91.1%). The median age of patients was 61.0 years (range: 31–84 years), with 96.9% of patients aged ≤75 years.³

In the FCR/BR arm, the majority of patients randomised were male (63.1%) and white (86.9%). The median age of patients was 61.0 years (range: 26–86 years), with 96.6% of patients aged ≤75 years.³

Table 6: Baseline patient demographic characteristics in AMPLIFY (full analysis set [FAS])^a

	Arm A (AV) (n=291)	Arm C (FCR/BR) (n=290)
Age (years)		
Mean (SD)	59.9 (9.4)	59.8 (9.7)

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	Arm A (AV) (n=291)	Arm C (FCR/BR) (n=290)
Median (Min, Max)	61.0 (31, 84)	61.0 (26, 86)
Age group, n (%)		
≤65	212 (72.9)	213 (73.4)
>65	79 (27.1)	77 (26.6)
■	■	■
■	■	■
Sex, n (%)		
Male	178 (61.2)	183 (63.1)
Female	113 (38.8)	107 (36.9)
Race, n (%)		
American Indian or Alaska Native	1 (0.3)	1 (0.3)
Asian	4 (1.4)	18 (6.2)
Black or African American	3 (1.0)	7 (2.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	2 (0.7)
White	265 (91.1)	252 (86.9)
Multiple	0 (0.0)	0 (0.0)
Not reported	18 (6.2)	10 (3.4)
Ethnicity, n (%)		
Hispanic or Latino	21 (7.2)	19 (6.6)
Not Hispanic or Latino	246 (84.5)	256 (88.3)
Not reported	24 (8.2)	15 (5.2)

^aResults for the AVO arm are presented in Appendix J.1.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; Max: maximum; Min: minimum; SD: standard deviation.

Source: Brown *et al.* (2025; Table 1; Table S1);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 12).²

Patient disease characteristics

Baseline patient disease characteristics for the AV and FCR/BR arms in the AMPLIFY trial are presented in Table 7.

Most patients in the AV arm (90.0%) had an ECOG PS ≤1 at baseline, with a median CIRS-Geriatric (CIRS-G) score of 2.0 and a median time from initial CLL diagnosis to randomisation of 28.52 months (interquartile range [IQR]: 8.0, 62.2). Less than half of the patients (38.8%) had bulky disease measuring ≥5 cm. The majority of patients were Rai stage ≤3 and did not carry del(11q) mutations (81.8%) or a complex karyotype (79.0%). A total of 167 patients (57.4%) had unmutated *IgHV* status at baseline.³

In the FCR/BR arm, most patients (90.3%) had an ECOG PS ≤1, with a median CIRS-G score of 2.0 and a median time from initial CLL diagnosis to randomisation of 29.55 months (IQR: 9.3, 53.9). Less than half of the patients (42.8%) had bulky disease measuring ≥5 cm. The majority of patients were Rai stage ≤3 and did not carry del(11q) mutations (83.4%) or a complex karyotype (74.8%). A total of 172 patients (59.3%) had unmutated *IgHV* status at baseline.

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Table 7: Baseline patient disease characteristics in AMPLIFY (FAS)^a

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
ECOG PS, n (%)		
≤1	262 (90.0)	262 (90.3)
2	28 (9.6)	26 (9.0)
Missing	1 (0.3)	2 (0.7)
Time from initial diagnosis to randomisation (months)		
Mean (SD)	██████████	██████████
Median (P25, P75)	28.52 (8.0, 62.2)	29.55 (9.3, 53.9)
Bulky disease, n (%)		
<5 cm	178 (61.2)	166 (57.2)
≥5 cm	113 (38.8)	124 (42.8)
<10 cm	271 (93.1)	269 (92.8)
≥10 cm	20 (6.9)	21 (7.2)
CIRS-G total score		
Mean (SD)	██████████	██████████
Median (P25, P75)	2.0 (1, 4)	2.0 (1, 4)
CIRS-G total score category, n (%)		
0	48 (16.5)	52 (17.9)
1–6	██████████	██████████
>6	██████████	██████████
CIRS3+, n (%)^b		
Yes	24 (8.2)	26 (9.0)
CIRS-G category by age group, n (%)^c		
Age group ≤65 years, n	██████████	██████████
≤6	██████████	██████████
>6	██████████	██████████
Age group >65 years, n	██████████	██████████
≤6	██████████	██████████
>6	██████████	██████████
Age group ≤75 years, n	██████████	██████████
≤6	██████████	██████████
>6	██████████	██████████
Age group >75 years, n	██████████	██████████
≤6	██████████	██████████
>6	██████████	██████████
Rai stage, n (%)		
0	3 (1.0)	4 (1.4)
I	47 (16.2)	62 (21.4)
II	104 (35.7)	97 (33.4)
III	69 (23.7)	59 (20.3)
IV	68 (23.4)	68 (23.4)

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Del(11q), n (%)		
Yes	51 (17.5)	46 (15.9)
No	238 (81.8)	242 (83.4)
Missing	2 (0.7)	2 (0.7)
IgHV mutational status, n (%)		
Mutated	124 (42.6)	118 (40.7)
Unmutated	167 (57.4)	172 (59.3)
Complex karyotype, n (%)		
Yes	45 (15.5)	42 (14.5)
Low (3 aberrations)	██████	██████
Medium (4 aberrations)	██████	██████
High (≥5 aberrations)	13 (4.5)	13 (4.5)
No	230 (79.0)	217 (74.8)
Missing	16 (5.5)	31 (10.7)
Beta-2 microglobulin (mg/L), n (%)		
≤3.5	103 (35.4)	107 (36.9)
>3.5	169 (58.1)	143 (49.3)
Missing	19 (6.5)	40 (13.8)
Creatine clearance <60 mL/min, n (%)		
Yes	38 (13.1)	30 (10.3)
No	253 (86.9)	260 (89.7)
Missing	0 (0.0)	0 (0.0)
Cytopenia, n (%)		
Neutropenia – ANC ≤1.5x10 ⁹ /L		
Yes	20 (6.9)	20 (6.9)
No	██████	██████
Missing	██████	██████
Anaemia – haemoglobin <11 g/dL		
Yes	103 (35.4)	94 (32.4)
No	██████	██████
Missing	██████	██████
Thrombocytopenia – platelets <100x10 ⁹ /L		
Yes	66 (22.7)	58 (20.0)
No	██████	██████
Missing	██████	██████
All of the above	██████	██████
Any of the above	██████	██████

^aResults for the AVO arm are presented in Appendix J.1.

^bCIRS3+ is defined as CIRS-G score of 3 or 4 in any single organ system.

^cPercentages are based on the number of patients in the age group.

Abbreviations: ANC: absolute neutrophil count; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab BR: bendamustine with rituximab; CIRS-G: Cumulative Illness Rating Scale-Geriatric; ECOG PS: Eastern Cooperative Oncology Group performance status; FAS: Full Analysis Set; FCR:

fludarabine with cyclophosphamide and rituximab; *IgHV*: immunoglobulin heavy-chain variable region gene; Max: maximum; Min: minimum; P25: 25th percentile; P75: 75th percentile; SD: standard deviation.
Source: Brown *et al.* (2025);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 13).²

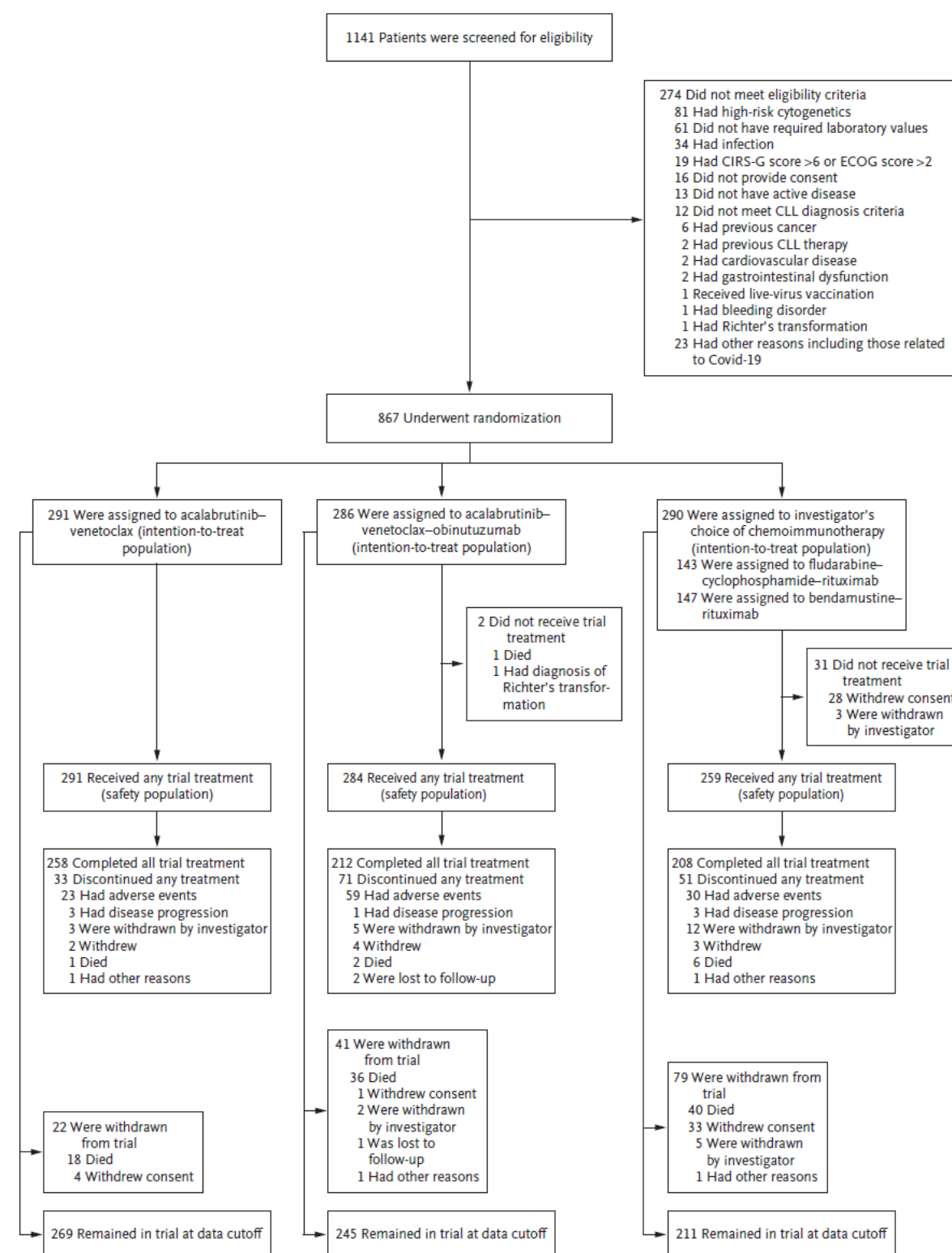
2.3.4 Patient flow

A total of 867 patients randomised on or before 5th May 2021 were included in the FAS of the interim analysis of the AMPLIFY trial, comprising 291 patients in Arm A (AV), 286 patients in Arm B (AVO) and 290 patients in Arm C (FCR/BR). Of these, 291 patients in the AV arm, 284 patients in the AVO arm and 259 patients in the FCR/BR arm received at least one dose of study treatment (safety population). The patient flow (CONSORT) diagram of the AMPLIFY trial is presented in Figure 4.

As of the DCO date of the interim analysis (30th April 2024), a total of 155 patients (18.6%) had discontinued study treatment in the AMPLIFY trial, of which 33 patients were in the AV arm, 71 were in the AVO arm and 51 were in the FCR/BR arm. The most frequently reported reason for discontinuation of study treatment in the AV arm was AEs (23 patients), followed by PD and investigator's decision (three patients each), then patient decision (two patients) and death (one patient). In the FCR/BR arm, the most frequently reported reason was AEs (30 patients), followed by investigator's decision (12 patients), then death (six patients), and PD and patient's decision (three each).

A total of 678 patients (82.7%) completed all treatments, whilst 22 patients (7.6%) in the AV arm and 79 patients (27.2%) in the FCR/BR arm withdrew from the study. Reasons for patient withdrawal from the study are detailed in Figure 4.

Figure 4: CONSORT diagram for AMPLIFY^a



^aAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. Reference to AVO is only included where necessary to accurately describe the methodology of the AMPLIFY trial.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; CIRS-G: Cumulative Illness Rating Scale-Geriatric; CLL: chronic lymphocytic leukaemia; ECOG: Eastern Cooperative Oncology Group.

Source: Brown *et al.* (2025) (Figure 1).³

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

Data cuts

The AMPLIFY study is still ongoing. Results presented in this submission are from the interim analysis (DCO: 30th April 2024). This interim analysis was planned to occur when approximately 141 IRC-assessed PFS events (75% of the 188 events required for final analysis) in the AV and FCR/BR arms had been observed. The median duration of follow-up from randomisation was [REDACTED] (range: [REDACTED] to [REDACTED]) for the AV arm and [REDACTED] (range: [REDACTED] to [REDACTED]) for the FCR/BR arm. The median duration of follow-up after treatment completion was [REDACTED] (range: [REDACTED] to [REDACTED]) for the AV arm.

The AMPLIFY trial is ongoing, [REDACTED]

Trial analysis populations and statistical methods

The definitions used for the statistical analysis populations in the trial are presented in Table 8. A summary of the statistical analysis methods used in the trial are presented in Table 9.

Table 8: Trial analysis populations in AMPLIFY

Analysis set	Definition	Outcomes analysed
FAS	All randomised patients regardless of the treatment actually received. Patients were analysed according to the arm to which they were randomised, following the 'intention-to-treat (ITT)' principle. FAS was the primary analysis set used for all efficacy analyses. Additionally, demographic and patient characteristics were summarised among the FAS.	• PFS • EFS • OS • ORR^a • DOR^a • TTNT • MRD • HRQoL
Safety population	All randomised patients who received any amount of study drug. Safety data were summarised using the safety population, according to the actual treatment that a patient received.	• AEs

^aPatients who were evaluable for the analysis of ORR were those with measurable disease at baseline. Patients who were evaluable for the analysis of DOR were those who had response of PR or better.

Abbreviations: AE: adverse event; DOR: duration of response; EFS: event-free survival; FAS: Full Analysis Set; HRQoL: health-related quality of life; ITT: intention-to-treat; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; TTNT: time to next treatment.

Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 6).²

Table 9: Statistical methods used for the primary analysis in AMPLIFY

Hypothetical objective	The primary objective of AMPLIFY is to demonstrate that AV is associated with a statistically significant improvement in PFS per IRC assessment compared with FCR/BR.
Statistical analysis	• All efficacy analyses were performed on the FAS and were analysed as randomised. • PFS, EFS, TTNT, and OS efficacy analyses were conducted using a stratified two-sided log-rank test, with the estimate of the HR for the AV arm versus the FCR/BR arm and its corresponding 95% CI computed using a stratified Cox proportional hazards model. ○ PFS: The distribution of IRC-assessed PFS was summarised for each treatment arm using the median and its corresponding 95% CI based on Kaplan-Meier estimates and the Brookmeyer-Crowley method for the CI. The proportion of patients who were progression-free and the associated 95% CI were estimated based on the Kaplan-Meier method at selected timepoints by treatment arm. IRC-assessed PFS was compared among the FAS using a stratified two-sided log-rank test and a method that corresponds to the Breslow approach for handling ties.⁹³ The estimate of the HR for the AV arm versus the FCR/BR arm and its corresponding 95% CI were computed using a stratified Cox proportional hazards model with ties=Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. ○ EFS: EFS was analysed using the same approach as that described for PFS, for both IRC- and investigator-assessed EFS, among the FAS. As this endpoint was not included in the multiple testing procedure (MTP), the p-value is considered descriptive. ○ ORR: ORR was summarised based on IRC and investigator assessment among the FAS. Descriptive statistics were provided for best overall response of each patient by treatment arm. The number and proportion of patients within each category of response were presented. ORR was summarised descriptively similarly by number and percentage of patients for each treatment arm, and its corresponding 95% CI was calculated based on the exact mid-p method. Response rate difference between treatment arms and 95% CI of the difference was calculated by exact methods. ORR was compared between treatment arms (AV versus FCR/BR) using the Cochran–Mantel–Haenszel chi-square test, adjusted for randomisation stratification factors as recorded in EDC/lab data. ○ DOR: DOR was summarised based on IRC and investigator assessment among the FAS, similar to PFS. Descriptive data were provided for DOR, including the associated Kaplan-Meier curves. ○ TTNT: TTNT was analysed among the FAS using the same method as for PFS. As this endpoint is not included in the MTP, the p-value is considered descriptive. ○ OS: OS was analysed among the FAS using the same method as for PFS. An exploratory analysis of OS in Arm A (AV) versus Arm C for FCR only and Arm A (AV) versus Arm C for BR only was also performed. ○ MRD: MRD negativity rate per peripheral blood was summarised among the FAS by number and percentage of patients, and its corresponding 95% CI was calculated based on the exact mid-p method. Peripheral blood MRD negativity rate was compared between treatment arms (AV versus FCR/BR) using the Cochran–Mantel–Haenszel chi-square test, adjusted for randomisation stratification factors as recorded in EDC/lab data.
Sample size, power calculation	• The study was expected to randomise approximately 260 patients per treatment arm. With a 1:1:1 randomisation ratio, the study was planned to randomise 780 patients in total. Under the exponential model assumptions, the study was sized to achieve approximately 90% power to detect a HR of 0.62 in PFS for AV versus FCR/BR at the two-sided significance level of 0.05 based on

	188 events at final analysis, which translates to a 61% improvement in median PFS from 44.7 months in the FCR/BR treatment arm to 72.1 months in AV treatment arm.
Data management, patient withdrawals	• The date a patient was withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation were recorded and described on the appropriate electronic case report form (eCRF). • The investigator, in consultation with the medical monitor, may have withdrawn any patient from study treatment, if, in the investigator's opinion, it was not in the patient's best interest to continue. • Any patient had the right to withdraw from the study at any time. Discontinuation of study treatment, for any reason, should not have impacted the patient's participation in the study. The patient had to continue attending subsequent study visits and data collection had to continue according to the study protocol. • Patients had the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator had the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may have included but were not limited to the following: ○ Patient's withdrawal of consent from study ○ Study termination or site closure ○ Patient lost to follow-up ○ Death • In case a patient was lost to follow-up, every possible effort was made by the study site personnel to contact the patient. The measures taken to follow-up were documented. • When a patient withdrew before completing the study, the reason for withdrawal was documented in the eCRF and in the source documents. Patients who withdrew consent were encouraged to complete the safety follow-up assessments before withdrawing consent, but these assessments were not mandated once consent was withdrawn. • Patients who were withdrawn or removed from study or study treatment were not replaced.
Multiplicity	• To adjust for multiplicity due to multiple endpoints, an alpha-exhaustive recycling strategy was utilised. If the primary efficacy endpoint, IRC-assessed PFS in AV treatment arm versus FCR/BR treatment arm, achieved statistical significance, the secondary endpoints were to be tested in a fixed sequential hierarchical manner.

Abbreviations: AV: acalabrutinib with venetoclax; BR: bendamustine with rituximab; CI: confidence interval; DOR: duration of response; EDC: electronic data capture (system); eCRF: electronic case report form; EFS: event-free survival; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; IRC: Independent Review Committee; MTP: multiple testing procedure; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment.

Source: AstraZeneca Data on File; AMPLIFY CSR (Section 9.5.2, 9.8.1.2, 9.8.1.3, 9.8.3).²

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality of the AMPLIFY trial, using the RoB-2 tool, is presented in Table 10.⁹⁴ The risk of bias across all five domains, and the overall risk of bias, was judged to be low.

Table 10: Risk of bias assessment for AMPLIFY trial (RoB-2 tool)

Study	D1	D2	D3	D4	D5	Overall
AMPLIFY						

Green: low risk of bias; yellow: medium risk of bias; red: serious risk of bias. D1: Bias arising from the randomisation process; D2: bias due to deviations from intended interventions; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result.⁹⁴

Abbreviations: D: domain.

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Primary endpoint: progression-free survival

At the DCO date of the interim analysis (30th April 2024), AMPLIFY met its primary objective; treatment with AV was associated with a statistically significant and clinically meaningful improvement in IRC-assessed PFS versus FCR/BR (HR: 0.65; 95% CI: 0.49, 0.87; p-value: 0.004).

The primary endpoint of the AMPLIFY trial was IRC-assessed PFS, as defined in Table 5. At the DCO date of the interim analysis (30th April 2024), and at a median follow-up of 40.8 months (range 0–59 months), 89 (30.6%) IRC-assessed PFS events were reported for AV and 95 (32.8%) for FCR/BR. The total number of IRC-assessed PFS events across the AV and FCR/BR arms was 184 (98% information fraction of 188 IRC-assessed PFS events required for the final analysis) (Table 11). Of note, 33 patients who did not receive FCR/BR treatment were censored at Day 1, as they did not have a post-baseline assessment.

AMPLIFY met its primary objective and treatment with AV was associated with a statistically significant improvement in IRC-assessed PFS compared with FCR/BR (HR: 0.65; 95% CI: 0.49, 0.87; p-value: 0.004 [p-value boundary: 0.0469]).

The Kaplan-Meier curve for IRC-assessed PFS demonstrates a separation between arms in favour of AV from approximately three months post-randomisation and throughout the remaining duration of follow-up (Figure 5). The PFS benefit observed for AV was sustained over time, as supported by the higher proportion of patients in the AV arm who were alive and progression-free at 24 and 36 months compared with patients in the FCR/BR arm (Table 11).

Table 11: IRC-assessed PFS for AV versus FCR/BR in AMPLIFY (FAS)^a

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Event^b		
Any	89 (30.6)	95 (32.8)
Progression		
Death without progression		
Censored observations		
Any	202 (69.4)	195 (67.2)

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Censored at Day 1	1 (0.3)	33 (11.4)
No baseline disease assessment	0 (0.0)	1 (0.3)
No post-baseline response assessment	1 (0.3)	32 (11.0)
Censored due to two or more consecutively missed response assessments ^c	20 (6.9)	31 (10.7)
Censored due to subsequent anti-CLL therapy	2 (0.7)	5 (1.7)
Progression-free ^d	179 (61.5)	126 (43.4)
Progression-free at time of the analysis	178 (61.2)	120 (41.4)
Early study discontinuation	1 (0.3)	6 (2.1)
Lost to follow-up	0 (0.0)	0 (0.0)
Withdrew consent	1 (0.3)	4 (1.4)
Study exit due to investigator decision or other	0 (0.0)	2 (0.7)
PFS, months ^{e, f}		
Median (95% CI)	NC (██████) ^g	47.6 (██████)
P25, P75	██████	██████
Comparison of treatment groups (AV versus FCR/BR)		
HR (95% CI) ^h	0.65 (0.49, 0.87)	
p-value ⁱ	0.004	
Kaplan-Meier estimates of PFS probability by timepoint (%)		
12 months (95% CI)	██████████	██████████
24 months (95% CI)	██████████	██████████
36 months (95% CI)	76.5 (██████)	66.5 (██████)
48 months (95% CI)	██████████	██████████

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bIncludes events that occur within 28 weeks of last evaluable assessment (in the first 3 years after randomisation) or within 56 weeks of last evaluable assessment (3 years and later from randomisation).

^cThe threshold for two or more consecutively missed response assessments is 28 weeks in the first three years after randomisation and 56 weeks thereafter.

^dProgression-free at time of analysis.

^eThe calculation is based on the Kaplan-Meier technique.

^fThe CI for median PFS is derived based on Brookmeyer-Crowley method.

^gMedian estimate for Arm A (AV) is unstable due to low number of patients at risk.

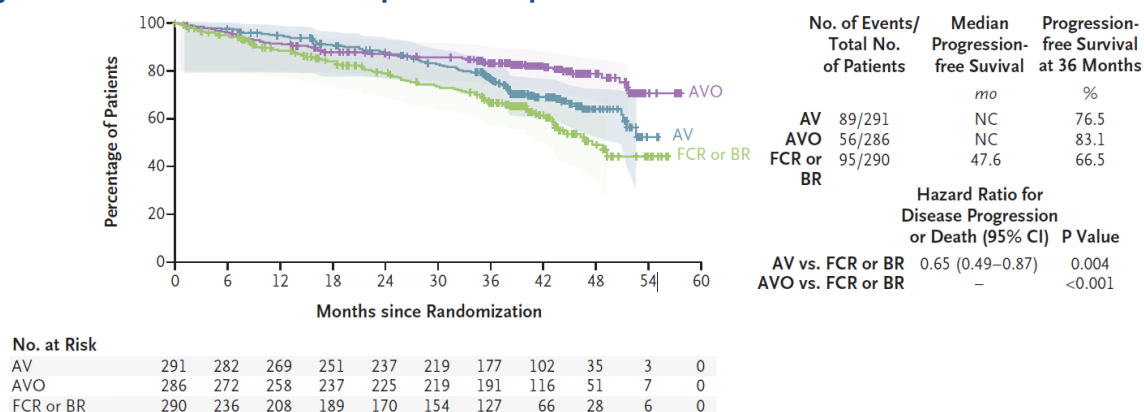
^hThe analysis is performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. Patients with no observed events are censored at the date of randomisation (if no baseline or post-baseline assessment) or last response assessment. An HR below 1 favours the AV arm over the FCR/BR arm.

ⁱThe analysis is performed using a stratified two-sided log-rank test and a method that corresponds to the Breslow approach for handling ties.⁹³

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CI: confidence interval; CLL: chronic lymphocytic leukaemia; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; NC: not calculable; P25: 25th percentile; P75: 75th percentile; PFS: progression-free survival.

Source: Brown *et al.* (2025) (Figure 2A, Table S18);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 18).²

Figure 5: IRC-assessed PFS Kaplan-Meier plot for AMPLIFY^a



^aAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. As such, results presented for AVO here are not directly relevant to the decision problem of this submission.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CI: confidence interval; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; IRC: Independent Review Committee; NC: not calculable; PFS: progression-free survival.

Source: Brown *et al.* (2025) (Figure 2A).³

2.6.2 Secondary endpoint: overall survival

At the DCO date of the interim analysis (30th April 2024), the AMPLIFY trial demonstrated that treatment with AV was associated with a statistically significant improvement in OS versus FCR/BR (HR: 0.33; 95% CI: 0.18, 0.56, nominal p-value: <0.001).

OS, as defined in Table 5, was a key secondary endpoint of the AMPLIFY trial. At the DCO date of the interim analysis (30th April 2024), 18 patients (6.2%) had died in the AV arm, and 42 patients (14.5%) had died in the FCR/BR arm (10% of maturity). The OS HR for AV versus FCR/BR was 0.33 (95% CI: 0.18, 0.56; nominal p-value: <0.001), representing a 67% reduction in the risk of death for patients who received AV versus FCR/BR. At 36 months, the Kaplan-Meier estimated probability of survival was numerically higher for AV (94.1%; 95% CI: ■■■%, ■■■%) than FCR/BR (85.9%; 95% CI: ■■■%, ■■■%) (Table 12, Figure 6).

Table 12: OS for AV versus FCR/BR in AMPLIFY (FAS)^a

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Event, n (%)		
Death	18 (6.2)	42 (14.5)
Censored observations, n (%)		
Any	273 (93.8)	248 (85.5)
Still in survival follow-up ^b	269 (92.4)	211 (72.8)
Early study discontinuation	4 (1.4)	37 (12.8)
Lost to follow-up	0 (0.0)	0 (0.0)
Withdrew consent	4 (1.4)	32 (11.0)
Study exit due to investigator decision or other	0 (0.0)	5 (1.7)
Overall survival (months)^{c, d}		
Median (95% CI)	57.8 ■■■ ^e	NC ■■■
P25, P75	■■■	■■■

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Comparison of treatment groups (AV versus FCR/BR)		
HR (95% CI) ^f	0.33 (0.18, 0.56)	
p-value ^g	<0.001	
Overall survival rate (%) ^c		
12 months (95% CI)		
24 months (95% CI)		
36 months (95% CI)	94.1	85.9
48 months (95% CI)		

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bIncludes patients not known to have died on or before DCO date.

^cThe calculation is based on the Kaplan-Meier technique.

^dThe CI for median overall survival is derived based on the Brookmeyer-Crowley method.

^eMedian estimate for Arm A (AV) is unstable due to low number of patients at risk.

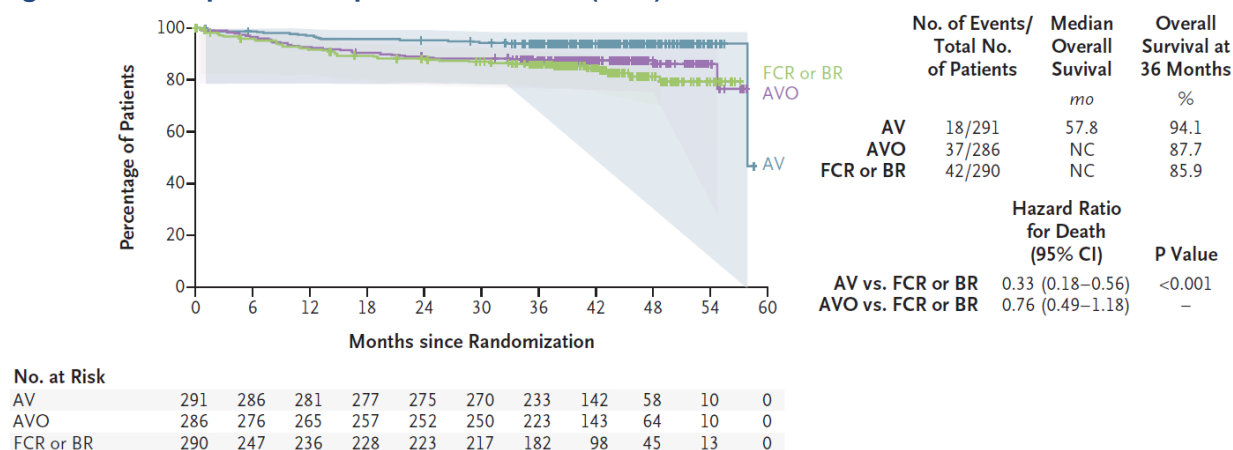
^fThe analysis is performed using a stratified Cox proportional hazards model with ties = Efron and the stratification variables included in the strata statement and the CI calculated using the profile likelihood approach. Patients with no observed events are censored at the last known alive date. A HR below 1 favours the AV arm over the FCR/BR arm.

^gThe p-value is based on the stratified log-rank test.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CI: confidence interval; DCO: data cut-off; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; NC: not calculable; P25: 25th percentile; P75: 75th percentile.

Source: Brown *et al.* (2025) (Figure 2C and Table S18);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 23).²

Figure 6: OS Kaplan-Meier plot for AMPLIFY (FAS)^{a, b}



^aAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. As such, results presented for AVO here are not directly relevant to the decision problem of this submission.

^bThe tail end of the Arm A (AV) curve is unstable due to low number of patients at risk.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CI: confidence interval; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; NC: not calculable; OS: overall survival.

Source: Brown *et al.* (2025) (Figure 2C).³

2.6.3 Secondary endpoint: MRD negativity rate

MRD negativity rate was a key secondary endpoint in the AMPLIFY trial (Table 5). A total of 78 (26.8%) patients who were treated with AV and 148 (51.0%) who were treated with FCR/BR achieved uMRD at Cycle 9 and at 12 weeks post-Cycle 6, respectively (see Figure 7). The risk ratio for uMRD with AV versus FCR/BR was in favour of FCR/BR (risk ratio: 0.5; 95% CI: 0.4,

0.7; p-value: <0.0001) (Table 13), despite the statistically significant improvement observed in PFS and OS for AV compared with FCR/BR.

Although uMRD has been previously suggested to correlate with PFS outcomes in patients with CLL, this connection is less clear for combination therapies with venetoclax and a BTKi than for combination therapies such as venetoclax and the anti-CD20 antibody, obinutuzumab.³ Further follow-up in the AMPLIFY trial is needed to determine how well uMRD is sustained, and the predictive implications of uMRD status on long-term outcomes. In addition, the uMRD data from the AMPLIFY trial should be interpreted with caution, as MRD assessments for the key secondary endpoint were made before treatment completion in the AV arm (Figure 7). This was done in order to align the assessment schedules for patients receiving AV and FCR/BR. Specifically, uMRD in peripheral blood was measured at the start of Cycle 9 in the AV group, but 12 weeks after the start of Cycle 6 (i.e., the last cycle of treatment) in the FCR/BR group. MRD assessments were also performed following treatment completion, and three months after treatment completion (Figure 7).

Ultimately, MRD negativity is not considered a key outcome for driving treatment decisions in UK clinical practice, with MRD testing not routinely conducted or funded by the NHS, as confirmed by clinical experts interviewed by AstraZeneca.¹⁵ This was further supported by feedback from UK clinical experts participating in a modified Delphi panel conducted by AstraZeneca, who agreed that MRD negativity is less important than PFS for guiding treatment decisions in patients with CLL (see Section 2.10.5). Further details regarding the utility of MRD assessment in clinical practice are provided in Section 2.13.1.

Table 13: Peripheral blood MRD for AV versus FCR/BR in AMPLIFY (FAS)^a

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Patients with MRD measurement, n (%)^b	244 (83.8)	190 (65.5)
uMRD, n (%)^c	78 (26.8)	148 (51.0)
95% CI	22.0, 32.1	45.3, 56.8
Comparison of treatment groups (AV versus FCR/BR)^d		
Risk ratio (95% CI)	0.5 (0.4, 0.7)	
p-value	<0.0001	

^aResults for the AVO arm are not presented but can be found in Brown *et al.* (2025).³

^bPatients with an MRD measurement at Cycle 9 (AV arm) or 12 weeks after the start of Cycle 6 (FCR/BR arm).

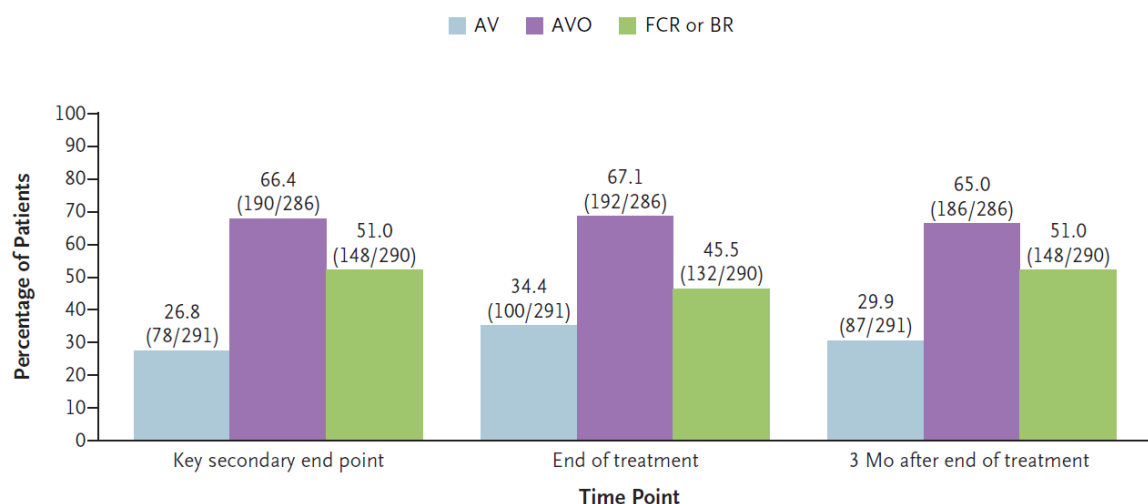
^cuMRD is defined as <1 CLL cell per 10,000 (10⁻⁴) leukocytes unless otherwise indicated. uMRD is based on the AV arm at the start of Cycle 9 and the FCR/BR arm at 12 weeks after the start of Cycle 6. The confidence interval for uMRD is derived based on exact methods.

^dThe CI for the risk ratio for AV versus FCR/BR is derived based on exact methods. The p-value for comparison versus the FCR/BR arm is based on the Cochran–Mantel–Haenszel test, adjusted for randomisation stratification factors.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BOR: best overall response; BR: bendamustine with rituximab; CI: confidence interval; CLL: chronic lymphocytic leukaemia; CR: complete response; CRi: complete response with incomplete marrow recovery; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; IRC: Independent Review Committee; MRD: minimal residual disease; uMRD: undetectable minimal residual disease.

Source: Brown *et al.* (2025) (Table S4).³

Figure 7: Percentage of patients in AMPLIFY with uMRD in the peripheral blood at the key secondary endpoint, at the end of treatment and three months after the end of treatment (FAS)^{a, b}



^aKey secondary endpoint based on peripheral blood MRD measurement at the start of Cycle 9 for the AV arm and at 12 weeks after the start of Cycle 6 for the FCR/BR arm.

^bAs detailed in Section 1.1, AstraZeneca are seeking reimbursement for AV only. As such, results presented for AVO here are not directly relevant to the decision problem of this submission.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FAS: full analysis set; FCR: fludarabine with cyclophosphamide and rituximab; uMRD: undetectable minimal residual disease.

Source: Brown *et al.* (2025) (Figure 3A).³

2.6.4 Exploratory endpoint: health-related quality of life

Treatment with AV was associated with no clinically meaningful deterioration in PROs, as measured by EQ-5D, EORTC QLQ-C30 and FACIT-Fatigue. Improvements in HRQoL during and after treatment were generally greater in the AV arm versus the FCR/BR arm, owing to fewer AEs and lower long-term toxicity.

Multiple HRQoL questionnaires were used to capture PROs at baseline and at scheduled assessments in AMPLIFY. The main HRQoL questionnaires relevant to this submission are the EQ-5D, EORTC QLQ-C30 and FACIT-Fatigue:

- EQ-5D-5L is a well-established generic instrument for describing and valuing HRQoL. It is based on a descriptive system that defines health in terms of five 'dimensions': Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has five response categories or 'levels', corresponding to no/slight/moderate/severe/extreme problems. Patients are also asked to rate how they feel on the day of assessment using a visual analogue scale (VAS).⁹⁵
- The EORTC QLQ-C30 is an internationally validated and widely used measure designed to assess the HRQoL of cancer patients participating in clinical trials.⁹⁶ The 30-item measure considers the global health status, and the physical, role, emotional, cognitive, and social functioning of patients, as well as common cancer symptoms experienced by patients. A higher overall QLQ-C30 summary score indicates better HRQoL (range: 0–100).⁹⁶
- FACIT-Fatigue is a validated 13-item instrument which assesses fatigue and its impact on cancer patients' quality of life. The fatigue measure uses a five-point Likert-type scale that

ranges from “not at all” to “very much,” giving patients the ability to grade their fatigue and how it impacts their daily activities and functions.⁹⁷

An overview of the PRO measures reported in the AMPLIFY trial is presented below, with full results presented in Appendix J.7.

EQ-5D

EQ-5D VAS scores gradually improved over the course of active treatment across the AV and FCR/BR arms, indicative of treatment effect on tumour burden reduction, and control of underlying CLL disease-related symptoms.

At the safety follow-up, patients who received AV experienced a greater improvement in VAS score from baseline [REDACTED] versus those receiving FCR/BR [REDACTED]. This may partially be due to the lower incidence of treatment-emergent adverse events (TEAEs) reported for the AV arm (see Section 2.10 for further details on TEAEs). Patients in the AV arm experienced an increase in VAS scores at 1-, 2 and 3-years post-treatment follow-up, whilst in the FCR/BR arm, an increase in scores started at around 2-years post-treatment follow-up, indicative of the treatment-related adverse impact on reported health status beyond the TEAE reporting period.

Overall, the scores indicate better patient-reported health status following the active treatment phase for AV and FCR/BR, suggesting an inherent benefit from treatment regimens with defined treatment duration. However, they also reflect the impact of FCR/BR-related toxicity on delaying this improvement in HRQoL following treatment.

EORTC QLQ-C30

Quality of life was measured using the two-item Global Health Status scale in the EORTC QLQ-C30. Overall, the mean change from baseline Global Health Status score showed a gradual improvement, reaching a maximum increase of [REDACTED] points at the safety follow-up, indicating a clinically meaningful improvement in health status for patients receiving AV. In the FCR/BR arm, the Global Health Status score had also gradually increased by the safety follow-up, though to a lesser extent than the AV arm, reaching [REDACTED]. At 3-years post-treatment follow-up, the mean change from baseline score remained higher in the AV arm compared with the FCR/BR arm ([REDACTED]).

FACIT-Fatigue

The FACIT-Fatigue scores, as measured by three different scales, Global Fatigue Scale (GFS), Fatigue Symptom Score (FSS), and Fatigue Impact Score (FIS) were evaluated in [REDACTED] and [REDACTED] patients treated with AV and FCR/BR, respectively.

The mean change from baseline in FACIT-Fatigue scores showed a small improvement in fatigue symptoms during treatment and follow-up for the AV and FCR/BR arms, although these changes were not clinically meaningful, as defined by an absolute change in score of five points in any arm. This highlights that the clinical benefit of active treatment was not associated with a clinically meaningful deterioration in HRQoL.

2.7 Subsequent treatments

At the DCO date of the interim analysis (30th April 2024), a total of [REDACTED]/291 ([REDACTED]) patients receiving AV, and [REDACTED]/290 ([REDACTED]) patients receiving FCR/BR, had experienced disease progression.

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In terms of subsequent therapies received in second-line, 100/291 (34%) patients in the AV arm and 100/290 (34%) patients in the FCR/BR arm received subsequent anti-cancer therapy, as shown in Table 14. Overall, the proportion of patients receiving subsequent therapies and the specific subsequent therapies received were well-balanced between treatment arms.

In clinical expert interviews conducted by AstraZeneca, it was noted that, given its global nature, the subsequent treatment distribution in the AMPLIFY trial was not fully reflective of UK clinical practice.¹⁵ For example, some patients received subsequent treatment with rituximab, obinutuzumab, nemtabrutinib and azacitidine, none of which are reimbursed for CLL in any setting in the UK. Moreover, due to the immaturity of data from the AMPLIFY trial, the overall proportion of patients who received subsequent treatment is lower than would be expected in clinical practice.¹⁵ Further details on the subsequent treatment distribution expected for the population of relevance to this submission based on feedback from UK clinical experts, and how this compares to the subsequent treatments in the AMPLIFY trial, are presented in Section 3.5.2.

Table 14: Subsequent anti-cancer treatments received in AMPLIFY (FAS)^{a, b}

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Any post-cancer therapy	100	100
Antineoplastic agents (L01)	100	100
Venetoclax	100	100
Acalabrutinib	100	100
Ibrutinib	100	100
Rituximab	100	100
Zanubrutinib	100	100
Obinutuzumab	100	100
Nemtabrutinib	100	100
Bendamustine	100	100
FCR	100	100
Rituximab; venetoclax	100	100
BR	100	100
Doxorubicin	100	100
Pirtobrutinib	100	100
Azacitidine	100	100
BGB 11417	100	100
Bleomycin; dacarbazine; doxorubicin hydrochloride; vinblastine sulphate	100	100
Cemiplimab	100	100
Chlorambucil	100	100
Cyclophosphamide	100	100
Idelalisib	100	100
Other antineoplastic agents	100	100
Vincristine	100	100
Investigational drug (V98)	100	100
Investigational drug	100	100

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bPatients are counted once per the Anatomical Therapeutic Chemical Classification and generic drug name regardless of the frequency of medication usage.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab.

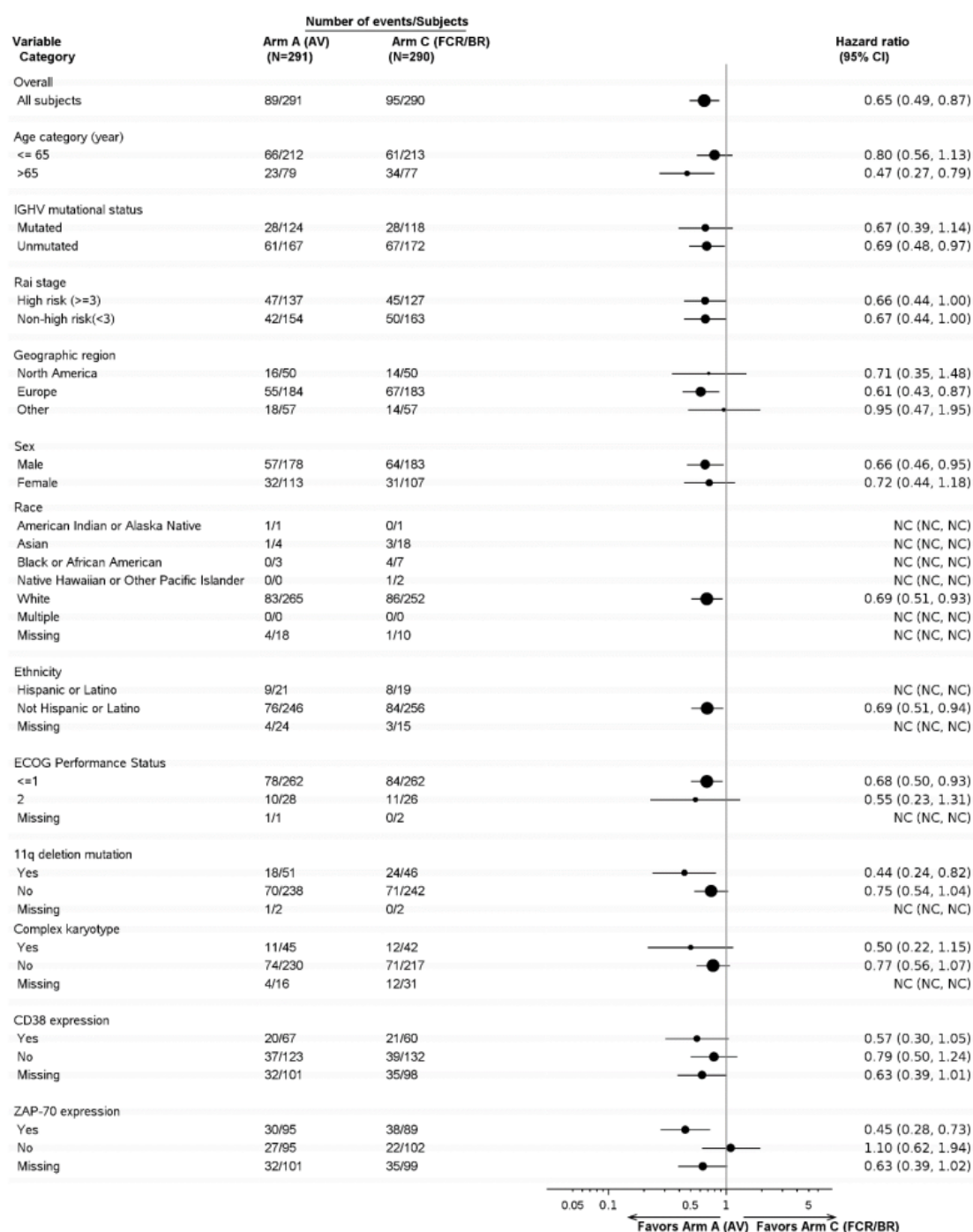
Source: AstraZeneca Data on File, 2025 (AMPLIFY TLF; Table 14.1.13).⁹⁸

2.8 Subgroup analysis

Subgroup analyses were conducted for the primary (IRC-assessed PFS) and key secondary (OS) endpoints. The results of the IRC-assessed PFS subgroup analyses are presented in this section, and the OS subgroup analyses are presented in Appendix C.

An improvement in PFS in favour of treatment with AV compared with treatment with FCR/BR was observed across the majority of the pre-specified subgroups (see Figure 8). This supports a treatment benefit for AV over FCR/BR that is consistent with the primary analysis. Some variability in PFS results was observed, but this can likely be attributed to the small sample size of some of the subgroups.

Figure 8: Forest plot for subgroup analyses of IRC-assessed PFS for AV and FCR/BR in AMPLIFY (FAS)^a



^aDue to too few events in some of the subgroups across both arms, HR and 95% CI are presented as NC.

Abbreviations: AV: acalabrutinib with venetoclax; BR: bendamustine with rituximab; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; *IgHV*: immunoglobulin heavy-chain variable region gene; NC: not calculable; PFS: progression-free survival.

Source: Brown *et al.* (2025) (Figure S3A).³

2.9 Meta-analysis

Although two studies were identified for AV (Swaminathan *et al.* [2024], AMPLIFY), only the AMPLIFY trial evaluated PFS and OS outcomes for AV in the relevant patient population and

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indication.^{3, 82} Therefore, conducting a meta-analysis was not necessary for this submission.

2.10 Indirect and mixed treatment comparisons

An SLR identified no head-to-head studies comparing AV with the relevant fixed-duration comparators VenI and VenO. As such, an indirect estimate of comparative efficacy was required for this submission.

- The SLR identified 53 unique studies which were screened for inclusion in a feasibility assessment to determine the feasibility of conducting a network meta-analysis (NMA).
- A total of 14 studies were included in the NMA feasibility assessment: 12 RCTs and two single-arm studies. Eight investigated interventions of relevance to this submission (AV, VenI, VenO); one study for AV (AMPLIFY),³ four studies for VenI (CAPTIVATE FD,⁸³ GLOW,³⁷ Jain *et al.* [2019]⁸⁷ and FLAIR)⁸⁶ and three studies for VenO (CLL13,⁸⁸ CLL14,⁵⁵ CRISTALLO).⁸⁹
- The studies were comprehensively assessed for similarity (no difference in known and unknown effect modifiers between studies) and homogeneity (the need for sufficient homogeneity in terms of trial eligibility criteria, study design and conduct, methods of treatment administration, and statistical variation).

Based on the NMA feasibility assessment, key assumptions for an NMA – homogeneity, similarity, exchangeability – were violated, rendering the conduct of an NMA infeasible.

- Substantial heterogeneity between studies was present in terms of patient inclusion criteria, trial design and intervention protocols. This was compounded by treatment switching in control arms, recruitment during the COVID-19 pandemic (potentially impacting outcomes) and varying follow-up periods.
- Several important prognostic factors and treatment effect modifiers (TEMs) also differed substantially between studies.

Given the infeasibility of conducting an NMA, population-adjusted indirect treatment comparisons (ITCs), such as matching-adjusted indirect treatment comparisons (MAIC) and simulated treatment comparisons (STC) were considered, focusing on studies investigating AV, VenI and VenO only.

- Due to poor overlap in key characteristics between AMPLIFY and the comparator studies, a MAIC was considered infeasible; this undermines the positivity assumption required for MAICs and would lead to substantial reductions in effective sample size and potential bias.
- Regression-based approaches such as STCs are more appropriate in this context, as they do not suffer from a reduction in effective sample size as a result of population adjustment, provided that extrapolation beyond the range of individual patient-level data is valid.⁹⁹

An STC was ultimately deemed the most suitable approach. Results of the STCs showed no statistically significant differences in the efficacy of AV in terms of PFS and OS compared with VenI and VenO.

- STCs were conducted between AV (based on the AMPLIFY trial),³ VenI (GLOW and CAPTIVATE FD)^{37, 83} and VenO (CLL14).⁵⁵ In addition, an anchored ITC using CLL13 (VenO) was deemed possible through the common comparator arm (FCR/BR) using the Bucher method.¹⁰⁰
- In the primary analyses, unanchored STCs were conducted to estimate restricted mean survival time (RMST) for each arm, and included all available covariates reported by the included studies.

- For PFS, at 55.1 months follow-up, there was no statistically significant difference in RMST for AV compared with VenI in the pooled analysis with CAPTIVATE FD and GLOW (RMST difference: [REDACTED] [95% CI: [REDACTED]]), or GLOW only (RMST difference: [REDACTED] [95% CI: [REDACTED]]). The findings were similar for the comparative analysis with CLL14 for VenO (RMST difference: [REDACTED] [95% CI: [REDACTED]]).
- For OS, at 57.7 months follow-up, there was no statistically significant difference in RMST for AV compared with VenI in the pooled analysis with CAPTIVATE FD and GLOW (RMST difference: [REDACTED] [95% CI: [REDACTED]]), or GLOW only (RMST difference: [REDACTED] [95% CI: [REDACTED]]). The findings were similar for the comparative analysis with CLL14 for VenO (RMST difference: [REDACTED] [95% CI: [REDACTED]]).
- Results of the Bucher ITC between AMPLIFY and CLL13 demonstrated that the difference in RMST for OS at 57.1 months follow-up was statistically significant and in favour of AV versus VenO (RMST difference: [REDACTED] [95% CI: [REDACTED]]), whereas the difference in RMST for PFS at 55.1 months follow-up was not statistically significant (RMST difference: [REDACTED] [95% CI: [REDACTED]]).

A modified Delphi panel was conducted with 22 UK clinical experts to explore clinical consensus on the expected comparative efficacy of AV versus VenI and VenO in real-world practice and validate the ITC findings. Consensus was reached in Round 1 of the Delphi panel that AV would be considered clinically comparable in terms of PFS and OS to VenI and VenO.

- 22 UK clinical experts took part in a modified Delphi panel across July and August 2025. All 22 took part in the first round; 16 took part in the second round.
- Results from Round 1 of the modified Delphi panel indicated that AV is considered clinically comparable to VenI and VenO in terms of PFS and OS.
- Whilst consensus was reached in Round 1 that AV and VenO would be considered clinically comparable in terms of safety, consensus was not reached for the same question versus VenI. In Round 2, consensus was obtained that fixed-duration AV would have a more favourable safety profile than fixed-duration VenI.

In conclusion, the results of the ITCs and the modified Delphi panel demonstrate that AV can be considered clinically comparable in terms of PFS and OS to VenI and VenO.

2.10.1 Identification and selection of relevant studies

As previously highlighted in Section 1.2.3, VenI and VenO are the only relevant comparators to AV in this submission. Since the efficacy of AV, VenI and VenO have not been directly compared in any head-to-head clinical studies, an ITC was required to determine the efficacy of AV compared with VenI and VenO for this submission.

An SLR was conducted in October 2024 and subsequently updated in June 2025 to identify studies on treatments in patients with untreated CLL. Full details of the methodology and results of the SLR are presented in Appendix B. The overall scope of the SLR was broad, as it was conducted from a global perspective, and therefore included studies that investigated therapies beyond AV, VenI and VenO. In total, 53 unique studies, including 27 RCTs, 24 single-arm trials and two non-randomised studies were identified.

Firstly, a feasibility assessment was conducted to determine the feasibility of conducting an NMA. The studies identified in the SLR were screened for inclusion within the feasibility

assessment, and initially excluded if they:

- Were an RCT that was disconnected from the network and did not evaluate a comparator treatment of interest (VenI or VenO). If a study could be connected to the network, and provided a potentially informative loop of evidence, this study was retained in the network even if it did not include VenI, VenO or AV.
- Were an RCT that compared two chemoimmunotherapy regimens, for example, variations of FCR treatment.
- Did not report PFS or OS outcomes.

Of the 53 studies identified in the SLR, 12 RCTs and two single-arm studies met the eligibility criteria for inclusion in the feasibility assessment. The characteristics of these studies are summarised in Table 15. As this feasibility assessment formed a part of a wider global exercise conducted by AstraZeneca, a number of therapies not relevant to this submission were included when assessing the feasibility of an NMA, and retained if they formed a potentially informative loop of evidence (as indicated by the green highlighting in Table 15).

Table 15: Study characteristics and key inclusion criteria for the 14 studies included in the feasibility assessment for ITC

Study	Study design	Country	Study enrolment period	Follow-up period as of the latest DCO (months)	Study inclusion criteria					Treatment arm	N
					Cytogenetics	Age	ECOG PS	CIRS	Creatinine clearance (mL/min)		
AMPLIFY³	Open-label phase III RCT	27 countries	2019–24	36	Without del(17p) or <i>TP53</i> mutation	≥18	≤2	<6	≥50	AV	291
										AVO	286
										FCR/BR	290
ELEVATE-TN¹⁰¹	Open-label phase III RCT	18 countries	2015–17	72	Not restricted	≥65, or ≥18 with comorbidities	≤2	>6	30–69	Acalabrutinib-Obinutuzumab	179
										Acalabrutinib	179
										OC1b	177
CLL11⁵⁷	Open-label phase III RCT	26 countries	2010–12	36	Not restricted	≥18	-	>6	<70	OC1b	333
										Rituximab-Chlorambucil	330
										Chlorambucil	118
CLL13⁸⁸	Open-label phase III RCT	9 EU countries & Israel	2016–19	48	Without del(17p) or <i>TP53</i> mutation	≥18	≤2	<6	≥ 70	FCR/BR	229
										Venetoclax-Rituximab	237
										VenO	229
										Venetoclax-Obinutuzumab-Ibrutinib	231
CLL14⁵⁵	Open-label phase III RCT	21 countries	2014–18	72	Not restricted	≥18		>6	<70	VenO	216
										OC1b	216
GLOW³⁷	Open-label phase III RCT	14 countries	2018–19	64	Not restricted	≥65, or ≥18 with comorbidities	≤2	>6	<70	VenI	106
										OC1b	105
ALLIANCE¹⁰²	Phase III RCT	USA & Canada	2013–16	55	Not restricted	≥65	≤2	-	≥ 40	BR	183
										Ibrutinib	182
										Ibrutinib-Rituximab	182
Change¹⁰³	Open-label phase III RCT	5 Asian countries	2020–24	–	Without del(17p) or <i>TP53</i> mutation	≥65, or ≥18 with comorbidities	–	>6	30–69	Acalabrutinib	77
										Rituximab-Chlorambucil	78
			2013–15	60		≥65	≤2	-		Ibrutinib	136

Study	Study design	Country	Study enrolment period	Follow-up period as of the latest DCO (months)	Study inclusion criteria					Treatment arm	N
					Cytogenetics	Age	ECOG PS	CIRS	Creatinine clearance (mL/min)		
RESONATE-2 ¹⁰⁴	Open-label phase III RCT	16 countries			Without del(17p) or TP53 mutation				Adequate renal function	Chlorambucil	133
CRISTALLO ⁸⁹	Open-label phase III RCT	5 countries	2020–23	Fit	≥18	-	≤6	≥ 70	-	VenO	80
										FCR/BR	86
FLAIR ⁸⁶	Open-label phase III RCT	UK	Ongoing	48	Without <i>TP53</i> abnormalities	≥18 to ≤75	WHO ≤2	-	-	VenI (MRD guided)	260
										FCR	263
E1912 ¹⁰⁵	Open-label phase III RCT	USA	2014–16	36	Without del(17p) or <i>TP53</i> mutation	<70	≤2	-	-	Ibrutinib-Rituximab	354
										FCR/BR	175
CAPTIVATE FD ⁸³	Open-label, phase 2 single-arm trial	5 countries	2016–20	36	Not restricted	≥18 to <70	≤2	-	Adequate renal function	VenI	159
Jain et al. (2019) ⁸⁷	Open-label, phase 2 single-arm trial	USA	2016–18	36	Not restricted	≥65, or ≥18 with >1 high-risk genetic feature	≤2	-	>50	VenI	80

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; ITC: indirect treatment comparison; OC1b: obinutuzumab with chlorambucil; RCT: randomised controlled trial; WHO: World Health Organization performance status; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

2.10.2 Feasibility assessment

A comprehensive assessment was conducted to determine the feasibility of conducting an ITC, and the most appropriate method of doing so. The feasibility assessment evaluated the similarity and homogeneity of the identified trials with respect to study design, eligibility criteria, treatment administration and study outcomes. Similarity and homogeneity were defined as:

- **Similarity:** Assumes that no differences exist in known and unknown treatment effect modifiers between studies
- **Homogeneity:** Refers to the need for sufficient homogeneity in terms of clinical, methodological and statistical variation across studies, to justify the combining of results

2.10.2.1 Similarity and homogeneity assessment across trials

Identification of potential prognostic factors and TEMs

To assess the similarity and homogeneity between studies, patient and disease characteristics that may act as potential prognostic factors and TEMs in CLL were first identified. Prognostic factors and/or TEMs in CLL were defined as:

- Prognostic factors: covariates that affect or are prognostic of outcomes
- TEMs: covariates that alter the effect of treatment on outcomes, so that the treatment is effective in different subgroups related to the effect modifier

Potential prognostic factors and TEMs were identified through a targeted review of the literature, clinical trials, clinical guidelines, previous NICE evaluations and clinician feedback (see Appendix B.5.1 for full details of the search methods and results of this targeted review). Based on these sources, the following factors were identified as being prognostic factors and/or TEMs in patients with CLL:

- Age group
- Clinical staging
- *TP53* mutational status
- *IgHV* mutational status
- β 2-microglobulin concentration
- Patient sex
- ECOG PS
- Comorbidities
- Bulky disease
- Creatinine clearance rate
- Chromosomal abnormalities (trisomy 12, del[11q], del[17p] and del[13q]).

Similarity and homogeneity assessment across trials

Study design and conduct

All of the RCTs reviewed as part of the feasibility assessment were phase III clinical trials, with the majority (11 out of 12) being open-label and conducted across multiple countries. Most

studies were multinational, although two were confined to a single country; one in the UK (FLAIR) and the other in the US (E1912).^{86, 105} A few studies were conducted across a single continent, such as ALLIANCE (US and Canada) and ChangE (Asia).^{102, 103}

Treatment switching from the comparator arm to the experimental therapy at disease progression was permitted in three trials, namely ELEVATE-TN, ALLIANCE, and CLL11.^{57, 101, 102} The inclusion of such crossover designs could introduce bias, particularly in estimates of OS, as exposure of patients in the comparator arm to the experimental treatment could diminish apparent differences.

All studies were conducted after 2010, with follow-up ranging from 36 to 72 months. Four of the studies recruited patients during the COVID-19 pandemic period (2020–2023), including AMPLIFY (enrolment 2019–2024), ChangE (enrolment 2020–2024), CRISTALLO (enrolment 2020–2023) and CAPTIVATE FD (enrolment 2016–2020).^{3, 83, 89, 103} In another two studies (CLL13 and GLOW), the follow-up period substantially overlapped with the COVID-19 pandemic.^{37, 88} Multiple real-world studies have found a statistically significant correlation between the use of anti-CD20 agents and venetoclax, and the risk or severity of COVID-19 infection.^{106, 107} Given that patients receiving anti-CLL treatment may exhibit a higher risk of severe COVID-19, the differential impact of COVID-19 on the trial conduct, processes and outcomes in these studies, but not on the others, could represent a potential source of bias in an ITC.

The majority of studies (n=12) fell into two broad categories in terms of their patient populations. Six studies (AMPLIFY, CLL13, CRISTALLO, FLAIR, E1912, and CAPTIVATE FD) considered predominantly younger patients (typically under 65 years old), with low comorbidity burden (CIRS score ≤ 6), and adequate renal function (creatinine clearance ≥ 70 mL/min).^{3, 83, 86, 88, 89, 108} Conversely, another six studies (ELEVATE-TN, CLL11, CLL14, GLOW, ChangE and Jain *et al.* [2019]), focused predominantly on older individuals (≥ 65 years), or those aged 18–65 with markers of higher disease burden or comorbidities, such as CIRS > 6 , creatinine clearance < 70 mL/min, or high-risk genetic features like *TP53* mutations or del(17p).^{37, 55, 57, 87, 101, 103}

Whilst the patient populations across most studies could generally be grouped based on those that were younger with low comorbidity burden versus those that were older with high comorbidity burden, other specific eligibility criteria varied significantly. For example, the inclusion/exclusion guidelines regarding cytogenetic abnormalities differed: no restrictions on any patients (four studies), complete exclusion on patients with high-risk genetic features such as del(17p)/*TP53* mutation (five studies) or del(17p) only (two studies), and age-based cytogenetic exclusions (two studies). FLAIR had a unique criterion of only excluding patients with $> 20\%$ del(17p) or *TP53* abnormality.⁸⁶ There were also differences in the inclusion criteria for age, varying from adults over 18 years (nine studies), adults excluding elderly patients (three studies), to only elderly patients over 65 years (two studies). In addition, some studies that recruited ≥ 18 years olds only included patients if they had comorbidities or high-risk genetic features, otherwise they had to be over the age of 65 (four studies). Most studies specified an ECOG PS of 0 to 2. However, there was a mix of criteria used for fitness level as measured by the CIRS, which was typically categorised as less than 6, or over 6, indicating low or high comorbidity burden, respectively. There were also different inclusion thresholds across studies for creatinine clearance, which measures renal function.

Baseline characteristics

As outlined in Section 2.10.1, several patient characteristics were identified as being prognostic factors and TEMs in CLL. The heterogeneity in some of these key characteristics is discussed

below. Further details are provided in Appendix B.5.2.

An overview of baseline characteristics for the studies included in the feasibility assessment is presented below in Table 16. Baseline patient characteristics highlighted notable heterogeneity across the studies. Median age ranged from approximately 57 to 74 years. The distribution of clinical stage, assessed by Binet or Rai classifications, ranged from 28% to 57% for patients presenting with advanced disease (Binet C or Rai III–IV). Regarding genetic markers, the proportion of patients with high-risk cytogenetic abnormalities like del(17p) or *TP53* mutations also varied, with some studies restricting inclusion to non-high-risk patients and others only including high-risk individuals. The prevalence of unmutated *IgHV* status ranged from 43% to 83%, reflecting the heterogeneity in disease biology among study populations (see Appendix B.5.2).

Additional baseline features also differed significantly. The proportion of males ranged from roughly 56% to 75%, and most patients had a good performance status, with ECOG scores of 0 or 1 in 87% to nearly 100% of cases. The burden of comorbidities, measured by CIRS, varied widely, with some studies including only patients with minimal comorbidities, while others allowed patients with high comorbidity scores (CIRS >6). The presence of bulky disease (≥ 5 cm) was reported in about 25% to nearly 43% of patients across five studies. Renal function, indicated by median creatinine clearance, also ranged from approximately 63 to 95 mL/min, influencing eligibility, especially in older or more frail populations.

Finally, other chromosomal abnormalities such as del(11q), del(13q), and trisomy 12 were documented across studies, with their proportions varying. For example, del(11q) was present in 12% to 25% of patients, while del(13q) ranged from 24% to over 56% (see Appendix B.5.2). These genetic features are important prognostic factors and could impact treatment responses and outcomes.

In summary, the trials incorporated diverse patient populations with significant variability in baseline characteristics, eligibility criteria, and disease features. Understanding these differences is important when interpreting the study results and considering their inclusion within an NMA.

Table 16: Baseline characteristics of the studies included in the feasibility assessment

Study	Treatment arm	N	Age (median)	Age >65 years (%)	Male sex (%)	ECOG PS 0–1 (%)	Rai stage III/IV (%)	Bulky disease ≥5cm (%)	CIRS >6 (%)	Creatinine clearance mL/min (median)	Beta-2 microglobulin > 3.5 mg/L (%)	TP53 mutation (%)	Del(17p) (%)
AMPLIFY³	AV	291	61	27.1	61.2	90.0	47.1	38.8	2.1	-	58.1	0.0	0.0
	AVO	286	61	26.6	69.2	95.1	40.6	35.0	0.3	-	52.8	0.0	0.0
	FCR/BR	290	61	26.6	63.1	90.3	43.8	42.8	1.0	-	49.3	0.0	0.0
ELEVATE-TN¹⁰¹	Acalabrutinib-Obinutuzumab	179	70	80.4	62	94.4	48.0 ^b	25.7	16.8	76.5	73.7	11.7	9.5
	Acalabrutinib	179	70	84.4	62	92.2	48.6 ^b	38.0	11.7	75	78.2	10.6	8.9
	OC1b	177	71	86.4	59.9	94.4	44.1 ^b	31.1	8.5	70	74.6	11.9	9
CLL11⁵⁷	OC1b	333	74	81	61	-	35 [*]	-	78	62.5	36	-	7
	Rituximab-Chlorambucil	330	73	78	62	-	37 [*]	-	75	62.6	39	-	7
	Chlorambucil	118	72	78	64	-	37 [*]	-	78	63.8	39	-	10
CLL13⁸⁸	Venetoclax-Rituximab	237	62	35.9	73.8	-	44.3	-	-	84.5	63.6	0.0	0.0
	Venetoclax-Obinutuzumab-Ibrutinib	231	60	35.9	68.4	-	44.3	-	-	86.2	63.8	0.0	0.0
	VenO	229	62	35.8	74.7	-	40.8	-	-	86.3	59.9	0.0	0.0
	FCR/BR	229	61	34.5	71.2	-	47.1	-	-	86.3	68.0	0.0	0.0
CLL14⁵⁵	OC1b	216	71	-	66.2	88.4 ^b	42.6 ^a	-	81.9	67.4	61.8	8.3	7.3
	VenO	216	72	-	67.6	87.0 ^b	43.1 ^a	-	86.1	65.2	59.4	11.1	8.5
GLOW³⁷	OC1b	105	71	89.5	60	88.5 ^b	52.5	36.2	58.1	63.2	73.3	1.9	0.0
	VenI	106	71	84.9	55.7	87.7 ^b	57.3	39.0	69.8	66.5	69.8	6.6	0.0
ALLIANCE¹⁰²	BR	183	70	-	65	95 ^b	54	-	-	67	-	9	8
	Ibrutinib	182	71	-	68	97 ^b	54	-	-	69	-	9	5
	Ibrutinib-Rituximab	182	71	-	69	99 ^b	54	-	-	67	-	12	6
ChangE¹⁰³	Acalabrutinib	77	-	-	-	-	-	-	-	-	-	0.0	0.0
	Rituximab-Chlorambucil	78	-	-	-	-	-	-	-	-	-	0.0	0.0

Study	Treatment arm	N	Age (median)	Age >65 years (%)	Male sex (%)	ECOG PS 0–1 (%)	Rai stage III/IV (%)	Bulky disease ≥5cm (%)	CIRS >6 (%)	Creatinine clearance mL/min (median)	Beta-2 microglobulin > 3.5 mg/L (%)	TP53 mutation (%)	Del(17p) (%)
RESONATE-2 ¹⁰⁴	Ibrutinib	136	73	-	65	92 ^b	44	40	31	-	62	-	0.0
	Chlorambucil	133	72	-	61	91 ^b	47	30	33	-	67	-	0.0
CRISTALLO ⁸⁹	Venetoclax–Obinutuzumab	80	62	33.8	68.8	-	-	-	0.0	-	-	0.0	0.0
	FCR/BR	86	61	33.7	66.3	-	-	-	0.0	-	-	0.0	0.0
FLAIR ⁸⁶	VenI (MRD guided)	260	62	31.2	71.5	96.1 ^b (WHO)	41.9 ^a	-	-	83.0	-	0.4	0.0
	FCR	263	62	31.2	71.1	95.0 ^b (WHO)	42.2 ^a	-	-	79.0	-	0.0	0.0
E1912 ¹⁰⁵	Ibrutinib–Rituximab	354	56.7 ^c	-	66.7	97.4 ^b	44.1	-	-	94.8	51.9	-	0.6
	FCR	175	56.7 ^c	-	68.6	98.3 ^b	41.1	-	-	94.5	48.0	-	0
CAPTIVATE FD ⁸³	VenI	159	60	28.0	67.0	100.0	28.0	30.0	-	-	-	10.0	13.0
Jain et al. (2019) ⁸⁷	VenI	80	65	54.0	71.0	-	51.0	-	-	-	-	14.0	18.0

^aBinet stage C.

^bSummed percentages from reported categories.

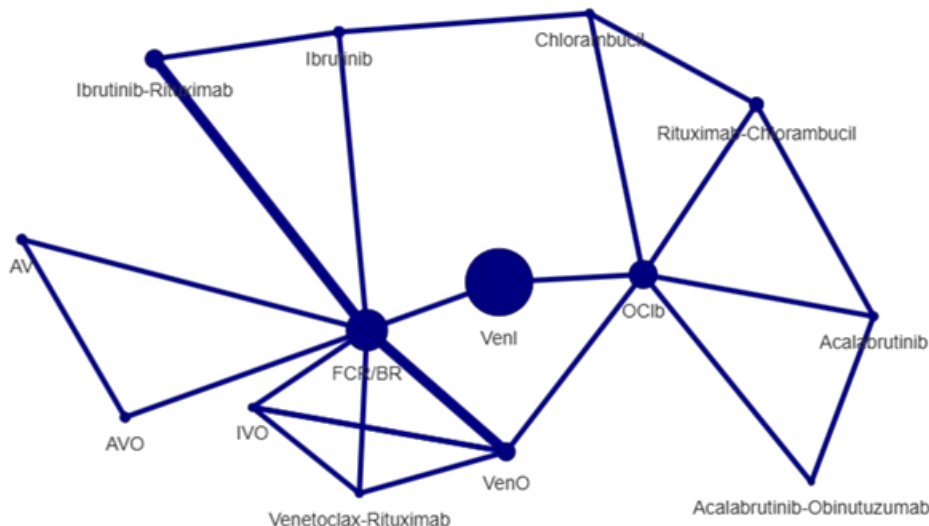
^cReported as mean.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; OClb: obinutuzumab with chlorambucil; RCT: randomised controlled trial; WHO: World Health Organization performance status; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Evidence networks for PFS and OS

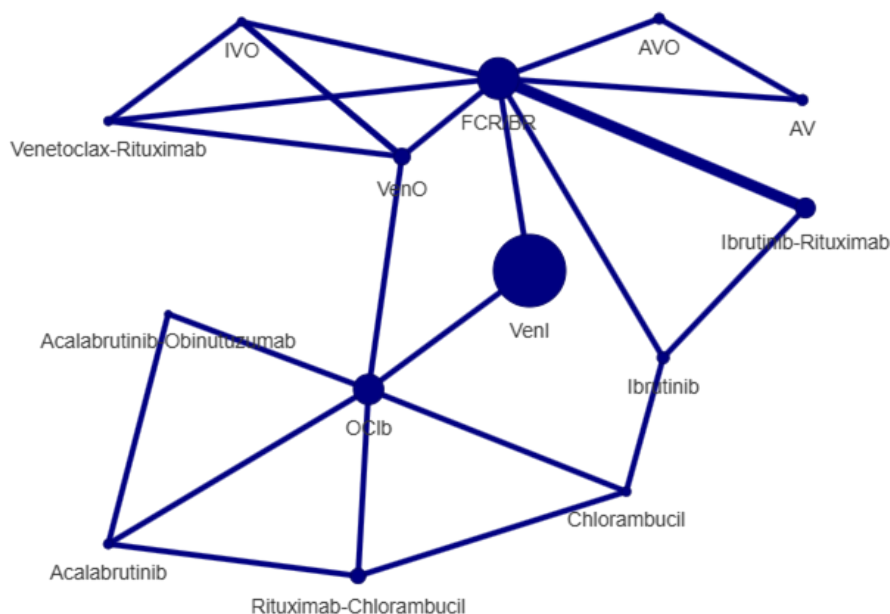
The evidence networks for PFS and OS are displayed in Figure 9 and Figure 10. These included all 12 RCTs for PFS, and 11 RCTs for OS (CRISTALLO did not report OS and was omitted).⁸⁹ The two single-arm studies, CAPTIVATE FD and Jain *et al.* (2019), could not be included as they were disconnected from the network.^{83, 87}

Figure 9: Evidence network for PFS



Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; IVO: ibrutinib with venetoclax and obinutuzumab; OC1b: obinutuzumab with chlorambucil; PFS: progression-free survival; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Figure 10: Evidence network for OS



Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; IVO: ibrutinib with venetoclax and obinutuzumab; OC1b: obinutuzumab with chlorambucil; OS: overall survival; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Definition of outcomes

In the AMPLIFY trial, the primary efficacy analysis was PFS assessed by IRC in the ITT population, using the iwCLL 2018 criteria.³ PFS was measured from the date of randomisation to either disease progression or death, with patients who had not progressed censored at their last IRC response assessment. Patients who initiated a new line of therapy or missed two or more consecutive response assessments before progression were censored at the last adequate IRC response assessment that occurred before these events. For patients lacking an adequate post-baseline IRC assessment, censored data were recorded at the date of randomisation.

Whilst the AMPLIFY trial assessed PFS by IRC using the iwCLL criteria, other trials employed various methods for evaluating progression events. Several studies, including GLOW and RESONATE-2 also used IRC-assessed PFS as their primary endpoint, aligning with AMPLIFY.^{37, 104} Conversely, studies such as CLL11, CLL13, and CLL14 relied on investigator-assessed progression as their main outcome, although they also reported IRC-based PFS curves.^{55, 57, 88} These differing assessment methodologies can produce similar but not identical efficacy estimates. Details of outcome definitions across all 14 studies are summarised in Appendix B.5.2.

OS was consistently defined across studies as the time from randomisation to death from any cause, with standard censoring rules; patients alive at last follow-up were censored at their most recent record date, aligning with the AMPLIFY trial.

Median follow-up

Median follow-up was assessed to ensure sufficient data for capturing events such as disease progression or death, which are critical for time-to-event analyses. Kaplan-Meier survival curves can change shape over different follow-up periods, as demonstrated in the CLL13 trial, where extended long-term data showed notable differences near the 36-month mark compared with earlier analyses.⁸⁸ This discrepancy was likely due to limited follow-up for some patients in the initial analysis, affecting the number at risk and the resulting HR estimates that would be used in an NMA. Similar trends were observed in other studies; for instance, the CLL14 trial reported HRs of 1.24 at 17.1 months, 1.03 at 39.6 months, and 0.69 at 76.4 months of median follow-up when comparing OS data for VenO with OC1b.⁵⁵ To avoid bias, it is essential that studies included in NMAs have sufficiently long and relatively similar median follow-up durations to accurately reflect treatment effects and ensure reliable indirect comparisons.

Consideration of non-proportional hazards

An estimated HR from an NMA or other indirect comparison depends on the follow-up time of the trials included in the synthesis. If there is evidence that the proportional hazards assumption may not be valid, results could therefore be confounded, and the HR may not give the best representation of treatment effect.¹⁰⁹

Visual inspection of the published Kaplan-Meier curves for PFS revealed divergence from proportionality in many studies, suggesting non-constant treatment effects over time. To further assess the assumption of proportional hazards, the Kaplan-Meier curves for key studies which included a VenI (GLOW) or VenO arm were digitised (CLL13, CLL14) and assessed for proportional hazards.^{37, 55, 88} The results indicated that it would not be appropriate to assume proportional hazards for PFS, although for OS the assumption appeared more reasonable. The detailed evaluations and results are summarised in Appendix B.5.2.

Risk of bias assessment

A risk of bias assessment for the studies included in the feasibility assessment was conducted using

Company evidence submission template for acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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the RoB-2 tool for RCTs and the JBI tool for non-randomised trials.^{94, 110}

Generally, the RCTs were well-conducted, some with limited reporting around generation of the randomisation schedule. Although raising some concerns, this was likely due to limited reporting rather than issues with the randomisation process. Similarly, there were some concerns indicated by the selection of reported results, largely due to the multiple data cuts provided by most trials. Only two studies that were identified as having high risk of bias were included in the feasibility assessment: FLAIR and ALLIANCE.^{86, 102}

Full details of the risk of bias assessments are presented in Appendix B.5.2.

2.10.2.2 Feasibility of conducting an NMA

Based on the similarity and homogeneity assessment described in Section 2.10.2 and Appendix B.5.2, the feasibility of conducting an NMA was assessed. An NMA combines all direct and indirect comparisons that are interlinked through a treatment node. NMAs are more commonly conducted on comparisons with three or more interventions simultaneously.

To create a connected network and perform an NMA, a number of assumptions must be met. These assumptions are presented in Table 17. Given the foundational assumptions for an NMA were violated, it is likely that treatment effect estimates produced using this method would be highly uncertain and potentially unreliable. Though a connected network could be formed, the overall evidence network was sparse with most nodes linked through single studies and weak assumptions were made regarding common comparator. The assessment also showed a high degree of clinical, methodological, or statistical variation between studies, as outlined in Table 17, which in turn violated the homogeneity or similarity and transitivity assumptions.

Furthermore, it was not feasible to assess all characteristics across all trials as some characteristics inevitably remained unreported. Indications of heterogeneity amongst hidden or uncaptured variables were shown by the wide ranges of survival probabilities studied across the evidence base. These indicators may introduce limitations in an NMA, thus compromising the robustness of the results produced. As such, an NMA was deemed unfeasible.

Table 17: Foundational assumptions required for an NMA

Assumption	Requirement based on structure of evidence network	Evidence base assessment
Network connectivity	- Equivalence of FCR/BR, FCR only and BR only arms which were combined into a single node in the network. - Equivalence of MRD-guided VenI and fixed-duration VenI which were combined into a single node in the network.	- Numeric differences between FCR and BR were observed in the non-inferiority trial CLL10.¹¹¹ - Treatment durations for fixed-duration and MRD-guided VenI varied significantly (~1.15 years versus up to 6 years). In the FLAIR study, the 3-year PFS rate for MRD-guided VenI was 97.2%, compared with a 30-month PFS rate in GLOW for fixed-duration VenI.^{37, 86}
Methodological variation	- Differences in eligibility criteria across trials did not affect treatment outcomes. - The COVID-19 pandemic did not impact treatment allocation and/or outcomes. - Treatment switching did not affect comparative treatment estimates.	As described in Section 2.10.2.1, there were several methodological variations between studies that may impact the feasibility of conducting an NMA, including eligibility criteria, time of trial (recruitment of patients during the COVID-19 pandemic), treatment switching and median follow-up duration.
Clinical variation	Known and unknown TEMs are comparable across patients in the evidence base.	Key prognostic factors and TEMs influencing patient outcomes were heterogeneous across trials as a result of differences in trials' eligibility criteria. These prognostic factors and TEMs included age, clinical stage (Binet B/C or Rai I–IV, <i>TP53</i> mutations, <i>IgHV</i> mutational status, beta-2 microglobulin concentration (>3.5 mg/L), patient sex, ECOG PS, comorbidities (CIRS), bulky disease, creatinine clearance and chromosomal abnormalities (trisomy 12, del[11q], del[17p], del[13q]) (see Section 2.10.2.1).
Statistical variation	- Heterogeneity across the survival estimates is solely due to random error. - HR estimates within the same pairs of interventions are similar across studies and all reported time points due to the assumption of proportional hazards. - Variations in median follow-up durations are not associated with HR estimates.	- While homogeneity and transitivity assumptions posit similar baseline risks and treatment effects should be reproducible across trials, substantial inconsistencies in reported PFS measures suggest otherwise. Many of these differences are likely related to prognostic factors and TEMs, which, given the sparse evidence network, could bias the NMA results and reduce their accuracy without covariate adjustment.^a - Divergence from proportional hazards was observed in many PFS Kaplan-Meier curves, which may introduce bias into the NMA (see Section 2.10.2.1). - Kaplan-Meier curves for time-to-event outcomes can shift over different follow-up periods, as demonstrated in CLL13.⁸⁸ HR estimates, in turn, can vary widely at different time points, as seen in the CLL14 trial (see Section 2.10.2.1).⁵⁵

^aTransitivity assumes that an unbiased ITC can be computed through a common comparator when no variation is expected across the TEMs between trials with a common treatment arm.

Abbreviations: BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; COVID-19: coronavirus disease 2019; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; *IgHV*: immunoglobulin heavy chain variable region; ITC: indirect treatment comparison; MRD: minimal residual disease; NMA: network meta-analysis; PFS: progression-free survival; SLR: systematic literature review; TEM: treatment effect modifier; VenI: venetoclax with ibrutinib.

2.10.2.3 Feasibility of conducting population-adjusted comparisons

Since an NMA was considered unfeasible, careful consideration was given to conducting population-adjusted analyses, including a MAIC and an STC. These methods would also facilitate comparison to single arm studies.

The feasibility of performing an anchored or unanchored population-adjusted ITC was explored using data from AMPLIFY and studies which included a VenI or VenO treatment arm. As well as addressing the issue of heterogeneity via population-adjustment, restricting the analysis to a smaller subset of studies that focus on the comparators of interest removed the need for the assumption of equivalence between FCR and BR, and avoided including trials that permitted treatment switching (none of these included VenI or VenO). The studies considered are listed in Table 18. Whilst FLAIR included a VenI arm, VenI treatment duration was informed by MRD status, which is not aligned with UK clinical practice.¹¹² Therefore, this trial was removed from consideration. Jain *et al.* (2019) and CRISTALLO were also removed from consideration – Jain *et al.* (2019) had a very short follow-up period (14.8 months) and followed MRD stopping rules,^{86, 87} while CRISTALLO also had a short median follow-up period (32 months), reported immature PFS data and no OS data.⁸⁹

An anchored indirect comparison relies on the presence of a common comparator (e.g., placebo), respecting randomisation within studies to remove bias due to imbalanced TEMs. An unanchored indirect comparison between two treatment arms does not rely on the presence of a common comparator and does not respect any randomisation within studies.⁹⁹ For an anchored ITC, the population adjustment should consider all TEMs; in addition, an unanchored ITC should include all prognostic factors. Whether an anchored or unanchored population-adjusted ITC could be possible is indicated in Table 18.

Table 18: Studies considered for a population-adjusted comparison with AMPLIFY

Study	Study design	Treatment arm	Number of patients	Type of comparison
AMPLIFY ³	RCT	AV	291	–
		AVO	286	
		FCR/BR	290	
CLL13 ⁸⁸	RCT	VenO	229	Anchored
		FCR/BR	229	
CLL14 ⁵⁵	RCT	VenO	216	Unanchored
GLOW ³⁷	RCT	VenI	106	Unanchored
CAPTIVATE FD ⁸³	Single-arm trial	VenI	159	Unanchored

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; RCT: randomised controlled trial; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Feasibility assessment of conducting a MAIC

The MAIC approach adjusts for imbalances in trial populations before performing a treatment comparison. Unlike an NMA which is based only on aggregate data, a MAIC incorporates individual patient data (IPD) from the index trial (AMPLIFY) and reweights outcomes based on published aggregate data from a comparator trial. Individuals in the AMPLIFY study are weighted by the inverse of their propensity score to balance the covariate distribution with that of the comparator trial. The propensity score is defined as the conditional probability that an individual from the IPD study would be assigned to the comparator study. Outcomes are then compared

across balanced trial populations.

A MAIC is only valid where there is sufficient overlap between the patient populations in both trials. As matching also reduces the effective sample size (ESS) for the IPD study; the degree of reduction will depend on the degree of “overlap” between the IPD trial and the comparator target population, therefore care must be taken not to over-match, or attempt to match between studies with insufficient overlap.

For the comparison of AV versus VenI, two studies in addition to AMPLIFY were available: CAPTIVATE FD and GLOW. Due to the different inclusion criteria of these studies, there was significant non-overlap of some study and baseline characteristics, as shown in Table 15 and Table 16, respectively. There are clear differences in the eligibility criteria related to age, cytogenetics, CIRS and creatinine clearance. It is crucial to note that a MAIC can only adjust IPD to meet the target populations of the aggregate-level data. Therefore, the more restrictive eligibility criteria for the AMPLIFY study cannot be adjusted to the broader patient groups in the target populations of CAPTIVATE FD and GLOW. Differences in eligibility criteria feed through into differences in age, Rai stage, ECOG PS and CIRS score.

For the comparison of AV versus VenO, two studies in addition to AMPLIFY were available: CLL13 and CLL14 (Table 18).^{35, 88} In the comparison between AMPLIFY and CLL14, differences in eligibility criteria led to differences in patient characteristics that have been identified as TEMs or prognostic factors (Table 15; Table 16). The distribution of baseline characteristics in the AMPLIFY and CLL13 trials was, however, more aligned.

Conducting an unanchored MAIC against the CLL14 trial population was assessed. However, unlike AMPLIFY which was restricted to patients without a del(17p) or *TP53* mutation, CLL14 did not apply any patient eligibility criteria on cytogenetics. In addition, CLL14 assessed patients with comorbidities, described by a criterion that patients must have >6 CIRS total score or creatinine clearance restrictions of 30-69 mL/min.³⁵ Adjusting for these factors in a MAIC would either not be possible or would reduce the ESS substantially. Given the common control arm between AMPLIFY and CLL13, and the comparability of the patient populations, a Bucher analysis was considered viable.

In conclusion, given the lack of overlap in characteristics, the positivity assumption required for a MAIC (i.e., that all patients in the target population are represented by patients in the matching cohort) would be undermined. Furthermore, as the distribution of matching covariates differ markedly, a MAIC may result in assigning extreme weights to a small subset of patients. This would dramatically reduce the ESS, potentially to a level where the resulting estimates would not be credible or statistically robust. Previous studies have attempted MAICs in this indication but issues with crossover led to significant reductions in ESS and hence considerable uncertainty in the results.^{8, 113} An example of this is evident in the NICE evaluation of zanubrutinib in CLL (TA931).⁸ The original matching exercise used in the evaluation resulted in an ESS of 31, and even after the number of covariates matched was reduced, the ESS only increased to 79, which the External Assessment Group (EAG) still deemed insufficient to detect differences in outcomes.

As a result of the limitations outlined above, a MAIC was deemed unfeasible for assessing the comparative efficacy of AV versus VenI and VenO.

Feasibility assessment of conducting an STC

An STC offers an alternative analytic approach if there is limited overlap between the baseline characteristics of IPD in the index study and aggregate data for comparator study populations, as observed here. This method uses predictive equations to explicitly model the relationship between outcomes and baseline characteristics in the index study (AMPLIFY). These equations can then be used to predict outcomes for patients receiving AV whilst applying the mean characteristics of the comparator study. The predicted outcome can then be compared against the outcome from the comparator study to obtain an estimated treatment effect.

There are some limitations which are inherent in both STCs and MAICs. These include the inability to overcome situations where the AMPLIFY eligibility criteria is more restrictive to that of other studies, and the inability to adjust for patient characteristics that are unreported. However, regression-based approaches such as STCs are not restricted to scenarios with close overlap, provided it is assumed that the relationship modelled between outcome and baseline characteristics still applies beyond the range of values seen in the IPD. In circumstances with small sample sizes, an STC has been shown to be superior (in terms of bias) to a MAIC.¹¹⁴ As such, a regression-based STC approach was deemed to be the most feasible and appropriate option for conducting an ITC of AV versus VenI and VenO. Unanchored analyses were required due to the lack of a common comparator between the studies.

Given the common FCR/BR control arm and the comparable patient baseline characteristics between the AMPLIFY and CLL13 trials, an anchored ITC using the method described by Bucher *et al.* (1997) was considered viable for this comparison (see Section 2.10.3.2).¹⁰⁰

2.10.3 Simulated treatment comparison (STC)

2.10.3.1 STC methodology

STC predictive equations

Full details of the predictive equations used in the STC are presented in Appendix B.5.3.

Parametric survival models

For the endpoints of interest (PFS and OS), parametric survival models were fitted to the survival data for AV using the flexsurv package in R.¹¹⁵ Parametric models recommended in the NICE TSD14 were used (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic; the generalised gamma model was explored, however this model was found not to converge).¹¹⁶ These models make explicit assumptions regarding the shape of the hazard by imposing a specific statistical model on the event times. For instance, an exponential distribution assumes a constant hazard of the event, while Weibull or Gompertz assume monotonic hazards. The choice of distribution in modelling the outcome determines how the relative effect of AV versus comparator treatments is expressed.

The best-fitting models were selected using the AIC. This assesses the goodness-of-fit of the model to the data using the likelihood function, whilst penalising models with a greater number of estimated parameters to avoid overfitting. A lower AIC suggests a more parsimonious model.

Given the finding that proportional hazards may not be considered a reasonable assumption, RMST was estimated from the best-fitting parametric model for AMPLIFY, and from digitised

Kaplan-Meier data for the comparator studies, using the minimum of the longest follow-up time between the two studies for each endpoint. The standard error (SE) and 95% CI for the RMST in AMPLIFY were estimated via sampling from the normal asymptotic distribution of the estimated parameters for each model.

Covariate selection

Baseline characteristics reported by both AMPLIFY and the comparator studies, and therefore available for inclusion in the predictive model, were compared across studies. For comparator studies evaluating the same treatment (i.e., VenI or VenO), the aggregate baseline data were combined to enable a pooled comparison (this was possible as all covariates were binary variables). In addition, separate analyses were conducted for GLOW (VenI) and CLL14 (VenO) as these studies reported more complete baseline data (including CIRS score).

For the unanchored STCs, the difference in RMST was calculated for three different models, which included:

- Full model: all available covariates reported by both studies were adjusted for
- Unadjusted model: no covariates were adjusted for
- AIC optimised model: the subset of covariates that resulted in the best (lowest) AIC following backwards stepwise selection, were adjusted for. The selection process was conducted using the parametric distribution from the best-fitting model using all covariates

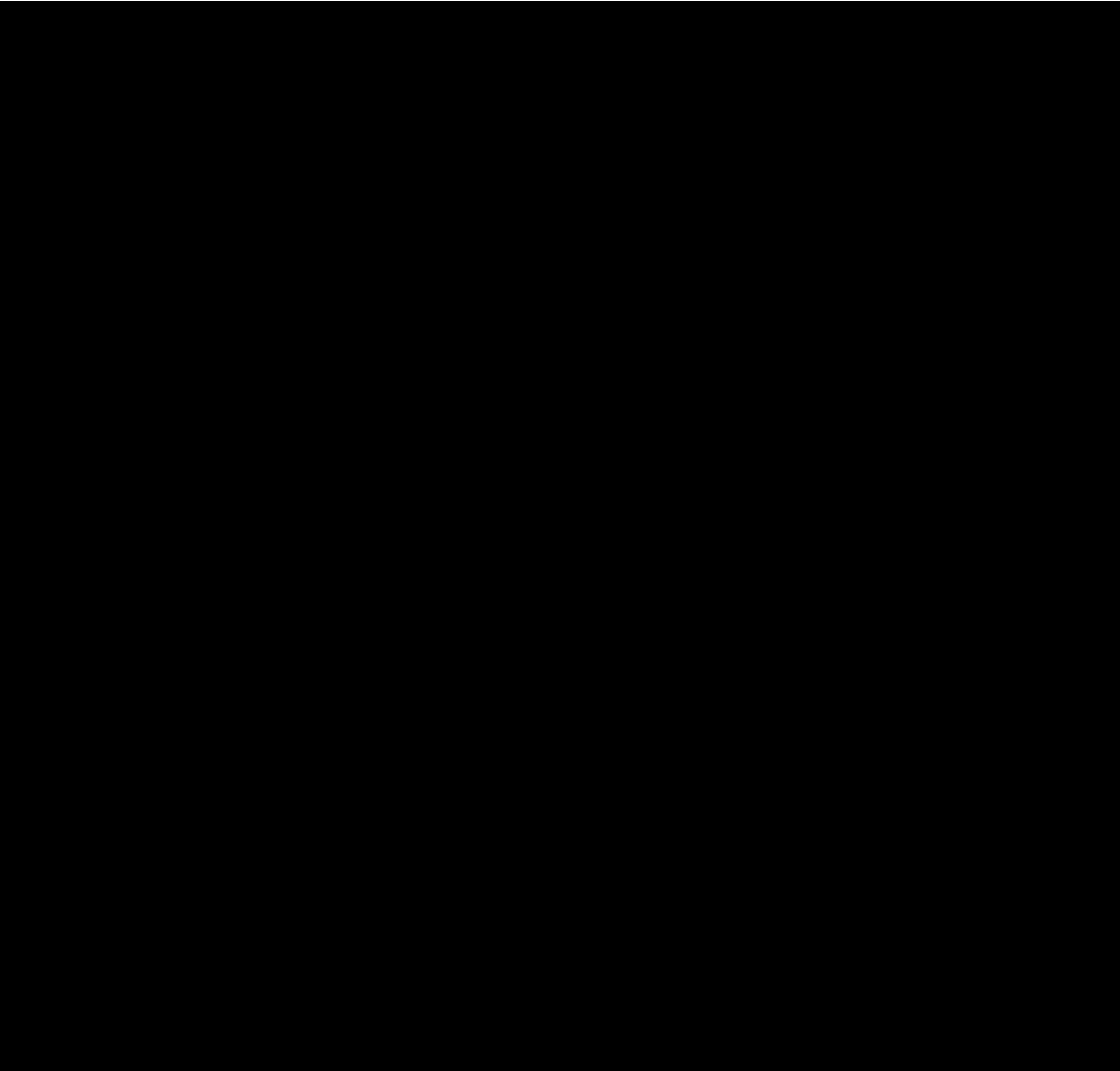
The baseline characteristics available for both AMPLIFY and the comparator studies are listed in Table 19, and the distributions across studies are displayed in Figure 11. For most characteristics, the distributions were similar to the AMPLIFY study, with the exception of age, creatinine clearance and CIRS score. These were notably different for CLL14 and GLOW which represent an older, sicker and less fit population of CLL patients compared with AMPLIFY.

Table 19: Baseline characteristics available for inclusion by study

Baseline characteristic	CAPTIVATE FD +GLOW (VenI)	GLOW (VenI)	CLL14 (VenO)
Age ≥65 yr	Y	Y	–
Age ≥75 yr	–	Y	Y
Beta-2 microglobulin >3.5 mg/L	–	Y	Y
Binet stage: C	–	–	Y
Bulky disease ≥5 cm	Y	Y	–
CIRS score	–	Y	Y
Creatinine clearance <70 mL/min	–	Y	Y
Del(11q)	Y	Y	Y
ECOG ≥1	Y	Y	Y
IgHV mutated	Y	Y	Y
Rai stage III/IV	Y	Y	–
Sex: male	Y	Y	Y

Abbreviations: CIRS: Cumulative Illness Rating Scale; ECOG: Eastern Cooperative Oncology Group; *IgHV*: immunoglobulin heavy chain variable region; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Figure 11: Distribution of baseline characteristics by treatment^a



^aAs outlined in Section 1.1, AstraZeneca are seeking reimbursement for AV only. As such, details relating to AVO are not relevant to this submission.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; *IgHV*: immunoglobulin heavy chain variable region; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

The subset of baseline characteristics retained following the AIC-based procedure using backwards stepwise selection on the best-fitting model for the AV arm are listed in Table 20, by endpoint and target study. ECOG PS, creatinine clearance and sex were dropped from all models.

Table 20: Subset of variables selected using AIC-based backwards stepwise regression for AV arm, by endpoint and target study

Endpoint	Parameter	CAPTIVATE FD + GLOW (VenI)	GLOW (VenI)	CLL14 (VenO)
OS	Age ≥65 yr			
	Age ≥75 yr			
	Beta-2 microglobulin >3.5 mg/L			
	Del(11q)			

Endpoint	Parameter	CAPTIVATE FD + GLOW (VenI)	GLOW (VenI)	CLL14 (VenO)
PFS	Beta-2 microglobulin >3.5 mg/L			
	Binet stage: C			
	Bulky disease ≥5cm			
	<i>IgHV</i> mutated			
	Rai stage III/IV			

Abbreviations: AIC: Akaike Information Criterion; *IgHV*: immunoglobulin heavy chain variable region; OS: overall survival; PFS: progression-free survival; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

RMST for comparator studies

For the endpoints of interest (PFS and OS) and each treatment arm (VenI and VenO) in CLL14, GLOW and CAPTIVATE FD, RMST was estimated non-parametrically from the Kaplan-Meier curves. RMST was also calculated for the Bucher analysis using CLL13. The curves were fitted to the reconstructed survival data from digitised published Kaplan-Meier curves using the survival package in R. The standard error and 95% CIs for the RMST were estimated via the method described in the vignette for the survival package in R.¹¹⁵

Sensitivity analyses

Sensitivity analyses were conducted whereby RMST was calculated based on the three types of model (full model, unadjusted model, AIC-optimised model) using the top three best-fitting parametric distributions for each endpoint/treatment combination (based on the model with all covariates). Further details of the methodology and results of these sensitivity analyses are presented in Appendix B.5.6.

2.10.3.2 STC results

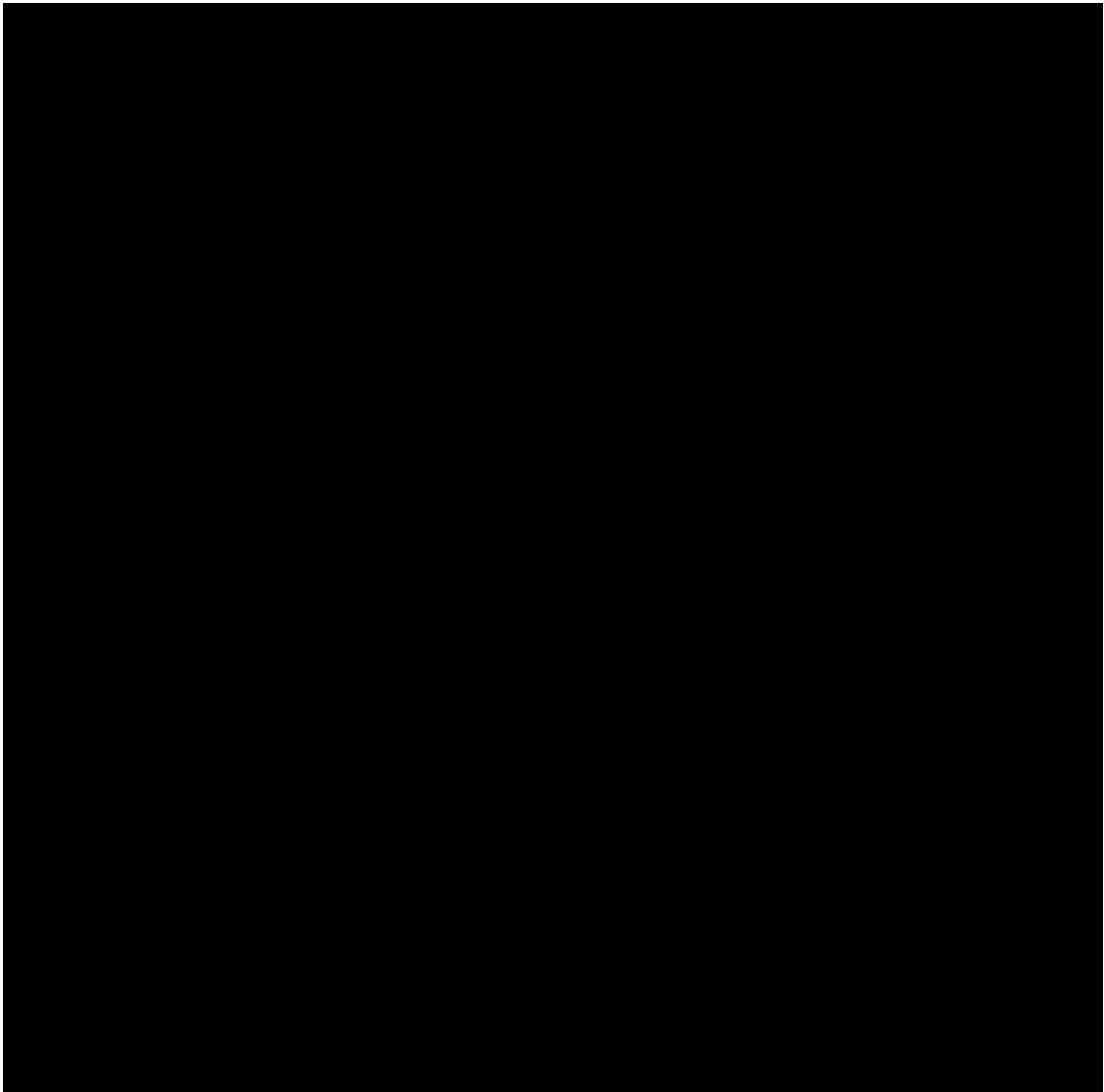
PFS

The forest plot in Figure 12 displays the RMST difference for PFS (Table 21) for the STCs of AV with VenI and VenO from the best-fitting parametric models. The STC adjusted survival curves for each comparison are reported in Figure 13.

At 55.1 months follow-up, there was no statistically significant difference in RMST for AV compared with VenI in the pooled analysis with CAPTIVATE FD and GLOW (RMST difference: [REDACTED] [95% CI: [REDACTED]]), or GLOW only (RMST difference: [REDACTED] [95% CI: [REDACTED]]). RMST was not significantly different between AV and VenO in the separate analysis with CLL14 (RMST difference: [REDACTED] [95% CI: [REDACTED]]).

Sensitivity analyses results were aligned with the results from the primary analysis (Appendix B.5.2.).

Figure 12: Forest plot of RMST difference for PFS from the STC with all covariates



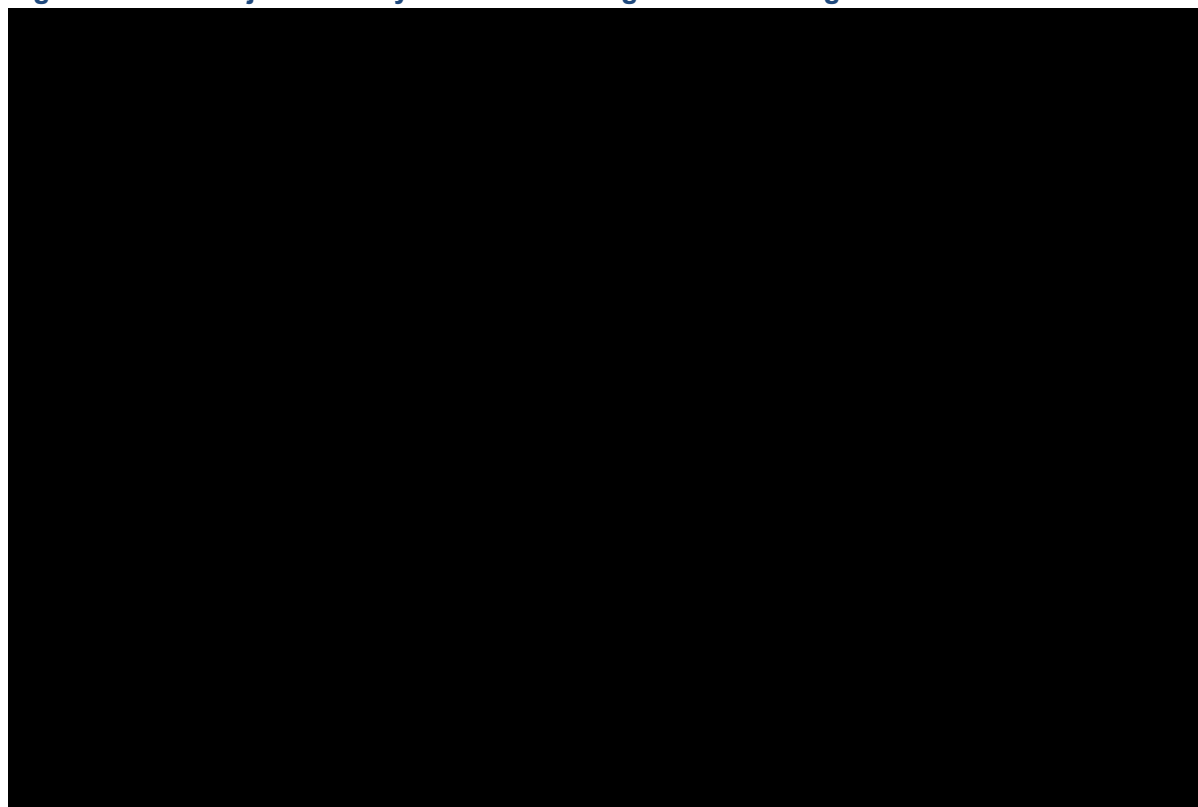
Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; IV: venetoclax with ibrutinib; PFS: progression-free survival; RMST: restricted mean survival time; STC: simulated treatment comparison; VO: venetoclax with obinutuzumab.

Table 21: RMST difference for PFS from the STC with all covariates (55.1-month cut-off)

Target study	Distribution	RMST difference, months (95% CI)
AV reference		
CAPTIVATE+GLOW (VenI)		
GLOW (VenI)		
CLL14 (VenO)		

Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; PFS: progression-free survival; RMST: restricted mean survival time; STC: simulated treatment comparison; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Figure 13: STC-adjusted analysis for PFS using the best-fitting model with all covariates



Abbreviations: AV: acalabrutinib with venetoclax; IV: venetoclax with ibrutinib; KM: Kaplan–Meier; PFS: progression-free survival; STC: simulated treatment comparison; VO: venetoclax with obinutuzumab.

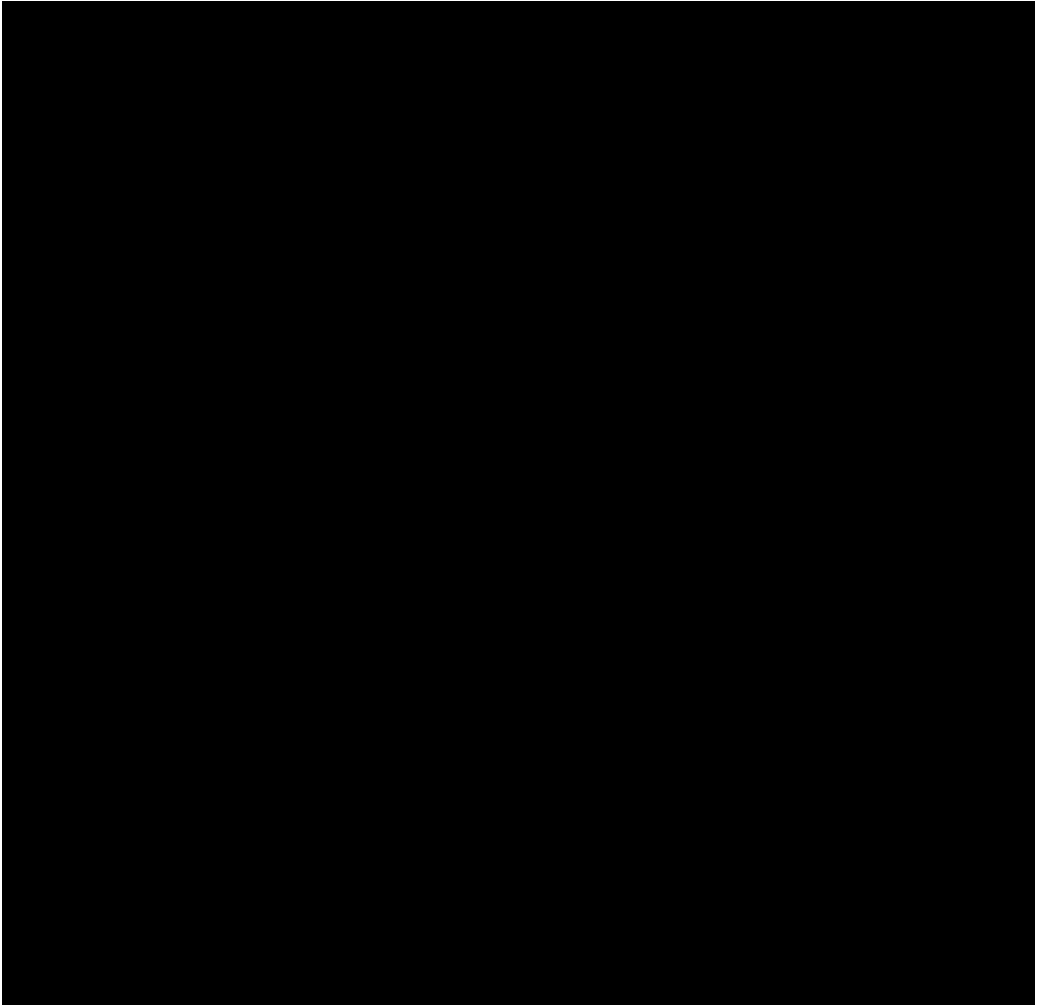
OS

The forest plot in Figure 14 displays the RMST difference for OS (Table 22) for the STCs of AV with VenI and VenO from the best-fitting parametric models. The STC adjusted survival curves for each comparison are reported in Figure 15.

At 57.7 months follow-up, there was no statistically significant difference in RMST for AV compared with VenI in the pooled analysis with CAPTIVATE FD and GLOW (RMST difference: [REDACTED] [95% CI: [REDACTED]]), or GLOW only (RMST difference: [REDACTED] [95% CI: [REDACTED]]). The findings were similar for the comparative analysis with CLL14 for the VenO comparator, with no significant difference in RMST (RMST difference: [REDACTED] [95% CI: [REDACTED]]).

Sensitivity analyses results were aligned with the results from the primary analysis (Appendix B.5.2).

Figure 14: Forest plot of RMST difference for OS from the STC with all covariates



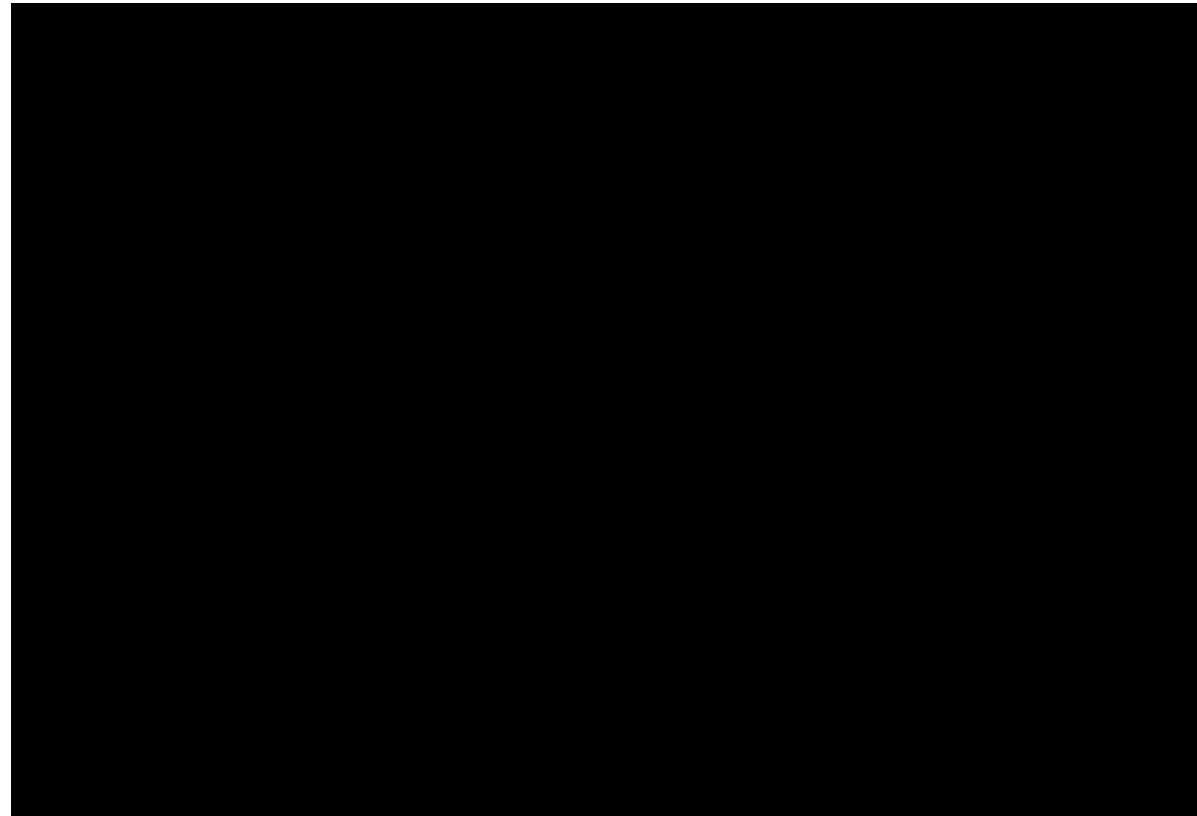
Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; IV: venetoclax with ibrutinib; OS: overall survival; RMST: restricted mean survival time; STC: simulated treatment comparison; VO: venetoclax with obinutuzumab.

Table 22: RMST difference for OS from the STC with all covariates (57.7-month cut-off)

Target study	Distribution	RMST difference, months (95% CI)
AV reference		
CAPTIVATE+GLOW (VenI)		
GLOW (VenI)		
CLL14 (VenO)		

Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; OS: overall survival; RMST: restricted mean survival time; STC: simulated treatment comparison; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Figure 15: STC-adjusted analysis for OS using the best-fitting model with all covariates



Abbreviations: AV: acalabrutinib with venetoclax; IV: venetoclax with ibrutinib; KM: Kaplan–Meier; OS: overall survival; STC: simulated treatment comparison; VO: venetoclax with obinutuzumab.

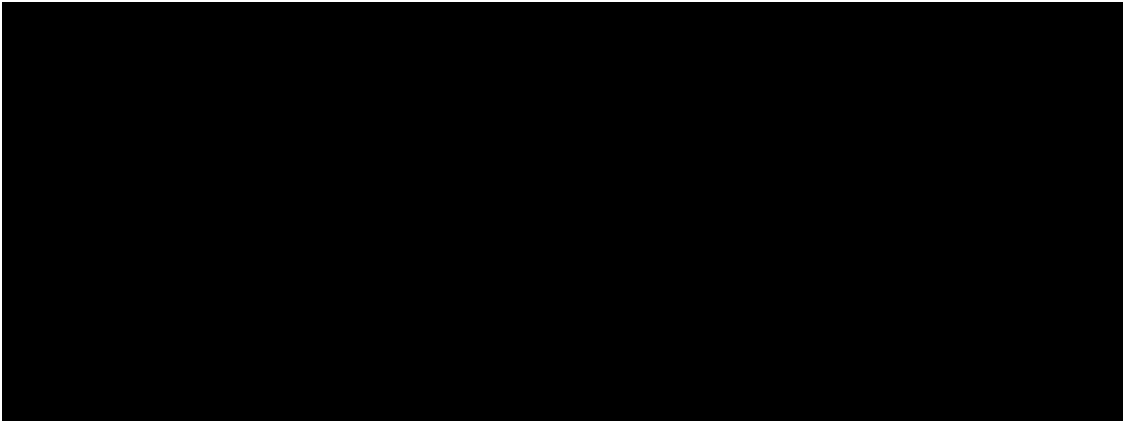
2.10.4 Anchored Bucher ITC with CLL13

OS

The forest plot in Figure 16 displays the RMST difference for OS for the anchored Bucher ITC of AV (AMPLIFY) versus VenO (CLL13).

At 57.1 months follow-up, RMST was significantly longer for AV compared with VenO (RMST difference: [REDACTED] [95% CI: [REDACTED]]).

Figure 16: Forest plot of RMST difference in OS from the anchored Bucher ITC of AV (AMPLIFY) versus VenO (CLL13)



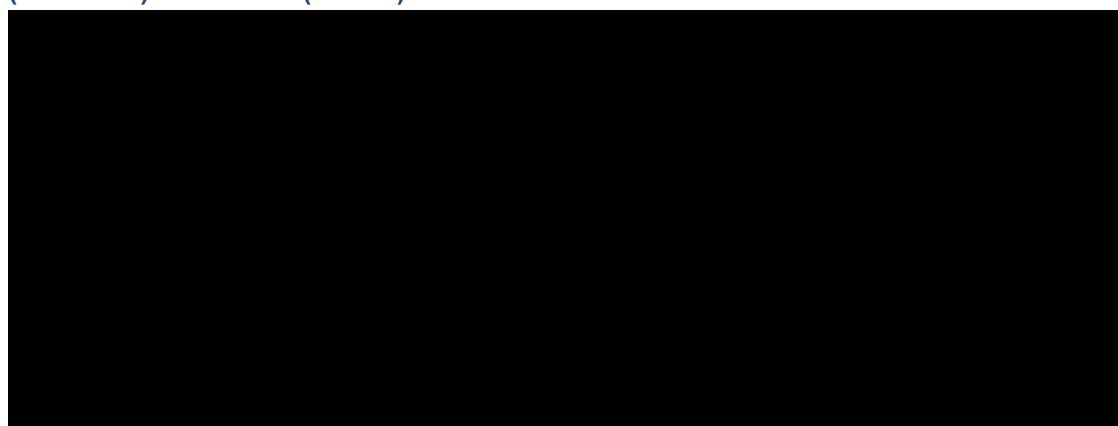
Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; ITC: indirect treatment comparison; OS: overall survival; RMST: restricted mean survival time; VO: venetoclax with obinutuzumab.

PFS

The forest plot in Figure 16 displays the RMST difference for IRC-assessed PFS for the anchored Bucher ITC of AV (AMPLIFY) with VenO (CLL13).

At 55.1 months follow-up, there was no significant difference in RMST for AV compared with VenO (RMST difference: [REDACTED] [95% CI: [REDACTED]]).

Figure 17: Forest plot of RMST difference in PFS from the anchored Bucher ITC of AV (AMPLIFY) with VenO (CLL13)



Abbreviations: AV: acalabrutinib with venetoclax; BICR: blinded independent central review; CI: confidence interval; ITC: indirect treatment comparison; PFS: progression-free survival; RMST: restricted mean survival time; VO: venetoclax with obinutuzumab.

2.10.5 Modified Delphi panel with UK clinical experts (2025)

The STC and Bucher ITC results provide indirect statistical evidence for the comparable efficacy of AV versus VenI and VenO. To provide further evidence and validate the outcomes of the STC and Bucher ITC, a *de novo* two-round modified Delphi panel was conducted with UK clinical experts to obtain clinical consensus on the comparative efficacy of AV versus VenI and VenO. The modified Delphi panel provides evidence on the comparative efficacy of AV versus VenI and VenO based on the clinical experts' experience with treatments for CLL in real-world practice.

2.10.5.1 Modified Delphi panel methodology

The objective of the Delphi panel was to collect clinical expert opinion on the relative efficacy and safety of AV versus VenI and VenO in patients with untreated non-high risk CLL.¹¹⁷ A modified Delphi panel is an iterative, anonymised approach to robustly elicit and synthesise responses over sequential survey rounds. Modified Delphi panels represent a widely adopted method for expert consensus and this approach was chosen over a 'classic' Delphi panel to ensure timely completion of the study. Full details of the methodology of the Delphi panel are provided within the reference pack accompanying this submission.¹¹⁸

Firstly, a pre-specified protocol for the Delphi panel was developed outlining the eligibility criteria for participation, methods of data collection and analysis of results.¹¹⁷ Four well-known UK clinical experts in the field of haematology were invited by AstraZeneca to participate as members of the steering committee (SC). The SC consulted on the scope and design of the statements for each round but did not participate in the consensus voting.

The eligibility criteria for the selection of panel participants included being UK based and having five or more years of experience in treating newly diagnosed patients with CLL. Recruitment of

Company evidence submission template for acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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participants in rural and less represented regions was also prioritised to ensure a wide geographic spread across the UK. Panellists were recruited via email by a third party and were not reimbursed for their time.

An initial scoping meeting was held with members of the SC to discuss the topics of interest for the Delphi panel. Initial Round 1 statements were discussed during this meeting and further refined over email. Topics covered by the statements included gathering expert opinion on comparing trial endpoints, such as PFS, OS and TTNT, between AV, VenI and VenO. The safety profile, healthcare resource use (HCRU) and HRQoL impacts of these treatments were also assessed. The statements were uploaded to the Costello Medical Delphi App, a bespoke web application to facilitate the delivery of Delphi panel projects and distributed to the panellists for completion over a 14-day time period. The majority of statements used the Likert scale, an 8-point scale ranging from 'Strongly agree' to 'Strongly disagree' as well as 'Do not wish to respond' and 'Insufficient expertise' response options. Some statements were also associated with a free-text comments box.

Following the completion of each round, the results were analysed and assessed as to whether they reached the pre-defined consensus threshold of $\geq 70\%$ agreement or disagreement. 'Strongly agree/agree' counted as agreement, and 'Strongly disagree/disagree' counted as disagreement in consensus calculations. Any 'Slightly agree' or 'Slightly disagree' responses to Likert scale statements were considered neutral and not included in the overall calculation of percentage 'agreement' or 'disagreement'. Ranking statements were able to reach consensus if Kendall's W $\geq 70\%$.

After Round 1, results were compiled and presented to the SC for discussion on whether to deprioritise or restructure statements with the aim of achieving consensus in Round 2. Consensus was not assessed for free-text comments but instead responses were used to inform Round 2 statement development. Statements achieving consensus in Round 1 were not included in Round 2. In Round 2, panellists were able to see their response and the overall group response to corresponding statements from Round 1. After the second and final round, the methodology and results from the Delphi panel were compiled into a summary report.¹¹⁸

At the time the Delphi panel was conducted, acalabrutinib had not yet received a marketing authorisation extension for use in combination with venetoclax for the treatment of untreated non-high risk CLL and had therefore not yet been used in clinical practice. As such, statements were formulated such that clinicians could draw on their clinical experience with VenI and VenO, their knowledge of the existing AMPLIFY trial data, and their experience with how CLL therapies perform outside RCTs.

2.10.5.2 Modified Delphi panel results

In total, 93 panellists from all four UK nations were invited to participate in the modified Delphi panel, of which 33 agreed to take part. The overall response rate for Round 1 was 22/33 and 16/22 for Round 2.

Background information was gathered on these individuals and is presented in Table 23, demonstrating a broad range of experience, geography and treatment setting across the panellists. Additionally, data on the distance travelled by patients was gathered to contextualise the impact that the treatments being discussed have on individuals (Table 23). Half of the clinical experts who responded to Round 1 indicated that patients would typically travel over 10 miles for treatment.

Company evidence submission template for acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Table 23. Background information of Delphi panellists

Characteristic	Round 1 (n=22)	Round 2 (n=16)
Years of experience		
5–10 years	36%	44%
11–15 years	32%	25%
>15 years	32%	31%
Region		
London	23%	19%
Midlands	9%	6%
North East and Yorkshire	14%	19%
East of England	9%	13%
North West	9%	6%
South East	9%	13%
South West	9%	6%
Scotland	9%	6%
Northern Ireland	9%	13%
Setting		
Cancer centre	36%	44%
District general hospital	23%	13%
Teaching hospital	41%	44%
Average patient journey (one-way trip)		
<10 miles	50%	56%
10–20 miles	36%	31%
21–40 miles	9%	13%
>60 miles	5%	0%

Results

Overall summary

Based on both the panellists' clinical experience and interpretation of the AMPLIFY trial data, consensus was reached that AV would be considered a suitable treatment alternative to both VenI and VenO in terms of both PFS and OS. There was also consensus that AV would be a suitable treatment alternative to both VenI and VenO when considering their associated safety profiles, and that AV would have a more favourable safety profile than VenI.

Table 24 summarises the key topics that reached consensus in this Delphi panel. All of these topics reached consensus in Round 1, unless otherwise indicated. The detailed statements and full results are discussed further below.

Table 24. Summary of key topics that reached consensus in the modified Delphi panel (% agreed)

Topic	AV versus VenI	AV versus VenO
PFS	- Suitable treatment alternative (91%) - Clinically comparable (95%)^a	- Suitable treatment alternative (77%) - Clinically comparable (88%)^a
OS	- Suitable treatment alternative (91%) - Clinically comparable (85%)^a	- Suitable treatment alternative (73%) - Clinically comparable (94%)^a
Safety	- Suitable treatment alternative (86%) - More favourable safety profile (88%)^b	- Suitable treatment alternative (77%) - Clinically comparable (76%)^a

^aThis was a branching question, with consensus calculated for the number of panellists responding to the question. In some instances, although these reached consensus when taking into account the number of panellists answering the specific branching statement, when calculating consensus using the entire cohort (n=22) the consensus threshold was not reached.

^bReached consensus in Round 2.

Abbreviations: AV: acalabrutinib with venetoclax; OS: overall survival; PFS: progression-free survival; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Round 1

The individual statements and outcomes for Round 1 are presented in Table 25. A total of 17 out of 22 (77%) statements reached the pre-determined consensus threshold of 70%.

Consensus was reached when considering AV as a suitable treatment alternative to both VenI (91% agreed) and VenO (77% agreed), in terms of PFS, based on panellist clinical experience and knowledge. When assessing clinical evidence presented in AMPLIFY, consensus was additionally reached in terms of considering AV to be clinically comparable in terms of PFS and OS versus both VenI (95% and 85% agreed for PFS and OS, respectively) and VenO (88% and 94% agreed for PFS and OS, respectively).

There was less certainty around AV proving a suitable treatment alternative to VenI and VenO with regards to TTNT, with consensus amounting to 59% and 55%, respectively. A number of panellists selected 'Insufficient Expertise' for these questions (6/22 for VenI and 5/22 for VenO), quoting the lack of published data on TTNT for these treatments in their rationale.

In terms of safety, AV was regarded as a suitable treatment alternative to VenI and VenO (86% agree and 77% agreed, respectively) based on panellist clinical experience and knowledge. Based on the clinical evidence in AMPLIFY, consensus was reached regarding clinical comparability of safety for AV and VenO (76% agreed, n=17) but not for AV and VenI (47% agreed, n=19).

In addition, AV was considered a suitable treatment alternative to both VenI and VenO in terms of HCRU burden, both within 6 months of treatment initiation and in the 6 months after this period.

Finally, in terms of HRQoL, although AV was found to be a suitable treatment alternative to VenI both during and after treatment, consensus was not reached when compared to VenO. Comparative HRQoL outcomes for AV and VenO were therefore explored in the subsequent round.

Table 25: Modified Delphi panel Round 1 results

Statement	Consensus reached
PFS	
Based on your clinical experience and knowledge of PFS associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI. ^a	Yes – consensus reached (91% agreed)
Those who answered 'Strongly Agree/Agree' to the previous question were met with the following: ^b Based on your assessment of the clinical evidence in AMPLIFY, you would consider AV and VenI to be clinically comparable in terms of PFS.	Yes – consensus reached (95% agreed, n=20; 86%, n=22)

Statement	Consensus reached
Based on your clinical experience and knowledge of PFS associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	Yes – consensus reached (77% agreed)
Those who answered ‘Strongly Agree/Agree’ to the previous question were met with the following: ^b Based on your assessment of the clinical evidence in AMPLIFY, you would consider AV and VenO to be clinically comparable in terms of PFS.	Yes – consensus reached (88% agreed, n=17; 68%, n=22)
OS	
Based on your clinical experience and knowledge of OS associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI.	Yes – consensus reached (91% agreed)
Those who answered ‘Strongly Agree/Agree’ to the previous question were met with the following: ^b Based on your assessment of the clinical evidence in AMPLIFY, you would consider AV and VenI to be clinically comparable in terms of OS.	Yes – consensus reached (85% agreed, n=20; 77%, n=22)
Based on your clinical experience and knowledge of OS associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	Yes – consensus reached (73% agreed)
Those who answered ‘Strongly Agree/Agree’ to the previous question were met with the following: ^b Based on your assessment of the clinical evidence in AMPLIFY, you would consider AV and VenO to be clinically comparable in terms of OS.	Yes – consensus reached (94% agreed, n=16; 68%, n=22)
TTNT	
Based on your clinical experience and knowledge of TTNT associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI.	No consensus (59% agreed) Strongly agree: 6/22 Agree: 7/22 Slightly agree: 2/22 Slightly disagree: 1/22 Insufficient expertise: 6/22
Based on your clinical experience and knowledge of TTNT associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	No consensus (55% agreed) Strongly agree: 2/22 Agree: 10/22 Slightly agree: 4/22 Slightly disagree: 1/22 Insufficient expertise: 5/22
Safety	
Based on your clinical experience and knowledge of the safety profile associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI.	Yes – consensus reached (86% agreed)
Those who answered ‘Strongly Agree/Agree’ to the previous question were met with the following: Based on your assessment of the clinical evidence in AMPLIFY, you would consider AV and VenI to be clinically comparable in terms of safety.	No consensus (47% agreed, n=19; 41% n=22) Strongly agree: 3/19 Agree: 6/19 Slightly agree: 2/19 Slightly disagree: 2/19

Statement	Consensus reached
	Disagree: 6/19
Based on your clinical experience and knowledge of the safety profile associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	Yes – consensus reached (77% agreed)
Those who answered ‘Strongly Agree/Agree’ to the previous question were met with the following: ^b Based on your assessment of the clinical evidence in AMPLIFY, you would consider AV and VenO to be clinically comparable in terms of safety.	Yes – consensus reached (76% agreed n=17; 59%, n=22)
HCRU	
Based on your clinical experience and knowledge of HCRU WITHIN 6 months of treatment initiation associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI.	Yes – consensus reached (86% agreed)
Based on your clinical experience and knowledge of HCRU AFTER 6 months of treatment initiation associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI.	Yes – consensus reached (82% agreed)
Based on your clinical experience and knowledge of HCRU WITHIN 6 months of treatment initiation associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	Yes – consensus reached (77% agreed)
Based on your clinical experience and knowledge of HCRU AFTER 6 months of treatment initiation associated with these treatment regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	Yes – consensus reached (73% agreed)
HRQoL	
Based on your clinical experience and knowledge of HRQoL DURING TREATMENT with these regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI.	Yes – consensus reached (82% agreed)
Based on your clinical experience and knowledge of HRQoL AFTER TREATMENT HAS BEEN COMPLETED with these regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenI	Yes – consensus reached (77% agreed)
Based on your clinical experience and knowledge of HRQoL DURING TREATMENT with these regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	No consensus (64% agreed) Strongly agree: 9/22 Agree: 5/22 Slightly agree: 7/22 Disagree: 1/22
Based on your clinical experience and knowledge of HRQoL AFTER TREATMENT HAS BEEN COMPLETED with these regimens in untreated standard-risk CLL patients, you would consider AV to be a suitable treatment alternative to VenO.	No consensus (59% agreed) Strongly agree: 5/22 Agree: 8/22 Slightly agree: 5/22 Slightly disagree: 3/22 Insufficient expertise: 1/22

All Statements in Round 1 used the Likert scale. The consensus threshold was set at ≥70% selecting ‘Strongly agree/agree’ for ‘agree’ consensus or ‘Strongly disagree/disagree’ for ‘disagree’ consensus for Likert scale questions.

^aOne participant responded to this question only so their results were removed.

^bThis was a branching question so consensus has been calculated for the number of panellists responding to the question in addition to the entire cohort (n=22). In some instances, although these reached consensus when taking into account the number of panellists answering the specific branching statement, when calculating

consensus using the entire cohort (n=22) the consensus threshold was not reached.

Abbreviations: AV: acalabrutinib plus venetoclax; CLL: untreated chronic lymphocytic leukaemia; HCRU: healthcare resource use; HRQoL: health related quality of life; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment; VenI: venetoclax plus ibrutinib; VenO: venetoclax plus obinutuzumab.

Round 2

The individual statements and outcomes for Round 2 are presented in Table 26. A total of 2 out of 6 (33%) statements reached the pre-determined consensus threshold of 70%.

Consensus was reached on fixed-duration AV having a more favourable safety profile than fixed-duration VenI (88% agreed).

No consensus was obtained on whether fixed-duration AV would have improved HRQoL during or after treatment versus fixed-duration VenO (44% agreed and 19% agreed for during, and after treatment, respectively).

There was consensus agreement that PFS would be a greater driver of treatment decisions than MRD negativity (81% agreed), however, the statement on whether safety would be a greater driver of treatment decisions than MRD negativity was just short of the consensus threshold (69% agreed). Consensus was not reached on the relative importance of PFS, safety and MRD negativity when selecting a treatment in clinical practice (Kendall's W 0.38); however, the most popular selection was, from most to least important, safety (9 participants), followed by PFS (9 participants) then MRD negativity (13 participants).

Table 26: Modified Delphi panel Round 2 results

Statement	Consensus reached
Safety	
Based on your clinical experience and knowledge of the safety profile associated with treatments used in untreated standard-risk CLL patients, you would consider fixed-duration AV to have a more favourable safety profile versus fixed-duration VenI treatment.	Yes – consensus reached (88% agreed)
HRQoL	
Based on your clinical experience and knowledge of HRQoL DURING TREATMENT in untreated standard-risk CLL patients, you would consider fixed-duration AV treatment to be associated with improved HRQoL compared with fixed-duration VenO treatment.	No consensus (44% agreed) Strongly agree: 1/16 Agree: 6/16 Slightly agree: 5/16 Slightly disagree: 1/16 Disagree: 1/16 Do not wish to respond: 1/16 Insufficient expertise: 1/16
Based on your clinical experience and knowledge of HRQoL AFTER TREATMENT HAS BEEN COMPLETED in untreated standard-risk CLL patients, you would consider fixed-duration AV treatment to be associated with improved HRQoL compared with fixed-duration VenO treatment.	No consensus (19% agreed) Agree: 3/16 Slightly agree: 8/16 Slightly disagree: 2/16 Disagree: 1/16 Do not wish to respond: 1/16 Insufficient expertise: 1/16
MRD	
Based on your clinical experience and knowledge of MRD negativity in untreated standard-risk CLL, you would consider safety to be of greater importance than MRD negativity when choosing a treatment in clinical practice.	No consensus (69% agreed) Strongly agree: 2/16 Agree: 9/16 Slightly agree: 3/16

Statement	Consensus reached
	Slightly disagree: 2/16
Based on your clinical experience and knowledge of MRD negativity in untreated standard-risk CLL, you would consider PFS to be of greater importance than MRD negativity when choosing a treatment in clinical practice.	Yes – consensus reached (81% agreed)
Based on your clinical experience and knowledge of PFS, safety, and MRD negativity rate in untreated standard-risk CLL, please rank the following endpoints in order of importance when choosing a treatment in clinical practice. 1 = of most importance; 3 = of least importance. ^a	No consensus (Kendall's W 0.38) Rank 1: Safety (9) Rank 2: PFS (9) Rank 3: MRD Negativity (13)

The consensus threshold was set at ≥70% selecting 'Strongly agree/agree' for 'agree' consensus or 'Strongly disagree/disagree' for 'disagree' consensus for Likert scale questions, or Kendall's W ≥70% for ranking questions.

^aRanking question. All other statements in Round 2 used the Likert scale.

Abbreviations: AV: acalabrutinib plus venetoclax; CLL: untreated chronic lymphocytic leukaemia; HRQoL: health related quality of life; MRD: minimal residual disease; VenO: venetoclax plus obinutuzumab.

2.10.6 Comparative evidence summary

Taken together, the results of the STC (Section 2.10.3.2), anchored Bucher ITC (Section 2.10.3.2), and modified Delphi panel provide substantial evidence for the clinical comparability of AV, VenI and VenO. This was in line with feedback from UK clinical experts who all agreed that they would not expect a clinically meaningful difference in terms of PFS and OS between AV, VenI and VenO.¹⁵ The modified Delphi panel also provided support for the favourable safety profile of AV versus VenI. It was not appropriate to include safety endpoints in the unanchored STC given that follow-up differed between trials and the timing of AEs was unknown in the comparator trials.

Additionally, feedback from UK clinical experts confirmed that acalabrutinib monotherapy and ibrutinib monotherapy can be considered at least clinically equivalent, and broadly agreed that this equivalence is not expected to change upon the addition of venetoclax.¹⁵ This evidence is further supported by the results of the phase III clinical trial investigating the safety and efficacy of ibrutinib and acalabrutinib in patients with relapsed/refractory CLL.⁸⁰ In this trial, acalabrutinib monotherapy demonstrated non-inferiority in terms of PFS, and fewer cardiac AEs, when compared with ibrutinib monotherapy.⁸⁰ Furthermore, the assumption of clinical equivalence between acalabrutinib monotherapy and ibrutinib monotherapy has been previously accepted in the NICE evaluation of acalabrutinib monotherapy in untreated and treated CLL (TA689), thus supporting its applicability in this submission as well.⁹

2.11 Adverse reactions

The safety profile observed with AV in the AMPLIFY trial aligned with that of previous studies for acalabrutinib, showing AV to be a well-tolerated treatment option for patients with CLL.^{2, 3}

- The most common AEs were headache (35.1%), diarrhoea (32.6%) and neutropenia (30.9%) for the AV arm, and neutropenia (38.2%), nausea (35.9%) and infusion-related reactions (32.8%) for the FCR/ BR arm. These were consistent with the known AE profiles of the individual study treatments.
- No new safety signals arose from the analysis of AEs of clinical or special interest, which included cardiac events such as ventricular arrhythmias, hypertension, haemorrhage and secondary primary malignancies.
- The incidence rates of grade ≥ 3 AEs, SAEs, AEs leading to dose reduction, and AEs leading to discontinuation of study drug were similar between the AV and FCR/BR arms.
 - Grade ≥ 3 AEs: 53.6% versus 60.6%, respectively
 - SAEs: 24.7% versus 27.4%, respectively
 - AEs leading to dose reduction: 14.1% versus 11.2%, respectively
 - AEs leading to discontinuation of study drug: 7.9% versus 10.8%
- Overall, the safety profile of AV was consistent with the known individual safety profiles of acalabrutinib and venetoclax.

2.11.1 Overview

At the DCO date of the interim analysis (30th April 2024), the incidence of any TEAE was comparable between the AV and FCR/BR arms of the AMPLIFY trial (92.8% versus 91.1%, respectively).

The incidence of AEs was collected as a safety endpoint in the AMPLIFY trial and full details of the safety results are presented in this section. All AEs presented are TEAEs experienced in the safety population, unless otherwise specified.

An overview of TEAEs for AV and FCR/BR in AMPLIFY is presented in Table 27.

- The majority of patients experienced at least one TEAE during the study (92.8% and 91.1% for AV and FCR/BR, respectively).
- There were ten (3.4%) and nine (3.5%) patients who had TEAEs that resulted in death in the AV and FCR/BR arms, respectively. [REDACTED] in the FCR/BR arm who received BR had a treatment-related AE (acute kidney injury) that resulted in death.
- The incidence of TEAEs leading to discontinuation of any study treatment was 7.9% for AV and 10.8% for FCR/BR.

Table 27: Overall summary of TEAEs for AV and FCR/BR in AMPLIFY (safety population)^a

	Arm A (AV) n=291	Arm C (FCR/BR)		
		Total n=259	FCR only n=122	BR only n=137
Any AE	270 (92.8)	236 (91.1)	[REDACTED]	[REDACTED]
Treatment-related	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

	Arm A (AV) n=291	Arm C (FCR/BR)		
		Total n=259	FCR only n=122	BR only n=137
Acalabrutinib-related	██████	N/A	N/A	N/A
Venetoclax-related	██████	N/A	N/A	N/A
Obinutuzumab-related	N/A	N/A	N/A	N/A
Bendamustine-related	N/A	██████	██████	██████
Rituximab-related	N/A	██████	██████	██████
Fludarabine-related	N/A	██████	██████	██████
Cyclophosphamide-related	N/A	██████	██████	██████
Any grade ≥3 AE	156 (53.6)	157 (60.6)	██████	██████
Treatment-related	██████	██████	██████	██████
Acalabrutinib-related	██████	N/A	N/A	N/A
Any SAE	72 (24.7)	71 (27.4)	██████	██████
Treatment-related	██████	██████	██████	██████
Acalabrutinib-related	██████	N/A	N/A	N/A
Any AE with outcome death	10 (3.4)	9 (3.5)	██████	██████
Treatment-related	██████	██████	██████	██████
Acalabrutinib-related	██████	N/A	N/A	N/A
Any AE leading to discontinuation of:				
Any treatment	23 (7.9)	28 (10.8)	██████	██████
Acalabrutinib	22 (7.6)	N/A	N/A	N/A
Venetoclax	18 (6.2)	N/A	N/A	N/A
Obinutuzumab	N/A	N/A	N/A	N/A
Bendamustine	N/A	10 (3.9)	██████	██████
Rituximab	N/A	27 (10.4)	██████	██████
Fludarabine	N/A	15 (5.8)	██████	██████
Cyclophosphamide	N/A	16 (6.2)	██████	██████

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; N/A: not applicable; SAE: serious adverse event.

Source: Brown *et al.* (2025) (Table 2, Table S11 and Table S17);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 45).²

2.11.2 Incidence of AEs

AEs of any grade

At the DCO of the interim analysis (30th April 2024), the proportion of patients experiencing ≥1 TEAE was comparable between the AV and FCR/BR arms (270 patients [92.8%]; 236 patients [91.1%], respectively).

The TEAEs experienced by $\geq 10\%$ of patients in any arm in the safety population are presented by system organ class and preferred term in Table 28.

The TEAEs with the highest incidences (reported in $\geq 20\%$ of patients in any arm) were as follows:

- For AV: headache (35.1%), diarrhoea (32.6%), and neutropenia (30.9%)
- For FCR/BR: neutropenia (38.2%), nausea (35.9%), and infusion-related reaction (32.8%)

Headache is a known, very common AE for acalabrutinib, however the majority of reported incidences of headache were low grade.

Table 28: TEAEs of any grade reported in $\geq 10\%$ of patients in any arm by system organ class and preferred term in AMPLIFY (safety population)^{a, b, c}

System organ class preferred term	Arm A (AV) n=291	Arm C (FCR/BR)		
		Total n=259	FCR only n=122	BR only n=137
Patients with ≥ 1 TEAE	270 (92.8)	236 (91.1)	██████	██████
Infections and infestations	██████	██████	██████	██████
COVID-19	55 (18.9)	6 (2.3)	████	████
COVID-19 pneumonia	21 (7.2)	7 (2.7)	████	████
Blood and lymphatic system disorders	██████	██████	██████	██████
Neutropenia	90 (30.9)	99 (38.2)	██████	██████
Thrombocytopenia	13 (4.5)	33 (12.7)	██████	██████
Febrile neutropenia	5 (1.7)	24 (9.3)	██████	████
Metabolism and nutrition disorders	██████	██████	██████	██████
Decreased appetite	████	████	████	██████
Nervous system disorders	██████	██████	██████	██████
Headache	102 (35.1)	20 (7.7)	████	██████
Cardiac disorders	██████	██████	██████	██████
Vascular disorders	██████	██████	██████	██████
Respiratory, thoracic and mediastinal disorders	██████	██████	██████	██████
Gastrointestinal disorders	██████	██████	██████	██████
Diarrhoea	95 (32.6)	28 (10.8)	██████	██████
Nausea	43 (14.8)	93 (35.9)	██████	██████
Constipation	██████	██████	██████	██████
Vomiting	██████	██████	██████	██████
Skin and subcutaneous tissue disorders	██████	██████	██████	██████
Rash	24 (8.2)	18 (6.9)	████	██████
Pruritus	32 (11.0)	14 (5.4)	████	██████

System organ class preferred term	Arm A (AV) n=291	Arm C (FCR/BR)		
		Total n=259	FCR only n=122	BR only n=137
Musculoskeletal and connective tissue disorders	██████	██████	██████	██████
Arthralgia	37 (12.7)	9 (3.5)	██████	██████
Back pain	31 (10.7)	14 (5.4)	██████	██████
General disorders and administration site conditions	██████	██████	██████	██████
Fatigue	43 (14.8)	35 (13.5)	██████	██████
Pyrexia	17 (5.8)	47 (18.1)	██████	██████
Investigations	██████	██████	██████	██████
Neutrophil count decreased	18 (6.2)	27 (10.4)	██████	██████
Injury, poisoning and procedural complications	██████	██████	██████	██████
Infusion-related reaction	0 (0.0)	85 (32.8)	██████	██████
Contusion	40 (13.7)	4 (1.5)	██████	██████

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

^cPatients with multiple occurrences are counted once per system organ class and preferred term regardless of the number of occurrences.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; TEAE: treatment-emergent adverse event.

Source: Brown *et al.* (2025) (Table S8);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 46).²

AEs of clinical or special interest

A number of AEs of clinical or special interest were pre-defined within the AMPLIFY trial statistical analysis plan based on non-clinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTKis.¹¹⁹ These AEs include ventricular arrhythmias, cardiac events, infection, secondary primary malignancies and tumour lysis syndrome (TLS).

A summary of the incidence of these AEs is presented in Table 29. Due to significant differences in exposure between the FCR/BR and AV arms, these AEs were also analysed via exposure-adjusted AE rates (i.e., events per 100 patient-years), as shown in Table 30.

The incidence of infections reported during the AMPLIFY trial were notably high due to the impact of the COVID-19 pandemic. Although haemorrhage occurred in a higher proportion of patients in the AV arm versus the FCR/BR arm, major haemorrhage events were infrequent across both arms. The proportion of patients experiencing any cardiac event was low across both arms, with ventricular arrhythmia occurring in fewer than 1% of patients in any arm.

Overall, no new safety signals arose from the analysis of AEs of clinical or special interest in the AMPLIFY trial. The greater proportion of events in the AV arm compared with the FCR/BR arm can, in part, be attributed to the longer duration of exposure to AV over FCR/BR.

Table 29: AEs of clinical or special interest (safety population)^{a, b, c}

System organ class preferred term	Arm A (AV) n=291	Arm C (FCR/BR)		
		Total n=259	FCR only n=122	BR only n=137
AEs of clinical interest				
Anaemia	20 (6.9)	25 (9.7)	████	████
Cardiac event	27 (9.3)	9 (3.5)	████	████
Atrial fibrillation	2 (0.7)	2 (0.8)	████	████
Haemorrhage	94 (32.3)	11 (4.2)	████	████
Major haemorrhage	3 (1.0)	2 (0.8)	████	████
Hypertension	12 (4.1)	7 (2.7)	████	████
Infections	148 (50.9)	82 (31.7)	████	████
Secondary primary malignancies (excluding non-melanoma skin cancer)	8 (2.7)	1 (0.4)	████	████
TLS	1 (0.3)	8 (3.1)	████	████
AEs of clinical interest <u>and</u> AEs of special interest				
Suspected transmission of an infectious agent via product	████	████	████	████
Ventricular arrhythmias ^d	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular tachycardia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

^cAEs of clinical or special interest with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.

^dDefined using the same collection of MedDRA preferred terms as the cardiac event of clinical interest subcategory of ventricular tachyarrhythmias.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine with cyclophosphamide and rituximab; TLS: tumour lysis syndrome.

Source: Brown *et al.* (2025) (Table 2, Table S8 and Table S13);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 60 and Table 14.3.2.11.4).²

Table 30: Exposure-adjusted incidence rate (events per 100 patient-years) of key AEs of clinical or special interest (safety population)

System organ class preferred term	Arm A (AV) n=291	Arm C (FCR/BR) N=259
AEs of clinical interest		
Cardiac event	████	████
Atrial fibrillation	████	████
Cytopenias		
Anaemia	████	████
Neutropenia	████	████
Thrombocytopenia	████	████

System organ class preferred term	Arm A (AV) n=291	Arm C (FCR/BR) N=259
Haemorrhage	████	████
Major haemorrhage	████	████
Hypertension	████	████
Infections	████	████
Secondary primary malignancies (excluding non-melanoma skin cancer)	████	████
TLS	████	████
AEs of clinical and special interest		
Suspected transmission of an infectious agent via product	█	█
Ventricular arrhythmias	████	█

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

^cAEs of clinical or special interest with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine with cyclophosphamide and rituximab; TLS: tumour lysis syndrome.

Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 61 and Table 14.3.2.11.4).²

Grade ≥3 AEs

The incidences of Grade ≥3 TEAEs experienced in the AMPLIFY trial were 53.6% and 60.6% for AV and FCR/BR, respectively, as shown in Table 31. The most common grade ≥3 TEAE reported in ≥5% of patients was neutropenia, occurring in 26.8% of patients in the AV arm and 32.4% of patients in the FCR/BR arm.

Grade ≥3 febrile neutropenia events were reported in 5 patients (1.7%) receiving AV and 24 patients (9.3%) receiving FCR/BR.

Table 31: Grade ≥3 TEAEs reported in ≥5% of patients in any arm in AMPLIFY (safety population)^{a, b, c}

Preferred term	Arm A (AV) n=291	Arm C (FCR/BR) n=290		
		Total n=259	FCR only n=122	BR only n=137
Patients with at least 1 Grade ≥ 3 TEAE	156 (53.6)	157 (60.6)	████	████
Neutropenia	78 (26.8)	84 (32.4)	████	████
COVID-19 pneumonia	16 (5.5)	7 (2.7)	████	████
Neutrophil count decreased	16 (5.5)	22 (8.5)	████	████
Anaemia	11 (3.8)	17 (6.6)	████	████
COVID-19	8 (2.7)	4 (1.5)	████	████
Febrile neutropenia	5 (1.7)	24 (9.3)	████	████
Thrombocytopenia	4 (1.4)	22 (8.5)	████	████
TLS	1 (0.3)	8 (3.1)	████	████

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

^cPatients with multiple occurrences are counted once per system organ class and preferred term regardless of the number of occurrences.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; TEAE: treatment-emergent adverse event; TLS: tumour lysis syndrome.

Source: Brown *et al.* (2025) (Table 2 and Table S8);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 47).²

Treatment-related AEs

The incidence of TEAEs assessed as possibly being related to acalabrutinib was 75.9% for AV (see Table 32). The most commonly reported TEAEs (occurring in ≥10% of patients) for AV were headache (■■■%), neutropenia (■■■%), diarrhoea (■■■%), and contusion (■■■%).

Table 32: Acalabrutinib-related AEs reported in ≥5% of patients in AMPLIFY (safety population)^{a, b, c}

Preferred term	Arm A (AV) n=291
Patients with ≥1 AE possibly related to any study treatment ^d	■■■■■
Patients with ≥1 AE possibly related to acalabrutinib ^d	■■■■■
Headache	■■■■■
Neutropenia	■■■■■
Diarrhoea	■■■■■
Contusion	■■■■■
Nausea	■■■■■
Fatigue	■■■■■
Arthralgia	■■■■■
Haematoma	■■■■■
Rash	■■■■■
Thrombocytopenia	■■■■■

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

^cPatients with multiple occurrences are counted once per system organ class and preferred term regardless of the number of occurrences.

^dPossibly related is defined as reasonable possibility that the AE was caused by investigational product, as assessed by investigator.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; TEAE: treatment-emergent adverse events.

Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 48).²

SAEs

SAEs were reported in 24.7% and 27.4% of patients receiving AV and FCR/BR, respectively.

The SAEs with the highest incidences (reported in ≥5% of patients) included the following:

- For AV: COVID-19 pneumonia (5.8%)
- For FCR/BR: febrile neutropenia (8.1%)

Company evidence submission template for acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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Febrile neutropenia SAEs were reported in five patients (1.7%) receiving AV and 21 patients (8.1%) receiving FCR/BR.

COVID-19 had a greater impact on the treatment-emergent SAEs for AV compared to FCR/BR, partly due to the longer duration of treatment exposure, and consequently the longer treatment-emergent observation period for AV compared to FCR/BR.

SAEs related to any study treatment occurred in █% (acalabrutinib-related: █%) and █% of patients receiving AV and FCR/BR, respectively (see Table 27).

2.11.3 Dose modification due to AEs

Dose modifications were permitted for all arms in the AMPLIFY trial. The criteria for dose modifications (withholding and reduction) differed by drug and are defined in the AMPLIFY statistical analysis plan Section 3.5, provided in the reference pack alongside this submission.¹¹⁹

Arm A (AV)

Dose withholding for AV was defined as a delay (withholding of treatment) of at least seven consecutive days. For AV, █ (█%) patients and █ (█%) patients had a dose withholding of acalabrutinib and venetoclax, respectively. At least one dose reduction was required in 41 (14.1%) patients for acalabrutinib and █ (█%) patients for venetoclax. AEs were the primary reason for dose withholding and dose reductions for acalabrutinib and venetoclax.

Arm C (FCR/BR)

For FCR/BR, rituximab, bendamustine, fludarabine, and cyclophosphamide dose withholding was defined as missing at least one scheduled infusion within a treatment cycle.

Among patients who were treated with FCR, █ (█%) patients, █ (█%) patients, and █ (█%) patient had a dose withholding of fludarabine, cyclophosphamide, and rituximab, respectively. There were █ (█%) patients, █ (█%) patients, and █ (█%) patients who had a dose reduction of fludarabine, cyclophosphamide, and rituximab, respectively.

Among patients who were treated with BR, █ (█%) patients and █ (█%) patients had a dose withholding of bendamustine and rituximab, respectively. There were █ (█%) patients and █ (█%) patients who had a dose reduction of bendamustine and rituximab, respectively.

Dose reduction of any study treatment due to AEs

The incidence of AEs leading to dose reduction of any study treatment was 14.1% for AV and 11.2% for FCR/BR (Table 33). Neutropenia was the only AE leading to dose reduction of any treatment that occurred in >3% of patients in both arms.

Table 33: AEs occurring in ≥1% of patients which led to dose reduction of any treatment by preferred term in AMPLIFY (safety population)^{a, b}

Preferred term	Arm A (AV) n=291	Arm C (FCR/BR) n=259
Any AE leading to dose reduction of any treatment	41 (14.1)	29 (11.2)
Neutropenia	█	█

Preferred term	Arm A (AV) n=291	Arm C (FCR/BR) n=259
Neutrophil count decreased	████	████
Diarrhoea	████	████
Thrombocytopenia	████	████
Nausea	████	████
White blood cell count decreased	████	████

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; TEAE: treatment-emergent adverse event.

Source: Brown *et al.* (2025);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 50).²

The incidence of AEs leading to dose withholding of any study treatment was higher for AV (████) than FCR/BR (████) (Table 34). However, a notably higher proportion of patients withheld doses due to COVID-19 in the AV arm versus FCR/BR arm (10.3% versus 0.4%, respectively). As noted above, the longer treatment-emergent observation period for AV compared to FCR/BR contributed to the higher rate of COVID-19 AEs in the AV arm and, as such, may have contributed to the higher rate of AEs leading to dose withholding.

Table 34: AEs occurring in ≥2% of patients which led to dose withholding of any treatment in any arm by preferred term in AMPLIFY (safety population)^{a, b}

Preferred term	Arm A (AV) n=291	Arm C (FCR/BR) n=259
Any AE leading to dose withholding of any treatment	████	████
Neutropenia	67 (23.0)	35 (13.5)
COVID-19	30 (10.3)	1 (0.4)
Neutrophil count decreased	14 (4.8)	9 (3.5)
COVID-19 pneumonia	11 (3.8)	0 (0.0)
Diarrhoea	8 (2.7)	0 (0.0)
Pyrexia	6 (2.1)	4 (1.5)
Thrombocytopenia	5 (1.7)	9 (3.5)
Alanine aminotransferase increased	5 (1.7)	1 (0.4)
Pneumonia	4 (1.4)	3 (1.2)
Febrile neutropenia	2 (0.7)	1 (0.4)
Platelet count decreased	2 (0.7)	4 (1.5)
Nausea	1 (0.3)	0 (0.0)

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in the AMPLIFY CSR.²

^bTEAEs were coded with MedDRA Version 26.1.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; TEAE: treatment-emergent adverse event.

Source: Brown *et al.* (2025);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 52).²

2.11.4 Treatment discontinuation due to AEs

There were 23 (7.9%) patients receiving AV and 28 (10.8%) patients receiving FCR/BR with at least one AE leading to discontinuation of any study treatment (Table 35 and Table 36).

Table 35: AEs leading to discontinuation of AV in ≥ 2 patients in AMPLIFY (safety population)^{a, b}

Preferred term	Arm A (AV) n=291
Patients with ≥ 1 AE leading to discontinuation of any study treatment	23 (7.9)
Patients with ≥ 1 AE leading to discontinuation of acalabrutinib	22 (7.6)
COVID-19 pneumonia	6 (2.1)
COVID-19	1 (0.3)
Thrombocytopenia	2 (0.7)
Neutrophil count decreased	0 (0.0)
Pneumonia	0 (0.0)
Pneumonitis	0 (0.0)
Patients with ≥ 1 AE leading to discontinuation of venetoclax	18 (6.2)
COVID-19 pneumonia	4 (1.4)
COVID-19	1 (0.3)
Thrombocytopenia	2 (0.7)
Neutropenia	1 (0.3)
Acute kidney injury	0 (0.0)
Diarrhoea	0 (0.0)
Pneumonia	0 (0.0)

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in Brown *et al.* (2025).³

^bTEAEs were coded with MedDRA Version 26.1.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; N/A: not applicable; TEAE: treatment-emergent adverse event.

Source: Brown *et al.* (2025) (Table S11).³

Table 36: AEs leading to discontinuation of FCR/BR in ≥ 2 patients in AMPLIFY (safety population)^a

Preferred term	Arm C (FCR/BR) n=259
Patients with ≥ 1 AE leading to discontinuation of any study treatment	28 (10.8)
Patients with ≥ 1 AE leading to discontinuation of fludarabine	15 (5.8)
Thrombocytopenia	4 (1.5)
Febrile neutropenia	2 (0.8)
Neutropenia	2 (0.8)
Patients with ≥ 1 AE leading to discontinuation of cyclophosphamide	16 (6.2)
Thrombocytopenia	5 (1.9)
Febrile neutropenia	2 (0.8)

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Preferred term	Arm C (FCR/BR) n=259
Neutropenia	2 (0.8)
Patients with ≥1 AE leading to discontinuation of rituximab	27 (10.4)
Thrombocytopenia	5 (1.9)
Neutropenia	3 (1.2)
Febrile neutropenia	2 (0.8)
Patients with ≥1 AE leading to discontinuation of bendamustine	10 (3.9)

Data are presented as n (%).

^aTEAEs were coded with MedDRA Version 26.1.

Abbreviations: AE: adverse event; BR: bendamustine/rituximab; FCR: fludarabine/cyclophosphamide/rituximab.

Source: Brown *et al.* (2025) (Table 2 and Table S11).³

2.11.5 Deaths

Patient deaths occurred in 18 patients receiving AV (6.2%) and 42 patients receiving FCR/BR (14.5%) in the FAS (see Table 37) and in ■■■ of patients receiving AV and ■■■ receiving FCR/BR in the safety population. None of the deaths for AV were considered to be causally related to acalabrutinib by the investigator.

COVID-19 and COVID-19 pneumonia are the only AEs with a fatal outcome that occurred in two or more patients in each arm.

Table 37: Summary of deaths in AMPLIFY (FAS)^a

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Deaths	18 (6.2)	42 (14.5)
Primary cause of death		
Disease progression ^b	0 (0.0)	4 (1.4)
Adverse event	16 (5.5)	28 (9.7)
Pre-treatment	0 (0.0)	0 (0.0)
On treatment ^{c, d}	10 (3.4)	9 (3.1)
After 30 days post-dose	6 (2.1)	19 (6.6)
Unknown	0 (0.0)	4 (1.4)
Other ^e	2 (0.7)	6 (2.1)
Acute respiratory failure	1 (0.3)	0 (0.0)
COVID-19	0 (0.0)	2 (0.7)
Cerebrovascular accident	0 (0.0)	1 (0.3)
Haemorrhagic stroke	0 (0.0)	1 (0.3)
Infection	0 (0.0)	0 (0.0)
Lung disorder	0 (0.0)	0 (0.0)
Neoplasm malignant	1 (0.3)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	1 (0.3)
Sudden death	0 (0.0)	1 (0.3)

	Arm A (AV) n=291	Arm C (FCR/BR) n=290
Death due to COVID-19^d	10 (3.4)	21 (7.2)
COVID-19	4 (1.4)	10 (3.4)
COVID-19 pneumonia	6 (2.1)	11 (3.8)
Suspected COVID-19	0 (0.0)	0 (0.0)

Data are presented as n (%).

^aResults for the AVO arm are not presented but can be found in Brown *et al.* (2025).³

^bDeath related to disease progression is as assessed by investigator.

^cIncludes AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent therapy, whichever comes first.

^dPatients who died due to confirmed/suspected COVID-19 are also included among those who died due to an AE or other reasons while on treatment.

^ePatients who died and are not captured in the earlier categories and reasons correspond with “other, specify” field in the eCRF.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; eCRF: electronic case report form; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab.

Source: Brown *et al.* (2025) (Table S18).³

2.12 Ongoing studies

The AMPLIFY trial is currently ongoing with a future data cut expected in [REDACTED]

[REDACTED] In addition, the MAJIC study (NCT05057494), a phase III RCT investigating the safety and efficacy of AV versus VenO in untreated CLL or small lymphocytic lymphoma, is ongoing.

Treatment duration in the MAJIC trial is guided by MRD status.¹²⁰

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the AMPLIFY trial

Strengths of the clinical evidence

The efficacy and safety of AV in patients with untreated non-high risk CLL has been demonstrated in the ongoing, multicentre, phase III AMPLIFY RCT.

AMPLIFY is a high quality, phase III RCT that enrolled a large patient sample (N=867) and was deemed to be at low risk of bias (Section 2.5), thus providing robust evidence on the efficacy and safety of AV versus FCR/BR. The primary outcome of PFS was assessed by blinded independent assessors and was consistent with investigator-assessed PFS, further supporting the robustness and reliability of the primary outcome. Furthermore, all randomised patients were included in the efficacy analyses, thus preserving randomisation. In addition, the AMPLIFY trial included [REDACTED] UK sites. Feedback from UK clinical experts indicated that baseline patient and disease characteristics from the AMPLIFY trial were representative of the UK patient population for whom fixed-duration therapies are considered more suitable than treat-to-progression therapies.¹⁵ As such, data from AMPLIFY are deemed generalisable to UK clinical practice.

Relevance of AMPLIFY endpoints

PFS and OS

IRC-assessed PFS was selected as the primary endpoint in the AMPLIFY trial. PFS is a

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commonly used endpoint for assessing the efficacy of CLL treatments in clinical trials, and was used in the CLL14 (VenO) and the GLOW (VenI) trials.^{35, 37} In addition, due to the indolent and chronic nature of CLL, patients tend to live for long periods of time beyond the trial follow-up, which can make it challenging to collect mature OS data in the timeframe of most CLL clinical trials.^{3, 55, 121, 122} Since PFS has been shown to have a robust correlation with OS, it has become a widely accepted surrogate endpoint for OS in CLL.⁵⁶ OS was a key secondary endpoint in the AMPLIFY trial as extension of survival is still considered a primary goal of treatment in CLL. Despite the immaturity of data, AV still achieved a statistically significant improvement in survival compared with FCR/BR (nominal p-value <0.001).

MRD negativity

MRD negativity rate was a key secondary endpoint in the AMPLIFY trial, as a number of prospective clinical trials have demonstrated that CLL treatments which lead to uMRD are associated with improved clinical outcomes, such as PFS. Additionally, the EMA, the BSH and the iwCLL have noted the potential of uMRD to assess treatment response in CLL clinical trials.^{26, 31, 123} However, the connection between uMRD and PFS is less clear for combination therapies of venetoclax and a BTKi, than for combination therapies such as venetoclax and the anti-CD20 antibody, obinutuzumab. Despite relatively low percentages of uMRD for AV in AMPLIFY, AV was associated with relatively high PFS and OS estimates and showed a statistically significant PFS and OS benefit versus FCR/BR.³ It should be considered that the anti-CD20 antibody treatment in the AVO arm, but not AV arm, may have “cleared” CLL cells from the blood, thus explaining the low MRD negativity rate observed in the AV arm. Use of a more stringent method for assessing MRD negativity in the AMPLIFY trial, for example assessing bone marrow samples as opposed to peripheral blood, may have yielded more clinically robust results.

Furthermore, the results for the uMRD endpoint should be interpreted with caution due to the timing of scheduled assessments. As discussed in Section 2.6.3, MRD rates for the key secondary endpoint were compared between AV and FCR/BR before treatment completion in the AV arm, and thus the results may not reflect the true effect of AV on MRD negativity. Additionally, the COVID-19 pandemic is likely to have compromised the ability to best assess treatment outcomes, due to the competing risk of death from COVID-19.

In addition, uMRD is not considered a key endpoint in driving treatment decisions in UK clinical practice.¹⁵ MRD assessment is not routinely conducted for patients with untreated non-high risk CLL in the UK and is not funded by the NHS, meaning that it is a less relevant endpoint than PFS and OS in UK clinical practice. This is supported by feedback from UK clinical experts participating in the modified Delphi panel conducted by AstraZeneca (see Section 2.10.5), who agreed that PFS is of greater importance than MRD negativity in guiding treatment decisions in patients with CLL.¹¹⁸

Clinical efficacy for AV in patients with untreated non-high risk CLL

The AMPLIFY study met its primary endpoint of IRC-assessed PFS. At the interim analysis (DCO date: 30th April 2024), patients in the AV arm experienced a statistically significant 35% reduction in the risk of progression or death compared with the FCR/BR arm (HR: 0.65; 95% CI: 0.49, 0.87; p=0.004; median follow-up: 40.8 months).³ The PFS benefit associated with AV was consistent across major subgroups, including age, *IgHV* mutational status and complex karyotype. Also at the interim analysis, the AMPLIFY trial demonstrated that treatment with AV was associated with an improvement in OS and a 67% reduction in the risk of death compared with FCR/BR (HR:

0.33; 95% CI: 0.18, 0.56; $p < 0.001$).³

Furthermore, results from the AMPLIFY trial highlight that the clinically significant efficacy benefit observed in the AV arm was not at the expense of patient HRQoL, with PRO data confirming that treatment with AV was not associated with a deterioration in HRQoL compared with FCR/BR. More broadly, the results also showed a HRQoL benefit associated with active treatment. At 3 years post-treatment follow-up, patients in both the AV and FCR/BR arms experienced an improvement in HRQoL as measured by EQ-5D, EORTC QLQ-C30 and FACIT-Fatigue.

Safety for AV in patients with untreated non-high risk CLL

The safety profile of AV in the AMPLIFY trial aligned with that of previous studies on acalabrutinib and no new safety signals were identified which impact the risk-benefit profile of AV.^{2, 3} The proportion of patients who had TEAEs that resulted in death was comparable in the AV and FCR/BR arms, whilst the proportion who had TEAEs resulting in discontinuation was slightly higher in the FCR/BR arm. The most commonly reported TEAEs were headache (35.1%), diarrhoea (32.6%), and neutropenia (30.9%) in the AV arm, and neutropenia (38.2%), nausea (35.9%), and infusion-related reactions (32.8%) in the FCR/BR arm, consistent with the known safety profiles of these treatments.

Furthermore, no new safety signals were identified when considering events of clinical interest, or AEs of special interest. The proportion of patients experiencing any cardiac event was low across both arms, with ventricular arrhythmias occurring in less than 1% of patients in either group. Major haemorrhages occurred in fewer than 2% of patients in either arm, and the proportion of secondary primary malignancies was also low. For various AEs, the higher incidence in the AV arm compared with the FCR/BR arm can be attributed, at least in part, to the longer duration of exposure to AV versus FCR/BR.³

2.13.2 Comparative efficacy of AV with VenI and VenO

The SLR detailed in Section 2.1 did not identify any head-to-head studies comparing AV to the relevant fixed-duration comparators: VenI and VenO. As such, an indirect estimate of comparative efficacy was required for this submission.

Indirect treatment comparison feasibility assessment

To determine the feasibility of conducting an ITC and the most suitable approach of doing so, a feasibility assessment was conducted (Section 2.10.2). This assessment considered the feasibility of the following ITC approaches: an NMA, an anchored or unanchored MAIC and an STC. Of these three approaches, an NMA was deemed unfeasible as the studies included in the feasibility assessment did not satisfy the foundational assumptions required for an NMA. A MAIC was also considered infeasible due to the significant non-overlap in study and baseline characteristics between these trials, which would result in drastic reductions in ESS and potential bias.

An STC was considered the most appropriate approach for comparing the efficacy of AV in the AMPLIFY trial with VenI in the CAPTIVATE FD and GLOW trials, and VenO in the CLL14 trial. This is because an STC is not restricted to scenarios with close overlap in baseline and study characteristics, and therefore would not reduce the ESS as a result of population adjustment. As the AMPLIFY and CLL13 trials shared a common FCR/BR control arm, and the distribution of prognostic factors and TEMs in these trials was more aligned compared with other trials, an anchored Bucher ITC was considered the most appropriate ITC approach for the comparison of

AV and VenO using data from these two trials.

Results of the ITCs conducted between AV, VenI and VenO

The STC analyses, based on patient-level data from AMPLIFY and published data from the comparator studies, showed no statistically significant differences in efficacy between AV and the comparators VenI and VenO, in terms of PFS and OS. Specifically, the relative treatment effect estimates at follow-up periods of approximately 55 months for PFS and 58 months for OS indicated no statistically significant differences: the RMST differences for AV versus VenI (from GLOW and CAPTIVATE FD) and VenO (from CLL14) were all within CIs crossing zero, reflecting clinical comparability.

The results of the anchored ITC comparing the efficacy of AV and VenO using data from the AMPLIFY and CLL13 trials demonstrated an improvement in OS for AV versus VenO at 57 months follow-up, and no statistically significant difference in PFS at 55 months follow-up, thus supporting the conclusion of clinical comparability.

Modified Delphi panel

A *de novo* two-round modified Delphi panel was conducted with UK-based clinical experts between July and August 2025 to obtain clinical consensus on the expected comparative efficacy of AV versus VenI and VenO in real-world practice, and validate the findings of the ITCs. In Round 1, consensus was achieved that AV would be considered clinically comparable to VenI and VenO in terms of PFS (95% and 88% agreed for VenI and VenO, respectively) and OS (85% and 94% agreed for VenI and VenO, respectively).

Participants also considered AV a suitable alternative regarding HCRU within the first and subsequent six months of treatment. Similarly, consensus on HRQoL comparisons was reached for AV versus VenI but not versus VenO.

Regarding safety, consensus was reached that AV and VenO can be considered clinically comparable, though agreement was not achieved for AV versus VenI. In Round 2, consensus was obtained that, based on panellists' clinical experience, fixed-duration AV would have a more favourable safety profile than fixed-duration VenI.

Summary

In conclusion, despite the absence of head-to-head trial data, the results of the ITCs and the modified Delphi panel demonstrate that AV can be considered clinically comparable in terms of PFS and OS to both VenI and VenO. This was further supported by feedback from UK clinical experts,¹⁵ and published evidence of clinical comparability in terms of PFS between acalabrutinib and ibrutinib monotherapy.^{9, 80}

3 Cost effectiveness

Summary

- A *de novo* economic analysis was conducted to assess the cost-effectiveness of AV versus the relevant fixed-duration comparator therapies used for untreated non-high risk CLL in UK clinical practice: VenI and VenO.
- The economic analysis was developed in line with the NICE reference case and from an NHS and PSS perspective. The model structure adopted a semi-Markov, state-transition cohort approach in line with previous NICE evaluations for therapies in untreated non-high risk CLL, with a lifetime time horizon and a 28-day cycle length.^{4, 8, 9}
- The model consisted of three mutually exclusive health states: progression-free (PF), PD and death.
 - For AV, transitions from the PF to PD health state, and the PF health state to death, were derived from time to progression (TTP) and pre-progression survival (pre-PS) data for AV reported in the AMPLIFY trial (DCO: 30th April 2024).² For the transition between PD and death, due to the immaturity of the post-progression survival (post-PS) data from the AMPLIFY trial,³ external OS data from the acalabrutinib arm in the second-line CLL setting from the ASCEND trial were used.¹²⁴
 - For VenI and VenO, TTP, pre-PS and post-PS were assumed to be clinically equivalent to AV. This was based on the results from a series of ITCs, including an STC (Section 2.10.3.2) and an anchored Bucher ITC (Section 2.10.4), as well as the results from a modified Delphi panel conducted with UK clinical experts (Section 2.10.5).
- Where feasible, health state utility values were based on EQ-5D-5L data collected in the AMPLIFY trial (DCO: 30th April 2024)² and mapped to the EQ-5D-3L, otherwise external sources identified in the literature were used. AE disutilities were derived from the literature.
- All relevant direct costs were considered, including intervention and comparator acquisition costs (at PAS price for acalabrutinib, and list price for all other therapies), intervention and comparator administration costs, subsequent treatment acquisition costs, health state follow-up and monitoring costs, AE management costs, and end-of-life costs.

Results of the economic analysis

- In the probabilistic base case analysis versus VenI, AV (at PAS price) was associated with [REDACTED] more quality-adjusted life years (QALYs) at a [REDACTED] cost of [REDACTED], therefore AV dominated VenI. This translates to a [REDACTED] net health benefit (NHB) at willingness-to-pay (WTP) thresholds of £20,000 and £30,000/QALY ([REDACTED] and [REDACTED], respectively) and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenI at both WTP thresholds was [REDACTED].
- In the probabilistic base case analysis versus VenO, AV (at PAS price) was associated with [REDACTED] QALYs and [REDACTED] total costs of [REDACTED], resulting in AV dominating VenO. This translates to a [REDACTED] NHB at WTP thresholds of £20,000 and £30,000/QALY ([REDACTED] and [REDACTED], respectively), and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenO at both WTP thresholds was [REDACTED].
- Deterministic sensitivity analysis (DSA) revealed the most influential drivers of the base case economic analysis versus VenI were the proportion of patients receiving subsequent

treatment with zanubrutinib monotherapy, and venetoclax with rituximab, for the VenI arm. Similarly, versus VenO, they were the proportion of patients receiving subsequent treatment with zanubrutinib monotherapy, and venetoclax with rituximab, for the VenO arm.

- Scenario analyses were conducted to assess the robustness of the base case economic analysis assumptions; across all scenario analyses AV remained dominant versus both VenI and VenO.

3.1 Published cost-effectiveness studies

An economic SLR was conducted in December 2024 and subsequently updated in August 2025 to identify relevant economic evaluations, utility studies, and cost and resource use studies in patients with untreated CLL.

Full details of the SLR search strategy, study selection process and results for the economic SLR can be found in Appendix E, Appendix F and Appendix G, for the economic evaluations, utility studies, and cost and resource use studies SLR streams, respectively.

In total, the economic evaluations SLR stream identified 47 records reporting on 47 unique economic evaluations. These included six budget impact models, one cost minimisation model, two trial based economic evaluations, two microsimulations, one discrete event simulation, nine partitioned survival models (PSM), four semi-Markov models and 22 Markov models. Additionally, the SLR identified 35 HTA submissions that included an economic evaluation, seven of which were made to NICE.^{4, 5, 8-10, 13, 14}

Full details of the economic evaluations and HTA submissions identified in the SLR are provided in Appendix E.

3.2 Economic analysis

Since none of the economic evaluations identified by the SLR addressed the exact decision problem relevant to this submission, a *de novo* economic analysis was conducted for the purpose of this evaluation.

The objective of the economic analysis was to determine the cost-effectiveness of AV compared to the relevant fixed-duration comparator therapies used to treat untreated non-high risk CLL in UK clinical practice: VenI and VenO.

The analysis was conducted from the perspective of the NHS and PSS, taking into account direct costs and benefits only. The economic evaluation was approached as follows, in line with the NICE reference case:¹²⁵

- Health outcomes were measured in both life years gained (LYG) and QALYs gained.
- The primary outcome measures for the economic evaluation were the incremental cost-effectiveness ratio (ICER; the cost per QALY gained), NHB and NMB for the comparisons of AV versus VenI, and AV versus VenO.
- The clinical effectiveness of AV and the relevant comparators was measured using TTP and pre-PS derived from the AMPLIFY trial (DCO: 30th April 2024) (see Section 3.3.2).²

- Due to the immaturity of post-PS data in the AMPLIFY trial, post-PS data in the model were informed by OS data from the ASCEND trial, which was conducted in patients with relapsed/refractory CLL.¹²⁴ The second-line setting of the ASCEND trial was considered to represent post-progression patients in the first-line CLL setting.¹²⁴
- All relevant direct costs were considered, including intervention and comparator acquisition costs, administration costs, subsequent treatment acquisition costs, health state follow-up and monitoring costs, AE management costs, and end-of-life costs (see Section 3.5).

Further methodological details for the economic analysis are provided below.

3.2.1 Patient population

The patient population considered in the economic analysis was adult patients with untreated *non-high risk* CLL, i.e., patients with untreated CLL and *without del(17p) or TP53 mutations*. As summarised in Section 1.1, this comprises a subset of the marketing authorisation extension for acalabrutinib relevant to this submission and aligns with the population enrolled in the AMPLIFY trial,^{2, 3} the pivotal clinical trial for AV in this indication.

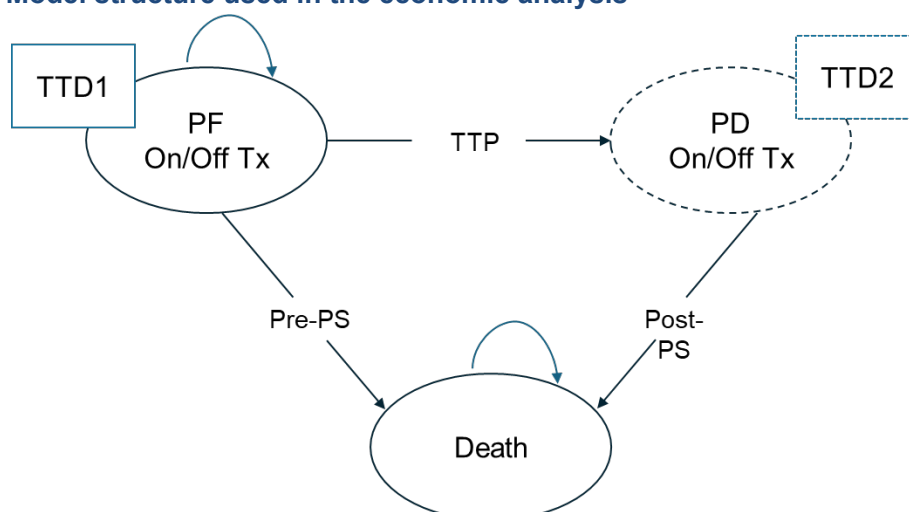
3.2.2 Model structure

The economic analysis utilised a semi-Markov, state-transition cohort model with three mutually exclusive health states: PF, PD and death (Figure 18).

Unlike a conventional Markov model, the semi-Markov model captures and follows each cohort of patients entering the PD health state in each model cycle using tunnel states. Transition probabilities between health states were time-dependent and applied over the course of the modelled time horizon. The PF and PD health states included health sub-states for patients being on- or off- treatment. This allowed for the explicit modelling of specific treatment-related costs, as well as the HRQoL implications associated with being on- or off-treatment. In the PF health state, time spent in the on-/off-treatment sub-states was informed by time to treatment discontinuation (TTD) data from the AMPLIFY trial (DCO: 30th April 2024).² In the PD health state, this was informed by a weighted average of median treatment duration from external sources.

Costs and health state utility values (HSUVs) were assigned to each health state, and the total costs and QALYs for each treatment were estimated by combining the proportion of patients in each health state over time with the appropriate HSUVs values or costs.

Figure 18: Model structure used in the economic analysis



Abbreviations: Post-PS: post-progression survival; Pre-PS: pre-progression survival; TTD: time to treatment discontinuation; TTP: time to progression; Tx, treatment.

Model health states

PF health state

All patients in the economic analysis begin on active first-line treatment in the PF health state, and continue treatment until discontinuation, disease progression or death (Figure 18). The PF health state comprises patients who are alive without PD and includes two health sub-states for patients being on-/off-treatment. From the PF health state, patients can transition to PD or death.

PD health state

Following progression on first-line treatment, patients enter the PD health state and undergo subsequent lines of treatment, remaining in this health state until death (Figure 18). From the PD health state, patients can only transition to death. Similar to the PF health state, the PD health state also includes two health sub-states for patients being on/off-treatment.

Death

The death state is modelled as an absorbing state (that is, patients cannot leave this state once they have entered it). Patients can enter this health state from either the PF or PD health states, depending on whether they die pre- or post-progression (Figure 18).

Transition probabilities

The following clinical parameters were used to model the transition probabilities between health states in the base case economic analysis:

- **Transitions from the PF to PD health state** were based on TTP data from the AMPLIFY trial (DCO: 30th April 2024).²
 - **TTP** was defined as the time from treatment initiation to disease progression (excluding death), based on IRC-assessed PFS.
- **Transitions from the PF health state to death** were based on pre-PS data from the AMPLIFY trial (DCO: 30th April 2024).²

- **Pre-PS** was defined as the time to death in the absence of disease progression, based on IRC-assessed PFS.
- To ensure survival did not exceed that expected for the general population, this transition probability to the death state was constrained by age- and gender-matched UK general population mortality.
- **Transitions from the PD health state to death** were based on post-PS from the ASCEND trial (DCO: 3rd September 2021).¹²⁴
 - **Post-PS** was defined as the time from disease progression to death from any cause. However, due to the immaturity of the post-PS data from the AMPLIFY trial (DCO: 30th April 2024),² an alternative source of post-PS data was used in the base case economic analysis. Specifically, external OS data from the acalabrutinib arm in the second-line CLL setting from the ASCEND trial was used (see Section 3.3.2 for further details).¹²⁴
 - This transition probability was constrained by age- and gender-matched UK general population mortality.

Choice of model structure

A semi-Markov, state-transition cohort model approach was deemed most appropriate for modelling the clinical outcomes for patients with untreated non-high risk CLL for the following reasons:

- **Addressing OS immaturity:** Whilst partitioned survival models (PSMs) are a commonly used modelling approach for the economic evaluation of oncology therapies, they require relatively mature long-term OS data. Due to the inherently indolent course of untreated CLL, OS data from the AMPLIFY trial remain immature from the latest DCO of the interim analysis (30th April 2024);² as such, the extrapolation of this OS data within a PSM approach would likely be associated with substantial uncertainty. A PSM is only appropriate when sufficient follow-up and numbers of events are available to reliably represent hazards. Given that this is unlikely to be achieved for untreated CLL, a PSM was not considered the most appropriate approach for this economic analysis. By contrast, a state-transition approach is not dependent on OS data and allows the use of data for intermediate endpoints, such as pre- and post-PS, to 'indirectly' inform OS as the product of multiple transitions between health states. As such, the structural link between PFS and OS in a state-transition model is expected to lead to more plausible long-term outcome estimates than in a PSM.

Data immaturity can further be addressed by the ability to incorporate external data into a state-transition model to inform transitions. A state-transition approach also avoids inconsistencies that may occur with a PSM in the context of untreated CLL, such as independently extrapolated OS based on immature trial data which, for example, may exceed the age-matched general population survival, or the crossing of independently extrapolated PFS and OS curves. These inconsistencies would result in a lack of clinical face validity and necessitate further adjustments to the economic analysis to reduce uncertainty.

- **Enables the modelling of the impact of subsequent treatment lines:** To reflect the indolent nature of CLL, where patients begin in a treatment-naïve setting (i.e., first-line treatment) then progress to the relapsed/refractory setting (i.e., second-line treatment), a semi-Markov state-transition model allows for the explicit modelling of the impact of subsequent treatment, implicitly capturing any effects thereafter.
- **Captures the costs and benefits of being on-/off-treatment, and the HRQoL impact of disease progression:** The semi-Markov state-transition approach with on- and off-treatment

health sub-states enables the explicit modelling of treatment-free periods and lines of subsequent treatment. This allows for a more granular assessment of the costs and HRQoL impact associated with being on treatment and experiencing disease progression.

- **Consistency with previously accepted approaches:** Finally, a semi-Markov state-transition model was the preferred approach in the three most recent NICE evaluations for therapies in previously untreated and/or treated CLL (TA931 [zanubrutinib monotherapy for treated and untreated CLL], TA891 [ibrutinib with venetoclax for untreated CLL], TA689 [acalabrutinib monotherapy for treated and untreated CLL]).^{4, 8, 9}

Summary of model features

The economic analysis was conducted from the perspective of the UK NHS and PSS according to the NICE reference case.¹²⁶

The model cycle length used in the economic analysis was four weeks (28 days). This is consistent with the four-weekly drug administration treatment cycles used for AV in the AMPLIFY trial,² and is in line with the model cycle length used in previous NICE evaluations for fixed-duration treatments in untreated CLL (VenI [TA891] and VenO [TA663]).^{4, 10} A half-cycle correction was implemented to account for the fact that transitions between health states can occur at any point during the model cycle, not necessarily at the start or end of each cycle, in line with recommended best practice.¹²⁷

A lifetime time horizon was adopted to reflect all differences in costs and health effects between the technologies being compared, in line with the NICE reference case.¹²⁶ The lifetime time horizon was estimated to be 40 years, based on the mean baseline age of the patients in the AMPLIFY trial (59.90 years) and allowing for a maximum age of 100 years.³ Costs and health outcomes were discounted at a 3.5% discount rate.¹²⁶

A summary of the key features of the economic analysis is provided in Table 38. The key features of the economic analyses from the NICE evaluations for the relevant comparator therapies (VenI [TA891] and VenO [TA663]), as well as the most recent evaluation in untreated CLL (zanubrutinib monotherapy [TA931]) are also presented in Table 38.^{4, 8, 10}

Table 38: Features of the economic analysis

Factor	Previous evaluations			Current evaluation	
	TA931 (zanubrutinib monotherapy) ⁸	TA891 (VenI) ⁴	TA663 (VenO) ¹⁰	Chosen values	Justification
Model design	State-transition	State-transition	Partitioned survival analysis	State-transition	- Overcomes the limitation of immature OS data by incorporating intermediate survival endpoints, such as pre- and post-PS. - Avoids inconsistencies associated with extrapolating PFS and OS using a PSM approach. - Allows for the explicit modelling of treatment-free periods and lines of subsequent treatment. - Aligned with precedent from previous NICE evaluations: TA931 (zanubrutinib monotherapy for treated and untreated CLL), TA891 (ibrutinib with venetoclax for untreated CLL), TA689 (acalabrutinib monotherapy for treated and untreated CLL).^{4, 8, 9}
Intervention	Zanubrutinib (treat-to-progression)	VenI (fixed-duration)	VenO (fixed-duration)	AV (fixed-duration)	In line with the decision problem addressed in this evaluation.
Comparators	Most relevant comparators preferred by committee: ^a - Acalabrutinib monotherapy - Ibrutinib monotherapy	- Acalabrutinib monotherapy - OC1b - VenO - Ibrutinib monotherapy - FCR	- OC1b - FCR - Ibrutinib monotherapy	- VenI - VenO	In line with the decision problem addressed in this evaluation.
Line of treatment	First-line	First-line	First-line	First-line	In line with the decision problem addressed in this evaluation.

Factor	Previous evaluations			Current evaluation	
	TA931 (zanubrutinib monotherapy) ⁸	TA891 (VenI) ⁴	TA663 (VenO) ¹⁰	Chosen values	Justification
Time horizon	Lifetime: 30 years	FCR suitable ^b - Lifetime: 40 years FCR unsuitable ^b /high-risk ^c - Lifetime: 30 years	Lifetime: 30 years	Lifetime: 40 years	In line with the NICE reference case, to capture all relevant differences in costs and outcomes between the technologies being compared. ¹²⁶
Model cycle length	28 days	28 days	28 days	28 days	In line with the model cycle length used in the NICE evaluations for the relevant fixed-duration comparator therapies (VenI [TA891] and VenO [TA663]) ^{4, 10} and consistent with the four-weekly drug administration treatment cycles for AV in AMPLIFY. ³
Discounting	3.5%	3.5%	3.5%	3.5%	In line with the NICE reference case.
Half-cycle correction	Yes	Yes	Yes	Yes	To account for health state transitions which may occur mid-model cycle. ¹²⁷
Perspective	UK NHS/PSS	UK NHS/PSS	UK NHS/PSS	UK NHS/PSS	In line with the NICE reference case.
Health effects measure	QALYs	QALYs	QALYs	QALYs	In line with the NICE reference case.
Source of pre-progression utilities	Acalabrutinib NICE evaluation (TA689) ⁹	FCR suitable ^a - GLOW trial (age-adjusted) FCR unsuitable ^b and high-risk patients ^b - GLOW trial	OC1b NICE evaluation (TA343) ⁵	EQ-5D-5L utility data collected from the AMPLIFY trial were used and mapped to the EQ-5D-3L	In line with the NICE reference case.
Source of post-	Published literature	FCR suitable ^b Published literature and previous NICE	OC1b NICE evaluation (TA343) ⁵	PD HSUV from Kosmas <i>et al.</i> (2015) ¹²⁸	Since only a few progression events were observed in the AMPLIFY trial, a reduction in utility associated with disease progression was not observed. As

Factor	Previous evaluations			Current evaluation	
	TA931 (zanubrutinib monotherapy) ⁸	TA891 (Venl) ⁴	TA663 (VenO) ¹⁰	Chosen values	Justification
progression utilities		evaluations FCR unsuitable ^b and high-risk patients ^c Published literature and previous NICE evaluations		was used to estimate the utility decrement associated with progression	such, a utility decrement from the published literature was applied to the pre-PS HSUV to inform the PD HSUV. The PF to PD HSUVs are in line with the previous NICE evaluation for fixed-duration Venl in untreated CLL (TA891) and validated by feedback from UK clinical experts. ^{4, 15}
Source of AE disutilities	Published literature and previous NICE evaluations	FCR suitable ^b - Previous CLL NICE evaluations FCR unsuitable ^b and high-risk patients ^c - Previous CLL NICE evaluations	Published literature and previous NICE evaluations	Published literature and previous NICE evaluations	The disutility associated with each therapy was calculated using published disutility values and durations associated with each TEAE used in the model.
Source of costs	- BNF - NHS reference costs	- Monthly Index of Medical Specialities (MIMS) - BNF - NHS reference costs	- MIMS - BNF - NHS reference costs	- eMIT - BNF - NHS reference costs 2023/24	In line with the NICE reference case.

^aComparison with VenO provided by the submitting Company as part of response to Appraisal Consultation Document (ACD) but not used in final decision making, as the Committee acknowledged zanubrutinib monotherapy was most likely to be used in place of ibrutinib or acalabrutinib monotherapy.

^bExcludes patients with del(17p) mutation.

^cHigh-risk patients were defined as patients with CLL carrying *TP53* or del(17p) mutations.

Abbreviations: ACD: Appraisal Consultation Document; AE: adverse event; AV: acalabrutinib with venetoclax; BNF: British National Formulary; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; eMIT: The drugs and pharmaceutical electronic market information tool; FCR: fludarabine with cyclophosphamide and rituximab; HSUV: health state utility value; MIMS: Monthly Index of Medical Specialities; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OClb: obinutuzumab with chlorambucil; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; post-PS: post-progression survival; pre-PS: pre-progression survival; PSS: Personal Social Services; QALY: quality-adjusted life years; TA: technology appraisal; UK: United Kingdom; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.2.3 Intervention technology and comparators

Intervention

The intervention in the economic analysis was AV, which was modelled in line with the dosing regimen detailed in the SmPC for acalabrutinib in this indication and that used in the AMPLIFY trial (see Table 39).^{1, 3}

Comparators

As discussed in Section 1.1, the relevant comparators to AV in this submission are VenO and VenI. All three treatments have fixed-duration dosing regimens, as summarised in Table 39.

Table 39: The dosing regimens for AV, VenI and VenO modelled in the economic analysis

Treatment regimen	Dosing regimen	Source
AV	Acalabrutinib (oral; 14x 28-day cycles) 100 mg administered twice daily for 14 treatment cycles, each lasting 28 days Venetoclax (oral; 12x 28-day cycles) - Initiated on Day 1 of Cycle 3 with a 5-week ramp-up until Day 1 of Cycle 4 (20 mg, 50 mg, 100 mg, 200 mg, 400 mg; once daily). Venetoclax treatment was continued at 400 mg once daily until Day 28 of Cycle 14	Acalabrutinib and venetoclax SmPCs ^{1, 129}
VenI	Ibrutinib (oral; 15x 28-day cycles) - Administered once daily (420 mg) - Ibrutinib is given as a monotherapy from Day 1 of Cycle 1 until Day 28 of Cycle 3, then in combination with venetoclax starting on Day 1 of Cycle 4 Venetoclax (oral; 12x 28-day cycles) - Initiated with a 5-week dose ramp-up period (20 mg, 50 mg, 100 mg, 200 mg, 400 mg; once daily), then 400 mg per day from Cycle 5 onward	Venetoclax and ibrutinib SmPCs ^{112, 129, 130}
VenO	Venetoclax (oral; 12x 28-day cycles) - Initiated with a 5-week dose ramp-up period starting on Day 22 of Cycle 1 until Day 22 of Cycle 2 (20 mg, 50 mg, 100 mg, 200 mg, 400 mg; once daily) - Dosage of 400 mg is maintained until the end of Cycle 12 Obinutuzumab (IV; 6x 28-day cycles) 1,000 mg administered on Days 1, 8 and 15 of Cycle 1, then on Day 1 of Cycles 2 through 6	Venetoclax and obinutuzumab SmPCs ^{129, 131, 132}

Abbreviations: AV: acalabrutinib with venetoclax; IV: intravenous; SmPC: summary of product characteristics; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.3 Clinical parameters and variables

3.3.1 Baseline characteristics

Baseline characteristics for the economic analysis population were informed by the AMPLIFY trial (all trial arms), as shown in Table 40.^{2, 3}

The economic analysis used the mean baseline age (59.90 years) of the AMPLIFY trial as the starting age in the first model cycle. Drug cost calculations, if not based on a flat dose, were

derived from the mean body surface area (BSA) () or the mean body weight () of patients in the AMPLIFY trial (all trial arms).²

Table 40: Baseline characteristics used in the economic analysis, based on the AMPLIFY trial (all trial arms)

Patient characteristics	Mean	SE
Age (mean)	59.90 years	0.32
BSA (mean)		
Weight (mean)		
Female patients	36%	0.036 ^a

^aSE assumed.

Abbreviations: BSA: body surface area; SE: standard error.

Source: Brown *et al.* (2025; Table 1);³ AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 12).²

3.3.2 Time-to-event outcomes

AV

For AV, the AMPLIFY trial reported data for TTP, pre-PS and post-PS for the duration of the follow-up period. However, since the data remain immature, extrapolation beyond the trial follow-up was necessary to estimate long-term treatment effects over a lifetime time horizon.

For TTP and pre-PS, standard parametric survival models (Weibull, exponential, Gompertz, gamma, log-normal, log-logistic, and generalised gamma) were fitted to patient-level data for TTP and pre-PS from the AV arm reported in the AMPLIFY trial (DCO: 30th April 2024).² For post-PS, due to the immaturity of the post-PS data from the AMPLIFY trial (DCO: 30th April 2024),² standard parametric survival models were instead fitted to external OS data from the acalabrutinib arm in the second-line CLL setting reported in the ASCEND trial (DCO: 3rd September 2021) (see Section 3.3.2.4 for further details).^{3, 124}

Whilst FCR/BR was the principal comparator in AMPLIFY, this was not considered a comparator for the decision problem of the current submission, due to its limited use in UK clinical practice (as discussed in Section 1.1). Given this, independent parametric survival models were fitted for the AV arm of the AMPLIFY trial only. Furthermore, joint models were considered unsuitable for all endpoints given the evidence of non-proportional hazards, particularly for PFS (see Appendix B.5.2).

The parametric survival model curve selection process was conducted in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14, and took into account the following criteria:¹¹⁶

- **Statistical fit:** Using the AIC¹³³ and Bayesian information criterion (BIC) statistics,¹³⁴ with the best statistical fit to the observed Kaplan-Meier data being the extrapolation with the lowest AIC and BIC
- **Visual fit:** Through visual inspection of goodness-of-fit of the predicted extrapolation to the observed Kaplan-Meier data and observed hazards
- **Clinical plausibility:** By validating the predicted outcomes of the extrapolations beyond the observed Kaplan-Meier data against published long-term survival curves and through clinical expert feedback, from interviews conducted by AstraZeneca between April and July 2025¹⁵

VenI and VenO

As detailed in Section 2.10, an STC, anchored Bucher ITC and modified Delphi panel were conducted to determine the comparative efficacy of AV versus VenI and VenO. Results of the STC demonstrated no statistically significant difference in PFS or OS between all three treatments (Section 2.10.3). The anchored Bucher ITC provided further evidence that the difference in PFS between AV and VenO was not statistically significant, whilst the difference in OS between the two therapies was statistically significant and in favour of AV (Section 2.10.4).

Furthermore, in the modified Delphi panel conducted with UK clinical experts across July and August 2025, the 22 experts reached consensus that AV can be considered clinically comparable in terms of PFS and OS versus both VenI (95% and 85% agreed for PFS and OS, respectively) and VenO (88% and 94% agreed for PFS and OS, respectively) (see Section 2.10.5).¹¹⁸ The assumption of clinical equivalence between AV, VenI and VenO was further supported by feedback from interviews with six UK clinical experts conducted by AstraZeneca between April and July 2025.¹⁵

As such, in the base case economic analysis, AV, VenI and VenO were deemed clinically equivalent in terms of TTP, pre-PS and post-PS. This was incorporated into the economic analysis by applying a HR of 1 to the relevant extrapolated curve for AV to derive the equivalent curve for VenI and VenO.

A detailed overview of the curve-fitting process for each time-to-event outcome is presented in the following sections.

3.3.2.1 Time to progression

TTP was defined as the time from treatment initiation to disease progression (excluding death). TTP was derived from the primary endpoint of the AMPLIFY trial – blinded IRC-assessed PFS.² As of the latest DCO of the AMPLIFY trial (30th April 2024), the median estimated TTP for the AV arm was not reached (Table 41).² The Kaplan-Meier curve for TTP is presented in Figure 19.

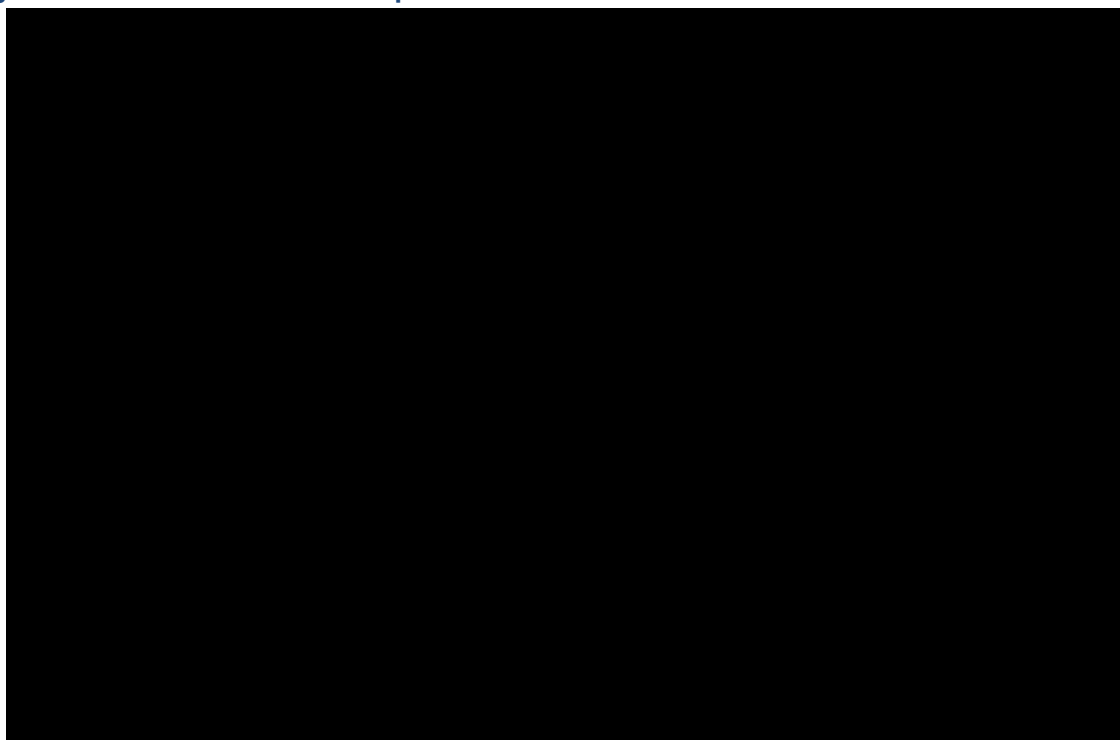
A plot of the raw and smoothed hazards (Figure 20) shows that the hazard increases over the duration of the trial. This hazard profile was considered relatively simple and did not warrant the exploration of more flexible survival models. Therefore, the analysis focussed on standard parametric models (Weibull, exponential, Gompertz, gamma, log-normal, log-logistic, and generalised gamma).

Table 41: Summary of TTP data for AV from the AMPLIFY trial

Arm	N	Events	Maturity	Median, months (95% CI)
AV	■	■	■	■

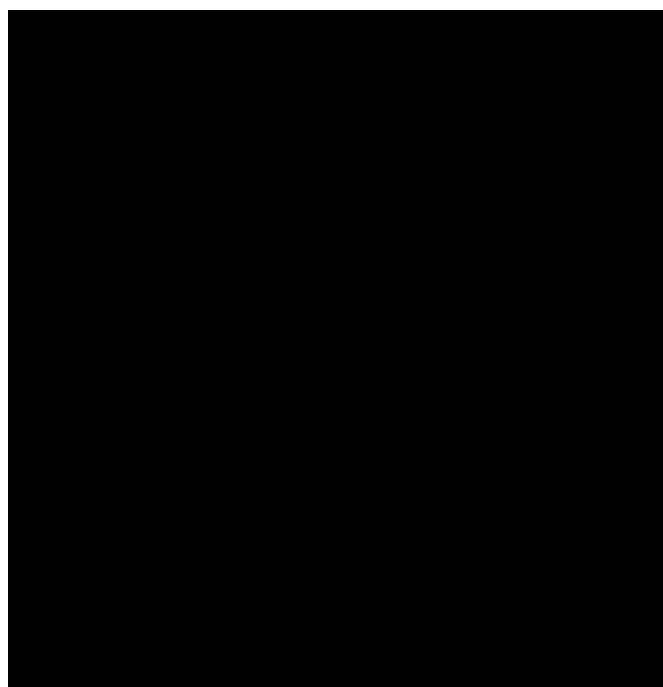
Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; NC: not calculable; TTP: time to progression.

Figure 19: IRC-assessed TTP Kaplan-Meier curve for AV from the AMPLIFY trial



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; TTP: time to progression.

Figure 20: IRC-assessed TTP raw and smoothed hazard plots for AV from the AMPLIFY trial



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; TTP: time to progression.

Statistical fit

According to AIC/BIC the Gompertz curve reflects the best statistical fit to the observed data for

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the AV arm of the AMPLIFY trial (Table 42). However, the top five best-fitting models all demonstrated a comparable goodness-of-fit with AIC/BIC values that differed only marginally.

Table 42: Statistical goodness-of-fit indicators (AIC/BIC) for the IRC-assessed TTP independent parametric models for AV from the AMPLIFY trial

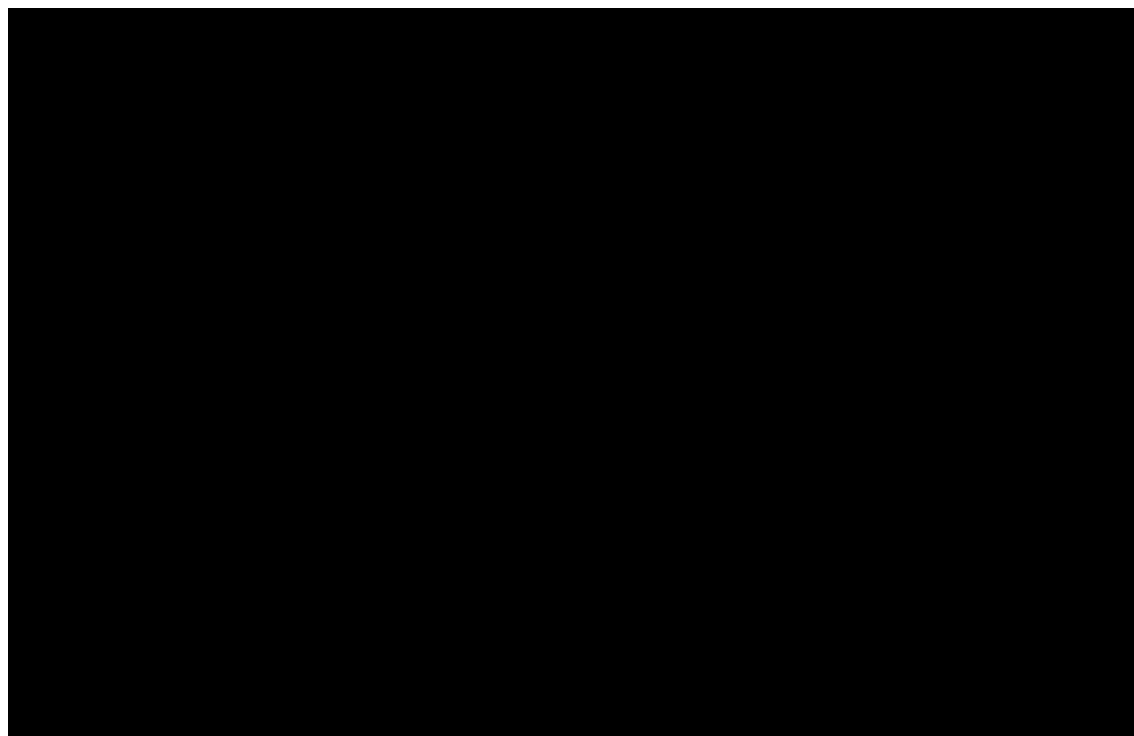
Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	911.5	7	915.2	7
Weibull	881.7	2	889.1	2
Log-normal	895.7	6	903.0	6
Log-logistic	884.1	4	891.5	3
Gompertz	878.0	1	885.3	1
Generalised gamma	881.9	3	892.9	5
Gamma	884.8	5	892.1	4

Abbreviations: AIC: Akaike Information Criterion; AV: acalabrutinib with venetoclax; BIC: Bayesian Information Criterion; IRC: Independent Review Committee; TTP: time to progression.

Visual fit

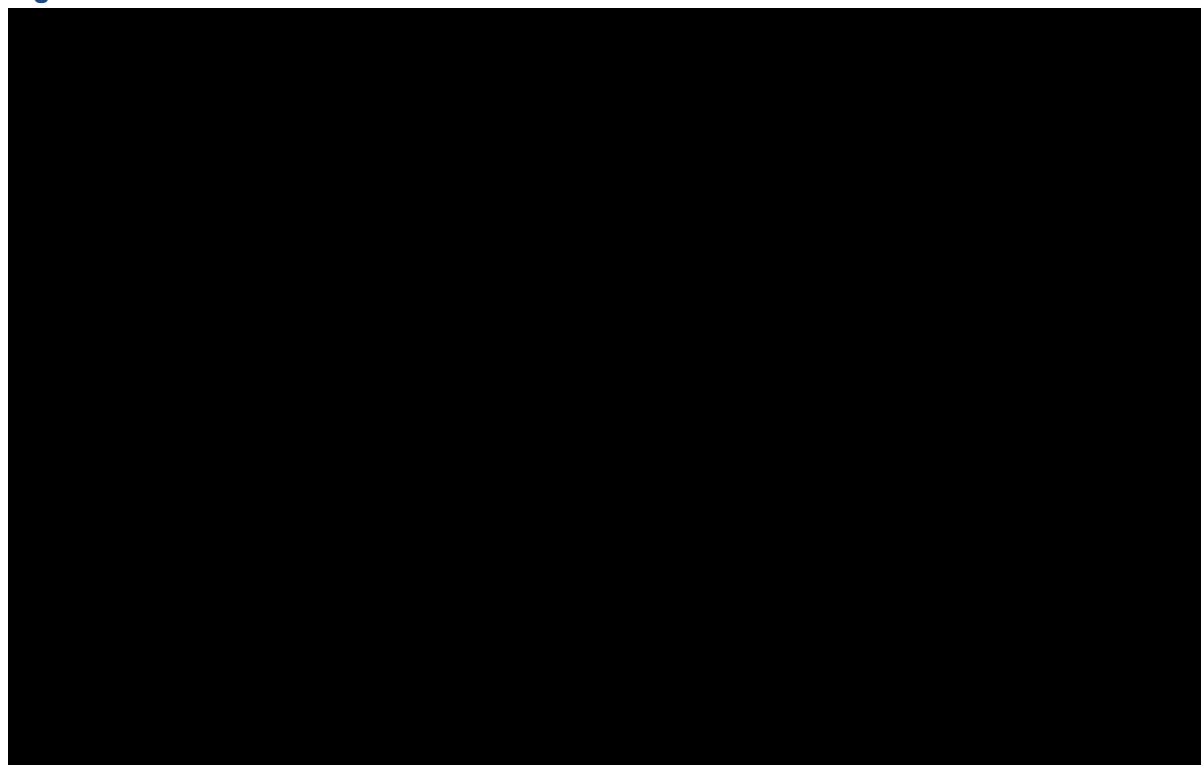
Visual inspection of the parametric models indicates that all distributions provide a similar visual fit to the observed Kaplan-Meier and hazard curves (Figure 21 and Figure 22), with the exception of the exponential and log-normal models. Both Kaplan-Meier curves underestimated time to progression during the first 36 months and overestimated it in the later follow-up period; similarly, both hazard profiles plateau, in contrast to the increased hazards observed in the trial. The smoothed hazard curves extrapolated over the modelled time horizon are presented in Appendix K.1.

Figure 21: Projections of AV IRC-assessed TTP based on parametric survival models fit to IRC-assessed TTP from the AMPLIFY trial



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; TTP: time to progression.

Figure 22: IRC-assessed TTP smoothed hazard curves for AV



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; TTP: time to progression.

Clinical plausibility of extrapolations and external evidence

UK clinical experts (N=6) with extensive experience of treating patients with CLL were interviewed by AstraZeneca between April and July 2025 to determine the clinical plausibility of the different parametric survival model extrapolations. Across all interviews, clinicians said that a subset of patients would experience sustained disease remission. The Gompertz and generalised gamma models predicted rapid progression (as reflected in the indefinitely increasing hazards seen in the smoothed hazard curves in Figure 22), with all patients experiencing progression within approximately 8 years. This was considered clinically implausible and inconsistent with the expectation of sustained disease remission. Conversely, the exponential and log-normal curves were considered to over-estimate the TTP curve beyond the trial period, particularly at the tail end of the extrapolations. All clinicians thought that the log-logistic curve provided the most clinically plausible extrapolation for TTP in UK clinical practice, followed by the gamma curve. However, the lack of durable remission predicted by the gamma curve was noted as an issue.

Given the relatively recent introduction of BTKi therapies, including VenI and VenO, external data supporting long-term survival are limited. Therefore, evidence from trials investigating the previous standard of care, FCR, was considered. This should be interpreted as the lower bound of clinically plausible survival for AV, given the statistically significantly improved PFS reported for AV versus FCR/BR in AMPLIFY (Section 2.6.1).

Two external data sources were identified by clinicians to inform plausible long-term extrapolations for PFS following treatment with FCR. The observed FCR outcomes in these studies have been compared to the TTP extrapolations in Table 43. Rossi *et al.* (2015) conducted an independent multicentre retrospective analysis of FCR-treated CLL patients

(N=317).¹³⁵ This study reported outcomes separately for patients by their del(11q), del(17p) and *IgHV* mutation status; the outcomes have been weighted across these patient subgroups for this comparison. At 72 months, 34% of the included patients were progression-free, while 31% were progression free at 96 months (Table 43). In the low-risk patient group alone, 71% of patients remained progression free at each of these timepoints.

The E1912 trial (Shanafelt *et al.* [2022]) was a prospective, randomised phase 3 study enrolling 529 generally fit patients aged ≤70 years with untreated CLL.¹⁰⁵ This study compared treatment with first-line ibrutinib-rituximab to standard FCR chemoimmunotherapy. Among patients who received FCR (n=158), PFS at 72 months was 31%.

As TTP censors death events, this comparison should be viewed as conservative. It should also be recognised that the number of patients at risk at later timepoints in these studies is relatively low. Given that these figures are considered as the lower bound of plausible survival, the comparison supports the exclusion of the Gompertz and generalised gamma curves, which underestimate survival at 72 and 96 months, and also suggests the Weibull may be implausible.

Table 43: Extrapolated outcomes of TPP for AV from AMPLIFY compared with external data for FCR

Study/Extrapolation	Treatment	Endpoint	Proportion at 72 months	Proportion at 96 months
External data				
E1912 (Shanafelt <i>et al.</i> , [2022]) ¹⁰⁵ N=158	FCR	PFS	31% ^a	NA
Rossi <i>et al.</i> (2015) ¹³⁵ N=317	FCR		34% ^b	31% ^b
AMPLIFY extrapolations				
Exponential	AV	TTP		
Generalised Gamma				
Gompertz				
Loglogistic				
Lognormal				
Weibull				
Gamma				

^aOverall population as reported by the E1912 trial.

^bWeighted outcomes across the three patient subgroups reported in Rossi *et al.* (2015).¹³⁵

Abbreviations: AV: acalabrutinib with venetoclax; FCR: fludarabine with cyclophosphamide and rituximab; PFS: progression-free survival; TTP: time-to-treatment progression;

Summary

The exponential and log-normal curves were disregarded from consideration due to the implausible hazard profiles and poor visual fit to the data. While the Gompertz, Weibull and generalised gamma models provided a good statistical fit to the observed data, all produced extrapolated outcomes that were inconsistent with clinical expectations. Clinicians anticipate a small subset of patients will experience sustained disease remission throughout the entire modelled period, which was not reflected in these models. Furthermore, external evidence identified for FCR showed that these models may underestimate TTP for AV.

The log-logistic model better captured the likelihood of long-term remission commonly experienced by clinicians treating in CLL and provided a sufficiently acceptable visual fit to the data and was selected to extrapolate TTP in the base case economic analysis.

The gamma curve was explored in scenario analyses as a more conservative model, predicting less sustained disease remission. It was also commonly selected by clinicians (n=3) as a plausible alternative.

3.3.2.2 Pre-progression survival

Pre-PS was defined as the time to death in the absence of progression and was based on the primary endpoint of the AMPLIFY trial – blinded IRC-assessed PFS.² Patients who experienced progression before death were censored at the time of progression. As of the latest DCO of the AMPLIFY trial (30th April 2024), the median estimated pre-PS for the AV arm was not reached (Table 44).² The Kaplan-Meier curve for pre-PS for the AV arm in the AMPLIFY trial is presented in Figure 23.

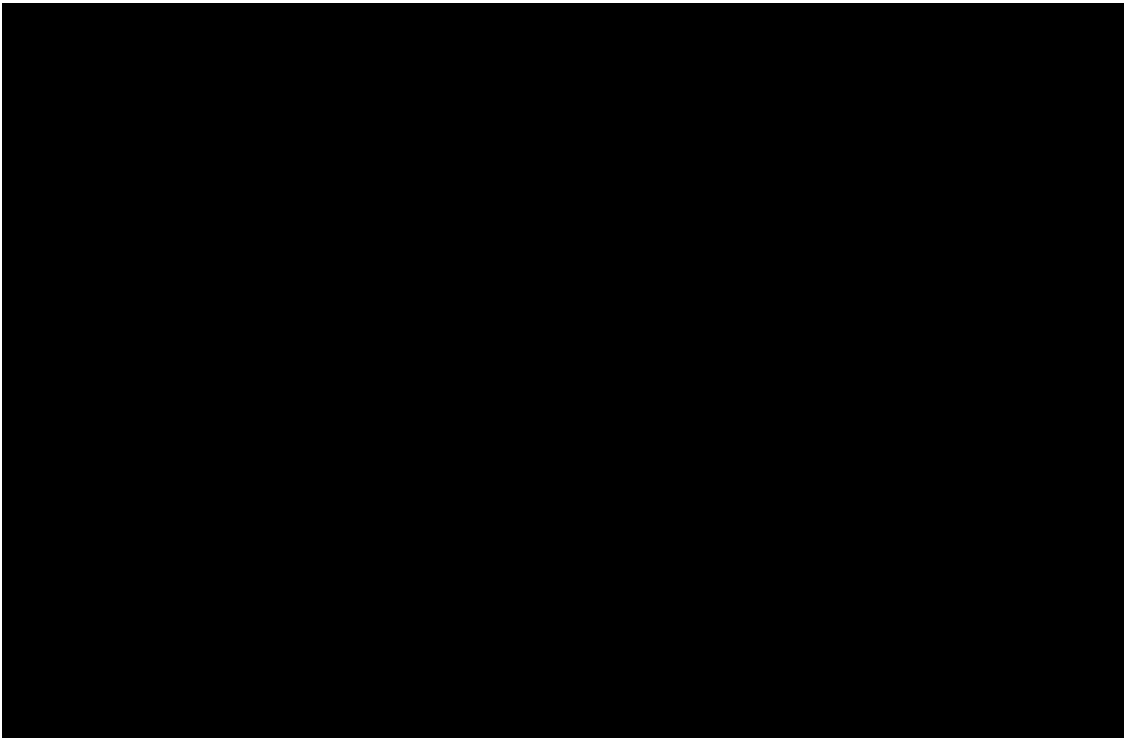
A plot of the raw and smoothed hazards (Figure 24) shows that the pre-PS hazard decreases over the duration of the trial. This hazard profile was considered relatively simple and did not warrant the exploration of more flexible survival models. Therefore, the analysis focused on standard parametric models.

Table 44: Summary of the pre-PS data for AV from the AMPLIFY trial

Arm	N	Events	Maturity	Median, months (95% CI)
AV				

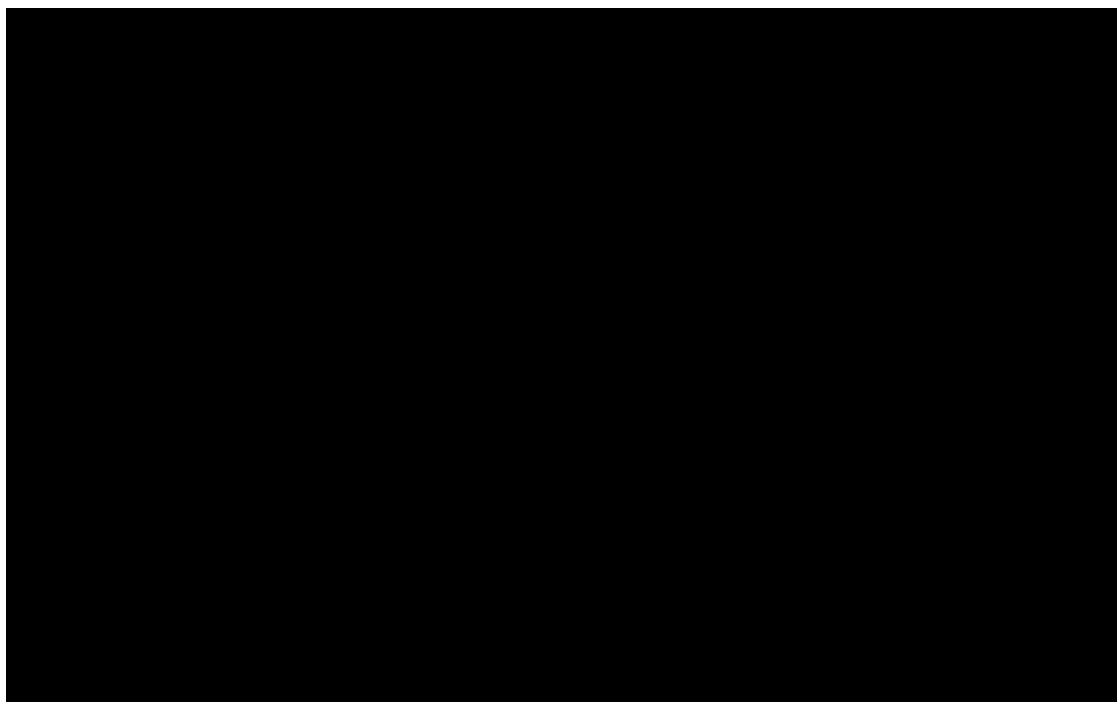
Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; NR: not reported; pre-PS: pre-progression survival.

Figure 23: IRC-assessed pre-PS Kaplan-Meier curve for AV from the AMPLIFY trial



progression survival.

Figure 24: IRC-assessed pre-PS raw and smoothed hazard curves for AV from the AMPLIFY trial



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; pre-PS: pre-progression survival.

Statistical fit

According to AIC/BIC (Table 45), the Gompertz curve provided the best statistical fit, with the remaining curves showing minimal variation in statistical fit across the models. This suggests that, although the Gompertz curve was optimal, several alternative models provide a broadly similar statistical fit to the observed data.

Table 45: Statistical goodness-of-fit indicators (AIC/BIC) for the independent IRC-assessed pre-PS parametric models for AV from the AMPLIFY trial

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	188.4	7	192.0	2
Weibull	187.1	5	194.4	5
Log-normal	186.1	3	193.4	3
Log-logistic	187.0	4	194.4	4
Gompertz	183.5	1	190.9	1
Generalised gamma	185.9	2	196.9	7
Gamma	187.2	6	194.5	6

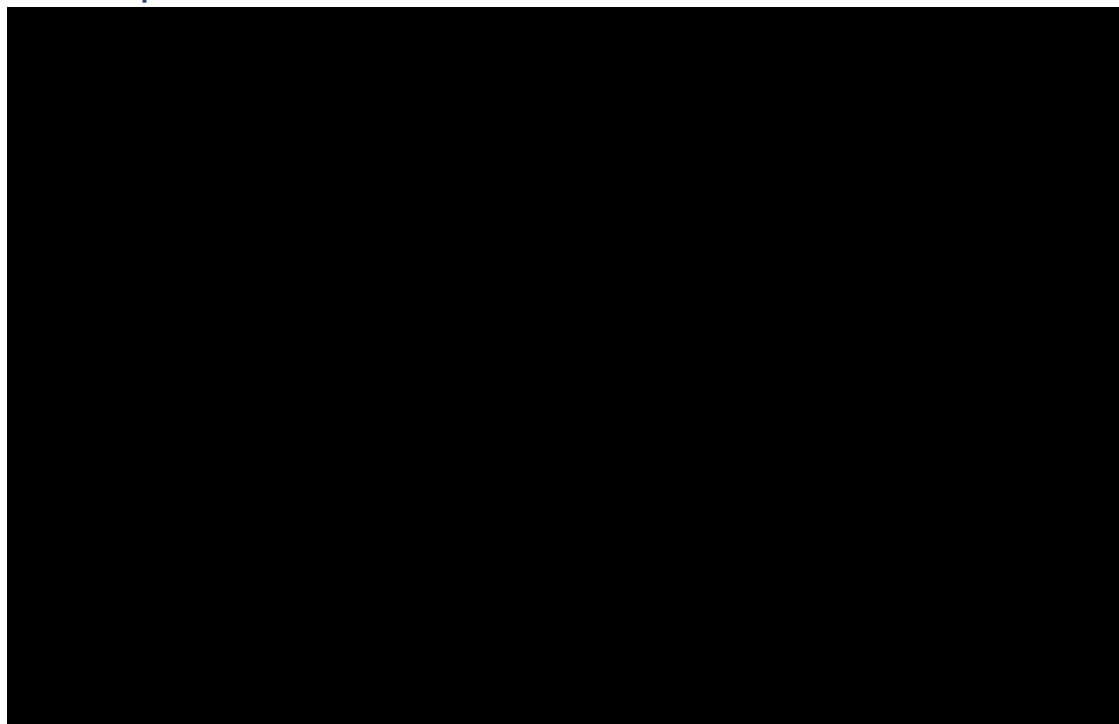
Abbreviations: AIC: Akaike Information Criterion; AV: acalabrutinib with venetoclax; BIC: Bayesian Information Criterion; IRC: Independent Review Committee; pre-PS: pre-progression survival.

Visual fit

All models provided a good fit to the observed Kaplan-Meier curve (Figure 25). Figure 26 shows the pre-PS smoothed hazard curve for AV from the AMPLIFY trial, which gradually decreases over time – a trend broadly reflected by all extrapolated curves except for the exponential model.

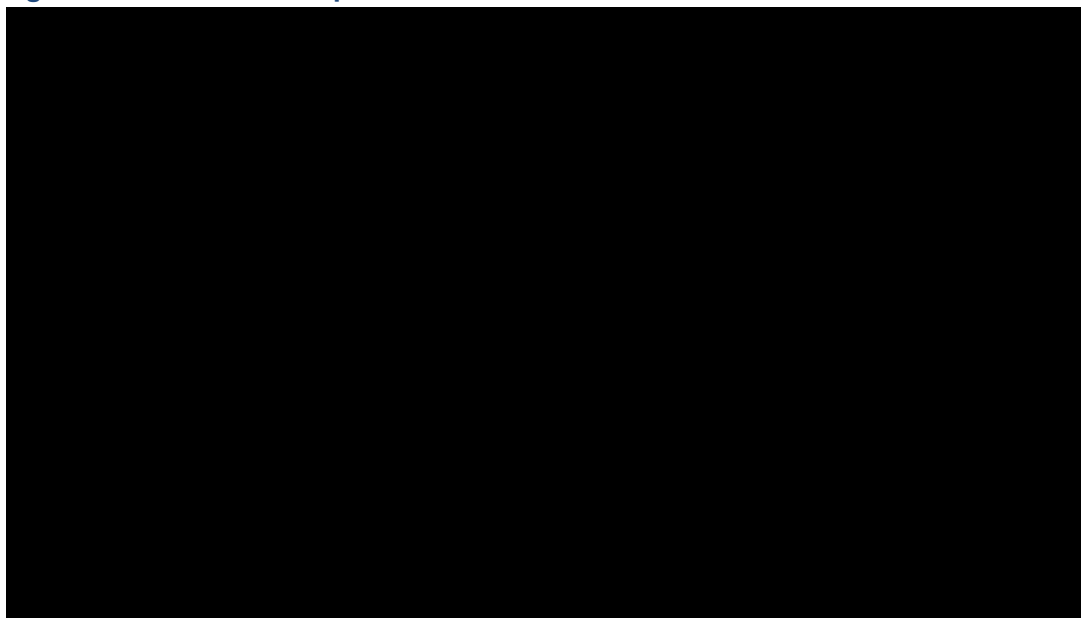
The smoothed hazard curves extrapolated over the modelled time horizon are presented in Appendix K.1.

Figure 25: Projections of AV pre-PS based on parametric survival distributions fit to IRC-assessed pre-PS from the AMPLIFY



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; pre-PS: pre-progression survival.

Figure 26: IRC-assessed pre-PS smoothed hazard curves for AV



Abbreviations: AV: acalabrutinib with venetoclax; IRC: Independent Review Committee; pre-PS: pre-progression survival.

Clinical plausibility of extrapolations

In the interviews carried out by AstraZeneca, UK clinical experts (N=6) anticipated an initial

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gradual decline in pre-PS resulting from infections and secondary malignancies, and a more stable mortality rate thereafter. This expectation is reflected in the Kaplan-Meier curve for pre-PS from the AMPLIFY trial (Figure 23), with a steeper decline in survival in the first 12-month period followed by more gradual decline thereafter. The AMPLIFY Kaplan-Meier curve predicts approximately 4% of patients were expected to have died in the AV arm by the end of the follow-up period, which UK clinicians said aligned with their expectations for pre-PS.

All clinicians considered the exponential curve clinically implausible, as it predicted an unrealistically high rate of pre-progression deaths throughout the modelled period. This is aligned with their expectations that there would be an early decrease in survival (due to secondary malignancies and treatment-related adverse events) followed by a stabilisation. Two curves (Gompertz and generalised gamma) predict sustained plateaus early on: all experts (N=6) believed that the Gompertz did not reflect the expected course of disease, and three clinicians excluded generalised gamma for the same reason. However, 2 clinicians believed the generalised gamma to be the most plausible, preferring a plateau starting in the early period of treatment. All clinicians agreed the Weibull, log-normal, log-logistic, and gamma curves were all clinically plausible, exhibiting only minor differences in their long-term predictions.¹⁵

Summary of curve choice

Within the follow-up period of the AMPLIFY trial, the Gompertz curve provided the best statistical fit to pre-PS data, although all curves had similar AIC/BIC statistics. Clinical expert interviews confirmed that Weibull, log-normal, log-logistic and gamma were all considered clinically plausible, as they produced comparable estimates in alignment with observed KM data and expected mortality trends. In practice, differences between these curves have minimal impact on long-term projections for pre-PS, as extrapolated estimates become capped by general population mortality, resulting in eventual convergence across all plausible models.

Taking all factors into account, the log-logistic curve demonstrated the best combination of statistical fit and clinical plausibility and was therefore selected as the base case model for pre-PS extrapolation in the economic analysis. The generalised gamma and gamma curves were explored in scenario analyses.

3.3.2.3 Time to treatment discontinuation

Time-on-treatment with AV was modelled based on TTD data from the AMPLIFY trial. As of the latest DCO (30th April 2024), TTD data for AV were complete because the fixed-duration regimen was fully captured within the trial follow-up period.² As such, there was no need to extrapolate TTD beyond the AMPLIFY trial, and the TTD Kaplan-Meier curve was used directly within the base case economic analysis to estimate the proportion of patients receiving AV in each model cycle (Table 46).

For VenI and VenO, only median and maximum TTD were publicly available – no TTD Kaplan-Meier data are published. It was therefore assumed that the trajectory for TTD for these therapies would be the same as for AV. However, in the GLOW trial, the per protocol treatment regimen was one cycle longer than the AV regimen in AMPLIFY (15 cycles versus 14 cycles).³⁷ This 15-cycle regimen is also consistent with the licensed dosing for VenI, as specified in the SmPC.¹¹² To account for this, the AV TTD Kaplan-Meier curve was extended by one cycle, to 15 cycles, assuming the same proportion of patients discontinue as in the proceeding cycle (Cycle 14). The treatment duration for VenI and AV was then assumed equal.

For VenO, median TTD is not publicly available. However, as the median and maximum treatment duration is shorter than for AV, and drug costs are capped at 12 cycles (i.e., the maximum administration for venetoclax), no adjustments were required for VenO.⁵⁵

Table 46: Summary of TTD data from the AMPLIFY trial

Arm	N	Events	Maturity	Median, months (95% CI)
AV (A)	■	■	■	■
AV (V)	■	■	■	■

Abbreviations: CI: confidence interval; AV: acalabrutinib with venetoclax; A: acalabrutinib; TTD: time to discontinuation; V: venetoclax.

3.3.2.4 Post-progression survival

Post-PS was defined as the time from disease progression to death from any cause. However, as of the latest DCO of the AMPLIFY trial (30th April 2024), post-PS data were immature, with a low number of death events (Table 47). As such, it was not considered appropriate to utilise the post-PS data from the AMPLIFY trial within the base case economic analysis and alternative sources of data were sought.

Table 47: Summary of the post-PS data for AV from the AMPLIFY trial

Arm	N	Events	Maturity	Median, months (95% CI)
AV	■	■	■	■

Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; NR: not reported; post-PS: post-progression survival.

Based on feedback from UK clinical experts, post-PS was assumed to be equal across the treatment arms, that is, once progressed on AV, VenI or VenO, patients were expected to experience the same outcomes regardless of first-line therapy.¹⁵ Given the insufficient post-PS data available from the AMPLIFY trial, external OS data for the acalabrutinib monotherapy arm in the second-line CLL setting from the ASCEND trial was used as a proxy for post-PS instead, given the trial had longer follow-up and greater event maturity at the final DCO (3rd September 2021) than post-PS in AMPLIFY.¹²⁴

Post-PS data from the ASCEND trial

The acalabrutinib monotherapy arm of the ASCEND trial was assumed to represent treatment with BTKi monotherapies in subsequent lines of treatment for CLL. Based on feedback from UK clinical experts during interviews conducted between April and July 2025, these are the most common subsequent treatments received following first-line treatment for CLL (see Section 3.5.2).¹⁵

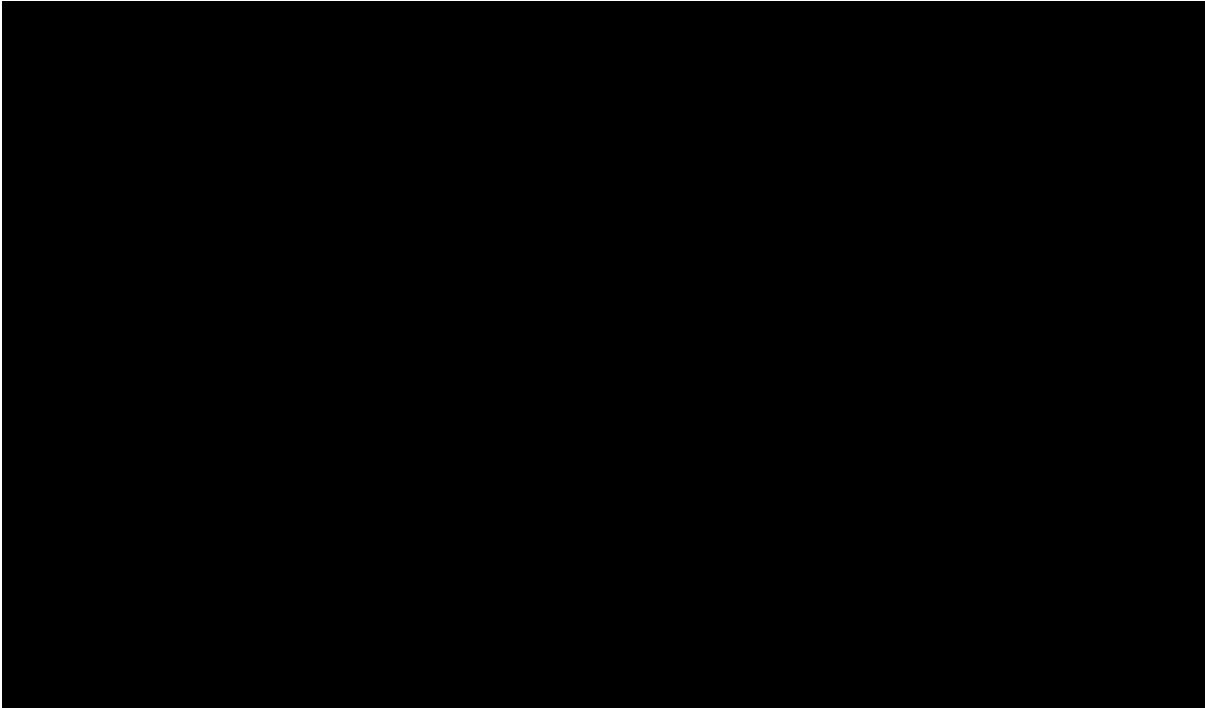
Median OS (defined as time from randomisation to death from any cause) for the acalabrutinib monotherapy arm was not reached in the ASCEND trial (Table 48). The Kaplan-Meier curves for OS are presented in Figure 27. The low maturity of these data reflects the indolent and chronic nature of CLL, as patients with the disease tend to live for long periods of time beyond the trial follow-up. However, maturity for these data was approximately ■ that of the post-PS AMPLIFY data. This hazard profile was considered relatively simple and did not warrant the exploration of more flexible survival models (Figure 28).

Table 48: Summary of OS data for acalabrutinib monotherapy from the ASCEND trial

Arm	N	Events	Maturity	Median, months (95% CI)
Acalabrutinib monotherapy	108	24	22.2%	NR (NR, NR)

Abbreviations: CI: confidence interval; NR: not reported; OS: overall survival.

Figure 27: OS Kaplan-Meier curves for acalabrutinib monotherapy from the ASCEND trial (without del[17p] or TP53 mutations)



Abbreviations: OS: overall survival.

Figure 28: Post-PS raw and smoothed hazard curves for acalabrutinib from the ASCEND trial



Abbreviations: AV: acalabrutinib with venetoclax; post-PS: post-progression survival.

Statistical fit

As shown in Table 49, the exponential curve provided the best statistical fit in terms of AIC/BIC, followed by the log-normal and log-logistic curves, with the remaining curves showing minimal differences in statistical fit.

Table 49: Statistical goodness-of-fit indicators (AIC/BIC) for the OS parametric models for acalabrutinib monotherapy from the ASCEND trial

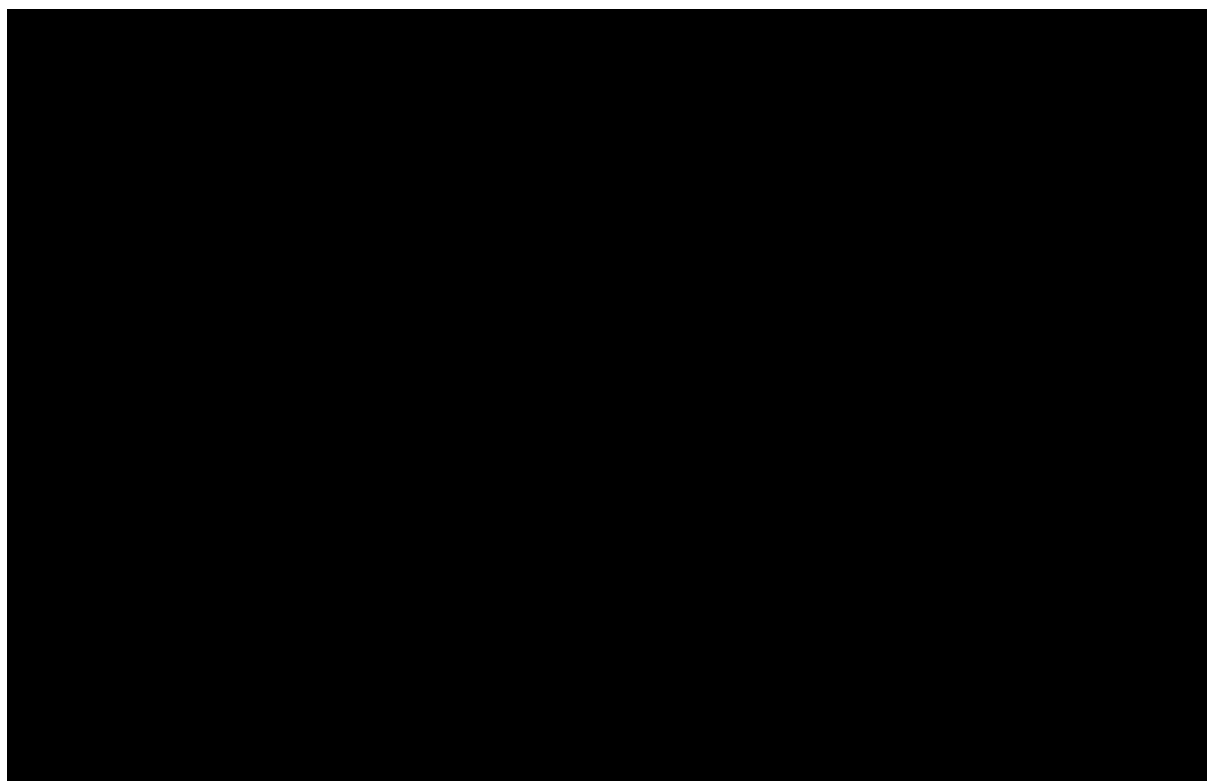
Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	299.9	1	302.6	1
Weibull	301.7	5	307.1	5
Log-normal	300.4	2	305.7	2
Log-logistic	301.4	3	306.8	3
Gompertz	301.9	6	307.2	6
Generalised Gamma	302.1	7	310.1	7
Gamma	301.7	4	307.1	4

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

Visual fit

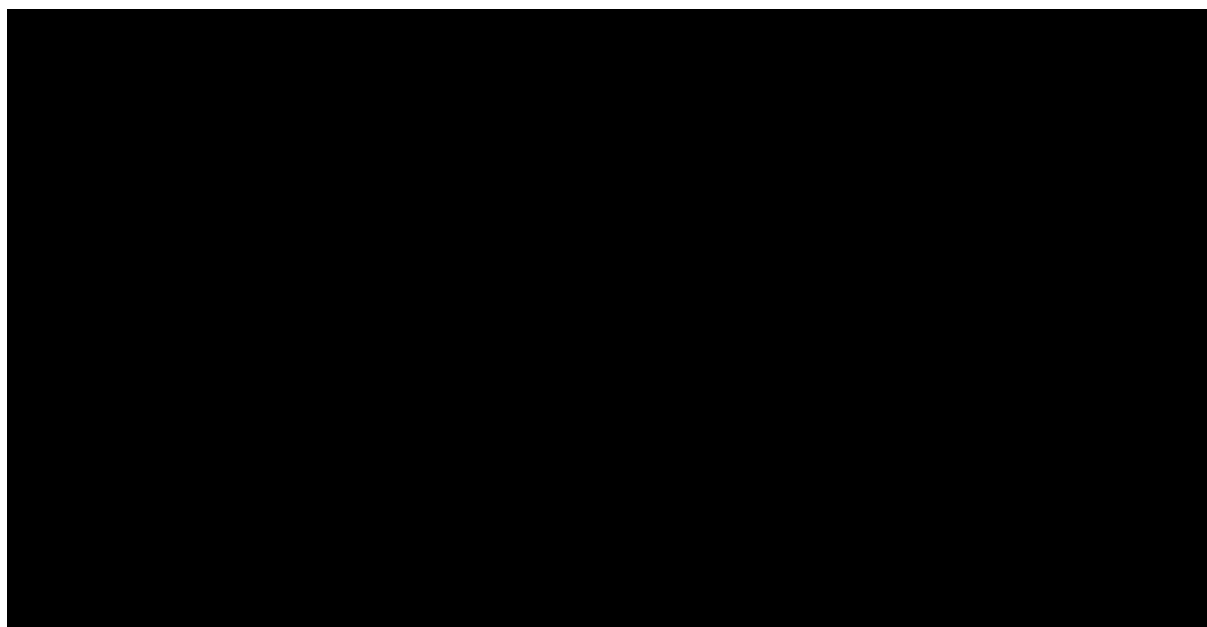
All curves provided a similar fit to the observed Kaplan-Meier curve for acalabrutinib monotherapy from the ASCEND trial (Figure 29), and predicted hazards followed the observed hazard reasonably well (Figure 30). This hazard profile was considered relatively simple and did not warrant the exploration of more flexible survival models. The smoothed hazard curves extrapolated over the modelled time horizon are presented in Appendix K.1.

Figure 29: Projections of post-PS based on parametric survival distributions fit to OS from the ASCEND trial



Abbreviations: OS: overall survival; post-PS: post-progression survival.

Figure 30: OS smoothed hazard curves for acalabrutinib monotherapy from the ASCEND trial



Abbreviations: OS: overall survival.

Clinical plausibility of extrapolations

Clinical expert feedback reflected a range of preferences regarding survival extrapolation, with the exponential and lognormal curves most frequently identified as clinically plausible. One

clinician specifically noted that any curve projecting higher long-term survival than the exponential resulted in implausibly high estimates at 30 years for CLL and recommended that only the exponential curve and those predicting survival lower than 15% at 30 years were deemed to be plausible for the AV arm.¹⁵

Additionally, the clinicians highlighted that there is no substantive evidence to suggest post-PS differs between AV, VenI, and VenO; and supported the assumption of equivalency of post-PS in modelling each regimen.¹⁵

Summary of curve choice

While all parametric models showed broadly similar visual fit to the observed data, the exponential curve provided the best statistical fit. Three clinicians confirmed that the exponential model produced realistic long-term survival estimates. In the cost-effectiveness model, each curve was capped by general population mortality, such that differences in the long-term extrapolations for the Gompertz, log-logistic, log-normal and gen gamma models were not material to the results. Accordingly, the exponential curve was selected to model overall survival from ASCEND as a proxy for post-PS in the base case economic analysis. The log-normal and Weibull curves were explored in scenario analyses.

3.3.3 Adverse events

Grade ≥ 3 TEAEs with an incidence of $\geq 5\%$ for each treatment arm (i.e., any incidence $< 5\%$ was considered as 0%) were included in the base case economic analysis. The incidence of each TEAE was derived from the key clinical trials for AV, VenI and VenO, respectively (Table 50).

Further details of the disutility values applied in the economic analysis for each TEAE and the costs associated with the management of each AE are presented in Section 3.4.4 and Section 3.5.4, respectively.

Table 50: Incidence of Grade ≥ 3 TEAEs for AV, VenI and VenO included in the economic analysis

AE	Proportion of patients (%)		
	AV (AMPLIFY) ³	VenI (GLOW) ³⁷	VenO (CLL14) ⁵⁵
Anaemia	0.00	0.00	8.00
Atrial fibrillation	0.00	6.60	0.00
Cardiac disorders	0.00	0.00	6.10
Diarrhoea	0.00	10.38	0.00
Febrile neutropenia	0.00	0.00	5.20
Hypertension	0.00	7.55	0.00
Hyponatremia	0.00	5.66	0.00
Infections and infestations	0.00	16.98	19.40
Infusion-related reactions	0.00	0.00	9.00
Malignant neoplasm	0.00	0.00	7.00
Neutropenia	26.80	34.91	52.80
Neutrophil count decreased	5.50	0.00	0.00
Thrombocytopenia	0.00	5.66	13.70

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; NHS: National Health Service; TEAE: treatment-emergent adverse event; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 14.3.2);² Brown *et al.* (2025; Table 2 and Table S8);³ Kater *et al.* (2022; GLOW);³⁷ Fischer *et al.* (2019; CLL14).⁵⁵

3.4 Health-related quality of life

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

In the AMPLIFY trial, EQ-5D-5L data were collected at each treatment cycle during the treatment phase and each follow-up visit during the post-treatment phase.² Post-treatment follow-up visits occurred approximately every 12 weeks for 3 years, and then every 24 weeks until disease progression.

In line with NICE-preferred methodology, the EQ-5D-5L data were mapped to EQ-5D-3L using the Hernandez-Alava *et al.* 5L to 3L mapping algorithm (see Section 3.4.2 for further details).^{126, 136, 137}

The statistical relationship between EQ-5D-3L scores, treatment and health status was assessed using regression analysis. To account for repeated utility measurements in the AMPLIFY trial, a mixed model for repeated measures (MMRM) method was used.¹³⁸ The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- *Randomised treatment*
- *Treatment progression by IRC status (pre-treatment and post-treatment IRC-assessed progression)*
- *Treatment + treatment progression by IRC status*
- *Treatment + treatment progression by IRC status + treatment * treatment progression by IRC status (both terms and their interaction included)*

The correlation of repeated utility measurements for patients over time was captured via the specification of covariance structures for the MMRM. AIC and BIC statistics were generated for from the MMRM for each covariate structure, and the best-fitting model was selected based on the lowest AIC and BIC values. Further details of the EQ-5D utility analysis are presented in Appendix K.

Treatment progression by IRC status was selected as the best-fitting model based on both AIC and BIC. HSUVs were therefore generated using the MMRM analysis with treatment progression by IRC status as fixed effects.^{32, 33} The marginal (or least square) mean was calculated to generate a model-based estimate of the mean HSUV averaged over observations, with the adjustment for repeated measures. The resulting marginal mean HSUVs for AV are summarised in Table 51, with results for the AVO and FCR/BR treatment arms also presented for completeness.

Table 51: HSUVs from the AMPLIFY trial generated using the MMRM analysis with treatment progression by IRC status as fixed effects

Treatment	PF utility value (95% CI)	PD utility value (95% CI)
AV		
AVO		
FCR/BR		

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; HSUV: health state utility value; IRC: Independent Review Committee; MMRM: mixed model for repeated measures.

3.4.2 Mapping

As detailed above, in accordance with the NICE methods manual regarding the use of EQ-5D-5L to derive utility values, the EQ-5D-5L data collected in the AMPLIFY trial were mapped onto the EQ-5D-3L UK value set using the mapping function developed by Hernández-Alava *et al.* (2017) through the NICE DSU, using the EEPRU dataset (Hernández-Alava *et al.* 2020).^{126, 136, 137}

3.4.3 Health-related quality-of-life studies

An SLR to identify studies reporting utility data in patients with CLL was conducted in December 2024 and subsequently updated in August 2025. Full details of the SLR search strategy, study selection process and results for the SLR can be found in Appendix F.

Overall, 45 records reporting on 45 unique studies were included in the utilities/HRQoL stream of the SLR (refer to Appendix F for further details). However, the majority of these studies were either investigating treatments not of interest for this submission, did not report novel utilities, or reported HSUVs for health states not used in the model structure.

The exception to this was Kosmas *et al.* (2015), a time trade-off study with a representative sample of 100 members of the general UK public.¹²⁸ In this study, CLL health states were assigned utility weights based on participants rankings of each health state, using the time trade-off methodology.

Notably, the value for the PD off-treatment health state in the Kosmas *et al.* (2015) study was estimated as the weighted average of HSUVs for PFS on second-line therapy, PFS without second-line treatment, further progression and relapsed line of treatment.¹²⁸ The weights were proportional to the time spent by an average patient in each health state, and were obtained from the NICE evaluation for OClb for untreated CLL (TA343), the first evaluation where these HSUVs were used.⁵ These HSUVs have been used in several prior economic evaluations identified in the SLR, as well as other NICE evaluations in untreated CLL (TA663 [VenO for untreated CLL]).^{5, 10, 128} The HSUVs reported by Kosmas *et al.* (2015) are presented in Table 52.

Table 52: HSUVs reported by Kosmas *et al.* (2015)^{5, 128}

Health state	Mean HSUV	Relative difference compared to PF on-treatment
PF on-treatment (oral treatment)	0.71	-
PF on-treatment (IV treatment)	0.67	-6%
PF off-treatment	0.82	15%
PD on-treatment	0.55	-23%
PD off-treatment	0.59	-16%

Abbreviations: HSUV: health state utility value; IV: intravenous; PD: progressed disease; PF: progression-free.

A further study identified in the SLR, Slot *et al.* (2023), used a HSUV of 0.77 for the PF off-treatment health state.¹³⁹ This value was derived from the NICE evaluation for VenO (TA663),¹⁰ which itself sourced HSUVs from Kosmas *et al.* (2015).^{10, 128} During the VenO NICE evaluation, the EAG considered it necessary to adjust the original PF off-treatment value (0.82) reported by Kosmas *et al.* (2015), as it exceeded the age-adjusted values for members of the UK general

public (0.76). The EAG's preferred approach for adjusting the PF off-treatment HSUV was to cap it to the value for the matched, gender-adjusted, age-specific UK general population, as per Ara and Brazier (2010).¹⁴⁰ This resulted in a gender-adjusted, age-specific HSUV of 0.77 for the matched UK general population. Similarly, the EAG for the NICE evaluation of OC1b (TA343) applied an upper bound of 0.76 to the PF off-treatment HSUV of 0.82 reported by Kosmas *et al.* (2015).⁵ However, it should be noted that in both of these economic analyses, the age of the matched, general UK population was assumed to range from 72–73.3 years, which is substantially higher than that of the starting age of patients in the current economic analysis (59.90 years).

3.4.4 Adverse events

AE disutility values were adopted in the economic analysis to account for the HRQoL loss resulting from AEs. A disutility value for each AE included in the economic analysis was sourced from the literature and multiplied by the anticipated duration of each AE to obtain a decrement that was used to calculate the total disutility for each AE (see Table 53).

The utility decrements were applied to the proportion of patients experiencing the AE in the first model cycle of the economic analysis, based on the assumption that AEs would occur during the first four weeks of treatment. A scenario analysis was explored without the incorporation of AE disutilities.

Table 53: Summary of AEs disutilities included in the economic analysis

AE	Disutility	Duration (days)	Source of disutility value and duration
Anaemia	−0.09	23.21	TA487 (sourced from TA891) ⁴
Atrial fibrillation	−0.22	14	TA891 (assumed to be the same as highest disutility [infection]) ⁴
Cardiac disorders	−0.22	14.00	TA891 (assumed to be the same as highest disutility [infection]) ⁴
Diarrhoea	−0.2	3	Disutility: TA359 (sourced from TA891) Duration: TA403 (sourced from TA891) ⁴
Febrile neutropenia	−0.16	15.09	TA487 (sourced from TA891) ⁴
Hypertension	−0.02	21	Disutility: Wehler <i>et al.</i> 2018 ¹⁴¹ (sourced from TA689) ⁹ Duration: TA931 (assumed) ⁸
Hyponatremia	−0.02	21	Assumed the same as hypertension ⁸
Infections and infestations	−0.22	14	Disutility: TA487 (sourced from TA891) ⁴ Duration: TA891 (assumed) ⁴
Infusion-related reaction	−0.2	3.5	TA487 (sourced from TA891) ⁴
Malignant neoplasm	−0.22	14	Same approach as TA891 (assumed to be the same as the highest disutility [infection]) ⁴
Neutropenia	−0.16	15.09	TA487 (sourced from TA891) ⁴
Neutrophil count decreased	−0.16	15.09	TA487 (sourced from TA891) ⁴
Thrombocytopenia	−0.11	23.21	TA487 (sourced from TA891) ⁴

Abbreviations: AE: adverse event.

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

A summary of the PF and PD HSUVs used in the base case economic analysis is presented in Table 54.

PF health state

In the base case economic analysis, the HSUV for the PF health state was derived from EQ-5D-5L data collected in the AMPLIFY trial (Section 3.4), mapped to the EQ-5D-3L (Section 3.4.2). This was considered to be the most appropriate source of HSUV data for consistency with the patient population and source of efficacy inputs used in the economic analysis.

In the Kosmas *et al.* (2015) study, being PF, and being off-treatment, resulted in a HSUV increase compared with having PD and being on-treatment.¹²⁸ The HSUV increase derived from the Kosmas *et al.* (2015) study was therefore subsequently applied to the PF on-treatment HSUV from AMPLIFY, an approach which was considered appropriate by UK clinical experts.¹⁵ However, this resulted in an overestimation of the PF off-treatment value (1.001) which lacked face value. As such, in the base case economic analysis, HSUVs associated with being on-treatment and off-treatment in the PF health state were ultimately assumed to be equal (Table 52).

Whilst a utility adjustment for the on-/off-treatment substates was not included, an adjustment was included in the base case economic analysis for patients receiving IV treatment (with obinutuzumab as part of VenO) versus oral treatments (AV and VenI). The Kosmas *et al.* (2015) study reported HSUVs for CLL patients who were progression-free and receiving oral or IV treatments.¹²⁸ The decrement associated with receiving IV versus oral therapy was therefore applied to the PF HSUV from the AMPLIFY trial, in line with the approach in the NICE evaluation for VenI (TA891), to reflect the reduced HRQoL associated with IV treatment administration.^{4, 128} This approach was validated by UK clinical experts who confirmed that the toxicity of IV treatment contributes to a worse HRQoL compared with oral therapies.¹⁵

PD health state

Disease progression is associated with a worsening in disease-related symptoms and increased medical care requirements, negatively impacting patient HRQoL. Therefore, in line with feedback from UK clinical experts, the HSUV used in the economic analysis for the PD health state should reflect this.¹⁵ The PD HSUV derived from the AMPLIFY trial was based on a very limited number of observations, and showed no disutility associated with progression. As such, this value was considered to lack face validity. Instead, an HSUV decrement associated with PD versus PF, derived from the Kosmas *et al.* (2015) study, was applied to the PF HSUV taken from the AMPLIFY trial.¹²⁸

A scenario analysis was explored using the HSUVs for PF and PD health states taken directly from the Kosmas *et al.* (2015) study.¹²⁸

Age-related utility decrement

Finally, in the base case economic analysis, age-related utility decrements were applied over the model time horizon, in line with NICE preferred methods and previous NICE evaluations in untreated CLL.^{4, 9, 142} The age decrement was derived from published population norms by Hernández-Alava *et al.* (2022).¹³⁶ The HSUVs were adjusted by applying a relative annual age

decrement. Given that the mean age of patients starting in the economic analysis was 59.90 years, in line with the AMPLIFY trial population, this adjustment is expected to account for the gradual reduction in HRQoL associated with ageing, independent of disease progression.

Table 54: Summary of HSUVs used in the economic analysis

Health state	Base case HSUVs (SE)	Source	Justification
PF on-treatment (oral treatment)	██████████	AMPLIFY trial ²	AMPLIFY trial used for consistency with patient population and efficacy inputs
PF on-treatment (IV treatment)	██████████	AMPLIFY trial; Kosmas <i>et al.</i> (2015) ^{2, 128}	Decrement associated with IV versus oral treatment applied, in line with accepted approach in previous NICE CLL evaluations ^{4, 5}
PF off-treatment	██████████	AMPLIFY trial ²	AMPLIFY trial used for consistency with patient population and efficacy inputs
PD on-treatment	██████████	AMPLIFY trial; Kosmas <i>et al.</i> (2015) ^{2, 128}	PD HSUV from AMPLIFY trial lacked face validity. Decrement associated with progression was applied to PF value, in line with accepted approach in previous NICE CLL evaluations ^{4, 9}
PD off-treatment	██████████	AMPLIFY trial; Kosmas <i>et al.</i> (2015) ^{2, 128}	

Abbreviations: CLL: chronic lymphocytic leukaemia; HSUV: health state utility value; IV: intravenous; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; SE: standard error.

3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was conducted in December 2024 and subsequently updated in August 2025 to identify relevant cost and resource use studies in patients with untreated CLL.

Full details of the SLR search strategy, study selection process and results for the cost and resource use SLR can be found in Appendix G.

In total, the SLR identified 65 records reporting on 65 unique cost and resource use studies. Given the availability of direct healthcare unit costs from the British National Formulary (BNF), the electronic Market Information Tool (eMIT) and NHS reference costs, no costs from the SLR were utilised within the economic analysis.

The following cost categories were included in the economic analysis:

- Intervention and comparator acquisition and administration costs
- Subsequent treatment acquisition costs
- Health state follow-up and monitoring costs
- AE management costs
- End-of-life costs

Full details of the costs utilised are presented in the following sections.

3.5.1 Intervention and comparator costs

Acquisition costs for the intervention and comparator therapies included in the economic analysis were calculated based on the dosing regimens from the respective SmPC for each therapy (Table 55). An overview of the intervention and comparator acquisition and administration costs included in this economic analysis are presented in Table 56.

Acquisition costs

The acquisition cost for acalabrutinib (both as part of the intervention and as a subsequent treatment) was included in the economic analysis at PAS price. Drug acquisition costs for venetoclax (as part of AV), and all comparators and subsequent treatments were included in the economic analysis at list price and were sourced from the BNF and eMIT.

In the base case economic analysis, it was assumed that vial sharing of IV treatments and pack sharing of oral treatments would not occur, that is, there would be drug wastage. This was in line with the EAG preferences in the NICE evaluation for VenI (TA891).⁴ A scenario analysis was conducted to explore the impact of no drug wastage from unused vials or packs.

To account for the fact that patients may not always receive the full dose of an assigned treatment, dose intensity was considered in the economic analysis by adjusting the drug acquisition cost in proportion to the relative dose intensity (RDI). RDI was calculated as the average number of doses received per treatment cycle, divided by doses per cycle, according to the trial design. The RDIs for acalabrutinib and venetoclax in the AV regimen were derived from the AMPLIFY trial.² In the absence of published data, the RDIs of ibrutinib, obinutuzumab and venetoclax in the VenI and VenO regimens were assumed to be 100%. This was consistent with the accepted approach taken in the NICE evaluation for VenI (TA891), where an RDI of 100% was assumed for the VenO regimen in the absence of published data.⁴

Administration costs

Administration costs were included in the economic analysis for the comparator treatments that are administered via IV infusion (obinutuzumab in VenO). The oral treatments acalabrutinib, ibrutinib and venetoclax were assumed to incur no administration costs.

Table 55: Intervention and comparator dosing regimens included in the economic analysis

Regimen	Drug	Administration method	Dose (mg)	Administrations per treatment cycle (first cycle) ^a	Administrations per treatment cycle (subsequent cycles) ^a	Maximum treatment cycles	RDI (%)	Source
AV	Acalabrutinib	Oral	100	56	56	14	■	SmPC ^{1, 2}
	Venetoclax	Oral	20	7	0	12	■	
			50	7	0			
			100	7	0			
			200	7	0			
			400	0	28			
VenI	Venetoclax	Oral	20	7	0	12	100	SmPCs ^{23, 112}
			50	7	0			
			100	7	0			
			200	7	0			
			400	0	28			
	Ibrutinib	Oral	420	28	28	15	100	
VenO	Venetoclax	Oral	20	7	0	12	100	SmPCs; ^{23, 132} TA891 ⁴
			50	7	0			
			100	7	0			
			200	7	0			
			400	0	28			
	Obinutuzumab	IV	1,000	3	1	6	100	

^aThe model cycle and treatment cycle for all interventions and comparators is 28 days.

Abbreviations: AV: acalabrutinib with venetoclax; IV: intravenous; RDI: relative dose intensity; SmPC: summary of product characteristics; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 56: Intervention and comparator acquisition and administration costs included in the economic analysis^a

Regimen	Drug	Drug acquisition costs					Drug administration costs			
		Pack/vial size (mg)	Units per pack/vial	Cost per pack/vial (£)	Drug acquisition cost (first model cycle) (£)	Drug acquisition cost (subsequent model cycles) (£)	Source	Drug administration cost (first model cycle) (£)	Drug administration cost (subsequent model cycles) (£)	Source
AV	Acalabrutinib	100	60				AstraZeneca	0.00	0.00	N/A
	Venetoclax	10	14	59.87	54.83	0.00	BNF 2025 ²⁸	0.00	0.00	N/A
		50	7	149.67	137.06	0.00		0.00	0.00	
		100	7	299.34	274.13	0.00		0.00	0.00	
					548.25	0.00		0.00	0.00	
					0.00	4,386.03		0.00	0.00	
VenI	Venetoclax	10	14	59.87	59.87	0.00	BNF 2025 ²⁸	0.00	0.00	N/A
		50	7	149.67	149.67	0.00		0.00	0.00	
		100	7	299.34	299.34	0.00		0.00	0.00	
					598.68	0.00		0.00	0.00	
					0.00	4,789.44		0.00	0.00	
	Ibrutinib	420	28	4,292.40	4,292.40	4,292.40	BNF 2025 ¹⁴³	0.00	0.00	N/A
VenO	Venetoclax	10	14	59.87	59.87	0.00	BNF 2025 ²⁸	0.00	0.00	N/A
		50	7	149.67	149.67	0.00		0.00	0.00	
		100	7	299.34	299.34	0.00		0.00	0.00	
					598.68	0.00		0.00	0.00	
					0.00	4,789.44		0.00	0.00	
	Obinutuzumab	1,000	1	3,312.00	9,936.00	3,312.00	BNF 2025 ¹⁴⁴	1,458.70	430.24	NHS reference costs 2023/24, deliver complex chemotherapy, including prolonged

Company evidence submission template for acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Regimen	Drug	Drug acquisition costs						Drug administration costs		
		Pack/vial size (mg)	Units per pack/vial	Cost per pack/vial (£)	Drug acquisition cost (first model cycle) (£)	Drug acquisition cost (subsequent model cycles) (£)	Source	Drug administration cost (first model cycle) (£)	Drug administration cost (subsequent model cycles) (£)	Source
										infusional treatment, at first attendance [SB14Z] & deliver subsequent elements of a chemotherapy cycle [SB15Z]

^aAcalabrutinib with-PAS price; list price for all other treatments.
Abbreviations: AV: acalabrutinib with venetoclax; BNF: British National Formulary; N/A: not applicable; NHS: National Health Service; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.5.2 Subsequent treatment costs

Subsequent treatment acquisition costs were included in the economic analysis and applied to patients in the PD health state (on-treatment) as a one-off cost at the time of progression.

At the DCO of the interim analysis (30th April 2024), █/291 (███) patients receiving AV, and █/290 (███) patients receiving FCR/BR, experienced disease progression.

In terms of subsequent therapies received in second-line, █/291 (███%) patients in the AV arm and █/290 (███%) patients in the FCR/BR arm received subsequent anti-cancer therapy (Section 2.7; Table 14).²³ Due to the immaturity of data from the AMPLIFY trial, the overall proportion of patients who received subsequent treatments in the trial is lower than would be expected in clinical practice. This was confirmed by UK clinical experts interviewed between April and July 2025.¹⁵ The experts also noted that the subsequent treatments received in the AMPLIFY trial were not reflective of the treatments that would be received in UK clinical practice, for example, monotherapy with rituximab, obinutuzumab, nemtabrutinib, and azacitidine are not reimbursed for the treatment of CLL in any setting in the UK.¹⁵

As such, the subsequent treatment distributions applied in the base case economic analysis were determined from the average of individual estimates provided by clinical experts for each treatment arm (Table 57).¹⁵ Subsequent treatment distribution across arms is well balanced – clinicians indicated that some level of BTKi rechallenge would be expected for patients with good outcomes from first-line treatment. This aligns with the increased use of acalabrutinib in the AV arm and ibrutinib in the VenI arm. Clinicians also noted that in the VenO arm, where patients have not had prior BTKi, increased subsequent BTKi use would be expected.

All clinical experts agreed that the sequencing of subsequent treatments is not expected to impact post-PS, as all patients will eventually receive all available classes of therapy, albeit in different sequences; there is no evidence that the specific ordering of treatments affects survival outcomes. Therefore, due to the immaturity of the AMPLIFY post-progression data, post-PS was modelled using data from the acalabrutinib monotherapy arm of the ASCEND trial (Section 3.3.2.4). Only the costs of subsequent treatments were adjusted in the model, with no modification required to the overall survival data.¹⁵

A scenario analysis was explored using the subsequent treatment distributions from the AMPLIFY trial but adjusted to exclude treatments which are not reimbursed by NICE, and therefore not relevant to UK clinical practice (Table 58).

Table 57: Subsequent treatment distributions used in the base case economic analysis based on estimates from UK clinical experts

Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with		
	AV	VenI	VenO
Acalabrutinib monotherapy	███	███	███
Ibrutinib monotherapy	███	███	███
Venetoclax monotherapy	███	███	███
Venetoclax with rituximab	███	███	███

Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with		
	AV	VenI	VenO
Zanubrutinib monotherapy	■	■	■

Abbreviations: AV: acalabrutinib with venetoclax; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 58: Subsequent treatment distributions based on AMPLIFY trial (adjusted to exclude treatments not relevant to UK clinical practice) – scenario analysis

Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with		
	AV	VenI	VenO
Acalabrutinib monotherapy	■	■	■
Ibrutinib monotherapy	■	■	■
Venetoclax monotherapy	■	■	■
Venetoclax with rituximab	■	■	■
Zanubrutinib monotherapy	■	■	■

Abbreviations: AV: acalabrutinib with venetoclax; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab; UK: United Kingdom.

Acquisition costs

Similar to the intervention and comparator treatments, acquisition costs for subsequent treatments were calculated based on the dosing regimens from the respective SmPC for each therapy (Table 59). An overview of these acquisition costs is provided in Table 60.

The costs of subsequent treatment were estimated as a weighted average of the total cost of each subsequent treatment regimen and the distribution of patients estimated to receive each one. The duration of treatment for each subsequent treatment was sourced from the literature and is presented in Table 59.

As noted above, in the base case economic analysis, the distribution of patients receiving each treatment following progression on first-line AV, VenI or VenO was based on estimates provided by UK clinical experts interviewed between April and July 2025 (see Table 57).¹⁵

Table 59: Dosing regimens for subsequent treatments included in the economic analysis

Subsequent treatment	Drug	Administration method	Dose (mg)	Per	Administrations per treatment cycle ^a	Median treatment duration (months)	Source
Acalabrutinib monotherapy	Acalabrutinib	Oral	100	Flat dose	56	39.10	SmPC, ¹ Davids <i>et al.</i> (2024) ¹⁴⁵
Ibrutinib monotherapy	Ibrutinib	Oral	420	Flat dose	28	41.00	SmPC, ¹¹² Munir <i>et al.</i> (2019) ¹⁴⁶
Venetoclax monotherapy	Venetoclax	Oral	20	Flat dose	7	24.84	SmPC, ²³ Kater <i>et al.</i> (2024) ¹⁴⁷
			50		7		
			100		7		
			200		7		
			400		28		
Venetoclax with rituximab	Venetoclax	Oral	20	Flat dose	7	22.10	SmPC, ²³ Seymour <i>et al.</i> (2018) ¹⁴⁸
			50		7		
			100		7		
			200		7		
			400		28		
	Rituximab	IV	375 ^b	mg/m ²	1	5.52	SmPC, ¹⁴⁹ Seymour <i>et al.</i> (2018) ¹⁴⁸
			500 ^b		1		
Zanubrutinib monotherapy	Zanubrutinib	Oral	160	Flat dose	56	41.20	SmPC, ¹⁵⁰ Brown <i>et al.</i> (2024) ¹⁵¹

^aTreatment cycle and model cycle length were 28 days for all subsequent treatments.

^bA dose of 375 mg/m² was used in Cycle 1, then 500mg/m² from Cycle 2 onwards.

Abbreviations: IV: intravenous; SmPC: summary of product characteristics.

Table 60: Acquisition costs for subsequent treatments included in the economic analysis

Subsequent treatment	Drug	Pack/vial size (mg)	Units per pack/vial	Cost per pack/vial (£)	Total drug acquisition cost (£)	Source
Acalabrutinib monotherapy	Acalabrutinib	100	60	██████	██████	AstraZeneca
Ibrutinib monotherapy	Ibrutinib	420	28	4,292.40	191,308.82	BNF 2025 ¹⁴³
Venetoclax monotherapy	Venetoclax	10	14	59.87	28,646.84	BNF 2025 ²⁸
		50	7	149.67		
		100	7	299.34		
Venetoclax with rituximab	Venetoclax	10	14	59.87	32,968.83	BNF 2025 ²⁸
		50	7	149.67		
		100	7	299.34		
	Rituximab	1,400	1	██████		BNF 2025 ¹⁵²
Zanubrutinib monotherapy	Zanubrutinib	80	120	4,928.65	206,021.68	BNF 2025 ¹⁵³

Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; FCR: fludarabine with cyclophosphamide and rituximab.

3.5.3 Health state follow-up and monitoring costs

Follow-up and monitoring costs were incorporated in the economic analysis separately for the PF and PD health states. In the absence of any more granular data, follow-up and monitoring costs were assumed to be the same for patients regardless of being on- or off-treatment.

In the base case economic analysis, follow-up and monitoring costs for both health states were derived based on the follow-up and monitoring categories and frequencies used in the NICE evaluation for VenI (TA891),⁴ adjusted based on clinical expert opinion to more accurately reflect clinical practice. The resulting frequencies were multiplied by current unit costs (see Table 61).

Total follow-up and monitoring costs for the PF and PD health states in the base case economic analysis are summarised in Table 62.

Table 61: Follow-up and monitoring – frequency and cost of resource use

Resource use	Cost (£)	Source	Frequency of use per model cycle by health state		Source
			PF	PD	
Laboratory tests					
Full blood count	3.10	NHS reference costs 2023/24; DAPS05, Haematology; Weighted average of all unit costs.	0.39	0.92	TA891 and clinical expert feedback ⁴
Lactate dehydrogenase	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.16	0.23	
Blood glucose	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.31	0.31	
Bone marrow exam	740.05	NHS reference costs 2023/24; SA33Z, Diagnostic Bone Marrow Extraction.	0.00	0.07	
Biopsy	763.73	NHS reference costs 2023/24; YJ04Z, Core Needle Biopsy of Axillary Lymph Nodes.	0.00	0.08	
Renal – urea electrolytes test	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.30	0.92	
Liver function	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.30	0.92	
Immunoglobulin blood test	7.74	NHS reference costs 2023/24; DAPS06, Immunology; Weighted average of all unit costs.	0.07	0.15	
Imaging					
Chest X-Ray	83.79	NHS reference costs 2023/24; RD50Z, DEXA Scan; As per TA689.	0.07	0.07	TA891 and clinical expert feedback ⁴
CT scan	136.24	NHS reference costs 2023/24; RD27Z, Computerised Tomography Scan of more than Three Areas.	0.04	0.16	
Hospital visits					
Haematologist visit	184.09	NHS reference costs 2023/24; Outpatient Care, 303, Clinical haematology, Weighted average of all unit costs.	0.30	0.39	TA891 and clinical expert feedback ⁴

Resource use	Cost (£)	Source	Frequency of use per model cycle by health state		Source
			PF	PD	
Other specialist visit	176.17	NHS reference costs 2023/24; Outpatient Attendances; 370, Medical Oncology Service, 800, Clinical Oncology Service; Weighted average of all units costs.	0.07	0.16	
Community visits					
General practitioner (GP) visit	45.00	PSSRU 2024, Table 9.4.2: Unit costs for a GP, per surgery consultation lasting 10 minutes including direct staff costs with qualification costs.	0.08	0.15	TA891 and clinical expert feedback ⁴
Transfusions					
Full blood transfusion	398.79	NHS reference costs 2023/24; Outpatient attendances: 303, Clinical Haematology: SA44A Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over.	0.00	0.07	TA891 and clinical expert feedback ⁴
Platelet transfusion	398.79	NHS reference costs 2023/24; Outpatient attendances: 303, Clinical Haematology: SA44A Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over.	0.15	0.08	

Abbreviations: CC: Complication and Comorbidity; CT: computed tomography; GP: general practitioner; NHS: National Health Service; PD: progressed disease; PF: progression-free; PSSRU: Personal Social Services Research Unit.

Table 62: Total health state follow-up and monitoring costs per model cycle

Health states	Sub-state	Total cost (£)
PF	On-treatment	148.33
	Off-treatment	
PD	On-treatment	313.85
	Off -treatment	

Abbreviations: PD: progressed disease; PF: progression-free.

3.5.4 Adverse event management costs

The costs of managing AEs were also included in the base case economic analysis, using the proportion of patients who experienced Grade ≥ 3 TEAEs with an incidence of $\geq 5\%$ in the intervention of interest (i.e., any incidence $< 5\%$ was considered as 0%), as reported in the key clinical trials for AV (AMPLIFY trial),^{2, 3} VenI (GLOW trial)³⁷ and VenO (CLL14 trial).⁵⁵

All patients experiencing Grade ≥ 3 TEAEs were assumed to require hospitalisation. The total costs associated with the management of AEs for AV, VenI and VenO were estimated as the weighted average of the individual TEAE costs and the proportion of patients experiencing these TEAEs for each treatment (Table 63).

Table 63: Incidence of Grade ≥3 TEAEs occurring in ≥5% of patients for AV, VenI and VenO and the associated hospitalisation costs included in the economic analysis

AE	Proportion of patients (%)			Cost (£)	Source
	AV (AMPLIFY) ³	VenI (GLOW) ³⁷	VenO (CLL14) ⁵⁵		
Anaemia	0.00	0.00	8.00	603.91	NHS reference costs 2023/24; SA09L, K, Other Red Blood Cell Disorders with CC Score 0-5, Non-Elective Inpatient Short Stay; As per NICE TA931.
Atrial fibrillation	■	6.60	0.00	1,333.98	NHS reference costs 2023/24; EB07A, B, C, D, E, Arrhythmia or Conduction Disorders; Weighted average of all unit costs.
Cardiac disorders	0.00	0.00	6.10	2,772.36	NHS reference cost 2023/24; EB03A, B, C, D, E; Heart Failure or Shock; Weighted average of all unit costs.
Diarrhoea	0.00	10.38	0.00	509.69	NHS reference costs 2023/24; FD10M; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; Non-elective inpatient short stay.
Febrile neutropenia	0.00	0.00	5.20	2,522.56	NHS reference costs 2023/24; SA35A, B, C, D, E, Agranulocytosis, Non-elective inpatient short stay and long stay; as per NICE TA931.
Hypertension	0.00	7.55	0.00	404.67	NHS reference costs 2023/24; EB04Z, Hypertension, Non-elective inpatient short stay; As per NICE TA931.
Hyponatremia	■	5.66	0.00	419.47	NHS reference costs 2023/24; KC04B, Inborn Errors of Metabolism with CC Score 0-2, Non-elective inpatient short stay; As per NICE TA931.
Infections and infestations	■	16.98	19.40	1,937.90	NHS reference costs 2023/24; WJ03A, B, C, D, E, F, G, Standard Infectious Diseases; Weighted average of all unit costs.
Infusion-related reaction	0.00	0.00	9.00	600.40	NHS reference costs 2023/24; JD07K; Skin Disorders without Interventions, with CC Score 0-1; Weighted average of all unit costs.
Malignant neoplasm	■	0.00	7.00	3,477.25	NHS reference costs 2023/24; WH14A, B, C, D, Other or Unspecified Neoplasm; Weighted average of all unit costs.
Neutropenia	26.80	34.91	52.80	695.84	NHS reference costs 2023/24; SA35A, B, C, D, E, Agranulocytosis, Non-elective inpatient short stay; As per NICE TA931.
Neutrophil count decreased	5.50	0.00	0.00	695.84	Assumed same as neutropenia.

AE	Proportion of patients (%)			Cost (£)	Source
	AV (AMPLIFY) ³	VenI (GLOW) ³⁷	VenO (CLL14) ⁵⁵		
Thrombocytopenia	5.50	0.00	0.00	752.52	NHS reference costs 2023/24; SA12G, H, J, K, Thrombocytopenia, Non-elective inpatient short stay; As per NICE TA931.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; NHS: National Health Service; TEAE: treatment-emergent adverse event; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.5.5 Miscellaneous unit costs and resource use

End-of-life costs

End-of-life costs were applied as a one-off cost, for all patients who transitioned to the death health state, in the model cycle before death. This cost was derived from the Health and Social Care 2024 manual (£11,278.00).¹⁵⁴

TLS management cost

TLS is a particularly detrimental AE associated with venetoclax treatment but is preventable with adequate prophylaxis. The cost of TLS management, assumed to be £2,612.40, was incorporated into the economic analysis as a one-time cost, based on the value used in the NICE evaluation of venetoclax with rituximab (TA561).¹⁵⁵ This value was derived using the risk distribution of TLS in the treated population of the MURANO trial and the use of oral acid reducers as prophylaxis. In the absence of alternative data, the TLS management costs were assumed to be the same as the prophylaxis costs.

3.6 Severity

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by McNamara *et al.* 2023.¹⁵⁶ The total life expectancy for the modelled population was calculated using population mortality data from the Office for National Statistics for 2021–2023.¹⁵⁷ The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava *et al.* (2022) through the NICE DSU.¹³⁶

The total discounted QALYs for the current untreated non-high risk CLL patient population in the UK were based on the results of the base case economic analysis for AV in this submission. As shown in Table 65, the absolute QALY shortfall and proportional QALY shortfall compared to the population receiving treatment with existing therapies (Table 64) were below the severity modifier threshold, therefore, no severity weights were used in the base case economic analysis.

Table 64: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Starting age (mean)	59.90 years	Section 3.3.1
Proportion of female patients	36%	Section 3.3.1

Abbreviations: QALY: quality-adjusted life year.

Table 65: Summary of QALY shortfall analysis

Treatment	QALE for general population	Total QALYs	Absolute shortfall	Proportional shortfall
VenI	12.46	■	■	■
VenO		■	■	■

Abbreviations: AV: acalabrutinib with venetoclax; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.7 Uncertainty

Whilst every effort was made to develop an economic analysis that is robust and utilises evidence-based assumptions, some areas of uncertainty remain.

As with the extrapolation of any trial data over a longer time horizon, there will be uncertainty around long-term estimates and their clinical plausibility. Given the indolent nature of CLL and the need to derive long-term estimates of TTP and pre-PS, the choice of curve to extrapolate these data is associated with uncertainty. All extrapolation choices were aligned with UK clinical expert feedback to assess clinical plausibility, NICE DSU TSD 14 guidance and external sources of data where available for TTP.^{15, 116}

The above area of uncertainty is extended to post-PS, where the immaturity of the AMPLIFY data necessitated the use of external, more mature OS data from the ASCEND trial. This trial explored the use of acalabrutinib monotherapy only, and therefore the use of these data as a proxy for post-PS for all subsequent treatments following first-line therapy is associated with uncertainty. The assumption that acalabrutinib monotherapy is representative of subsequent treatments can be considered reasonable given that it was the most commonly used treatment, based on estimates from UK clinical experts (Section 3.5.2). Alternative BTKis (e.g., ibrutinib) were also commonly used – the comparable efficacy of acalabrutinib and ibrutinib in the relapsed/refractory CLL setting is well-established.^{9, 80, 82} Overall, using ASCEND OS data as a proxy for post-PS leverages data from a robust, phase III RCT in an appropriate population and disease setting and, as such, can be considered the most accurate modelling approach given the available data.

The distribution of subsequent treatments observed within the AMPLIFY trial was not considered generalisable to UK clinical practice for a number of reasons as discussed in Section 3.5.2. To improve the clinical plausibility of the modelled subsequent treatments, treatment distributions were instead informed by estimates provided by UK clinical experts. Although, the modelled subsequent treatments included regimens typically received for longer than one year, their associated costs were applied as a one-off cost at progression rather than being discounted over time. Whilst potentially a source of uncertainty, this was considered a reasonable simplification to prevent introducing unnecessary complexity into the model structure. Furthermore, AEs associated with subsequent treatments were not explicitly included within the model. Whilst not discounting the subsequent treatment costs may slightly overestimate costs, the exclusion of subsequent treatment-related AE costs may slightly underestimate them, thereby balancing the impact on the final model results.

All key areas of uncertainty within the model were explored in scenario analyses, and the results of these are presented in Section 3.11.3.

3.8 Managed access proposal

The clinical evidence informing this submission for AV derives from the AMPLIFY trial latest DCO (30th April 2024). These data and their adoption in the economic analysis are considered suitably mature (see PFS data in Section 3.3.2.1) and reliable to allow the Committee to recommend AV via routine commissioning.

However, the AMPLIFY trial is ongoing and an [REDACTED]

[REDACTED]

[REDACTED]

3.9 Summary of base case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

A summary of all key model inputs is presented in Table 66.

Table 66: Summary of key inputs applied in the base case economic analysis

Variable	Value				Reference to section in submission
Model settings					
Discount rate, %	3.5				Section 3.2.2
Time horizon, years	40				
Perspective	UK NHS and PSS				
Patient baseline characteristics					
Mean age (SE), years	59.90 (0.32)				Section 3.2.1
Mean BSA (SE), m²	██████████				
Mean weight (SE), kg	██████████				
Female patients (SE), %	36 (0.036)				
Survival inputs					
	TTP	Pre-PS	Post-PS	TTD	Section 3.3.2
AV	Log-logistic	Log-logistic	Exponential	Median: ██████ (95% CI: ██████)	
VenI	Assumed clinically equivalent to AV				
VenO	Assumed clinically equivalent to AV				
HSUV inputs					
PF on-treatment (oral treatment)	██████████				Section 3.4.5
PF on-treatment (IV treatment)	██████████				
PF off-treatment	██████████				
PD on-treatment	██████████				
PD off-treatment	██████████				
AE disutility					
	Disutility		Duration (days)		Section 3.4.4
Anaemia	−0.09		23.21		
Atrial fibrillation	−0.22		14		
Cardiac disorders	-0.22		14		
Diarrhoea	−0.2		3		
Febrile neutropenia	−0.16		15.09		
Hyperglycaemia	−0.06		14		
Hyponatremia	−0.02		21		
Infections and infestations	−0.22		14		
Infusion-related reaction	−0.2		3.5		

Variable		Value			Reference to section in submission	
Malignant neoplasm		-0.22	14			
Neutropenia		-0.16	15.09			
Neutrophil count decreased		-0.16	15.09			
Thrombocytopenia		-0.11	23.21			
AEs						
		Frequency			Costs (£)	
		AV	VenI	VenO		
Anaemia		0.00	0.00	8.00	603.91	Sections 3.3.3 and 3.5.4
Atrial fibrillation		■	6.60	0.00	1,333.98	
Cardiac disorders		0.00	0.00	6.10	2,772.36	
Diarrhoea		0.00	10.38	0.00	509.69	
Febrile neutropenia		0.00	0.00	5.20	2,522.56	
Hypertension		0.00	7.55	0.00	404.67	
Hyponatremia		■	5.66	0.00	419.47	
Infections and infestations		■	16.98	19.40	1,937.90	
Infusion-related reactions		0.00	0.00	9.00	600.40	
Malignant neoplasm		■	0.00	7.00	3,477.25	
Neutropenia		26.80	34.91	52.80	695.84	
Neutrophil count decreased		5.50	0.00	0.00	695.84	
Thrombocytopenia		0.00	5.66	13.70	752.52	
Drug acquisition costs						
Regimen		Dose (mg)	First model cycle (£)		Subsequent model cycles (£)	Section 3.5.1
AV	Acalabrutinib	100	■		■	
	Venetoclax	10	54.83		0.00	
		50	137.06		0.00	
		100	274.13		0.00	
			548.25		0.00	
			0.00		4,386.03	
VenI	Venetoclax	10	59.87		0.00	
		50	149.67		0.00	
		100	299.34		0.00	
			598.68		0.00	
			0.00		4,789.44	
	Ibrutinib	420	4,292.40		4,292.40	
VenO	Venetoclax	10	59.87		0.00	
		50	149.67		0.00	
		100	299.34		0.00	
			598.68		0.00	

Variable			Value		Reference to section in submission	
			0.00	4,789.44		
	Obinutuzumab	1,000	9,936.00	3,312.00		
Drug administration cost (IV-administered drugs only)						
		First model cycle (£)	Subsequent model cycles (£)		Section 3.5.1	
VenO	Venetoclax	0.00	0.00			
	Obinutuzumab	1,458.70	430.24			
Subsequent treatments						
		Distributions (% of patients)			Acquisition costs (£)	Section 3.5.2
		AV	VenI	VenO		
Acalabrutinib monotherapy						
Ibrutinib monotherapy					191,308.82	
Venetoclax monotherapy					28,646.84	
Venetoclax with rituximab					32,968.83	
Zanubrutinib monotherapy					206,021.68	
Health state follow-up and monitoring						
		Cost (£)	Frequency		Section 3.5.3	
			PF	PD		
Laboratory tests						
Full blood count		3.10	0.39	0.92		
Lactate dehydrogenase		1.53	0.16	0.23		
Blood glucose		1.53	0.31	0.31		
Bone marrow exam		740.05	0.00	0.07		
Biopsy		763.73	0.00	0.08		
Renal – urea electrolytes test		1.53	0.30	0.92		
Liver function		1.53	0.30	0.92		
Immunoglobulin blood test		7.74	0.07	0.15		
Imaging						
Chest X-Ray		83.79	0.07	0.07		
CT scan		136.24	0.04	0.16		
Hospital visits						
Haematologist visit		184.09	0.30	0.39		
Other specialist visit		176.17	0.07	0.16		
Community visits						
GP visit		45.00	0.08	0.15		
Transfusions						
Full blood transfusion		398.79	0.00	0.07		
Platelet transfusion		398.79	0.15	0.08		
Disease management costs						
End-of-life costs						

Variable	Value	Reference to section in submission
	£11,278.00	Section 3.5.5
TLS management cost		
	£2,612.40	

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; BSA: body surface area; CI: confidence interval; CT: computed tomography; GP: general practitioner; HSUV: health state utility value; IV: intravenous; PD: progressed disease; PF: progression-free; SE: standard error; TLS: tumour lysis syndrome; TTD: time to discontinuation; TTP: time to progression; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.9.2 Assumptions

A summary of the key assumptions utilised in the base case economic analysis is presented in Table 67.

Table 67: Summary of key assumptions used in the base case economic analysis

Parameter	Assumption	Justification
Clinical effectiveness		
Pre-PS, post-PS, TTD and TTP	AV is assumed to be clinically equivalent to its comparators, VenI and VenO	As described in Section 2.10.3, results of the STC indicated that there was no statistically significant difference between AV and VenI or VenO in terms of PFS or OS. The clinical equivalence of these interventions was further confirmed by the results of a modified Delphi panel with UK clinical experts (Section 2.10.5) and separate interviews conducted with UK clinical experts. ¹⁵ As such, this assumption has been informed via quantitative analysis and robust expert elicitation, so does not represent a significant source of uncertainty.
Survival extrapolations		
TTP curves	AV TTP was modelled by independent extrapolation of TTP data from the AMPLIFY trial using the log-logistic curve. VenI and VenO were assumed to have the same TTP as AV	As described in Section 3.3.2.1, the log-logistic curve was deemed to be the most clinically plausible to extrapolate TTP, by closely representing the proportion of patients expected to experience long-term remission, whilst remaining statistically acceptable. When compared with external sources, the log-logistic curve also represented a conservative estimate of progression. A scenario analyses was conducted using the gamma curve. Given the assumption of clinical equivalence between AV, VenI and VenO, a HR of 1 was applied to the above AV extrapolation for TTP to derive equivalent curves for VenI and VenO.
Pre-PS	AV pre-PS was modelled by independent extrapolation of TTP data from the AMPLIFY trial using the log-logistic curve. VenI and VenO were assumed to have the same pre-PS as AV	As described in Section 3.3.2.2, the log-logistic curve was one of the most clinically plausible extrapolations identified by UK clinical experts to extrapolate pre-PS, whilst also providing good statistical performance. Scenario analyses were conducted using the Generalised gamma and gamma curves. Given the assumption of clinical equivalence between AV, VenI and VenO, a HR of 1 was applied to the above AV extrapolation for pre-PS to derive equivalent curves for VenI and VenO.
Post-PS	OS data from the ASCEND trial, which assessed acalabrutinib monotherapy for patients with CLL in the second-line setting,	External post-PS data was incorporated into the model due to the immaturity of post-PS data from the AMPLIFY trial (■%). The second-line setting of the ASCEND trial was considered to represent post-progression patients in the first-line setting, whilst

Parameter	Assumption	Justification
	were used as a proxy for post-PS data. VenI and VenO were assumed to have the same post-PS as AV	acalabrutinib monotherapy was assumed to represent treatment with BTKI monotherapies in subsequent lines of treatment. As shown in Table 57, over 50% of patients receive BTKI monotherapies following first-line treatment. Scenario analyses were conducted using the log-normal and Weibull curves.
TTD	AV TTD was modelled using data from the AMPLIFY trial. VenI and VenO were assumed to have equal TTD to AV	Extrapolation of data from the AMPLIFY trial was not required as these data were fully captured within the trial follow-up period (Section 3.3.2.3). The same TTD for AV and its comparators was used given the assumption of clinical equivalence between AV, VenI and VenO, and the paucity of publicly available TTD data for VenI and VenO. However, the Kaplan-Meier curve for AV TD was extended by one cycle to account for the longer maximum TTD of VenI versus AV. A scenario analysis was conducted without this TTD extension.
Costs		
Drug wastage	Wastage for IV drugs was assumed	Aligned with the accepted approach in previous NICE evaluation in untreated CLL. ^{4, 10} A scenario analysis was conducted where no drug wastage was assumed.
Resource use estimates	Resource use estimates were estimated by health state, and assumed to be equal irrespective of first-line treatment received	Frequencies for resource use were taken from a previous NICE evaluation in the untreated CLL setting (TA891), and adapted following input from UK clinical experts to more accurately reflect clinical practice. ^{4, 15} Furthermore, the clinical experts confirmed that patients in the PF and PD health states would have different medical requirements which should be reflected through different levels of resource use in the economic analysis. ¹⁵
HSUVs		
HSUVs	HSUVs were derived from the AMPLIFY trial for the PF on-treatment health state. The following adjustments were made to this value to derive HSUVs for other health state: - PF on-treatment (IV): applied as utility decrement associated with IV treatment, versus oral treatment, derived from the Kosmas <i>et al.</i> 2015 study.¹²⁸ - PF off-treatment: assumed equal to HSUV for PD on-treatment (oral). - PD on-treatment: applied as utility decrement associated with disease progression, derived from the Kosmas <i>et</i>	Adjustments were applied using increments/decrements from the Kosmas <i>et al.</i> (2015) study, which have been used in several prior NICE evaluations^{5, 10, 128} Input from UK clinical experts confirmed that use of a lower HSUV for IV treatment versus orally-administered treatment is appropriate, and that a utility decrement associated with disease progression is appropriate.¹⁵ The HSUV for PF off-treatment was assumed equal to that of PF on-treatment (oral), because applying the utility increase associated with being off-treatment resulted in an HSUV which lacked validity. Scenario analyses were conducted using utilities reported in the Kosmas <i>et al.</i> (2015) study,¹²⁸ and without the application of AE-related disutilities.

Parameter	Assumption	Justification
	<i>al.</i> 2015 study. ¹²⁸ • PD off-treatment: utility increase associated with being off-treatment was derived from Kosmas <i>et al.</i> 2015 study was applied.¹²⁸	

Abbreviations: AV: acalabrutinib with venetoclax; HSUV: health state utility value; IV: intravenous; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; post-PS: post-progression survival; pre-PS: pre-progression survival; STC: simulated treatment comparison; TTD: time to discontinuation; TTP: time to progression; UK: United Kingdom; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.10 Base case results

3.10.1 Base case incremental cost-effectiveness analysis results

Probabilistic base case results

Probabilistic base case results for the economic analysis of AV versus VenI and VenO are presented in Table 68 (ICER) and in Table 69 (NHB and NMB). These results align with the deterministic base case analysis.

The ICERs for AV versus VenI and VenO indicate dominance however due to the small incremental QALY, NMB at a WTP threshold of £30,000 is presented as an informative measure of cost-effectiveness.

In the probabilistic base case analysis versus VenI, AV was associated with [REDACTED] QALYs at a [REDACTED] total cost of [REDACTED], resulting in AV dominating VenI. This translates to a [REDACTED] NHB at WTP thresholds of £20,000 and £30,000 per QALY ([REDACTED] and [REDACTED], respectively) and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenI at both WTP thresholds was [REDACTED].

In the probabilistic base case analysis versus VenO, AV was associated with [REDACTED] QALYs at a [REDACTED] total cost of [REDACTED], resulting in AV dominating VenO. This translates to a [REDACTED] NHB at WTP thresholds of £20,000 and £30,000/QALY ([REDACTED] and [REDACTED], respectively) and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenO at both WTP thresholds was [REDACTED].

The economic analysis included the existing PAS price for acalabrutinib and list prices of comparator therapies.

Table 68: Probabilistic base case results for AV versus VenI and VenO (acalabrutinib with-PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) ^a
AV	[REDACTED]	12.398	[REDACTED]	-	-	-	-
VenI	[REDACTED]	12.398	[REDACTED]	[REDACTED]	0.000	[REDACTED]	Dominant
VenO	[REDACTED]	12.398	[REDACTED]	[REDACTED]	0.000	[REDACTED]	Dominant

^a [REDACTED]
Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 69: Probabilistic NHB and NMB results for AV versus VenI and VenO (acalabrutinib with-PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000	NMB at £30,000 (£)
AV	[REDACTED]	[REDACTED]	-	-	-	-	-
VenI	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
VenO	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: AV: acalabrutinib with venetoclax; Incr: incremental; NHB: net health benefit; NMB: net monetary

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benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Deterministic base case results

Deterministic base case results for the economic analysis of AV versus VenI and VenO are presented in Table 70 (ICER) and Table 71 (NHB and NMB).

In the deterministic base case analysis versus VenI, AV was associated with [REDACTED] QALYs at a [REDACTED] total cost of [REDACTED], resulting in AV dominating VenI. This translates to a [REDACTED] NHB at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY ([REDACTED] and [REDACTED], respectively) and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED].

In the deterministic base case analysis versus VenO, AV was associated with [REDACTED] QALYs at a [REDACTED] total cost of [REDACTED], resulting in AV dominating VenO. This translates to a [REDACTED] NHB at WTP thresholds of £20,000 and £30,000/QALY ([REDACTED] and [REDACTED], respectively) and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED].

Table 70: Deterministic base case results for AV versus VenI and VenO (acalabrutinib with-PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) ^a
AV	[REDACTED]	12.399	[REDACTED]	-	-	-	-
VenI	[REDACTED]	12.399	[REDACTED]	[REDACTED]	0.000	[REDACTED]	Dominant
VenO	[REDACTED]	12.399	[REDACTED]	[REDACTED]	0.000	[REDACTED]	Dominant

^a [REDACTED]
Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 71: Deterministic NHB and NMB results for AV versus VenI and VenO (acalabrutinib with-PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	NHB at £20,000	NHB at £30,000	NMB at £30,000 (£)
AV	[REDACTED]	[REDACTED]	-	-	-	-	-
VenI	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
VenO	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: AV: acalabrutinib with venetoclax; Incr: incremental; NHB: net health benefit; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

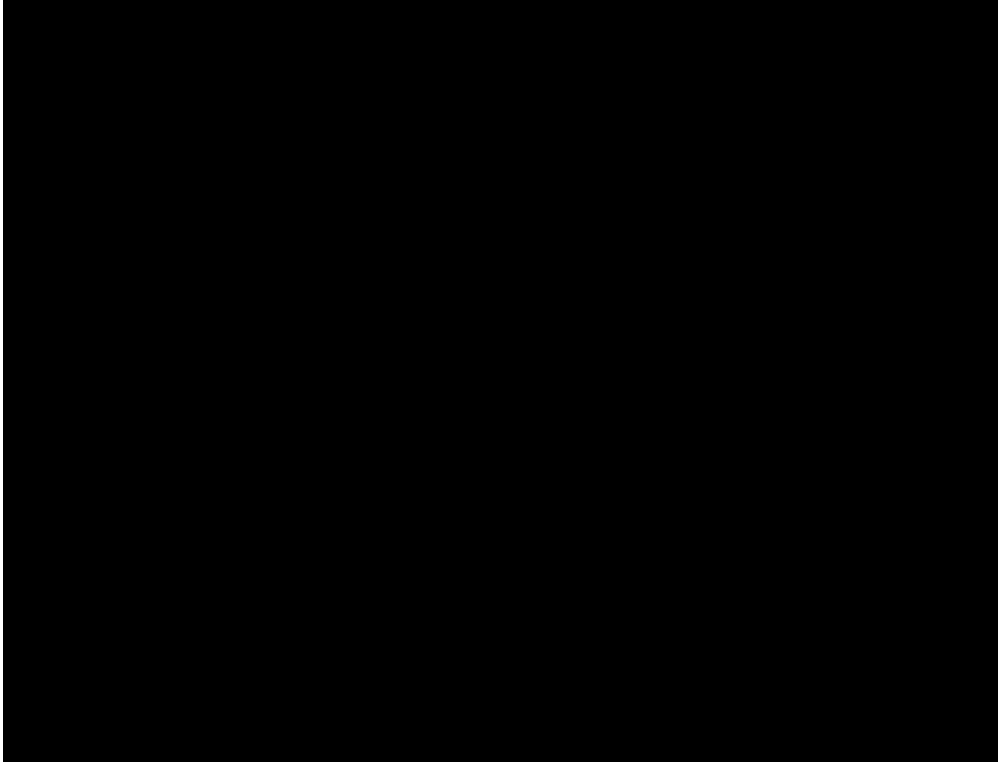
A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results were robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions.

Estimates of model parameters were based on the uncertainty in the source data (where data availability permitted). Where no such data were available, SEs were estimated as 10% of the

mean value.

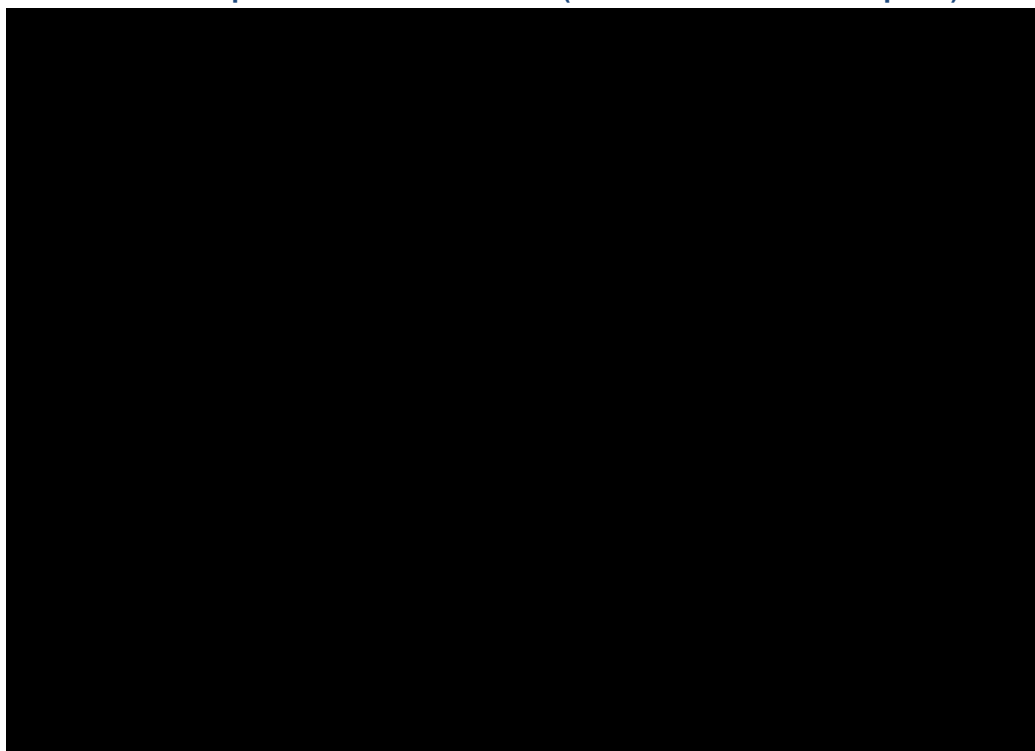
A scatter plot showing the incremental costs and QALYs from the 1,000 iterations of the PSA for AV versus VenI, and VenO, are presented in Figure 31 and Figure 32, respectively.

Figure 31: PSA scatter plot for AV versus VenI (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay; VenI: venetoclax with ibrutinib.

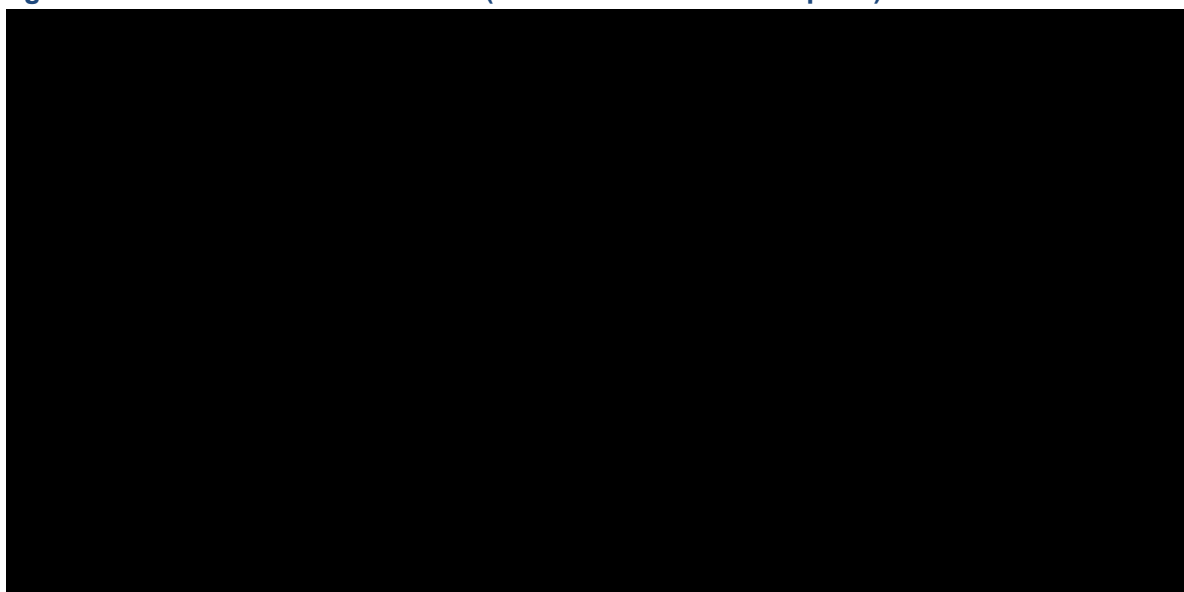
Figure 32: PSA scatter plot for AV versus VenO (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay; VenO: venetoclax with obinutuzumab.

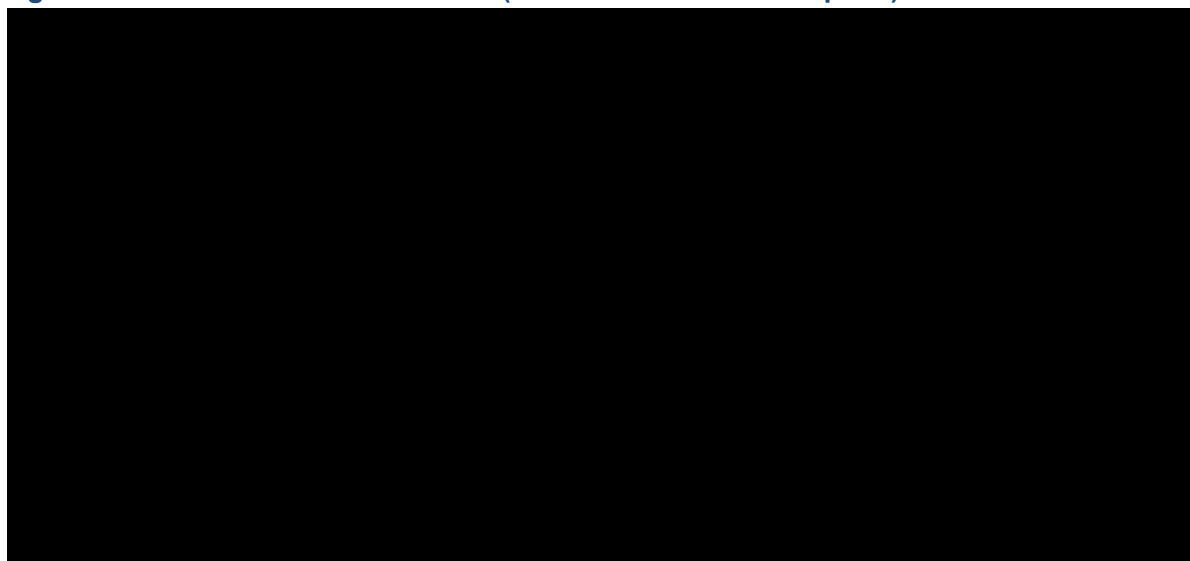
The cost-effectiveness acceptability curve (CEAC) for AV versus VenI, and VenO, are presented in Figure 33 and Figure 34, respectively.

Figure 33: CEAC for AV versus VenI (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenI: venetoclax with ibrutinib.

Figure 34: CEAC for AV versus VenO (acalabrutinib with-PAS price)



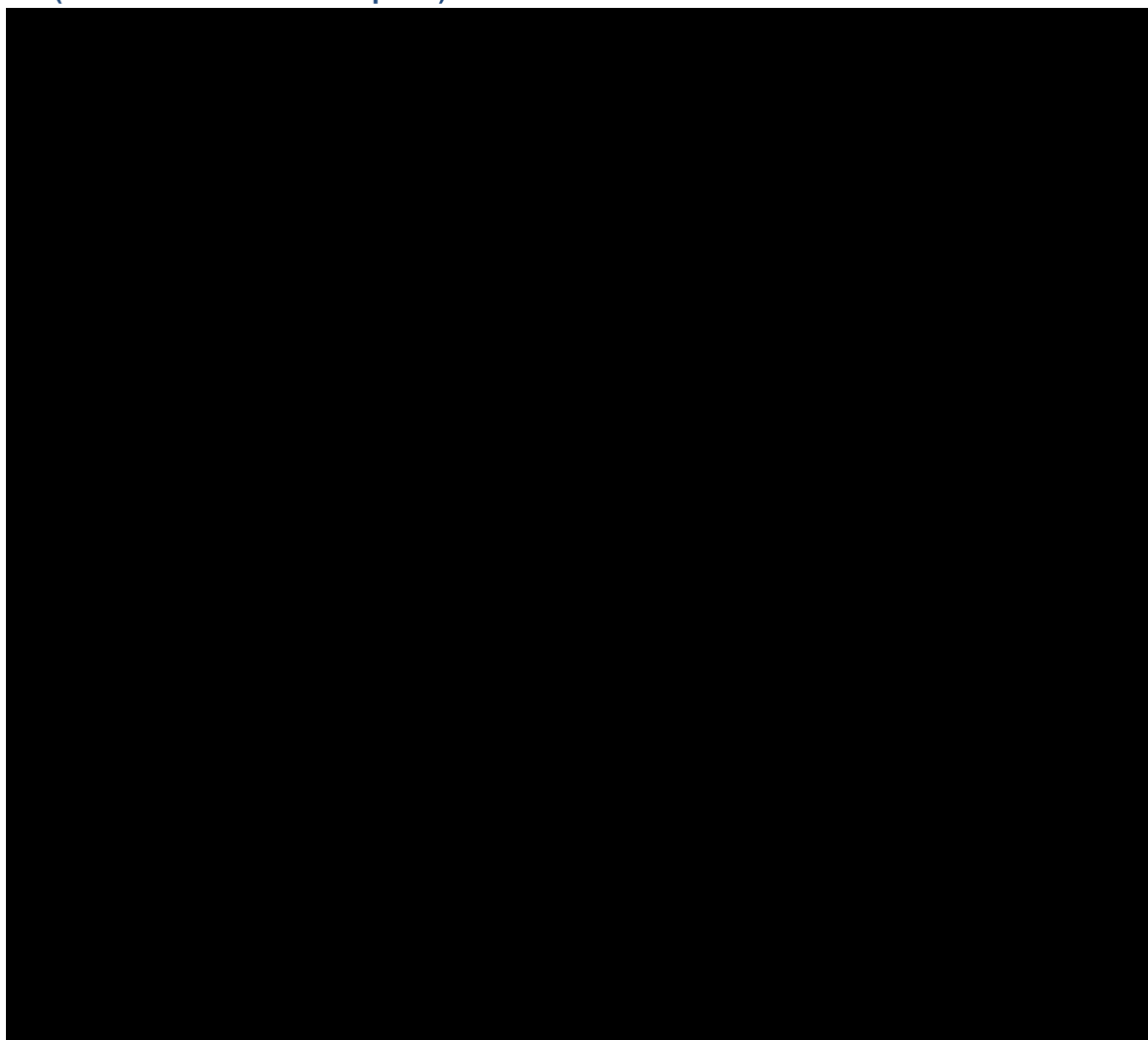
Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenO: venetoclax with obinutuzumab.

3.11.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis (DSA) was undertaken to explore the impact of varying key model parameter values by +/- 10% on the NHB for each comparison. A tornado diagram showing the key drivers of the DSA in the base case economic analysis of AV versus VenI, and versus VenO, are presented in Figure 35 and Figure 36, respectively. The WTP is assumed to be £20,000 per QALY.

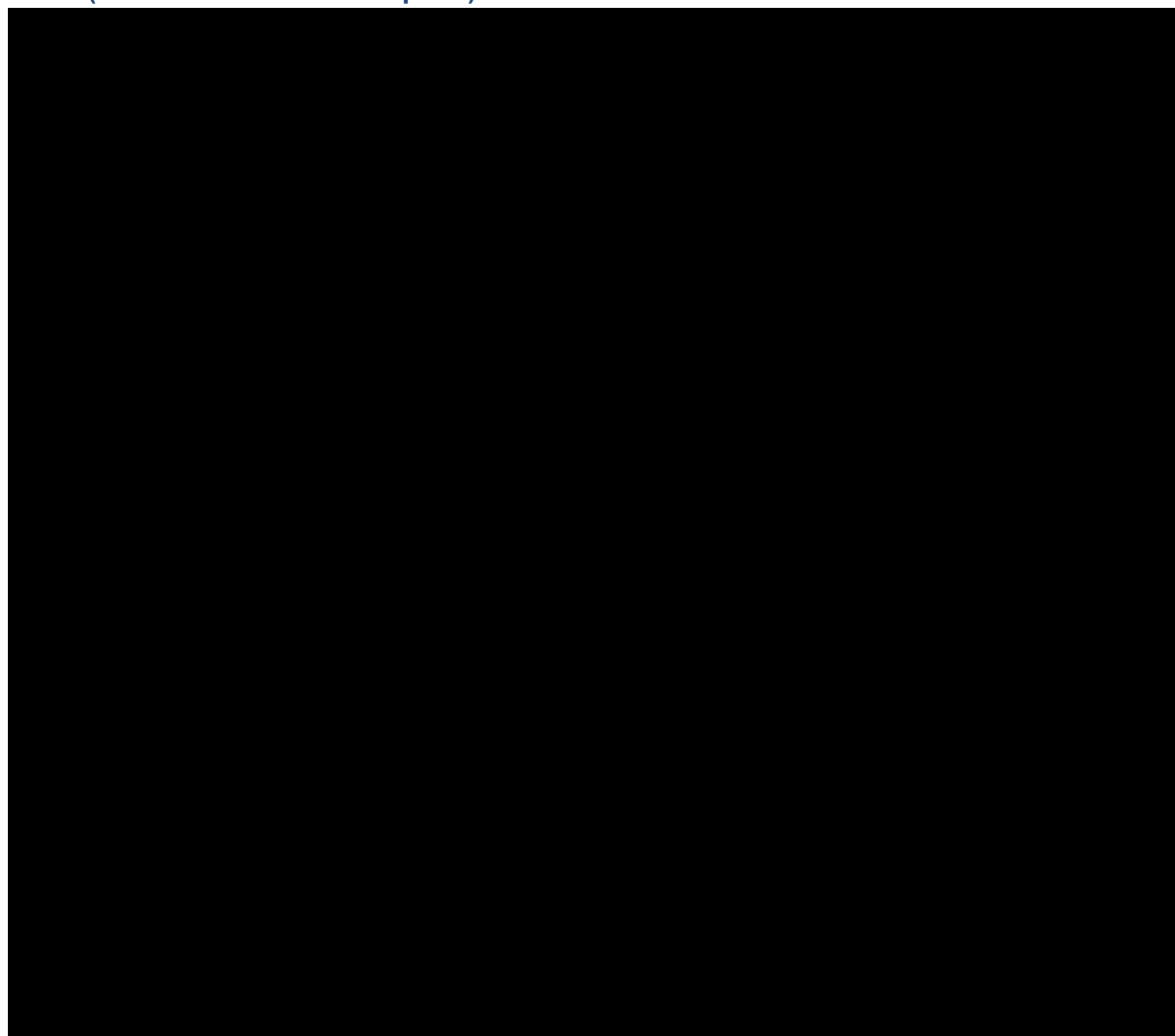
The most influential drivers of the base case economic analysis versus VenI were the proportion of patients receiving subsequent treatment with zanubrutinib monotherapy, and venetoclax with rituximab, for the VenI arm. Similarly, versus VenO, the most influential drivers were the proportion of patients receiving subsequent treatment with zanubrutinib monotherapy, and venetoclax with rituximab, for the VenO arm.

Figure 35: NHB (WTP threshold of £30,000 per QALY) DSA tornado diagram for AV versus VenI (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; WTP: willingness-to-pay.

Figure 36: NHB (WTP threshold of £30,000 per QALY) DSA tornado diagram for AV versus VenO (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenO: venetoclax with obinutuzumab; WTP: willingness-to-pay.

3.11.3 Scenario analysis

A series of scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the base case economic analysis.

A complete list of the scenario analyses explored is provided in Table 72 (versus VenI) and Table 73 (versus VenO). In all scenarios, AV remained dominant versus both VenI and VenO. The results remain stable across the majority of scenarios because of the underlying assumption of equivalence in efficacy between AV, VenI, and VenO.

Redistributing subsequent treatments based on the AMPLIFY trial rather than clinical expert opinion had the biggest impact on incremental costs. This scenario weights the use of BTKi therapies more evenly across the treatment arms, which drives a greater change in cost outcomes. However, feedback from UK clinical experts indicated that patients who have not received first-line therapy with a BTKi would be expected to receive a BTKi in subsequent lines of therapy. This supports the increased use of BTKis in subsequent lines for patients who received

first-line therapy with VenO, compared with AV or VenI, in the base case economic analysis.¹⁵ Applying HSUVs reported by Kosmas *et al.* (2015; Table 52)¹²⁸, rather than those derived from the AMPLIFY trial (Table 54), had the greatest impact on incremental QALYs. However, given the assumption of equal efficacy between AV, VenI and VenO in the economic analysis, the use of different HSUVs had a minimal impact on overall results.

Overall, the results of the scenario analyses demonstrate that the results of the base case analysis are robust to uncertainties in the model inputs and assumptions (Section 3.9.2).

Table 72: Scenario analysis results – AV versus Venl (acalabrutinib with-PAS price)

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	INHB (£20,000 WTP)	INHB (£30,000 WTP)	NMB at £30,000 (£)	ICER (£/QALY) ^a
Base case analysis		████	██	██	██	██	Dominant
TTP curve selection (log-logistic distribution)	Alternative TTP curve selection (gamma)	████	██	██	██	██	Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gen gamma)	████	██	██	██	██	Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gamma)	████	██	██	██	██	Dominant
Post-PS curve selection (exponential distribution)	Alternative post-PS curve selection (lognormal)	████	██	██	██	██	Dominant

Table 73: Scenario analysis results – AV versus VenO (acalabrutinib with-PAS price)

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	INHB (£20,000 WTP)	INHB (£30,000 WTP)	NMB at £30,000 (£)	ICER (£/QALY) ^a
Base case analysis		████	████	████	████	████	Dominant
TTP curve selection (log-logistic distribution)	Alternative TTP curve selection (gamma)	████	████	████	████	████	Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gamma)	████	████	████	████	████	Dominant
Pre-PS (log-logistic distribution)	Alternative pre-PS curve selection (gamma)	████	████	████	████	████	Dominant
Post-PS (exponential distribution)	Alternative post-PS curve selection (lognormal)	████	████	████	████	████	Dominant
Post-PS (exponential distribution)	Alternative post-PS curve selection (Weibull)	████	████	████	████	████	Dominant
Wastage assumed	Assume no wastage	████	████	████	████	████	Dominant
Subsequent treatment distribution based on clinician feedback	Subsequent treatment distributions from AMPLIFY	████	████	████	████	████	Dominant
Utility data collected from the AMPLIFY trial	Health state utilities from Kosmas <i>et al.</i> (2015)	████	████	████	████	████	Dominant

3.12 Subgroup analysis

As noted in Section 1.1, no economic subgroup analyses have been conducted for this submission.

3.13 Benefits not captured in the QALY calculation

Whilst the clinical effectiveness of AV has been comprehensively incorporated within the base case economic analysis, a key benefit that has not been fully captured in the comparison versus VenO is the impact on HRQoL of patients being able to take an all-oral therapy versus an oral-IV combination therapy. As an all-oral combination therapy, patients can take AV at home without the need to visit the hospital. This means that, unlike therapies administered via an IV infusion, such as obinutuzumab, AV does not require any nursing resources to administer, and frees up chemotherapy day units for other much-needed treatments to be delivered, therefore alleviating capacity constraints on the NHS. Additionally, AV is more comfortable for patients to take themselves, without needing to travel to hospital for administration, and is not associated with a risk of infusion-related reactions or bloodstream infection.⁸¹ Whilst the impact of this has been incorporated through the inclusion of an IV utility decrement for VenO, this decrement may not reflect the full impact of IV administration on patients. Feedback from clinical experts interviewed by AstraZeneca supported the fact that the toxicity and administrative burden associated with IV treatment contributes to a worse HRQoL compared with oral therapies.¹⁵ As such, it should be considered that this impact may not have been fully captured within the QALY calculation.

Similarly, the impact of the improved safety profile associated with AV versus VenI and VenO is not fully captured within the QALY calculation. Feedback from UK clinical experts interviewed by AstraZeneca between April and July 2025 indicated that AV is associated with an improved tolerability profile compared with VenI and VenO.¹⁵ Moreover, in a modified Delphi panel conducted by AstraZeneca with 22 UK clinical experts between July and August 2025, consensus was reached that fixed-duration AV would have a more favourable safety profile than fixed-duration VenI (88% agreed), further supporting this view. Whilst cost differences can be observed, the utility decrements applied for TEAEs have a minimal impact on the overall QALY difference, and therefore this does not translate to reduced QALYs for VenI and VenO overall.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Technical validation

In line with best practice, the structure of the economic analysis was fully validated by an independent health economist prior to submission. In addition, quality control checks were conducted; these included technical cell by cell verification of all input data, calculations, data references, model interface and Visual Basic for Applications code. Results generated by the economic analysis were all checked to ensure accuracy and consistency, and the correct functionality of the sensitivity and scenario analyses was also reviewed.

Clinical validation

Feedback from six UK clinical experts on the structure of the economic analysis was collected by AstraZeneca in validation exercises conducted between April and July 2025.¹⁵ Clinical experts reviewed and validated all key inputs and assumptions that were incorporated into the analysis,

including HSUVs, distribution of subsequent treatment and survival curve extrapolations.¹⁵

3.15 Interpretation and conclusions of economic evidence

Strengths of the economic analysis

The principle evidence base informing the economic analyses was the AMPLIFY trial, a large, robust phase 3 RCT conducted in a broad population of patients with untreated non-high risk CLL, which was considered representative of the UK patient population (N=867; Section 2.3.3). The trial was used to inform key efficacy inputs in the economic analysis. Furthermore, TTD data in AMPLIFY were complete at the latest DCO (30th April 2024), so TTD in the model were derived directly from the Kaplan-Meier curve from the trial. No parametric distribution extrapolations were necessary, limiting the uncertainty associated with this endpoint. In addition, HRQoL was assessed in the trial using EQ-5D, so HSUVs used in the analysis were derived directly from patients in a generalisable population which was also the source of most efficacy data, in line with the NICE reference case, rather than relying on published HSUVs from the literature.

The model structure used for the economic analysis was consistent with structures used in previous NICE evaluations in the untreated CLL setting.^{4, 8, 9} A key strength of the economic analyses also includes the numerous features that were conducted in line with the NICE reference case, including the time horizon, discount rate, perspective, and derivation of HSUVs using EQ-5D data.

Limitations of the economic analysis

The median follow-up of the AMPLIFY trial was 40.8 months at the latest DCO (30th April 2024).³ Despite this follow-up, the immaturity of post-PS data necessitated the use of external data sources. As noted in Section 3.7, the use of the acalabrutinib ASCEND trial represents a potential source of uncertainty in the model. However, data were derived from the subgroup of patients without del(17p) or *TP53* mutations, enhancing generalisability to the population of interest in this submission. The use of acalabrutinib monotherapy as a proxy for subsequent treatments was also considered appropriate, given that over 50% of patients receive a BTKi monotherapy following first-line treatment in UK clinical practice (Section 3.5.2).¹⁵

Given that the median follow-up of AMPLIFY and ASCEND was shorter than the total time horizon of the economic analysis, long-term extrapolation of clinical data from these trials was required. This is associated with uncertainty, given the indolent nature of CLL (Section 3.7). To address this limitation, selection of the most appropriate parametric survival functions followed the recommendations outlined by the NICE DSU TSD 14.¹¹⁶ Specifically, selection was informed by a combination of goodness-of-fit statistics, inspection of visual fit (internal validity) as well as feedback received from clinical experts on the relative clinical plausibility of each curve (external validity). Furthermore, uncertainty surrounding the long-term survival estimates of AV were explored in several scenario analyses which demonstrated the base case results to be robust to variations in these estimates.

Finally, although the AMPLIFY trial population was considered to be broadly generalisable to the UK untreated CLL population expected to be eligible for fixed-duration treatments, the distribution of subsequent treatments observed in the trial was not considered to be representative of those received in UK clinical practice. Instead, distributions in the economic analysis were informed by estimates from UK clinical experts.¹⁵ However, to avoid overcomplicating the model structure, the

costs associated with these modelled treatments were applied as a one-off cost rather than being discounted over time. Nevertheless, this is balanced by the exclusion of treatment-related AE costs for subsequent treatments, meaning the overall impact of this on the final model results is negligible.

Results of the economic analysis

In the probabilistic base case analysis versus VenI, AV was associated with [REDACTED] QALYs at a [REDACTED] cost of [REDACTED], therefore treatment with AV dominated VenI. This translates to a [REDACTED] NHB at WTP thresholds of £20,000 and £30,000/QALY of [REDACTED] and [REDACTED], respectively, and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenI at both WTP thresholds was [REDACTED]. Similarly, in the probabilistic base case analysis versus VenO, AV was associated with [REDACTED] QALYs at a [REDACTED] cost of [REDACTED], hence AV also dominated VenO. This translates to a [REDACTED] NHB at WTP thresholds of £20,000 and £30,000/QALY of [REDACTED] and [REDACTED], respectively, and a NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenO at both WTP thresholds was [REDACTED].

Conclusion

An unmet need exists for effective, more convenient and well-tolerated treatment options, in line with patient preferences, for patients with untreated non-high risk CLL. These patients experience a substantial disease burden, compounded by the impact of IV administration and AEs associated with existing treatments.

Recommending the use of AV in this patient population would address the current unmet need and offer an effective, convenient and well-tolerated fixed-duration treatment option, alongside VenI and VenO, for patients with untreated non-high risk CLL.

4 References

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Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232] – Managed access proposal

As outlined in the Company Submission, clinical evidence informing the submission for acalabrutinib with venetoclax (AV) are from the latest data cut-off of the AMPLIFY trial (interim analysis, 30th April 2024). The Company anticipate that these data are suitably mature and reliable to allow the Committee to recommend AV via routine commissioning.

However, should the Committee deem managed access necessary, a managed access proposal for the Cancer Drug's Fund (CDF) for AV in adults with untreated CLL without a 17p deletion (del[17p]) or TP53 mutation is provided below. The primary data sources anticipated to resolve any clinical uncertainty identified by the NICE Committee are the AMPLIFY trial (which is currently ongoing) and data from the Systemic Anti-Cancer Therapy (SACT) dataset.

An overview of potential clinical uncertainties and outcome data and data sources that could resolve the uncertainties is presented in Table 1. An overview of the AMPLIFY trial and the SACT dataset are presented in Table 2 and Table 3, respectively.

As AV is an all-oral, well-tolerated fixed duration treatment, a managed access agreement for AV in adults with untreated CLL without a del(17p) or *TP53* mutation is not anticipated to be associated with any additional burden to patients or clinicians in NHS clinical practice. In addition, no barriers to or ethical concerns associated with a managed access agreement for AV have been identified.

Table 1: List of uncertainties and the data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
Long-term efficacy of AV	OS and PFS data with longer follow-up	AMPLIFY trial
Generalisability of AMPLIFY trial to UK clinical practice	Baseline characteristics of patients receiving AV in UK clinical practice	SACT
Modelling of time on treatment for VenI and VenO	Time on treatment for patients receiving VenI and VenO in UK clinical practice	SACT

Abbreviations: AV: acalabrutinib with venetoclax; OS: overall survival; PFS: progression-free survival; SACT: Systemic Anti-Cancer Therapy; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 2: Overview of AMPLIFY trial

Study	AMPLIFY trial
Study design	Phase 3, randomised, controlled, international trial
Population	Adults with untreated CLL without TP53 mutation or del(17p)
Intervention(s)	AV (and AVO) ^a
Comparator(s)	FCR/BR
Outcomes	PFS and OS
Indicate if study used in the NICE economic model	Yes
Trial start date	February 2019
Data cut submitted to NICE	Interim analysis – 30th April 2024

Study	AMPLIFY trial
Anticipated data cut after a period of managed access	Anticipated [REDACTED] – but subject to change and event-driven

^a As outlined in the Company Submission (Section 1.1), AstraZeneca is not seeking reimbursement for acalabrutinib with venetoclax and obinutuzumab (AVO). This is based on the feasibility of demonstrating cost-effectiveness as well as feedback from UK clinical experts who indicated that treatment with AV would be preferred over acalabrutinib with venetoclax and obinutuzumab (AVO) in the majority of patients, as the efficacy benefit associated with the addition of obinutuzumab does not outweigh the associated adverse event (AE) burden.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; OS: overall survival; PFS: progression-free survival.

Table 3: Overview of SACT dataset

Registry	Systemic Anti-Cancer Therapy (SACT)
Type of registry	Mandated dataset as part of the Health and Social Care Information Standards
Population	All patients who use systemic anti-cancer therapies across all NHS England trusts
Relevant data items collected	Baseline characteristics of patients receiving AV Survival data for patients receiving AV, VenI and VenO
Data analysis	The company will not have access to the NHS Digital patient data, but will receive de-personalised summary data
Governance	All necessary governance arrangements through SACT, and other datasets brought together by NHS Digital, have been established with NHS trusts and NHSE&I
Indicate if registry previously used within a NICE managed access	Yes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia

ID6232

Summary of Information for Patients (SIP)

September 2025

File name	Version	Contains confidential information	Date
ID6232_Acalabrutinib_NICE_SIP [NoCON]	Final	No	17 th September 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):

Generic name: Acalabrutinib with venetoclax (AV)

Brand name: Calquence® with Venclyxto®

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

In this submission, the medicine AV is being proposed as a treatment for adult patients with **untreated chronic lymphocytic leukaemia (CLL) without a 17p deletion (del[17p]) or TP53 mutation**. If patients do not have these del17(p) or TP53 mutations, this document will refer to them as having **non-high risk** CLL.

Terms highlighted in bold throughout this document are explained in the glossary found in **Section 4b**.

CLL is a blood cancer (**leukaemia**) that affects **white blood cells**. White blood cells are a type of blood cell that help the body to fight infections.¹ In patients with CLL, these blood cells have abnormalities that make them multiply uncontrollably. This leads to a build-up of abnormal cells in the **bone marrow** (the production centre of most blood cells), blood, **spleen** (an organ that filters blood and fights off infections) and **lymph nodes** (microbes filtered out of the blood are trapped here and killed by white blood cells).

Patients with CLL often do not experience any **symptoms** (noticeable changes that a patient can see or feel themselves) at first and are instead diagnosed when visiting the doctor for other reasons.² Patients do not always receive treatment when they are first informed that they have CLL. Instead, patients only receive treatment for CLL when they start developing symptoms.²

CLL generally gets worse over time. Some patients have genetic changes that make their disease grow and spread faster. These changes include del17(p) or *TP53* mutations. When this happens, doctors call the disease **high-risk**.^{1, 3}

Depending on whether patients have received treatment for CLL before, their disease is classified as being either previously treated or untreated.

The target population for the medicine AV is adult patients with untreated non-high risk CLL.

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.

Acalabrutinib's current **marketing authorisation** (approval for use) covers its use:

- As **monotherapy** (given on its own) for the treatment of CLL in:⁴
 - Patients with untreated CLL
 - Patients with previously treated CLL
- Or in combination with venetoclax for the treatment of adult patients with untreated CLL⁴

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:

AstraZeneca UK Ltd engages with the following patient advocacy groups in haematology, with the aims of improving patient insights and responding to requests for information: Blood Cancer UK, Lymphoma Action, CLL Support, and Leukaemia Care.

Funding provided to United Kingdom (UK) patient groups is published annually on AstraZeneca's website: <https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups>.

SECTION 2: Current landscape

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.

AV is anticipated to be used for the treatment of untreated non-high risk CLL

What is CLL?

CLL is a type of leukaemia. It affects white blood cells called '**B-lymphocytes**'.¹ These types of white blood cell help the body to fight infections. **B-lymphocytes** are produced in the bone marrow, which is the soft tissue inside of bones. **B-lymphocytes** are then released into the blood stream to travel to other parts of the body. In CLL, B-lymphocytes have changes in their genes. These changes cause the cells to multiply too much and can lead to a build-up of these

abnormal cells.¹ As a result, there is less space for other healthy B-lymphocytes and blood cells to develop. People with CLL often have fewer red blood cells (which carry oxygen around the body), which can lead to **anaemia**, and a weakened immune system which means it is more difficult for the body to fight infections.

CLL often develops slowly, and patients can live for months or years with the disease before developing symptoms. However, each patient with CLL has a different experience. This can be because of changes in a patient's genes, enlargement of their lymph nodes or spleen, the presence of other health conditions and the **clinical staging** of the disease (see **Section 2b**).⁵ For example, in patients with CLL who have abnormalities in their *TP53* gene, the disease often grows and spreads more quickly. As a result, these patients get sicker more quickly.

The population of interest in this submission is patients with untreated non-high risk CLL. Non-high risk disease means there are no *TP53* abnormalities, as described in **Section 1b**.

What are the signs and symptoms of CLL?

CLL usually grows slowly, so most patients with CLL may not experience any symptoms. Doctors often find the disease when looking for other problems.² For patients who do experience symptoms, these may include losing weight without trying, fever, night sweats, significant fatigue (feeling tired) and getting sick often with infections like colds and flu.⁵ Doctors may also see that the patient has other symptoms, like anaemia, or that the liver, spleen and lymph nodes are bigger than usual.

How many people are affected by CLL in the UK?

CLL is the most common type of adult leukaemia in the UK. One in four people with leukaemia have CLL.⁶ Each year, about 4,500 people are told they have CLL in the UK.⁷ Most patients do not have symptoms when they find out that they have CLL. Doctors may refer to this as **asymptomatic, early-stage** disease.^{2, 8} CLL can affect anyone, but there are some factors which make a person more likely to develop CLL. CLL is most common in people who are male, people who are 70 years of age or older, or people who have a close family member with the disease.

What is the impact of CLL on a patient's life (disease burden)?

CLL can impact a patient's **quality of life**, which is a measure of a person's wellbeing. This happens due to the unpleasant symptoms caused by the disease, the **side effects** of treatment and the worries about the disease.

Impact of disease on quality of life

The symptoms of CLL can stop patients from going about their daily lives which affects their quality of life. For example, fatigue can make it difficult for patients to work and do their usual day-to-day tasks. Fatigue can get worse as the disease becomes more advanced.⁹ Stomach aches and dizziness caused by CLL can also make it difficult for patients to do their daily activities.¹⁰ This can stop patients spending time with their family and friends, making them feel more lonely. Patients with CLL also have a weakened immune system, which can make them more likely to get infections such as the flu or common cold.¹¹ Since patients with CLL are often older and may have other health conditions, CLL puts them at an even greater risk of developing serious infections. As a result, patients can often become isolated from family and friends to protect themselves from infection.¹²

CLL is a disease that cannot be cured, so there is a significant emotional impact.¹³ The knowledge that the disease can **relapse** (when patients become sick again) can cause a lot of stress and anxiety. In the UK, people with CLL often do not receive treatment until they start experiencing symptoms.¹⁴ This period of knowing that they have the disease but cannot have treatment can be stressful. Patients can sometimes feel that nothing is being done (see **Section 2d** for more details).¹⁵

People with CLL often need to go to the hospital to manage their symptoms, get tests or receive treatment. This can take time for many patients. If they are employed, patients may have to take time off work for these hospital visits. All of these factors can impact their quality of life.¹⁶

Patients with CLL often require full-time support from families and carers. This means caregivers may have to take time off work,¹⁶ or leave their jobs. This can impact the quality of life of patients' families and carers. One study that looked at the quality-of-life impact of CLL showed that family members caring for patients with CLL had a lower quality of life, compared with the general population.¹⁷

Impact of treatment

Current treatments for CLL have side effects which may affect patients' health and wellbeing. Sometimes, people have to stop their treatment because of these side effects (see **Section 3h** for more details).¹⁸ Some treatments need to be given by injection into a vein (called an **intravenous or IV injection**). Patients have to travel to hospital to receive these treatments, which can add to the overall impact of the disease for patients.¹⁹ Treatments given by IV injection may also lead to **infusion-related reactions** (side effects that can occur after receiving a treatment by IV injection).²⁰ If someone has an infusion-related reaction, they may have to stop treatment until they feel better.

CLL can have a greater impact on quality of life compared with other types of cancer because of the symptoms, side effects from treatment, and knowing that their disease cannot be cured.²¹

Life expectancy

CLL affects patients in different ways. For some patients, their condition will not have any impact on how long they live, while others will not live as long as people without CLL. On average:

- For every 20 patients diagnosed with CLL over the age of 60, about 19 patients are alive at five years
- For every 10 patients diagnosed with CLL over the age of 80, about seven patients are alive at five years²²

What are the financial and societal costs of CLL?

CLL is linked with significant direct and indirect costs for healthcare systems and society. Direct costs include the cost of treatment and hospital care. Indirect costs include patients being less able to continue work. CLL therapies can cause side effects which require further treatments to help reduce their impact.²³

Since most patients with CLL are elderly, they rely on friends and family to support with medical care, such as going to doctors' appointments or for treatment. For caregivers and

patients of working age, this can mean taking time off work,¹⁶ which can reduce their income and have an economic impact on society.

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?

Diagnosis

CLL usually progresses slowly. Most patients find out they have the disease when visiting the doctor for other reasons and often do not have symptoms at that time.² To find out if a patient has CLL, a doctor may carry out tests, which include:⁵

- Checking the number of B-lymphocytes in a patient's blood sample
- Checking for changes in the appearance of a patient's B-lymphocytes
- Checking for the disease signs described in **Section 2a**

Clinical staging

When doctors confirm a patient has CLL, they may check how advanced the disease is. This is called 'staging' and can suggest how the disease might progress. CLL staging is normally done using one of two staging systems: the **Binet system** and the **Rai classification system**.⁵ Both systems divide CLL into three stages:

- The Binet system divides CLL into Stage A (which is low-risk), Stage B (which is intermediate-risk) and Stage C (which is high-risk disease)⁵
- The Rai system divides CLL as being low-risk (often referred to as Stage 0), intermediate-risk (often referred to as Stage I or Stage II) or high-risk (often referred to as Stage III or Stage IV)⁵

Most doctors in the UK and Europe use the Binet system. Most doctors in the United States use the Rai classification system. These disease staging systems help doctors to decide the best treatment and predict how the disease might progress.

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.

Although CLL cannot be cured, it can be well managed with treatment. Most CLL treatments work by either destroying the cancer cells or stopping them from multiplying to produce more cells.

Watch and Wait

In the UK, patients with CLL who do not have any symptoms will typically not receive treatment until they start showing signs of their disease getting worse.¹⁴ This approach to treatment is known as 'Watch and Wait.' It has been shown to be an effective way of managing CLL in patients whose disease is still at an early stage.²⁴⁻²⁶

Choosing the most suitable treatment

The current treatment options for CLL can be split into two types of **regimen** based on how long the treatment course lasts. They can either be **fixed-duration** regimens (where patients receive treatment for a set amount of time) or **treat-to-progression** regimens (where patients receive treatment until they experience **disease progression** [their illness gets worse] or the side effects of treatment become too severe). Doctors will choose a fixed-duration or treat-to-progression treatment option based on a patient's age, whether a patient has any genetic abnormalities, and whether a patient has any other health conditions.

In the past, fixed-duration treatment options mainly included **chemoimmunotherapy**. These regimens combine **chemotherapy** (drugs that kill or slow down the growth of cancer cells) with **immunotherapy** (drugs that help a patient's immune system to identify and destroy abnormal B cells). More recently, newer treatments known as **targeted therapies** (treatments which specifically target B-lymphocytes), such as venetoclax with ibrutinib (VenI) and venetoclax with obinutuzumab (VenO), have been developed. Targeted therapies are now used instead of chemoimmunotherapy regimens as they are better at controlling disease and have fewer severe side effects.²⁷

Like VenI and VenO, AV is a fixed-duration, targeted therapy. It is expected that AV will be an alternative treatment option to VenI and VenO for patients with untreated non-high risk CLL (see blue box below for more information about VenI and VenO).

VenI

- VenI is a combination of two treatments, venetoclax and ibrutinib, which are given orally. It is therefore known as an **all-oral** combination
 - Venetoclax is a drug which stops abnormal B cells from surviving and multiplying. It blocks a **protein** called **BCL2**, which is found in B-lymphocytes, and is known as a **BCL2 inhibitor**²⁸
 - Ibrutinib is another drug that stops the survival and multiplication of abnormal B-lymphocytes, however it does this by blocking another protein called **bruton tyrosine kinase** (BTK). Ibrutinib is referred to as a **first-generation BTK inhibitor** (BTK), meaning that it was one of the earlier drugs developed to target BTK²⁹

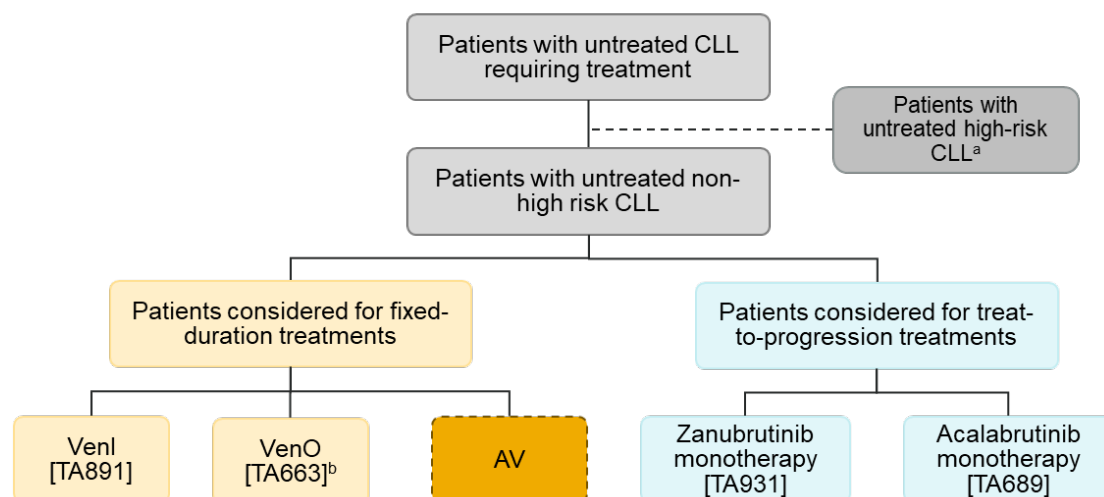
VenO

- VenO is a combination treatment of venetoclax (which is given as a tablet) and obinutuzumab (which is given as an IV injection)
 - Obinutuzumab is an **antibody** that interacts with a protein called **CD20**, found on the surface of B-lymphocytes, to help the immune system find and destroy cancerous B-lymphocytes³⁰

Figure 1 illustrates the treatments currently used for untreated non-high risk CLL in the UK and shows where AV would be offered as a treatment option. Since zanubrutinib monotherapy and acalabrutinib monotherapy (shown below in Figure 1) are treat-to-progression regimens, AV is

not expected to displace the use of these treatments. Therefore, they are not considered relevant in this submission.

Figure 1: Pathway showing the available treatments for patients with untreated non-high risk CLL in the UK, and the position where AV would be offered



Abbreviations: AV: acalabrutinib with venetoclax; CLL: chronic lymphocytic leukaemia; UK: United Kingdom; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

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 from a patient perspective

CLL has a significant physical, mental and emotional burden for patients living with the disease and the people who care for them. The fatigue experienced by patients with CLL often means that they cannot work or perform day-to-day activities.⁵ In patient interviews conducted in 2022 as part of the **NICE** evaluation for VenI, one patient said, "I felt so tired all the time – all my energy was going into work. I had to have some energy for my family, so I stopped working."¹⁹ Furthermore, during the NICE evaluation of ibrutinib monotherapy, which is a treatment given to patients with high risk CLL (i.e., patients who have *TP53* abnormalities), patient experts described how the uncertainty of living with CLL can greatly affect patients' quality of life and wellbeing. This is because CLL forces patients to isolate themselves from family and friends to protect themselves from getting an infection.¹²

In the UK, patients who do not have symptoms are often put on 'Watch and Wait' (see **Section 2a**). This means doctors wait before starting treatment.¹⁴ About 13,300 patients with CLL are

on 'Watch and Wait' in the UK.³¹ Although this has been shown to be an effective CLL management strategy,²⁴⁻²⁶ 'Watch and Wait' can still be stressful for those involved. Patients often feel that 'nothing is being done'.¹⁵ In the UK, one in two patients on 'Watch and Wait' say they feel anxious. One in ten people say they feel depressed all the time.³¹ This mental health burden is often made worse for patients because they know that CLL cannot be cured, and the disease may return even after treatment.¹³

Patients have also expressed preference for treatments that are easier to receive and do not require going to the hospital. In 2022 interviews conducted for the NICE evaluation for Venl, one patient said, "it's inconvenient to go to hospital, to drive there and pay for parking... not having these trips to hospital is just easier on the mind".¹⁹ This shows that patients want to have less hospital visits, as these can cause anxiety and disruption to their lives. Hospital visits are also costly and difficult to organise.

CLL from a carer perspective

Due to the physical impact of CLL, family members often play an important role in caring for patients. This can be very stressful, as they may need to miss work to support patients with disease management and hospital visits.^{16, 19} In a patient interview that was conducted during the NICE evaluation for ibrutinib monotherapy, they said, "My wife worries so much about what might happen next, she doesn't say anything to me but she tells our children who then worry too."¹⁵ This highlights the far-reaching impact that CLL can have for not just patients, but also their carers and families.

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.

The new treatment being considered in this submission is AV, a combination of acalabrutinib with venetoclax.

Acalabrutinib

Acalabrutinib is a second-generation (i.e., newer) BTK inhibitor that works like ibrutinib. For more information on how BTK inhibitors (e.g., ibrutinib and acalabrutinib) work, see **Section 2c**. Acalabrutinib monotherapy (on its own, rather than in combination with another treatment) is already used to treat CLL in some patients (see **Section 1c** for more details).³²

Venetoclax

For more details about how venetoclax works, see **Section 2c**. Venetoclax, either monotherapy or in combination with other drugs, is already used to treat CLL in some patients.³²

AV

AV is a combination of acalabrutinib and venetoclax. Both medicines are given as tablets that patients can take at home without going to the hospital. Acalabrutinib and venetoclax work together in two different ways to kill the cancer cells. Acalabrutinib slows down the multiplication of CLL cells, while venetoclax causes them to destroy themselves. These different but complementary mechanisms make AV more effective at killing CLL cells compared with other treatments.³³

3b) Combinations with other medicines

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

- 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.

The treatment of interest in this submission is AV (acalabrutinib in combination with venetoclax). AV is not intended to be used with any other CLL treatments in this patient population.

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?

Acalabrutinib

- Acalabrutinib is available as a 100 mg film-coated tablet, which is taken orally.⁴ Patients should take one tablet (100 mg) twice a day, and each tablet should be taken about 12 hours apart. Acalabrutinib is taken every day of the 28-day **treatment cycle**⁴
- Acalabrutinib should be taken for a total of 14 treatment cycles⁴

Venetoclax

- Venetoclax is available as a 10 mg, 50 mg and 100 mg film-coated tablet, which is taken orally. Patients should start taking venetoclax 20 mg once daily at the start of treatment cycle 3 with a 5-week gradual increase in dosage to reach a dose of 400 mg by Day 1 of treatment cycle 4 (20 mg, 50 mg, 100 mg, 200 mg, 400 mg)⁴
- Patients should continue to take venetoclax 400 mg until the end of treatment cycle 14⁴

What is a treatment cycle?

Many cancer treatments are given in cycles. Each cycle is usually split into a period where patients receive a treatment, followed by a period where the treatment is stopped to allow their body to recover. The length of a treatment cycle, and the duration of time spent taking treatment within each cycle can be different based on the type of treatment being given. One complete treatment cycle with acalabrutinib and venetoclax lasts 28 days.

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.

AMPLIFY trial details

The **AMPLIFY** trial is the key **clinical trial** testing the **efficacy** (how well a treatment works) of AV in patients with untreated non-high risk CLL.

AMPLIFY is an **ongoing, Phase III, randomised, multicentre, open-label** clinical trial, which compared AV with chemoimmunotherapy.³⁴ This means that the AMPLIFY trial is still happening (ongoing), includes patients across many clinical trial centres and regions (multicentre), and that patients taking part in the trial were randomly assigned to receive either AV or chemoimmunotherapy (randomised). As an open-label study, patients know which treatment they are receiving. In general, the aim of Phase III trials is to compare the efficacy and safety of a new treatment with another treatment that is already available. In AMPLIFY, the efficacy and safety of AV is being compared with chemoimmunotherapy.

Although chemoimmunotherapy is not a standard treatment for CLL in the UK now (see **Section 2c**), it was still often used when the AMPLIFY trial was designed. This is why chemoimmunotherapy was chosen as the most appropriate treatment to compare AV to in the AMPLIFY trial.

Further details in the AMPLIFY trial can found here:

- <https://clinicaltrials.gov/study/NCT05197192>

Inclusion criteria

Patients who fulfilled the following criteria were able to take part in AMPLIFY:³⁴

- Men and women aged 18 years or older
- Patients must have a diagnosis of non-high risk CLL (see **Section 2b**)
- Patients' CLL must be symptomatic and requiring treatment (see **Section 2a**)
- Patients must not have received any prior CLL treatment

Outcomes being assessed in AMPLIFY

The main outcome that was being assessed in the AMPLIFY trial was **progression-free survival** (PFS).³⁴ PFS is the length of time from the start of treatment until patients experience signs of their disease getting worse (progression). In the AMPLIFY trial, this was measured by

a group of medical experts who were not involved in the study and did not know which treatment each patient received.

The AMPLIFY trial also measured other outcomes, including

- **Overall survival (OS):** The length of time patients lived after starting treatment
- Quality of life
- Safety: How many side effects there were and how severe they were for patients

Since the AMPLIFY trial is still ongoing, an **interim analysis** was done based on the data available up until 30th April 2024, instead of waiting until the very end of the study. The results for the outcomes from AMPLIFY at this interim analysis are presented in **Section 3e**, **Section 3f** and **Section 3g**.

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.

Results from the AMPLIFY trial

As discussed in **Section 3d**, the AMPLIFY trial compared the efficacy of AV and chemoimmunotherapy in patients with non-high risk CLL. Key results from the trial are presented below. For more details about the other outcomes that were tested in the AMPLIFY trial, see **Section 2.6** of the **Company Evidence Submission**.

PFS

At 36 months after starting treatment, more patients taking chemoimmunotherapy experienced disease progression (had their disease get worse) when compared with patients taking AV.³⁴ Patients receiving AV were one-third less likely to have their disease get worse, compared with patients receiving chemoimmunotherapy during the study.³⁴ The reduced risk of disease progression was **statistically significant** and **clinically meaningful**. **Statistically significant** means that these results are most likely to be because of the treatment and are unlikely to have been due to chance. **Clinically meaningful** means that these results are impactful for patients.

OS

At 36 months after starting treatment, more patients taking AV were alive when compared with patients receiving chemoimmunotherapy.³⁴ Patients taking AV were two-thirds less likely to die during the study compared with those on chemoimmunotherapy.³⁴

Overall, the results of the AMPLIFY trial show that patients receiving AV are likely to live longer than those receiving chemoimmunotherapy, and their disease is less likely to progress.

Comparing AV with VenI and VenO

The AMPLIFY trial did not compare AV with VenI or VenO, the other relevant treatments in this submission (see **Section 2c**). As a result, a type of statistical analysis called a **simulated treatment comparison** (STC) was conducted. This type of analysis matches the patient populations from the trials for AV, VenI and VenO to make a fairer comparison between the treatments.

The results from the STC comparing AV with VenI and VenO showed that there were no statistically significant differences in the efficacy of AV, VenI and VenO in terms of both PFS and OS. This means that, based on the data available, we cannot confidently say that VenI or VenO are more effective than AV and vice versa. Instead, it is likely that any differences which might be seen between AV and VenI and VenO are random or due to chance.

In addition to the STC, a second statistical analysis known as a Bucher indirect treatment comparison or ITC was conducted to compare the efficacy of AV and VenO. Similar to the STC, this analysis showed that there was no statistically significant difference between AV and VenO in terms of PFS. However, unlike the STC, the Bucher ITC showed that AV led to a statistically significant improvement in OS compared with VenO, meaning that patients taking AV had a lower risk of dying than patients taking VenO.

Overall, we can conclude that AV is the same as VenI and VenO when looking at the impact they have on PFS and OS.

To confirm the results of the STC, the Company asked a group of UK doctors multiple rounds of questions about how safe and effective AV is compared with VenI and VenO. This process is called a **Delphi panel**. The aim is to complete several rounds of questions until experts can agree on the answer to these questions. In this Delphi panel, the experts agreed in the first round that AV was similar to VenO and VenI in terms of both PFS and OS. The results of the Delphi panel are therefore in line with the results of the STC described above. Doctors also agreed that AV is generally easier for patients to tolerate than VenI.

Overall, based on the evidence from the AMPLIFY trial and the Delphi panel, we can say that AV, VenI and VenO are the same when looking at the impact they have on PFS and OS. When considering safety, AV can be considered a suitable alternative to VenO and has a more favourable safety profile than VenI.

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.

Quality of life was measured at different timepoints in the AMPLIFY trial using several questionnaires about patient wellbeing.

The results show that both AV and chemoimmunotherapy improved quality of life compared with the start of treatment (known as 'baseline'). However, the improvement in quality of life was generally larger in patients taking AV compared with patients taking

chemoimmunotherapy. This is likely due to fewer serious side effects with AV than chemoimmunotherapy.

Overall, the results show that AV reduced disease progression and improved survival compared with chemoimmunotherapy, as described in **Section 2e**, as well as improved patient wellbeing.

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.

Each medicine has its own side effects. The same medicine can produce different reactions in different people.

In the AMPLIFY trial, the number of patients experiencing side effects in patients receiving AV was tested. These results showed AV to be well-tolerated among patients, with no new side effects seen with acalabrutinib or venetoclax. This means that the types of side effects, and the number of patients who had these side effects were similar to what was expected.

Some of the side effects that patients most often said they had with acalabrutinib or venetoclax are:

Venetoclax:³⁵

- Diarrhoea
- Nausea or vomiting
- Constipation
- Tiredness
- Pneumonia

Acalabrutinib:³²

- Bleeding
- Infection
- Signs of heart rhythm problems, such as fast heart rate or missed heart beats
- Dizziness
- Chest discomfort or shortness of breath

Side effects of currently available CLL treatments

As discussed in **Section 2a**, some of the currently available treatments for CLL can cause unpleasant side effects. For example, ibrutinib (I in VenI) can lead to cardiac side effects (problems with the heart).¹⁸ Obinutuzumab (O in VenO) can cause infusion-related reactions and is associated with a risk of infection.²⁰ These side effects mean that some patients are

more likely to stop taking their treatment before the treatment course is finished. UK doctors that were interviewed by the Company between May and July 2025 have said they expect AV to be better tolerated by patients than VenI and VenO.

Managing side effects

A common side effect of venetoclax (V in AV, Ven in VenI and VenO) treatment is **tumour lysis syndrome** (TLS).³⁵ This can happen when cancer cells are destroyed too quickly and release their contents into the blood. The risk of TLS is higher in the first few days or weeks of treatment with venetoclax, as the dose is higher. To reduce the risk of TLS, patients should drink plenty of water and take certain medicines (allopurinol and rasburicase) that can help remove the harmful contents released by cancer cells that have been destroyed.

If patients taking AV, VenI or VenO have severe or intolerable side effects, their doctor may advise interrupting treatment until these side effects are resolved, or stopping treatment.

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 mentioned previously, currently available fixed-duration treatments for CLL can be associated with unpleasant side effects, such as cardiac side effects (ibrutinib) and infusion-related reactions (obinutuzumab). In addition, obinutuzumab (O in VenO) is administered via IV injection (injected into the vein) which means patients must travel to hospital to receive treatment. This can impact the daily lives of patients and carers, as they need to travel and potentially take time off work. AV addresses the current need for an easy-to-administer, well-tolerated and effective treatment, as it:



Provides a convenient way to receive treatment: Acalabrutinib and venetoclax are both given as tablets, which means that patients can take them at home without having to travel to the hospital



Extends life and delays disease getting worse:

- Results from the AMPLIFY trial showed that patients taking AV had a lower risk of their disease getting worse, and a lower risk of dying, compared with chemoimmunotherapy
- Results from an STC and Delphi panel showed that there was no statistically significant difference between AV, VenI and VenO, in terms of PFS and OS. This is also supported by the results from the Bucher ITC which showed that AV was comparable to VenO in terms of PFS and better in terms of OS



Is associated with tolerable side effects: AV is associated with fewer unpleasant side effects than VenI and VenO. During interviews held between May and July 2025, UK doctors indicated that AV would be better tolerated than VenI and VenO

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

In the AMPLIFY trial, AV was shown to be well-tolerated and effective in patients with untreated non-high risk CLL. As with all treatments, AV is associated with some common side effects, as described in **Section 3g**. However, these side effects can be managed with support from doctors. Most patients do not need to stop treatment because of them.

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.

Introduction for patients

An **economic model** was developed to reflect the key features of the CLL pathway in the UK and assess whether AV is a good use of NHS resources (i.e., **cost-effective**). The model compared the effectiveness, costs and impact on quality of life of AV with Venl and VenO – the fixed-duration treatments currently available to patients in the UK.

How the model reflects the condition

A **state-transition model** was selected as the most appropriate type of model to assess the cost-effectiveness of AV. A state-transition model divides a patient's journey into different **health states**. These states represent the different stages of disease that a patient with CLL might go through. For example, it includes periods of time which patients are likely to experience in real life, such as:

- A patient's disease is stable (not getting worse)
- A patient's disease gets worse after it had started to improve
- A patient's disease continues to get worse until they die

Each health state is assigned a specific quality of life value, reflective of the patient's well-being at each point in their treatment journey.

Patients 'enter' the model and are assumed to receive an initial treatment. The benefits and costs associated with treatment are added for either AV, VenI or VenO. After patients start treatment, they can move into other health states in the economic model, either to reflect their disease getting worse or to reflect them dying. If a patient has disease progression in the model, they are assumed to start taking a second treatment (called a **subsequent treatment**) that is usually different to the initial one they had been receiving. The benefits and costs of this second treatment are also added.

In summary, the economic model is designed to show the different stages of CLL, and the costs and benefits patients with CLL might experience in each of these stages. This information helps us to understand how cost-effective AV is, compared with VenI and VenO.

Modelling the effectiveness and safety of AV, VenI and VenO

Results from the AMPLIFY trial were used in the economic model, including how long patients survived without their disease getting worse and how long it takes for patients to progress. The results from another clinical trial, called the **ASCEND trial**,³⁶ were used to estimate how long patients survive after their disease progressed. The AMPLIFY trial is still ongoing so very few patients have progressed and died so far. This means that, if data from the AMPLIFY trial were used, the economic model would not have enough data to make accurate suggestions regarding cost-effectiveness. Results from the ASCEND trial were used as the trial has been going on for longer than AMPLIFY, so there is more time for patients to progress and die, and therefore more data to use in the economic model. More details on the ASCEND trial are available here:

- <https://clinicaltrials.gov/study/NCT02970318>

In the economic model, VenI and VenO were assumed to have the same effectiveness as AV. This was based on the results of the STC and Delphi panel, as discussed in **Section 3e**.

To estimate how safe each treatment was, information relating to side effects experienced by patients in the AMPLIFY trial, as well as clinical trials which investigated VenI and VenO, were included in the economic model. Specifically, the proportion of patients who experienced different side effects following treatment were used. The trial used to show how safe VenI was called GLOW and the trial for VenO was called CLL14. More details on these trials are available here:

- **GLOW:** <https://clinicaltrials.gov/study/NCT03462719>
- **CLL14:** <https://clinicaltrials.gov/study/NCT02242942>

In summary, results from different clinical trials were used in the economic model to predict how long patients would survive, with or without their disease getting worse. In addition, results from different clinical trials were used to estimate the side effects patients would experience while receiving AV, VenI or VenO.

Modelling the impact of AV, VenI and VenO on quality of life

A change in quality of life was modelled based on which health state in the economic model patients were in, and whether or not they were receiving treatment. This is because the physical, mental and emotional impact of CLL often increases if a patient's disease progresses. The quality of life data used in the model came from the AMPLIFY trial as well as another study which looked at how individuals value quality of life in the UK.³⁷

Modelling how the costs of AV differ from VenI and VenO

The costs included in the economic model were:

- Costs of the medicines and how much it costs to give them to patients
- Costs of subsequent treatment: this included the cost of treatments patients may receive if their disease gets worse after their first CLL treatment
- Disease management costs: this included the cost of hospital visits and regular check-ups such as blood tests and scans
- The costs of managing side effects that patients experience while receiving treatment
- The costs incurred when a patient dies

Overall, various types of costs were included in the economic model to reflect how much of the NHS's resources are spent treating patients with CLL at the different stages of their disease.

Economic model results

AV was estimated to provide a greater health benefit, measured in **quality-adjusted life years** (QALYs), at a lower cost compared with VenI and VenO.

These cost-effectiveness results are an estimate based on a confidential discounted price for acalabrutinib. They do not account for any other potential confidential discounted prices that may be available for some drugs considered in the model.

Uncertainty

Several assumptions had to be made in the economic model. These assumptions are described in more detail in **Section 3.7** of the **Company Evidence Submission**. Several inputs in the economic model were also varied to assess their impact on the cost-effectiveness of AV. Further details are provided in **Section 3.11** of the **Company Evidence Submission**.

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)

Although current fixed-duration treatment options for CLL (VenI and VenO) are effective, they can be associated with challenging side effects, such as cardiac side effects, infection risk and infusion-related side effects (see **Section 3g**).^{18, 20} In addition, obinutuzumab (O in VenO) is administered via an IV injection, which means patients need to travel to the hospital to receive treatment. This can further increase the impact of CLL on patients' lives and the NHS. The availability of more treatment options for CLL which are well-tolerated and easy-to-administer, such as AV, would improve the lives of patients with CLL.

Acalabrutinib and venetoclax work together to destroy CLL cells by targeting two different proteins (see [Section 3a](#)).^{38, 39} If recommended, AV would be the second fixed-duration, all-oral treatment available for patients with non-high risk CLL in the UK, after VenI. However, compared with ibrutinib (I in VenI), acalabrutinib is better tolerated and more suitable for patients with cardiac conditions.^{18, 40} Additionally, as an all-oral treatment, AV does not have the same challenges as those associated with obinutuzumab (O in VenO), which patients must receive via an injection.

The results of the AMPLIFY trial have shown that AV is an effective, well-tolerated treatment, which leads to an improvement in the quality of life of patients compared with when they started treatment (see [Section 3e](#), [Section 3f](#) and [Section 3g](#)).

Benefits not captured in the economic model

AV treatment offers some further benefits that are not captured by the economic model.

Since AV is an all-oral combination, patients do not have to receive injections. This means they are not at risk of developing infusion-related reactions and do not have to visit the hospital as often as patients receiving IV-administered treatment. Switching from an IV to an all-oral treatment can also lead to a reduction in the overall time spent in hospital, which means less disruption to daily lives of patients, and can also release time of NHS staff to help other patients. Not having to visit the hospital as frequently can help patients return to work or resume their usual activities more quickly. It also means fewer NHS resources need to be used to give treatments to patients with CLL. This positive impact of an all-oral treatment option for patients was not fully captured in the model. Additionally, an all-oral treatment would improve the lives of carers as they do not need to spend as much time taking patients to hospital.⁴¹ This benefit for carers was not captured in the model at all.

As discussed in [Section 3g](#), patients receiving AV are likely to experience fewer side effects, which have a negative impact on their quality of life, than patients receiving VenI or VenO.^{18, 42-45} Although this benefit was included in model, its impact on patients' quality of life was not as significant as indicated by feedback from UK clinical experts interviewed by AstraZeneca between April and July 2025. This might suggest that the model was unable to fully capture the benefit of a reduction in side effects on the quality of life for patients receiving AV.

3I) 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](#)

No equality issues related to the use of AV are anticipated in this indication.

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:

- Cancer Research UK: <https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll>
- Macmillan Cancer Support: <https://www.macmillan.org.uk/cancer-information-and-support/leukaemia/chronic-lymphocytic-leukaemia-cll>
- Blood cancer UK: <https://bloodcancer.org.uk/understanding-blood-cancer/leukaemia/chronic-lymphocytic-leukaemia-cll/>

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

This glossary explains the terms highlighted in bold blue text throughout this summary of information for patients.

Term	Definition
17p deletion	A genetic abnormality where part of chromosome number 17 is missing. Chromosomes are the structures where genes are found.
All-oral	A combination therapy made up of medications which are administered orally.
AMPLIFY trial	The key clinical trial that compared the effectiveness and safety of AV with chemoimmunotherapy in patients with untreated non-high risk CLL.

Anaemia	A condition where a person has too few red blood cells, causing tiredness or weakness.
Antibody	A protein made by the body to fight infections or cancer cells.
ASCEND trial	A clinical trial that investigated the effectiveness and safety of acalabrutinib as a subsequent treatment in patients with CLL.
Asymptomatic	Having CLL but not showing any symptoms.
BCL2	A protein that stops cells from dying. In CLL, this protein is produced in high quantities, making them survive for longer and harder to kill.
BCL2 inhibitor	A medicine that blocks the BCL2 protein to help destroy CLL cells.
Binet system	A system that assesses how advanced CLL is based on the severity of the symptoms and signs. This system is mostly used in Europe.
B-lymphocytes	A type of white blood cell responsible for fighting infections. B-lymphocytes are the main type of cell affected in CLL.
Bone marrow	The soft tissue inside bones where blood cells are made.
Bruton tyrosine kinase	A protein that helps B-lymphocytes grow and survive.
BTK inhibitor	A medicine that blocks Bruton tyrosine kinase.
CD20	A protein found on B-lymphocytes. It can be targeted by CLL treatments to kill cancer cells.
Chemoimmunotherapy	A combination of chemotherapy and immunotherapy.
Chemotherapy	Medicines that kill fast-growing cells, including CLL cells.
Chronic lymphocytic leukaemia	A slow-growing blood cancer where abnormal B-lymphocytes build up in the blood and bone marrow.
Clinical staging	The process of determining how advanced a cancer is.
Clinical trial	A study where new treatments are tested for safety and effectiveness.
Clinically meaningful	Observed changes due to treatment that make a real, noticeable difference to a patient's health or daily life.
Cost-effective	A treatment that offers clinical benefit at a reasonable price compared with other available treatments.
Delphi panel	A method of collecting opinions from a group of experts by asking several rounds of questions, sharing the results, and repeating until the experts agree on an answer.
Disease course	The way a disease is going to progress and change over time.
Disease progression	This happens when a disease becomes more advanced.
Early-stage disease	Cancer that has not spread far or caused many symptoms.
Economic model	A tool researchers use to estimate the cost-effectiveness of a treatment.
Efficacy	How well a treatment works to improve an individual's condition or symptoms.
First-generation BTK inhibitor	One of the earlier drugs developed to inhibit BTK.
Fixed-duration treatment regimen	A treatment that is given for a specific, limited period of time.

Genetic abnormality	A change in the genes of cells that can cause disease or affect how a disease behaves.
Health state	Health states represent the different health conditions that a patient can exist in.
High risk	Patients with CLL who have an abnormality in their <i>TP53</i> gene.
Immunotherapy	Treatment that helps the body's immune system find and destroy cancer cells.
Infusion-related reactions	Side effects that happen during or soon after receiving medicine through a drip (IV).
Interim analysis	A type of analysis where results from an ongoing clinical trial are investigated before the trial is completed.
Intravenous injection	A way to give medicine directly into a vein using a small needle.
Leukaemia	A type of cancer that affects blood cells.
Lymph nodes	Small glands that are part of the immune system. These glands trap microbes filtered out of the blood, so that they can be destroyed by white blood cells.
Marketing authorisation	The approval given to a medicine, allowing it to be prescribed to patients in a particular country.
Monotherapy	A type of treatment regimen that consists of a single drug.
Multicentre clinical trial	A clinical trial carried out at several different hospitals or clinics.
NICE	An organisation in the UK that reviews and decides which treatments should be used in the NHS.
Non-high risk CLL	Patients with CLL who do not have an abnormality in their <i>TP53</i> gene.
Ongoing clinical trial	A clinical trial that is still running and has not ended yet.
Open-label clinical trial	A clinical trial where both doctors and patients know which treatment is being given.
Overall survival	The length of time patients are alive for after starting treatment.
Phase III clinical trial	A clinical trial that aims to compare the efficacy and safety of a new treatment with the currently available treatment options.
Progression-free survival	The length of time following the start of treatment until patients experience signs of worsening disease (progression).
Protein	An essential substance made and used by the body as a building block.
Quality of life	A measure of a person's well-being.
Quality-adjusted life years	A way to measure both how long and how well a patient lives for.
Rai classification system	A system that assesses how advanced CLL is based on the severity of the symptoms and signs. This system is mostly used in America.
Randomised clinical trial	When the treatment choice for patients taking part in a clinical trial is decided randomly.
Red blood cells	Cells that carry oxygen around the body.
Regimen	A planned schedule for how and when to take the drugs a patient has been prescribed.

Relapse	When a cancer comes back again after a patient has finished their treatment and got better.
Side effects	Unwanted, and often unpleasant, effects caused by treatment.
Signs	Things a doctors can see or measure to help him diagnose a patient's disease.
Simulated treatment comparison	A statistical method that indirectly compares two treatments by using data from separate clinical trials. In order to have a fair comparison, simulated treatment comparisons balance patient characteristics from the different clinical trials first.
Spleen	An organ that filters blood and fights off infections.
State-transition model	A type of economic model where patients move between health states over time based on the effectiveness of the treatment being investigated.
Statistically significant	The observed changes are because of treatment and are unlikely to have been due to chance.
Subsequent treatment	Additional treatment that is given to patients after they have experienced disease progression.
Symptoms	Noticeable changes that a patient can see or feel themselves.
Targeted therapy	Treatments which specifically target the cells affected by a disease.
TP53 mutation	A change in the <i>TP53</i> gene.
Treatment cycle	A repeated schedule of taking medicine for a set period of time, followed by a break, and then starting again, as part of a treatment plan.
Treat-to-progression regimen	A treatment regimen where patients receive treatment until the side effects become too severe, or they experience disease progression.
Tumour lysis syndrome	A serious problem that can happen if cancer cells are destroyed too quickly, releasing too much body salts into the blood.
Untreated	When patients have a disease but have not received treatment for it before.
White blood cells	A type of cell that is responsible for fighting infections.

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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Clarification questions

October 2025

File name	Version	Contains confidential information	Date
ID6232 acalabrutinib EAG Clarification Questions [CON]	Final	Yes	24 th October 2025

Section A: Clarification on effectiveness data

A1. Please confirm the total number of UK patients included in the AMPLIFY trial, and specifically the A+Ven and FCR/BR arms.

The AMPLIFY trial was conducted at [REDACTED] study sites across the UK, with [REDACTED] UK patients in the full analysis set (FAS). In the acalabrutinib with venetoclax (AV) and fludarabine with cyclophosphamide and rituximab/bendamustine with rituximab (FCR/BR) arms, [REDACTED]% ([REDACTED]) and [REDACTED]% ([REDACTED]) of patients were enrolled in the UK, respectively.¹

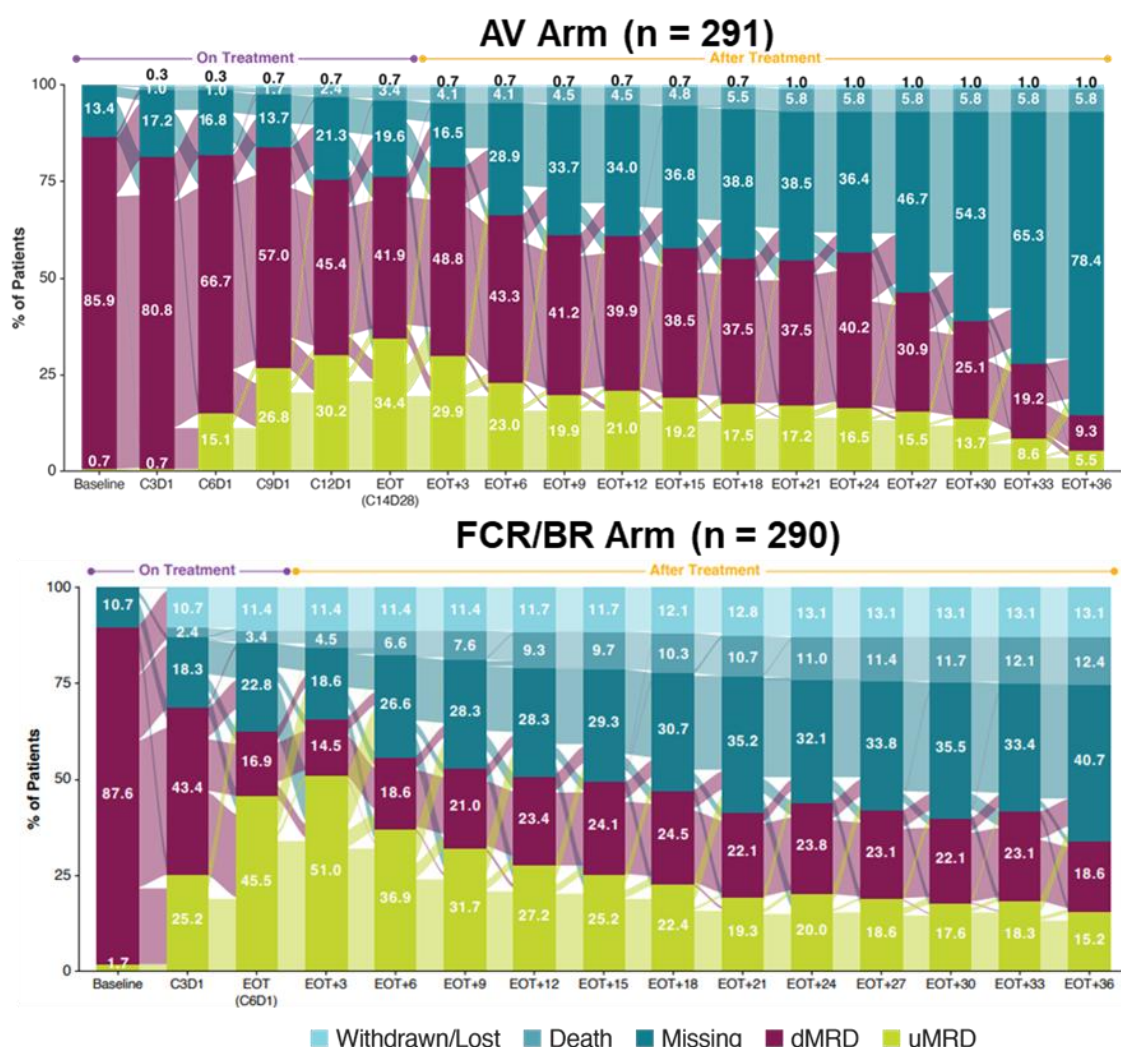
A2. Please provide the proportion of people who have MRD negativity at each point this was assessed across the trial follow-up, including a Kaplan-Meier plot showing duration of MRD negative status.

In the AMPLIFY trial, minimal residual disease (MRD) status was assessed in the peripheral blood and bone marrow using flow cytometry (cutoff $<10^{-4}$) and in peripheral blood by next-generation sequencing (ClonoSEQ assay; $<10^{-4}$, $<10^{-5}$, $<10^{-6}$).¹ Undetectable MRD (uMRD) was defined as <1 chronic lymphocytic leukaemia (CLL) cell per 10,000 (10^{-4}) leukocytes unless otherwise indicated.

Figure 1 presents the uMRD rates in peripheral blood over time by flow cytometry in each treatment arm (intent-to-treat [ITT] analysis set) of the AMPLIFY trial.² uMRD rates (peripheral blood by flow cytometry) at the end of therapy (EOT) and EOT + 12 weeks (EOT+3) were 34.4% and 29.9% for AV and 45.5% and 51.0% for FCR/BR. By EOT + 144 weeks (EOT+36), uMRD rates were 5.5% and 15.2% for AV and FCR/BR, respectively. Similar trends were observed in the MRD evaluable set for uMRD rates in the peripheral blood, and bone marrow, by flow cytometry.² Discussion of the association between uMRD and long-term progression-free survival (PFS) and overall survival (OS) outcomes for AV specifically is provided in response to Clarification Question A3.

Kaplan-Meier plots showing duration of MRD negative status are not available as the duration of uMRD was not an endpoint in the AMPLIFY trial.

Figure 1: uMRD rates in peripheral blood over time in evaluable patients by flow cytometry in each treatment arm



Abbreviations: AV: acalabrutinib with venetoclax; BR: bendamustine with rituximab; CXDX: Cycle X Day X; dMRD: detectable minimal residual disease; EOT: end of therapy; EOT + X: end of therapy + X months; FCR: fludarabine, cyclophosphamide and rituximab; uMRD: undetectable minimal residual.

Source: Ghia *et al.* 2025.²

A3. Please evaluate and report the association between MRD status and clinical outcomes, particularly OS and PFS events, in AMPLIFY.

The association between MRD status and long-term survival outcomes, specifically PFS and OS, in patients with untreated non-high risk CLL receiving treatment with AV is not known. Further follow-up of the AMPLIFY trial is needed to determine how well uMRD is sustained following treatment with AV specifically, and the predictive implications of uMRD status on long-term clinical outcomes.

MRD status has been previously suggested to correlate with long-term clinical outcomes, such as PFS and OS, following treatment with other therapies such as VenI and VenO untreated CLL, suggesting that uMRD status can serve as a predictor for long-term outcomes.³⁻⁵ However, this association has been found to be less clear for combination therapies with venetoclax and a bruton tyrosine kinase inhibitor (BTKi; such as VenI) than for combination therapies such as venetoclax and the anti-CD20 antibody, obinutuzumab.⁶ This highlights that the value of uMRD

status as a predictor of long-term outcomes can vary based on the treatment being considered. As such, it is not considered appropriate to extrapolate any association between MRD status and PFS or OS from VenI or VenO to AV as they are different treatment regimens; this was highlighted by UK clinical experts interviewed by the Company who emphasised that the relationship between uMRD status and long-term PFS/OS outcomes observed for VenI/VenO will not necessarily be observed for AV.⁷

In summary, the relationship between MRD status and long-term clinical outcomes for AV is unknown. Nevertheless, the available evidence from the AMPLIFY trial demonstrates a statistically significant PFS and OS benefit with AV versus FCR/BR, and the relatively low percentages of uMRD for patients receiving treatment with AV in AMPLIFY should not negate this observed benefit.⁶ MRD testing is not routinely conducted or funded by the NHS and,⁷ as confirmed by UK clinical experts interviewed by the Company and validated through the results of a Delphi panel conducted with over 22 UK clinical experts, MRD status is not considered a key outcome for driving treatment decisions in UK clinical practice.^{7, 8}

A4. Please confirm how many patients received IVIG from randomisation to the latest data cut-off.

At the interim analysis data cut-off (DCO; 30th April 2024), ■■■ patients in the AV arm and ■■■ patient in the FCR/BR arm received intravenous immunoglobulin (IVIG) in the AMPLIFY trial.¹

A5. Please provide details of SAEs captured post-progression.

The Company understands, following clarification from the EAG, that this question is to assess whether the serious adverse events (SAEs) presented in the Company Submission (CS; Section 2.11) were reported from both the pre- and post-progression periods and whether these SAEs included those observed whilst patients were receiving subsequent anti-cancer therapy.

As per Section 5.3.1 of the AMPLIFY clinical study protocol (CSP), all SAEs after the first dose of study drug until 30 days after the last dose of the last study drug or the start of a new anti-cancer therapy (whichever came first) were reported.⁹ This is referred to as the treatment-emergent period and a summary of treatment-emergent SAEs was presented in the CS, Section 2.11.2. As such, these treatment-emergent SAEs do not include any SAEs that started while patients were on subsequent anti-cancer therapy; however, they may include SAEs that occurred after progression if a patient experienced disease progression in the 30 days after the last dose of the last study drug.

Per the CSP, after the treatment-emergent period, SAEs that were believed to be related to prior treatment with the study drugs, or SAEs that could be relevant to the study regardless of their relationship to the study drugs (e.g. secondary primary malignancies), were reported. Such SAEs reported after the treatment-emergent period may be influenced by subsequent anti-cancer therapy. As such, these SAEs were not provided in the CS. The SAEs presented in Section 2.11.2 in the CS represent the SAEs observed in the AV and FCR/BR arms during the treatment-emergent period of the AMPLIFY trial before the initiation of subsequent anti-cancer therapy.⁹

A6. Please include Kaplan–Meier curves from AMPLIFY for PFS/OS stratified by MRD status.

PFS

PFS Kaplan-Meier curves stratified by MRD status from the AMPLIFY trial are presented in Figure 2. Relative PFS results for AV versus FCR/BR were consistent between patients with uMRD and those with detectable MRD (dMRD).¹⁰ Irrespective of MRD status, AV was associated with an improvement in PFS compared with FCR/BR, with a hazard ratio (HR) of 0.43 (95% confidence intervals [CIs]: 0.24, 0.76) in the uMRD subgroup and 0.44 (95% CIs: 0.28, 0.71) in the dMRD subgroup. This corresponds to a 57% reduction in the hazard of disease progression for AV versus FCR/BR in patients with uMRD and a 56% reduction in patients with dMRD.¹⁰

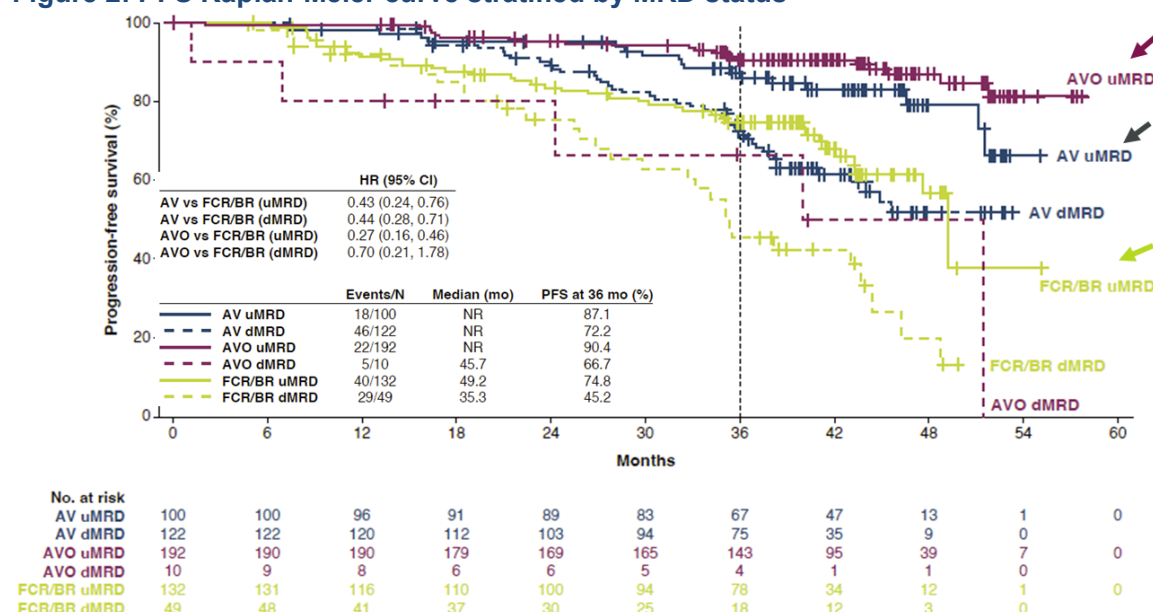
Across both the AV and FCR/BR arms, a higher proportion of patients with uMRD were progression-free at 36 months follow-up compared with those with dMRD (AV: 87.1% versus 72.2%, respectively; FCR/BR: 74.8% versus 45.2%, respectively). This suggests that achieving uMRD is associated with improved PFS prognosis, regardless of the treatment received.¹⁰ However, there are a relatively small number of events in each subgroup and these analyses were not statistically powered to detect differences between subgroups. As such, these results should be interpreted with caution.

OS

OS Kaplan-Meier curves stratified by MRD status from the AMPLIFY trial are presented in Figure 3. In line with the PFS results, relative OS results for AV versus FCR/BR were broadly consistent across MRD subgroups. Across both subgroups, AV was associated with an improvement in OS compared with FCR/BR, with an HR of [REDACTED] (95% CI: [REDACTED]) in the uMRD subgroup and [REDACTED] (95% CIs: [REDACTED]) in the dMRD subgroup. Variation in the point estimate and the wide CIs are likely due to the very low number of events in some of the subgroups (e.g., [REDACTED] for the uMRD AV subgroup; [REDACTED] for the dMRD FCR/BR subgroup). As such, these results should be interpreted with caution.

Overall, and as detailed in response to Clarification Question A3, MRD testing is not routinely conducted or funded by the NHS and, as confirmed by UK clinical experts interviewed by the Company and validated through the results of the Delphi panel conducted with over 22 UK clinical experts, MRD status is not considered a key outcome for driving treatment decisions in UK clinical practice (see Section 2.10.5 of the CS).^{7, 8}

Figure 2: PFS Kaplan-Meier curve stratified by MRD status^a

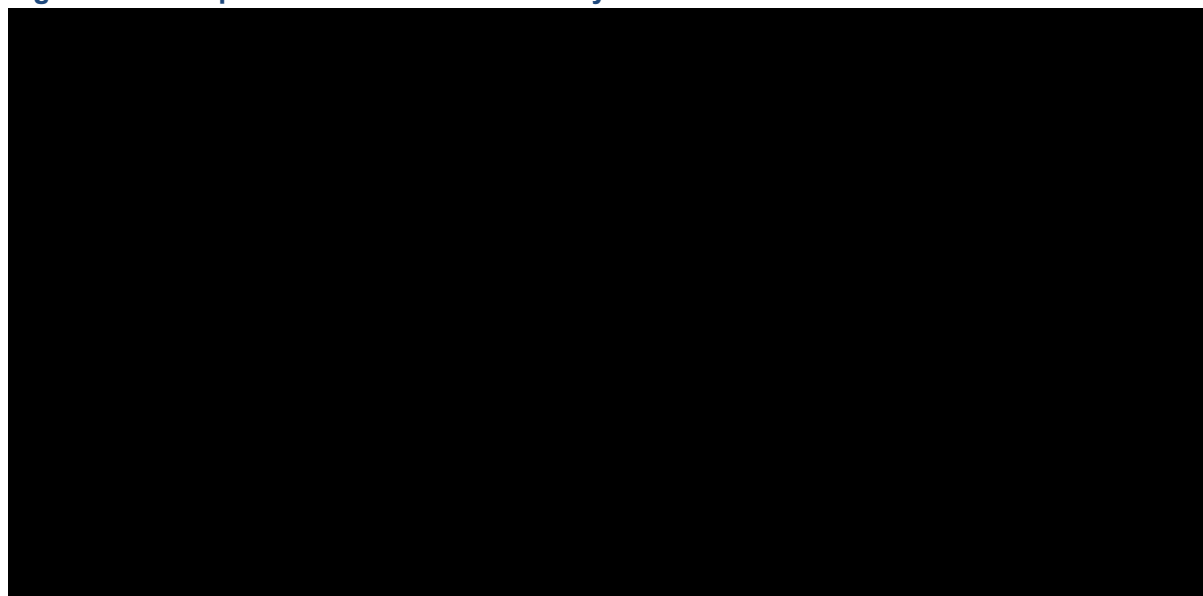


^aAs detailed in Section 1.1 of the CS, the Company is seeking reimbursement for AV only. As such, results presented for AVO here are not directly relevant to the decision problem of this submission.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BICR: Blinded Independent Central Review; BR: bendamustine with rituximab; CI: confidence interval; dMRD: detectable minimal residual disease; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; PFS: progression-free survival; uMRD: undetectable minimal residual disease.

Source: Ghia *et al.* (2025).¹⁰

Figure 3: OS Kaplan-Meier curve stratified by MRD status



^aAs detailed in Section 1.1 of the CS, the Company is seeking reimbursement for AV only. As such, results presented for AVO here are not directly relevant to the decision problem of this submission.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CI: confidence interval; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; OS: overall survival; uMRD: undetectable minimal residual disease.

Source: AstraZeneca Data on File.

A7. In relation to the CS, Figure 4:

- a) Please clarify the discrepancy in the AVO arm between the sum of safety population discontinuation reasons (59+1+5+4+2+2=73) and the 71 patients who discontinued any treatment.**

In Figure 4 of the CS (Section 2.3.4), reasons for treatment discontinuation were reported for each drug discontinued, so patients were counted a maximum of once per discontinuation reason and could have been counted under multiple discontinuation reasons. As such, if patients discontinued different components of a combination therapy regimen for different reasons, they would be counted under multiple different reasons for discontinuation.

- b) Please clarify the difference between discontinuations in the safety population and withdrawals in the ITT population across all arms.**

Definitions of study treatment discontinuation and study withdrawal based on the CSP (Section 4.6) are provided below.⁹

Discontinuation of study treatment: The investigator, in consultation with the medical monitor, may have withdrawn any patient from study treatment, if, in the investigator's opinion, it was not in the patient's best interest to continue. Any patient had the right to withdraw from the study at

any time. Discontinuation of study treatment, for any reason, should not have impacted on the patient's participation in the study. The patient continued attending subsequent study visits and data collection continued according to the study protocol.⁹

Withdrawal from study: Patients had the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator had the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may have included but were not limited to the following: patient's withdrawal of consent from study; study termination or site closure; patient lost to follow-up; death.⁹

The **ITT (FAS) population** comprised: All randomised patients regardless of the treatment actually received. Patients were analysed according to the arm to which they were randomised, following the 'intention-to-treat' principle. As of the DCO date of the interim analysis (30th April 2024), a total of 867 patients were included in the ITT (full analysis set [FAS]) population of AMPLIFY, comprising 291 patients in Arm A (AV), 286 patients in Arm B (acalabrutinib with venetoclax and obinutuzumab [AVO]) and 290 patients in Arm C (FCR/BR). Within the ITT (FAS) population, a total of 142 patients withdrew from the study (16.4%), of which 22 patients were in the AV arm, 41 patients were in the AVO arm, and 79 patients were in the FCR/BR arm.⁶

The **safety population** comprised: All randomised patients who received any amount of study drug. Safety data were summarised using the safety population, according to the actual treatment that a patient received. As of the DCO date of the interim analysis (30th April 2024), a total of 834 patients were included in the safety population, comprising 291 patients in Arm A (AV), 284 patients in Arm B (AVO) and 259 patients in Arm C (FCR/BR). Within the safety population, a total of 155 patients (18.6%) discontinued study treatment, of which 33 patients were in the AV arm, 71 were in the AVO arm and 51 were in the FCR/BR arm.⁶

c) Please clarify the discrepancy in the chemoimmunotherapy arm between the sum of safety population discontinuation reasons (30+3+12+3+6+1=55) and the figure of 51 patients who discontinued any treatment.

Please refer to the response to part a); patients could be counted multiple times under different reasons for treatment discontinuation.

d) Please clarify the discrepancy in the total deaths reported in the CSR (Table 22) and Figure 4 for both AVO and chemoimmunotherapy ITT populations (AVO: 37 vs 36; chemoimmunotherapy: 42 vs 40).

Table 22 of the clinical study report (CSR) reports the total number of deaths across all treatment arms of the AMPLIFY trial.¹ Figure 4 of the CS presents the reasons for withdrawal from the study; this includes death for some patients, but it does not represent a complete summary of deaths. Three patients withdrew from the AMPLIFY trial for a non-death reason and then died, but death data were allowed to be collected after study exit in certain circumstances. These patients are captured in the summary of deaths data (Table 22 of the CSR), but death is not documented as their reason for study withdrawal in Figure 4 of CS. Details on these three patients are provided in Table 1.

Table 1: Details of patients who withdrew from the AMPLIFY trial for a non-death reason and then died

Arm	Study exit date	Study exit reason	Death date
AVO	██████████	Lost to follow-up	██████████
FCR/BR	██████████	Withdrawal by subject	██████████
FCR/BR	██████████	Physician decision	██████████

Abbreviations: AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab.

A8. PRIORITY QUESTION: Please present NMA results for PFS, OS, PFS2, TOT/TTD OR, DOR and CRR, if the network permits all these outcomes to be compared, for A+Ven vs all relevant comparators, including Acalabrutinib and Zanubrutinib monotherapy. The company should highlight any potential bias, and the expected direction and magnitude of effect. Please undertake sensitivity analyses by excluding studies whose inclusion would require the strongest breach of the assumptions of the NMA.

Feasibility assessment for an NMA

As detailed in the CS, an extensive feasibility assessment was conducted to assess the possibility of conducting a network meta-analysis (NMA) to compare the relative efficacy of AV versus the relevant comparators for untreated non-high risk CLL, VenI and VenO. There are a number of foundational assumptions required to conduct a valid NMA, centred around network connectivity, study methodological variation, clinical variation and statistical variation. As detailed in Table 17 of the CS and restated below, all of these foundational assumptions were violated when considering an NMA to assess the relative efficacy of AV, VenI and VenO:

- **Meaningful differences in FCR/BR efficacy:** Numeric differences between FCR and BR were observed in the non-inferiority trial CLL10, undermining any assumption of equivalence between these regimens.¹¹
- **Substantial variation in treatment duration:** Treatment durations for fixed-duration and MRD-guided VenI varied significantly (~1.15 years versus up to 6 years). Reported outcomes also varied significantly, for example in the FLAIR study, the 3-year PFS rate for MRD-guided VenI was 97.2%, compared with a 30-month PFS rate in GLOW for fixed-duration VenI.^{12, 13}
- **Major methodological inconsistencies:** Studies differed in key design elements, including eligibility criteria, timing of recruitment (with some conducted during COVID-19), treatment switching policies, and median follow-up duration, all of which preclude a valid NMA.
- **Marked heterogeneity in prognostic factors and treatment effect modifiers (TEMs):** Key prognostic factors and TEMs influencing patient outcomes were identified through a targeted review of the literature, previous NICE evaluations and clinical expert feedback (see Appendix B.5.1 of the CS). The distribution of these factors was heterogeneous across trials as a result of differences in trial eligibility criteria. These included age, clinical stage (Binet B/C or Rai I–IV), *TP53* mutations, *IgHV* mutational status, beta-2 microglobulin concentration (>3.5 mg/L), patient sex, ECOG PS, comorbidities (CIRS), bulky disease, creatinine clearance and chromosomal abnormalities (trisomy 12, del[11q], del[17p], del[13q]).

- **Violation of homogeneity and transitivity assumptions:** Differences in baseline risk and effect modifiers undermine the assumption that treatment effects are transferable across studies, and the wide range of reported PFS outcomes supports this inconsistency. Many of these differences are likely related to prognostic factors and TEMs, which, given the sparse evidence network, could bias the NMA results and reduce their accuracy without covariate adjustment.

Taken together, the substantial heterogeneity in trial design, patient populations, and treatment effects violate the key assumptions underpinning a valid NMA. Any such analysis would produce biased and unreliable estimates with limited interpretability. For these reasons, an NMA has not been conducted and is not considered methodologically appropriate.

Endpoints considered

In terms of the outcomes considered within the indirect treatment comparisons (ITCs), OS and PFS were selected given they are the most relevant endpoints for patients with untreated CLL in UK clinical practice and are the most relevant to inform the cost-effectiveness analysis. Progression-free survival-2 (PFS2), time-on-treatment (TOT)/time-to-discontinuation (TTD), overall response rate (ORR), duration of response (DOR) and complete response rate (CRR) are not considered to be the key clinically important endpoints in the treatment of untreated CLL, as confirmed by UK clinical experts interviewed by the Company, and were therefore not explored in an ITC.⁷ Moreover, given the notable heterogeneity in outcome definitions, assessment methods and follow-up timing across the studies included in the feasibility assessment, conducting an ITC between these endpoints would have also been challenging. NMA results for PFS2, TOT/TTD, OR, DOR and CRR have, therefore, not been explored or presented here.

Treatments considered

Finally, acalabrutinib and zanubrutinib monotherapy are not deemed relevant comparators to AV in this submission, as discussed in detail in the CS. Therefore, an NMA (or any other type of ITC) of AV versus acalabrutinib and zanubrutinib monotherapy has not been explored.

This is supported by feedback from UK clinical experts, who indicated that fixed-duration therapies are considered more suitable in younger, fitter patients, and as such are the only relevant comparators in this submission. UK clinical experts also confirmed that treat-to-progression therapies are generally used in older, less fit patients, and that the introduction of AV is unlikely to influence treatments options for the vast majority of patients considered more suitable for treat-to-progression therapies.⁷ This is also supported by the recently updated British Haematological Society (BSH) guidelines. Furthermore, in the NICE evaluation of zanubrutinib monotherapy in CLL (TA931), the Committee accepted that the decision between treat-to-progression and fixed-duration therapies remains unchanged by the introduction of a new treatment.¹⁴ Detailed discussion of why zanubrutinib and acalabrutinib are not deemed relevant comparators in this appraisal is presented in response to Clarification Question B1.

A9. PRIORITY QUESTION: Please carry out ML-NMR for the network, comparing ORR, DOR and CRR for all treatments in the connected network, adjusting for key prognostic and effect modifying differences in the trials, reporting either in odds ratios or risk ratios. Please also perform ML-NMR for

time-to-event outcomes: PFS, OS, PFS2 and TOT/TTD, reporting the corresponding hazard ratios.

A multilevel network meta-regression (ML-NMR) is a population-adjusted network meta-regression that combines individual patient data (IPD) from at least one trial, with aggregate data from other trials to compare multiple treatments while adjusting for cross-trial population differences.

The key assumptions underlying an ML-NMR are as follows:

- **Conditional constancy of relative effects assumption:** After adjusting for observed effect modifiers, there are no remaining unobserved effect modifiers that would impact the relative treatment effects.
- **Shared TEM assumption:** If a separate treatment-by-covariate interaction for each treatment cannot be estimated because of the lack of access to IPD for all studies other than AMPLIFY in the network, as is the case here, an assumption can be made that treatments within the same class share identical interaction terms with the TEMs (e.g., AV and VenI have the same interaction with *IgHV* status). This is a strong assumption that must be clinically defensible and empirically supported.

It is recognised that the assumption that there are no unobserved TEMs is required for an unanchored simulated treatment comparison (STC), the population-adjustment method used in the CS. This was considered a reasonable assumption for this analysis, and all covariates which were identified as being prognostic factors or TEMs and were available in the included studies were considered in the STC.

For both the STC and ML-NMR methodologies, the population-adjustment can only be applied to covariates that are reported for all studies in each respective analysis. By performing the STC as an unanchored comparison, due to the absence of a common control arm between the AV and VenI studies, the list of potential covariates could be drawn from the available baseline data for GLOW and AMPLIFY, and CLL14 and AMPLIFY. For an anchored ML-NMR, the analysis requires access to baseline data from a broader set of studies (see Feasibility Assessment included in the Company Submission Appendices) because of the need to create a connected network. As noted in Table 19 in the CS, not all identified covariates were consistently available across studies. To include all studies in a single ML-NMR, the intersection set of covariates would be reduced to a very small subset. .

The studies included in the ITCs between AV, VenI and VenO (and FCR/BR in the comparison to CLL13) mix different treatment classes and combination therapies. Acalabrutinib and ibrutinib are different BTKis with known tolerability differences,^{7, 15-20} and obinutuzumab introduces infusion-related effects and infection risks, which are otherwise absent in all-oral regimens.^{7, 21} Section 1.2.4 in the CS explains why AV is more tolerable than VenI and VenO, which is driven by differing class components, undermining the principal assumption that must be made when data are insufficient, which is that interactions are shared across treatment classes. The shared TEM assumption is challenging to assess, since it is typically used to identify the model when data are insufficient.²²

In the absence of available data on covariate correlations in the VenI and VenO populations, the correlation structure would need approximating.²² The standard approach would be to use a correlation matrix computed from AMPLIFY (i.e., the IPD study) and apply it as a proxy for the VenI and VenO trials. The full joint covariate distribution in each VenI and VenO study would

then be reconstructed by assuming specific marginal distributions and imposing the approximated correlation structure. These additional distributional assumptions introduce further uncertainty and potential misspecification, especially when key covariates are missing or defined inconsistently between studies.

One of the benefits of ML-NMR is when there are complex networks of evidence with consistent reporting of covariates and endpoints, but given there are only two treatments of interest, each with two studies informing the evidence, and with the limited availability of IPD, it was not considered warranted to explore a more complex ITC when there was uncertainty about whether all the assumptions could be met.

In conclusion, given the lack of IPD for comparator studies, inconsistent covariate reporting and uncertain validity of the shared TEM assumption, the complexity of an ML-NMR was not considered warranted.

For the appropriateness of performing comparisons using the ORR, DOR, CRR, and TOT/TTDT endpoints, please see the response to Clarification Question A8. For the appropriateness of using a HR to compare between studies please see response to Clarification Question A10.

A10. Please present hazard ratio output from the current indirect treatment comparisons presented.

As detailed in the CS Appendix B, an assessment of the proportional hazards assumption was carried out for studies which assessed AV, VenI or VenO, and reported PFS and OS, and were therefore considered for inclusion in the ITCs. Overall, there was evidence of non-proportional hazards across all of the studies. The presence of non-proportional hazards indicates that the treatment effect varies throughout trial follow-up, and therefore any point estimate HR would be highly misleading as it would not capture this variation.

Whilst it is possible to generate HRs at landmark timepoints from Bucher ITCs and STCs, these would only provide an estimate of relative hazards at the chosen timepoint rather than reflecting the treatment effect across the study period. An HR at a single landmark timepoint would lack a clear clinical interpretation and would be highly dependent on the timepoint(s) selected, therefore reducing the robustness of results.

Given this, the RMST analysis conducted by the Company captures average PFS and OS over the full follow-up period and, as such, does not rely on the proportional hazards assumption. The Company therefore maintains that the chosen STC reporting RMST approach to assess comparative efficacy of AV and the relevant comparators, VenI and VenO, is the most methodologically robust given the available evidence. Moreover, the results of the STCs and Bucher ITCs presented in the CS, which demonstrate clinical comparability in terms of both PFS and OS between AV and VenI and VenO, were further validated by a modified Delphi panel and feedback from 22 UK clinical experts, confirming the reliable and clinically meaningful nature of these results.^{7, 8}

A11. Please confirm why patients with del(17p)/TP53 mutation are excluded from this appraisal, given they are included in EMA approval.

The UK and European marketing authorisation of relevance to this submission is “acalabrutinib in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult

patients with previously untreated chronic lymphocytic leukaemia (CLL)".^{23, 24} This is based on an assessment by the relevant regulatory authorities of all relevant studies for acalabrutinib (as AV or AVO), which includes trials that did not specify the presence or absence of 17p deletion (del[17p]) or *TP53* mutations (for AVO only).²⁵

Based on the totality of evidence available for AV and AVO, the marketing authorisation wording is broad and does not specify the presence or absence of del(17p) or *TP53* mutations. This is consistent with the marketing authorisation of other BTKis, including ibrutinib.²⁶ However, the decision problem in this appraisal must be aligned and supported by the evidence base, which is the AMPLIFY trial. As such, the company are only seeking reimbursement for AV in patients with untreated non-high risk CLL (i.e. those without a del[17p] or *TP53* mutation) in line with the AMPLIFY trial (NCT03836261).^{1, 6} Patients with untreated high-risk CLL (i.e. those with a del[17p] or *TP53* mutation) were not eligible for inclusion in the AMPLIFY trial and are therefore not included in the target population for AV in this submission.

In addition, as detailed in the response to Clarification Question B1, treat-to-progression and fixed-duration therapies are typically used in separate untreated CLL patient populations. Of relevance to this response, treat-to-progression therapies are generally preferred over fixed duration therapies in patients with high-risk CLL (i.e. those with a del[17p] or *TP53* mutation), in order to maximise their treatment response.²⁷ This was confirmed by UK clinical experts interviewed by the Company between April and July 2025, and highlighted in the NICE evaluation of zanubrutinib monotherapy in CLL (TA931).^{7, 14} Given that AV is a fixed-duration therapy, it is not expected to be used in patients with high-risk disease; UK clinical experts confirmed that the positioning of AV for non-high risk patients is reflective of the expected use of AV in UK clinical practice.⁷ As such, patients with untreated high-risk CLL (i.e. those with a del[17p] or *TP53* mutation) are excluded from this submission.

Finally, acalabrutinib is currently indicated and reimbursed in patients with untreated high risk CLL (TA689).²⁸

A12. Please implement a Bucher ITC or NMA of PFS for people aged ≥ 65 using CLL13 (Ven+O) and AMPLIFY (A+Ven):

The requested subgroup (age ≥65 years) is not relevant for decision making in this evaluation. The target population for AV is all patients with untreated CLL without *TP53* mutations or 17p deletion. Consistent with prior NICE evaluations for fixed-duration therapies in fitter populations of patients with untreated CLL (e.g. the NICE evaluation for VenI [TA891], which reported a starting age of 58 years for FCR/BR-eligible patients), the Company base case economic analysis for this submission adopted a starting age of 59.90 years based on all patients in the AMPLIFY trial, which was confirmed by UK clinical experts to align with the AV-eligible population in UK clinical practice.^{7, 29}

The age ≥65 years subgroup is small in the AMPLIFY and CLL13 trials. In AMPLIFY, patients over 65 years comprise approximately 25% of the full analysis set (79 patients in the AV arm).⁶ Similarly, in CLL13, patients over 65 years represent a minority (~35%) of the intent-to-treat (ITT) analysis set.³⁰ Small subgroup sizes increase imprecision, undermining the reliability of an indirect comparison. Furthermore, the feasibility for a Bucher ITC or NMA on PFS in this subgroup is limited by data availability and endpoint reporting. For CLL13, Kaplan-Meier subgroup curves and numbers-at-risk for patients aged ≥65 are not available, precluding the reconstruction of patient data and RMST estimation in this subgroup.³⁰ As detailed in response to

Clarification Question A10, RMST was preferred in the Company's comparative efficacy analyses because it does not rely on the proportional hazards assumption. The ITCs of HRs would be inappropriate due to likely proportional hazards violations across studies (see proportional hazards diagnostics in Appendix B [Figures 2–7]) and heterogeneity in assessment schedules, which are further exacerbated in small subgroups.

Given these constraints, the Company did not consider it clinically meaningful or appropriate to generate subgroup results for patients aged ≥65 years.

A13. Based on the available evidence, do patients with *del(17p)* or *TP53* mutation typically derive greater, lesser, or similar benefit from these treatments compared to those without?

Following the clarification call with the EAG, the Company understands that this question intends to address whether *del(17p)* or *TP53* alterations are considered prognostic factors or TEMs, and if so, the potential direction of the effect.

The Company presented a comprehensive feasibility assessment which included the consideration of prognostic factors and TEMs in CLL within the CS Appendices, Section B.5.1. This concluded that there was evidence that *del(17p)* and *TP53* mutations could be considered a prognostic factor and, for some treatments, a TEM. The implications of this finding for the ITC analyses conducted within the CS are discussed below, based on the pivotal studies included in the ITCs: AMPLIFY, CAPTIVATE-FD, GLOW, CLL13 and CLL14.^{6, 20, 21, 31, 32}

***del(17p)* or *TP53* mutation as a prognostic factor**

The presence of a *del(17p)* or *TP53* mutation (i.e., high-risk disease) is a well-established predictor for poor prognosis in CLL and, as outlined in the response to Clarification Question A11, guides treatment choice in UK clinical practice.^{33, 34} AMPLIFY, GLOW and CLL13 excluded patients with *del(17p)* or known *TP53* mutations at baseline.^{6, 20, 32} Conversely, CAPTIVATE-FD and CLL14 both included patients with *del(17p)* or known *TP53* mutations, however these patients only made up a small proportion of the overall cohort (n= 27 [17%] in CAPTIVATE-FD, and n= 46 [11%] in CLL14).^{21, 35}

Given that these patients only made up a small proportion of each trial, the expected impact on the results of the trial and subsequent impact on the unanchored STC is anticipated to be minimal.

***del(17p)* or *TP53* mutation as a TEM**

The influence of the presence of *del(17p)* or *TP53* mutations as a TEM in the untreated CLL setting appears to vary between the regimens included in the feasibility assessment. This was assessed through consideration of pre-specified subgroup analyses in the studies considered in the feasibility assessment provided in the CS. All results should be interpreted with caution, as patient numbers were low across several subgroups and analyses were not powered to capture differences in treatment effect.

When considering the intervention and comparators included in this evaluation, pre-specified subgroup analyses can be considered for the response and PFS outcomes. For VenI, CAPTIVATE-FD presents subgroup results for complete response (CR) (Figure 4), which

demonstrates that rates of CR is consistent in del(17p) and del(17p)/*TP53* mutation subgroups versus all treated patients, although as noted above, these subgroups are small.³⁵

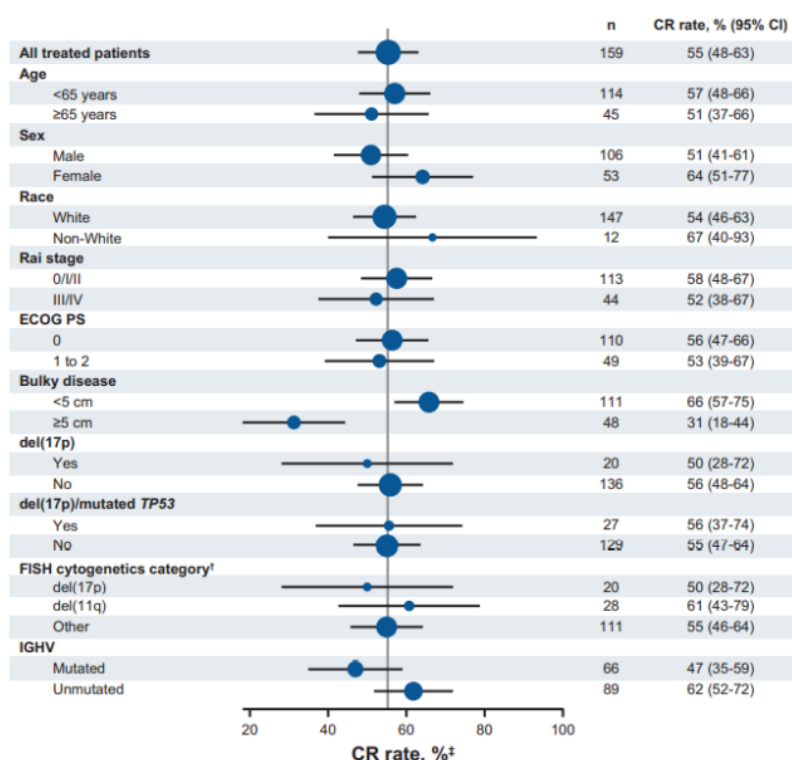
For VenO, CLL14 presents subgroup results for PFS (Figure 5) and MRD negativity (Figure 6). For PFS, the treatment effect in the *TP53* deletion and/or mutation subgroup appears broadly consistent with the overall population; however, the confidence intervals are wider, likely reflecting the smaller subgroup sample size (N=46). For MRD negativity, the odds ratio is higher in the *TP53* deletion subgroup, but the confidence intervals overlap those of the subgroup without *TP53* alterations, suggesting imprecision due to limited numbers.²¹

There are no subgroup results from GLOW or CLL13, given that they excluded patients with del(17p)/*TP53* mutation at baseline.^{12, 32} It is also not known how the treatment effect of AV varies between patients with and without *TP53* alterations, as the AMPLIFY trial did not include patients with del(17p) or *TP53* mutations.⁶ Additionally, the treatment benefit of AV observed in patients with untreated high-risk CLL is not of relevance to this submission, as AV is positioned as a fixed-duration therapy in patients with untreated non-high risk CLL only (i.e., no del(17p) or *TP53* mutations) – please refer to the response to Clarification Question A11 for further details.

For reference only and as requested by the EAG, subgroup results from other treatments used in untreated CLL have been provided in Figure 7 for zanubrutinib monotherapy and Figure 8 for acalabrutinib monotherapy.^{31, 36} In UK clinical practice, these treat-to-progression regimens are generally favoured for patients with del(17p) or *TP53* mutations, with fixed-duration therapies (i.e., VenI and VenO) more commonly used in those without these *TP53* alterations.⁷ Further details regarding the suitability for fixed-duration and treat-to-progression therapies have been provided in the response to Clarification Question B1.

In conclusion, whilst there is no compelling evidence that del(17p) or *TP53* mutations are TEMs for fixed-duration therapies. There is more evidence that they may alter the treatment effect for treat-to-progression options, which is why treat-to-progression therapies are generally reserved for patients who have high-risk CLL (i.e., those with del(17p) or *TP53* mutations).

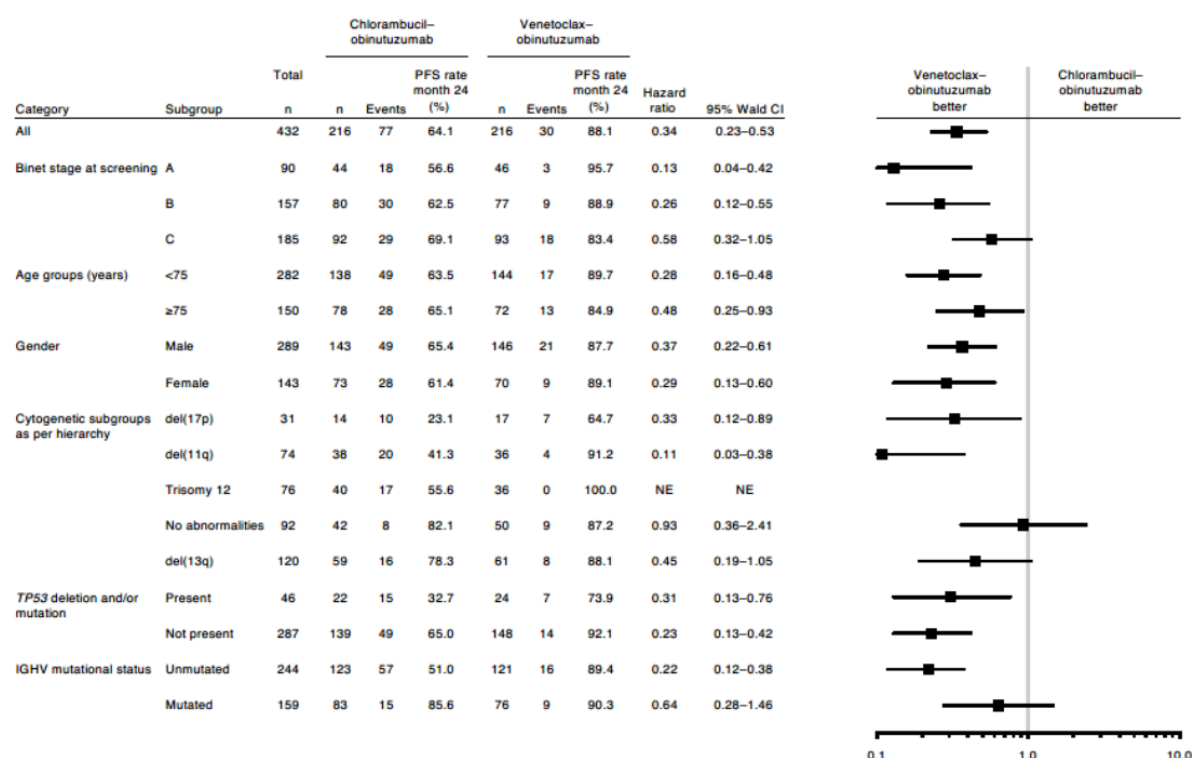
Figure 4: Forest plot of investigator-assessed CR/CRi by pre-specified subgroups (Venl: CAPTIVATE-FD)



Abbreviation: CI: confidence interval; CR: complete response; CRi : complete response with incomplete bone marrow recovery; del11q: 11q deletion; del17p: 17p deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FISH: fluorescence in situ hybridisation; *IGHV*: immunoglobulin heavy chain variable; INV: investigator; TP53: tumour protein p53; Venl: venetoclax with obinutuzumab.

Source: Tam 2022.³⁵

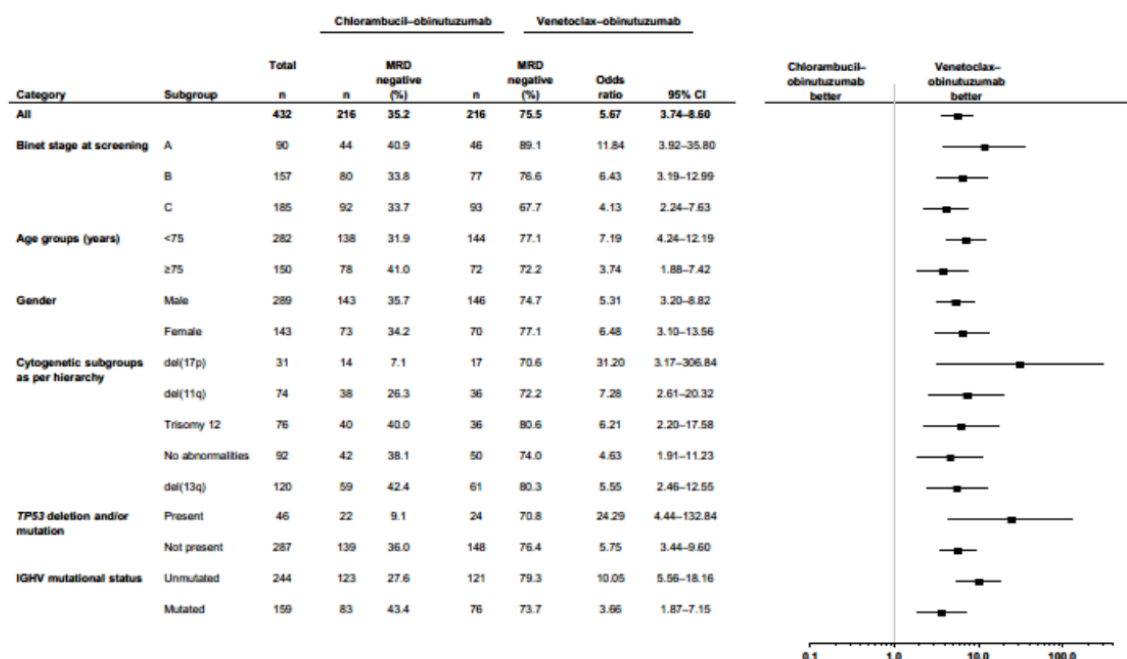
Figure 5: Investigator-assessed PFS by pre-specified subgroups (VenO; CLL14)



Abbreviations: CI: confidence interval; del(11q): chromosome 11q deletion; del(13q): chromosome 13q deletion; del(17p): chromosome 17p deletion; *IgHV*: immunoglobulin heavy-chain variable region; PFS: progression-free survival; VenO: venetoclax with obinutuzumab.

Source: Fischer 2019.²¹

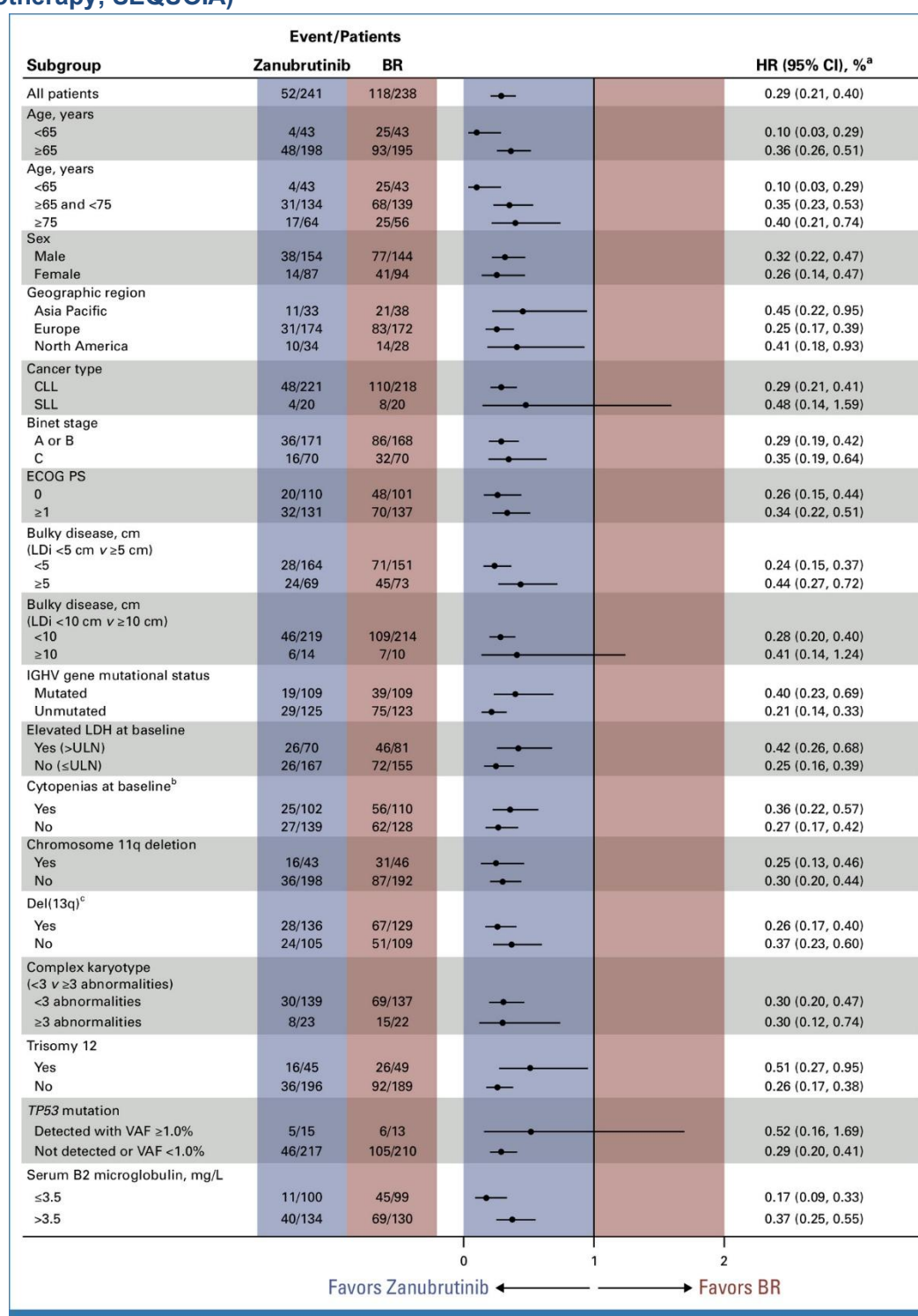
Figure 6: MRD negativity three months after completion of treatment by pre-specific subgroups (VenO; CLL14)



Abbreviations: CI: confidence interval; del(11q): chromosome 11q deletion; del(13q): chromosome 13q deletion; del(17p): chromosome 17p deletion; *IgHV*: immunoglobulin heavy-chain variable region; MRD: minimal residual disease; VenO: venetoclax with obinutuzumab.

Source: Fischer 2019.²¹

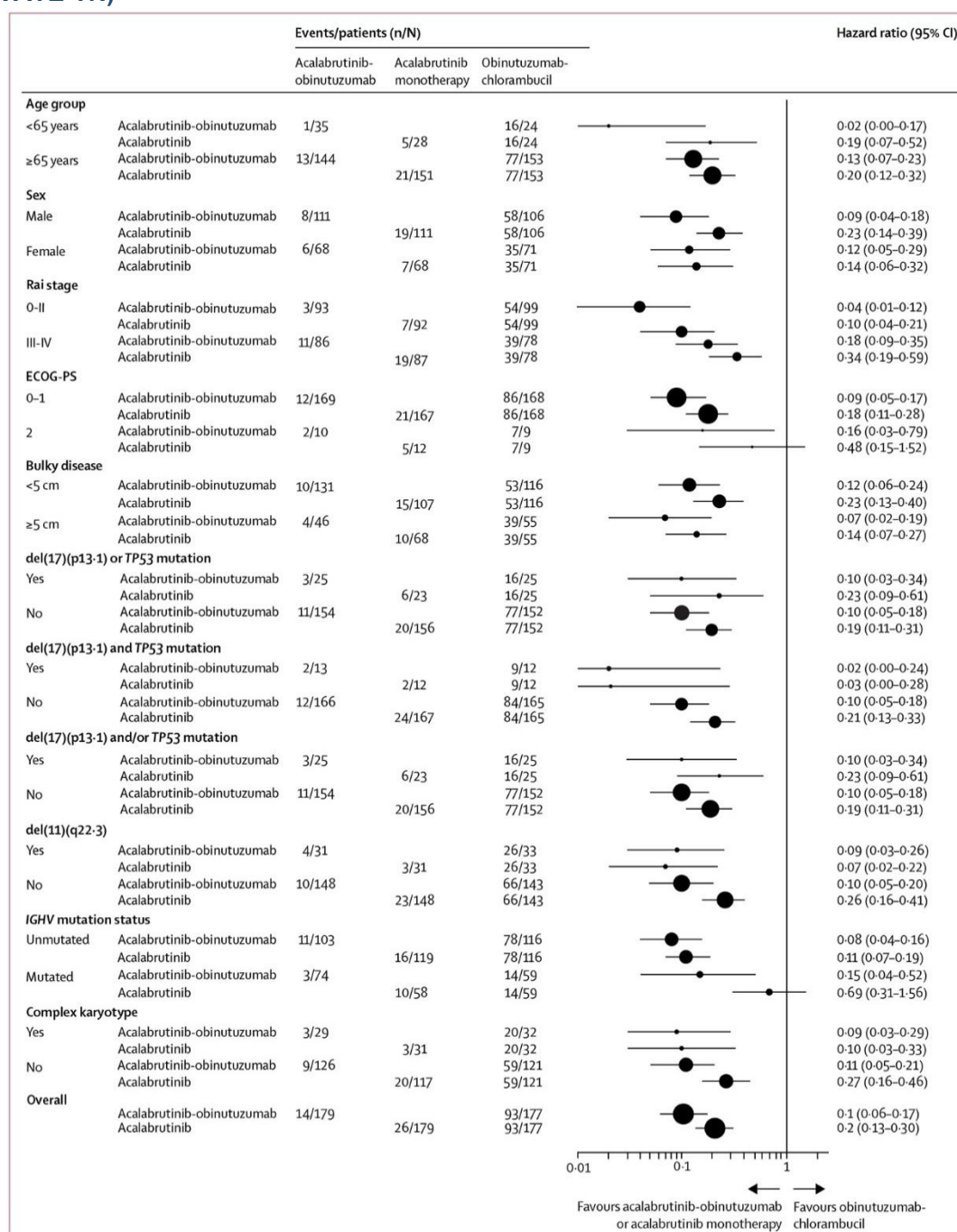
Figure 7: Investigator-assessed PFS by pre-specified subgroups (zanubrutinib monotherapy; SEQUOIA)



Abbreviations: BR: bendamustine plus rituximab; CLL: chronic lymphocytic leukaemia; ECOG P: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; *IgHV*: immunoglobulin heavy chain variable region; ITT: intent-to-treat; LDH: lactate dehydrogenase; LDi: longest diameter; PFS: progression-free survival; SLL: small lymphocytic lymphoma; TP53: tumour protein 53; ULN: upper limit of normal; VAF: variant allele frequency.

Source: Shadman 2024.³⁷

Figure 8: IRC-assessed PFS by pre-specified subgroups (acalabrutinib monotherapy; ELEVATE-TN)



Abbreviations: *IgHV*: immunoglobulin heavy chain variable gene; IRC: independent review committee; NE: not evaluable; TP53: cellular tumour antigen p53 gene; ECOG PS: Eastern Cooperative Oncology Group performance status; PFS: progression-free survival.

Source: Sharman 2020.³⁸

Section B: Clarification on cost-effectiveness data

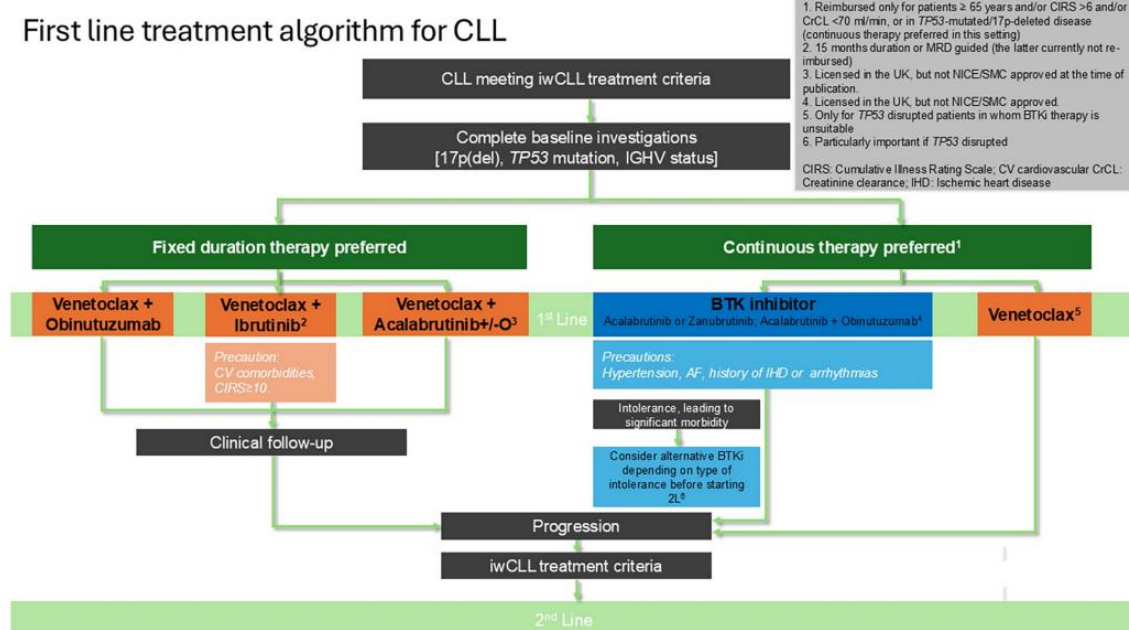
B1. PRIORITY QUESTION: Please perform a cost-effectiveness analysis versus both Acalabrutinib and Zanubrutinib monotherapy. The EAG clinical experts stated that the benefits of AV mean it is likely to broaden the pool of people receiving a dual therapy beyond those currently receiving Ven+O or I+Ven, and also that these monotherapies (treat-to-progression) are more likely to be used in settings with limited access to hospitals offering the necessary supporting services.

As detailed in Section 1.2.3 of the CS, treatment choice for patients with untreated, non-high risk CLL in UK clinical practice is informed by a broad assessment of fitness, which encompasses factors such as age, comorbidities, genetic factors, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score.^{7, 28, 34} In addition, suitability for fixed-duration versus treat-to-progression therapies plays a key role in informing treatment choice, with these two regimens typically used in distinct patient populations, as confirmed by UK clinical experts interviewed by the Company.⁷

Feedback from UK clinical experts indicated that the introduction of AV is unlikely to influence treatment options for the majority of patients deemed more suitable for treat-to-progression therapies.⁷ This view is consistent with the NICE evaluation of zanubrutinib monotherapy in CLL (TA931), in which the Committee similarly concluded that the decision to use a treat-to-progression or fixed-duration regimen is unchanged by the availability of new therapies.¹⁴ Since the CS was submitted, the BSH CLL treatment guidelines have also been updated.³⁴ In this update, the guidelines explicitly separate the untreated CLL treatment pathway according to suitability for fixed-duration versus treat-to-progression regimens (Figure 9), reinforcing the importance of this suitability classification in clinical decision making and treatment choice.^{7, 34}

As such, the introduction of fixed-duration AV is not expected to displace treat-to-progression therapies such as acalabrutinib or zanubrutinib monotherapy. This is consistent with UK clinical practice, where VenO and VenI, both fixed-duration therapies, have been available on the NHS for at least two years and five years, respectively, without displacing treat-to-progression therapies that are, as highlighted above, typically considered more suitable for less fit patients or those with high-risk disease. On this basis, the relevant comparators to AV in UK clinical practice are other fixed-duration treatment regimens (i.e., VenI and VenO). Treat-to-progression regimens acalabrutinib and zanubrutinib monotherapy, are not considered relevant comparators and therefore the economic analysis has only been conducted versus VenI and VenO. All UK clinical experts consulted by the Company confirmed that VenI and VenO represent the relevant comparators to AV in this indication.⁷

Figure 9: BSH treatment algorithm for patients with untreated CLL



Abbreviations: AF: atrial fibrillation; BTK(i): Bruton tyrosine kinase (inhibitor); CIRS: Cumulative Illness Rating Score; CLL: chronic lymphocytic leukaemia; CrCL: creatine clearance; CV: cardiovascular; IHD: ischaemic heart disease; iwCLL: International Workshop on chronic lymphocytic leukaemia; 2L: second-line.
Source: 2025 BSH Guideline for the treatment of CLL.³⁴

B2. Please explain why a standard partitioned survival model approach was not taken, i.e. where post-progression survival is directly informed by the extrapolation of OS and PFS.

As outlined in Section 3.2.2 of the CS, a semi-Markov state-transition model was deemed more appropriate than a partitioned survival model (PSM) to evaluate the cost-effectiveness of AV versus VenI and VenO in patients with untreated, non-high risk CLL.

Due to the indolent and chronic nature of CLL, OS data from the AMPLIFY trial were immature (6.2% maturity [18/291] in the AV arm) at the latest DCO of the interim analysis (30th April 2024).⁶ A PSM approach would require mature follow-up to reliably estimate hazards; extrapolating immature OS within a PSM framework would introduce substantial uncertainty and raise face validity concerns, such as OS projections that exceed age-matched general population survival or crossings between independently extrapolated PFS and OS curves. In contrast, the semi-Markov state-transition model employed in the CS does not depend on mature OS data. It uses intermediate endpoints (pre-PS and post-PS) to inform OS indirectly, leveraging IPD to anchor directly observed transition periods, and it permits post-PS to be informed by external data from the ASCEND trial to address OS immaturity.³⁶

Guidance from the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19 supports this approach, stating that a “a state-transition model allows fuller and more explicit use of information on prognostic intermediate endpoints, such as progression, to inform mortality extrapolations”, and that a state-transition approach is more commonly used when OS data are immature.³⁹ The semi-Markov state-transition approach also affords a more granular view of the natural history of CLL by explicitly capturing the impact of subsequent treatment lines, recognising that patients with untreated CLL will progress to relapsed/refractory disease requiring additional therapy, and by accounting for the costs and health-related quality of life (HRQoL)

associated with being on or off treatment, which reflects the real-world benefit clinicians and patients associate with treatment-free periods.²⁹ Taken together, this modelling framework minimises uncertainty in line with NICE DSU guidance and ensures that the relevant costs and benefits associated with AV, VenI, and VenO are accurately captured.

Finally, the use of a standard PSM approach would overlook the indolent nature of the disease, and associated immaturity of the OS AMPLIFY data, resulting in uncertain extrapolations which lack clinical plausibility.⁴⁰ Accordingly, the semi-Markov state-transition approach is the preferred modelling framework for this analysis, as it robustly integrates IPD, intermediate endpoints, and external data to inform OS whilst avoiding inappropriate extrapolations. This approach also aligns with the three most recent NICE evaluations for therapies in previously untreated and/or treated CLL (TA931 [zanubrutinib monotherapy for treated and untreated CLL], TA891 [ibrutinib with venetoclax for untreated CLL], TA689 [acalabrutinib monotherapy for treated and untreated CLL])^{14, 28, 29} and supports a credible, clinically plausible assessment of AV, VenI, and VenO in this indication.

B3. Can the company please explain why they preferred to use TA561 as the source of TLS instead of AMPLIFY trial data? Additionally, could the company provide justification for using TA561 as the source of TLS rather than STAs related to VenO and VenI?

Tumour lysis syndrome (TLS) prophylaxis and management costs were applied as a one-off cost in the first model cycle of the Company's base case economic analysis, with costs assumed to be the same for all three treatment regimens (AV, VenI and VenO). As clinical trials, including the AMPLIFY trial, do not typically collect AE management costs, TA561 (the NICE evaluation of venetoclax with rituximab in CLL) was selected as an appropriate source to inform TLS prophylaxis and management costs. In TA561, the average TLS prophylaxis cost (£1,975.45 in 2018 GBP) was calculated based on the TLS risk distribution among patients in the MURANO trial.^{41, 42} TA561 defined patients at lower risk of TLS as patients with a lymph node diameter ≤5 cm and an absolute lymphocyte count (ALC) <25 x10⁹, while greater risk patients were defined by a node diameter >5 cm or an ALC >25 x10⁹.⁴²

A similar approach, based on the TLS risk distribution in the CLL14 trial,⁴³ was used to calculate TLS prophylaxis costs in the NICE evaluation of VenO in untreated CLL (TA663) (£1,933 for VenO in 2019 GBP; £1,694 for obinutuzumab with chlorambucil [OClb] in 2019 GBP).⁴⁴ These costs are very similar to those used in TA561 and the Company's base case economic analysis. The NICE evaluation of VenI in untreated CLL (TA891) also used a similar TLS risk segmentation approach;²⁹ however, only patients at high risk of TLS were assumed to receive TLS prophylaxis and therefore incur the associated costs (£3,796.00 in 2022 GBP) in the base case economic analysis.²⁹ In addition, and unlike TA561 and TA663, a one-off cost for hospitalisation due to treatment-emergent TLS was incorporated into the economic analysis in TA891.²⁹

The rate of TLS in the safety population of the AMPLIFY trial was low, with only one patient (0.3%) in the AV arm and eight patients (3.1%) in the FCR/BR arm experiencing TLS. Given this, and the assumption that TLS prophylaxis and management costs applied in the Company's economic analysis are the same for AV, VenI and VenO, the source of this cost (i.e., TA561, TA891, or TA663)^{29, 42, 44} is not expected to have a meaningful impact on the cost-effectiveness results. This is supported by the results of the deterministic sensitivity analysis, which

demonstrate that TLS costs are not a key driver of the model results (Figure 18 and Figure 19 in Appendix 1).

B4. Can the company please provide the formula and the exact annual decrement values used in the section “Age-related utility decrement” for adjusting the utility values? Furthermore, it appears that the utility value applied by the company for “Progression-free on treatment” is higher than the general population utility estimated from both Ara and Brazier (2010) and Hernández-Alava et al. (2022). Can the company provide justification for this?

The formula used to calculate the age-related utility decrement for each age beyond the starting age applied in the model (59.90 years) was as follows:

$$\text{Decrement} = \frac{U(\text{age})}{U(\text{base})}$$

where $U(\text{age})$ is the baseline utility for any given age, and $U(\text{base})$ is the baseline utility for the starting age in the model. The calculated decrements can be found in Table 2.

Table 2: Age-related utility decrements applied in the Company base case economic analysis

Age (years)	Baseline utility general population	Relative utility decrement
0.00	0.93	1.00
1.00	0.93	1.00
2.00	0.93	1.00
3.00	0.93	1.00
4.00	0.93	1.00
5.00	0.93	1.00
6.00	0.93	1.00
7.00	0.93	1.00
8.00	0.93	1.00
9.00	0.93	1.00
10.00	0.93	1.00
11.00	0.93	1.00
12.00	0.93	1.00
13.00	0.93	1.00
14.00	0.93	1.00
15.00	0.93	1.00
16.00	0.93	1.00
17.00	0.93	1.00
18.00	0.93	1.00
19.00	0.93	1.00
20.00	0.93	1.00
21.00	0.92	1.00

Age (years)	Baseline utility general population	Relative utility decrement
22.00	0.92	1.00
23.00	0.92	1.00
24.00	0.92	1.00
25.00	0.92	1.00
26.00	0.92	1.00
27.00	0.92	1.00
28.00	0.92	1.00
29.00	0.91	1.00
30.00	0.91	1.00
31.00	0.91	1.00
32.00	0.91	1.00
33.00	0.91	1.00
34.00	0.91	1.00
35.00	0.90	1.00
36.00	0.90	1.00
37.00	0.90	1.00
38.00	0.90	1.00
39.00	0.90	1.00
40.00	0.89	1.00
41.00	0.89	1.00
42.00	0.89	1.00
43.00	0.89	1.00
44.00	0.89	1.00
45.00	0.88	1.00
46.00	0.88	1.00
47.00	0.88	1.00
48.00	0.87	1.00
49.00	0.87	1.00
50.00	0.87	1.00
51.00	0.87	1.00
52.00	0.86	1.00
53.00	0.86	1.00
54.00	0.86	1.00
55.00	0.85	1.00
56.00	0.85	1.00
57.00	0.85	1.00
58.00	0.84	1.00
59.00	0.84	1.00
60.00	0.84	1.00
61.00	0.83	0.99
62.00	0.83	0.99
63.00	0.83	0.98

Age (years)	Baseline utility general population	Relative utility decrement
64.00	0.82	0.98
65.00	0.82	0.97
66.00	0.82	0.97
67.00	0.81	0.96
68.00	0.81	0.96
69.00	0.80	0.95
70.00	0.80	0.95
71.00	0.79	0.94
72.00	0.79	0.94
73.00	0.79	0.93
74.00	0.78	0.93
75.00	0.78	0.92
76.00	0.77	0.92
77.00	0.77	0.91
78.00	0.76	0.91
79.00	0.76	0.90
80.00	0.75	0.89
81.00	0.75	0.89
82.00	0.74	0.88
83.00	0.74	0.87
84.00	0.73	0.87
85.00	0.72	0.86
86.00	0.72	0.85
87.00	0.71	0.85
88.00	0.71	0.84
89.00	0.70	0.83
90.00	0.69	0.82
91.00	0.68	0.81
92.00	0.68	0.81
93.00	0.67	0.80
94.00	0.66	0.79
95.00	0.66	0.78
96.00	0.65	0.78
97.00	0.65	0.77
98.00	0.64	0.76
99.00	0.63	0.75
100.00	0.63	0.75
101.00	0.62	0.74

Source: Hernández-Alava 2022.⁴⁵

While the progression-free on-treatment health-state utility values (HSUVs) used within the model are greater than the estimated general population utility from Hernández-Alava (2022),⁴⁵ these values more accurately represent the population being modelled within the CS, as they are

sourced from the AMPLIFY trial.^{1, 6} Given that these HSUVs are applied to all treatments, it is important for the increment between each value to be maintained so that the model accurately captures the differences in QALYs between treatments, which occur due to differences in the time spent in each health state.

Further to this, the Company economic analysis already explores the impact of an alternative HSUV source in a scenario analysis (Kosmas *et al.*, [2015]),⁴⁶ where HSUVs, including the progression-free on-treatment HSUV, were generally below general population utility values. Results of this scenario analysis were presented in Section 3.11.3 of the CS and demonstrated minimal impact on net monetary benefit (NMB). A further scenario analysis has been included in the revised Company economic analysis so that a cap is applied to HSUVs over the time horizon of the model, such that HSUV in the progression-free health states is never greater than the age-related baseline general population utility in any given model cycle. To further confirm that results of the revised Company economic analysis are robust to both the source of HSUVs and the use of capping, an additional scenario analysis has been conducted using the Kosmas *et al.*, (2015) HSUVs capped by general population utility values.⁴⁶ The results of these scenario analyses are presented in Appendix 1 and demonstrate minimal impact on the revised Company base case NMB.

B5. Can the company please provide further details on the mixed model for repeated measures (MMRM) used in the EQ-5D utility analysis? Specifically, please provide the full set of parameter estimates (e.g., regression coefficients, standard errors, and p-values) for all fixed effects and covariates included in the model.

The statistical relationship between EQ-5D-3L scores, treatment and health status was assessed using regression analysis, with a mixed model for repeated measures (MMRM) method used to account for repeated utility measurements (Section 3.4.1 of the CS).⁴⁷ A full set of parameter estimates are presented in Table 3.

Table 3: Summary of fixed effect parameter estimates derived from the MMRM analysis of AMPLIFY EQ-5D analysis

Parameter	Treatment	Treatment progression by IRC status	Treatment + Treatment progression by IRC status	Treatment * Treatment progression by IRC status
(Intercept)	████ (SE: █████; p<0.001)	████ (SE: █████; p<0.001)	████ (SE: █████; p<0.001)	████ (SE: █████; p<0.001)
AVO	-0.002 (SE: 0.011; p=0.832)	-	-0.003 (SE: 0.011; p=0.783)	-0.003 (SE: 0.011; p=0.792)
AV	-0.004 (SE: 0.011; p=0.738)	-	-0.004 (SE: 0.011; p=0.740)	-0.004 (SE: 0.011; p=0.747)
Post-progression	-	-0.022 (SE: 0.009; p=0.014)	-0.022 (SE: 0.009; p=0.014)	-0.021 (SE: 0.013; p=0.107)

Parameter	Treatment	Treatment progression by IRC status	Treatment + Treatment progression by IRC status	Treatment * Treatment progression by IRC status
AVO: Post-progression	-	-	-	-0.005 (SE: 0.034; p=0.878)
AV: Post-progression	-	-	-	-0.002 (SE: 0.018; p=0.920)
AIC	-24361.4	-24377.2	-24360.7	-24349.0

Abbreviations: AIC: Akaike Information Criterion; AV: acalabrutinib with venetoclax; AVO: acalabrutinib, venetoclax and obinutuzumab; IRC: independent review committee; MMRM: mixed model for repeated measures; SE: standard error.

B6. Can the company please provide the evidence supporting the use of 100% relative dose intensity for the comparators and a lower percentage for AV arm? Furthermore, can the company confirm that the relative dose intensity was calculated based on the received dose across all treatment cycles in which the patient received the drug, rather than over the full treatment duration, regardless of whether the patient was on or off treatment?

Justification for use of 100% RDI for comparators

As detailed in Section 3.5.1 of the CS, relative dose intensities (RDIs) were available for AV from the AMPLIFY trial and applied in the base case economic analysis.

In the NICE evaluation for VenI in untreated CLL (TA891), in the absence of published data, an RDI of 100% was assumed for the comparator regimen VenO and this was accepted by the Committee.²⁹ As RDIs for VenO and VenI are not publicly available, and could therefore not be applied in the current economic analysis, a similar approach to that used in the VenI NICE evaluation (TA891) was used in the Company base case economic analysis, whereby the RDIs for VenI and VenO were assumed to be 100%.²⁹

Nevertheless, to explore the impact of varying the RDI for VenI and VenO, a scenario analysis has been conducted whereby the RDI for AV is applied to VenO and VenI. The RDI for venetoclax across all three regimens was set to [REDACTED], in line with the RDI reported for venetoclax in the AMPLIFY trial. For ibrutinib and obinutuzumab, the RDI was assumed to be equal to the RDI for acalabrutinib in the AMPLIFY trial ([REDACTED]). The results of this scenario analysis are presented in Appendix 1 and demonstrate minimal impact on the revised Company base case NMB, thus confirming that RDI is not a key model driver.

Calculation of RDI in AMPLIFY

RDI in the AMPLIFY trial was defined as the dose patients received for the full treatment duration, compared with the standard treatment protocol, and was calculated as follows:⁴⁸

- RDI for acalabrutinib from Cycle 1 through Cycle 14 was calculated as (total cumulative dose received [mg] / (duration of exposure [days] * 100 [mg] * 2) * 100)

- RDI for venetoclax was calculated as (total cumulative dose received [mg] / 2,590 [mg]) *100) for Cycle 3 and (total cumulative dose received [mg] / (duration of exposure [days] * 400 [mg]) *100) for Cycles 4 through 14. RDI for venetoclax will be summarised for Cycle 3 and Cycle 4 through Cycle 14 separately.

B7. The model functionality is very limited for exploring options beyond the assumption of equal efficacy. Please add into the model functionality to easily explore alternative approaches for modelling time-to-event outcomes for the comparators, i.e. through applying hazard ratios to the A+Ven extrapolations, and using separate parametric extrapolations for the comparators.

As detailed in response to Clarification Question B2, a semi-Markov state-transition model was chosen to evaluate the cost-effectiveness of AV versus VenI and VenO in patients with untreated, non-high risk CLL. Given the immaturity of OS data from the AMPLIFY trial, due to the inherently indolent course of untreated CLL,⁶ this approach was considered the most appropriate and robust alternative to a PSM.

The model comprises pre-progression (pre-PS) and post-progression (post-PS) health states, with time to progression (TTP) acting as the key intermediate endpoint. Pre-PS and TTD data were derived from AMPLIFY,⁶ while post-PS survival was informed by external OS data from the acalabrutinib arm of the ASCEND trial in the second-line CLL setting, enabling plausible long-term extrapolation without relying on immature OS from AMPLIFY.³⁶

As detailed in Section 3.3.2 of the CS, equivalent efficacy was assumed across AV, VenI, and VenO, with the extrapolated AV time-to-event curves considered representative of outcomes for all regimens. This assumption reflects the clinical equivalence between these regimens in terms of TTP, pre-PS and post-PS outcomes, supported by results from the STCs, Bucher ITCs, modified Delphi panel, and UK clinical expert input (see Section 2.10 of the CS), which demonstrated clinical comparability in terms of both PFS and OS between all treatments.^{7, 8} Given this evidence, separate parametric extrapolations or alternative HRs were not considered appropriate.

Furthermore, none of the comparator studies (for VenI or VenO) have published Kaplan-Meier curves for TTP or post-progression survival (post-PS), meaning independent extrapolation for these regimens could not be undertaken. Even if it were assumed that the TTP treatment effect is comparable to that for PFS, it would still not be appropriate to apply HRs derived from ITCs, as detailed in response to Clarification Question A10. This is because the proportional hazards assumption was violated across trials, indicating that treatment effects vary over time. As such, any HRs would depend on the timepoint chosen, undermining their validity and reliability. Consequently, HRs derived from ITCs were not applied in the economic analysis, even for hypothetical non-equivalence scenarios.

B8. Can the company please justify the approach to discounting in the model, where values remain undiscounted for the first two years and then discounting

is applied for each 28-day cycle rather than annually, as this does not appear to align with the NICE reference case?

The approach to discounting in the model has been updated such that discounting occurs from Year 1 onwards. It has also been updated to be applied annually. Results of the revised Company base case are presented in Appendix 1.

B9. Please provide UK real-world evidence supporting the company's preferred starting age used in the model is consistent with UK clinical practice for the same patient population, or compare with values used in other NICE STAs?

As described in the response to Clarification Question B1, AV is a fixed-duration therapy positioned as a treatment option for patients with untreated non-high risk CLL. UK clinical expert feedback confirmed that the age of the AMPLIFY patient population (59.90 years) is reflective of the patients expected to receive AV, or any fixed-duration therapy, in UK clinical practice. Specifically, UK clinical experts noted that this population of patients is generally younger and fitter than the overall UK CLL population as well as the separate population of patients who are more suitable for treat-to-progression therapies.^{7, 14} This was also confirmed by UK clinical experts interviewed as part of the NICE evaluation of zanubrutinib monotherapy in CLL (TA931).

Given that patient suitability for fixed-duration versus treat-to-progression therapies has only recently been used to segment patients in UK clinical practice, with suitability for FCR/BR used historically, the Company is not aware of any real-world evidence from the UK in the population of interest to this submission (i.e., untreated non-high risk CLL). Similarly, no NICE evaluations have been submitted for patients with untreated non-high risk CLL who are eligible for fixed-duration therapies to compare against. However, results from the international CLL Collaborative Study of Real-World Evidence (CORE) confirm that patients receiving fixed-duration therapies are, on average, younger than those receiving treat-to-progression options.⁴⁹ Furthermore, in the NICE evaluation for Venl (TA891), a starting age of 58 years was used for the FCR/BR-eligible population, which has typically comprised 'fitter' patients and therefore is most analogous to the AV-eligible population.²⁹ This starting age is very similar to the starting age of 59.90 years used in the Company base case economic analysis, which was based on the mean baseline age of patients in the AMPLIFY trial.⁶

As the pivotal trial for AV, AMPLIFY was used to source evidence for key clinical parameters, such as TTP and pre-PS, which informed the model. Age and other baseline characteristics for the modelled patient population should therefore remain consistent with those of the AMPLIFY trial, which, as noted above, aligned with the population in UK clinical practice who would be eligible to receive AV. This consistency ensures methodological coherence across the economic analysis inputs, to ensure generalisability and integrity of the results.

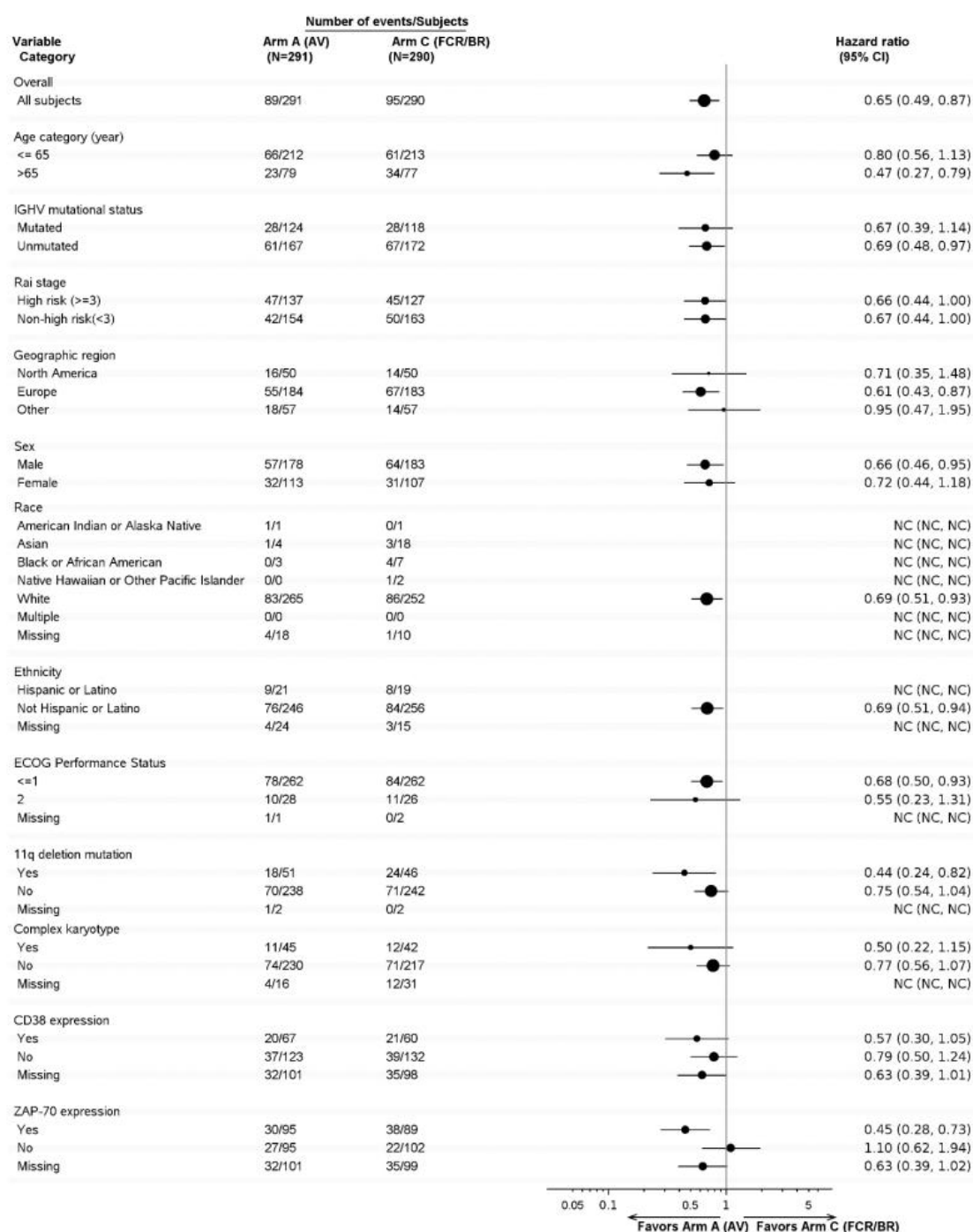
B10. Can the company please provide its viewpoint (with supporting clinical evidence if available) on whether prognosis, adverse events and discontinuation and treatment effect (e.g. response rate and duration, PFS, OS,

MRD) differ between an older and younger population (e.g. average age of 60 vs 70).

Subgroup analyses from the AMPLIFY trial for the primary endpoint, independent review committee (IRC)-assessed PFS, and the key secondary endpoint, OS, indicate a numerical benefit for AV over FCR/BR across both the ≤ 65 and > 65 years subgroups. These subgroup analyses are presented in Figure 10 and Figure 11 below (and in the CS, Section 2.8, and the CS Appendix C, respectively). Whilst it is noted that there is a lack of statistical power to detect differences in treatment effects within these subgroups due to the small sample sizes, taken together, these subgroup analyses confirm that a numerical benefit in favour of AV over FCR/BR for PFS and OS is maintained regardless of age.

Data on treatment discontinuation and adverse events (AEs) by age are not available from the AMPLIFY trial. Regardless, these data are not considered relevant to the decision problem of this submission. AV is positioned as a treatment for all patients with untreated CLL without TP53 alterations, and is anticipated to be used in patients deemed more suitable for fixed-duration therapies. Given that the majority of patients receiving fixed duration therapies are relatively younger than those receiving treat-to-progression therapies (which are not relevant comparators to AV in this submission), these data are not considered relevant to the decision problem of this submission.⁷

Figure 10: Forest plot for subgroup analyses of IRC-assessed PFS for AV and FCR/BR in AMPLIFY (FAS)^a

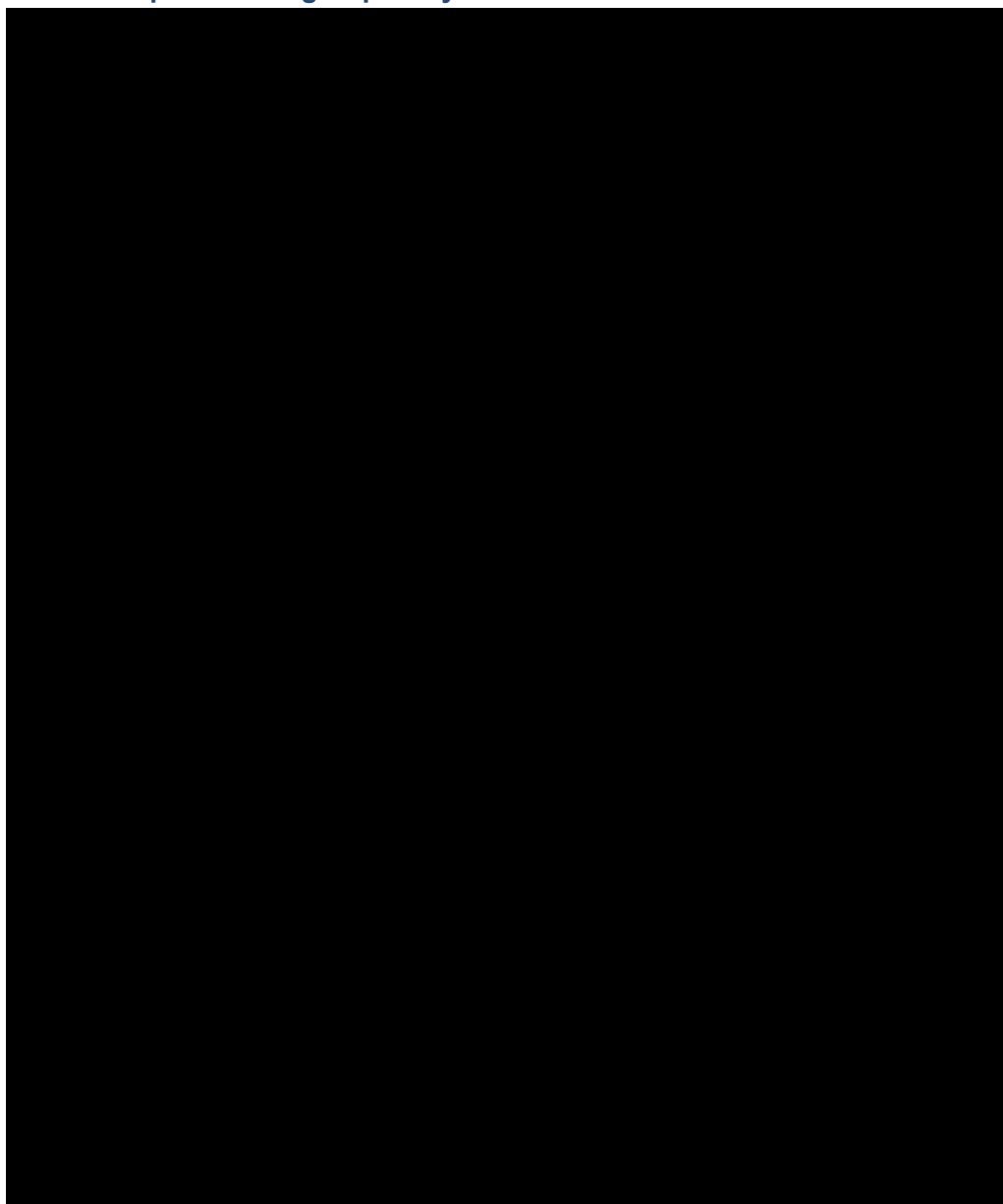


^aDue to too few events in some of the subgroups across both arms, HR and 95% CI are presented as NC.

Abbreviations: AV: acalabrutinib with venetoclax; BR: bendamustine with rituximab; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FAS: Full Analysis Set; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; *IgHV*: immunoglobulin heavy-chain variable region gene; NC: not calculable; PFS: progression-free survival.

Source: Brown *et al.* (2025) (Figure S3A).⁶

Figure 11: Forest plot for subgroup analyses of OS for AV and FCR/BR in AMPLIFY (FAS)^a



^aDue to too few events in some of the subgroups across both treatment arms, HR and 95% CI are presented as NC.

Abbreviations: AV: acalabrutinib with venetoclax; BR: bendamustine with rituximab; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; FCR: rituximab with fludarabine and cyclophosphamide; HR: hazard ratio; *IgHV*: immunoglobulin heavy chain variable region gene; NC: not calculable; OS: overall survival.

Source: AstraZeneca Data on File, 2025 (AMPLIFY CSR; Figure 10).¹

B11. Could the company please confirm the calculations in the model linked to TTD1, as the EAG notes likely errors, in particular the life-years and QALYs. For example, Ven+O and A+Ven appear identical (Detailed results cell F23 and F25) despite having different treatment durations. I+Ven also appears incorrect.

The Company thanks the EAG for noting these errors in the model. Following further investigation, the following errors were identified:

1. TTD for venetoclax was incorrectly modelled for AV
2. The model was applying one additional cycle for all treatments by starting in Cycle 0

These errors have now been corrected in the version of the model submitted alongside this response, and all model traces have been adjusted to start from Cycle 1, not Cycle 0. Venetoclax costs in the AV and VenI arms are now applied from Cycle 3 and Cycle 4, respectively, aligned with each regimen's SmPC, while all other treatments start in Cycle 1.^{23, 26, 50, 51}

The maximum number of treatment cycles for AV, VenI and VenO is 14 cycles, 15 cycles and 12 cycles, as per the respective SmPCs, respectively.^{23, 26, 50, 51} In the CS, the TTD curves for VenI and VenO were set equal to the TTD curve for AV, with TTD for VenI undergoing an exponential decline after the maximum treatment duration for AV, in order to capture the patients receiving VenI after Cycle 14.

While treatment costs for all treatments were capped by the maximum number of treatment cycles in the CS, this cap was not applied directly to the TTD curve, meaning that LYs and QALYs were still accumulated after the maximum treatment duration had been reached, as some patients were still 'on-treatment' as defined by the TTD curve. To accurately reflect the different treatment durations for VenI and VenO, the TTD curves in the model shared alongside this response are now capped by the maximum number of treatment cycles for VenI and VenO. As such, once this point is reached, the TTD curve is set to 0. This means that TTD, which informs estimated LYs and QALYs, is capped in the same way as costs in the progression-free (on-treatment) health state. This change is reflected in differences in the benefits accumulated in this health state in the revised Company base case presented in Appendix 1.

B12. Could the company please clarify the value (£598.22) for Deliver Complex Chemotherapy at First Attendance (Treatment Costs sheet cell F43) in the model, as this is given in the report as £1,458.70 (Table 56, NHS reference costs 2023/24, deliver complex chemotherapy, including prolonged infusional treatment, at first attendance [SB14Z])

As detailed in Table 4, the cost of the first administration of obinutuzumab is £598.22 as per Treatment Costs sheet cell F43 of the model. The cost of all subsequent administrations is £430.24 (Treatment Costs sheet cell F44). As per the summary of product characteristics (SmPC), obinutuzumab is administered three times in the first cycle. Therefore, the total administration cost of £1,458.70 in the first treatment (and model) *cycle*, detailed in Table 56 of the CS, is derived from the sum of one first administration cost and two subsequent administration costs (Table 4).

Table 4: Administration costs for obinutuzumab (in VenO) during first treatment cycle

	Cost	Source
First administration	£598.22	NHS reference cost 2023/24, SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
Subsequent administrations	£430.24	NHS reference cost 2023/24, SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle

Total cost in first cycle (three administrations)	Cost of first administration and two subsequent administrations: £1,458.70

Abbreviations: VenO: venetoclax with obinutuzumab.

B13. Please amend adverse event costs in the sensitivity analysis to be disaggregated to include the cost of each AE, its probability, disutility, and duration, as this approach would provide insights into the overall impact of each of these parameters in the OWSA.

The model has been updated to incorporate disaggregated AE costs, probabilities, disutilities and durations into the deterministic sensitivity analysis (DSA). An updated Company model has been submitted alongside this response, and results of the revised Company base case are presented in Appendix 1.

B14. The EAG notes no uncertainty has been applied to the survival curves (PFS, OS, TTD) for VenI and VenO. Please could the company allow for this uncertainty to be explored, through uncertainty around a hazard ratio, or allowing independent sampling of the preferred extrapolation parameters for each treatment.

Please refer to the responses to Clarification Question A10 and B7, which detail why the inclusion of HRs and separate extrapolation parameters for each treatment were not considered appropriate.

B15. Please could the company run a PSA for 10,000 iterations for the company base-case (revised base case if necessary, based on these questions) to give greater confidence in the model results.

Results of the revised Company base case probabilistic analysis run with 10,000 iterations are presented in Appendix 1.

B16. Could the company please add a macro that can reset the model to default values, and a references sheet added.

A 'reset to default' macro and a references sheet have been added to the model.

B17. The company model includes rituximab as the 1400mg subcutaneous solution for injection, however the SMPC for this particular formulation does not appear to include CLL. Please comment on whether the subcutaneous formulation would be used in this population and if so what proportions of people in the model would have subcutaneous rituximab as opposed to

intravenous infusion? Please update the model to allow modelling of intravenous rituximab.

The company thank the EAG for highlighting that subcutaneous rituximab is not used for CLL. Clinical experts consulted by the company confirmed that intravenous rituximab is used when given as a subsequent treatment for CLL. As such, the model has been updated to reflect this formulation. Results of the revised Company base case incorporating this change are presented in Appendix 1.

Section C: Literature searching, Textual clarification and additional points

C1. Please provide references and PDFs of the identified SLRs/NMAs used for handsearching of bibliographies (CS Appendices, section B.2. 'Reference list searches') and clarify if there were 15 (CS Appendices, figure 1 'PRISMA flow diagram').

Yes, 15 SLRs/NMAs were identified for handsearching of bibliographies. The PDF files of the reviews have been included in the reference pack accompanying this response.⁵²⁻⁶⁶

C2. Please clarify which of the following highlighted numbers are correct.

	PRISMA Flow diagram (figure 1)	Table / section in CS appendices
Records from database searching		Table 1 MEDLINE and Embase (via Embase.com):
	MEDLINE 5563	Line 61 (MEDLINE) 5246 250 5496
	Embase 6504	Line 60 (Embase) 6254 317 6571
	TOTAL 12067	TOTAL 12067
	Cochrane: 1709 Pre-prints: 5 INAHTA: 78	Table 2 Cochrane: 1675 Table 1 line 62: 5 INAHTA: 78
Records identified through other sources	Peer reviewed publications from bibliographic search: 3 Conference abstracts: 72 Clinical study reports: 2	No details of numbers from bibliographic search or searches of clinical trials registers in text or tables. Table 5 conference hand searches: 32
Records screened		B.3.1 Original SLR: 7766 SLR update: 418

	PRISMA Flow diagram (figure 1)	Table / section in CS appendices
	8260	TOTAL: 8184
Records excluded [Ti/Ab]	8119	B.3.1 Original SLR: 7638 SLR update: 405 TOTAL: 8043
Studies included	53 studies reported across 161 references: 81 peer-reviewed 72 conference abstracts 2 CSRs TOTAL: 155	Table 8: 53 studies (161 references) Of the 161: 84 for 'Database Searches', 71 for 'Conference proceeding', 1 for 'Peer reviewed publication', 3 for 'Bibliography searches', 2 for 'CSR'.
	15 SLR/ITCs	

The company thanks the EAG for flagging these discrepancies, which were due to a calculation error. A corrected version of the PRISMA diagram, aligned with the results of Table 1 from the CS Appendices, is presented in Figure 12. An amended version of Table 8 from the CS Appendices is also presented in Appendix 2, and an amended description of the SLR results has been provided below.

With regards to the Cochrane hits, the correct total number of hits is 1,709, as stated in the PRISMA diagram. This calculation is based on the sum of the number of hits from the original SLR (line 19 of the search strategy: 1,617 hits) and the SLR update (line 20 of the search strategy: 92 hits) (see Table 2 in the CS Appendices).

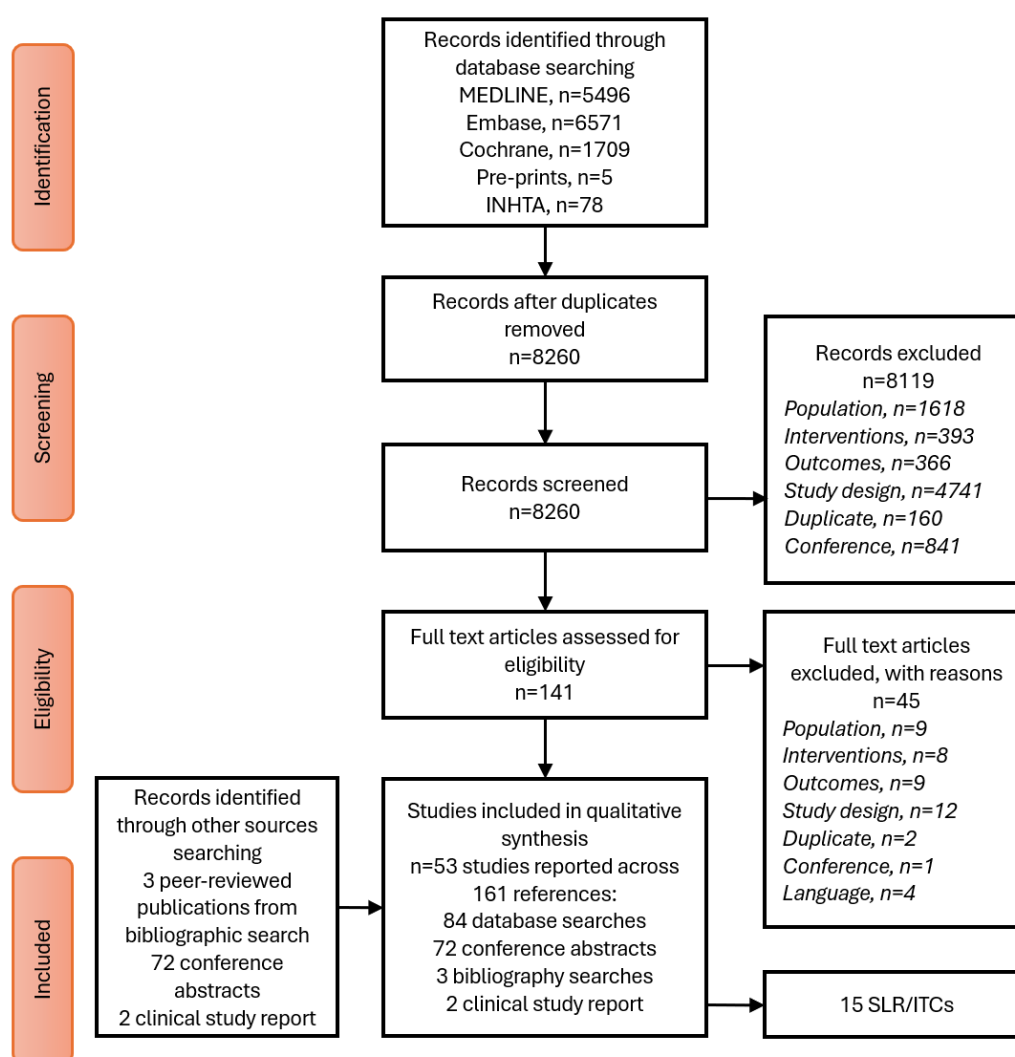
Original SLR

In the original SLR (11th October 2024), a total of 7,842 records were retrieved from database searches. Of these, 7,714 were removed after screening at the title/abstract stage. The remaining 128 full texts were screened for eligibility, of which 43 were excluded. A total of 63 records were identified through supplementary searches.

SLR update

In the SLR update (24th June 2025), a total of 418 records were retrieved through database searches. Of these, 13 were identified as being potentially relevant, and their full texts were screened for eligibility. Out of the 13 full texts, 11 met the eligibility criteria and were included in the SLR. An additional 14 records were identified through supplementary searches.

Figure 12: PRISMA flow diagram for original and updated clinical SLRs



Abbreviation: SLR: systematic literature review.

C3. Exclusion criteria are given in general in the introduction to section B.5 for the feasibility assessment. Please give reasons for exclusion for individual studies.

Details of studies excluded from the feasibility assessment and the rationale for exclusion are presented in Appendix 2

C4. Please clarify if the bibliographies of 11 reviews reported in figure 18 ‘PRISMA flow diagram’ were hand-searched to identify any additional studies of interest and provide references and PDFs of these reviews.

The bibliographies of all 11 reviews presented in Figure 18 of the CS Appendices were hand searched. However, no additional, potentially relevant studies were identified from these. The PDF files of the 11 reviews have been included in the reference pack accompanying this response.⁶⁷⁻⁷⁷

C5. Please clarify which of the following highlighted numbers are correct.

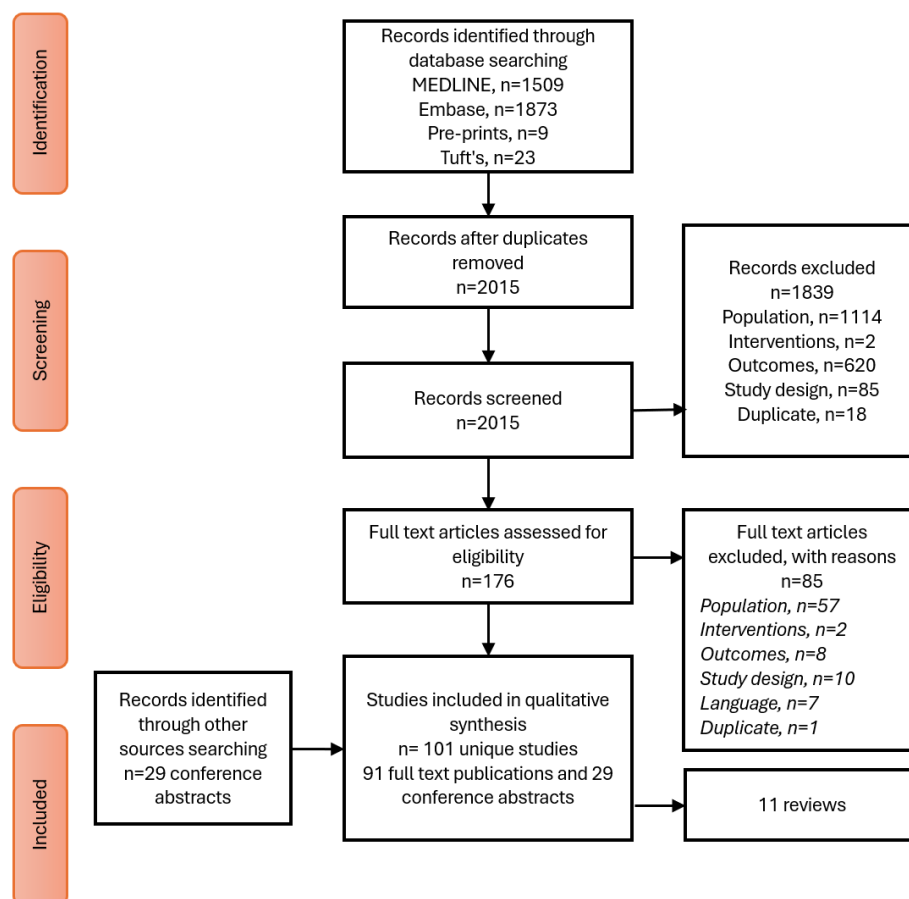
	Flow diagram (figure 18)	Tables or text in appendices
Records from database searching		Table 19 MEDLINE and Embase (via Embase.com):
	MEDLINE 1534	Line 67 (MEDLINE) 1396 138 1534
	Embase 1848	Line 66 (Embase) 1735 157 1892
	TOTAL	TOTAL
	CEA Registry: 23 Pre-prints: 9	Table 20 CEA Registry: 25 Table 19, line 68 (Pre-prints): 3 + 113 = 116 Table 21 INAHTA: 77
Records identified through other sources	Conference abstracts: 29	No details of numbers from conference hand searches in text or tables.
Records after duplicates removed	2015	
Records screened	2017	1857 + 158 = 2015 (CS Appendix E.1.3)
Full text excluded	85	84
Studies included	101 (120 publications)	47 (47 publications) economic evaluations (Table 25) 45 (45 publications) utilities/HRQoL (Table 31) 65 (65 publications) (Table 34) Note in introduction (CS Appendix E.1, that 'Each study identified could therefore be included in one or more streams')
	11 reviews	

The Company thanks the EAG for flagging these errors. A corrected PRISMA diagram is presented in Figure 13, and corrected versions of the search strategies have been provided in Appendix 2.

Additionally, one study was missing from the excluded studies table in the CS (Table 26 in the CS), hence the discrepancy in the number of records excluded at the full-text stage, as noted by the EAG. The reference for the missing record has been provided below:

Shadman M, Salkar M, Srivastava B, et al. Real-world outcomes following ibrutinib dose reduction in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia & Lymphoma* 2025;66:44-53.

Figure 13: PRISMA flow diagram for original and updated economic SLRs



Abbreviation: SLR: systematic literature review.

C6. For CS Table 50, the CSR (ref 2) is cited, but the table number given in the citation is not in the CSR or TLF document. Please clarify if 'Table 14.3.2' is referring to all the tables starting with 14.3.2 in the TLF document.

The Company thanks the EAG for flagging this. The AMPLIFY trial data in Table 50 of the CS was sourced from Table 14.3.2.4 of the CSR.

C7. In Appendix G, could you please include a table summarizing resource use and intervention name for each study, along with details on how the various cost items were measured in the included studies?

A summary of the interventions, resource use and cost items for each study included in the cost and resource use stream of the economic SLR is presented in Table 13 of Appendix 2.

Appendix 1

Revised Company base case results

The Company has updated its base case as follows:

- Discounting occurs from Year 1 onwards and is now applied annually (Clarification Question B8)
- All model traces now start from Cycle 1 (previously Cycle 0) (Clarification Question B11)
- Venetoclax costs in the AV and VenI arms are now applied from Cycle 3 and Cycle 4, respectively, aligned with each regimen's SmPC, while all other treatments start in Cycle 1 (Clarification Question B11)
- The maximum number of treatment cycles is now aligned with each regimen's SmPC: AV: 14 cycles; VenI: 15 cycles; VenO: 12 cycles (Clarification Question B11)
- TTD curves are capped at the maximum number of cycles for each treatment (set to zero beyond that point), ensuring consistency between costs and accrued benefits in the progression-free (on-treatment) health state (Clarification Question B11)
- Rituximab administration has been updated from subcutaneous to intravenous (Clarification Question B17)

Results of the revised Company base case are presented below.

Deterministic base case results (revised Company base case)

Deterministic base case results for the economic analysis of AV versus VenI and VenO are presented in Table 5.

In the deterministic base case analysis versus VenI, AV was associated with █████ QALYs at a █████ total cost of █████, resulting in AV dominating VenI. This translates to an NMB at a WTP threshold of £30,000 per QALY of █████.

In the deterministic base case analysis versus VenO, AV was associated with █████ QALYs at a █████ total cost of █████, resulting in AV dominating VenO. This translates to an NMB at a WTP threshold of £30,000 per QALY of █████.

Table 5: Deterministic base case results for AV versus VenI and VenO (acalabrutinib with-PAS price)

Technologies	Total costs (£)	Total LYG	Total QAL Ys	Incr. costs (£)	Incr. LYG	Incr. QAL Ys	ICER (£/QALY) ^a	NMB at £30,000/QALY
AV	█████	12.592	█████	—	—	—	—	—
VenI	█████	12.592	█████	█████	0.000	█████	Dominant	█████
VenO	█████	12.592	█████	█████	0.000	█████	Dominant	█████

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Probabilistic base case results (revised Company base case)

Probabilistic base case results for the economic analysis of AV versus VenI and VenO are presented in Table 6. These results align with the deterministic base case analysis.

In the probabilistic base case analysis versus VenI, AV was associated with [REDACTED] QALYs at a [REDACTED] total cost of [REDACTED], resulting in AV dominating VenI. This translates to an NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenI at the same WTP threshold was [REDACTED].

In the probabilistic base case analysis versus VenO, AV was associated with [REDACTED] QALYs at a [REDACTED] total cost of [REDACTED], resulting in AV dominating VenO. This translates to an NMB at a WTP threshold of £30,000 per QALY of [REDACTED]. As such, the probability of AV being cost-effective versus VenO at the same WTP threshold was [REDACTED].

The economic analysis included the existing PAS price for acalabrutinib and list prices of comparator therapies.

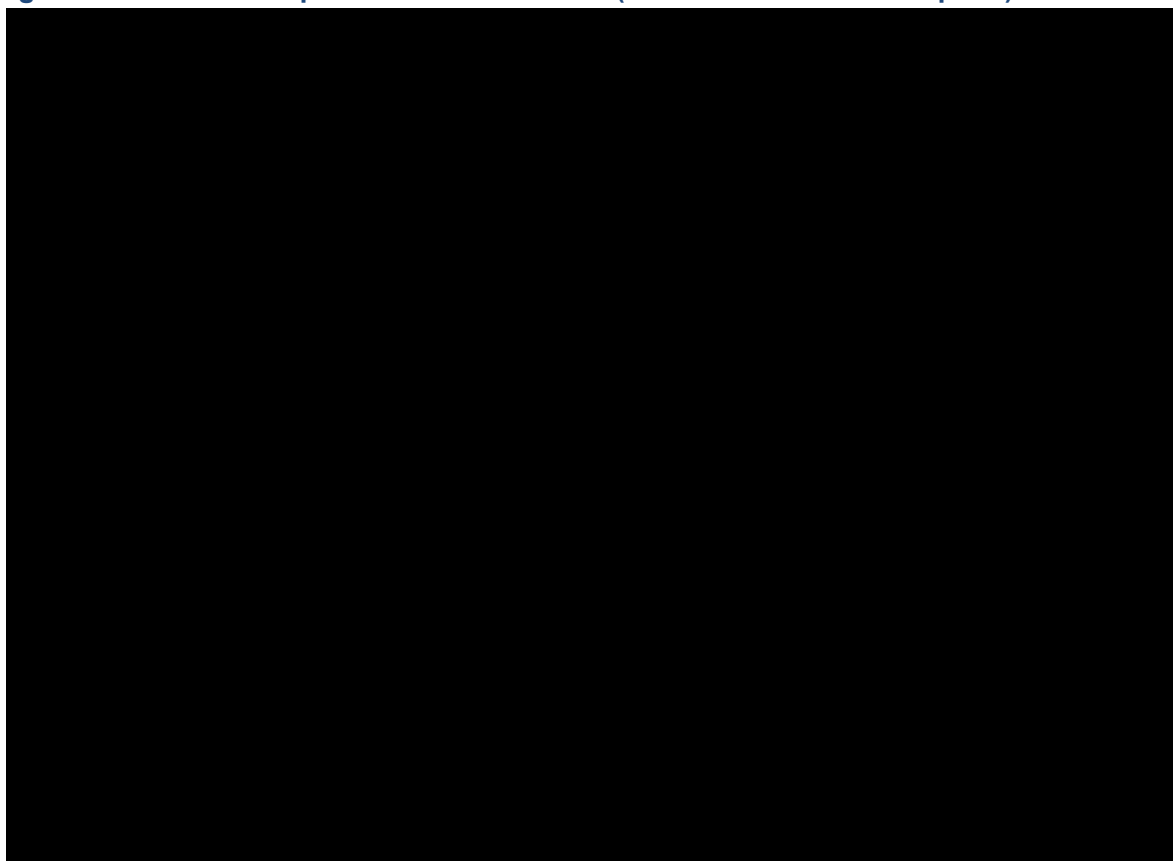
Table 6: Probabilistic base case results for AV versus VenI and VenO (acalabrutinib with-PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) ^a	NMB at £30,000 /QALY
AV	[REDACTED]	12.591	[REDACTED]	-	-	-	-	-
VenI	[REDACTED]	12.591	[REDACTED]	[REDACTED]	0.000	[REDACTED]	Dominant	[REDACTED]
VenO	[REDACTED]	12.591	[REDACTED]	[REDACTED]	0.000	[REDACTED]	Dominant	[REDACTED]

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

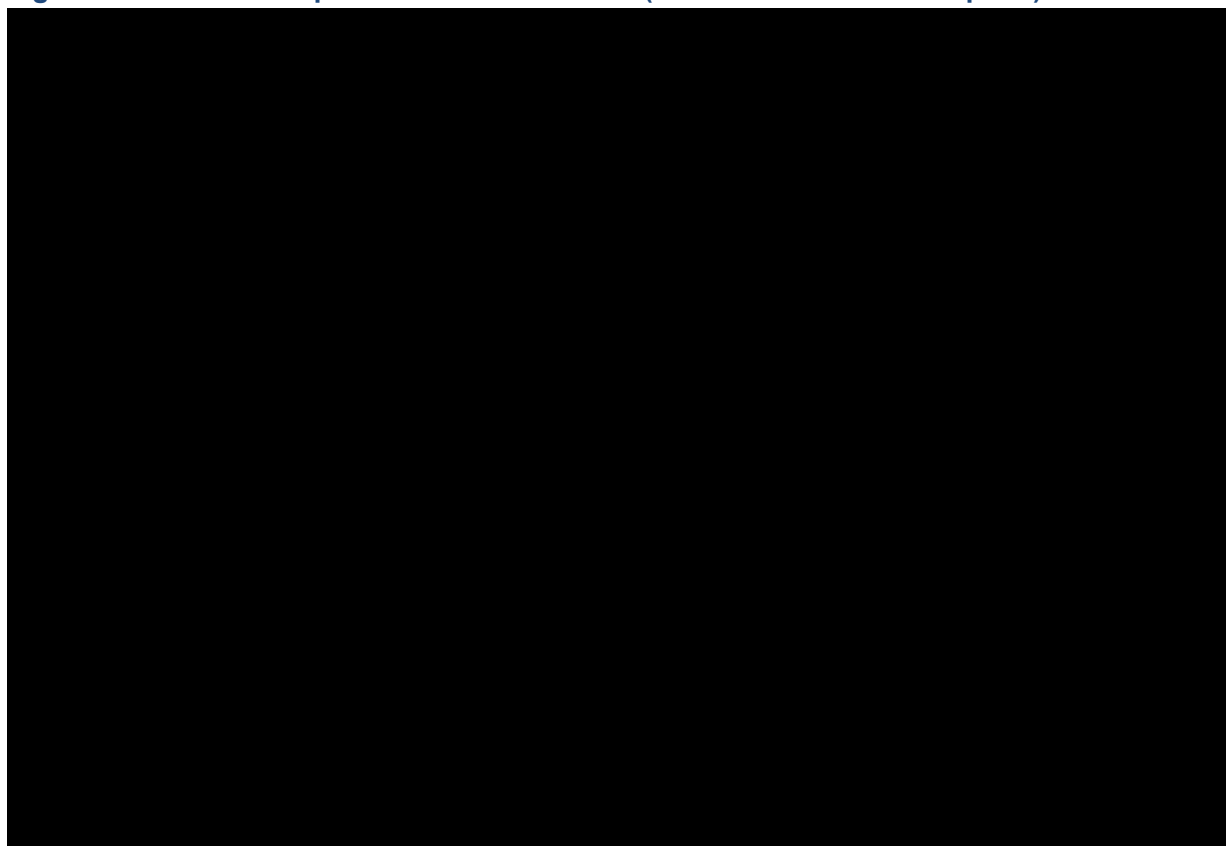
A scatter plot showing the incremental costs and QALYs from the 10,000 iterations of the PSA for AV versus VenI, and VenO, are presented in Figure 14 and Figure 15, respectively.

Figure 14: PSA scatter plot for AV versus VenI (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay; VenI: venetoclax with ibrutinib.

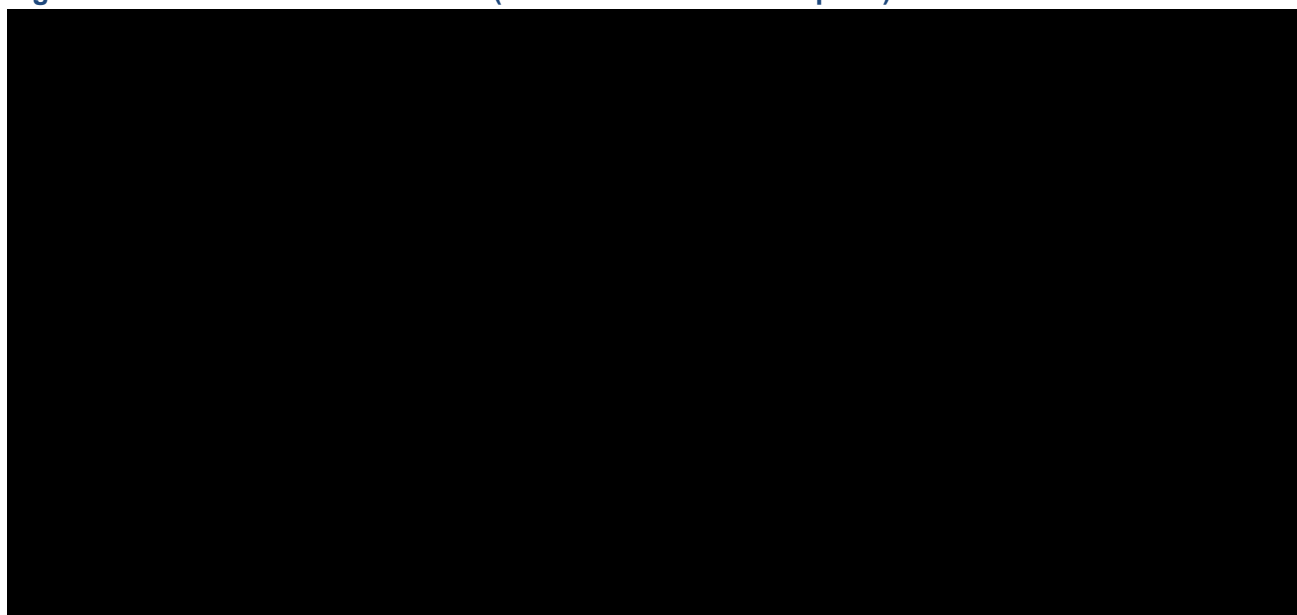
Figure 15: PSA scatter plot for AV versus VenO (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay; VenO: venetoclax with obinutuzumab.

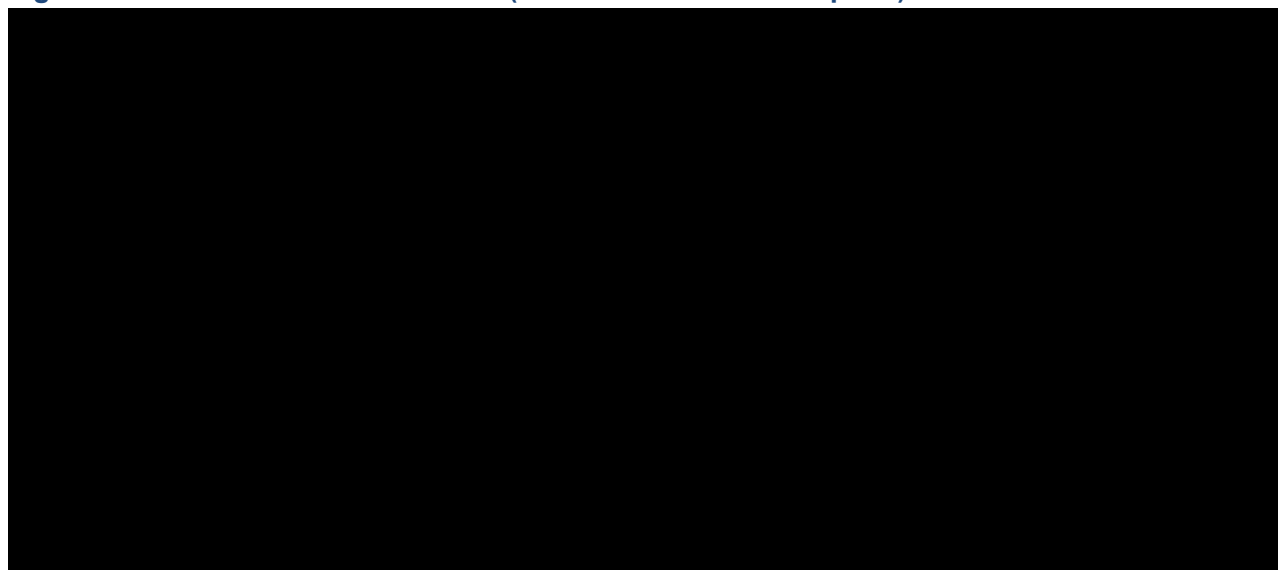
The cost-effectiveness acceptability curve (CEAC) for AV versus VenI, and VenO, are presented in Figure 16 and Figure 17, respectively.

Figure 16: CEAC for AV versus VenI (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenI: venetoclax with ibrutinib.

Figure 17: CEAC for AV versus VenO (acalabrutinib with-PAS price)



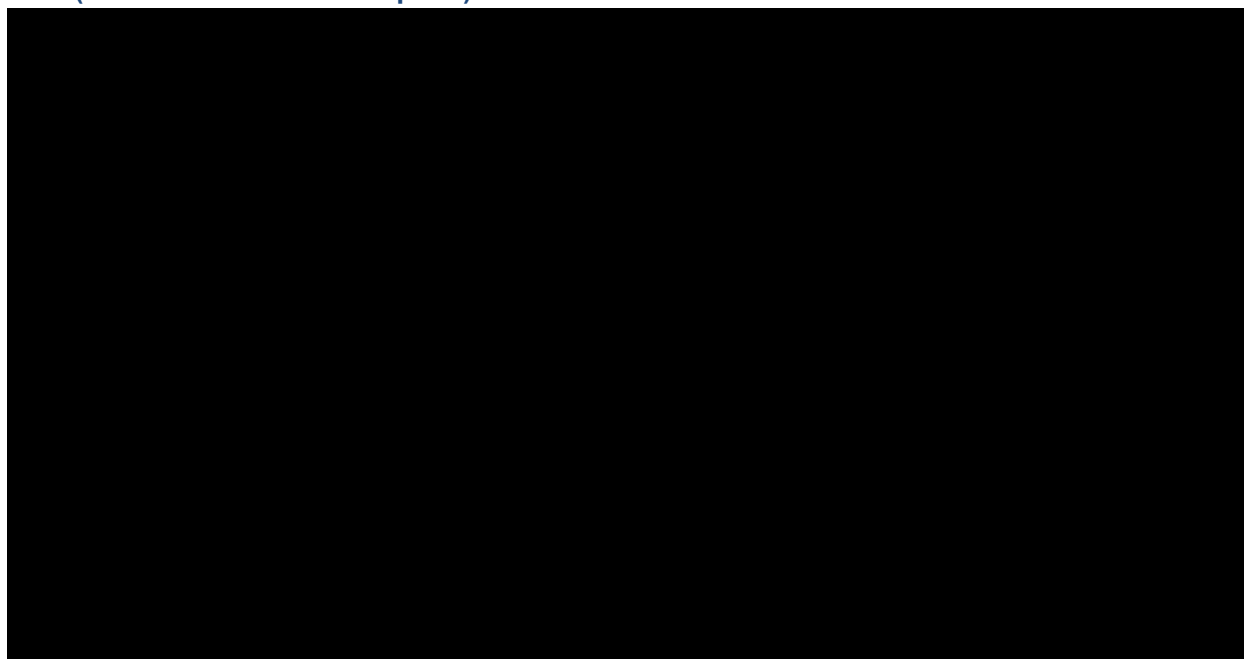
Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenO: venetoclax with obinutuzumab.

Deterministic sensitivity analysis (revised Company base case)

A deterministic sensitivity analysis (DSA) was undertaken to explore the impact of varying key model parameter values by +/- 10% on the NMB for each comparison. A tornado diagram showing the key drivers of the DSA in the base case economic analysis of AV versus VenI, and versus VenO, are presented in Figure 18 and Figure 19, respectively. The WTP is assumed to be £30,000 per QALY.

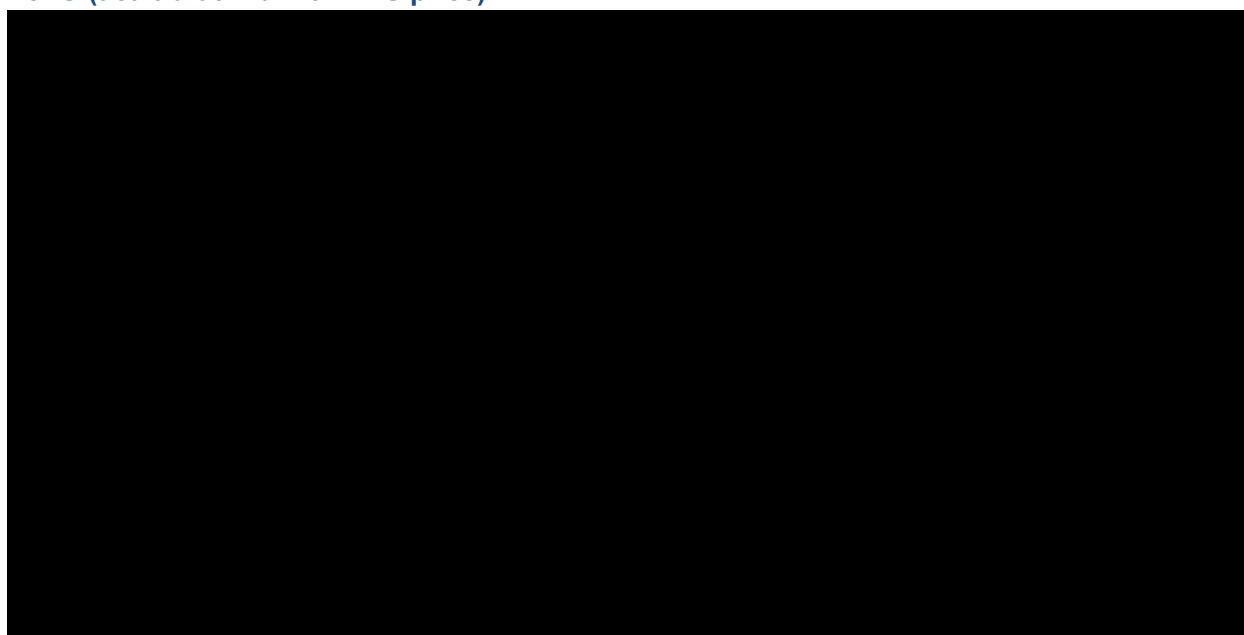
The most influential drivers in the base case economic analysis versus VenI were the proportion of patients receiving subsequent treatment with zanubrutinib monotherapy, and venetoclax with rituximab, for the VenI arm. Similarly, versus VenO, the most influential drivers were the proportion of patients receiving subsequent treatment with zanubrutinib monotherapy, and venetoclax with rituximab, for the VenO arm.

Figure 18: NMB (WTP threshold of £30,000 per QALY) DSA tornado diagram for AV versus VenI (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; WTP: willingness-to-pay.

Figure 19: NMB (WTP threshold of £30,000 per QALY) DSA tornado diagram for AV versus VenO (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenO: venetoclax with obinutuzumab; WTP: willingness-to-pay.

Scenario analyses

Scenario analyses results for the revised Company base case are provided in Table 7 (versus VenI) and Table 8 (versus VenO). In the vast majority of scenarios, AV remained dominant

versus both VenI and VenO. The results remain stable across the majority of scenarios because of the underlying assumption of equivalence in efficacy between AV, VenI, and VenO.

Table 7: Scenario analysis results – AV versus VenI (acalabrutinib with-PAS price)

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	NMB at £30,000/QALY (£)	ICER (£/QALY) ^a
Base case analysis		████	████	████	Dominant
TTP curve selection (log-logistic distribution)	Alternative TTP curve selection (gamma)	████	████	████	Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gen gamma)	████	████	████	Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gamma)	████	████	████	Dominant
Post-PS curve selection (exponential distribution)	Alternative post-PS curve selection (lognormal)	████	████	████	Dominant
Post-PS curve selection (exponential distribution)	Alternative post-PS curve selection (Weibull)	████	████	████	Dominant
Wastage assumed	Assume no wastage	████	████	████	Dominant
Subsequent treatment distribution based on clinician feedback	Subsequent treatment distributions from AMPLIFY	████	████	████	Dominant
Utility data collected from the AMPLIFY trial	Health state utilities from Kosmas <i>et al.</i> (2015)	████	████	████	Dominant
AE-related disutility applied	No AE-related disutility	████	████	████	Dominant
3.5% discount for costs and benefits	1.5% discount for costs and benefits	████	████	████	Dominant
100% RDI for VenI and VenO, AMPLIFY RDIs for AV	AV RDIs applied to VenI and VenO	████	████	████	Dominant
Uncapped utilities	General population capped utilities	████	████	████	████
Uncapped utility data collected	Health state utilities from	████	████	████	████

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	NMB at £30,000/QALY (£)	ICER (£/QALY) ^a
from the AMPLIFY trial	Kosmas <i>et al.</i> (2015); capped by general population capped utilities				

^a **Abbreviations:** AE: adverse event; AV: acalabrutinib with venetoclax; incr: incremental; INHB: incremental net health benefit; N/A: not applicable; NMB: net monetary benefit; PAS: patient access scheme; post-PS: post-progression survival; QALY: quality-adjusted life year; WTP: willingness to pay; VenI: venetoclax with ibrutinib.

Table 8: Scenario analysis results – AV versus VenO (acalabrutinib with-PAS price)

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	NMB at £30,000/QALY (£)	ICER (£/QALY) ^a
Base case analysis					Dominant
TTP curve selection (log-logistic distribution)	Alternative TTP curve selection (gamma)				Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gamma)				Dominant
Pre-PS (log-logistic distribution)	Alternative pre-PS curve selection (gamma)				Dominant
Post-PS (exponential distribution)	Alternative post-PS curve selection (lognormal)				Dominant
Post-PS (exponential distribution)	Alternative post-PS curve selection (Weibull)				Dominant
Wastage assumed	Assume no wastage				Dominant
Subsequent treatment distribution based on clinician feedback	Subsequent treatment distributions from AMPLIFY				Dominant
Utility data collected from the AMPLIFY trial	Health state utilities from Kosmas <i>et al.</i> (2015)				Dominant
AE-related disutility applied	No AE-related disutility				Dominant

Appendix 2

Clinical SLR

List of included studies

A corrected version of the list of studies included in the original and updated clinical SLRs is presented in Table 9.

Table 9: List of studies included in clinical SLR (161 records reporting on 53 unique studies)

No.	Study name	Clinical trial number	Citations	Source
1.	ACE-CL-001	NCT02029443	Byrd, et al. 2021. Acalabrutinib in treatment-naïve chronic lymphocytic leukemia. Blood.	Database searches
			Byrd, et al. 2022. Final Results of the Phase 1/2 Study of Acalabrutinib Monotherapy in Treatment-Naïve Chronic Lymphocytic Leukemia with >6 Years of Follow-up. ASH.	Conference proceeding
2.	ADMIRE	ISRCTN 42165735	Munir, et al. 2017. Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL. Leukemia.	Database searches
3.	Ahn 2018	NCT01500733	Ahn, et al. 2018. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood.	Database searches
			Ahn, et al. 2020. Ibrutinib for Chronic Lymphocytic Leukemia with TP53 Alterations. New England Journal of Medicine.	Bibliography searches
			Itsara, et al. 2023. Long-Term Outcomes in Chronic Lymphocytic Leukemia Treated with Ibrutinib: 10-Year Follow-up of a Phase 2 Study. Blood.	Conference proceeding
4.	ALLIANCE	NCT01886872	Woyach, et al. 2018. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. New England Journal of Medicine.	Database searches
			Woyach, et al. 2024. Follow-up from the A041202 study shows continued efficacy of ibrutinib regimens for older adults with CLL. Blood.	Database searches
5.	AMPLIFY	NCT03836261	Brown, et al. 2025. Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia. New England Journal of Medicine.	Database searches
			Brown, et al. 2024. Fixed-Duration Acalabrutinib Plus Venetoclax with or without Obinutuzumab Versus Chemoimmunotherapy for First-Line Treatment of Chronic Lymphocytic Leukemia: Interim Analysis of the Multicenter, Open-Label, Randomized, Phase 3 AMPLIFY Trial. ASH.	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
			AstraZeneca. 2024. A Randomized, Multicenter, Open-Label, Phase 3 Study to Compare the Efficacy and Safety of Acalabrutinib (ACP-196) in Combination with Venetoclax with and without Obinutuzumab Compared to Investigator's Choice of Chemoimmunotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia Without del(17p) or TP53 Mutation (AMPLIFY). Interim Clinical Study Report.	CSR
6.	ARCTIC	ISRCTN 16544962	Howard, et al. 2017. Results of the randomized phase IIB ARCTIC trial of low-dose rituximab in previously untreated CLL. Leukemia.	Database searches
7.	AU-003	NCT02343120	Cull, et al. 2022. Zanubrutinib for treatment-naïve and relapsed/refractory chronic lymphocytic leukaemia: long-term follow-up of the phase I/II AU-003 study. British Journal of Haematology.	Database searches
			Tam, et al. 2019. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood .	Database searches
8.	Burger 2019	NCT02007044	Burger, et al. 2019. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood.	Database searches
			Kim, et al. 2025. 10-year follow-up of a randomized phase-2 study of ibrutinib or ibrutinib plus rituximab in patients with chronic lymphocytic leukemia (CLL). EHA.	Conference proceeding
9.	Burger 2022	NCT04505254	Burger, et al. 2022. Time-limited treatment with acalabrutinib plus obintuzumab in treatment-naïve chronic lymphocytic leukemia patients induces deep remissions: early results of an ongoing phase 2 trial. EHA.	Conference proceeding
			Burger, et al. 2024. A phase II study of time-limited treatment with acalabrutinib plus obinutuzumab in patients with treatment-naïve chronic lymphocytic leukemia. EHA.	Conference proceeding
			Burger, et al. 2024. A Phase II Study of Time-Limited Treatment with Acalabrutinib Plus Obinutuzumab in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia. ASH.	Conference proceeding
10.	CAPTIVAT E FD	NCT02910583	Ghia, et al. 2025. Final analysis of fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in the phase 2 CAPTIVATE study.. ASCO.	Conference proceeding
			Wierda, et al. 2025. Final analysis of fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
			lymphoma (SLL) in the phase 2 CAPTIVATE study. EHA.	
			Allan, et al. 2022. Treatment Outcomes after Undetectable MRD with First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Fixed Duration Treatment (Placebo) Versus Continued Ibr with up to 5 Years Median Follow-up in the CAPTIVATE Study. ASH.	Conference proceeding
			Allan, et al. 2023. Outcomes in Patients with High-Risk Features after Fixed-Duration Ibrutinib plus Venetoclax: Phase II CAPTIVATE Study in First-Line Chronic Lymphocytic Leukemia. Clinical Cancer Research.	Database searches
			Barr, et al. 2023. Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study. ASCO.	Conference proceeding
			Ghia, et al. 2023. Relapse after First-Line Fixed Duration Ibrutinib + Venetoclax: High Response Rates to Ibrutinib Retreatment and Absence of BTK Mutations in Patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) with up to 5 Years of Follow-up in the Phase 2 Captivate Study. ASH.	Conference proceeding
			Ghia, et al. 2023. Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from fd cohort of phase 2 CAPTIVATE study. EHA.	Conference proceeding
			Ghia, et al. 2023. Fixed-duration ibrutinib + venetoclax in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the fd cohort of the phase 2 CAPTIVATE study. ICML.	Conference proceeding
			Jacobs, et al. 2024. Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia/small lymphocytic lymphoma: up to 5.5 years of follow-up in the phase 2 CAPTIVATE study. EHA.	Conference proceeding
			Moreno, et al. 2022. Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 3-year follow-up from the phase 2 CAPTIVATE study FD cohort. EHA.	Conference proceeding
			Tam, et al. 2022. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood.	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
			Wierda, et al. 2022. Fixed-duration (FD) ibrutinib (I) + venetoclax (V) for first-line (1L) treatment (tx) of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Three-year follow-up from the FD cohort of the phase 2 CAPTIVATE study. ASCO.	Conference proceeding
			Wierda, et al. 2024. 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. ASCO.	Conference proceeding
			Wierda, et al. 2024. Consistently High 5.5-Year Progression-Free Survival (PFS) Rates in Patients with and without Bulky Baseline Lymphadenopathy ≥5 Cm Are Associated with High Undetectable Minimal Residual Disease (uMRD4) Rates after First-Line Treatment with Fixed-Duration Ibrutinib + Venetoclax for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) in the Phase 2 CAPTIVATE Study. ASH.	Conference proceeding
11.	CAPTIVAT E MRD	NCT029 10583	Wierda, et al. 2021. Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results From the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. Journal of Clinical Oncology.	Database searches
12.	Castro 2022	NCT023 15768	Castro, et al. 2022. Ibrutinib plus Obinutuzumab as Frontline Therapy for Chronic Lymphocytic Leukemia Is Associated with a Lower Rate of Infusion-Related Reactions and with Sustained Remissions after Ibrutinib Discontinuation: A Single-Arm, Open-Label, Phase 1b/2 Clinical Trial NCT0231576. Advances in Hematology.	Database searches
13.	ChangE	NCT040 75292	Qiu, et al. 2024. Acalabrutinib Versus Chlorambucil Plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia: A Randomized, Multicenter, Open-Label, Phase 3 Study. ASH.	Conference proceeding
14.	CLL10	NCT007 69522	Eichhorst, et al. 2016. First-line chemoimmunotherapy with bendamustine and rituximab versus fl udarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial . Lancet Oncology.	Database searches
			Kutsch, et al. 2020. Long term follow-up data and health-related quality of life in frontline	Database searches

No.	Study name	Clinical trial number	Citations	Source
			therapy of fit patients treated with FCR Versus BR (CLL10 Trial of the GCLLSG). HemaspHERE.	
15.	CLL11	NCT01010061	Goede, et al. 2014. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. New England Journal of Medicine.	Database searches
16.	CLL12	NCT02863718	Langerbeins, et al. 2025. Ibrutinib in Early-Stage Chronic Lymphocytic Leukemia: The Randomized, Placebo-Controlled, Double-Blind, Phase III CLL12 Trial. Journal of clinical oncology.	Database searches
			Goergen, et al. 2025. Impact of ibrutinib on quality of life in patients with early-stage, asymptomatic chronic lymphocytic leukemia: results from the phase III CLL12 trial – matching safety to patient-reported outcomes. EHA.	Database searches
			Goergen, et al. 2024. Impact of Ibrutinib on Quality of Life in Patients with Early-Stage, Asymptomatic Chronic Lymphocytic Leukemia: Results from the Phase III CLL12 Trial. ASH.	Conference proceeding
			Langerbeins, et al. 2022. The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia. Blood.	Database searches
			Langerbeins, et al. 2023. Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): final results of the phase 3, double-blind, placebo-controlled CLL12 trial. EHA.	Conference proceeding
			Langerbeins, et al. 2023. Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): final results of the CLL12 trial. ICML.	Conference proceeding
			Riecke, et al. 2023. Genetic markers and ibrutinib vs placebo treatment in early stage chronic lymphocytic leukemia -results from the GCLLSG CLL12 trial. ASH.	Conference proceeding
17.	CLL13	NCT02950051	Fürstenau, et al. 2025. The triple combination of venetoclax-ibrutinib-obinutuzumab prolongs progression-free survival compared to venetoclax-cd20-antibody combinations and chemoimmunotherapy in treatment-naïve chronic lymphocytic leukemia: final analysis from the phase 3 GAIA/CLL13 trial. EHA.	Conference proceeding
			Fürstenau, et al. 2025. The triple combination of venetoclax ibrutinib-obinutuzumab prolongs PFS compared to venetoclax-CD20-antibody combinations and chemoimmunotherapy in treatment-naïve CLL. ICML.	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
18.	CLL14	NCT02242942	Eichhorst, et al. 2022. Time-limited venetoclax-obinutuzumab +/- ibrutinib is superior to chemoimmunotherapy in frontline chronic lymphocytic leukemia (CLL): PFS co-primary endpoint of the randomized phase 3 GAIA/CLL13 trial. EHA.	Conference proceeding
			Eichhorst, et al. 2023. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. NEJM.	Database searches
			Fürstenau, et al. 2023. First-Line Venetoclax Combinations in Fit Patients with CLL: 4-Year Follow-up and NGS-Based MRD Analysis from the Phase 3 GAIA/CLL13 Trial. ASH.	Conference proceeding
			Fürstenau, et al. 2024. 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. Lancet Oncology.	Database searches
			Fürstenau, et al. 2024. Patient-Reported Quality of Life Outcomes with Venetoclax-Based First-Line Combinations in CLL: An Analysis from the Phase 3 GAIA/CLL13 Trial. ASH.	Conference proceeding
18.	CLL14	NCT02242942	Al-Sawaf, et al. 2020. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncology.	Database searches
			Al-Sawaf, et al. 2021. Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study. Journal of Clinical Oncology.	Database searches
			Al-Sawaf, et al. 2021. Health-related quality of life with fixed-duration venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: Results from the randomized, phase 3 CLL14 trial. Am J Hematol.	Database searches
			Al-Sawaf, et al. 2022. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 5- year results of the randomized CLL14 study. EHA.	Conference proceeding
			Al-Sawaf, et al. 2023. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. Nat Commun.	Database searches
			Al-Sawaf, et al. 2023. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study. EHA.	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
			Al-Sawaf, et al. 2023. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study. ICML.	Conference proceeding
			Al-Sawaf, et al. 2024. Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the phase 3 CLL14 study. Blood.	Database searches
			Fischer, et al. 2019. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. New England Journal of Medicine.	Database searches
19.	CLL2007F MP	NCT005 64512	Feugier, et al. 2018. Long-term follow up of the CLL2007FMP trial evaluating fludarabine and cyclophosphamide in combination with either rituximab or alemtuzumab in previously untreated patients with chronic lymphocytic leukemia. Haematologica.	Database searches
			Lepretre, et al. 2012. Excess mortality after treatment with fludarabine and cyclophosphamide in combination with alemtuzumab in previously untreated patients with chronic lymphocytic leukemia in a randomized phase 3 trial. Blood.	Database searches
20.	CLL2-GiVe	NCT027 58665	Huber, et al. 2022. Final Analysis of the Prospective Multicenter CLL2-Give Trial of Obinutuzumab (GA101, G), Ibrutinib (I), and Venetoclax (Ve) in Untreated Patients with CLL with 17p Deletion/TP53 Mutation. ASH.	Conference proceeding
			Huber, et al. 2022. Obinutuzumab (GA-101), ibrutinib, and venetoclax (GiVe) frontline treatment for high-risk chronic lymphocytic leukemia. Blood.	Database searches
			Huber, et al. 2023. Final analysis of the CLL2-GiVe trial: obinutuzumab, ibrutinib, and venetoclax for untreated CLL with del(17p)/TP53mut. Blood.	Database searches
21.	CLL7	NCT002 75054	Herling, et al. 2020. Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial. Leukemia.	Database searches
22.	CLL8	NCT002 81918	Fischer, et al. 2016. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood.	Database searches
			Hallek, et al. 2010. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. The Lancet.	Database searches

No.	Study name	Clinical trial number	Citations	Source
			Kutsch, et al. 2017. FCR front-line therapy and quality of life in patients with chronic lymphocytic leukemia. Leukemia & lymphoma.	Database searches
23.	CRISTALLO	NCT04285567	Sharman, et al. 2024. 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. ASH.	Conference proceeding
			Sportoletti, et al. 2024. Reduction of Tumor Lysis Syndrome Risk after Debulking with Obinutuzumab in Patients Treated with Venetoclax–Obinutuzumab in the Randomized Phase 3 CRISTALLO Trial. ASH.	Conference proceeding
24.	Danilov 2017	-	Danilov, et al. 2017. A phase I dose-ranging study of bendamustine and rituximab in chronic lymphocytic leukemia patients with comorbidities. British journal of haematology.	Database searches
25.	Davids 2021	NCT03580928	Davids, et al. 2021. Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study. The Lancet Oncology.	Database searches
			Davids, et al. 2024. Primary Endpoint Evaluation of a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease. ASH.	Conference proceeding
			Davids, et al. 2025. Phase II Study of Acalabrutinib, Venetoclax, and Obinutuzumab in a Treatment-Naive Chronic Lymphocytic Leukemia Population Enriched for High-Risk Disease. Journal of Clinical Oncology.	Database searches
			Ryan , et al. 2022. Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease. Blood.	Conference proceeding
26.	E1912	NCT02048813	Shanafelt, et al. 2019. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. NEJM.	Database searches
			Shanafelt, et al. 2022. Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood.	Database searches
			Shanafelt, et al. 2024. Tolerability & long-term disease control by IGHV mutation status among CLL patients on ibrutinib arm of E1912. Blood advances.	Database searches

No.	Study name	Clinical trial number	Citations	Source
27.	ELEVATE-TN	NCT024 75681	AstraZeneca. 2022. A Randomized, Multicenter, Open-Label, 3 Arm Phase 3 Study of Obinutuzumab in Combination with Chlorambucil, ACP-196 in Combination with Obinutuzumab, and ACP-196 Monotherapy in Subjects with Previously Untreated Chronic Lymphocytic Leukemia. CSR.	CSR
			Follows, et al. 2023. Elevate-TN: Impact of First-Year Dose Modifications in Patients with Treatment-Naive Chronic Lymphocytic Leukemia Treated with Acalabrutinib. ASH.	Conference proceeding
			Sharman, et al. 2020. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. Lancet.	Database searches
			Sharman, et al. 2022. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia.	Database searches
			Sharman, et al. 2022. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN. ASCO.	Conference proceeding
			Sharman, et al. 2022. Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: 5-year follow-up of ELEVATE-TN. EHA.	Conference proceeding
			Acalabrutinib-Obinutuzumab Improves Survival vs Chemoimmunotherapy in TN CLL in the 6-year Follow-up of ELEVATE-TN	Database searches
			Sharman, et al. 2023. Acalabrutinib ± Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN. ASH.	Conference proceeding
28.	ERADIC	NCT040 10968	Michallet, et al. 2023. Minimal Residual Disease-Guided Combination of Ibrutinib and Venetoclax Compared to FCR in Untreated Patients with CLL of Intermediate Risk : Interim Results of MRD Kinetics in the Eradic Trial from the Filo Group. Blood.	Database searches
			Michallet, et al. 2023. Minimal residual disease-guided combination of ibrutinib plus venetoclax compared to FCR in untreated patients with CLL of intermediate risk: interim results from the phase II FILO trial. EHA.	Conference proceeding
		NCT028 63718	Michallet, et al. 2024. Minimal Residual Disease-Guided Combination of Ibrutinib and	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
			Venetoclax Compared to FCR in Untreated Patients with CLL of Intermediate Risk : Final Results of the Eradic Trial from the Filo Group. ASH.	
29.	FILO	NCT01370772	Cartron, et al. 2018. Increased rituximab exposure does not improve response and outcome of patients with chronic lymphocytic leukemia after fludarabine, cyclophosphamide, rituximab. A French innovative leukemia organization (FILO) study. Haematologica.	Database searches
30.	Fischer 2012	-	Fischer, et al. 2012. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. Journal of Clinical Oncology.	Database searches
31.	FLAIR	ISRCTN 01844152	Dalal, et al. 2023. Ibrutinib and Rituximab Versus Fludarabine, Cyclophosphamide, and Rituximab for Patients in NCRI FLAIR Study with Previously Untreated CLL: Assessment of Mutational Landscape of Patients at Baseline and Prognostic Impact. ASH.	Conference proceeding
			Hillmen, et al. 2022. THE COMBINATION OF IBRUTINIB PLUS VENETOCLAX RESULTS IN A HIGH RATE OF MRD NEGATIVITY IN PREVIOUSLY UNTREATED CLL: THE RESULTS OF THE PLANNED INTERIM ANALYSIS OF THE PHASE III NCRI FLAIR TRIAL. EHA.	Conference proceeding
			Munir, et al. 2025. Ibrutinib plus venetoclax with MRD-guided duration of treatment is superior to both continuous ibrutinib monotherapy and FCR for previously untreated CLL: report of the phase III UK FLAIR study. EHA.	Conference proceeding
			Hillmen, et al. 2023. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. The Lancet. Oncology.	Database searches
			Hillmen, et al. 2023. Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study. ASH.	Conference proceeding
			Munir, et al. 2022. Combination of Ibrutinib Plus Venetoclax with MRD-Driven Duration of Treatment Results in a Higher Rate of MRD Negativity in IGHV Unmutated Than Mutated	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
			CLL: Updated Interim Analysis of FLAIR Study. ASH.	
			Munir, et al. 2024. Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease. New England Journal of Medicine.	Database searches
			Rawstron, et al. 2023. Using Peripheral Blood (PB) Measurable Residual Disease (MRD) Levels to Predict <0.01% Bone Marrow Disease (BM uMRD4): Identification of Effective PB Targets for CLL Treatment Cessation in the Ibrutinib+Venetoclax Arm of the FLAIR Trial. ASH.	Conference proceeding
32.	Flinn 2019	NCT01685892	Flinn, et al. 2019. Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. Blood.	Database searches
33.	GALTON	NCT01300247	Brown, et al. 2015. Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase 1b GALTON trial. Blood.	Bibliography searches
			Brown, et al. 2019. Durable remissions with obinutuzumab-based chemoimmunotherapy: long-term follow-up of the phase 1b GALTON trial in CLL. Blood.	Database searches
34.	GIBB	NCT02320487	Danilov, et al. 2022. Improvements in Health-related Quality of Life and Symptoms in Patients With Previously Untreated Chronic Lymphocytic Leukemia: Final Results From the Phase II GIBB Study of the Combination of Obinutuzumab and Bendamustine. Clinical Lymphoma, Myeloma and Leukemia.	Database searches
			Sharman, et al. 2021. Phase 2, multicenter GIBB study of obinutuzumab plus bendamustine in previously untreated patients with chronic lymphocytic leukemia. Leukemia and Lymphoma.	Database searches
35.	GIMEMA LLC1114	NCT02232386	Mauro, et al. 2022. Efficacy of Front-Line Ibrutinib and Rituximab Combination and the Impact of Treatment Discontinuation in Unfit Patients with Chronic Lymphocytic Leukemia: Results of the Gimema LLC1114 Study. Cancers.	Database searches
			Mauro, et al. 2021. Efficacy of Front-Line Ibrutinib and Rituximab Combination and the Impact of Treatment Discontinuation in Unfit Patients with Chronic Lymphocytic Leukemia: Results of the GimemaLLC1114 Study. Cancers.	Database searches
36.	GIMEMA LLC1518	NCT03455517	Maoro, et al. 2023. 36-Month Follow-up Results of the Gimema 'Veritas' Trial of Front-Line Venetoclax and Rituximab (VenR) in	Conference proceeding

No.	Study name	Clinical trial number	Citations	Source
	VERITAS trial		Young and Fit Patients with Chronic Lymphocytic Leukemia and an Adverse Biologic Profile. Blood.	
			Mauro, et al. 2023. High rate of durable responses with undetectable minimal residual disease with front-line venetoclax and rituximab in young, fit patients with chronic lymphocytic leukemia and an adverse biological profile: results of the GIMEMA phase II LLC1518 – VERITAS study . Haematologica.	Database searches
			Kater, et al. 2022. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evidence.	Database searches
			Moreno, et al. 2023. First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): 55-Month Follow-up from the Glow Study. ASH.	Conference proceeding
			Munir, et al. 2023. Impact of Minimal Residual Disease on Progression-Free Survival Outcomes After Fixed-Duration Ibrutinib-Venetoclax Versus Chlorambucil-Obinutuzumab in the GLOW Study. Journal of Clinical Oncology.	Database searches
37.	GLOW	NCT034 62719	Niemann, et al. 2022. Residual Disease Kinetics Among Patients with High-Risk Factors Treated with First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): The Glow Study. ASH.	Conference proceeding
			Niemann, et al. 2023. Fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncology.	Database searches
			Niemann, et al. 2024. First-Line Ibrutinib Plus Venetoclax Vs Chlorambucil Plus Obinutuzumab in Elderly or Comorbid Patients (Pts) with Chronic Lymphocytic Leukemia (CLL): Glow Study 64-Month Follow-up (FU) and Adverse Event (AE)-Free Progression-Free Survival (PFS) Analysis. ASH.	Conference proceeding
38.	GREEN	NCT019 05943	LeBlonde, et al. 2018. Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIb GREEN study. Haematologica.	Database searches

No.	Study name	Clinical trial number	Citations	Source
			Stilgenbauer, et al. 2021. Safety and efficacy of obinutuzumab alone or with chemotherapy in previously untreated or relapsed/refractory chronic lymphocytic leukaemia patients: Final analysis of the Phase IIIb GREEN study. British Journal of Haematology.	Database searches
39.	Herishanu 2019	-	Herishanu, et al. 2019. Low-dose fludarabine and cyclophosphamide combined with standard dose rituximab (LD-FCR) is an effective and safe regimen for elderly untreated patients with chronic lymphocytic leukemia: The Israeli CLL study group experience. Hematological Oncology.	Database searches
40.	ICLL07	NCT02666898	Michallet, et al. 2019. Obinutuzumab and ibrutinib induction therapy followed by a minimal residual disease-driven strategy in patients with chronic lymphocytic leukaemia (ICLL07 FILO): a single-arm, multicentre, phase 2 trial. The Lancet Haematology.	Database searches
			Michallet, et al. 2022. A Fixed-Duration Immunochemotherapy Approach Combined with Ibrutinib in CLL Produces Deep and Sustained MRD Responses: 5.5-Year Results from the Icll-07 Filo Trial. Blood.	Conference proceeding
			Michallet, et al. 2023. A fixed-duration immunochemotherapy approach in CLL: 5.5-year results from the phase 2 ICLL-07 FILO trial. Blood advances.	Database searches
41.	iLLUMINATE	NCT02264574	Moreno, et al. 2019. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet.	Database searches
			Moreno, et al. 2022. First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: final analysis of the randomized, phase III iLLUMINATE trial. Haematologica.	Database searches
42.	Izutsu 2021	JapicCTI-132285	Izutsu, et al. 2021. A phase II Japanese trial of fludarabine, cyclophosphamide and rituximab for previously untreated chronic lymphocytic leukemia. Japanese Journal of Clinical Oncology.	Database searches
43.	Jain 2019	NCT02756897	Jain, et al. 2019. Ibrutinib and Venetoclax for First-Line Treatment of CLL. New England Journal of Medicine.	Database searches
			Jain, et al. 2021. Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic	Database searches

No.	Study name	Clinical trial number	Citations	Source
			Leukemia A Nonrandomized Phase 2 Trial. JAMA Oncology.	
			Jain, et al. 2023. Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): 5-Year Follow-up Data. ASH.	Conference proceeding
			Jain, et al. 2022. Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): 4-Year Follow-up Data. ASH.	Conference proceeding
44.	MABLE	NCT01056510	Michallet, et al. 2018. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica.	Database searches
45.	O'Brien 2014	NCT01105247	O'Brien, et al. 2014. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet.	Database searches
			Byrd, et al. 2020. Ibrutinib Treatment for First-Line and Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Analysis of the Pivotal Phase Ib/II PCYC-1102 Study. Clinical Cancer Research.	Bibliography searches
46.	RESONAT E-2	NCT01722487	Burger, et al. 2015. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. The New England Journal of Medicine.	Database searches
			Burger, et al. 2020. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia.	Database searches
			Burger, et al. 2024. Final analysis of the RESONATE-2 study: up to 10 years of follow-up of first-line ibrutinib treatment in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA.	Conference proceeding
			Woyach, et al. 2023. Characteristics and Clinical Outcomes of Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Receiving Ibrutinib for 5 Years in the RESONATE-2 Study. Cancers.	Database searches
			Barr, et al. 2018. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica.	Database searches
			Barr, et al. 2022. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for	Database searches

No.	Study name	Clinical trial number	Citations	Source
			patients with chronic lymphocytic leukemia. Blood advances.	
47.	Roeker 2023-ASH	NCT044 47768	Roeker, et al. 2023. A Phase 2 Study of Minimal Residual Disease (MRD)-Adapted Front Line Venetoclax and Obinutuzumab in Fit Patients with Chronic Lymphocytic Leukemia (CLL): Effect of Obinutuzumab on Tumor Lysis Syndrome (TLS) Risk and Safety of Outpatient Venetoclax Dose Escalation. ASH.	Conference proceeding
			Roeker, et al. 2024. Minimal Residual Disease (MRD)-Adapted Duration of Front-Line Venetoclax and Obinutuzumab Treatment for Fit Patients with Chronic Lymphocytic Leukemia (CLL). ASH.	Conference proceeding
48.	SAWYER	NCT012 92603	Assouline, et al. 2016. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. The Lancet. Haematology.	Database searches
49.	SEQUOIA	NCT033 36333	Ghia, et al. 2022. PATIENT-REPORTED OUTCOMES FROM A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE PLUS RITUXIMAB (BR) IN PATIENTS WITH TREATMENT-NAÏVE (TN) CLL/SLL. EHA.	Conference proceeding
			Munir, et al. 2023. Zanubrutinib (ZANU) vs bendamustine + rituximab (BR) in patients (pts) with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): extended follow-up of the SEQUOIA study. EHA.	Conference proceeding
			Ramakrishnan, et al. 2023. Broad Superiority of Zanubrutinib (Zanu) Over Bendamustine + Rituximab (BR) Across Multiple High-Risk Factors: Biomarker Subgroup Analysis in the Phase 3 SEQUOIA Study in Patients With Treatment-Naive (TN) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) without del(17p). ASH.	Conference proceeding
			Shadman, et al. 2024. Sustained Superiority of Zanubrutinib vs Bendamustine + Rituximab in Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (TN CLL): 5-Year Follow-Up of Cohort 1 from the SEQUOIA Study. ASH.	Conference proceeding
			Tam, et al. 2021. Zanubrutinib monotherapy for patients with treatment-naïve chronic lymphocytic leukemia and 17p deletion. Haematologica.	Database searches

No.	Study name	Clinical trial number	Citations	Source
			Aldairy, et al. 2025. Adverse events of interest (AEIs) with zanubrutinib vs fixed-duration combination of venetoclax + obinutuzumab in treatment-naïve (TN) chronic lymphocytic leukemia (CLL). ASCO.	Conference proceeding
			Shadman, et al. 2025. Zanubrutinib Versus Bendamustine and Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: median 5-Year Follow-Up of SEQUOIA. Journal of Clinical Oncology.	Database searches
			Tam, et al. 2025. SEQUOIA 5-year follow-up in arm C: Frontline zanubrutinib monotherapy in patients with del(17p) and treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). ASCO.	Conference proceeding
			Tam, et al. 2025. SEQUOIA 5-year follow-up in arm C: frontline zanubrutinib monotherapy in patients with del(17p) and treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). EHA.	Conference proceeding
			Tam, et al. 2025. SEQUOIA 5 - year follow - up in arm C: Frontline zanubrutinib in patients with del(17p) And treatment - naïve chronic lymphocytic Leukemia/small lymphocytic lymphoma (CLL/SLL). ICML.	Conference proceeding
			Shadman, et al. 2025. Zanubrutinib and Venetoclax for Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del(17p)/TP53 Mutation: SEQUOIA Arm D Results. Journal of Clinical Oncology.	Database searches
			Shadman, et al. 2025. Combination of zanubrutinib (zanu) + venetoclax (ven) for treatment-naïve (TN) CLL/SLL: Results in SEQUOIA arm D. ASCO.	Conference proceeding
			Shadman, et al. 2025. Combination of zanubrutinib + venetoclax for treatment-naïve CLL/SLL: results in SEQUOIA arm D. EHA.	Conference proceeding
			Shadman, et al. 2025. Combination of zanubrutinib + venetoclax for treatment-naïve CLL/SLL: results in SEQUOIA arm D. ICML.	Conference proceeding
			Tam, et al. 2022. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncology.	Database searches
50.	Shibayama 2019	NCT025 56892	Shibayama, et al. 2019. Phase I study of ibrutinib in Japanese patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma.	Database searches

No.	Study name	Clinical trial number	Citations	Source
			Journal of clinical and experimental hematopathology : JCEH.	
51.	Short 2015	NCT00794820	Short, et al. 2015. Fludarabine, cyclophosphamide, and multiple-dose rituximab as frontline therapy for chronic lymphocytic leukemia. Cancer.	Database searches
52.	Swaminathan 2024-ASH	NCT04169737	Swaminathan, et al. 2024. Early Obinutuzumab Significantly Increases Bone Marrow Undetectable MRD (10-4 sensitivity) (uMRD4) Rate When Combined with Acalabrutinib and Venetoclax in a Randomized Phase II Trial for Treatment Naïve CLL. ASH.	Conference proceeding
53.	Takizawa 2024	NCT03198650	Takizawa, et al. 2024. Safety and efficacy of acalabrutinib and obinutuzumab in treatment-naïve chronic lymphocytic leukemia: a Japanese phase 1 study. Leukemia & lymphoma.	Database searches

Abbreviation: SLR: systematic literature review.

Studies excluded from the feasibility assessment

Full reference details of studies excluded from the feasibility assessment, as well as reason for exclusion is presented in Table 10 below.

Table 10: Studies excluded from the feasibility assessment

Study name	Citations	Reason for exclusion
ACE-CL-001	Byrd, et al. 2022. Final Results of the Phase 1/2 Study of Acalabrutinib MonDisconnected from the network / Did not provide an informative loop of evidence in Treatment-Naïve Chronic Lymphocytic Leukemia with >6 Years of Follow-up. ASH.	Disconnected from the network / Did not provide an informative loop of evidence
ADMIRE	Munir, et al. 2017. Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL. Leukemia.	Comparing two chemoimmunotherapy regimens
Ahn 2018	Ahn, et al. 2018. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood.	Disconnected from the network / Did not provide an informative loop of evidence
ARCTIC	Howard, et al. 2017. Results of the randomized phase IIB ARCTIC trial of low-dose rituximab in previously untreated CLL. Leukemia.	Comparing two chemoimmunotherapy regimens
AU-003	Cull, et al. 2022. Zanubrutinib for treatment-naïve and relapsed/refractory chronic lymphocytic leukaemia: long-term follow-up of the phase I/II AU-003 study. British Journal of Haematology.	Disconnected from the network / Did not provide an informative loop of evidence
Burger 2019	Burger, et al. 2019. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood.	Disconnected from the network / Did not provide

Study name	Citations	Reason for exclusion
		an informative loop of evidence
Burger 2022	Burger, et al. 2022. Time-limited treatment with acalabrutinib plus obintuzumab in treatment-naïve chronic lymphocytic leukemia patients induces deep remissions: early results of an ongoing phase 2 trial. EHA.	Disconnected from the network / Did not provide an informative loop of evidence
CAPTIVA TE-MRD	Wierda, et al. 2021. Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results From the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. Journal of Clinical Oncology.	Disconnected from the network / Did not provide an informative loop of evidence
Castro 2022	Castro, et al. 2022. Ibrutinib plus Obinutuzumab as Frontline Therapy for Chronic Lymphocytic Leukemia Is Associated with a Lower Rate of Infusion-Related Reactions and with Sustained Remissions after Ibrutinib Discontinuation: A Single-Arm, Open-Label, Phase 1b/2 Clinical Trial NCT0231576. Advances in Hematology.	Disconnected from the network / Did not provide an informative loop of evidence
CLL10	Eichhorst, et al. 2016. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncology.	Disconnected from the network / Did not provide an informative loop of evidence Comparing two chemoimmunotherapy regimens
CLL12	Langerbeins, et al. 2022. The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia. Blood.	Disconnected from the network / Did not provide an informative loop of evidence
CLL2007 FMP	Lepretre, et al. 2012. Excess mortality after treatment with fludarabine and cyclophosphamide in combination with alemtuzumab in previously untreated patients with chronic lymphocytic leukemia in a randomized phase 3 trial. Blood.	Comparing two chemoimmunotherapy regimens
CLL2-GIVe	Huber, et al. 2022. Obinutuzumab (GA-101), ibrutinib, and venetoclax (GIVe) frontline treatment for high-risk chronic lymphocytic leukemia. Blood.	Disconnected from the network / Did not provide an informative loop of evidence
CLL7	Herling, et al. 2020. Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial. Leukemia.	Comparing two chemoimmunotherapy regimens
CLL8	Hallek, et al. 2010. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. The Lancet.	Comparing two chemoimmunotherapy regimens
Danilov 2017	Danilov, et al. 2017. A phase I dose-ranging study of bendamustine and rituximab in chronic lymphocytic leukemia patients with comorbidities. British journal of haematology.	No PFS/OS
Davids 2025	Davids, et al. 2025. Phase II Study of Acalabrutinib, Venetoclax, and Obinutuzumab in a Treatment-Naïve Chronic Lymphocytic Leukemia Population Enriched for High-Risk Disease. Journal of Clinical Oncology.	Disconnected from the network / Did not provide an informative loop of evidence

Study name	Citations	Reason for exclusion
ERADIC	Michallet, et al. 2023. Minimal Residual Disease-Guided Combination of Ibrutinib and Venetoclax Compared to FCR in Untreated Patients with CLL of Intermediate Risk : Interim Results of MRD Kinetics in the Eradic Trial from the Filo Group. Blood.	No PFS/OS
FILO	Cartron, et al. 2018. Increased rituximab exposure does not improve response and outcome of patients with chronic lymphocytic leukemia after fludarabine, cyclophosphamide, rituximab. A French innovative leukemia organization (FILO) study. Haematologica.	Comparing two chemoimmunotherapy regimens
Fischer 2012	Fischer, et al. 2012. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. Journal of Clinical Oncology.	Disconnected from the network / Did not provide an informative loop of evidence
Flinn 2019	Flinn, et al. 2019. Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. Blood.	Disconnected from the network / Did not provide an informative loop of evidence
GALTON	Brown, et al. 2015. Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase 1b GALTON trial. Blood.	Comparing two chemoimmunotherapy regimens
GIBB	Sharman, et al. 2021. Phase 2, multicenter GIBB study of obinutuzumab plus bendamustine in previously untreated patients with chronic lymphocytic leukemia. Leukemia and Lymphoma.	Disconnected from the network / Did not provide an informative loop of evidence
GIMEMA LLC1114	Mauro, et al. 2022. Efficacy of Front-Line Ibrutinib and Rituximab Combination and the Impact of Treatment Discontinuation in Unfit Patients with Chronic Lymphocytic Leukemia: Results of the Gimema LLC1114 Study. Cancers.	Disconnected from the network / Did not provide an informative loop of evidence
GIMEMA LLC1518 VERITAS trial	Mauro, et al. 2023. High rate of durable responses with undetectable minimal residual disease with front-line venetoclax and rituximab in young, fit patients with chronic lymphocytic leukemia and an adverse biological profile: results of the GIMEMA phase II LLC1518 – VERITAS study . Haematologica.	Disconnected from the network / Did not provide an informative loop of evidence
GREEN	LeBlonde, et al. 2018. Safety of obinutuzumab alone or combined with chemDisconnected from the network / Did not provide an informative loop of evidence	Disconnected from the network / Did not provide an informative loop of evidence
Herishanu 2019	Herishanu, et al. 2019. Low-dose fludarabine and cyclophosphamide combined with standard dose rituximab (LD-FCR) is an effective and safe regimen for elderly untreated patients with chronic lymphocytic leukemia: The Israeli CLL study group experience. Hematological Oncology.	Disconnected from the network / Did not provide an informative loop of evidence
ICLL07	Michallet, et al. 2019. Obinutuzumab and ibrutinib induction therapy followed by a minimal residual disease-driven strategy in patients with chronic lymphocytic leukaemia (ICLL07 FILO): a single-arm, multicentre, phase 2 trial. The Lancet Haematology.	No PFS/OS
iLLUMINATE	Moreno, et al. 2019. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic	Disconnected from the network

Study name	Citations	Reason for exclusion
	lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet.	/ Did not provide an informative loop of evidence
Izutsu 2021	Izutsu, et al. 2021. A phase II Japanese trial of fludarabine, cyclophosphamide and rituximab for previously untreated chronic lymphocytic leukemia. Japanese Journal of Clinical Oncology.	Disconnected from the network / Did not provide an informative loop of evidence
MABLE	Michallet, et al. 2018. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica.	Comparing two chemoimmunotherapy regimens
O'Brien 2014	O'Brien, et al. 2014. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet.	Disconnected from the network / Did not provide an informative loop of evidence
Roecker 2024	Roeker, et al. 2024. Minimal Residual Disease (MRD)-Adapted Duration of Front-Line Venetoclax and Obinutuzumab Treatment for Fit Patients with Chronic Lymphocytic Leukemia (CLL). ASH.	Disconnected from the network / Did not provide an informative loop of evidence
SAWYER	Assouline, et al. 2016. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. The Lancet. Haematology.	Disconnected from the network / Did not provide an informative loop of evidence
SEQUOIA	Tam, et al. 2022. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncology.	Disconnected from the network / Did not provide an informative loop of evidence
Shibayama 2019	Shibayama, et al. 2019. Phase I study of ibrutinib in Japanese patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma. Journal of clinical and experimental hematopathology : JCEH.	No PFS/OS
Short 2015	Short, et al. 2015. Fludarabine, cyclophosphamide, and multiple-dose rituximab as frontline therapy for chronic lymphocytic leukemia. Cancer.	Disconnected from the network / Did not provide an informative loop of evidence
Swaminathan 2024-ASH	Swaminathan, et al. 2024. Early Obinutuzumab Significantly Increases Bone Marrow Undetectable MRD (10 ⁻⁴ sensitivity) (uMRD4) Rate When Combined with Acalabrutinib and Venetoclax in a Randomized Phase II Trial for Treatment Naïve CLL. ASH.	No PFS/OS
Takizawa 2024	Takizawa, et al. 2024. Safety and efficacy of acalabrutinib and obinutuzumab in treatment-naïve chronic lymphocytic leukemia: a Japanese phase 1 study. Leukemia & lymphoma.	Disconnected from the network / Did not provide an informative loop of evidence

Economic SLR

Search strategies

Corrected versions of the search strategies for MEDLINE and Embase (Table 11) and the Tufts CEA registry (Table 12) are presented below.

With regards to the MEDLINE and Embase search strategy, search terms that were originally missing in the CS Appendices have been highlighted in green in Table 11.

Table 11: Search terms used in MEDLINE and Embase (via Embase.com)

#	Searches	Results (Original SLR: 10 th December 2024)	Results (SLR update: 14 th August 2025)
1	'chronic lymphatic leukemia'/exp	58352	62451
2	'chronic leukaemia, lymphatic':ti,ab OR 'chronic leukemia, lymphatic':ti,ab OR 'chronic lymphatic leucemia':ti,ab OR 'chronic lymphatic leukaemia':ti,ab OR 'chronic lymphocyte leukaemia':ti,ab OR 'chronic lymphocyte leukemia':ti,ab OR 'chronic lymphocytic leukaemia':ti,ab OR 'chronic lymphocytic leukemia':ti,ab OR 'chronic lymphoid leukaemia':ti,ab OR 'chronic lymphoid leukemia':ti,ab OR 'leukaemia, chronic lymphatic':ti,ab OR 'leukaemia, lymphocytic, chronic':ti,ab OR 'leukemia, chronic lymphatic':ti,ab OR 'leukemia, lymphocytic, chronic':ti,ab OR 'lymphatic chronic leukaemia':ti,ab OR 'lymphatic chronic leukemia':ti,ab OR 'lymphatic leukaemia, chronic':ti,ab OR 'lymphatic leukemia, chronic':ti,ab OR 'chronic lymphatic leukemia':ti,ab OR 'cll':ti,ab	50017	52777
3	#1 OR #2	70693	75063
4	'economics'/de	248591	250797
5	'cost'/de	68626	69878
6	'health economics'/exp	1122693	1185916
7	'budget'/de	35304	37162
8	economic*:ti,ab OR cost:ti,ab OR costs:ti,ab OR costly:ti,ab OR costing:ti,ab OR price:ti,ab OR prices:ti,ab OR pricing:ti,ab OR pharmacoeconomic*:ti,ab OR 'pharmaco economic':ti,ab OR expenditure:ti,ab OR expenditures:ti,ab OR expense:ti,ab OR expenses:ti,ab OR financial:ti,ab OR finance:ti,ab OR finances:ti,ab OR financed:ti,ab	1725181	1869601
9	(cost* NEAR/2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)):ti,ab	333809	367658
10	(value NEAR/2 (money OR monetary)):ti,ab	4389	4664
11	'statistical model'/de	178551	182017
12	'economic model':ti,ab	7065	7571
13	'probability'/de	163122	176085
14	markov:ti,ab	39731	42043
15	'monte carlo method'/de	55628	58648
16	'monte carlo':ti,ab	66046	69233
17	'decision theory'/de	1895	1932

#	Searches	Results (Original SLR: 10 th December 2024)	Results (SLR update: 14 th August 2025)
18	'decision tree'/de	26533	29814
19	(decision* NEAR/2 (tree* OR analy* OR model*)):ti,ab	59491	66703
20	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	2907838	3104727
21	'socioeconomics'/de	178775	186846
22	'quality of life'/exp	727889	830164
23	'quality of life':ti	143957	157096
24	(instrument* NEAR/3 'quality of life'):ti,ab	6474	6936
25	'quality adjusted life year'/de	38670	41572
26	'quality adjusted life year':ti,ab	9816	10460
27	qaly*:ti,ab OR qald*:ti,ab OR qale*:ti,ab OR qtime*:ti,ab OR 'life year*':ti,ab	48917	54086
28	'disability adjusted life' OR daly*:ti,ab	11238	14024
29	sf36:ti,ab OR 'sf 36':ti,ab OR 'short form 36':ti,ab OR 'shortform 36':ti,ab OR 'short form36':ti,ab OR 'shortform36':ti,ab OR 'sf thirtysix':ti,ab OR sfthirtysix:ti,ab OR 'sfthirty six':ti,ab OR 'sf thirty six':ti,ab OR 'shortform thirtysix':ti,ab OR 'shortform thirty six':ti,ab OR 'short form thirtysix':ti,ab OR 'short form thirty six':ti,ab	52408	57037
30	sf6:ti,ab OR 'sf 6':ti,ab OR 'short form 6':ti,ab OR 'shortform 6':ti,ab OR 'sf six':ti,ab OR sfsix:ti,ab OR 'shortform six':ti,ab OR 'short form six':ti,ab OR shortform6:ti,ab OR 'short form6':ti,ab	3250	3459
31	sf8:ti,ab OR 'sf 8':ti,ab OR 'sf eight':ti,ab OR sfeight:ti,ab OR 'shortform 8':ti,ab OR shortform8:ti,ab OR 'short form8':ti,ab OR 'shortform eight':ti,ab OR 'short form eight':ti,ab	1240	1305
32	sf12:ti,ab OR 'sf 12':ti,ab OR 'short form 12':ti,ab OR 'shortform 12':ti,ab OR 'short form12':ti,ab OR shortform12:ti,ab OR 'sf twelve':ti,ab OR sftwelve:ti,ab OR 'shortform twelve':ti,ab OR 'short form twelve':ti,ab	13097	14470
33	sf16:ti,ab OR 'sf 16':ti,ab OR 'short form 16':ti,ab OR 'shortform 16':ti,ab OR 'short form16':ti,ab OR shortform16:ti,ab OR 'sf sixteen':ti,ab OR sfsixteen:ti,ab OR 'shortform sixteen':ti,ab OR 'short form sixteen':ti,ab	85	91
34	sf20:ti,ab OR 'sf 20':ti,ab OR 'short form 20':ti,ab OR 'shortform 20':ti,ab OR 'short form20':ti,ab OR shortform20:ti,ab OR 'sf twenty':ti,ab OR sftwenty:ti,ab OR 'shortform twenty':ti,ab OR 'short form twenty':ti,ab	549	591
35	hql:ti,ab OR hqol:ti,ab OR 'h qol':ti,ab OR hrqol:ti,ab OR 'hr qol':ti,ab	42711	46837
36	hye:ti,ab OR hyes:ti,ab	205	225
37	(health* NEAR/2 year* NEAR/2 equivalent*):ti,ab	51	51
38	pqol:ti,ab OR qls:ti,ab	1024	1098

#	Searches	Results (Original SLR: 10 th December 2024)	Results (SLR update: 14 th August 2025)
39	'quality of wellbeing':ti,ab OR 'quality of well being':ti,ab OR 'index of wellbeing':ti,ab OR 'index of well being':ti,ab OR qwb:ti,ab	629	657
40	'nottingham health profile':ti,ab	1700	1801
41	'nottingham health profile'/de	695	804
42	'sickness impact profile':ti,ab	1249	1270
43	'sickness impact profile'/de	2354	2383
44	'health status indicator'/de	3607	3672
45	(health NEAR/3 (utilit* OR status)):ti,ab	128705	139836
46	(utilit* NEAR/3 (valu* OR measur* OR health OR life OR estimat* OR elicit* OR disease OR score* OR weight)):ti,ab	27679	29790
47	(preference* NEAR/3 (valu* OR measur* OR health OR life OR estimat* OR elicit* OR disease OR score* OR instrument OR instruments)):ti,ab	20788	22461
48	disutilit*:ti,ab	1421	1515
49	rosser:ti,ab	154	161
50	'willingness to pay':ti,ab	14433	15658
51	'standard gamble':ti,ab	1210	1242
52	'time trade off' OR 'time tradeoff':ti,ab	2603	2734
53	tto:ti,ab	2449	2634
54	hui OR hui1 OR hui2 OR hui3:ti,ab	354092	375266
55	eq:ti,ab OR euroqol:ti,ab OR 'euro qol':ti,ab OR eq5d:ti,ab OR 'eq 5d':ti,ab OR euroqual:ti,ab OR 'euro qual':ti,ab	44316	49704
56	'duke health profile':ti,ab	124	128
57	'functional status questionnaire':ti,ab	182	193
58	'dartmouth coop functional health assessment*':ti,ab	14	14
59	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	1438662	1584738
60	#20 OR #59	4069713	4382803
61	#3 AND #60	5370	5864
62	#61 NOT 'case report'	5139	5544
63	#62 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	3082	3420
64	#63 AND [2014-2024]/py	1840	–
65	#63 AND [10-12-2024]/sd NOT [14-08-2025]/sd	–	358
66	#65 NOT 'clinical trial':dtype	–	157
67	#64 AND [embase]/lim	1735	–
68	#66 AND [embase]/lim	–	138

#	Searches	Results (Original SLR: 10 th December 2024)	Results (SLR update: 14 th August 2025)
69	#64 AND ([medline]/lim OR [pubmed-not-medline]/lim)	1396	–
70	#66 AND ([medline]/lim OR [pubmed-not-medline]/lim)	–	113
71	#64 AND [preprint]/lim	3	–
72	#66 AND [preprint]/lim	–	6

Table 12: Search terms used in Tufts CEA registry

#	Searches	Results (Original SLR: 10 th December 2024)	Results (SLR update: 14 th August 2025)
1	CLL	23	0

Cost and resource use studies

Table 13: Overview of cost items and resource use data reported across studies included in the cost and resource use stream of the economic SLR

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
Adena 2014	FCR	FC	• Total direct medical costs • Drug cost • Administration cost • AE management costs • Monitoring costs	-	-	-	-
Allan 2022	VenO	VenR	• Total direct medical costs • Treatment costs • Drug cost	-	VenO - on treatment: 3.3 PPPM VenO - off treatment: 2.3 PPPM VenR - on treatment: 3.2 PPPM VenR - off treatment: 1.4 PPPM	-	-
Alrawas hdh 2022	All	-	• Drug cost • Administration cost • Inpatient visits costs • ER visits costs • Outpatient visits costs • HCP costs • AE management costs	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
Bakker 2021	Usual care	Care with analytics	- Total direct medical costs - Treatment costs - Drug cost - Administration cost - AE management costs - Monitoring costs	-	-	-	-
Barnes 2018	Ibrutinib	-	- Drug cost - Administration cost - HCP costs - AE management costs - Monitoring costs	-	-	-	-
Becker 2016	-	-	- Drug cost - AE management costs	-	-	-	-
Blomme stein 2016	OC1b	Clb + rituximab	- Drug cost - Administration cost - AE management costs	-	-	-	-
Casado 2016	OC1b	Clb + rituximab	- Drug cost - Administration cost - AE management costs	-	-	-	-
Chanan-Khan 2023	-	-	-	Chemotherapy: 0.45 PPPM (2.24) Anti-CD20: 0.41 PPPM (2.50) BTKi: 0.31 PPPM (1.74) Vene: 0.62 PPPM (3.37)	Chemotherapy: 2.86 PPPM (3.75) Anti-CD20: 2.88 PPPM (3.36) BTKi: 1.07 PPPM (1.63) Vene: 1.75 PPPM (3.10)	-	-
Chatterjee 2021	VenO	OC1b	- Drug cost - AE management costs	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			- Monitoring costs - End of life care costs				
Chen 2017	FCR	CIb	- Total direct medical costs - Administration cost - Outpatient visits costs - AE management costs - Monitoring costs - Out of pocket costs	-	-	-	-
Cheung 2021	BR	Ibrutinib ± rituximab	- Total direct medical costs - Drug cost - Inpatient visits costs - Outpatient visits costs - Monitoring costs	-	-	-	-
Cho 2020	FCR	- BR - OCib	- Total direct medical costs - Treatment costs - Drug cost - Administration cost	-	-	-	-
Crawford 2025	Ibrutinib	- Acalabrutinib - Zanubrutinib	-	-	-	-	-
Do 2023	VenO	OCib	- Drug cost - Inpatient visits costs - Outpatient visits costs - AE management costs	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			- Monitoring costs - End of life care costs - Caregiver burden				
Emond 2019	Ibrutinib	BR	Monitoring costs	-	-	-	-
Ermann 2025	Acalabrutinib	Ibrutinib	-	-	-	Acalabrutinib: 5 (median) Ibrutinib: 17 (median)	Median clinic visits: Acalabrutinib: 12 Ibrutinib: 9 Median hospital admissions for medical events of interest: Acalabrutinib: 34 Ibrutinib: 42 Median specialist admissions: Acalabrutinib: 39 Ibrutinib: 48
Fariman 2023	Ibrutinib	BR	- Drug cost - HCP costs - AE management costs - Monitoring costs	-	-	-	-
Fitzgerald 2025	Acalabrutinib	Ibrutinib	- Total direct medical costs - Treatment costs	-	-	-	-
George 2025	- VenO - BR - FCR	-	-	-	Within 1st year of treatment VenO- 1.2	-	Median duration of any 1L FD therapy: 5.8 months

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
	• OC1b				FD chemotherapy-5.4		
Goyal 2021	-	-	- Total direct medical costs - AE management costs	-	-	-	-
Guinan 2024	VenO	- BTKis - CIT	- Drug cost - Administration cost - Inpatient visits costs - HCP costs - AE management costs - Monitoring costs - Palliative care costs	-	-	-	-
Hegde 2023	Ibrutinib	- BR - Clb + rituximab	- Treatment costs - Drug cost - AE management costs - Total indirect costs	-	-	-	-
Herring 2016	Ofatumumab + Clb	Clb	- Drug cost - Administration cost - AE management costs	-	-	-	-
Holtzer-Goor 2014	-	-	- Drug cost - Inpatient visits costs - ER visits costs - Outpatient visits costs - HCP costs - Monitoring costs	17.3	37.85	-	Visit to nurse practitioner: 0.15 Telephone contact: 1.52 Day care visit: 7.91 ICU per day: 0.41 Diagnostic tests: 83.23
Hong 2023	Ibrutinib	BR	- Treatment costs - Drug cost	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			- Administration cost - Inpatient visits costs - ER visits costs - AE management costs - End of life care costs				
Howard 2017	FCR	FCM-miniR	- Total direct medical costs - Drug cost - Administration cost - Inpatient visits costs - ER visits costs - Outpatient visits costs - HCP costs	-	-	-	-
Hoxha 2025	-	-	Monitoring costs	-	-	-	-
Huang 2020	Ibrutinib	CIT	- Total direct medical costs - Treatment costs - Drug cost - Administration cost - Inpatient visits costs - ER visits costs - Outpatient visits costs	-	-	-	-
Huntington 2024	VenO	BTKis	- Drug cost - HCP costs - AE management costs - Monitoring costs - Total direct medical	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			costs • Treatment costs • Drug cost • HCP costs				
Huntington 2025	Ibrutinib	• Acalabrutinib • Venetoclax	• Total direct medical costs	-	-	-	-
Irwin 2021	Ibrutinib	BR	• Total direct medical costs • Treatment costs • Inpatient visits costs • Outpatient visits costs	All cause (PPPM): Ibrutinib: 0.13 (0.08) BR: 0.11 (0.06) CLL related (PPPM): Ibrutinib: 0.12 (0.08) BR: 0.10 (0.05)	-	All cause (PPPM): Ibrutinib: 0.18 (0.24) BR: 0.14 (0.11) CLL related (PPPM): Ibrutinib: 0.15 (0.34) BR: 0.10 (0.04)	-
Kittai 2025	Ibrutinib	• Acalabrutinib • Zanubrutinib	• Total direct medical costs • Drug cost • AE management costs	-	-	-	-
Kongnakorn 2014	Bendamustine	• Alemtuzumab • Clb	• Treatment costs • Drug cost • Administration cost • AE management costs	-	-	-	-
Lachaine 2021	Watch and wait	-	• Drug cost • Administration cost • HCP costs • AE management costs • Monitoring costs	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			Palliative care costs				
Lachaine 2023	Watch and wait	-	- Drug cost - Administration cost - HCP costs - AE management costs - Monitoring costs - Palliative care costs	-	-	-	-
Lee 2024	-	-	- Total direct medical costs - Drug cost - Inpatient visits costs - ER visits costs - Outpatient visits costs - HCP costs - Home health costs - Hospice costs	0 (1)	21 (24)	0 (1)	Healthcare provider total claim counts: 39 (33) Durable medical equipment: 2 (4) Laboratory claim counts: 4 (6) Radiology claim counts: 1 (2)
Leslie 2022	-	-	- Total direct medical costs - Treatment costs - Administration cost - Inpatient visits costs - ER visits costs - Outpatient visits costs - HCP costs	PPPM: 0.08 (0.15)	-	PPPM: 0.04 (0.08)	Cancer-related HCRU (PPPM): Physician office visits: 1.21 (0.97) Other outpatient services: 3.23 (2.95) Antineoplastic drug administration related visits (specific): 0.80 (0.84) CLL-related HCRU (PPPM):

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
							Physician office visits 0.94 (0.83) Other outpatient services 2.49 (2.65) Antineoplastic drug administration related visits (specific) 0.68 (0.82)
Leslie 2022	-	-	• Total direct medical costs • Treatment costs • Administration cost • Inpatient visits costs • ER visits costs • Outpatient visits costs • HCP costs	PPPM: 0.07 (0.16)	-	PPPM: 0.03 (0.05)	Cancer-related HCRU (PPPM): Physician office visits mean (SD) 1.33 (1.13) 1.47 (1.27) 1.21 (0.97) 0.031 Other outpatient services 3.87 (3.27) Antineoplastic drug administration related visits (specific) 1.10 (1.03) CLL-related HCRU (PPPM): Physician office visits 1.09 (1.12) Other outpatient services 2.87 (2.74) Antineoplastic drug administration related visits (specific) 0.95 (1.04)

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
Li 2024	Acalabrutinib	• AO • CIT	• Drug cost • Administration cost • AE management costs • Monitoring costs • Palliative care costs	-	-	-	-
Mandrik 2015	FCR	FC	• Drug cost • Inpatient visits costs • AE management costs	-	-	-	-
Manzoor 2023	VenO	-	• Total direct medical costs • Treatment costs • Drug cost	-	-	-	-
Mariotto 2020	-	-	• Total direct medical costs • Treatment costs • Drug cost • End of life care costs	-	-	-	-
McBride 2021	Rituximab-abbs	Rituximab	• Total direct medical costs	-	-	-	-
Montañés 2022	Fixed-duration therapies	-	• Drug cost • Administration cost • Monitoring costs	-	-	-	-
Moreno-Martínez 2022	VenO	-	• Drug cost • AE management costs • Monitoring costs • End of life care costs	-	-	-	Annual units with progression/ without progression Complete blood count: 8/10

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
							Lactate dehydrogenase test: 7/8 Chest X-ray: 1/1 Bone marrow study: 0/1 Haematologist visit: 8/10 Other specialist visits: 1/3 Blood transfusion: 0/1 Computed axial tomography (CAT) scan: 2/2 Biochemistry: 8/9 Liver function tests: 7/7 Blood immunoglobulin test: 2/3
Muller 2016	FCR	FC	- Total direct medical costs - Drug cost - Administration cost - AE management costs	-	-	-	-
Muluneh 2023	Ibrutinib	Acalabrutinib	Total direct medical costs	-	PPPM Ibrutinib: 0.68 Acalabrutinib: 1.09	-	Physician office visits, PPPM Ibrutinib: 0.62 Acalabrutinib: 0.83
Munir 2023	Acalabrutinib	AO	- Drug cost - Administration cost - AE management	-	-	-	Per cycle (PFS/PD) Full blood count: 0.31/0.61

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			- Monitoring costs - End of life care costs				LDH: 0.23/0.00 Chest x-ray: 0.00/0.15 Bone marrow exam: 0.00/0.08 Hematologist visit: 0.15/0.46 Inpatient visit (nonsurgical): 0.00/0.31 Full blood transfusion: 0.00/0.84
Nie 2024	Zanubrutinib	BR	- Drug cost - AE management costs - Monitoring costs - End of life care costs	-	-	-	-
Paquete 2017	OC1b	Clb ± rituximab	- Treatment costs - Drug cost - Administration cost - Inpatient visits costs - ER visits costs - HCP costs - AE management costs - Monitoring costs	-	-	-	-
Patel 2020	Ibrutinib	BR	- Treatment costs - Drug cost - Administration cost - HCP costs - Monitoring costs	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			End of life care costs				
Rogers 2021	-	-	- Total direct medical costs - Treatment costs - Drug cost - Inpatient visits costs - ER visits costs - Outpatient visits costs - Monitoring costs	-	-	-	Number of blood and metabolic tests (per month): 3.07 (2.84)
Rogers 2023	Ibrutinib	Acalabrutinib	Total direct medical costs	PPPM Ibrutinib: 0.42 Acalabrutinib: 0.49	PPPM Ibrutinib: 1.47 Acalabrutinib: 2.06	-	-
Rogers 2025	Ibrutinib	Acalabrutinib	- Total direct medical costs - Treatment costs - Drug cost - Administration cost - Inpatient visits costs - Outpatient visits costs	All cause (PPPM) IQVIA- Ibrutinib: 0.08 (0.22) Acalabrutinib: 0.07 (0.18) Acentrus- Ibrutinib: 0.06 (0.17) Acalabrutinib: 0.06 (0.18) CLL/SLL-related HCRU PPPM IQVIA Ibrutinib: 0.03 ± (0.13) Acalabrutinib: 0.03 (0.13) Acentrus	All cause outpatient and ER visits (PPPM) IQVIA- Ibrutinib: 2.27 (2.20) Acalabrutinib: 2.41 (2.20) Acentrus Ibrutinib: 1.47 (1.94) Acalabrutinib: 2.06 (2.83) CLL/SLL-related outpatient and ED visits PPPM IQVIA Ibrutinib: 0.86 (0.90)	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
				Ibrutinib: 0.03 ± 0.11 (n = 710) Acalabrutinib: 0.04 ± 0.15 (n = 373)	Acalabrutinib: 1.09 (1.04) Acentrus Ibrutinib: 0.57 (0.96) Acalabrutinib: 0.74 (1.19)		
Ronconi 2021	Ibrutinib	-	• Total direct medical costs • Drug cost • Inpatient visits costs • Outpatient visits costs	-	-	-	-
Santos 2023	FCR	FC	• Treatment costs • Drug cost • Administration cost • AE management costs	-	-	-	-
Scortichi ni 2025	-	-	• Total direct medical costs • Treatment costs • AE management costs • Home health costs • Hospice costs • Palliative care costs • Total indirect costs • Absenteeism • Presenteeism • Activity impairment • Indirect costs due to work loss	-	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			Caregiver burden				
Shadman 2025	Ibrutinib	-	- Total direct medical costs - Treatment costs - Drug cost - Inpatient visits costs - ER visits costs - Outpatient visits costs	PPPM patients with dose reduction/without dose reduction Optum CDM All cause: 0.05 (0.10)/0.14 (0.41) CLL related: 0.04 (0.08)/0.09 (0.29) ConcertAI All cause: 0.52 (1.29)/0.54 (1.26) CLL related: 0.16 (0.46)/0.15 (0.53) Medicare FFS All cause: 0.04 (0.08)/0.04 (0.19) CLL related: 0.03 (0.07)/0.03 (0.16)	PPPM patients with dose reduction/without dose reduction Optum CDM All cause: 2.71 (1.68)/2.87 (3.24) CLL related: 1.14 (1.13)/1.33 (2.43) ConcertAI All cause: 0.31 (0.49)/0.45 (0.87) CLL related: 0.06 (0.17)/0.07 (0.21) Medicare FFS All cause: 0.81 (0.85)/0.80 (0.85) CLL related: 0.40 (0.48)/0.37 (0.50)	PPPM patients with dose reduction/without dose reduction Optum CDM All cause: 0.10 (0.15)/0.22 (1.41) CLL related: 0.03 (0.09)/0.04 (0.30) ConcertAI All cause: 0.03 (0.12)/0.05 (0.18) CLL related: 0.00 (0.00)/0.00 (0.02) Medicare FFS All cause: 0.04 (0.08)/0.04 (0.19) CLL related: 0.03 (0.07)/0.03 (0.16)	PPPM patients with dose reduction/without dose reduction (visits for other services) Optum CDM All cause: 0.58 (0.68)/0.73 (1.70) CLL related: 0.20 (0.35)/0.24 (0.66) ConcertAI All cause: 0.82 (0.97)/0.70 (0.98) CLL related: 0.08 (0.34)/0.03 (0.12) Medicare FFS All cause: 0.32 (0.52)/0.31 (0.55) CLL related: 0.32 (0.52)/0.06 (0.22)
Sinha 2018	Ibrutinib	OC1b	- Drug cost - Administration cost - AE management costs - End of life care costs	-	-	-	-
Slot 2023	VenO	Ibrutinib	- Drug cost - Inpatient visits costs - Outpatient visits costs - AE management costs	VenO Treatment onset C1: 4/cycle Controls 2–5: 2/cycle	-	-	-

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
			- Monitoring costs - End of life care costs	Controls 6: 1/cycle OC1b Treatment onset 1: 4/cycle Controls 2-6: 2/cycle Ibrutinib Treatment onset 1: 2/cycle Controls 2-36: 1 every three cycles 3 VenR, 2L Treatment onset 1: 4/cycle Controls 2-5: 2/cycle Controls 6-12: 1/cycle Ibrutinib, 2L Treatment onset 1: 2/cycle			
Soini 2016	All	-	- Drug cost - Administration cost - AE management costs	-	-	-	-
Tapaninen 2024	-	-	-	-	-	-	Healthcare contacts PPY unmutated <i>IgHV</i> : 25.5 unmutated <i>IgHV</i> with Infectious AEs: 28.1

Study name	Intervention	Comparator	Cost items	Resource use (mean [SD])			
				Number of inpatient visits	Number of outpatient visits	Number of ED visits	Other resource use
							unmutated <i>IgHV</i> with haematological AE: 27.6 unmutated <i>IgHV</i> with infectious AE: 33.6
Wang 2018	-	-	• Total direct medical costs • Drug cost • Inpatient visits costs • ER visits costs • Outpatient visits costs • Home health costs	-	-	-	-
Yang 2025	Zanubrutinib	Acalabrutinib	-	Zanubrutinib: 2.6 PPPY Acalabrutinib: 3.6 PPPY Ibrutinib: 4.6 PPPY	-	-	-

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; AO: acalabrutinib with obinutuzumab; AVO: acalabrutinib with venetoclax and obinutuzumab; B: bendamustine; BR: bendamustine with rituximab; BTKi: bruton tyrosine kinase inhibitor; CIT: chemoimmunotherapy; Clb: chlorambucil; CLL: chronic lymphocyte leukaemia; ED: emergency department; ER: emergency room; FCR: fludarabine; FCM-miniR: fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab; FCR: fludarabine with cyclophosphamide and rituximab; HCP: healthcare provider; HCRU: healthcare cost and resource use; OC1b: ofatumumab with chlorambucil; PPPM: per patient per month; PPPY: per patient per year; SD: standard deviation; SLL: small lymphocytic lymphoma; VenR: venetoclax with rituximab; VenO: venetoclax with obinutuzumab.

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Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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

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- 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	
2. Name of organisation	Leukaemia Care. Submission also submitted on behalf of Blood Cancer UK, Leukaemia UK, CLL Support and Lymphoma Action
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care Leukaemia Care is the UK's 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 (as detailed in the charity's 2024 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. 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.] If so, please state the name of the company, amount, and purpose of funding.	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-TPAG 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, 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 Gilead Sciences (idelalisib) - £10,451 in 2024 for community champions, CLL Support 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 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?	Patients are keen to see treatments that work, but also favour those with better side effect profiles, seeing the two as a balancing act. Given this is a long term illness and many people undergo several treatments, it is important that a number of options are available to clinicians and patients to maximise their quality of life at each stage of their disease – initial treatment and at relapse. Adding this treatment to the list of available options would generally offer patients and clinicians more choice depending on their personal circumstances and thereby maximise quality of life. 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 a survey 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. This demonstrates the need to keep personalising treatment to meet patients goals, as each patient will need something different. "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?	The range of treatments available means that most patients have access to a treatment appropriate for their personal CLL, previous treatments and existing comorbidities. However, there remain several groups in need of further options including those with high risk disease, especially at first treatment to limit their exposure to both long- and short-term side effects. Younger, fitter patients with several poor prognostic markers (TP53 disruption, 17Pdel or complex karyotype) may benefit more from an intensive doublet or triplet targeted therapy which aggressively treats their disease. This would hopefully produce deep remissions, long periods of minimal residual disease negativity and remission. While the AMPLIFY Phase III trial demonstrated the efficacy of acalabrutinib, venetoclax, and obinutuzumab (AVO) in the broader frontline CLL population, it excluded patients with TP53 mutations. Evidence from smaller but important studies highlights the potential of AVO in this subgroup: the dedicated Phase II trial (NCT04505254) specifically designed for TP53-aberrant patients showed encouraging results, and other early-phase data, including the CLL2-BAAG study in relapsed/refractory disease, suggest that responses are achievable even in this high-risk setting. Although numbers remain limited, these findings underscore the rationale for offering acalabrutinib and venetoclax (with or without obinutuzumab) as a promising approach for patients whose disease biology confers unmet need. There are fewer targeted options available for patients with no genetic mutations at diagnosis, compared to those with higher risk genetics. The treatments that are approved have come to be known for significant side effects, as their use in the real world increases and more long term data is accumulated. Ibrutinib is known for significant challenges in those with heart conditions, affecting a large number of those with CLL. The AMPLIFY trial again highlights that targeted therapies, such as AVO, are effective options. The older a patient is, the more likely they are to have comorbidities that make treating their CLL a challenge, so personalising treatment through multiple options available is still important. Younger patients in all the subgroups listed often suffer from treatment anxiety and worry about what effective treatment will be available to them when they need it. Clinicians prefer to use their best available treatment as first line and patients are now generally well informed of treatment options. Therefore, it is important to ensure there are a number of options for younger patients, who expect to live a long time with their CLL now.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The Amplify trial showed this is an effective treatment compared to chemotherapeutic option in those without TP53 and 17p del mutations. There is little evidence regarding a comparison to other targeted treatments now available in the UK, but we believe, based on clinical and patient advice, there to be a benefit of acalabrutinib over ibrutinib regimens, particularly for patients requiring anticoagulation or with cardiovascular co-morbidities One patient reported that they started treatment with neutropenia and thrombocytopenia barely acceptable for the trial but saw a rapid improvement in all parameters and “I began to really recover around the time of my first Obinutuzumab infusion. I felt I could relax after that and the treatment was obviously working” The addition of Obintuzumab showed an additional benefit for patients with unmutated IGHV status and would offer a valuable alternative to IV. Aside from clinical effectiveness, acalabrutinib 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 a treatment-free period as a positive. Acalabrutinib has a different side effect profile to existing targeted therapies, so could be beneficial for older patients particularly, who have co-morbidities that can impact side effects experienced or treatment for those effects. AVO would provide an option to allow effective tailoring for all the groups mentioned above.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	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. A patient on the AMPLIFY trial reported early nausea and ongoing diarrhoea which was slightly inconvenient and that this continued for a while after the end of treatment period. This patient also required GCSF support during the venetoclax ramp up. This was a commonly reported adverse event in the AMPLIFY trial, Patients, especially older people, are cautious of the side effects and adverse events of an intensive regime such as this technology and clinicians may restrict its use based on fitness levels and this seems entirely appropriate.

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 timely access to a wide range of effective options. Therefore, we ask that NICE ensures there is equal access among patients who are newly diagnosed to access a targeted therapy or targeted therapy combination especially now it is the preferred option by both clinicians and patients.

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?	N/a

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	1. This is a novel, time limited, drug combination that has shown itself to be effective with a 92% response rate as a first line treatment and a PFS advantage at 36 months. 2. Although the grade3 adverse events were 69% and 53% (for +/- Obin) they were not dissimilar to that for chemoimmunotherapy (60%) 3. Acalabrutinib + Venetoclax +/- Obintuzumab would offer a valuable additional therapeutic option for patients, especially those with cardio-vascular co-morbidities who are unable to tolerate Ibrutinib. 4. Patients with high risk CLL would also benefit from additional options to maximise their chance of a long term remission. 5. Younger patients with CLL require the most effective treatment possible upfront.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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	
2. Name of organisation	UK CLL Forum & British Society of Haematology
3. Job title or position	
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 a framework whereby the UK CLL clinical and scientific acommunity, 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 a specific focus in CLL. The British Society of Haematology (BSH) brings haematology professionals together since 1960 to transform the care our members provide to haematology patients. With over 3,000 members worldwide, it is the largest UK haematology organisation and the only society to cover all aspects of the speciality. BSH is funded via royalties, subscriptions, education events, investment income (including bank interest), BSHE Gift Aid and the Annual Sponsorship Programme.

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.	The UK CLL Forum has received funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months as follows: Anticipated funding in 2025: <table data-bbox="568 395 1265 571"> <tr> <td>Astra Zeneca</td><td>£12,000</td></tr> <tr> <td>AbbVie</td><td>£7,500</td></tr> <tr> <td>BeOne Medicines (formerly Beigene)</td><td>£12,000</td></tr> <tr> <td>Johnson and Johnson</td><td>£1,500</td></tr> </table> The purpose of the funding is to support the independent educational activities of the UK CLL Forum. BSH received £69,810 from Astra Zeneca for a Gold sponsorship package and they funded one education session at the Annual Scientific BSH meeting.	Astra Zeneca	£12,000	AbbVie	£7,500	BeOne Medicines (formerly Beigene)	£12,000	Johnson and Johnson	£1,500
Astra Zeneca	£12,000								
AbbVie	£7,500								
BeOne Medicines (formerly Beigene)	£12,000								
Johnson and Johnson	£1,500								
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No								

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 an incurable 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 to obtain 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, make the assessment of survival based on the effect of a single technology, impractical. With the approval of fixed duration treatment regimens in CLL, the treatment free period (assessed by Time to Next Treatment, TTNT) has become an increasingly valuable endpoint for CLL patients. CLL patients value the opportunity to achieve a prolonged time off treatment and thus the associated absence of side effects. Patients of any age can be affected by CLL, though it is typically a disease of older patients with the median age of diagnosis being 70 years.

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). This takes into account reduction in lymph node, liver and spleen size; resolution of symptoms; and restoration of normal blood counts. Partial or complete responses are clinically acceptable responses 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. 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 1×10^{-4} CLL cells/total WBC in peripheral bloods. MRD can be measured by flow cytometry or next-generation sequencing, with the former much more widely used in practice in the UK.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Patients with high risk genetic features (specifically TP53 aberration, or unmutated IGHV status) remain an unmet need. Despite the ready availability of novel agents in the CLL treatment pathway, many of these patients still typically experience shorter duration of response overall than patients lacking high risk features. Some of these patients will exhaust all available treatment options and die from progressive CLL. Furthermore, effective fixed duration treatment options for patients with high risk genetic features are especially limited. Continuous BTKi therapy seems to go some way towards mitigating the adverse impact of TP53 aberration and unmutated IGHV status (as demonstrated in the SEQUOIA (Tam <i>et al</i>, 2022 Lancet Oncol 23(8):1031-1041) and ELEVATE TN (Sharman <i>et al</i>, 2025 Blood 146(11):1276-1285) clinical trials in treatment naïve patients), but this approach comes at the expense of exposing patients indefinitely to side effects of the drug and ongoing selective pressure that facilitates emergence of resistant CLL clones. Using continuous therapy in the first line of treatment also commits a patient to indefinite CLL treatment as they will typically move directly from continuous therapy to another treatment regimen at the time of progression. Fixed duration treatments allow considerable time off therapy and avoidance of cumulative therapy related toxicity. Currently available fixed duration regimens include venetoclax-obinutuzumab (Ven-O) and venetoclax-ibrutinib (I+V). Ven-O does not overcome the adverse impact of either unmutated IGHV or TP53 aberrations and PFS is impaired in these patient groups compared to patients with mutated IGHV or wildtype TP53 respectively (CLL14 trial (Al-Sawaf <i>et al</i>, 2024 Blood 144(18): 1924-1935); CLL13 trial (Furstenau <i>et al</i> 2024 Lancet Oncol 25(6) 744-759). Ven-O also requires 6 months of intravenous infusion, frequent attendance to hospital and significant day unit capacity to deliver. I+V has been shown in the CAPTIVATE (Tam <i>et al</i>, 2022, Blood 139(22):3278-3289) and GLOW (Niemann <i>et al</i>, 2023 Lancet Oncol 24(12): 1423-1433) studies to deepen remissions (as measured by MRD, see below) in unmutated IGHV patients, but PFS in these patients still compares unfavourably to patients with mutated IGHV. Furthermore, the use of I+V is cautioned in older patients or those with cardiovascular comorbidities in view of the risk of significant cardiac toxicity including sudden cardiac death.

Another relevant unmet need in the management of CLL 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 when length of therapy with Ibrutinib-Venetoclax was determined by MRD kinetics during treatment. Studies are ongoing by other international CLL groups that will likely corroborate FLAIR findings and consolidate MRD guided treatment as a therapeutic approach in CLL.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?

In making a treatment choice in CLL, patients are divided into 3 therapeutic groups: patients with TP53 gene aberrations, patients with mutated IGHV genes and patients with unmutated IGHV genes. Furthermore, treatment options are divided into fixed duration (venetoclax-based) and continuous (BTK inhibitor based) regimens, and patient preference in regard to the duration of treatment is an important factor. National updated BSH guidelines in CLL (currently in print), acknowledge the efficacy of all available first line 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 second generation covalent 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). Chemoimmunotherapy is no longer recommended for use in treatment naïve CLL patients in either national or international guidelines and its value as a comparator to novel targeted therapies is debatable.

Expanding each of the subgroups the recommendations of the most recent BSH guidelines are as follows:

Continuous therapy preferred

BTKi therapy is favoured for patients with **TP53 aberrations**. Among continuous treatment options, second generation covalent BTKi (acalabrutinib or zanubrutinib) are preferred due to their side effect profile and ibrutinib 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 latter is not a formal recommendation due to the lack of randomised evidence to support it. The current technology would likely enter the treatment algorithm in this space, competing with the other fixed duration regimens in first line.

The BSH 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 continuous 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. <u>Patients with relapsed CLL are recommended to be treated as follows:</u> • 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 <i>TP53</i> status • For patients relapsing following fixed-duration venetoclax-based therapy consider either a BTKi (Grade III) or venetoclax re-treatment depending on duration of PFS1 prior response, tolerance and patient preference. • For relapsed patients who are intolerant of 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 but use is very limited due to concerns regarding toxicity. • Pirtobrutinib is a potential future option given recent licensing by MHRA where it can be used following failure of covalent BTKi. It is currently undergoing NICE TA evaluation and the final commissioning position of Pirtobrutinib will affect this algorithm.
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) lwCLL 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 is from outside England.)	The pathway of treatment is well defined. The new guidelines reflect the importance of patient choice in the selection of treatment, given the excellent efficacy and minor differences in toxicity between the first line therapeutic options for CLL. Patient preference is becoming increasingly relevant and is often a strong decision maker in the setting of first line therapy. The venetoclax-based fixed-duration regimens 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 (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?	The technology would introduce a novel fixed duration therapy regimen comprising venetoclax in combination with a second generation covalent BTKi +/- obinutuzumab. Currently, fixed duration venetoclax is only available for use in treatment naïve patients alongside either obinutuzumab (Ven-O) or first generation BTKi, ibrutinib (I+V). A+V+/- obinutuzumab is indicated as a licensed option for potential treatment choice in treatment naïve patients without TP53 aberration, in the updated BSH guidelines in CLL.

Second generation covalent BTKi are typically preferred to ibrutinib when delivered as continuous monotherapy, because of their improved toxicity profile. Similarly, the toxicity profile of fixed duration A+V looks favourable in the AMPLIFY study when compared with fixed duration I+V in the CAPTIVATE study. The rates of any grade bleeding, hypertension and atrial fibrillation were all favourable in the AMPLIFY study (32% versus 59%; 4.1% versus 16%; 0.7% versus 4% respectively). I+V is used currently in carefully selected patients because of the cardiovascular risks including sudden deaths, which were observed in the GLOW study. No sudden cardiac deaths have been reported in the AMPLIFY study. This technology would make the BTKi-venetoclax fixed duration regimen more readily available to a greater number of patients due to the favourable toxicity profile of A+V compared with I+V. While the AMPLIFY study comprised a population of fit patients, with patients over the age of 65 years excluded if they had a Cumulative Illness Rating Score (CIRS) of greater than 6, the study included patients up to the age of 86 years. Furthermore, the improved toxicity profile of acalabrutinib in comparison with ibrutinib is also seen in a randomised head to head comparison in the ELEVATE RR study in relapsed refractory CLL patients, where the incidence of AF, hypertension and confusion/bleeding were all reduced in the acalabrutinib arm. The ELEVATE RR study included patients up to the age of 89 years in the acalabrutinib arm. The improved toxicity profile of the A+V compared with I+V combination in older patients including those with comorbidities thus might be reasonably extrapolated from the available data.

In addition to the benefits in toxicity profile, the AMPLIFY study demonstrated that the addition of obinutuzumab to the A+V combination appeared to benefit genetically high risk patients with unmutated IGHV: estimated 36 month PFS in mutated IGHV and unmutated IGHV patients was 83.6% and 82.8% respectively in patients receiving AVO. In contrast, currently available fixed duration venetoclax-based regimens do not overcome the adverse impact on PFS of unmutated IGHV as demonstrated in the CLL13 and CLL14 trials (Ven-O regimen) and in the CAPTIVATE and GLOW trials (I+V regimen). A Phase 2 study of A+V+obinutuzumab in treatment naïve patients enrolled 72 patients enriched for high

	risk genetic features (Davids et al). 54 (75%) of the patients had unmutated IGHV and a 4 year PFS of 81% was observed in this group. This data is in keeping with the findings of the AMPLIFY study, though notably this study used an MRD guided approach to treatment duration and 42 of the total 72 patients received longer than 15 months treatment i.e. longer than the treatment regimen described in the AMPLIFY study. Longer follow up is needed to determine the longer term impact of the addition of obinutuzumab to the A+V combination in unmutated IGHV, but this triplet potentially offers an active treatment regimen in this high risk group who are otherwise less well served by currently available fixed duration regimens. Patients with TP53 aberrations were excluded from the AMPLIFY study. 45 patients were included in the phase 2 study (Davids et al) with 4 year PFS in this patient group of 70%. However, 15 of these patients received more than 15 cycles of treatment using an MRD guided duration of therapy approach. Treatment options in the relapsed/refractory setting would not be impacted by the introduction of this technology. Patients relapsing after I+V have been successfully retreated both with BTKi and with venetoclax-based therapies, albeit with short follow up. The fixed duration therapy option does not appear to infer any additional mutation burden at relapse that would render subsequent therapy options obsolete. It would be anticipated that patients relapsing after AV+/-Obinutuzumab could be similarly retreated.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No current use of the A+V combination in the NHS
10a. How does healthcare resource use differ between the technology and current care?	The availability of this technology may impact on the use of obinutuzumab in treatment naïve CLL patients which requires day unit attendances in the first 6 months of treatment. An all-oral A+V fixed

	duration combination will be attractive to some CLL patients who would otherwise have received Ven-O.
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 example, for facilities, equipment, or training.)	No additional investment is foreseen to introduce this technology, as clinical staff treating CLL are already familiar with the drugs comprising the regimen.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The technology could potentially offer an all oral fixed duration regimen (A+V) to a wider group of patients than are currently able to safely receive the oral fixed duration regimen I+V. A+V has a favourable toxicity profile in regard to hypertension, bleeding, AF, and other cardiac toxicity and is likely to be more widely applicable for patients than I+V. In combination with obinutuzumab as a triplet regimen, the technology offers a fixed duration therapy with clinically meaningful benefits in PFS for unmutated IGHV patients compared to current fixed duration options (see 9c above).
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?	Many patients prefer a fixed duration treatment regimen in order to enjoy a period of time off treatment which is beneficial to quality of life and reduces exposure to cumulative drug toxicity, development of additional co-morbidities and therapies required to manage these e.g AF and hypertension.

	Furthermore, A+V is an all oral fixed duration option which negates the need for patients to attend and spend significant time on the day unit for infusions.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Unmutated IGHV patients may derive specific benefit from the addition of obinutuzumab to A+V though longer term follow up will be important. Mutated IGHV patients experience long PFS and TTNT with a range of treatments and Ven-O is a highly effective regimen which is commonly recommended for these patients. However, for patients unable to attend the day unit/ hospital for regular infusions, A+V would offer an all oral alternative fixed duration option. There is insufficient data to comment on the benefit or otherwise of this technology on the TP53 patient group as they were excluded from the AMPLIFY study. Despite the better safety profile, there remains a subgroup of CLL patients with cardiovascular comorbidities for whom BTK inhibitors in general (including A+V regimen) remain unsuitable.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare 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)	All the drugs in the regimen are already commonly used in current UK CLL practice. Practical implications for use include enhanced monitoring for neutropaenia and associated infections particularly in patients receiving A+V+obinutuzumab during the treatment period. Concomitant antimicrobial prophylaxis e.g. co trimoxazole may be recommended as per local guidance.

or additional tests or monitoring needed.)	
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 (indications for treatment) is based on the internationally accepted IWCLL criteria. Treatment will be stopped after the fixed duration regimen has been completed (14 cycles months of therapy in the published regimen). Genetic testing before starting therapy is not mandatory but is recommended, including TP53 gene 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 life year (QALY) calculation?	There are no health related benefits to this technology that would not be anticipated to be captured by QALY.
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?	A+V is an example of an all oral targeted therapy combination that has superseded the use of chemoimmunotherapy in clinical practice. The use of both classes of novel agents in this fixed-duration regimen provides a treatment free period for patients that results in a meaningful reduction in hospital visits following cessation of therapy, avoidance of cumulative toxicity and avoidance of resistance selection on the CLL clone.
16a. Is the technology a 'step-change' in the management of the condition?	The technology is not a 'step change' in that a fixed duration BTKi-venetoclax regimen (I+V) is already available. However the current available regimen (I+V) must be used in carefully selected patients in

	view of the observed cardiac risks in clinical trials. Hypertension, AF, bleeding events are all observed more frequently with I+V than with A+V. The current technology would therefore widen the availability of a highly effective BTKi-venetoclax-based fixed duration regimen for CLL patients. Fixed duration regimens are often favoured by patients for allowing them time off treatment and shorter exposure to drug related side effects. A+V+obinutuzumab would be a step change in current UK practice as there is no other available triplet combination available in CLL.
16b. Does the use of the technology address any particular unmet need of the patient population?	A+V offers an all oral fixed duration combination regimen for patients who wish to avoid frequent hospital attendance for the obinutuzumab infusions delivered in fixed duration Ven-O, but who are unsuitable for I+V due to age or cardiac risk. AV also an all-oral option for hospitals where day unit capacity is an issue for delivering infusions or where safety concerns about safe delivery of obinutuzumab is an issue(due to frequency of infusion related reactions). The triplet fixed duration combination (AVO) provides an effective fixed duration option for patients with high risk unmutated IGHV though longer term follow up data are awaited.
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?	Neutropaenia and associated infection were the most commonly reported adverse events in the AMPLIFY trial. The trial was conducted in the early stages of the Covid pandemic (patients recruited 2019-2021) and there were a number of Covid deaths in all arms of the trial (including the

	chemoimmunotherapy comparator arm). Rates of neutropaenia and infection were highest in the triplet acalabrutinib-venetoclax-obinutuzumab arm. Monitoring for hypertension and bleeding events is essential for all patients receiving a BTKi. Patients receiving obinutuzumab are at risk of infusion related reactions at the time of treatment, which requires day unit attendance and monitoring. Typically infusion related reactions are manageable with pre-medication and a managed infusion rate according to standard practice.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The population in the AMPLIFY study is representative of the wide age range of CLL patients treated in the UK with patients up to 86 years included in the study. Patients over the age of 65 years were excluded if they had a CIRS score (Cumulative Illness Rating Scale for Geriatrics score) of greater than 6 and therefore the older patients in the study were typically 'fitter' and without a heavy burden of comorbidities. The dosing regimen for the three drugs included in the technology, including venetoclax ramp-up, reflects current UK clinical practice. The regimen echoes that used in fixed duration I+V in current practice with a 'lead-in' of BTKi prior to venetoclax starting.
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, overall response rates, time to next treatment, MRD negativity rates are all important outcomes. These were all explored and reported in the AMPLIFY study with the exception of time to next treatment, though duration of response was reported.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA931, TA891, TA796, TA689, TA663, TA429, TA359, TA343, TA216, TA174]?	Since publication of TA931 zanubrutinib in CLLpatients Nov 2023, there has been an updated report of the SEQUOIA cohort C trial at ASCO 2025: Tam <i>et al</i>, JCO 43(16) https://doi.org/10.1200/JCO.2025.43.16_suppl.7011 Since publication of TA891 ibrutinib and venetoclax May 2023, there have been updates to the CAPTIVATE study presented at ASCO 2025: Ghia <i>et al</i>, JCO 43(16) https://doi.org/10.1200/JCO.2025.43.16_suppl.7036 and of the GLOW study at ASH 2024: Niemann <i>et al</i>, Blood 144(1) p1871.

	Since publication of TA 663 venetoclax obinutuzumab Dec 2020 there have been published updates of the CLL14 study (Al-Sawaf et al, 2024 Blood 144(18):1924-1935 and of the CLL 13 study (Furstenau et al, 2024 Lancet Onol 25(6) 744-759.
21. How do data on real-world experience compare with the trial data?	Aside from the exclusion of elderly patients with heavy burden of comorbidity, 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 in AMPLIFY. It is hopeful that the impact of Covid might be significantly less in RWE, given that the AMPLIFY study was conducted in the early stages of the Covid pandemic, prior to wide availability of vaccination and improved Covid treatment pathways.

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 Obinutuzumab infusions and need for TLS monitoring alongside venetoclax delivery, require appropriate day unit time. 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 may have an impact on the potential use of this technology, in comparison to continuous BTKi therapy which can be delivered wholly in the outpatient clinic setting. Reduced availability of daycare and inpatient beds may dissuade clinicians to use the current technology.
22b. Consider whether these issues are different from issues with current care and why.	These issues are no different to those of current care, as obinutuzumab is already delivered to treatment naïve patients as part of Ven-O regimen.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• AV+/- obinutuzumab is a fixed duration regimen for treatment naïve patients with CLL. Patients typically prefer fixed duration regimens where available, in order to achieve time off treatment and reduced exposure to drugs and their associated toxicities. Further, current European guidelines state preference should be given to time limited therapies if efficacy appears equivalent. • AV offers an all oral fixed duration regimen with favourable toxicity profile compared to the currently available BTKi/venetoclax combination of I+V. I+V can only be safely delivered to select patient groups because of cardiac risk and sudden death associated. There have been no sudden cardiac deaths reported in the AMPLIFY study, which contrasts with the sudden cardiac deaths reported with the fixed duration I+V combination trialled in the GLOW study. All any grade adverse events of special interest (including hypertension, bleeding, atrial fibrillation) occurred less frequently in the AMPLIFY study compared to the CAPTIVATE study (I+V in an equivalent population). This is in keeping with the ELEVATE RR study which indicates improved safety profile of acalabrutinib in comparison with ibrutinib. Due to this overall favourable toxicity profile, the current technology is therefore likely to widen the availability of an all oral fixed duration regimen for patients. • Patients with high risk genetic feature (unmutated IGHV) may benefit from the triplet AV+obinutuzumab regimen which overcomes the adverse impact of unmutated IGHV. This is in contrast to the other available approved fixed duration venetoclax-based regimens (Ven-O and I+V) where PFS is still adversely affected by unmutated IGHV status. • AVO carries increased risk of neutropaenia and infection . The risk of greater immunocompromise with AVO needs to be carefully balanced compared to its increased efficacy, and overall AVO and may not be appropriate for all patients. The AMPLIFY study excluded elderly patients with heavy burden of comorbidity. The Covid pandemic had a significant impact on outcomes in the AMPLIFY study with Covid deaths observed in all study arms. •

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Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Clinical expert statement

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Part 1: Treating chronic lymphocytic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Nicolas Martinez-Calle
2. Name of organisation	Nottingham University Hospitals NHS Trust and UK CLL Forum
3. Job title or position	Consultant Haematologist, UK CLL Forum Chair
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic lymphocytic leukaemia? ☐ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or technology? ☒ Other (please specify): Astra Zeneca nominated expert.
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

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8. What is the main aim of treatment for untreated chronic lymphocytic leukaemia? (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. This leads to progressive bone marrow failure and/or worsening lymphadenopathy. The aim of treatment is to induce remission by clearing disease within the bone marrow and nodes and improve both progression free and overall survival. There is no cure currently for CLL and treatments have limited efficacy and associated toxicities. A regime with greater efficacy leads to resolution and maintenance of normal marrow function, control of lymphadenopathy and improved overall survival. In addition, as survival improves, the impact of therapies on longer term effects such as secondary cancer, cardiovascular health and Richter's transformation are increasingly important.
9. 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)	In addition to resolution of lymphadenopathy and bone marrow function, we now can now also look for very deep remissions in the blood and bone marrow, using flow cytometry or next generation sequencing. We know that inducing these very deep remissions leads to improved PFS and OS.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	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, CLL17, FLAIR, 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

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	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. The present technology is not directly addressing an unmet need for CLL community, but providing an alternative for a very successful combination of drugs (Ibrutinib-venetoclax), allowing the patients who are not ideal candidates for treatment with Ibrutinib the possibility of using a BTKi with an improved safety profile and still benefit from the paradigm of an all-oral fixed duration therapy. As for the AVO combination, it will mostly offer an alternative therapy for patients with high risk CLL features (TP53 mutation and IGVH unmutated category), allowing them to benefit for a fixed duration paradigm with good clinical efficacy and high rate of MRD-negative remission.
11. How is untreated chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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 is from outside England.) • What impact would the technology have on the current pathway of care?	Chemo-immunotherapy is now rarely used following studies showing major superiority of non-chemotherapy regimens including BTKi and BCL2 inhibitors and their combination, which have been assessed in a number of previous technology appraisals (TA359, TA429, TA487, TA561, TA663, TA 689). The current proposed BCSH first line recommendations are: • Venetoclax-obinutuzumab (VenO), Ibrutinib-Venetoclax (VI), Zanubrutinib or acalabrutinib are recommended and NICE-approved options as initial therapy in patients unsuitable for CIT irrespective of TP53 status.

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	• Bendamustine or chlorambucil-based CIT are no longer recommended. • NICE-approved treatment options for fit patients with TP53 disruption include acalabrutinib, ibrutinib or venetoclax monotherapy for those with a contra-indication to B-cell receptor inhibitor. Relapsed patients 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 (Grade III) or venetoclax re-treatment depending on duration of PFS1 • For relapsed patients who are intolerant to ibrutinib, offer either venetoclax-based therapy or acalabrutinib depending on the reason for intolerance • For patients relapsing on BTKi, continue treatment until alternative therapy is initiated • Idelalisib-rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi and BCL2i-based treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology has two different regimens.

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• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	For Acababrutinib-Venetoclax (AV), the use is identical to the use of Ibrutinib-Venetoclax, and NHS funded regimen for untreated CLL, no additional health care resource will be needed for this patients. For AV+Obinutuzumab (AVO), administration of Obinutuzumab will require additional health care resource to delivery as compared to AV, but the delivery of Obinutuzumab already occurs within the NHS in other regimens such as Venetoclax-Obinutuzimab. The delivery of this monoclonal antibody does not differ in the context of AVO and hence there is no additional resource that is needed for its delivery, except in cases where additional capacity of day-units for delivery is required, depending on the penetration of this combination in the treatment pathway and the result of the present appraisal. This treatments will continue to be delivered in secondary and tertiary centres under specialist haematology guidance. No additional investment for the technology is foreseen.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The results of the AMPLIFY trial, demonstrated a 77% reduction in the risk of death for the AV combination in comparison with the chemoimmunotherapy (CIT) arm. This significant result has the main caveat of the inappropriateness of the comparison of AV with CIT, the later currently not recommended in the BSH guidelines. With a median follow-up of 40.8 months, the trial reported the 36-month overall survival rates of 94.1% for AV and 87.7% for AVO. This survival figures are comparable to that of other fixed duration alternatives and demonstrate the lack of utility of overall survival to evaluate technologies in CLL where CLL-related deaths are infrequent. The progression free survival followed a similar pattern as the overall survival with a 45% and 58% reduction in the risk of progression for AV and AVO respectively compared to the control arm. Again this apparent significant benefit

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	is unlikely to aid the evaluation of this technology as the comparator of CIT is not used in routine practice anymore. In order to establish if AV and AVO provide benefit in terms of PFS with the current care, indirect comparisons should be undertaken with data from the CLL17 trial, the GLOW trial and the CAPTIVATE trial. At this early timepoint, these trials suggest similar efficacy data as compared to AV combination in terms of response rates and PFS. With respect to quality of life, in comparison with VI combination, AV is likely to improve quality of life of patients, acalabrutinib is a second generation BTKI with a more favourable safety profile, which is translated into the dual combination. This benefit is somewhat lost with the triplet combination once the additional side effects from the monoclonal antibody Obinutuzumab are added to the AV combination. Hence the impact on quality of life improvement of AVO might be less evident than that of AV, in relation with the closest comparison of fixed-duration VI regimen.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The lack of randomised data in the AMPLIFY trial for patients with TP53 mutations makes it difficult to assess with scientific rigor, the impact of the triplet therapy in the context of high risk CLL, hence this population remain underserved and will not likely benefit for this technology until evidence becomes available. IGHV mutation is emerging as a differentiating factor in efficacy for fixed duration regimens. AV and AVO follow this same pattern with a shorter PFS for patients who lack IGHV mutation. Nonetheless the PFS and OS in this group of patients remains significantly improved when compared historically with CIT and hence it is difficult to recommend strongly that IGHV unmutated patients should not have venetoclax-based fixed duration regimens.

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	Quite the opposite, the significant benefit observed of fixed duration combinations in patients with IGHV mutation (of which AV is only one example), makes it more imperative to offer finite therapy to these patients, which will have an impact in their quality of life as these group will benefit the most of the treatment free (and most likely symptom- free) period. There is no data to compare the relative performance of available fixed duration regimens in IGHV mutated patients, as there is no clear standardisation between different trials and the statistical power of smaller groups is compromised.
15. Will the technology be easier or more difficult to use for patients or healthcare 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)	There will be no additional difficulties for the use of the present technology as CLL clinicians will have ample experience with each of the components of the AV/AVO regimens. The burden of health care resource if of these regimens is likely to be equivalent to already existing regimens, there is no significant challenge expected for patients in this respect
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is a fixed duration therapy, hence no rules to start or stop will apply.
17. 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 life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	From prior experiences, the health-related benefits of fixed-duration regimens have been appropriately captured in the QALY models, including the effect of the treatment free-period and the burden of the clinical visits of certain regimens that need closer monitoring at the start of therapy (Venetoclax dose escalation and use of Obinutuzumab)
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	The use if Venetoclax-fixed duration therapy is currently well established as an option for untreated CLL patients and continues to represent a significant

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impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	improvement in the therapy of CLL, due to the demonstration of improvement of clinical outcomes with venetoclax-based therapy when compared to CIT. The recent demonstration of non-inferiority of fixed duration regimens to continuous therapy in certain patient subgroups, converts fixed duration alternatives the desirable choice of therapy where available and appropriate. The benefits of BCL2/BTKi combinations has been widely demonstrated for untreated CLL, hence in this respect the present a significant innovation in this respect. It is possible plausible that there will be clinical benefit with the combination of 3 agents from the outset, in patients without TP53 abnormalities, but definitive data is at present, lacking. There is Phase 2 data on the use of AVO in patients with TP53 aberrations (Davids et al, DOI: 10.1200/JCO-24-02503) but this lacks the appropriate comparators to demonstrate if triple therapy derives significant benefit in this subgroup of high-risk CLL.
19. 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 AMPLIFY trial are summarised below: Neutropenia: G3 neutropenia occurred in 32.3% of the AV arm and 46.1% of the AVO arm. A higher incidence of overall infections was seen in the AVO arm compared to the AV arm G3 atrial fibrillation was uncommon, rates of 0.7% in AV, 2.1% in AVO. Hypertension (Grade 3 or higher) occurred in 2.7% (AV) and 2.1% (AVO). Overall it is believed that the adverse event profile of AV is favourable compared to that of VI. Whereas AVO will add haematological toxicity and risk of infections

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	to the AV combination, likely moving it to rates more similar to those observed in Venetoclax-Obinutuzumab studies.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The AMPLIFY clinical trials have been conducted with scientific rigour and the population accurately reflects a typical CLL population with respect to age, CLL risk features and comorbidities.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Nil
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA663, ID6291 and TA891?	The main new evidence has been the publication of the results of the CLL17 study later last year. The main results of this study are the non-inferiority approach of fixed duration regimens over continuous BTKi in terms of PFS in patients with untreated CLL. There is now data, albeit with a shorter follow-up, that demonstrated the efficacy and safety of Ibrutinib and Venetoclax combinations in a multicentre randomised study with good numbers to establish subgroup comparisons, particularly for IGHV mutation status. It provides a benchmark of efficacy of BCL2/BTKi combinations with a 3-year PFS rates of 81.1% (VO), 79.4% (VI), and 81.0% (continuous ibrutinib) and a rate of undetectable MRD of 47% with VI. This is also a benchmark for the safety of VI combination with a rate of cardiac events of 23%, including a similar rate of atrial fibrillation compared to the

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	Ibrutinib arm. There was also a reduced incidence of infections and cytopenias in comparison to Venetoclax-Obinutuzumab.
23. How do data on real-world experience compare with the trial data?	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. There is also a higher expected rate of infections and hospitalisation in the real world as compared to that reported in the studies, due to increased age and higher comorbidity burden of the patients in routine practice.
24. NICE considers whether there are any equality issues at each stage of an evaluation. 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. Please state if you think this evaluation could	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 Obinutuzumab 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

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• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	inpatient beds will clearly dissuade clinicians to use the current technology.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

AV and AVO regimens represent a novel combination of novel agents for the therapy of CLL, with VI as the closest comparator in terms of efficacy and safety.

AV and AVO will fill the gap in the treatment pathway for patients who desire a fixed duration therapy but are not good candidates for Ibrutinib, given poorer tolerability and higher impact in terms of side effects

Clinical efficacy compares favourably with existing results of other fixed duration regimens, with still immature follow-up. Rigorous indirect trial comparison will be required to assess whether or not AV/AVO provides clinical benefit when compared to the currently available technologies.

AV combination side effect profile is favourable compared to that of existing VI regimen, whereas that difference will be less pronounced with AVO. The addition of Obinutuzumab resulted in an increase in adverse effects with the triple combination that should be analysed in light of the added benefit of the triple combination.

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Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with chronic lymphocytic leukaemia. The text boxes will expand as you type.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Friday 23 January 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Part 1: Living with this condition or caring for a patient with chronic lymphocytic leukaemia

Table 1 About you, chronic lymphocytic leukaemia, current treatments and equality

1. Your name	Hugh Pender
2. Are you (please tick all that apply)	☒ A patient with chronic lymphocytic leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with chronic lymphocytic leukaemia? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Leukaemia UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

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	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with chronic lymphocytic leukaemia? If you are a carer (for someone with chronic lymphocytic leukaemia) please share your experience of caring for them	Summary: I was diagnosed in 2008 with Chronic lymphocytic leukaemia (with monoallelic 13q 14, TP53 not deleted and unmutated IGHV gene). I spent 13 years on 'watch and wait' with blood tests and face to face haematologist appointments varying from 3, 6, or 12 months which varied over the 13 years. On diagnosis my lymphocytes were around 4.5, other blood readings normal and no noticeable lymphadenopathy or other issues on examination. Over the course of the 13 years my lymphocytes climbed to 232 following a steep exponential curve in the 12th and 13th year and my haemoglobin and platelets dropped to 111 and 129 respectively. I had significant lymphadenopathy and an enlarged spleen. I was treated with obinutuzumab in June 2021 until November 2021 and venetoclax from July 2021 till May 2022. The treatment was successful. Experience living with CLL: The first few weeks and months after diagnosis were the hardest because of the shock of the diagnosis and the lack of a clear prognosis. The main issues were psychological rather than physical. There was anger and disappointment, fear and uncertainty. During the first year following diagnosis I read all I could on CLL including treatments available and I had good discussions with my haematologist who was a great help in providing context to any of my negative scenarios. I immersed myself in various hobbies and by the end of that first year I was totally accepting of the diagnosis. I was over the shock and life was great. Not so much for my wife and daughters who struggled with it. I was grateful that it was me who had leukaemia and not one of them.

Patient expert statement

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

	For the rest of the 13 years of watch and wait CLL didn't worry me. It was always in my mind and I viewed it as a challenge that I was well prepared for. There were ups and downs and that's reflected in my blood results graph. Every time I had a blood test the results went on the chart. I was ever hopeful when there was a lymphocyte drop and slightly disappointed when there was a rise. My experience of the NHS during 'watch and wait' and during treatment was all positive.
7a. What do you think of the current treatments and care available for untreated chronic lymphocytic leukaemia on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Note: My experience is as a CLL patient treated with obinutuzumab and venetoclax. NOT alcabrutinib. Current treatments like ibrutinib, alcabrutinib, obinutuzumab and venetoclax really seem much better than the 'older' FCR I had read about upon first diagnosis. And for me with the unmutated IGHV gene so much better as there are less side effects and better chance of remission. In my discussions with others their views are similar to mine with regard to current treatments.
8. If there are disadvantages for patients of current NHS treatments for chronic lymphocytic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Note: My experience is as a CLL patient treated with Obinutuzumab and Venetoclax. NOT alcabrutinib. I didn't consider any of my treatments as having disadvantages as it was all necessary if I was to recover. Side effects for me were as follows: Obinutuzumab: Acute sensitivity to sound and light especially at night preventing

Patient expert statement

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	sleep. After 3 nights without sleep my GP diagnosed zopiclone sleeping tablets which allowed me to sleep for the duration of the obinutuzumab treatment. Venetoclax: Queasy/sickly feeling for a few hours after taking the tablet. I found an easy way to manage and minimise this side effect. Infusions mean travelling to hospital, which can be difficult for some people whereas some oral treatments can be taken at home which is easier. I did have to travel to hospital 3 times per week for a couple of weeks when starting infusions of obinutuzumab and again with venetoclax. This was for blood tests to check I was not in danger of TLS. For me, I didn't see this as a problem. My treatment was a fixed duration which as a patient is better than continuous treatment.
9a. If there are advantages of acalabrutinib and venetoclax with or without obinutuzumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does acalabrutinib and venetoclax with or without obinutuzumab help to overcome or address any of the	Fixed duration treatment Less side effects than traditional chemotherapy Better quality of life. 9b. Fixed duration

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listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of acalabrutinib and venetoclax with or without obinutuzumab over current treatments on the NHS please describe these. For example, are there any risks with acalabrutinib and venetoclax with or without obinutuzumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from acalabrutinib and venetoclax with or without obinutuzumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering chronic lymphocytic leukaemia and acalabrutinib and venetoclax with or without obinutuzumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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	I hadn't realised until I got involved with the leukaemia community, (patients, researchers, NHS staff) that equality is a big issue. Particularly when it comes to affordability. e.g travelling, parking, time off work, time away from family, child care etc. The people at a disadvantage are those without financial means, who can't access the internet, who are not confident to attend appointments or to join support groups for help.

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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.	
13. Are there any other issues that you would like the committee to consider?	I can't think of any.

Patient expert statement

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I was treated with obinutuzumab and venetoclax. NOT alcabrutinib. My experience was positive
- My treatment was a fixed duration which as a patient is better than continuous treatment
- As I had unmutated IGHV gene my particular treatment meant there were less side effects than the older FCR and better chance of remission
- My experience of the NHS during 'watch and wait' and during treatment was all positive
- In my involvement with patient groups I came to realise that there are disadvantaged groups who are unable to benefit from treatment as I did

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Patient expert statement

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with chronic lymphocytic leukaemia

Table 1 About you, chronic lymphocytic leukaemia, current treatments and equality

1. Your name	Jackie Martin
2. Are you (please tick all that apply)	☒ A patient with chronic lymphocytic leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with chronic lymphocytic leukaemia? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

Patient expert statement

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	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with chronic lymphocytic leukaemia? If you are a carer (for someone with chronic lymphocytic leukaemia) please share your experience of caring for them	My experience of living with CLL over 13 years and very many treatments is that of realising that this cycle of watch and wait then relapse, treatment and another watch and wait, never ends. It results in a never ending constant, low level of anxiety which peaks at blood test/hospital visit times. This is true for the patients and their families. There is never any certainty that a particular treatment will be effective and the cumulative effect of the heterogeneity of CLL, of multiple treatments and aging comorbidities mean that not all treatments are suitable for everyone.
7a. What do you think of the current treatments and care available for untreated chronic lymphocytic leukaemia on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	The current targeted and immuno treatments available on the NHS have moved therapy away from chemotherapy for which CLL patients are very grateful. However, there are still significant concerns about side effects, particularly in the elderly patients who may have several co-morbidities and so, are unable to tolerate various treatments. There are a range of fixed length and continuous treatments which is good and preference will depend on individual circumstances, fitness, disease and support. It's very important that there is a wide a range of therapies available so that there is something suitable for everyone that needs treatment.
8. If there are disadvantages for patients of current NHS treatments for chronic lymphocytic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Considerations of the advantages and disadvantages of various treatments will vary from patient to patient depending on their individual circumstances. Most patients prefer oral and fixed length treatment regimes and others will see the intensive monitoring and possible hospitalisation during treatment ramp ups to be a disadvantage. That may depend of how accessible the hospital is, travelling time etc, the degree of support the patient has to attend hospital appointments may influence that too.

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	Side effects affect people differently but cardiovascular side effects such as hypertension and AF that continue to affect quality of life after treatment is stopped or finished is particularly egregious and can be debilitating. Side effects can mean that treatment is stopped prematurely (rather than paused) and a persisting side effect means other treatments can no longer be considered. I myself developed severe hypertension whilst on Ibrutinib that requires four anti HT medications each day 10 years after I was prescribed it. Bone marrow suppression can be a significant side effect of many treatments but can usually be managed by pausing treatment for a short period or reducing the dose. Some patients having treatment need to take an extended period of sick leave from work and rely on carers due to side effects which patients see as a disadvantage.
9a. If there are advantages of acalabrutinib and venetoclax with or without obinutuzumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does acalabrutinib and venetoclax with or without obinutuzumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	These advantages stated are taken from two patients who have experienced this treatment and who have given me permission to share their story. Both received A+V+O and their experiences are remarkably similar. Both patients were relatively young, in their 50's. One patient commenced the treatment in a clinical trial in 2019 and remains fit and well. The other is almost coming to the end of the treatment period. <i>"At my age, the idea of taking indefinite therapy was emotionally difficult and concerning. My Dr and I felt that a fixed-duration regimen offered the best chance at achieving a deep remission while avoiding years of continuous drug exposure, cumulative toxicity, and the risk of developing resistance to chronic therapy."</i> (64% of CLL patients would consider a treatment-free period as a positive) One patient was able to continue to work almost continuously during the treatment and felt this was a huge advantage for his mental and financial wellbeing.

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	Both patients noticed a dramatic improvement in energy levels and shrinkage of their lymph nodes early during the acalabrutinib phase which they found very reassuring. The opportunity for a deep remission and the possibility of years without treatment is very important to patients who are fit enough for this regime. Acalabrutinib appears to have less cardiovascular side effects than Ibrutinib and would possibly be a preferred option over Ibrutinib + Venetoclax which is approved by NICE. From the AMPLIFY trial it appears that the addition of Obintuzumab offers additional benefits for Unmutated IGHV patients despite the additional toxicity. Some patients with high risk disease may benefit from doublet or triplet therapy which has the potential to induce rapid, deep responses.
10. If there are disadvantages of acalabrutinib and venetoclax with or without obinutuzumab over current treatments on the NHS please describe these. For example, are there any risks with acalabrutinib and venetoclax with or without obinutuzumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	One patient had only worked from home prior to treatment due to severe neutropenia and this neutropenia continued until after the second Obintuzumab infusion, when, with GCSF, support they recovered. The other patient said <i>"the early obinutuzumab phase was difficult, and my neutropenia required careful management. The most difficult period was cycle 6 due to neutropenia, fatigue, and the bone pain from growth-factor injections."</i> There is often the need for GCSF support with this regime (ref AMPLIFY trial). One patient reported nausea and diarrhoea requiring treatment. From experience with Venetoclax + Obintuzumab the ramp up is seen as a disadvantage but tolerable due to the potential benefits.

Patient expert statement

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11. Are there any groups of patients who might benefit more from acalabrutinib and venetoclax with or without obinutuzumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with unmutated IGHV appear to benefit from the addition of Obintuzumab despite the concerns about additional toxicity. Younger patients with high risk disease may benefit but there is no trial evidence that we are aware of. However, all patients would benefit from and need timely access to a wide range of effective options. Therefore, we ask that NICE ensures there is equal access among patients who are newly diagnosed to access a suitable targeted therapy or targeted therapy combination as it is the preferred option by both clinicians and patients.
12. Are there any potential equality issues that should be taken into account when considering chronic lymphocytic leukaemia and acalabrutinib and venetoclax with or without obinutuzumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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	Not aware of any.

Patient expert statement

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	none

Patient expert statement

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This is a novel, time limited, drug combination that has shown itself to be effective with a 92% response rate as a first line treatment and a PFS advantage at 36 months. Time limited treatment is preferred by a majority of patients.

Although in the AMPLIFY trial the grade3 adverse events were 69% and 53% (for +/- Obin) they were not dissimilar to that for chemoimmunotherapy (60%). The two patients quoted here both needed GCSF support as did many patients in the trial.

- Acalabrutinib + Venetoclax +/- Obintuzumab would offer a valuable additional therapeutic option for patients, especially those with cardio-vascular co-morbidities who would benefit from a doublet or triplet therapy but are unable to tolerate Ibrutinib + Venetoclax.
- Patients with high risk CLL would also benefit from additional options to maximise their chance of a long term remission.
- All patients with CLL but especially younger ones require the most effective time limited treatment possible upfront.

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Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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Patient expert statement

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

NDRS-NICE partnership report

Background

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). NDRS and NICE have established a partnership focused on routinely collected data to support NICE decision making on the appraisals of cancer treatments. The partnership uses NDRS datasets, including the information submitted by trusts to the Systemic Anti-Cancer Therapy (SACT) dataset¹, to provide an understanding of current practice.

To determine a severity modifier, NICE considers factors such as the age, gender, and overall survival of the patient cohort affected by the disease. Additionally, knowing the time-on-treatment for each therapy is useful, as it validates assumptions made in technology appraisal evaluations about the duration of treatment use.

This partnership is focused on producing demographic and survival information using NDRS data, alongside supplementary information tailored to each technology appraisal. These may include, for example, the time patients spend on particular treatments, genetic data where this is available, or other information on real-world care pathways. Interpretation of the data is not included in this report, it is the information as provided to the NICE technology appraisal committees. Detail on how NICE health technology appraisals use this data can be found in the NICE health technology evaluations manual², with specific information relating to the survival analysis modelling available in Technical Support Document (TSD)³.

The focus of this report is the indication **ID6232: Acalabrutinib and venetoclax (AV) with or without obinutuzumab for untreated chronic lymphocytic leukaemia (CLL)**

Two cohorts were assessed for this indication:

- Cohort 1: Adults with untreated chronic lymphocytic leukaemia who have received venetoclax with obinutuzumab (VenO).

¹ Chloe J. Bright et al., “Data Resource Profile: The Systemic Anti-Cancer Therapy (SACT) dataset,” *International Journal of Epidemiology* 49, no. 1 (February 2020): 15–15l, <https://dx.doi.org/10.1093/ije/dyz137>.

² *NICE health technology evaluations: the manual (2025) NICE process and methods PMG36*. Last updated 23 October 2025, n.d., <https://www.nice.org.uk/process/pmg36>.

³ Latimer Nicholas, *NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data*, 2011, <http://www.nicedsu.org.uk/>.

- Cohort 2: Adults with untreated chronic lymphocytic leukaemia who have received venetoclax with ibrutinib (VenI).

Age and overall survival for untreated chronic lymphocytic leukaemia treated with venetoclax with obinutuzumab (VenO; cohort 1)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival and age distributions among patients aged 18 or over with untreated chronic lymphocytic leukemia (CLL) who have received venetoclax with obinutuzumab (VenO; cohort 1).

Method

A snapshot of SACT data was taken on 7th December 2025 and made available for analysis on 19th December 2025. SACT data is only considered complete when 90% of trusts have submitted data. As a result, SACT data is considered complete up to 31st March 2025. Patients were traced for their vital status on 5th October 2025.

Descriptive statistics of age were computed, along with Kaplan-Meier estimates and parametric fits for overall survival (OS). Patients were censored at the date of the most recent trace (5th October 2025), representing the last date on which vital status was confirmed. Given the high survival rate in this population, the fitted curves were extrapolated to cover a 10-year period following treatment initiation.

Cohort inclusions / exclusions

Patients were included if they met all of the following:

- Diagnosed between 1st April 2018 and 31st December 2023
- Gender recorded as male or female
- Country code was 'England', based on postcode of residence at diagnosis
- Age at diagnosis date was 18 or over
- Diagnosis of CLL confirmed by an ICD-10 code 'C91.1' (Chronic lymphocytic leukaemia of B-cell type) and ICD-O-3 morphology code '9823/3' (Chronic lymphocytic leukaemia/small lymphocytic lymphoma)
- Only one CLL neoplasm recorded during the study period
- No registration for another malignant neoplasm within the 36 months preceding CLL diagnosis
- VenO treatment was initiated on or after 9th December 2020 (NICE TA663 publication date). Usage before this point is assumed to be through compassionate use schemes.
- VenO treatment was initiated on or before the point at which SACT is considered complete (31st March 2025).

- Individuals were untreated, and had received no prior systemic anti-cancer therapy in the period between 1st April 2018 and the date of VenO initiation. Qualifying prior therapies included:
 - Monotherapies: acalabrutinib, zanubrutinib, fludarabine, bendamustine, venetoclax, ibrutinib, chlorambucil, rituximab, idelalisib, or cyclophosphamide
 - Combination therapies: venetoclax + ibrutinib, cyclophosphamide + obinutuzumab, rituximab + venetoclax, rituximab + fludarabine, rituximab + bendamustine, rituximab + chlorambucil, rituximab + idelalisib, or rituximab + cyclophosphamide. Combination therapies may also include other drugs (e.g. rituximab + cyclophosphamide + other) would also be considered a viable treatment.

Note: A potential limitation of this study is that treatments were identified using the 'regimen' table. As individual drug administrations in the 'drug_detail' table were not reviewed, some individuals who met the inclusion criteria but were only identifiable through drug administration records may have been missed.

Flow chart

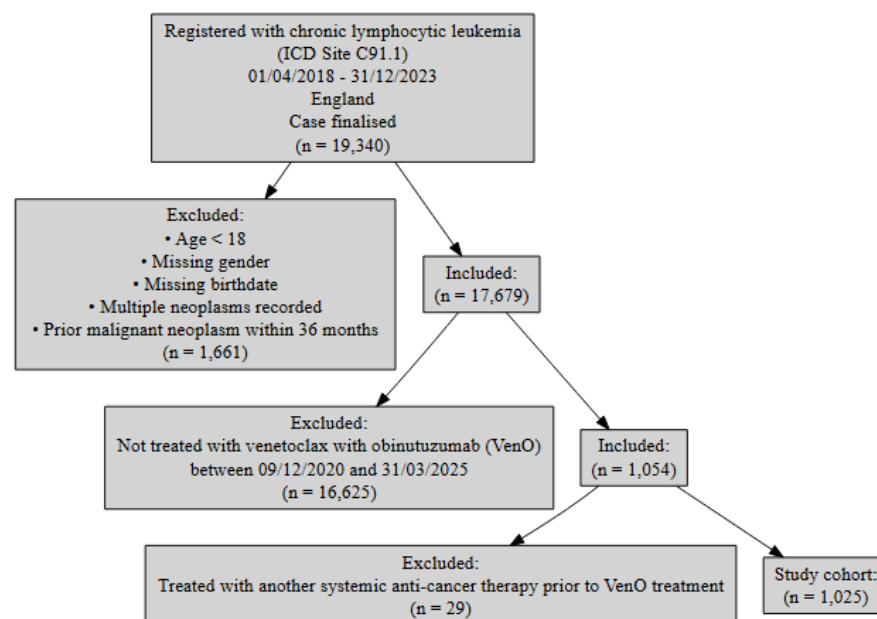


Figure 1: Inclusion / Exclusion Flow Chart

Patient acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

Results

Age at start of treatment

The table below sets out the mean age, standard deviation, median age and interquartile range (IQR) of patients who have received VenO for chronic lymphocytic leukemia, split by gender. Age is measured at the commencement of the first VenO treatment regimen.

Characteristic	Female N = 310 ¹	Male N = 715 ¹
Age at start of regimen	64, (10) : 65 (57, 73)	65, (10) : 65 (58, 72)

¹Mean, (SD) : Median (Q1, Q3)

Table 1: Mean age, standard deviation, median age and IQR of patients who have received venetoclax with obinutuzumab, split by gender

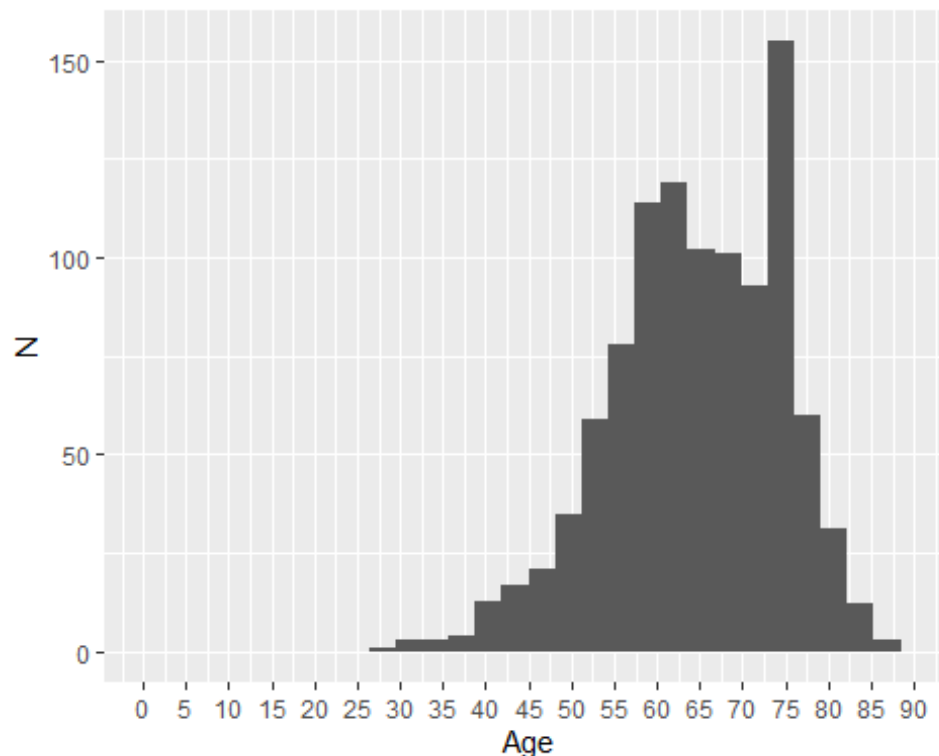


Figure 2: Age distribution of patients who have received venetoclax with obinutuzumab

Overall survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a VenO treatment regimen.

Median survival was not reached. Restricted mean survival (over the whole curve) was 54.38 months. The minimum follow-up time was 0.1 months, median 30.3 months, and maximum follow-up time of 57.8 months.

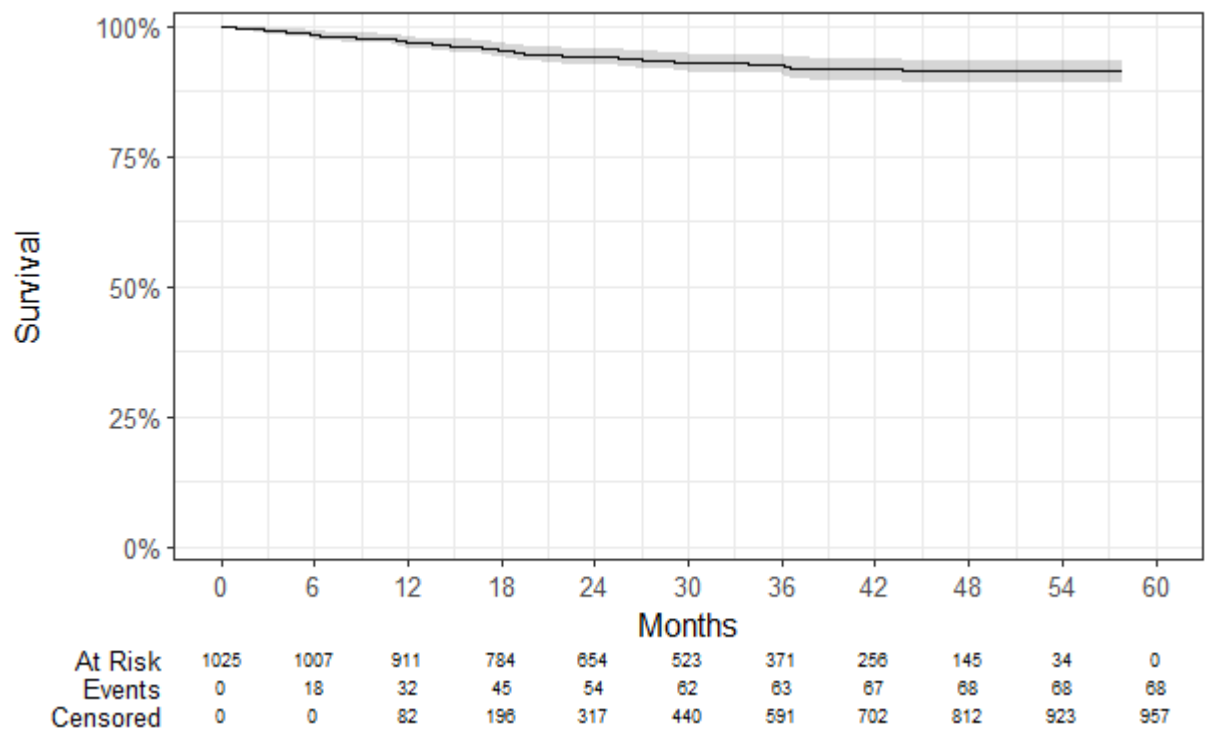


Figure 3: Overall survival amongst patients who have received venetoclax with obinutuzumab

Exponential

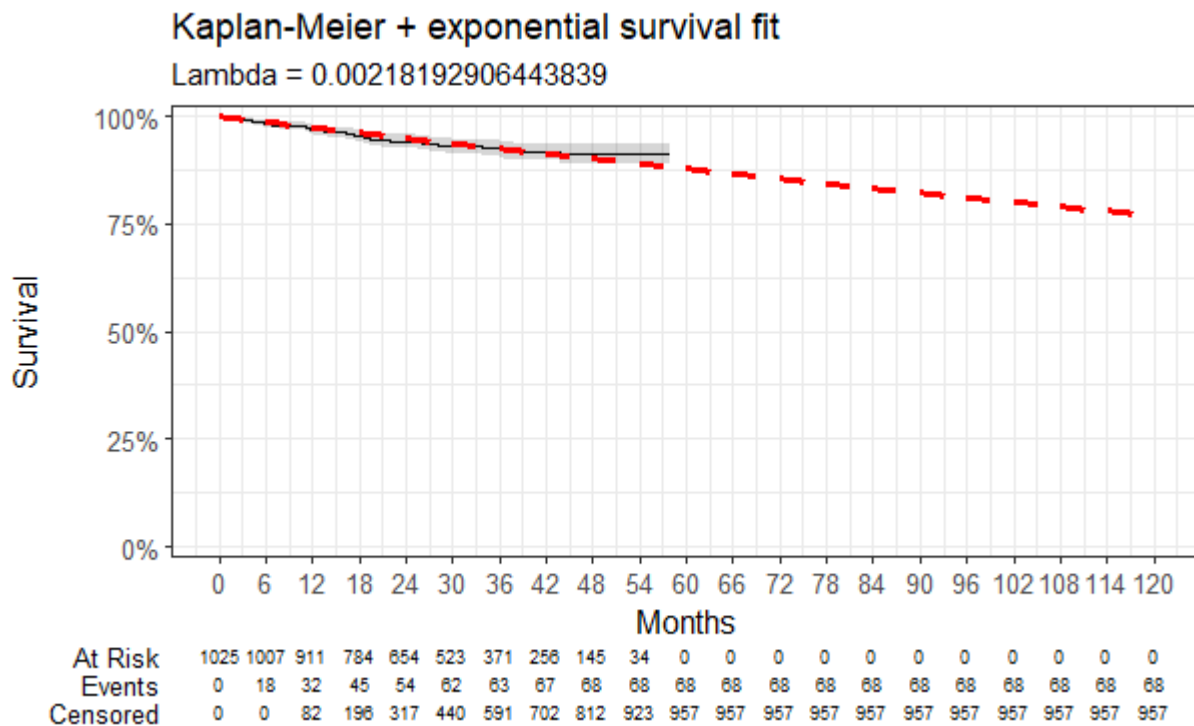


Figure 4: Overall survival against exponential survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.128	0.121	50.52904	0

log-likelihood = -484.673121304121
AIC = 971.346242608241
BIC = 976.278690499814

Table 2: Survival model fit summary (exponential distribution)

Weibull

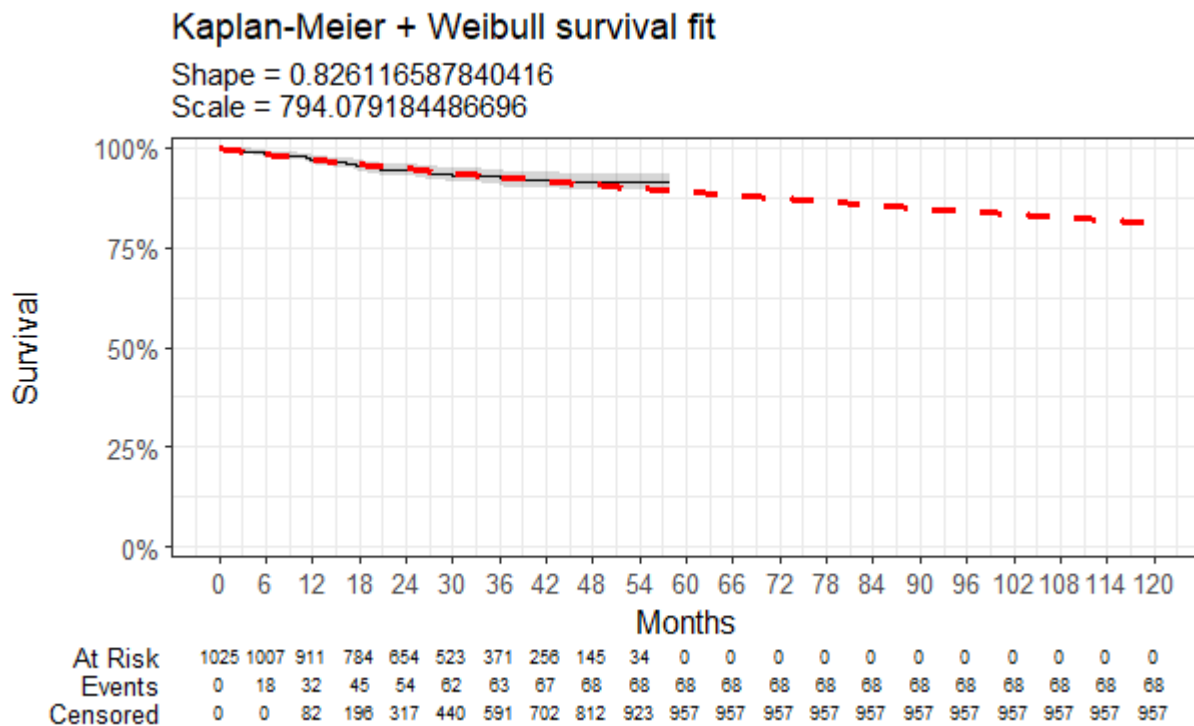


Figure 5: Overall survival against Weibull survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.677	0.389	17.146002	6.732785e-66
Log(scale)	0.191	0.113	1.683175	9.234116e-02

log-likelihood = -483.143652732327

AIC = 970.287305464655

BIC = 980.1522012478

Table 3: Survival model fit summary (Weibull distribution)

Log-normal

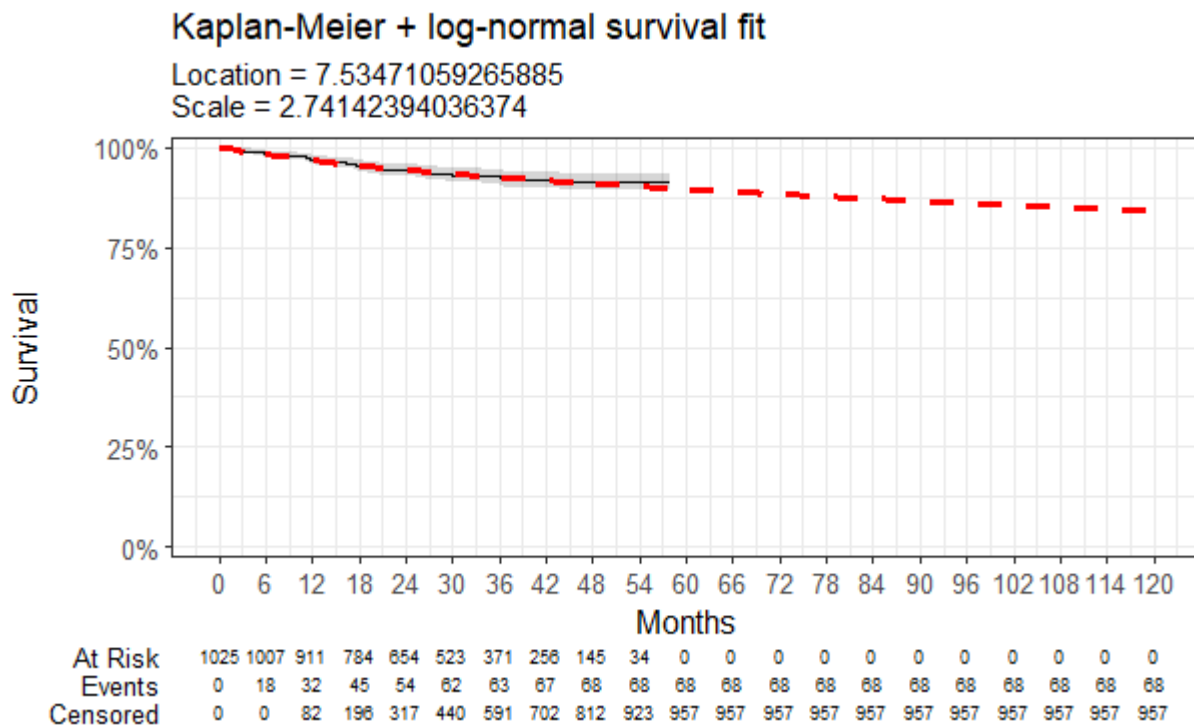


Figure 6: Overall survival against log-normal survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	7.535	0.478	15.763128	5.580098e-56
Log(scale)	1.008	0.103	9.817792	9.438847e-23

log-likelihood = -482.376500353882

AIC = 968.753000707764

BIC = 978.617896490909

Table 4: Survival model fit summary (log-normal distribution)

Log-logistic

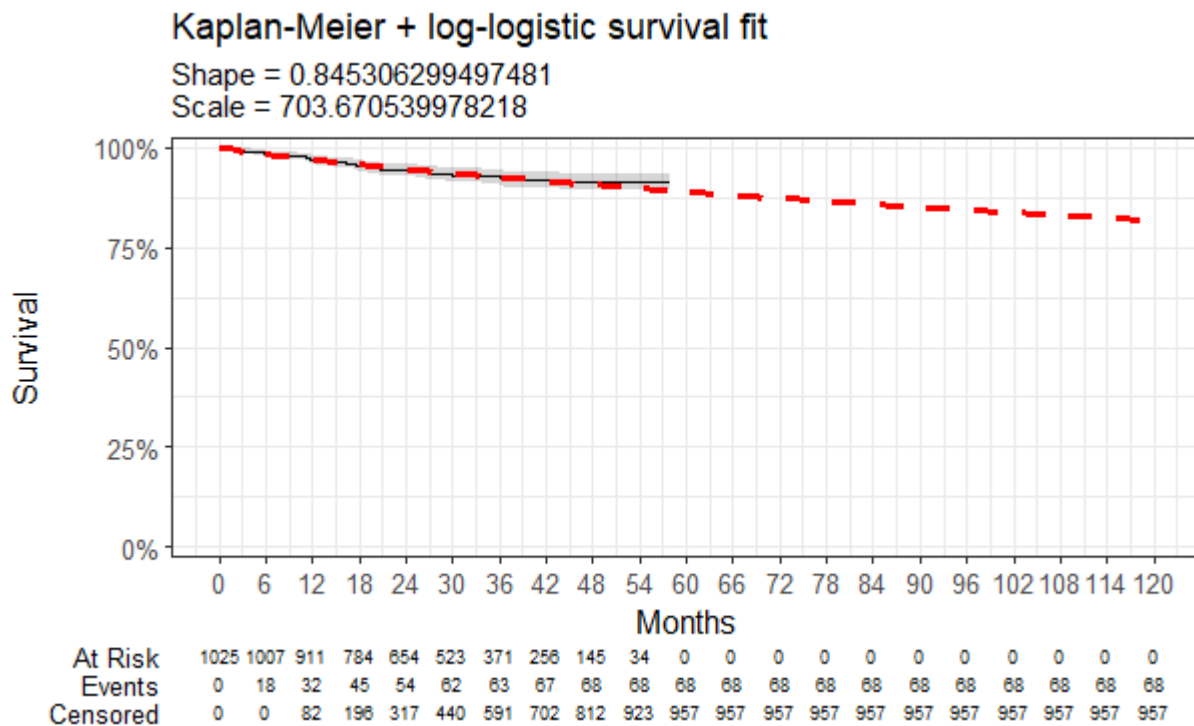


Figure 7: Overall survival against log-logistic survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.556	0.380	17.268389	8.138264e-67
Log(scale)	0.168	0.113	1.489928	1.362431e-01

log-likelihood = -482.970732564199

AIC = 969.941465128397

BIC = 979.806360911542

Table 5: Survival model fit summary (log-logistic distribution)

Gaussian

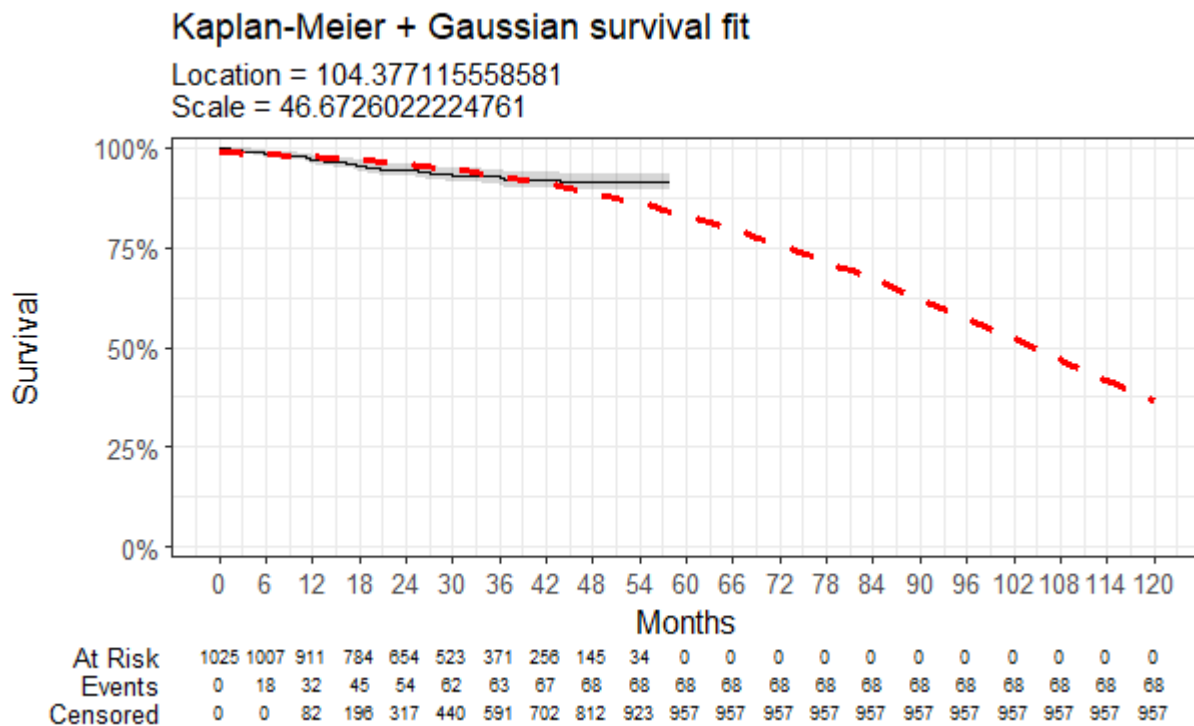


Figure 8: Overall survival against Gaussian survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	104.377	7.913	13.18992	1.002961e-39
Log(scale)	3.843	0.101	38.16480	0.000000e+00

log-likelihood = -518.043265032592

AIC = 1040.08653006518

BIC = 1049.95142584833

Table 6: Survival model fit summary (Gaussian distribution)

Gamma

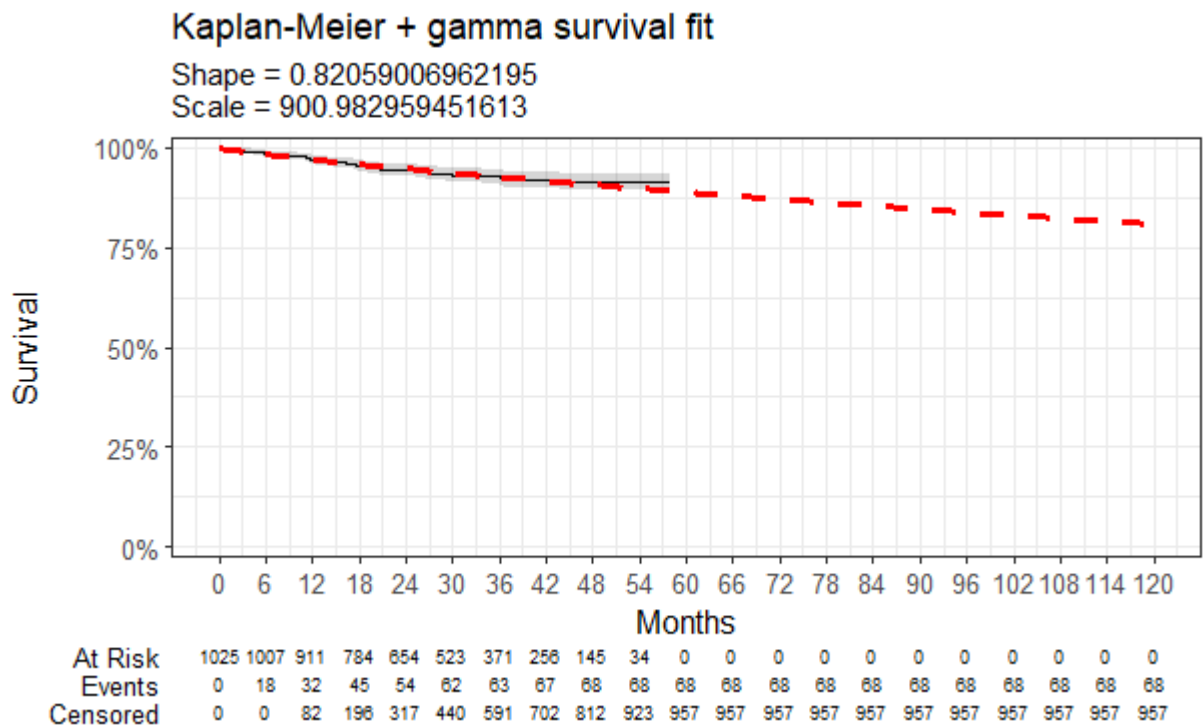


Figure 9: Overall survival against gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	0.821	0.098	0.6497614987	1.03633112
rate	0.001	0.001	0.0004485289	0.00274648

log-likelihood = -483.214908148409

AIC = 970.429816296819

BIC = 980.294712079964

Table 7: Survival model fit summary (gamma distribution)

Generalised gamma

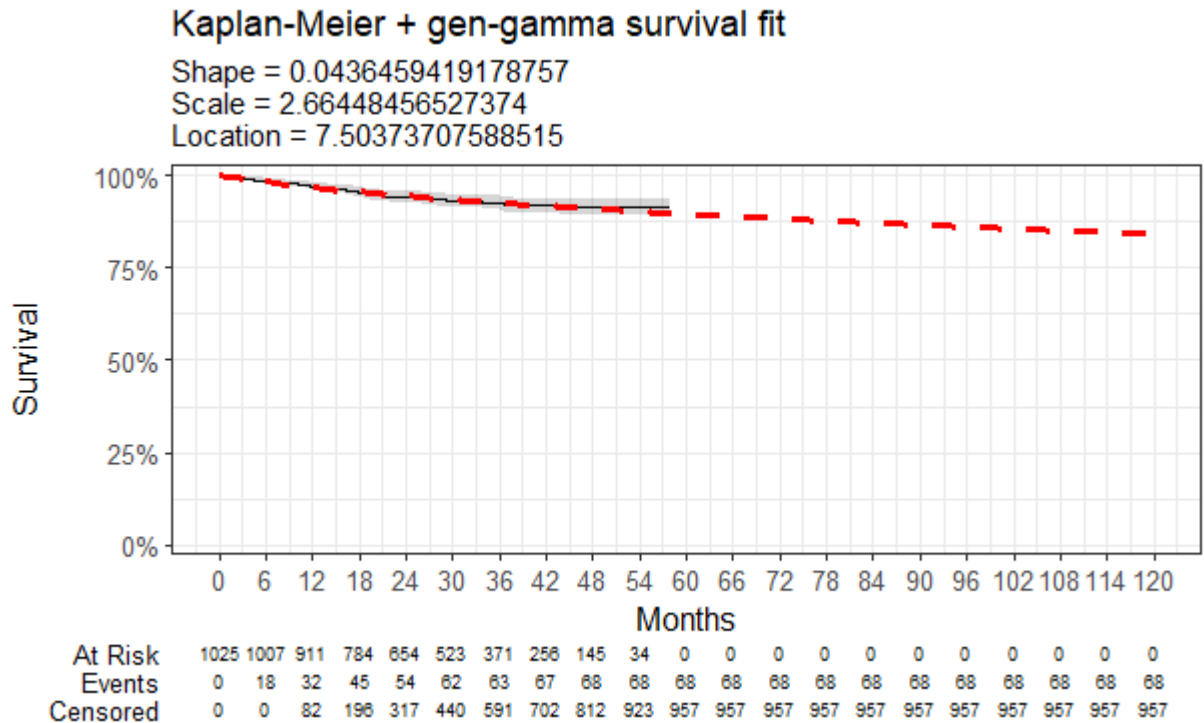


Figure 10: Overall survival against generalised gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
mu	7.504	0.713	6.106526	8.900948
sigma	2.664	1.315	1.012828	7.009563
Q	0.044	0.729	-1.385697	1.472989

log-likelihood = -482.374742889401

AIC = 970.749485778802

BIC = 985.546829453519

Table 8: Survival model fit summary (generalised gamma distribution)

Gompertz

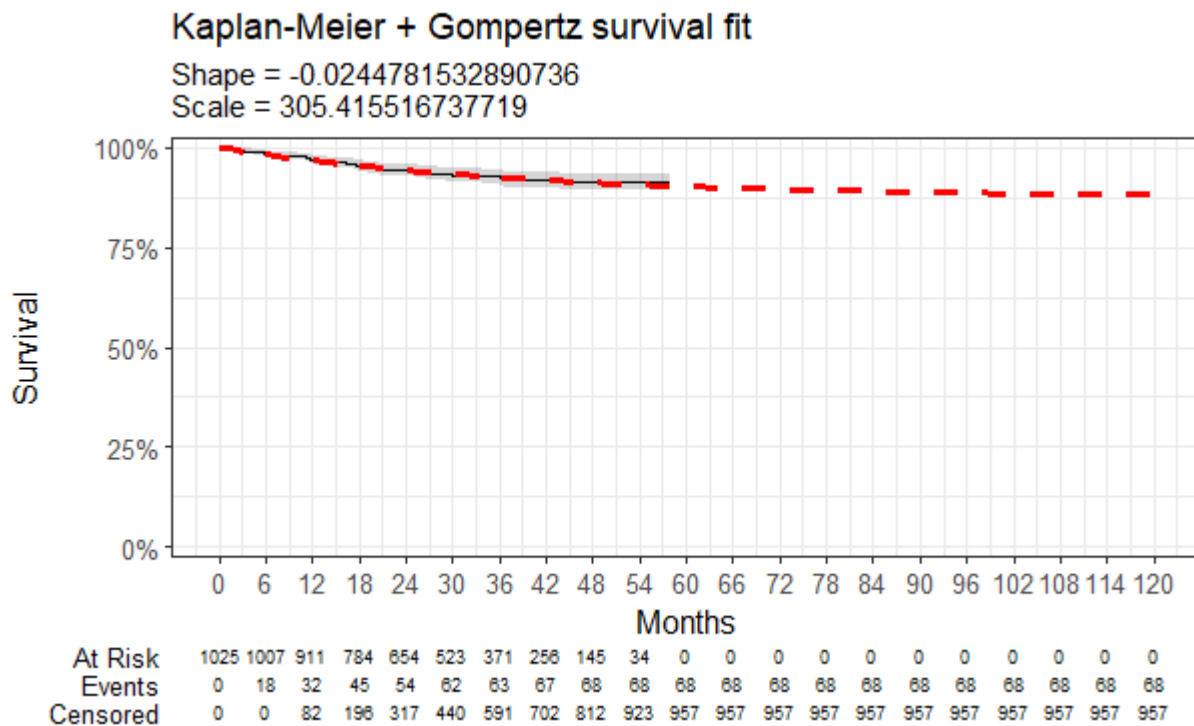


Figure 11: Overall survival against Gompertz survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.024	0.011	-0.045065864	-0.003890443
rate	0.003	0.001	0.002224395	0.004819543

log-likelihood = -481.725071988334

AIC = 967.450143976668

BIC = 977.315039759813

Table 9: Survival model fit summary (Gompertz distribution)

Age and overall survival for untreated chronic lymphocytic leukaemia treated with venetoclax with ibrutinib (VenI; cohort 2)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival and age distributions among patients aged 18 or over with untreated chronic lymphocytic leukemia (CLL) who have received venetoclax with ibrutinib (VenI; cohort 2).

Method

A snapshot of SACT data was taken on 7th December 2025 and made available for analysis on 19th December 2025. SACT data is only considered complete when 90% of trusts have submitted data. As a result, SACT data is considered complete up to 31st March 2025. Patients were traced for their vital status on 5th October 2025.

Descriptive statistics of age were computed, along with Kaplan-Meier estimates and parametric fits for overall survival (OS). Patients were censored at the date of the most recent trace (5th October 2025), representing the last date on which vital status was confirmed. Given the high survival rate in this population, the fitted curves were extrapolated to cover a 10-year period following treatment initiation. The generalised gamma model was excluded from the VenI cohort because it produced unreliable results and an implausible survival curve beyond the observed data.

Cohort inclusions / exclusions

Patients were included if they met all of the following:

- Diagnosed between 1st April 2018 and 31st December 2023
- Gender recorded as male or female
- Country code was 'England', based on postcode of residence at diagnosis
- Age at diagnosis date was 18 or over
- Diagnosis of CLL confirmed by an ICD-10 code 'C91.1' (Chronic lymphocytic leukaemia of B-cell type) and ICD-O-3 morphology code '9823/3' (Chronic lymphocytic leukaemia/small lymphocytic lymphoma)
- Only one CLL neoplasm recorded during the study period
- No registration for another malignant neoplasm within the 36 months preceding CLL diagnosis
- VenI treatment was initiated on or after 31st May 2023 (NICE TA891 publication date). Usage before this point is assumed to be through compassionate use schemes.
- VenI treatment was initiated on or before the point at which SACT is considered complete (31st March 2025).

- Individuals were untreated, and had received no prior systemic anti-cancer therapy in the period between 1st April 2018 and the date of VenI initiation. Qualifying prior therapies included:
 - Monotherapies: acalabrutinib, zanubrutinib, fludarabine, bendamustine, venetoclax, ibrutinib, chlorambucil, rituximab, idelalisib, or cyclophosphamide
 - Combination therapies: venetoclax + obinutuzumab, cyclophosphamide + obinutuzumab, rituximab + venetoclax, rituximab + fludarabine, rituximab + bendamustine, rituximab + chlorambucil, rituximab + idelalisib, or rituximab + cyclophosphamide. Combination therapies may also include other drugs (e.g. rituximab + cyclophosphamide + other) would also be considered a viable treatment.

Note: A potential limitation of this study is that treatments were identified using the 'regimen' table. As individual drug administrations in the 'drug_detail' table were not reviewed, some individuals who met the inclusion criteria but were only identifiable through drug administration records may have been missed.

Flow chart

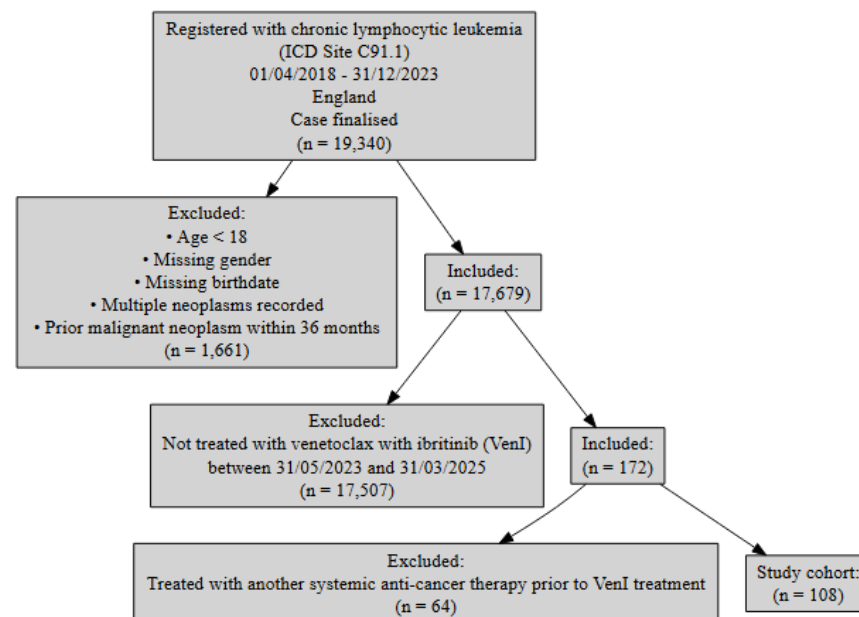


Figure 12: Inclusion / Exclusion Flow Chart

Patient acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

Results

Age at start of treatment

The table below sets out the mean age, standard deviation, median age and interquartile range (IQR) of patients who have received VenI for chronic lymphocytic leukemia, split by gender. Age is measured at the commencement of the first VenI treatment regimen.

Characteristic	Female N = 33 ¹	Male N = 75 ¹
Age at start of regimen	66, (9) : 67 (59, 71)	62, (10) : 63 (57, 68)

¹Mean, (SD) : Median (Q1, Q3)

Table 10: Mean age, standard deviation, median age and IQR of patients who have received venetoclax with ibrutinib, split by gender

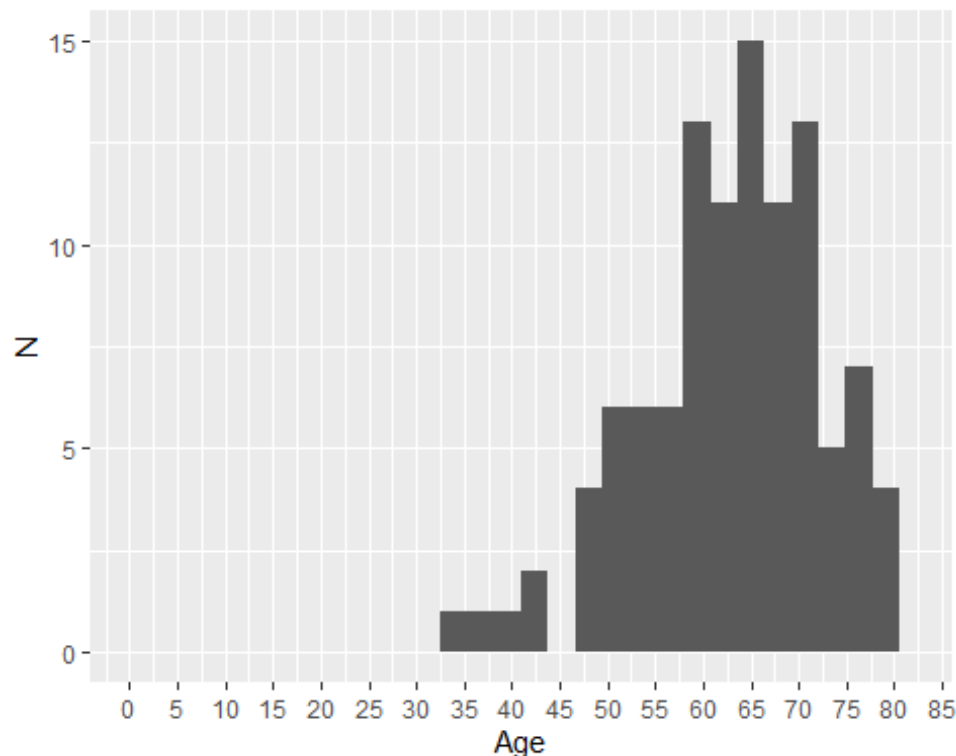


Figure 13: Age distribution of patients who have received venetoclax with ibrutinib

Overall survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a VenI treatment regimen.

Median survival was not reached. Restricted mean survival (over the whole curve) was 27.26 months. The minimum follow-up time was 4.3 months, median 19.4 months, and maximum follow-up time of 28 months.

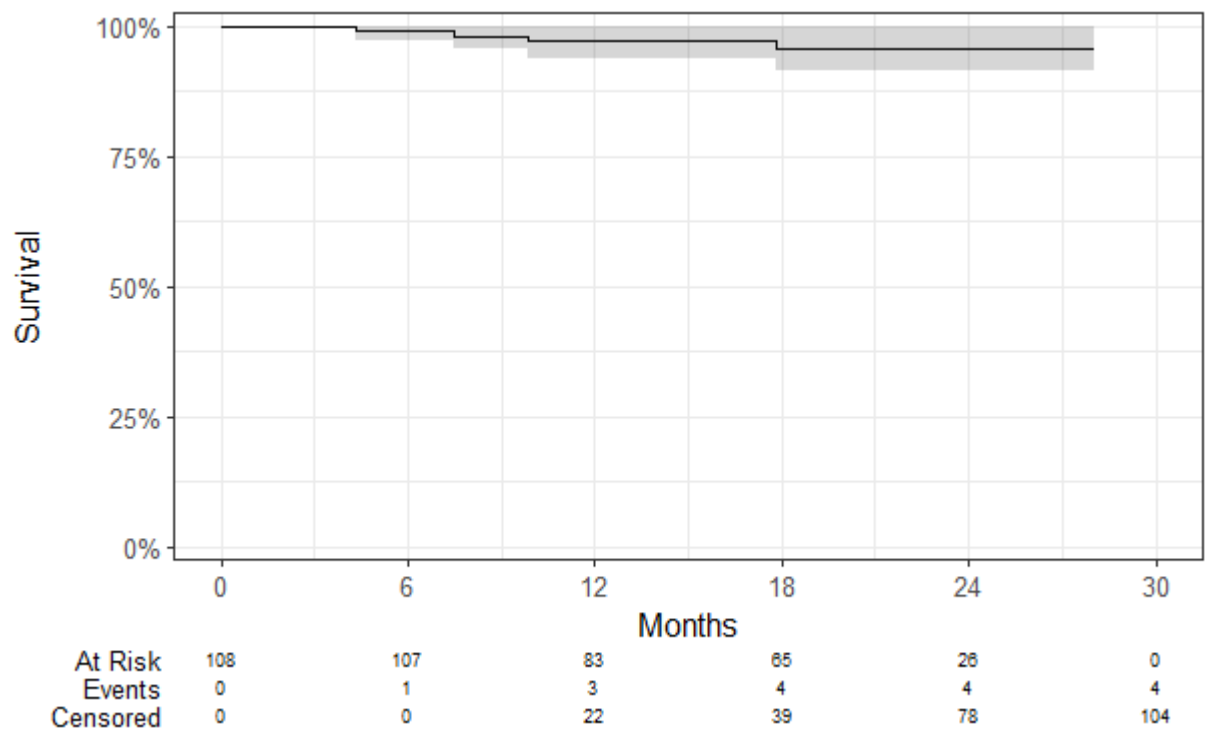


Figure 14: Overall survival amongst patients who have received venetoclax with ibrutinib

Exponential

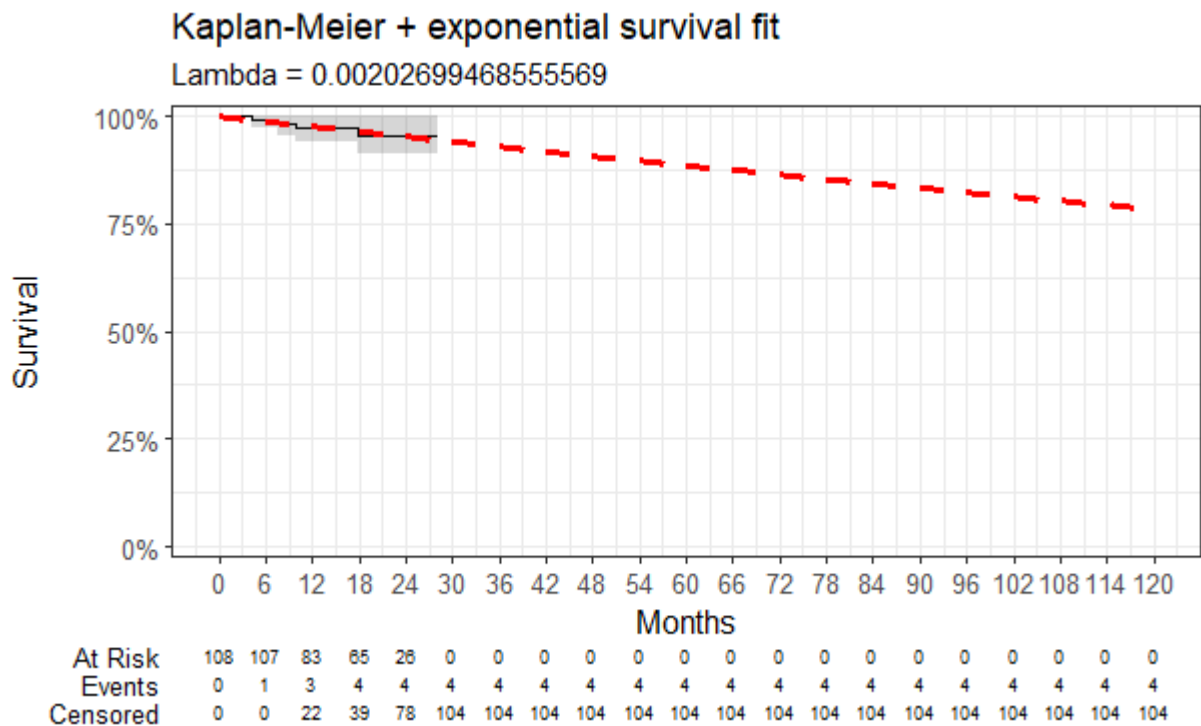


Figure 15: Overall survival against exponential survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.201	0.500	12.4024	2.536054e-35

log-likelihood = -28.8048041333728
AIC = 59.6096082667456
BIC = 62.2917394938698

Table 11: Survival model fit summary (exponential distribution)

Weibull

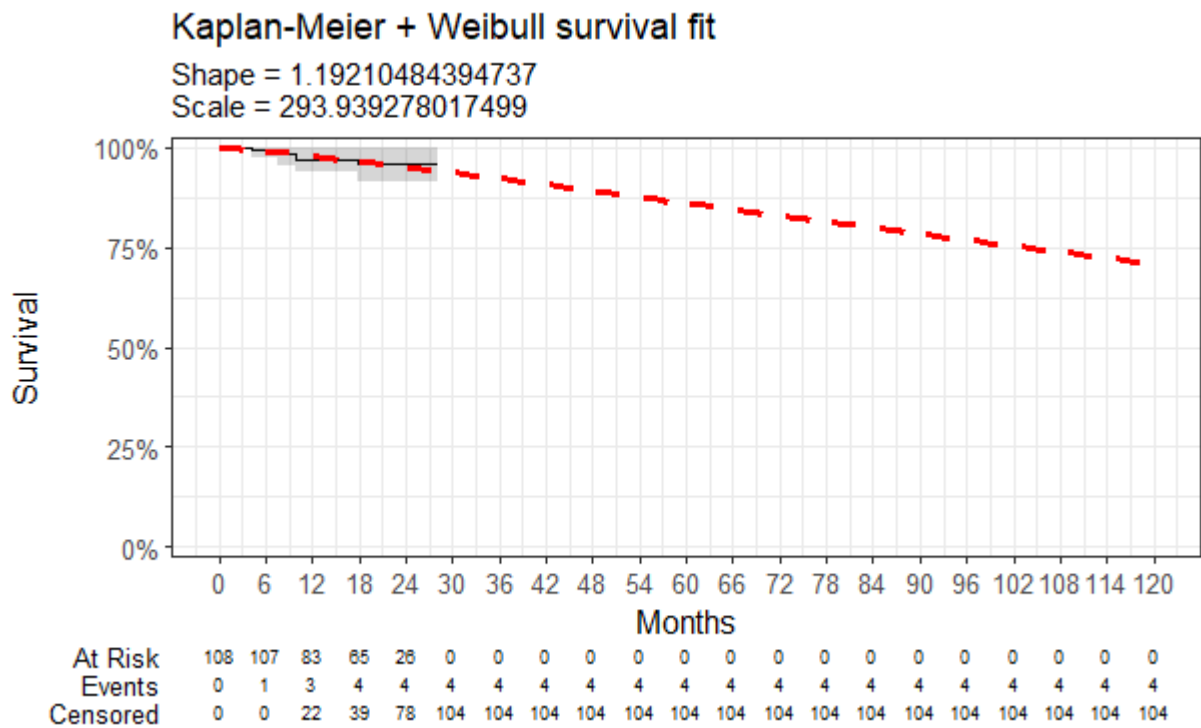


Figure 16: Overall survival against Weibull survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	5.683	1.319	4.3091393	1.638911e-05
Log(scale)	-0.176	0.466	-0.3772957	7.059539e-01

log-likelihood = -28.7383083624217

AIC = 61.4766167248434

BIC = 66.8408791790919

Table 12: Survival model fit summary (Weibull distribution)

Log-normal

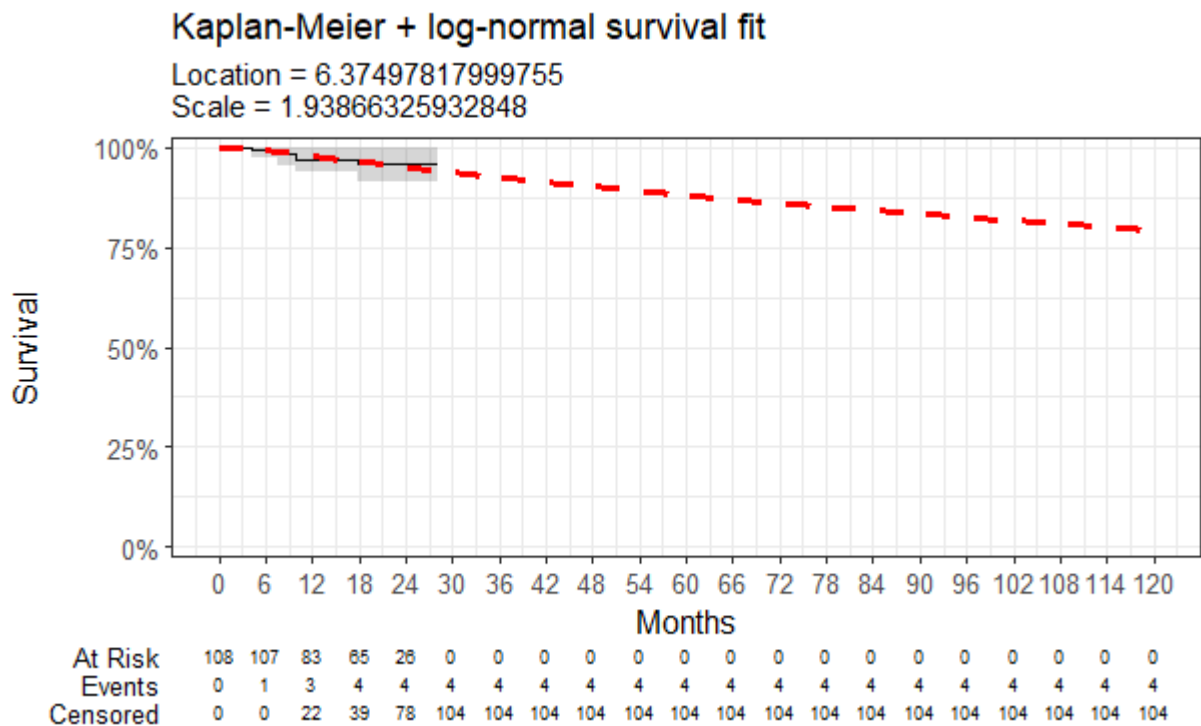


Figure 17: Overall survival against log-normal survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.375	1.606	3.970512	7.171839e-05
Log(scale)	0.662	0.433	1.529804	1.260653e-01

log-likelihood = -28.5284350897398

AIC = 61.0568701794795

BIC = 66.421132633728

Table 13: Survival model fit summary (log-normal distribution)

Log-logistic

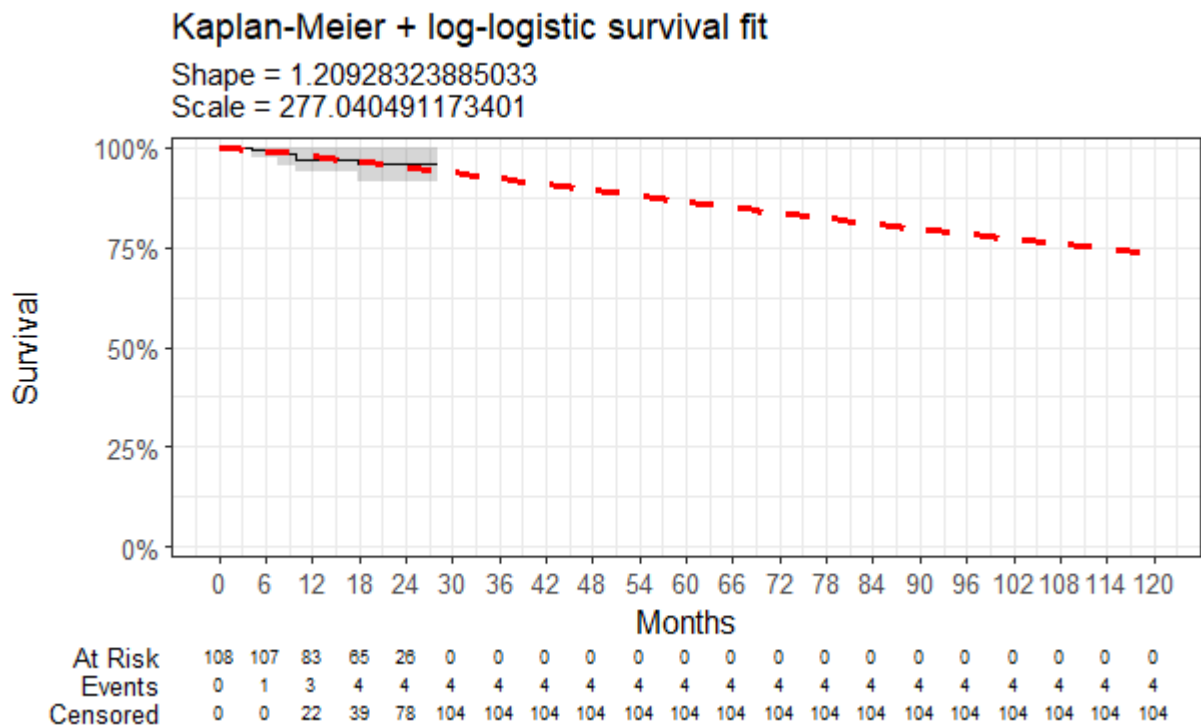


Figure 18: Overall survival against log-logistic survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	5.624	1.295	4.3424529	1.409007e-05
Log(scale)	-0.190	0.463	-0.4100564	6.817646e-01

log-likelihood = -28.7236159283733

AIC = 61.4472318567465

BIC = 66.811494310995

Table 14: Survival model fit summary (log-Logistic distribution)

Gaussian

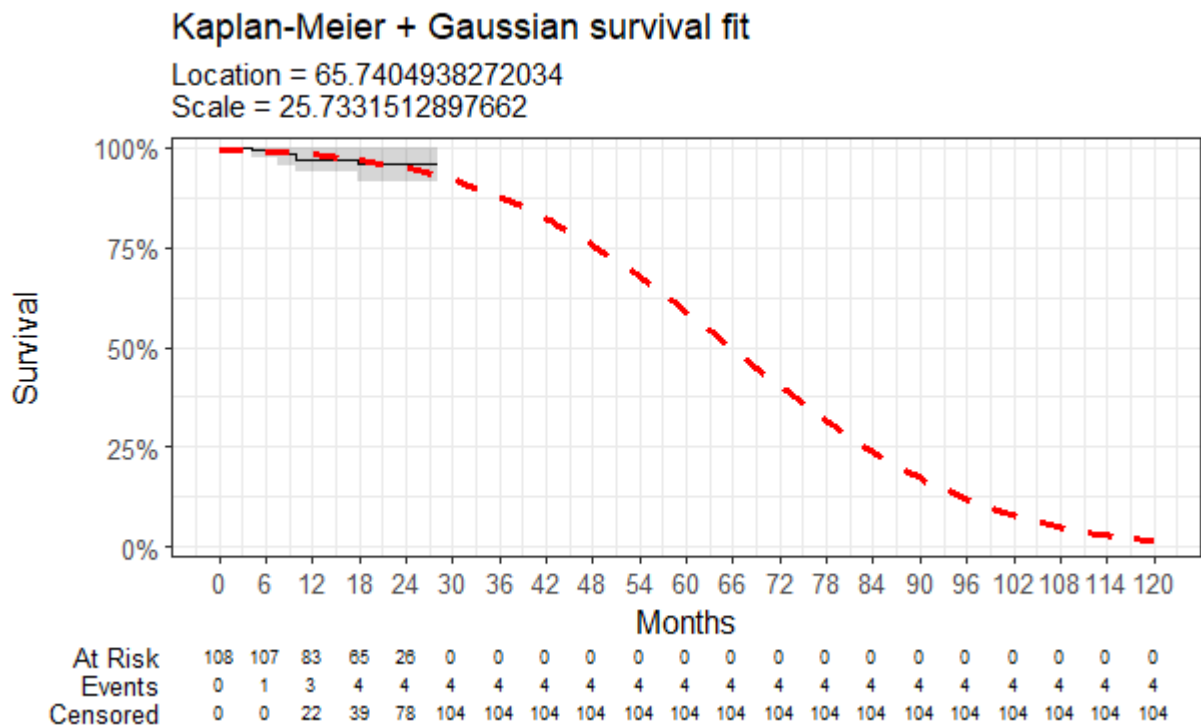


Figure 19: Overall survival against Gaussian survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	65.740	20.951	3.137860	1.701861e-03
Log(scale)	3.248	0.427	7.611054	2.718686e-14

log-likelihood = -30.1690705828917

AIC = 64.3381411657834

BIC = 69.7024036200318

Table 15: Survival model fit summary (Gaussian distribution)

Gamma

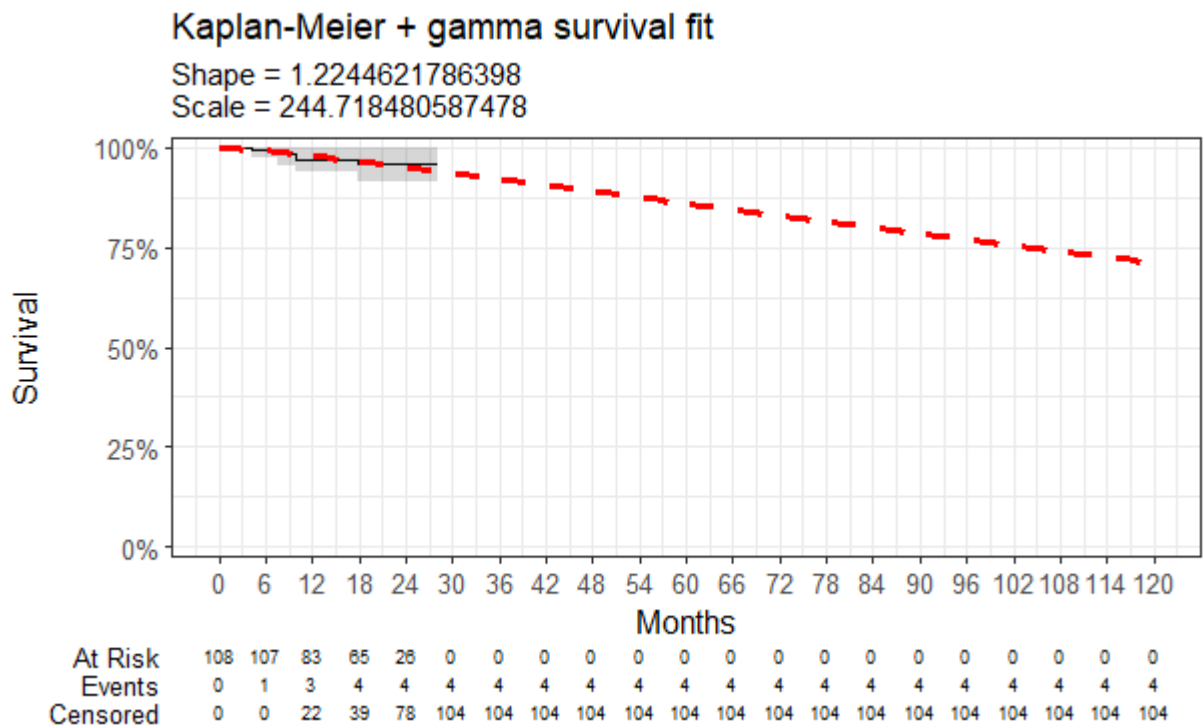


Figure 20: Overall survival against gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	1.224	0.618	0.4551392375	3.294174
rate	0.004	0.007	0.0001538979	0.108501

log-likelihood = -28.7286998442331

AIC = 61.4573996884663

BIC = 66.8216621427147

Table 16: Survival model fit summary (gamma distribution)

Gompertz

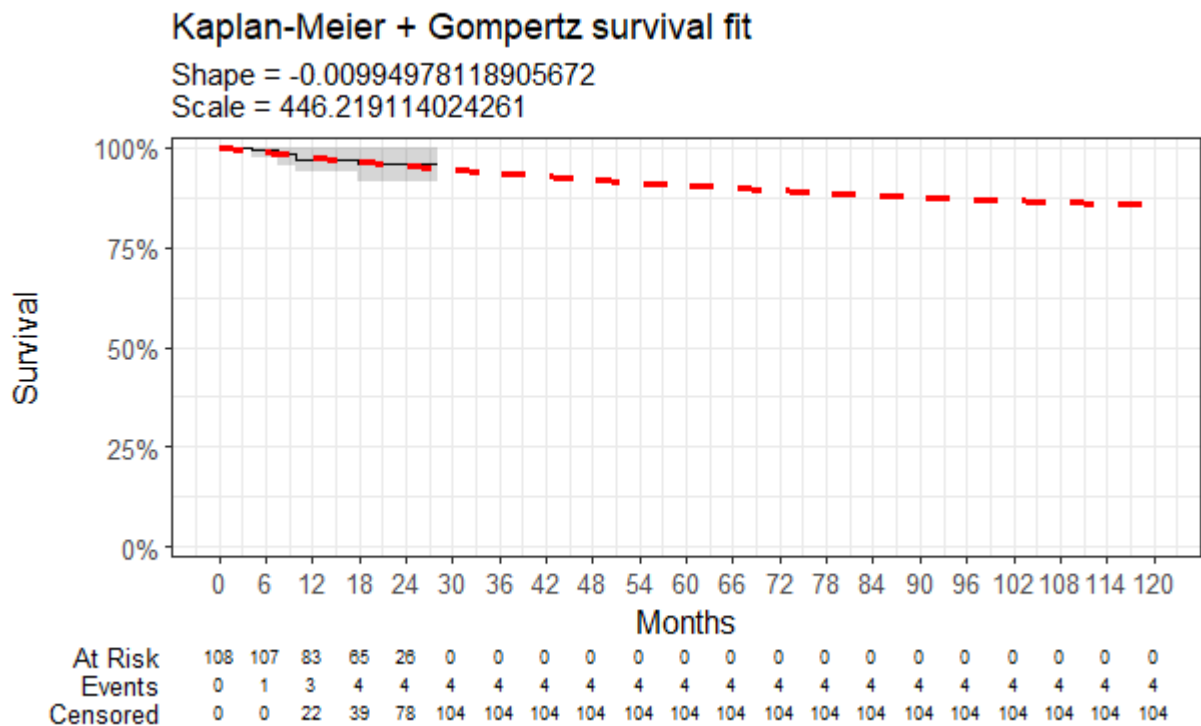


Figure 21: Overall survival against Gompertz survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.010	0.075	-0.1565310504	0.13663149
rate	0.002	0.002	0.0003906724	0.01285556

log-likelihood = -28.7958623310017

AIC = 61.5917246620033

BIC = 66.9559871162517

Table 17: Survival model fit summary (Gompertz distribution)

External Assessment Group (EAG) Report

Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
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Date completed	Date completed (20/11/2025)

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Declared competing interests

Authors have no competing interests.

Dr Satyen Gohil (clinical advisor) has declared the following conflicts of interest:

AbbVie (venetoclax) - Travel to conferences, honoraria and speakers fees;
AstraZeneca - Travel to conferences, honoraria and speakers fees; Beigene (zanubrutinib) - Travel to conferences, honoraria and speakers fees; Johnson &

Johnson Innovative Medicine (ibrutinib) - Travel to conferences, honoraria and speakers fees.

Dr Scott Marshall (clinical advisor) has declared the following conflicts of interest:

AbbVie - Advisory board for treatment of previously untreated patients with CLL 2025, Paid delivery of education lectures on CLL 2025, 2024, Sponsored Conference attendance 2025; AstraZeneca UK (acalabrutinib) - Advisory board for treatment of previously untreated patients with CLL, 2025.

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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.

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Contributions of authors

Mehdi Yousefi and Andrew Sutton critiqued the company's model, corrected identified errors and undertook EAG economic modelling. Adel Elfeky and Amin Mehrabian critiqued the clinical effectiveness evidence. Rachel Court critiqued the company's searches and conducted additional EAG searches. Daniel Gallacher

critiqued the company's indirect treatment comparisons. Adel Elfeky coordinated the EAG team. All authors contributed to the writing and editing of the report.

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Figure 1 is adapted from the 2025 British Society for Haematology (BSH) Guideline for the treatment of chronic lymphocytic leukaemia.

Figure 2 is adapted from Tedeschi, A. et al. Fixed-duration therapy of chronic lymphocytic leukemia with venetoclax and Bruton tyrosine kinase inhibitors: an insight into differences between ibrutinib and acalabrutinib. *Leukemia* 39, 2618–2621 (2025). <https://doi.org/10.1038/s41375-025-02778-1>.

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Table of Abbreviations

Abbreviation	Definition
2L	Second line
A	Acalabrutinib
ACD	Appraisal Consultation Document
AE	Adverse event
AIC	Akaike information criterion
ANC	Absolute neutrophil count
AO	Acalabrutinib with obinutuzumab
AV	Acalabrutinib with venetoclax
AVO	Acalabrutinib with venetoclax and obinutuzumab
BCL2	B-cell lymphoma 2
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BOR	Best overall response
BR	Bendamustine with rituximab
BSA	Body surface area
BSH	British Society for Haematology
BTK	Bruton tyrosine kinase
BTKi	Bruton tyrosine kinase inhibitor
CC	Complication and Comorbidity
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CLL	Chronic lymphocytic leukaemia
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CR	Complete response
CRi	Complete response with incomplete marrow recovery
CSR	Clinical study report
CT	Computed tomography

CX	Cycle X
DCO	Data cut-off
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DX	Day X
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
PS	Performance Status
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic Medicines Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
FCR	Fludarabine with cyclophosphamide and rituximab
FIS	Fatigue impact score
FSS	Fatigue symptom score
GFS	Global fatigue scale
GP	General practitioner
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgHV	Immunoglobulin heavy-chain variable region
IL27	Item Library 27
Incr	Incremental
INHB	Incremental net health benefit

IPD	Individual patient data
IQR	Interquartile range
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVO	Ibrutinib with venetoclax and obinutuzumab
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
Max	Maximum
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
Min	Minimum
ML-NMR	Multilevel Network Meta-Regression
MMRM	Mixed-model repeated measures
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nPR	Nodular partial response
NR	Not reported
OC1b	Obinutuzumab with chlorambucil
ORR	Overall response rate
OS	Overall survival
P25	25th percentile
P75	75th percentile
PAS	Patient access scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PGIC	Patient Global Impression of Change

PGIS	Patient Global Impression of Severity
PO	Oral administration
PR	Partial response
Pre-PS	Pre-progression survival
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial
RDI	Relative dose intensity
REML	Restricted maximum likelihood
RMST	Restricted mean survival time
SAE	Serious adverse event
SC	Steering committee
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STC	Simulated treatment comparison
REML	Restricted maximum likelihood
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
TLS	Tumour lysis syndrome
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTP	Time to progression
UK	United Kingdom
uMRD	Undetectable minimal residual disease
US	United States
V	Venetoclax

VAS	Visual analogue scale
VenI	Venetoclax with ibrutinib
VenO	Venetoclax with obinutuzumab
WHO	World Health Organization
WTP	Willingness-to-pay

1 Executive summary

This report summarises the critique of the company submission (CS), including the company's response to clarification questions, by the External Assessment Group (EAG).

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

Table 1: Summary of key issues

ID6232	Summary of issue	Impact on results	Report sections
Issue 1	Lack of comparison to acalabrutinib and zanubrutinib monotherapies (treat-to-progression therapies)	Unknown	1.3, 2.3, 4.2.4.3
Issue 2	Generalisability of AMPLIFY trials to target NHS population (age)	Small	3.2, 3.4, 4.2.3.1
Issue 3	Reliance on assumption of equal efficacy for AV, VenI and VenO	Unknown	3.5, 3.6
Issue 4	Modelling of time-on-treatment and relative dose intensity for AV, VenI and VenO	Moderate	4.2.4.1, 4.2.4.2, 4.2.5.3
Issue 5	Choice of health state utility values used in the model	Small	4.2.6.1
Issue 6	Proportion and distribution of subsequent treatments	Moderate	4.2.7.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The source of health state utility values
- The starting age of the model population

- The approach to modelling of time-on-treatment and incorporating relative dose intensity into the model
- The proportions receiving subsequent treatments and the distribution of treatments received.
- The EAG consider the assumption of equal efficacy is likely biased in favour of AV, however due to a lack of an alternative with increased certainty, the assumption is maintained in the EAG base case. The EAG does, though, allow the TTP, PrePS, and PPS curves to vary independently for each arm in the PSA.

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 a different time on treatment to the comparator treatments
- Having a different adverse event profile to the comparator treatments

Overall, the technology is modelled to affect costs by:

- Having a different mode of administration and time on treatment to the comparator treatments
- Having a different adverse event profile to the comparator treatments
- Having a different acquisition cost to the comparator treatments
- Having a different proportion of people receiving subsequent treatments, and a different distribution of subsequent treatments received

The modelling assumptions that have the greatest effect on the ICER are:

- The assumption of equal efficacy across the treatments
- The modelling of time on treatment or completion rate for each treatment
- The modelling of subsequent treatments

1.3 EAG's key issues

Issue 1: Lack of comparison to acalabrutinib and zanubrutinib monotherapies (treat-to-progression therapies)

Report section	1.3, 2.3, 4.2.4.3
Description of issue and why the EAG has identified it as important	The company claim that the only relevant comparators are Venl and VenO, which are the two dual therapies currently approved for untreated CLL. Whilst acalabrutinib and zanubrutinib monotherapies are approved as first line therapies, they are given to patients who are less fit, though there are no clear criteria for this assessment. The company consider that the availability of AV will not affect whether patients receive dual or mono therapy. The EAG clinical experts state that the more tolerable safety profile of AV compared to Venl and VenO means it is likely to broaden the potential patient pool for dual therapies, beyond those currently considered for Venl or VenO. This means that acalabrutinib and zanubrutinib monotherapies are relevant comparators to AV. The experts also highlighted that these monotherapies are often chosen in settings with limited access to hospitals able to provide the supporting services required for dual therapies.
What alternative approach has the EAG suggested?	The EAG requested that the company undertake an analysis comparing to acalabrutinib and zanubrutinib monotherapies. The company did not provide the requested analysis. Alternatively, AV access could be restricted to people considered eligible for Venl or VenO, however this may require clear eligibility criteria to be established.
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this key issue?	The company could provide the analyses requested by the EAG to allow a comparison to acalabrutinib and zanubrutinib.

Issue 2: Generalisability of AMPLIFY trial to target NHS population (age, fitness)

Report section	3.2, 3.4, 4.2.3.1
Description of issue and why the EAG has identified it as important	AV is licensed for all patients with untreated CLL, however the population of AMPLIFY is not representative of this group. The mean age of patients included in the AMPLIFY trial (59.9 years) is significantly lower than mean age of UK patients at presentation in clinical practice (around 70 years) as confirmed by our clinical experts. This raises concerns about the generalisability of trial findings, and it is difficult to gauge whether treatment benefit extends to older patients. The company conducted a subgroup analysis by age and an improvement in progression free survival (PFS) and overall survival (OS) in favour of treatment with AV compared with chemoimmunotherapy was observed. The EAG, however, notes that the sample size of most of the subgroups was small with few events in the subgroup of patients older than 65 years. As such, these analyses were not statistically powered to detect differences between subgroups and results should be interpreted with caution. The license for AV does not reference fitness, however the characteristics for AMPLIFY match closely to trials for other regimens which target people who are suitable for FCR/BR, loosely aligning with fitness assessment, which are now used to decide on dual or mono first line therapy.
What alternative approach has the EAG suggested?	The EAG acknowledges that in TA891, GLOW (mean age 71) was used for the FCR-unsuitable/high-risk population and CAPTIVATE FD (mean age 58) for the FCR-suitable population. However, recent BSH 2025 guidance and expert opinion confirm that fitness is no longer a key factor in treatment choice because targeted therapies are well tolerated across all fitness levels and age groups. As noted in the company's submission (section 1.2.3) and supported by BSH 2025 and the EAG's clinical experts, categorising patients by age or fitness would not reflect NHS practice. The EAG has amended the starting age in the economic model to 71 years, matching the age used in the appraisal of VenI (TA891), which has the same license as AV. This value is the median age of patients in the GLOW trial of VenI.
What is the expected effect on the cost-effectiveness estimates?	Small, but the effect of age is dependent on the assumptions around relative efficacy.
Could any additional evidence or analyses be provided to resolve this key issue?	The availability of real-world data from the use of VenI could inform the model starting age, and inform the efficacy of VenI, which could serve as the anchor for modelling the efficacy of AV. The EAG considers that the age of the AV population is likely to be older than those receiving VenI given the more tolerable safety profile.

Issue 3: Reliance on assumption of equal efficacy for AV, VenI and VenO

Report section	3.5, 3.6
Description of issue and why the EAG has identified it as important	The company relies on the assumption of equal efficacy of AV to VenI and VenO to inform the cost-effectiveness modelling. This assumption is made across pre-progression survival, time-to-progression, and post-progression survival. This assumption remains highly uncertain and is not well supported with strong evidence. The supporting analyses provided by the company are based on a limited presentation of STCs and a Bucher ITC. Additional input from six UK clinical experts and a modified Delphi panel is offered, but this input is uncertain and mainly reflects uncertain opinions and speculative assumptions, such as no biological reason for AV to be inferior and hypothetical gains from better tolerability. All of which the EAG consider likely to overestimate the benefits of AV due to clear biases. In addition, a recent unanchored MAIC suggests PFS and uMRD superiority of VenI over AV.
What alternative approach has the EAG suggested?	The EAG maintains this assumption in the EAG base case but explores a range of scenarios modelling inferior efficacy outcomes for AV to assess the impact on the ICER. In the EAG PSA, the strict assumption of equivalence is relaxed, with each treatment's efficacy coming from the same distribution and parameters but being sampled independently across each iteration, meaning the impact of potential superiority/inferiority is captured.
What is the expected effect on the cost-effectiveness estimates?	Unknown, though any deviation from equal efficacy could plausibly have a moderate to large impact on the cost-effectiveness results.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG requested that the company perform multi-level network meta-regression to provide a more reliable estimate of relative efficacy; however, the company did not provide this.

Issue 4: Modelling of time-on-treatment and relative dose intensity for AV, VenI and VenO

Report section	4.2.4.1, 4.2.4.2, 4.2.5.3
Description of issue and why the EAG has identified it as important	For AV, the company use information from AMPLIFY to inform the usage of acalabrutinib and venetoclax, combining information on time-to-treatment discontinuation (TTD) and relative dose intensity (RDI). For VenI and VenO, as no TTD information is reported, the company uses the same TTD curve but adjusts it for the number of cycles. The company assumes 100% RDI for VenI and VenO. The EAG considers that the assumptions of equal TTD and 100% RDI are unrealistic, given that AV is considered more tolerable than VenI and VenO. The company approach is likely to be overestimating the usage of VenI and VenO, overestimating their costs.
What alternative approach has the EAG suggested?	The EAG uses reported information for the treatment completion rates for AV, VenO and VenI, and assumes a linearly decreasing rate from 100% across the relevant number of cycles. This is combined with an assumption of 100% RDI for all treatments.
What is the expected effect on the cost-effectiveness estimates?	Moderate
Could any additional evidence or analyses be provided to resolve this key issue?	Real-world data could inform the completion rates for VenO and VenI in the relevant population.

Issue 5: Choice of health state utility values used in the model

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	The company derived HSUVs from EQ-5D-5L data collected in AMPLIFY, mapped these to EQ-5D-3L, and estimated utilities using a mixed model for repeated measures. However, the resulting values appear implausible: PF on-treatment utilities exceed age-matched population norms, and the assumption of equal PF utilities for on- and off-treatment states conflicts with expected improvements once treatment-related toxicity resolves. The AMPLIFY post-progression data were sparse, requiring external adjustments that add further uncertainty. In addition, the company did not fully report key elements of the mixed-model specification, making it unclear whether the estimates are appropriately adjusted for baseline factors influencing HRQoL. The EAG therefore considers that the company's approach risks overstating quality of life and inflating QALY estimates.
What alternative approach has the EAG suggested?	Use the HSUVs reported by Kosmas et al. (2015) in the base case, as these values fall within plausible population limits. Scenario analyses included AMPLIFY-derived utilities capped at age-matched population norms.
What is the expected effect on the cost-effectiveness estimates?	Small, because under the equal-efficacy assumption the QALY differences between treatments are minimal.
Could any additional evidence or analyses be provided to resolve this key issue?	Real-world evidence on HRQoL in people with CLL would help validate the plausibility of the utility inputs.

Issue 6: Proportion and distribution of subsequent treatments

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	The company assumes that almost all patients who progress receive subsequent therapy, applying this proportion equally across AV, VenI, and VenO. This exceeds what is observed in trial data (in all related trials), and the EAG's clinical advisers consider it unrealistic for UK practice. The company also models different distributions of subsequent therapies across comparators, despite advisers indicating that prescribing patterns are unlikely to vary meaningfully between these treatment sequences. In addition, the company's distribution overstates venetoclax monotherapy and underrepresents venetoclax-rituximab and allocates more zanubrutinib than clinical advisers believe is currently used.
What alternative approach has the EAG suggested?	The EAG adopts a more plausible estimate of the proportion receiving subsequent therapy by using the midpoint between trial-reported proportions and the company's assumptions for each arm. For the distribution of specific treatments, the EAG applies a revised allocation based on clinical-adviser feedback, assuming the same distribution across AV, VenI, and VenO.
What is the expected effect on the cost-effectiveness estimates?	Moderate
Could any additional evidence or analyses be provided to resolve this key issue?	More mature follow-up from relevant trials, UK real-world evidence on rates and patterns of subsequent therapy, and clearer justification from clinicians for expected sequencing would support a more robust estimation of both the proportion and distribution of subsequent treatments.

1.4 Secondary issues identified by the EAG

Issue 7: Extending consideration to people with untreated CLL with 17p deletion or TP53 mutation

Report section	Sections 2, 2.1.2 and 2.3
Description of issue and why the EAG has identified it as important	The company submission and clinical evidence focus solely on people without the 17p deletion or TP53 mutation. However, acalabrutinib and venetoclax have individually demonstrated efficacy in the patient subgroup with this deletion/mutation, and the AV combination has been licensed to include this subgroup on this basis. Acalabrutinib and venetoclax are both independently recommended by NICE for people with 17p deletion/TP53 mutation. The company was unable to identify evidence that deletion/mutation status was an effect modifier for fixed duration therapies. The EAG recommends that the committee should consider extending any decision to include people with the deletion or mutation.
What alternative approach has the EAG suggested?	The EAG has not been able to implement any analysis specific to this subgroup. Broadening the population for this appraisal would offer patients and clinicians additional options, simplify decision-making, and is likely of low-risk to the NHS, affecting the treatment decision of a relatively small number of people (5-10%). These patients may otherwise never be able to access this combination. It avoids the need for a repeated NICE appraisal and may represent an efficient use of decision-making resources.
What is the expected effect on the cost-effectiveness estimates?	Unknown
Could any additional evidence or analyses be provided to resolve this issue?	Evidence specific to this subgroup would be required to assess the efficacy and cost-effectiveness in this population.

1.5 Company's modelling errors identified by the EAG

The EAG identified several modelling errors and inconsistencies in the company's submission.

Incorrect implementation of discounting: The company applied no discounting for the first two years and then applied discount factors at the 28-day cycle level, contrary to NICE requirements. Discounting was not implemented consistently across the model (Resolved by the company at clarification).

Errors in time-to-treatment discontinuation (TTD): Venetoclax TTD was incorrectly modelled for AV, the model began at Cycle 0 (adding an extra cycle for all treatments), and TTD curves were not capped at SmPC-defined treatment durations. This led to patients remaining on treatment beyond allowable limits and inflated life-years and QALYs. These issues were corrected after clarification (Resolved after clarification).

Errors in the PSA implementation: The EAG identified errors in the PSA which led to implausible survival extrapolations being used for the different time-to-event outcomes. This error was corrected in a subsequent version (A corrected PSA with 10,000 iterations) of the economic model shared by the company.

Incorrect handling of survival uncertainty under the equal-efficacy assumption: All TTP, PrePS, and PPS curves referenced the same calculations in both deterministic and probabilistic analyses, preventing any uncertainty from being explored. The EAG addressed this by allowing the curves to vary independently in the PSA.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of EAG's preferred assumptions using company's base case- AV versus VenI (acalabrutinib with-PAS price)

Changes applied to company's base case**		Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)***	ICER £/QALY
The company's base case (from the version after clarification stage)		██████	██████	██████	Dominant
1	Using 71 years as starting age using in the model	██████	██████	██████	Dominant
2	Apply an RDI of 100% for all treatments	██████	██████	██████	Dominant
3	Using █████%, 85.0%, and 84.9% for AV, VenI, and VenO, respectively, as the proportion of patients completing treatment	██████	██████	██████	Dominant
4	Using HSUVs reported by Kosmas <i>et al.</i> (2015)	██████	██████	██████	Dominant
5	Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	██████	██████	██████	Dominant
Combined 1-5 (EAG's base case)		██████	██████	██████	Dominant

Key: AV: acalabrutinib plus venetoclax; VenI: ibrutinib plus venetoclax; VenO: venetoclax plus obinutuzumab; RDI: relative dose intensity; HSUV: health-state utility value; EAG: Evidence Assessment Group; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit.

*The severity modifier of 1 is applied for all exploratory analyses.

** The technical guidance related to the model changes can be found in the 'EAG-Technical report' worksheet and appendix 6.3 EAG Technical report in this report.

Table 3: Summary of EAG's preferred assumptions using company's base case- AV versus VenO (acalabrutinib with-PAS price)-pairwise

Changes applied to company's base case**		Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)***	ICER £/QALY
The company's base case (from the version after clarification stage)		██████	██████	██████	Dominant
1	Using 71 years as starting age using in the model	██████	██████	██████	Dominant
2	Apply an RDI of 100% for all treatments	██████	██████	██████	Dominant
3	Using █████%, 85.0%, and 84.9% for AV, VenI, and VenO, respectively, as the proportion of patients completing treatment	██████	██████	██████	Dominant
4	Using HSUVs reported by Kosmas <i>et al.</i> (2015)	██████	██████	██████	Dominant
5	Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	██████	██████	██████	Dominant
Combined 1-5 (EAG's base case)		██████	██████	██████	Dominant

Key: AV: acalabrutinib plus venetoclax; VenI: ibrutinib plus venetoclax; VenO: venetoclax plus obinutuzumab; RDI: relative dose intensity; HSUV: health-state utility value; EAG: Evidence Assessment Group; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit.

*The severity modifier of 1 is applied for all exploratory analyses.

** The technical guidance related to the model changes can be found in the 'EAG-Technical report' worksheet and appendix 6.3 EAG Technical report in this report.

Table 4: EAG- Deterministic base case results for AV versus Venl and VenO (acalabrutinib with-PAS price)-pairwise comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs*	ICER (£/QALY) ^a	NMB at £30,000/QALY**
AV	████	10.61	████	-	-	-	-	-
Venl	████	10.61	████	████	-0.001	████	Dominant	████
VenO	████	10.61	████	████	0.000	████	Dominant	████

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

*The severity modifier of 1 is applied for all exploratory analyses.

Table 5: EAG- Deterministic base case results for AV versus Venl and VenO (acalabrutinib with-PAS price)-Fully incremental analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs*	ICER (£/QALY) ^a	NMB at £30,000/QALY**
AV	████	10.61	████	-	-	-	-	-
VenO	████	10.61	████	████	0.000	████	Dominated	████
Venl	████	10.61	████	████	0.001	████	Dominated	████

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

*The severity modifier of 1 is applied for all exploratory analyses.

1.7 Outline of confidential comparator or subsequent treatment prices

There is a confidential appendix to this EAG report which includes analyses using confidential prices for comparator and subsequent treatments. Further detail can be found in section 5.4.

2 Background

This appraisal evaluates the clinical and cost effectiveness of acalabrutinib plus venetoclax (AV) for patients with previously untreated chronic lymphocytic leukaemia (CLL), in accordance with its marketing authorisation. The Medicines and Healthcare products Regulatory Agency (MHRA) approved AV [REDACTED] on 27 August 2025. At the time of submission, the indicated population comprises adults with untreated CLL without 17p deletion or TP53 mutations.

However, the exclusion of both continuous comparators (i.e., treatment-to-progression) and studies involving patients with TP53 mutations appears inconsistent with the European Medicines Agency's European Public Assessment Report (EPAR, Section 3.7.1),¹ which states:

“While patients with del(17p) or TP53 mutations were excluded from the AMPLIFY study due to an unsuitable comparator, the efficacy of acalabrutinib and venetoclax in the claimed indication has been characterised in other studies (ELEVATE-TN, CLL14, and SAT NCT03580928). Therefore, beneficial effects of the proposed new treatment regimens may be extrapolated to these patients as well.”

2.1 Critique of the company's description of underlying health problem

2.1.1 Condition, incidence and prognosis

Chronic lymphocytic leukaemia (CLL) is a monoclonal malignancy characterised by the progressive accumulation of mature but functionally impaired lymphocytes. It is the most prevalent adult leukaemia in Western countries, often asymptomatic at diagnosis and typically identified incidentally through routine blood tests.^{2, 3} Whilst some patients experience disease-related mortality within a few years, the majority survive at least five years (83.2%).⁴⁻⁶

Staging in the UK follows the Binet system (Stages A–C, based on lymphatic involvement and cytopenia), while the Rai classification is used in the US (low, intermediate, or high risk, based on lymphocytosis, lymphadenopathy, hepatosplenomegaly, and cytopenia).⁷⁻⁹

CLL progression is driven by genetic and cytogenetic heterogeneity. TP53 aberrations are associated with poor prognosis and define high-risk disease.^{10 11} This appraisal focuses on patients with untreated CLL without high-risk genetic abnormalities. Key adverse prognostic factors include age, clinical stage (Rai or Binet), serum β 2-microglobulin level, IGVH mutational status, and 17p deletion and/or TP53 mutation.

CLL predominantly affects older adults, with a median age at diagnosis of 70 years and a higher incidence among white race.¹² In the UK, approximately 4,000 new cases are diagnosed annually (2017–2019), with 63% in males and 37% in females. Incidence peaks in those aged 85–89, and 41% of cases occur in individuals aged ≥ 75 .⁷ CLL is typically diagnosed in individuals aged over 35 in the UK, whereas patients enrolled in the AMPLIFY trial included individuals as young as 26 years in the FCR/BR arm and 31 years in the AV arm. Mortality data show 61% of CLL-related deaths occur in males and 39% in females (2017–2019).⁷

2.1.2 TP53 mutations

TP53 mutations are present in over half of all human cancers. The TP53 gene encodes the tumour-suppressor protein p53, which plays a critical role in regulating the cell cycle, promoting apoptosis, and facilitating DNA repair in response to cellular stress, such as DNA damage.^{13, 14}

In chronic lymphocytic leukaemia (CLL), approximately 5–10% of patients are classified as having high-risk disease.¹⁵ This classification is typically based on cytogenetic abnormalities, including 17p deletions or TP53 mutations. These genetic alterations are associated with increased cellular proliferation and resistance to conventional therapies. Additionally, the presence of an unmutated immunoglobulin heavy chain variable region (IGHV) gene is linked to poorer clinical outcomes.^{13, 14}

Although TP53 aberrations are relatively uncommon at initial diagnosis, their prevalence increases significantly in advanced or treatment-refractory CLL, affecting up to 40–50% of such cases. This progression is likely driven by exposure to therapeutic stressors, such as cytotoxic agents. Consequently, reassessing TP53 status before initiating each new line of treatment is essential, as resistant clones may emerge or expand during relapse or disease progression.^{13, 14}

2.2 Critique of the company's overview of current service provision

2.2.1 Management of disease

Treatment of CLL is complex and influenced by multiple factors, including disease stage, prior therapies, patient age, symptom burden, and overall health. Patients with early-stage, asymptomatic disease without evidence of active progression are typically managed through surveillance, known as the watch-and-wait approach, and may be monitored until treatment becomes clinically necessary.

According to previous clinical guidelines,^{16, 17} fludarabine, cyclophosphamide, and rituximab (FCR) was recommended as first-line therapy for fit patients.¹⁸ However, recent updates, aligned with statements from EAG clinical experts, indicate that targeted combination regimens, such as venetoclax plus ibrutinib (VenI) and venetoclax plus obinutuzumab (VenO), have largely replaced chemoimmunotherapy approaches (e.g., FCR). The British Society for Haematology (BSH) guidelines highlight that treatment selection is influenced by availability, toxicity profiles, regimen duration (fixed vs continuous), and patient preferences.

2.2.2 Choosing patients by their fitness

The company challenged the fitness definitions that classify patients as either fit or unfit for chemoimmunotherapy (e.g., FCR/BR). The EAG clinical experts noted that fitness is no longer a primary determinant in treatment selection, especially with the availability of well-tolerated targeted therapies suitable even for frail individuals. Instead, fitness should be viewed broadly, incorporating patient preferences (e.g., fixed vs. continuous treatment), socioeconomic factors, ECOG performance status, and more.

The recent ESMO guideline¹⁹ supports this approach, recommending treatment decisions based on the intention to use fixed-duration venetoclax-based or continuous BTKi therapy.

The EAG concluded that fitness should not be used as a limiting criterion for this population.

2.2.3 Treatment pathway

In section 1.2.3 of the company submission, it is stated that targeted therapies for untreated, non-high-risk chronic lymphocytic leukaemia (CLL) in the UK are currently classified by dosing strategy as either treat-to-progression (TTP) or fixed-duration (FD). According to the 2025 BSH guideline (Figure 1),¹⁹ both approaches are appropriate for treatment-naïve patients without TP53 disruption, with no single regimen universally preferred.

Several therapies are NICE-approved, including venetoclax-obinutuzumab (VenO), venetoclax-ibrutinib (VenI), acalabrutinib, and zanubrutinib.

VenO is particularly effective in patients with mutated IgHV, while VenI is effective across IgHV subgroups, though caution is advised in older patients with cardiovascular comorbidities due to increased toxicity. Venetoclax-acalabrutinib, with or without obinutuzumab (AV±O), is licensed by EMA and MHRA but not NICE-approved; long-term efficacy and MRD kinetics remain uncertain.

Among continuous therapy options, acalabrutinib and zanubrutinib show comparable efficacy. Acalabrutinib-obinutuzumab (AO), although licensed (not NICE-approved), may offer higher efficacy but is associated with increased toxicity. MRD-guided VenI appears clinically relevant with an acceptable safety profile but remains unlicensed.

Treatment selection should be guided by IgHV status, comorbidities, concurrent medications, and individual patient preferences. A shared decision-making approach is strongly encouraged, and clinical trial participation should be considered where available. The potential benefit of a treatment-free interval may also influence therapeutic choice.

First line treatment algorithm for CLL

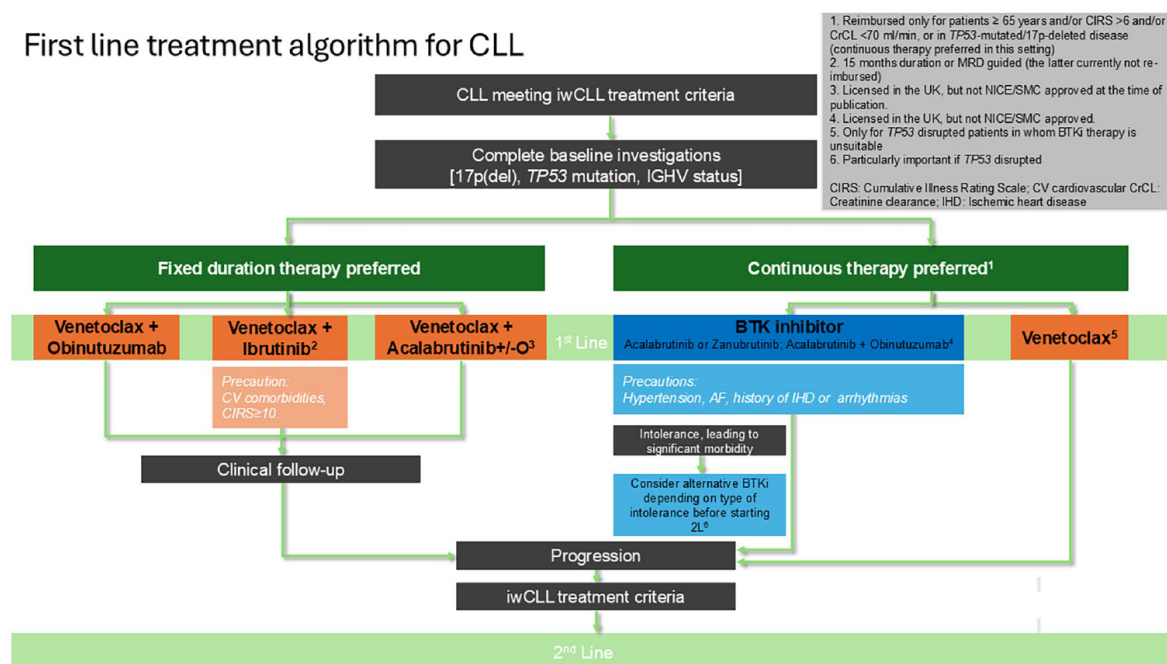


Figure 1. 2025 British Society for Haematology (BSH) Guideline for first-Line treatment algorithm for CLL.

Note: AstraZeneca are not submitting for reimbursement in the high-risk population (i.e., patients with mutated *TP53* or del[13p]), therefore the treatment pathway for patients with high-risk CLL has not been described in the diagram above.

Abbreviations: AF: atrial fibrillation; BTK(i): Bruton tyrosine kinase (inhibitor); CIRS: Cumulative Illness Rating Score; CLL: chronic lymphocytic leukaemia; CrCL: creatine clearance; CV: cardiovascular; IHD: ischaemic heart disease; iwCLL: International Workshop on chronic lymphocytic leukaemia; 2L: second-line.

2.3 Critique of the company's definition of decision problem

The EAG's comments on the company's decision problem are presented in Table 6.

The company's decision problem is narrower than NICE's across all categories.

Given the limited population and comparators, and in line with both NICE and the EAG's clinical experts, the exclusion of *tp53*-mutated patients (high-risk) and acalabrutinib and zanubrutinib monotherapies as potential comparators is a concern.

Table 6: 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 CLL.	Adult patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation.	The target population in this submission is adult patients with untreated CLL without a del(17p) or TP53 mutation. This aligns with the population included in the pivotal clinical trial for AV in this indication (the AMPLIFY trial) and is referred to in this submission as untreated non-high risk CLL	Narrower than NICE's decision problem, the company followed the AMPLIFY trial population. As noted in the CS, Appendix A1, the marketing authorisation includes untreated patients without excluding high-risk groups. Similarly, EPAR imposes no restrictions and supports extrapolating benefits to high-risk patients. The EAG agrees with NICE's recommendation.
Intervention	Acalabrutinib and venetoclax with/without obinutuzumab	AV	The AMPLIFY trial provides efficacy and safety data for AV and AVO in patients with untreated non-high risk CLL. However, AstraZeneca is seeking reimbursement in this new indication for AV only. This is based on the feasibility of demonstrating cost-effectiveness. Additionally, UK clinical experts indicated that treatment with AV would be preferred over AVO in the majority of patients as the efficacy	Narrower than NICE's decision problem. The company excluded the AVO combination, citing that its benefits do not outweigh associated adverse events. EAG clinical experts noted AV may be preferred due to its oral administration and potentially fewer adverse events, although AVO appears clinically relevant.

			benefit associated with the addition of obinutuzumab does not outweigh the associated AE burden .	The EAG agrees with the company.
Comparator(s)	1. For adults with untreated CLL where mutation is not specified: • Venetoclax with ibrutinib (VenI) (TA891) • Obinutuzumab with chlorambucil (OC1b; for adults who have comorbidities that make full-dose fludarabine-based therapy unsuitable, and only if bendamustine-based therapy is not suitable) (TA343) • Bendamustine (for whom fludarabine combination chemotherapy is not appropriate) (TA216) • Fludarabine with cyclophosphamide and rituximab (FCR) (TA174) • Bendamustine with rituximab (BR) • Acalabrutinib with obinutuzumab (AO)	For adult patients with untreated CLL without a 17p deletion or TP53 mutation: • VenI • VenO	As outlined above, the target population for AV in this submission is patients with untreated CLL without a del(17p) or TP53 mutation. As such, only treatments included under subheading 2 in the NICE final scope represent possible relevant comparators to AV. In addition, based on treatment guidelines and feedback from UK clinical experts, VenI is used in patients without a del(17p) or TP53 mutation and is therefore also a relevant comparator to AV in this submission. Discussion of treatments included within the NICE final scope that are not considered comparators is provided below: Treat-to-progression therapies The NICE final scope does not reflect the importance of different dosing	Narrower than NICE's decision problem. Based on the 2025 BSH guideline and in line with EAG clinical expert opinion, all NICE-approved treatments for untreated patients without TP53 mutations, namely VenO, VenI, acalabrutinib, and zanubrutinib, should be considered without restriction. While no formal preference exists between these regimens, treatment choice is typically guided by clinical judgment and patient preferences. Factors such as IgHV status, comorbidities, concurrent medications, and the potential for a treatment-free interval may influence selection. A shared decision-making approach is encouraged to tailor therapy to individual needs (<i>see Treatment pathway</i>). Whilst AVO, AO, and MRD-guided VenI are licensed by EMA and MHRA and may offer potentially higher efficacy, they are not

	2. For adults with untreated CLL without a 17p deletion or TP53 mutation only: • Zanubrutinib (for whom FCR or BR is unsuitable) (TA931) • Acalabrutinib (if FCR or BR is unsuitable) (TA689) • Venetoclax with obinutuzumab (VenO; if FCR or BR is unsuitable) (TA663) • VenO (if FCR or BR is suitable) (ID6291); subject to NICE evaluation 3. For adults with untreated CLL with a 17p deletion or TP53 mutation only: • Zanubrutinib (TA931) • Acalabrutinib (TA689) • VenO (TA663) • Idelalisib with rituximab (TA359) • Venetoclax (if a B-cell receptor pathway inhibitor is unsuitable) (TA796)		regimens, namely fixed-duration or treat-to-progression. In non-high risk CLL, fixed-duration therapies are generally used in younger, fitter patients, whereas treat-to-progression therapies are favoured in older, less-fit patients. This was confirmed by UK clinical experts interviewed by AstraZeneca, highlighted in the NICE evaluation of zanubrutinib in CLL (TA931), and is expected to be reflected in the upcoming update to the British Society for Haematology (BSH) CLL treatment guidelines. Feedback from UK clinical experts interviewed between April and July 2025 indicated that the introduction of AV, which is a fixed-duration therapy, is not expected to affect treatment choice in patients for whom treat-to-progression therapies (i.e., acalabrutinib monotherapy [TA689] and zanubrutinib monotherapy [TA931]) are deemed more suitable. As outlined and accepted by	approved by NICE. The EAG's clinical experts also acknowledged occasional use of O-CIb, bendamustine monotherapy, and FCR or BR in specific cases. The EAG's clinical expert noted that treatment options for patients with TP53 mutations would generally be similar, with venetoclax monotherapy also considered. However, there may be greater emphasis on continuous or MRD-guided therapies in this subgroup rather than FD treatments. The EAG partly agrees with NICE's list of comparators, acknowledging that while most are appropriate, some are infrequently used in clinical practice.

	Ibrutinib (if chemoimmunotherapy is unsuitable) (TA429)		the Committee in TA931, the decision of whether to use a treat-to-progression or fixed-duration therapy will be unchanged by the introduction of a new therapy, such as AV. As such, the treat-to-progression therapies included in the NICE final scope under subheading 2 (i.e., acalabrutinib monotherapy and zanubrutinib monotherapy) are not relevant comparators to AV in this indication. Treatments not used in clinical practice In addition to the treat-to-progression therapies listed above, the following therapies should not be included as comparators within any subgroups, for the reasons detailed below: OC1b is rarely used in UK clinical practice since the introduction of targeted therapies (i.e., acalabrutinib monotherapy,	

			zanubrutinib monotherapy, Venl and VenO). This was confirmed by UK clinical experts. • For the same reason, bendamustine monotherapy is not used in UK clinical practice for untreated CLL. Bendamustine monotherapy was also not considered a relevant comparator in the recent NICE evaluations of CLL therapies in FCR/BR unsuitable patients (e.g., VenO, Venl and zanubrutinib monotherapy). • Whilst FCR/BR represent treatment options for patients without a del(17p) or TP53 mutation, feedback from UK clinical experts indicated that FCR/BR are rarely used in UK clinical practice. In addition, this	

			feedback highlighted that FCR/BR are expected to be excluded from the upcoming update to the BSH CLL treatment guidelines. Finally, AO has not been evaluated or recommended by NICE in this indication and so is not available or used in National Health Service (NHS) clinical practice. In summary, the relevant comparators to AV in this submission are VenO and VenI.	
Outcomes	The outcome measures to be considered include: Overall survival (OS) Progression-free survival (PFS) Minimal residual disease (MRD) levels Event-free survival (EFS) Overall response rate (ORR) and complete response (CR) rate	The outcome measures included in this submission are: OS PFS MRD levels EFS ORR and CR rate Time to treatment failure	Infection-free survival is not a standard outcome measure in CLL and was not collected in the AMPLIFY trial. In addition, data on infection-free survival are unlikely to be publicly available for the relevant comparators. As such, infection-free survival outcomes specifically have not been included in this submission. Data on	Outcomes covered by the company submission are mostly consistent with NICE. Time to treatment failure and infection-free survival has not been collected per AMPLIFY protocol. The EAG agrees with the company.

	Time to treatment failure Duration of response (DOR) Time to next treatment (TTNT) AEs of treatment Infection free survival Health-related quality of life (HRQoL)	DOR TTNT AEs of treatment HRQoL	infections as AEs have been collected as part of the safety outcomes. Time to treatment failure was also not collected as part of the AMPLIFY trial, and as such, is not presented in this submission.	
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. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per the NICE final scope.	N/A	The company's model in general (regarding model structure, time horizon, sources of costs, sources of HRQoL, and providing incremental cost per quality-adjusted life year) was developed in line with the NICE final scope.

	The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	If evidence allows the following subgroups will be considered: People with and without a 17p deletion or TP53 mutation According to immunoglobulin heavy chain variable region gene (<i>IgHV</i>) mutation status (mutated or unmutated) People with complex or high-complex karyotype (those with more than 3 or more than 5 chromosomal aberrations respectively)	No economic subgroup analyses have been conducted for this submission. Clinical effectiveness data by <i>IgHV</i> mutational status (mutated or unmutated) and complex karyotype status are presented where available.	As the target population for AV is adults with untreated CLL without a del(17p) or <i>TP53</i> mutation, the presence or absence of a del(17p) or <i>TP53</i> mutation is not a relevant subgroup to this submission. Clinical effectiveness subgroup analyses by <i>IgHV</i> mutation and complex karyotype, status from AMPLIFY are presented in Section 2.8 for PFS and Appendix C for OS. Economic subgroup analyses in these subgroups have not been conducted due to the lack of comparator data by <i>IgHV</i> mutation or complex karyotype status.	Narrower than NICE's decision problem. As patients with del(17p) or <i>TP53</i> mutations were excluded from the AMPLIFY trial, no subgroup analysis has been provided for this population.

Abbreviations: AE: adverse event; AO: acalabrutinib with obinutuzumab; AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; CR: complete response; CS: company submission; DOR: duration of response; EFS: event-free survival; FCR: fludarabine with cyclophosphamide and rituximab; HRQoL: health-related quality of life; *IgHV*: immunoglobulin heavy chain variable region gene; MRD: minimal residual disease; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OClb: obinutuzumab with chlorambucil; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment; UK: United Kingdom; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3 Clinical effectiveness

Section 3.1 reviews the company's literature review of clinical and safety evidence. Sections 3.2 and 3.3 critique the methodology and clinical effectiveness of the pivotal AMPLIFY trial. Sections 3.4 and 3.5 examine any indirect comparisons presented by the company, and section 3.6 outlines additional analyses conducted by the EAG.

3.1 Critique of the methods of review

3.1.1 Systematic literature review methodology

A summary of the EAG's quality assessment of the company's SLR using the modified risk of bias assessment tool for systematic reviews (ROBIS)²⁰ is presented in Table 7. The full EAG assessment using the modified ROBIS is in the Table 61. Overall, the EAG found the company's SLR to have some risk of bias concerns.

Table 7: Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS, appendix B, section B.3	Some concern
Searches and selection of studies	CS, appendix B, section B.1 and B.2	Low concerns
Data extraction and risk of bias assessment	CS, appendix B, section B.3 and CS, section 2.5	Some concerns
Evidence synthesis	CS, appendix B, sections B.5.3, B.5.6, and CS, section 2.10	Some concerns

Abbreviations: CS, company submission; EAG, external assessment group; SLR, systematic literature review.

Eligibility criteria

Post hoc adjustments to the eligibility criteria appear to have included stratification of the population by TP53 mutation status into low- and high-risk groups, as well as differentiation between fixed-duration and continuous treatment regimens. Evidence related to the high-risk and continuous treatment subgroups was subsequently excluded. As a result, comparators

such as zanubrutinib and acalabrutinib monotherapies, which had been previously identified, were not reported.

Searches and selection

Broad searches in an appropriate range of sources were undertaken in October 2024 and updated in June 2025, then supplemented by reference checking of identified reviews. No date or language limits were applied.

Data extraction and risk of bias assessment

Title and abstract screening, as well as full-text review, were conducted independently by two reviewers. However, the processes for data extraction and risk of bias assessment were not clearly described. The risk of bias assessments lacks sufficient detail.

Synthesis and findings

The exclusion of continuous treatment regimens and TP53 mutation-related studies, lacks clear justification and appears inconsistent with regulatory guidance.¹ Additionally, statistical methods to assess heterogeneity were not applied. While risk of bias was assessed, its findings were not integrated into the SLR, nor was a sensitivity analysis conducted to explore its impact

3.2 Critique of the methods of the trials of the technology of interest

The main source of clinical evidence presented in the CS comes from the AMPLIFY trial (NCT03836261). AMPLIFY is an ongoing, phase III, multicentre, randomised, open-label study that provides efficacy and safety data for acalabrutinib–venetoclax (AV) in patients 18 years of age or older with untreated CLL who had an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (range, 0 to 5, with higher numbers indicating greater disability) and who did not have a 17p deletion or TP53 mutation.²¹

Patients were randomly assigned, in a 1:1:1 ratio, to receive AV, acalabrutinib–venetoclax–obinutuzumab (AVO), or chemoimmunotherapy (investigator’s choice of fludarabine–cyclophosphamide–rituximab (FCR) or bendamustine–rituximab (BR)). All the treatments received in the AMPLIFY trial were administered in 28-day cycles. Patients in the AV group received oral acalabrutinib at a dose of 100 mg twice daily during cycles 1 to 14 and oral venetoclax once daily during cycles 3 to 14 (including a 5-week ramp-up of venetoclax from 20 mg once daily to the target dose of 400 mg once daily). Patients in the AVO arm received the same doses of acalabrutinib and venetoclax as described for the AV arm plus 1,000 mg IV obinutuzumab on Days 1, 2, 8 and 15 of Cycle 2, then on Day 1 of Cycles 3 to 7. The patients in the chemoimmunotherapy arm received intravenous FCR or BR during cycles 1 to 6 according to standard dosing protocols (see CS, page 31).

While AMPLIFY trial provides efficacy and safety data for AV and AVO in patients with untreated non-high risk CLL, the company is seeking reimbursement in this submission for AV only. The company highlighted that UK clinical experts indicated that treatment with AV would be preferred over AVO in the majority of patients as the efficacy benefit associated with the addition of obinutuzumab does not outweigh the associated adverse events burden and this is underlined in recent UK guidelines.¹⁹

A total of 291 patients were randomised to receive AV treatment; 290 were assigned to the chemoimmunotherapy arm and were included in the ITT population for the safety and efficacy analysis.

Patients were recruited to the AMPLIFY trial from 133 hospital centres across 27 countries (including the UK). In response to clarification question A1, the company confirmed that only [REDACTED] UK patients were included in the full analysis set [(REDACTED)] in the AV arm and [(REDACTED)] in the chemoimmunotherapy arm].

Demographic and baseline clinical characteristics were balanced across trial arms. Most patients included in the trial were male (61.2% in the AV arm and 63.1% in the chemoimmunotherapy arm) and white (91.1% in the AV arm and 86.9% in the chemoimmunotherapy arm) with a median age of 61 years. Only 3.3% of randomised patients were older than 75 years. The EAG notes that the mean age for treatment of CLL in the UK is significantly higher (70's) as confirmed by our clinical experts. This is in line with data from real world evidence studies in other European settings which suggest that the median age at diagnosis is around 70 years, with the highest number of cases identified in the 65-74 years age group.^{22 23} Experts also highlighted that the lower toxicity profile of AV could result in AV being the choice for older fitter patients wanting a fixed term all oral therapy.

At baseline, most patients in the AV (90.0%) and chemoimmunotherapy arms (90.3%) had an ECOG PS ≤ 1 . Most patients did not have del(11q) mutations (81.8% in the AV arm and 83.4% in the chemoimmunotherapy arm). 57.4% of patients in the AV arm and 59.3% in the chemoimmunotherapy arm had unmutated IgHV status at baseline (Mutation is associated with lower risk disease). Detailed baseline demographic and patient disease characteristics are provided in CS, table 6 and 7.

The following efficacy endpoints were evaluated in the AMPLIFY trial:

- Progression-free survival (PFS, primary endpoint), as assessed by blinded Independent Review Committee (IRC)
- Overall survival (OS)
- Minimal residual disease (MRD) negativity rate
- Investigator-assessed PFS
- Event-free survival (EFS)

- Overall response rate (ORR)
- Duration of response (DOR)
- Time to next treatment (TTNT)
- Health-related quality of life (HRQoL)
- Other exploratory endpoints including plasma concentrations of acalabrutinib and venetoclax and hospitalisations/resource use

3.2.1 Risk of bias AMPLIFY

Critical appraisal of the AMPLIFY trial was undertaken using the revised Cochrane risk-of-bias tool for randomised trials (RoB2).²⁴ Risk of bias assessment of the trial is summarised in the CS Table 10.

The EAG agrees with the company's judgements. Overall, AMPLIFY was a well-designed trial with the appropriate steps taken to minimise bias where possible. The trial was deemed to be at low risk of bias across all domains. The comparison of the company's assessment and the EAG's assessment of risk of bias in the trial using the revised Cochrane RoB2 tool can be seen in Table 8.

Table 8. Comparison of company and EAG risk of bias assessment of AMPLIFY trial

Checklist questions	Company assessment	EAG assessment
1. Randomisation		
1.1 Was the allocation sequence random?		Y- A central interactive voice-response or Web-based response system was used for randomisation.
1.2 Was the allocation sequence concealed until participants were		Y

enrolled and assigned to interventions?		
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N- The demographic and baseline characteristics of the patients were well balanced between the groups
Risk of bias judgement	Low	Low
2. Deviations from intended interventions		
2.1 Were participants aware of their assigned intervention during the trial?		Y-open label trial
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y-open label trial
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y- intention-to-treat analysis
Risk of bias judgement	Low	Low
3. Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y- Efficacy analyses were performed in the intention-to-treat population (all the patients who underwent randomisation) and were analysed according to trial group
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		

Risk of bias judgement	Low	Low
4. Measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N- Treatment responses were assessed by blinded independent central review and by investigators who were aware of the group assignments according to the 2018 criteria from the International Workshop on CLL
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		
Risk of bias judgement	Low	Low
5. Selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y- AMPLIFY Clinical Trials.gov number, NCT03836261
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		PN
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?		PN
Risk of bias judgement	Low	Low
Overall bias	Low	Low

Abbreviations: CLL, chronic lymphocytic leukaemia; N, No; NI, no information; PN, probably no; PY, probably yes; Y, yes.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Efficacy results AMPLIFY

Results presented in this submission are from the interim analysis (DCO: 30th April 2024). At a median follow-up of 40.8 months from randomisation, treatment with AV showed superiority over chemoimmunotherapy with respect to IRC-assessed PFS (HR: 0.65; 95% CI: 0.49, 0.87; P= 0.004). The improvement in PFS associated with AV was sustained over time, as higher percentage patients in the AV arm were alive and progression-free at 24 [██████████] vs ██████████ and 36 months [76.5 [██████████] vs 66.5 (██████████)] compared with patients in the chemoimmunotherapy arm.

Treatment with AV resulted in a significant improvement in OS compared with chemoimmunotherapy [HR 0.33 (95% CI: 0.18, 0.56; P <0.001]. The estimated OS at 36 months was 94.1% (95% CI, █████, █████) with AV, and 85.9% (95% CI, █████, █████) with chemoimmunotherapy.

A key secondary endpoint in the AMPLIFY trial was MRD negativity rate. Despite improvement in PFS and OS, the percentage of patients with undetectable MRD in peripheral blood was significantly lower in the AV arm (26.8%), compared with the chemoimmunotherapy arm (51.0%). The risk ratio (RR) for undetectable MRD favoured chemoimmunotherapy (RR: 0.5; 95% CI: 0.4, 0.7; P <0.0001).

The estimated IRC assessed event-free survival at 36 months was 75.9% with AV and 64.5% with chemoimmunotherapy. The percentage of patients with IRC assessed overall response was higher with AV (92.8%) compared with chemoimmunotherapy (75.2%). The median duration of response was 50.4 months with AV and 47.6 months with chemoimmunotherapy. The percentage of responders who subsequently progressed or died was slightly lower in the AV arm (28.1%) compared with chemoimmunotherapy (33.9%).

Improvements in HRQoL during and after treatment were generally greater in the AV arm compared with the chemoimmunotherapy arm. The company attributed this improvement to fewer AEs and lower long-term toxicity with AV. An overview of the patient reported outcome measures reported in the AMPLIFY trial, can be found the CS, page 59, with full results presented in Appendix J.7.

3.3.2 Safety outcomes

The AMPLIFY trial demonstrated that AV is a well-tolerated treatment option for patients with CLL with the safety profile aligned with that of previous studies for acalabrutinib.²¹

The percentage of patients who experienced any treatment emergent adverse events (TEAEs) were comparable between the AV and chemoimmunotherapy arms (92.8% versus 91.1%, respectively). The most common AEs that emerged during AV treatment were headache (35.1%), diarrhoea (32.6%) and neutropenia (30.9%). In the chemoimmunotherapy arm, neutropenia (38.2%), nausea (35.9%) and infusion-related reactions (32.8%) were the most commonly reported AEs.

TEAEs $\geq$ Grade 3 (severe to death) were comparable between the AV arm (53.6%) and the chemoimmunotherapy arms (60.6%). The incidence rates of severe adverse events (SAEs) were also similar between the AV arm (24.7 %) and the chemoimmunotherapy arms (27.4 %). AMPLIFY reported that 3.4% of patients in the AV arm and 3.5% in the chemoimmunotherapy arm had TEAEs that resulted in death.

Among adverse events of clinical interest prespecified within the AMPLIFY trial, cardiac events of any grade were more common with AV treatment than with chemoimmunotherapy (9.3% vs 3.5%). Secondary primary cancers excluding non-melanoma skin cancer were also more common with AV treatment than with chemoimmunotherapy (2.7% vs 0.4%). A summary of the incidence of these AEs is presented in CS, Table 29.

3.3.3 Subsequent treatments

At the DCO date of the interim analysis (30th April 2024), [REDACTED] of patients in AV arm ([REDACTED]/291), and [REDACTED] of patients in the chemoimmunotherapy ([REDACTED]/290), had experienced disease progression. Following progression, [REDACTED]% of patients in the AV arm ([REDACTED]/291) and [REDACTED]% of patients in the chemoimmunotherapy arm ([REDACTED]/290) received subsequent anti-cancer therapy.

The company noted that the subsequent treatment distribution in the AMPLIFY trial was not fully reflective of UK clinical practice as some patients received subsequent anti-cancer treatments which are not reimbursed in the UK for the treatment of CLL (rituximab, obinutuzumab, nemtabrutinib and azacitidine). Details of subsequent treatments received by patients in the AMPLIFY trial are presented in CS, Table 14.

3.3.4 Subgroup analyses

AMPLIFY included prespecified subgroup analyses of the primary outcome (IRC-assessed PFS) and key secondary endpoints (OS) to assess the consistency of the results across clinically relevant patient subgroups. These included age, *IgHV* mutational status, Rai stage, geographic region, sex, race, ethnicity, ECOG PS, complex karyotype, CD38 expression, ZAP-70 expression and Del(11q).

Across most of the pre-specified subgroups, an improvement in PFS in favour of treatment with AV compared with treatment with FCR/BR was observed (CS, Figure 8). An improvement in OS in favour of treatment with AV was also consistently observed across the vast majority of the pre-specified subgroups (see Appendix C, Figure 17). The EAG, however, notes that the sample size of most of the subgroups was small and these analyses were not statistically

powered to detect differences between subgroups. As such, results should be interpreted with caution.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The EAG has reproduced and updated Tables 15 and 16 from the CS, section 2.10, in the *Summary of comparator studies*. An overview is reported in Table 9, Table 10 and Table 12. Additionally, the most recent follow-up data have been used to report OS and PFS for relevant comparators.

3.4.1 Study and baseline characteristics

The majority of included studies were phase III RCTs, with 11 of 12 being open-label and multinational. All trials commenced enrolment post-2014, with follow-up durations ranging from 36 to 72 months. CLL14 reported the longest follow-up (76.4 months). Five of the eleven studies listed in Table 62 overlapped with the COVID-19 pandemic (2020–2023). Among those selected by the company for indirect treatment comparison (AMPLIFY, CAPTIVATE FD, GLOW, CLL13, and CLL14), only AMPLIFY and CAPTIVATE FD had enrolment periods overlapping with the pandemic. However, ongoing follow-up in other studies may also coincide.

Eligibility criteria varied considerably across trials. AMPLIFY and CLL13 excluded patients with del(17p) or TP53 mutations, while CAPTIVATE FD, CLL14, and ELEVATE-TN imposed no such restrictions. GLOW excluded high-risk patients but still included 6.6% with TP53 mutations. Comorbidity burden also differed: AMPLIFY, CLL13, and CRISTALLO included patients with CIRS <6, whereas GLOW and CLL14 had higher proportions with CIRS ≥6. Renal function appeared better in AMPLIFY and CLL13 compared to GLOW and CLL14.

Performance status and age distributions further highlight heterogeneity. ECOG scores were not reported for CLL13; CLL14 and GLOW included more patients with ECOG 2, while all CAPTIVATE FD patients had ECOG 0–1. AMPLIFY, CAPTIVATE FD, and CLL13 included younger populations, while CLL14 and GLOW had higher proportions of patients aged ≥65. Notably, only █% of AMPLIFY AV patients were over 75, compared to 33% in both CLL14 and GLOW.

3.4.2 Safety outcomes

The safety profiles across treatment arms reveal substantial heterogeneity, both in reported rates and in the scope of adverse events (AEs) captured. Venetoclax + ibrutinib (VenI) combinations consistently show elevated toxicity, particularly for atrial fibrillation, hypertension, diarrhoea, and cardiac events. This pattern suggests a class effect, though the magnitude varies across studies, likely influenced by differences in population characteristics and follow-up duration.

Venetoclax + obinutuzumab (VenO) regimens generally show lower cardiovascular and bleeding risks, but higher rates of anaemia and tumour lysis syndrome (TLS) with infection rates vary widely (8.9-79%).

AMPLIFY's AV arm shows low rates of atrial fibrillation, cardiac events, TLS, and hypertension, which appear consistent with the acalabrutinib monotherapy safety profile reported in ELEVATE-TN and ASCEND.²⁵⁻²⁸

However, interpretation is limited as the acalabrutinib–venetoclax combination has only been evaluated in a single trial. Broader assessment across diverse cohorts would help confirm its tolerability and generalisability.

Several studies did not report key safety outcomes, such as haemorrhage, which limits the ability to compare across trials. Inconsistent definitions and reporting of adverse events, along with differences in follow-up duration, further complicate interpretation and introduce uncertainty into indirect treatment comparison.

Table 9: Overview of safety outcomes of trials used in company's indirect comparison

Study	AE of Special Interest*									
	Atrial fibrillation (%)	Cardiac event (%)	Anaemia (%)	Infections (%)	Haemorrhage (%)	Major haemorrhage (%)	Hypertension (%)	SPM (%)	Diarrhoea	TLS (%)
AMPLIFY (AV) (CS, Table 29)	0.7	9.3	6.9	50.9	32.3	1.0	4.1	2.7	32.6	0.3
CLL13 (VenO) ²⁹⁻³²	0.9	1.3**	8.3	10.5***	NR	NR	10.1	5.7	32.9	11.4
CLL14 (VenO) ³³⁻³⁵	0.5	2.4	16.5	8.9	NR	NR	6.6%	14.2	27.8	0.5
GLOW (VenI) ³⁶⁻³⁸	14.2	2.8	17.9	12.3	NR	NR	13.2	7.5	50.9	0
CAPTIVATE FD ³⁹⁻⁴³	4.4\$	18.24\$	6.92\$	67	NR	2	16	6.3	62	0

Abbreviations: AE, adverse events; AV, acalabrutinib plus venetoclax; CS, company submission; NR, not reported; SPM, secondary primary malignancy; TLS, tumour lysis syndrome; VenI, ibrutinib plus venetoclax; VenO, venetoclax plus obinutuzumab.

3.4.3 Survival outcomes

Naïve comparison of overall survival (OS) and progression-free survival (PFS) outcomes across studies shows generally favourable outcomes, with most treatment arms not reaching median OS or PFS, suggesting durable disease control. However, interpretation is complicated by differences in follow-up durations, assessment methods (investigator vs. independent review), and incomplete reporting. VenO regimens (CLL13, CLL14,) consistently show high OS and PFS rates, though missing confidence intervals in some cases limit comparability. VenI regimens (CAPTIVATE FD and GLOW) also demonstrate efficacy, but variability across timepoints and studies introduces uncertainty.

At 48 months, VenO (CLL13) reported 95.1% OS and 81.8% investigator-assessed PFS, and VenI (CAPTIVATE FD) showed 98% OS and 79% investigator-assessed PFS. In comparison, AV (AMPLIFY) reported █% OS and █% investigator-assessed PFS, though differences in population may contribute. Median OS was not reached in most studies, except for AV (57.8 months).

Table 10: Overview of survival outcomes of trials used in company's indirect comparison

Study	Overall survival	Progression-free survival
AMPLIFY (AV) (CS, Table 11-12; CSR TLF, Table 14.2.1.1, 14.2.1.6, and 14.2.6.1)	Median OS: 57.8 54 months (investigator): █ (95% CI, █ 48 months (investigator): █ (95% CI, █	Median PFS*: Not reached 54 months (investigator): █ (95% CI, █; IRC: █ (95% CI, █ 48 months (investigator): █ █ (95% CI, █ █; IRC: █ (95% CI, █ █
CLL13 (VenO) ²⁹⁻³²	Median OS*: Not reached 60 months (investigator): 93.6% (97.5% CI, NR)	Median PFS*: Not reached 60 months (investigator): 69.8% (97.5% CI, NR)

Study	Overall survival	Progression-free survival
	48 months (investigator): 95.1% (97.5% CI, 91.9-98.3)	48 months PFS rates (investigator): 81.8% (97.5% CI, 75.8-87.8)
CLL14 (VenO) ³³⁻³⁵	Median OS*: NR 72 months (investigator): 78.7% (95% CI, NR)	Median PFS: 76.2 months 72 months (investigator): 53.1% (95% CI, 45.9-60.3)
GLOW (VenI) ³⁶⁻³⁸	Median OS*: Not reached 60 months (investigator): 81.6% (95% CI, NR) 42 months (investigator): 87.5% (95% CI, 79.4-92.5)	Median PFS*: Not reached 60 months (investigator): 59.9% (95% CI, NR) 42 months (IRC): 74.6% (95% CI, 65.0-82.0)
CAPTIVATE FD ³⁹⁻⁴³	Median OS*: Not reached 66 months (investigator): 96.1% (95% CI, 91.4-98.2) 48 months (investigator): 98% (95% CI, 94-99)	Median PFS*: Not reached 66 months (investigator): 60.2% (95% CI, 51.7 to 67.7) 48 months (investigator): 79% (95% CI, 71-84)

3.5 EAG critique of the indirect comparison or multiple treatment comparison

The company selected a simulated treatment comparison (STC) as the most suitable method to compare AV with VenI and VenO. The unanchored STCs were based on data from AMPLIFY (AV), GLOW and CAPTIVATE FD (VenI), and CLL14 (VenO). The company also undertook a Bucher ITC to compare AV to VenO using data from AMPLIFY and CLL13 (FCR/BR common

comparator). The primary analyses used unanchored STCs to estimate restricted mean survival time (RMST), rather than hazard ratios, as the company reported that the assumption of proportional hazards (PH) was violated. The EAG notes that the assessment of hazard proportionality is often subjective and considers that presentation of hazard ratios would be beneficial to decision-making given that for the majority of relevant comparisons, strong evidence was not identified (Table 15, Company Appendices), and that the PH assessment does not appear to factor in unanchored comparisons.

3.5.1 Feasibility of indirect treatment comparisons (ITCs)

A feasibility assessment is provided in Document B, Section 2.10.2 and in response to clarification questions A8 and A9 to support not using NMA, MAIC, or ML-NMR by the company for an ITC. The company concludes that heterogeneity in study designs, follow-up durations, and the distribution of treatment effect modifiers (TEMs) violates the key assumptions of transitivity and homogeneity required for a robust network meta-analysis (NMA).

The EAG considers that heterogeneity between studies does not inherently preclude the conduct of an NMA and maintains that the output may be helpful for decision-making. To explore their concerns, the company could have explored excluding studies that most strongly violate NMA assumptions (see Clarification Question A8). The company declined to undertake such analyses.

Regarding the feasibility of conducting a matching-adjusted indirect comparison (MAIC), the company reported that the poor overlap of covariates across relevant studies would result in a small effective sample size (ESS), rendering the MAIC infeasible. The EAG has outlined relevant covariates in Table 11. While not all TEMs are consistently reported across published trials, a MAIC may still have been feasible, given that the company did not provide any estimate of ESSs. Instead, the company opted to use a STC. The EAG notes that a STC is subject to a similar assumption relating to the extent of

overlapping data in that whilst extrapolation beyond the range of patient-level data is possible, it is necessary for the relationships to be consistent with those within the observed data. When populations overlap, this extrapolation is of much lower concern, but in this instance, it remains a potential source of bias.

Table 11: Overview of potential indirect treatment comparison approaches

	Feasible	Undertaken	Key Strengths	Key Limitations or Assumptions
Bucher ITC	Yes	Yes	Preserves randomisation	Pairwise comparison. Assumes effect modifiers are balanced across studies.
NMA	Yes	No	Preserves randomisation	Assumes effect modifiers are balanced across studies.
Unanchored MAIC	Yes	No	Can adjust for differences in trials populations	Pairwise comparison. Requires all effect modifiers and prognostic factors to be adjusted for.
Unanchored STC	Yes	Yes	Can adjust for differences in trials populations	Pairwise comparison. Requires all effect modifiers and prognostic factors to be adjusted for. Requires an assumed parametric form.
ML-NMR	Yes	No	Preserves randomisation Can adjust for differences in populations when estimating relative effect	Requires all effect modifiers and prognostic factors to be adjusted for.

ITC: Indirect treatment comparison, MAIC: Matching adjusted indirect comparison, ML-NMR: Multi-level network meta-regression, NMA: Network meta-analysis, STC: Simulated treatment comparison. Red indicates that the EAG considers the assumption to be violated.

The EAG considers that the availability of a connected network, albeit with some heterogeneity, means a multi-level network regression (ML-NMR) was the optimal ITC for this setting, and requested the company perform this analysis (clarification A9). The company declined outlining the requirements to undertake a ML-NMR. However, from the EAG perspective, the only limitation beyond those which also apply to the company's STC was the limited reporting of covariates across the network of studies. The company has not presented a clear assessment of the potential covariates, and some of their concerns relate to studies which are not necessary for inclusion in the network in order to connect AV to VenI and VenO.

Table 12: Overview of trials included in company indirect treatment comparisons (adapted from Table 15 of CS)

Study	Arm	N	Age (median)	Age >65 years (%)	Male sex (%)	ECOG PS 0–1 (%)	Rai stage III/IV (%)	Bulky disease $\geq 5\text{cm}$ (%)	CIRS >6 (%)	Creatinine clearance mL/min (median)	Beta-2 microglobulin > 3.5 mg/L (%)	TP53 mutation (%)	Del(17p) (%)	General Population Description
AMPLIFY	AV	291	61	27.1	61.2	90.0	47.1	38.8	2.1	-	58.1	0.0	0.0	No mutation
	FCR/BR	290	61	26.6	63.1	90.3	43.8	42.8	1.0	-	49.3	0.0	0.0	
CLL13	VenO	229	62	35.8	74.7	-	40.8	-	-	86.3	59.9	0.0	0.0	No mutation + Suitable for FCR/BR
	FCR/BR	229	61	34.5	71.2	-	47.1	-	-	86.3	68.0	0.0	0.0	
CLL14	OC1b	216	71	-	66.2	88.4 ^b	42.6 ^a	-	81.9	67.4	61.8	8.3	7.3	Mutation, or No mutation + unsuitable for FCR/BR
	VenO	216	72	-	67.6	87.0 ^b	43.1 ^a	-	86.1	65.2	59.4	11.1	8.5	
GLOW	OC1b	105	71	89.5	60	88.5 ^b	52.5	36.2	58.1	63.2	73.3	1.9	0.0	Unsuitable for FCR/BR
	VenI	106	71	84.9	55.7	87.7 ^b	57.3	39.0	69.8	66.5	69.8	6.6	0.0	
CAPTIVATED	VenI	159	60	28.0	67.0	100.0	28.0	30.0	-	-	-	10.0	13.0	Fit

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; ITC: indirect treatment comparison; OC1b: obinutuzumab with chlorambucil; RCT: randomised controlled trial; WHO: World Health Organization performance status; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

3.5.2 Use of simulated treatment comparison (STC)

The company relied primarily on unanchored STCs, which are among the least robust forms of ITC. These rely entirely on the assumption that all relevant TEMs are observed and adjusted for, an assumption NICE TSD 18⁴⁴ explicitly warns is rarely met in practice, particularly in oncology, where unmeasured confounding is common. The company asserts this assumption is “*reasonable*” but provides no empirical validation or structured sensitivity analyses to support it.

The EAG suggested conducting an ML-NMR (Clarification Question A8), which the company declined. The company’s preference for STC over more robust methods such as MAIC or ML-NMR is not adequately justified, especially given the availability of IPD for at least one trial (AMPLIFY).

3.5.3 Results of company’s STC

The company’s STCs included between 7 and 11 covariates, depending on the comparison.

Table 13: Covariates included in the company's STC

Baseline characteristic	CAPTIVATE FD +GLOW (VenI)	GLOW (VenI)	CLL14 (VenO)
Age ≥65 yr	Y	Y	–
Age ≥75 yr	–	Y	Y
Beta-2 microglobulin >3.5 mg/L	–	Y	Y
Binet stage: C	–	–	Y
Bulky disease ≥5 cm	Y	Y	–
CIRS score	–	Y	Y
Creatinine clearance <70 mL/min	–	Y	Y
Del(11q)	Y	Y	Y
ECOG ≥1	Y	Y	Y
IgHV mutated	Y	Y	Y
Rai stage III/IV	Y	Y	–
Sex: male	Y	Y	Y
Total Number	7	11	9

The EAG notes that each of the three STC comparator trials included people with TP53 mutation or del(17p), a known prognostic factor. Since AMPLIFY did not include this subgroup of people, it could not be included in the adjustment; however, this remains a source of bias, likely overestimating the efficacy of AV. Additional prognostic factors, such as complex karyotypes, trisomy 12, and del(13q), were not included in the STC but have been acknowledged by both EAG and the company's clinical experts (AstraZeneca 2025 Clinical Expert Validation Report [data on file]).

Whilst many of the baseline characteristics between CLL13 and AMPLIFY appear similar, the EAG notes an imbalance in the proportion of people with ECOG =0. In the AV arm of AMPLIFY ██████% of people had ECOG = 0, compared with 72.1% of the VenO arm of CLL13.³⁰ Additionally, AMPLIFY had a higher proportion with Rai stage III/IV (47.1% vs 40.8%). The higher prevalence of FCR usage in CLL13 (65.5% vs 49.3%) also suggests a fitter population. This is supported by the consistently lower estimates of PFS from the FCR arm of AMPLIFY (Table 14). The EAG considers that this imbalance is likely to be an effect modifier, as in survival analysis treatment effects are more evident when a higher number of events have occurred, which is the case in a higher risk population. If AV was included in the CLL13 trial, the effect size vs FCR/BR would likely be less than was observed in the AMPLIFY study. This means that in this anchored Bucher ITC, the benefits of AV are likely to be overestimated.

Table 14: Comparison of PFS rates for FCR/BR arms of CLL13 and AMPLIFY

	FCR/BR arm of CLL13	FCR/BR arm of AMPLIFY
30 months	~78%	~████%
36 months	~76%	~66%
48 months	~61%	~████%

The results of the company's STC and Bucher ITC are reported in CS, section 2.10.3.2 and appendices section B.4.6, which the EAG summarises in Table 15.

Table 15: RMST difference for OS and PFS from company STCs and Bucher ITC

Comparison	PFS			OS		
	Follow-up (months)	Distribution	RMST difference, months (95% CI)	Follow-up (months)	Distribution	RMST Difference (months) for OS
CAPTIVATE FD + GLOW						
AV vs VenI	55.1	Gompertz	()	57.7	Gompertz	()
GLOW only						
AV vs VenI	55.1	Gompertz	()	57.7	Gompertz	()
CLL14						
AV vs VenO	55.1	Gompertz	()	57.7	Gompertz	()
CLL13						
AV vs VenO (Bucher ITC)	55.1		()	57.1		()

Abbreviations: AV: acalabrutinib with venetoclax; CI: confidence interval; OS: overall survival; RMST: restricted mean survival time; STC: simulated treatment comparison; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

The median follow-up durations reported in Table 62 are as follows: AMPLIFY, 40.8 months (range 0 to 59); CLL14, 76.4 months; CLL13, 63.8 months; GLOW, 64 months; and CAPTIVATE FD, 69.0 months. Despite the availability of longer-term data in the comparator trials, the company's STC analyses are based on truncated follow-up periods of 55.1 months for PFS and 57.7 months for OS. This appears to reflect the maximum follow-up available in AMPLIFY, which is still ongoing and has immature survival data, with a median follow-up of only 40.8 months. Whilst this is necessary for a fair analysis, it also fails to include the long-term data from more mature

comparator trials, which may underestimate their long-term efficacy. This is particularly relevant in a chronic condition such as CLL, where durability of response is a key consideration. The EAG is unclear why the follow-up for the OS Bucher ITC was restricted to 57.1 months rather than 57.7 months as was used in the OS STCs; however, this is unlikely to have a meaningful impact on the analysis.

3.5.4 Sensitivity Analyses for STC

The company reports sensitivity analyses in Document B, Section 2.10.3.1 and Appendix B.5.6. These analyses compare full, unadjusted, and AIC-optimised models, and explore different parametric distributions for the STC models. Overall, the results were broadly consistent, with AIC-optimised models occasionally changing the direction of the relative effect estimate but not impacting statistical significance. The AIC optimised models selected between two and four covariates, depending on the comparison.

While these analyses provide some insight into model fit and covariate selection, it does not address the most critical assumptions of unanchored STC including assessment of unmeasured or unreported TEMs, or exploration of non-linear/linear treatment-covariate interactions, which are essential in STC models. Given that no alternative, more robust ITC methodology was provided (e.g. ML-NMR, MAIC), and key assumptions were neither tested nor empirically validated, the consistency and credibility of the STC results remain uncertain.

3.5.5 Additional EAG Comment on Company ITCs

The EAG requested that the company perform a Bucher ITC to estimate relative efficacy of AV and VenO in the populations aged ≥ 65 years of AMPLIFY and CLL13 (clarification A12). This was of interest given the profile of AV may mean it is given predominantly in older frailer patients, compared with VenO and VenI, and reduce other differences in baseline characteristics.

Furthermore, the EAG considers this older population to be more representative of the general real-world CLL population. However, the company declined to present this analysis, citing small sample size of this subgroup across the relevant trials.

Regarding the presented STCs, it is concerning why the company opted to pool GLOW and CAPTIVATE for the comparison to VenI, rather than present a separate analysis comparing CAPTIVATE alone. A naïve comparison of these data undertaken by the EAG suggests that, at a comparable time point (48 months, investigator-assessed), CAPTIVATE FD VenI shows superior OS (98% vs ██████%) and PFS (79% vs ██████%) compared to AMPLIFY AV (see Table 10). Whilst GLOW's OS appears lower, its IRC-assessed PFS at 42 months is comparable to AMPLIFY's 36-month PFS, despite GLOW's older population and the expectation of fewer events with shorter follow-up (42 months VenI 74.6% vs 76.5% AV). A similar pattern is observed when comparing GLOW at 60 months with AMPLIFY at 54 months (Table 10).

The conclusion of equal efficacy is based on highly uncertain analyses, which are likely to be overestimating the benefits of AV and are not supported by external analyses (see section 3.6). The company has not provided comprehensive analyses or justification for not providing these analyses. Additional input from six UK clinical experts and a modified Delphi panel is offered, but this input is uncertain and mainly reflects uncertain opinions and speculative assumptions, such as no biological reason for AV to be inferior and hypothetical gains from better tolerability.

The EAG recommends the company consider presenting hazard ratio output, undertaking ML-NMR, and performing a comparison to the CAPTIVATE FD population without pooling with GLOW. Anchored and unanchored MAIC analyses would also support the current conclusions.

Exploratory analyses comparing to subgroup results from the comparator studies which exclude people with del(17p)/TP53 mutation will also be helpful

to explore the impact of this current source of bias but require assumptions of generalisability of baseline characteristics from the whole population.

Ultimately the evidence provided by the company is only a weak justification of equal efficacy and should be treated as such.

3.5.6 Delphi panel results

The company conducted a Delphi panel, reported in Document B, section 2.10.5.1, to assess the comparability of AV versus VenI and VenO. Of the 93 experts invited, only 33 (35%) agreed to participate, with response rates of 67% in Round 1 (22/33) and 48% in Round 2 (16/33), raising concerns about the representativeness and robustness of the findings.

Responses were collected via an online platform using an 8-point Likert scale, with consensus defined as $\geq 70\%$ agreement or disagreement. However, the panel did not elicit quantitative estimates (e.g., survival differences), limiting its value in informing comparative effectiveness.

The panel reached consensus that AV is a suitable treatment alternative to VenI and VenO in terms of PFS, OS, and healthcare resource use. AV was also considered to have a more favourable safety profile than VenI and to be a suitable alternative to VenO from a safety perspective. However, consensus was not reached for time to next treatment (TTNT), with several panellists citing insufficient data. HRQoL was considered similar between AV and VenI, but no consensus was reached for AV versus VenO.

EAG summary:

More robust and reliable statistical methods such as NMA, MAIC, or ML-NMR should have been employed, with STC used as a supplementary approach. Instead, the company relied primarily on STCs, with clinical expert opinion and a modified Delphi panel as complementary evidence. Reliance on caveated STC and Bucher ITC as the main statistical analyses without more rigorous methods limits the robustness of the evidence base.

3.6 Additional work on clinical effectiveness done by the EAG

3.6.1 EAG validation of equal efficacy

In this appraisal, the company has assumed equal efficacy between acalabrutinib-venetoclax (AV), ibrutinib-venetoclax (VenI), and venetoclax-obinutuzumab (VenO). The face validity and robustness of this assumption have been questioned by the EAG clinical experts. AV's improved cardiovascular safety profile is acknowledged and attributed to its more selective inhibition of Bruton's tyrosine kinase (BTK). The BSH 2025 guidance advises that *"the use of V+I in older patients with comorbidities should be carefully weighed against the potential risk of cardiovascular complications"*. However, the clinical relevance of this advantage may be limited, as such events are generally manageable within NHS practice. Whilst evidence remains limited, some studies suggest potential superiority of VenI over AV, aligning with the views of EAG's clinical experts (see section 3.6.2). AMPLIFY enrolled a relatively young and fit population and showed relatively lower PFS rates at 36 months compared with VenI (76.5% for AV vs 88% for VenI at 3 years).⁴⁵

These differences may reflect pharmacodynamic distinctions between ibrutinib and acalabrutinib.⁴⁶ Ibrutinib has been shown to more effectively induce a *"compartment shift"*, a process in which CLL cells are mobilised from the protective environment of the lymph nodes into the bloodstream. This occurs through downregulation of CXCR4, a receptor that helps CLL cells remain in lymphoid tissues. Once in the bloodstream, these cells become more susceptible to venetoclax, which promotes cell death by inhibiting Bcl-2, a protein that helps cancer cells survive. Ibrutinib may further enhance venetoclax sensitivity by reducing other survival proteins (e.g., Mcl-1, Bcl-XL) and increasing pro-death proteins (e.g., BIM), thereby priming CLL cells for

apoptosis.⁴⁷⁻⁴⁹ The differences in the mechanism of action are depicted in Figure 2 sourced from Tedeschi et al. (2025).⁴⁵

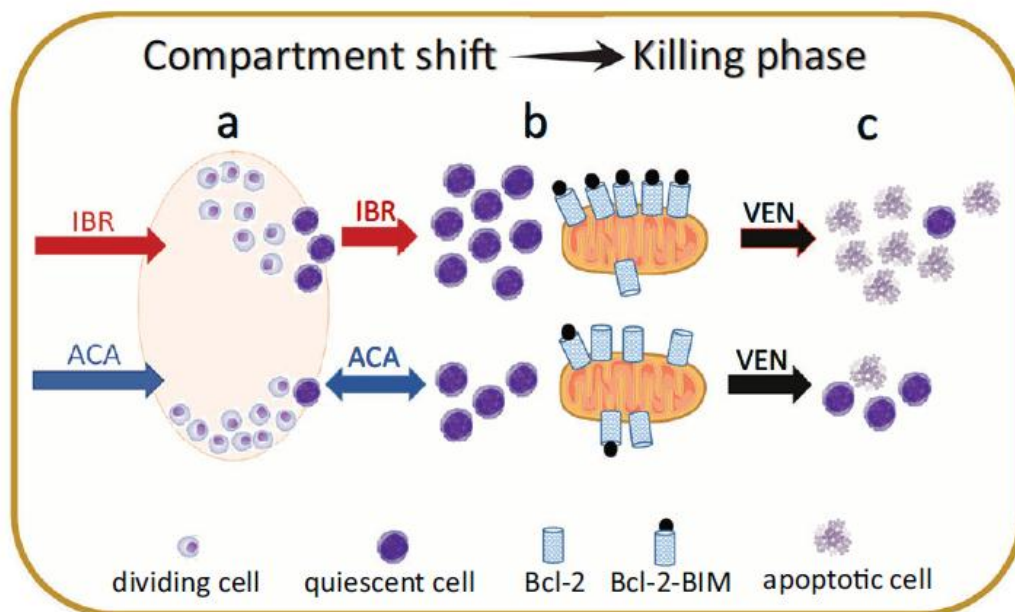


Figure 2: Possible mechanisms for the superior outcomes of fixed duration Venl over AV in trials (copied from Tedeschi et al. (2025) ⁴⁵)

Note: Compared to acalabrutinib, ibrutinib: **a)** causes more vigorous and unidirectional mobilization of quiescent cells from lymph nodes (compartment shift), **b)** induces higher upregulation of BIM, which occupies mitochondrial Bcl-2 and makes CLL cells more dependent on residual unoccupied Bcl-2, and **c)** provides venetoclax with more numerous and sensitive cells to commit to facilitated apoptosis (killing phase).

As for the atrial fibrillation (AF),⁴⁵ a known side effect of BTK inhibitors due to off-target kinase inhibition, this occurred less frequently with AV (any grade: 0.7%, grade ≥ 3 : 0.3%) than with Venl (4% and 1%, respectively), consistent with acalabrutinib's greater selectivity. However, these differences may be less clinically meaningful given the low absolute event rates and the fact that AF is generally manageable in NHS settings. Importantly, no studies have specifically evaluated AV in older, comorbid patients such as those enrolled in GLOW. This concern is underscored by the demographic profile of AMPLIFY, the only source of data for AV, which included substantially fewer elderly

patients: only 27.1% were aged over 65 and [REDACTED]% over 75, compared with 84.9% and 33.0% in GLOW, respectively. Additionally, patients in AMPLIFY had a CIRS score below 6, whereas those in GLOW had scores above 6, indicating a higher burden of comorbidities and impairments in the GLOW population. These differences, particularly the limited representation of older and more comorbid patients in AMPLIFY, warrant caution when extrapolating AV's safety and efficacy to the broader, more vulnerable population seen in GLOW.

3.6.2 Unanchored MAIC between CAPTIVATE + GLOW IPD and AMPLIFY

An unanchored MAIC comparing AV and VenI by Munir et al. (2025; conference abstract) ⁵⁰ reported significantly superior PFS and uMRD (Table 17) for individual patient-level data (IPD) of VenI (pooled GLOW and CAPTIVATE FD) compared to AV in the AMPLIFY after excluding patients who could not be matched for biological and clinical characteristics (

Table 16). Munir et al. (2025) highlight limitations favouring the AV arm: progression was assessed more rigorously in GLOW and CAPTIVATE (CT/MRI at predefined intervals), and follow-up was longer for VenI, potentially biasing PFS results toward AV. Additionally, unreported prognostic factors, due to incomplete data collection (CIRS data in CAPTIVATE), were not accounted for.⁵⁰

In

Table 16, covariates from pooled GLOW and CAPTIVATE IPD (median follow-up: 55.7 months) were adjusted to AMPLIFY aggregated data (median follow-up: 41 months). Patients with del17p/TP53 mutations, CIRS >6, CrCl <50 ml/min, or missing data were excluded from the VenI IPD pool (impact assessed separately). Eight covariates were adjusted with an effective sample size (ESS) of 101. The sensitivity analysis for additional matching to the ECOG PS score and exclusion of small lymphocytic lymphoma (SLL) showed poor overlap, and the ESS was reduced to 62.

Table 16: Patient baseline characteristics before and after matching

Characteristic	AMPLIFY (AV) (N=291)	GLOW + CAPTIVATE (Pooled VenI IPD) (N=265)	After reweighting (N=146, ESS=101)
Age			
Median	61	65	61
≤65 years	73%	55%	73%
Unmutated IGHV	57%	61%	57%
CrCl <60 ml/min	13%	17%	13%
del11q	18%	19%	18%
Male	61%	62%	61%
Rai Stage			
0–I	17%	28%	17%
II	36%	33%	36%
III	24%	21%	24%
IV	23%	19%	23%
Bulky Disease (≥5cm)	39%	34%	39%
Median Time from Diagnosis (months)	28.5m	35.5m	26.8m
ECOG PS			
0–1	90%	95%	90%
2	10%	5%	10%

Abbreviations: AV, acalabrutinib plus venetoclax; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy chain variable region; IPD, individual patient data; N, number of patients; Rai, Rai staging system; VenI, ibrutinib plus venetoclax

Table 17: Outcomes of unanchored MAIC between VenI IPD and AV aggregate data

N=146; ESS=101	95% CI; p-value
uMRD relative risk at EOT+3 in PB	1.56 (1.23; 1.98; 0.0002)
uMRD relative risk at EOT+3 in BM	1.54 (1.20; 1.99; 0.0008)
PFS hazard ratio of VenI vs AV	0.53 (0.33; 0.85; 0.0085)

Abbreviations: AV, acalabrutinib plus venetoclax; BM, bone marrow; CI, confidence interval; EOT+3, end of trial + 3 months; ESS, effective sample size; IPD, individual patient data; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable minimal residual disease; VenI, ibrutinib plus venetoclax

3.7 Conclusions of the clinical-effectiveness section

The AMPLIFY study shows a clear benefit of AV over FCR/BR for people with untreated CLL who do not have del(17p) or TP53 mutation. There are concerns around the representativeness of the AMPLIFY population compared to the eligible NHS patients in terms of average age and fitness. The limited ITC analyses presented by the company suggest very similar efficacy of AV to VenO and VenI, however these are likely subject to bias of an unknown magnitude in favour of AV. No comparison of AV to acalabrutinib or zanubrutinib monotherapy has been presented, despite the possibility of their displacement should AV be approved. There is the potential to extend the evidence of AV's efficacy to include people who have del(17p) or TP53 mutation, matching the licensed population.

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

The CS (Appendices E, F and G) provides detailed reports of three systematic reviews, aimed at identifying 'relevant economic evaluations, utilities studies and cost and resource use studies in patients with previously untreated CLL'.

Search strategy

Searches in an appropriate range of databases and other sources were conducted simultaneously for the three SLRs in December 2024 and updated in August 2025. They were limited by date to 2014 onwards.

Searches combining thesaurus and free text terms for CLL with CADTH search filters designed to identify economic evaluations and models,⁵¹ or health utilities/quality of life and HRQoL studies,⁵² have been combined correctly in searches of medical databases (MEDLINE and Embase via Embase.com). These filters do not contain specific 'resource use' or 'burden of illness' terms. Despite this, table 13 of the CS response to clarification questions indicates that 65 cost and resource use studies were retrieved. However, in the summary of included cost and resource-use studies (original CS appendix), the company has reported only bibliographic information. Details of the interventions assessed, and the specific cost and resource-use items extracted are not provided and should be included. Abstracts for the most recent two years of relevant conferences were also sought and other additional searches undertaken (checking Tufts CEA Register and the references of 11 identified reviews). The EAG identified an error in the INAHTA search (combining CLL thesaurus and free text terms with an 'AND'

rather than an 'OR' in lines 1 and 2), which would have effectively restricted the search to records indexed as CLL. However, the majority of relevant records in this database are still likely to have been retrieved. Additionally, hand-searching of five HTA organisations was reported for these cost-effectiveness SLR searches, which will have helped identify any others from those organisations (see CS appendix E, tables 28 and 29).

Overall, the eligibility criteria and study selection process were acceptable and broadly aligned with recognised methodological standards. The scope was sufficiently wide to capture a comprehensive set of studies relevant to untreated CLL, and the use of dual-reviewer screening added a reasonable level of robustness to the identification and inclusion process. The inclusion approach did not appear overly restrictive, and the breadth of permitted study designs, outcomes and comparators supported a wide evidence base.

In the utilities SLR, the intervention (and where relevant, the comparator) for each included study is not reported, despite being part of the stated PICO. This information should be added to improve clarity.

One flow diagram covering the search and selection process for the three SLRs is provided. Some minor discrepancies in numbers between the tables/text and flow diagram were corrected at clarification stage and an updated flow diagram and search strategies were provided.

4.2 Critique of the submitted economic evaluation

The EAG reviewed the company's economic evaluation model to assess alignment with NICE standards. The company constructed a de novo economic model to evaluate the cost-effectiveness of acalabrutinib plus venetoclax (AV) compared with ibrutinib plus venetoclax (VenI) and venetoclax plus obinutuzumab (VenO). This evaluation was based on the AMPLIFY clinical trial populations. The licensing criteria and the decision problem are outlined in the submission. The EAG provided a summary of the

model structure and critically appraised the clinical evidence (e.g., efficacy, treatment pathway, and mortality) and economic evidence (e.g., drug costs, health state resource use and costs, and utility values). The EAG critiqued the methods and inputs used in the analysis.

4.2.1 NICE reference case checklist

The EAG undertook an evaluation of the company's submission against the NICE reference case. Findings are summarised in the Table 18.

Table 18: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	The company's decision problem is narrower than NICE's across all categories, especially population and comparators
Comparator(s)	As listed in the scope developed	The comparators included in the company's economic analysis were acalabrutinib and venetoclax (AV); ibrutinib plus venetoclax (VenI); and venetoclax plus obinutuzumab (VenO). Company excluded acalabrutinib and zanubrutinib monotherapies.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model captures all relevant patient health effects that occur following treatment
Perspective on costs	NHS and Personal Social Services	The NHS and PSS perspective is utilized which aligns with NICE requirements.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company only reported pairwise comparisons, a fully incremental analysis is also included in the model as set out by the NICE requirements.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The time horizon (lifetime) aligns with NICE's requirement to capture all relevant costs and outcomes.
Synthesis of evidence on health effects	Based on systematic review	Feasibility of a NMA, ML-NMR and MAIC has been considered by the company. Ultimately, an unanchored simulated treatment comparison (STC) was utilised to compare AMPLIFY (AV), GLOW and CAPTIVATE FD (VenI), and CLL14 (VenO). The company also undertook a

		Bucher ITC to compare AV to VenO using data from AMPLIFY and CLL13 (FCR/BR common comparator).
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.	Measuring and valuing health effects aligns with NICE requirements.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Collected from patients using EQ-5D-5L in the AMPLIFY trial; also supported by secondary sources.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	AMPLIFY trial mapped EQ-5D-5L data to EQ-5D-3L using Hernández-Alava (2017) ⁵³
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	The company's approach aligns with the NICE reference case requirements.
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	Resource use clearly reported and valued appropriately using current prices and is in line with the NHS and PSS perspective
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	A discount rate (for both costs and health effects) of 3.5% per annum is used.

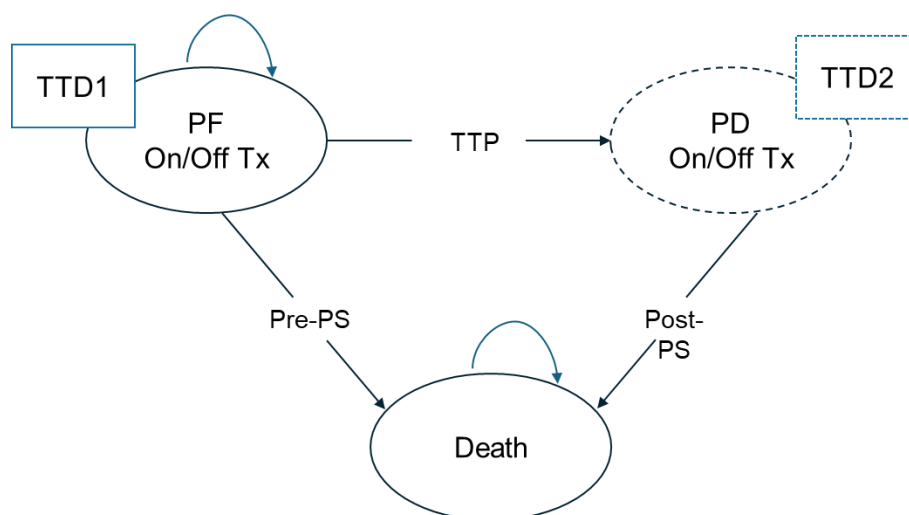
Abbreviations: AV, acalabrutinib plus venetoclax; BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukaemia; EQ-5D, EuroQol 5-Dimension; EQ-5D-3L, EuroQol 5-Dimension 3-Level; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FCR, fludarabine plus cyclophosphamide plus rituximab; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; N, number of patients; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PSS, Personal Social Services; QALY, quality-adjusted life year; STC, simulated treatment comparison; VenI, ibrutinib plus venetoclax; VenO, venetoclax plus obinutuzumab

4.2.2 Model structure

The company stated that it developed a de novo semi-Markov state-transition cohort model to evaluate the cost-effectiveness of AV compared with VenI and VenO for previously untreated, non-high-risk chronic lymphocytic leukaemia (CLL). The company noted that no published economic evaluations

addressed the specific decision problem, and therefore, a new model was required to reflect the key clinical and economic features of the UK CLL treatment pathway.

According to the company, the model comprised three mutually exclusive health states: progression free (PF), progressed disease (PD), and death, with additional 'on' and 'off' treatment sub-states within PF and PD. The company stated that this structure allows for explicit modelling of treatment duration, associated costs, and health-related quality of life (HRQoL) impacts, stratified by whether patients are on or off treatment. The company described that all patients entered the model in the PF on-treatment state and could transition between states according to disease progression or death.



Abbreviations: Post-PS: post-progression survival; Pre-PS: pre-progression survival; TTD: time to treatment discontinuation; TTP: time to progression; Tx, treatment.

Figure 3: Model structure used in the economic analysis (Obtained from CS, section 3.2.2)

The company justified the use of a semi-Markov approach rather than a partitioned survival model (PSM), citing immature overall survival (OS) data from the AMPLIFY trial (data cut-off: 30 April 2024). The company stated that a PSM would require more mature OS data for reliable long-term

extrapolations, whereas the semi-Markov framework allowed transitions to be informed by intermediate endpoints such as time to progression (TTP), pre-progression survival (pre-PS), and post-progression survival (post-PS). The company also noted that this approach allowed incorporation of external data sources where trial data were limited and ensured consistency between PFS and OS. The company highlighted that this approach is aligned with guidance in NICE TSD 19 and semi-Markov models accepted in recent NICE appraisals for CLL (TA689, TA891, TA931).

The company reported that transition probabilities were derived from the AMPLIFY trial data for PF-to-PD and PF-to-death transitions, and from the ASCEND trial for post-progression survival due to immaturity of AMPLIFY post-progression data. The company stated that transition probabilities were constrained by age and sex adjusted UK general population mortality to ensure plausible long-term survival estimates.

The company indicated that the model was conducted from the UK NHS and Personal Social Services (PSS) perspective, in line with the NICE reference case. The company reported using a 28-day cycle length, consistent with AV treatment cycles in AMPLIFY and previous NICE evaluations, applied a half-cycle correction, and adopted a lifetime time horizon of 40 years. Both costs and health outcomes were discounted at 3.5% per annum, according to NICE guidance.

EAG comment

The EAG considers the company's use of a semi-Markov state-transition model generally appropriate for assessing AV in untreated, non-high-risk CLL. The model captures key disease stages, including progression free, progressed disease, and death, and the on-/off-treatment sub-states allow more detailed modelling of costs and HRQoL, reflecting periods off treatment. The EAG agrees that avoiding a partitioned survival model (PSM) due to immature AMPLIFY OS data is reasonable. The semi-Markov approach

enables use of data describing intermediate endpoints and external data, improving long-term survival plausibility and avoiding inconsistencies from immature OS data. However, regarding the modelling of the discount rate, the EAG has the following concern:

4.2.2.1 EAG concern 1: Inappropriate incorporation of discount factors into the model

- **Company's Approach:** The company applies discounting starting from year three, with values remaining undiscounted for the first two years. In addition, discounting is implemented for each 28-day cycle rather than on an annual basis.
- **EAG's Critique, Assumptions, and Justification:** The EAG considers that discounting should be applied in line with the NICE reference case, that is, with a discount factor of 1.0 (i.e. no discounting) applied only for the first year. Furthermore, the EAG believes that discounting should be implemented consistently across the entire model. If the assumption of no time preference is applied to the first year (i.e. no discounting), the same assumption should extend to all cycles up to one full year. Then from the second year, a uniform annual discount factor should be applied to all cycles from that year onwards. This approach ensures internal consistency.
- **EAG's Proposed Solution:** The EAG's recommended approach is that discounting should be applied correctly for each intervention, either on a per-cycle basis or by using a single annual factor from the second year onwards. This issue was raised earlier at the clarification stage under question B8 and was addressed by the company by applying no discount in the first year and then using a fixed annual discount factor thereafter.

4.2.3 Population

The company stated that the patient population of interest for this submission comprises adult patients with untreated, non-high-risk chronic lymphocytic leukaemia (CLL), defined as patients without a del(17p) or TP53 mutation. The company stated that this population represents a subset of the marketing authorisation extension for acalabrutinib and aligns with the population enrolled in the AMPLIFY trial, which provides the key clinical evidence supporting the submission. The company explained that, in clinical practice, patients with CLL typically begin treatment only once their disease becomes symptomatic and requires intervention. Patients with high-risk cytogenetic abnormalities (del[17p] or TP53 mutations) were excluded from the target population, as these are associated with a poorer prognosis and different treatment approaches.

For the economic analysis, the company used baseline characteristics derived from the AMPLIFY trial to inform model inputs. The mean age of 59.9 years was applied as the starting age in the first model cycle. Where relevant, drug cost calculations were based on the trial-reported mean body surface area (██████ m²) and body weight (██████ kg). The company reported that 36% of participants in the AMPLIFY trial were female. These parameters were used consistently across the company’s cost-effectiveness model (Table 19).

Table 19: Baseline characteristics used in the economic analysis, based on the AMPLIFY trial (all trial arms) (obtain from CS, section 3.3.2)

Patient characteristics	Mean	SE
Age (mean)	59.90 years	0.32
BSA (mean)	██████	██████
Weight (mean)	██████	██████
Female patients	36%	0.036 ^a

^aSE assumed.
Abbreviations: BSA: body surface area; SE: standard error.
Source: Brown et al. (2025; Table 1) ²¹; AstraZeneca Data on File, 2025 (AMPLIFY CSR; Table 12); AstraZeneca 2024 AMPLIFY CSR TLF [Tables, Listings, and Figures].

The company described AMPLIFY trial as an ongoing Phase III, randomised, multicentre, open-label study comparing AV with chemoimmunotherapy,

which was selected as the comparator at trial design despite not being current UK standard of care. Inclusion criteria included adult patients with symptomatic, untreated non-high risk CLL. Further details of the AMPLIFY trial were reported in Section 3 of this report.

4.2.3.1 EAG concern 2: Appropriateness of using 59.9 years as the reference age for the CLL population

- **Company's approach and main rationale:** The company applied a starting age of 59.9 years in its economic model, reflecting the mean baseline age reported in the AMPLIFY trial. The company stated that this aligns with UK clinical expert opinion suggesting that patients considered suitable for fixed-duration therapy in first-line, non-high-risk CLL tend to be younger and fitter. The company notes that this perspective is consistent with the position taken in NICE TA931(zanubrutinib) and claim further support from international real-world evidence (RWE) for adopting a younger population profile.
- **EAG critique, assumptions, and justification:** The EAG considers the company's assumed starting age to be substantially lower than would be expected in routine UK practice. Some UK real-world evidence places the median age at diagnosis at 71.3 years ⁵⁴, with similar estimates seen internationally (70.4 years in Finland (overall untreated CLL/SLL population)⁵⁵ and 72 in the CORE study (CLL/SLL; treatment line unclear from referenced publication)⁵⁶). The EAG clinical advisers report that the mean age at treatment in the UK is around 70 years. Previous NICE appraisals of fixed-duration regimens have also considered older populations, including TA663 (VenO; median 72) and TA891 (VenI; mean 71.0, SD 8.02 in the GLOW trial). These data collectively indicate that a starting age of 59.9 years is not representative of UK clinical practice.

EAG assumption: Treatment outcomes do not appear to vary meaningfully between younger and older patients (for more details see *section 4.2.5*).

- **EAG proposed approach:**

- **Base case:** Apply the mean age reported in TA891 (VenI): 71.0 years (SD 8.02).¹⁵

- **Scenario analysis:** Retain the company's preferred starting age of 59.9 years (AMPLIFY trial mean).

4.2.4 Interventions and comparators

The company stated that the intervention under assessment is acalabrutinib with venetoclax (AV), a fixed-duration, all-oral, targeted therapy for adults with untreated chronic lymphocytic leukaemia (CLL) without a 17p deletion or TP53 mutation (i.e., non-high-risk CLL). The company explained that its submission aligns with the current treatment pathway in the UK, which distinguishes between fixed-duration and treat-to-progression therapies. According to UK clinical experts consulted by the company, fixed-duration therapies are generally used in younger, fitter patients with untreated non-high risk CLL, whereas treat-to-progression therapies are used in older or less-fit patients. As AV is a fixed-duration regimen, the company considered that its introduction would not displace the use of treat to progression options (e.g., acalabrutinib or zanubrutinib monotherapy).

Based on this, the company identified venetoclax with obinutuzumab (VenO) and venetoclax with ibrutinib (VenI) as the only relevant comparators for AV. These are currently recommended by NICE as fixed-duration therapies for untreated non-high-risk CLL and reflect standard UK clinical practice (for more details see *section 2.3*).

Other regimens listed in the NICE final scope (e.g., fludarabine, cyclophosphamide and rituximab (FCR); bendamustine with rituximab (BR); obinutuzumab with chlorambucil (OC1b); and acalabrutinib with obinutuzumab (AO)) were excluded by the company as relevant comparators. The company justified this on the basis that:

- Chemoimmunotherapy regimens (FCR, BR, OC1b) are no longer routinely used in UK practice and are expected to be removed from upcoming BSH CLL guidelines.
- AO has not been appraised by NICE in this indication and is not available in NHS practice.
- Treat to progression therapies (acalabrutinib or zanubrutinib monotherapy) are used in a different patient population and therefore not appropriate comparators.

The company noted that the AMPLIFY trial did not directly compare AV with VenI or VenO. For economic modelling, dosing regimens for AV, VenI and VenO were derived from product SmPCs (Table 20), and time to treatment discontinuation (TTD) for AV was based on AMPLIFY data. As no TTD Kaplan-Meier data were available for VenI or VenO, the company assumed a similar TTD trajectory to AV, adjusting for differences in treatment duration where relevant.

Table 20: The dosing regimens for AV, VenI and VenO modelled in the economic analysis (obtained from CS, section 3.2.3)

Treatment regimen	Dosing regimen
AV	Acalabrutinib (oral; 14x 28-day cycles) • 100 mg administered twice daily for 14 treatment cycles, each lasting 28 days Venetoclax (oral; 12x 28-day cycles) • Initiated on Day 1 of Cycle 3 with a 5-week ramp-up until Day 1 of Cycle 4 (20 mg, 50 mg, 100 mg, 200 mg, 400 mg; once daily). Venetoclax treatment was continued at 400 mg once daily until Day 28 of Cycle 14

Treatment regimen	Dosing regimen
VenI	Ibrutinib (oral; 15x 28-day cycles) - Administered once daily (420 mg) - Ibrutinib is given as a monotherapy from Day 1 of Cycle 1 until Day 28 of Cycle 3, then in combination with venetoclax starting on Day 1 of Cycle 4 Venetoclax (oral; 12x 28-day cycles) - Initiated with a 5-week dose ramp-up period (20 mg, 50 mg, 100 mg, 200 mg, 400 mg; once daily), then 400 mg per day from Cycle 5 onward
VenO	Venetoclax (oral; 12x 28-day cycles) - Initiated with a 5-week dose ramp-up period starting on Day 22 of Cycle 1 until Day 22 of Cycle 2 (20 mg, 50 mg, 100 mg, 200 mg, 400 mg; once daily) - Dosage of 400 mg is maintained until the end of Cycle 12 Obinutuzumab (IV; 6x 28-day cycles) 1,000 mg administered on Days 1, 8 and 15 of Cycle 1, then on Day 1 of Cycles 2 through 6

Abbreviations: AV: acalabrutinib with venetoclax; IV: intravenous; SmPC: summary of product characteristics; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

EAG comments

Whilst the company aligned with AMPLIFY, neither the marketing authorisation nor the European Medicines Agency's (EMA) European Public Assessment Report (EPAR)¹ imposed restrictions on high-risk patients. Given their small proportion (5–10%) (see *section 2.1.2*), they should have been included to support extrapolation of benefits to this subgroup.

According to the 2025 BSH guideline and EAG expert opinion, all NICE-approved first-line options, VenO, VenI, acalabrutinib, and zanubrutinib, should have been considered without restriction. While choice depends on clinical judgment and patient factors, AV's more tolerable safety profile may broaden eligibility, making acalabrutinib and zanubrutinib relevant comparators (see *section 2.3*).

4.2.4.1 EAG concern 3: Proportion of patients completing treatment

- Company's approach and main rationale:** The company derived treatment duration for AV from the AMPLIFY trial (14 cycles for acalabrutinib and 12 cycles for venetoclax). TTD data were taken directly from the trial without extrapolation, as the fixed-duration regimen was fully observed. For VenI and VenO, in the absence of trial-level TTD data, the company assumed that the TTD trajectory was equivalent to AV. For VenI, the AV TTD curve was extended by one additional cycle (15 total) to reflect trial protocol differences (see more details in section 4.2.5.3). Table 21 summarises the proportion of patients completing treatment as estimated within the company's model for each regimen, drug component, and corresponding maximum number of treatment cycles.

Table 21: Proportion of patients who completed treatment as extracted from the company's model

Regimen	Drugs	Maximum treatment cycles (trial protocol)	Proportion of patients who completed treatment
Acalabrutinib + venetoclax	Acalabrutinib	14.00	██████████
	Venetoclax	12.00	██████████
Ibrutinib + venetoclax	Ibrutinib	15.00	██████████
	Venetoclax	12.00	██████████
Venetoclax + obinutuzumab	Obinutuzumab	6.00	██████████
	Venetoclax	12.00	██████████

- EAG critique, assumptions, and justification:** The EAG considers the implicit assumption of TTD equivalence across all regimens to be unsupported and inconsistent with available evidence. Published trial data and clinical experience show clear differences in discontinuation patterns between AV, VenI, and VenO. The EAG also questions the abrupt drop in completion between cycles 13 and 14 for AV (from ██████% to ██████%), which appears clinically implausible, as patients on fixed-duration regimens are generally encouraged to complete a treatment if they can tolerate it

(section 4.2.5.3). Evidence from AMPLIFY, GLOW, and CLL14 shows substantial variation in completion rates: █% for AV, 77.4% for VenI, and 77.8% for VenO. EAG clinical experts highlighted that discontinuation is primarily driven by adverse events, suggesting that a less toxic regimen such as AV, would be expected to have higher completion rates. The company's assumption of equivalence therefore likely overestimates completion for VenI and VenO, which in turn inflates their treatment costs and creates a bias in favour of AV.

EAG assumption: Patients receiving AV experience fewer adverse events, leading to higher completion rates. Completion rates for VenI and VenO are expected to fall more steeply due to increased toxicity and tolerability challenges.

- **EAG proposed approach**

Base case: Incorporate TTD using a linear decline from full completion at cycle 1 to match observed trial-based completion estimates:

- VenI: average of GLOW and CAPTIVATE FD
- VenO: average of CLL14 and CLL13

Table 22: Proportion of patients completing treatment (EAG base case)

Regimen	Drugs	Completion (%)
Acalabrutinib + venetoclax	Acalabrutinib	█
	Venetoclax	█
Ibrutinib + venetoclax*	Ibrutinib	85.0%
	Venetoclax	85.0%
Venetoclax + obinutuzumab**	Obinutuzumab	84.9%
	Venetoclax	84.9%

*Completion rate for VenI:

- GLOW: Kater et al. (2022),³⁶ Figure 1, reports that 82 out of 106 patients completed treatment (77.4%).
- CAPTIVATE FD: Tam et al. (2022),⁴² reports that 147 out of 159 patients completed treatment (92.5%).
- Average completion: $(77.4 + 92.5) \div 2 = 85.0\%$

**Completion rate for VenO:

- CLL13: Eichhorst et al. (2023)³⁰, Figure 1, reports that for the VenO arm, 214 out of 229 patients completed the trial (93.4%).
- CLL14: Fischer et al. (2019),³⁴ Figure 1, reports that 165 out of 216 patients in the VenO arm completed treatment (76.4%).
- Average completion: $(93.4 + 76.4) \div 2 = 84.9\%$

Scenario analysis:

- Scenario 1: Apply the company's approach.
- Scenario 2: Apply AV completion rates across all treatment arms.
- Scenario 3: Apply observed trial-based rates for VenI (GLOW) and VenO (CLL14).

Table 23: Proportion of patients completing treatment (EAG scenario 3)

Regimen	Drugs	Completion (%)
Acalabrutinib + venetoclax	Acalabrutinib	██████
	Venetoclax	██████
Ibrutinib + venetoclax	Ibrutinib	77.4%
	Venetoclax	77.4%
Venetoclax + obinutuzumab	Obinutuzumab	76.4%
	Venetoclax	76.4%

4.2.4.2 EAG concern 4: Discrepancies in Relative Dose Intensity (RDI)

- **Company's approach and main rationale:** The company reports that RDI estimates for AV were taken directly from the AMPLIFY trial, with values of ██████ % for acalabrutinib and ██████ % for venetoclax. For VenI and VenO, the company assumed an RDI of 100% for both venetoclax and the partner drugs. Their justification relies on the precedent set in NICE TA891 (VenI), where a 100% RDI was also applied to VenO due to the absence of publicly available RDI data. As no trial-based RDI

information is available for VenI or VenO, the company carried this assumption of full dose intensity into their base case analysis.

- **EAG critique, assumptions, and justification:** The EAG considers the rationale for assuming 100% RDI for VenI and VenO and lower value for AV to be weak. The precedent cited from TA891 reflects a pragmatic decision driven by data gaps rather than evidence of equivalent dose intensity across regimens. The EAG notes that RDI represents the ratio of delivered to planned dose intensity, capturing any dose reductions or treatment delays. The company's implementation, which multiplies RDI directly by drug acquisition cost, incorrectly implies that delays reduce cost, when in practice they do not. It remains unclear what proportion of the reported RDI represents true dose reduction rather than scheduling adjustments. Assuming full dose intensity for VenI and VenO likely overestimates the amount of drug received in routine practice, creating a cost bias that favours AV. Clinical evidence and expert opinion indicate that VenI and VenO have at least comparable, and possibly greater, toxicity than AV; consequently, lower dose intensity for these regimens is plausible. Applying a consistent approach to RDI across all arms better reflects real-world treatment patterns and avoids introducing unwarranted advantages for any specific regimen.

EAG assumption: VenI and VenO are associated with toxicity profiles that make lower dose intensity more plausible than the 100% assumed by the company. A consistent approach to RDI across all arms provides a more realistic reflection of clinical practice and avoids bias in comparative cost estimates.

- **EAG proposed approach**

Base case: Apply an RDI of 100% for all treatments.

Scenario analysis:

- Apply an RDI of [REDACTED] % for venetoclax in all arms and an RDI of [REDACTED] % for ibrutinib and obinutuzumab (mirroring the value reported for acalabrutinib in AV).
- Alternatively, apply the company's original assumption of 100% RDI for VenI and VenO and [REDACTED] % for acalabrutinib and [REDACTED] % for venetoclax

4.2.4.3 EAG Concern 5: Exclusion of Treat-to-Progression (TTP) Comparators

- **Company's approach and main rationale:** The company excluded Treat-to-progression (TTP) comparators- specifically acalabrutinib and zanubrutinib monotherapy- from the base-case analysis. The company argued that fixed-duration (FD) and TTP regimens are used in different patient groups, with FD therapies viewed as more appropriate for younger and fitter patients, and TTP monotherapies reserved for older or less-fit individuals. The company stated that this position was supported by the company with reference to UK clinical expert opinion and the precedent set in NICE TA931, in which similar distinctions were drawn.
- **EAG critique, assumptions, and justification:** The EAG considers the company's rationale for excluding TTP therapies insufficient. Although FD and TTP regimens differ in intent and duration, both are legitimate first-line options for untreated non-high-risk CLL. In NHS practice, treatment selection is often driven by clinical judgement rather than rigid stratification based solely on age or fitness. Excluding TTP comparators therefore risks failing to capture the breadth of real-world practice. The EAG clinical experts stated that the benefits of AV mean it is likely to broaden the pool of people receiving a dual therapy beyond those currently receiving VenO or VenI, and also that these monotherapies (treat-to-progression) are more

likely to be used in settings with limited access to hospitals offering the necessary supporting services.

EAG assumption: Acalabrutinib and zanubrutinib monotherapies are relevant comparators for untreated, non-high-risk CLL. Ideally, they would be included in the comparative assessment, but suitable data or models are lacking.

- **EAG proposed approach:** Maintain analysis restricted to FD regimens due to the absence of usable data or models enabling robust inclusion of TTP therapies. However, acknowledge that acalabrutinib and zanubrutinib monotherapy should have been considered as comparators.

4.2.5 Treatment effectiveness and extrapolation

The company's model structure meant extrapolation was needed for four time-to-event outcomes: time-to-progression, pre-progression survival, time-to-treatment discontinuation and post-progression survival.

The company assumed equal efficacy between AV and the main comparators VenI and VenO, by applying the same survival curves within the model (namely TTP, PrePS, and PPS) to each of the interventions.

A modified Delphi panel of 22 UK clinical experts conducted by the company reached consensus (80%+) to describe AV as "*clinically comparable*" to VenI and VenO for PFS and OS. However, the EAG notes this wording does not mention "*equivalence*". However, the assumption of equivalence is described as being "*supported*" by feedback from interviews with six UK clinical experts by the company.

The company did not present any functionality to permit a comparison to monotherapies (acalabrutinib and zanubrutinib), despite the EAG requesting this (clarification request B1).

The company's model structure means a form of competing risk modelling is required, where patients have two routes out of the progression-free health state, through death events or disease progression events. The company's approach is to model these outcomes in two separate analyses, censoring people who experience the other type of event. An adjustment is then applied when applying these transition probabilities to account for the other types of transition.

4.2.5.1 Time to progression

Summary of company approach

The company defined TTP as being the time from treatment initiation to disease progression, excluding death, and utilised blinded IRC assessed PFS data from the AMPLIFY trial.

The observed data suggested a low but increasing hazard rate over time (see Figure 20 of CS). The company explored the fit of a regular set of parametric survival models through comparison of information criterion (AIC, BIC) and examination of fit of the survival functions and hazard functions to the Kaplan-Meier estimator and smoothed hazard.

The increasing hazard rate of the Gompertz and generalised gamma models were deemed too pessimistic as they predicted all patients would progress around 8 years. After ruling out the exponential and log-normal models for being too optimistic, the company was left with the log-logistic and gamma model. Based on feedback from their panel of clinical experts (n=6), the company selected the log-logistic model as this predicted that there would be a small group of people with sustained response beyond 20 years, whilst the gamma model did not.

EAG Comment

Ultimately, under the assumption of equivalence, the choice of curve for TTP has minimal influence on the cost-effectiveness outcomes. The long term (20+ years) durability of response to this specific combination remains unknown, and the EAG considers it equally possible that the gamma model may be the most appropriate extrapolation. Without stronger rationale, the EAG maintains the use of the log-logistic model in the EAG base case.

In a scenario analysis, the EAG explores the impact of applying the gamma extrapolation for AV, whilst maintaining the log-logistic extrapolation for VenI and VenO.

4.2.5.2 Pre progression survival

Summary of Company Approach

The company defined pre progression survival (Pre-PS) as the time to death prior to disease progression. This was modelled using data from AMPLIFY, using information for people who died without experiencing disease progression.

The decision to distinguish between causes of death means each estimate was associated with high uncertainty resulting from the low number of events to estimate the hazard rate. Pre-PS was informed by [REDACTED] events from a population of [REDACTED] people.

From the set of typical candidate parametric survival models, the company was largely guided by clinical plausibility as assessed by their panel of experts, but also presented information criterion (AIC and BIC) and considered visual fit.

All models could be considered a good fit and plausible according to AIC and BIC. The exponential model was deemed too pessimistic by the company's experts, with the Gompertz and generalised gamma largely considered too optimistic. Out of the remaining models, the choice has little effect due to the

constraints of background mortality. The company opted for the log-logistic model based on a balance of clinical expert preference and statistical goodness of fit.

Under the company's preferred model, background mortality informs pre-progression mortality at around ■ years.

EAG Comment

Again, under the assumption of equivalence, the choice of model for pre-PS is inconsequential, particularly when combined with the effects of background mortality based on the general population. Given the EAG's preference to increase the model starting age, background mortality has an even stronger influence on this outcome, with the higher hazard rate of background mortality from this older age coming into effect earlier than under the company's preferred assumptions.

The EAG maintains the company's preferred model of log-logistic for pre-PS in the EAG base case.

In a scenario analysis, the EAG explores the impact of using the exponential model for AV whilst using the log-logistic for VenI and VenO. This curve may be considered pessimistic, but it is the only model available to represent any noticeable decrease in relative efficacy and explore the impact on the cost-effectiveness outcomes.

4.2.5.3 Time to treatment discontinuation

Summary of Company Approach

For TTD, the company used the Kaplan-Meier estimator for the AV arm of the AMPLIFY trial. These estimates were applied for 14 cycles for AV. The company also assumed equivalence for the TTD curves; however, assumptions were necessary given that the number of cycles the different drug combinations are typically given for differs from AV. For VenO, the company only used TTD estimates for the first 12 cycles, whilst for VenI, the company estimated the 15th cycle TTD by applying the discontinuation rate between the 13th and 14th cycle onto the 14th cycle TTD estimate to cycle 15 to account for the fact that active treatment is given for 15 cycles. This resulted in an estimate of ■% of people receiving the 15th cycle of VenI.

EAG Comment

The EAG considers the company approach to be reasonable, but heavily reliant on the assumption of equivalence to TTD across the three regimens, which appears to be based on necessity rather than plausibility, as the company concluded that no detailed information was reported for VenI or VenO.

The EAG notes that some information was available for VenI from the CAPTIVATE study, where it is reported that 92% of people completed all cycles of VenI.⁴² For GLOW, it is reported that 77.4% of people completed all cycles of VenI,³⁶ with the lower completion rate to be expected due to the decreased fitness of the patients in GLOW. The population under consideration in this appraisal is somewhere in between the GLOW and CAPTIVATE populations (Table 12). Equivalent information was also available for CLL13 and CLL14, which share similar population differences to AMPLIFY.

The EAG queried the assumption of equal TTD with their clinical experts, and the consensus was that the more tolerable safety profile of AV meant it was expected that more people would complete the full number of cycles, relative to VenI or VenO, which are associated with greater toxicities. It was

concluded that the company's approach likely overestimated the costs of the comparators, introducing bias in favour of AV.

Table 24: Treatment completion rates across relevant trials

Trial name	Completion rate
AMPLIFY (AV)	
CLL13 (VenO) ²⁹⁻³²	214/229 (93.4%)
CLL14 (VenO) ³³⁻³⁵	165/216 (76.4%)
GLOW (VenI) ³⁶⁻³⁸	82/106 (77.4%)
CAPTIVATE FD (VenI) ³⁹⁻⁴²	147/159 (92.5%)

To improve on the company's approach and obtain a more balanced approach to modelling duration of treatment, the EAG utilises the completion rate information available for all three first line regimens. For VenI, for example, the EAG takes the midpoint of two reported values for treatment completion at 84.7% after 15 cycles. The EAG assumes a linearly decreasing time on treatment to estimate proportions for each cycle up to cycle 15.

For VenO and AV, the EAG undertake the same approach, based on the reported trial information (*see section 4.2.4.1*).

4.2.5.4 Post-progression survival

Summary of company approach

For the modelling of transition probabilities for survival from the post-progression health state, the company first considered the relevant

information from the AMPLIFY trial for people receiving AV. However, the low number of events and people at risk (■ and ■ respectively), meant these data were not suited for extrapolation purposes.

The company identified the ASCEND trial as a suitable source to provide information on survival outcomes for people who had progressed following first line treatment. The trial investigated acalabrutinib monotherapy for relapsed/refractory CLL, and the company considered that the acalabrutinib arm would be suitable to represent BTKi monotherapies generally, which are the most common subsequent treatment.

The company applied a regular set of parametric models and considered goodness of fit and plausibility of the extrapolations. The company selected the exponential model

The same post-progression survival transition probabilities were assumed for VenI and VenO (i.e. equivalency was assumed). This assumption is reasonable but has some uncertainty, as it is possible that subsequent BTKi efficacy may be linked to whether BTKis were used in the first line setting.

EAG Comment

The EAG accepts that company's approach is broadly adequate for modelling purposes and maintains it in the EAG base case. Given the uncertainty around relative efficacy, the EAG explores applying the slightly more pessimistic gamma extrapolation for AV, whilst maintaining the exponential scenario for the comparators.

4.2.6 Health-related quality of life

The company provides two alternative sources to inform the health-related quality of life values used in the model: 1. Data from the AMPLIFY trial, and 2. Values informed by the Kosmas et al. (2015)⁵⁷ study, which was identified as

part of the SLR (conducted by the company). The company reports that EQ-5D-5L data were collected in the AMPLIFY trial at each treatment cycle during the treatment phase and each follow-up visit during the post-treatment phase. As recommended by NICE these data were mapped from 5L to 3L using the Hernandez-Alava et al. ⁵³ mapping algorithm.

Table 25: HSUVs from the AMPLIFY trial generated using the MMRM analysis with treatment progression by IRC status as fixed effects (obtained from CS, Section 3.4.1)

Treatment	PF utility value (95% CI)	PD utility value (95% CI)
AV		
AVO		
FCR/BR		

Abbreviations: PD, progressive disease; PF; progression free; CI, confidence interval; HSUV: health state utility value;

The company reports that an SLR to identify studies reporting utility data in patients with CLL was conducted but only one study was found to be of interest - Kosmas et al. (2015) ⁵⁷. The company reports that the values in Kosmas et al. (2015) have been used in several prior economic evaluations identified in the SLR, as well as other NICE evaluations in untreated CLL (TA663 [VenO for untreated CLL]). The utility values reported in Kosmas et al. (2015) and utilized in the economic model as a scenario are shown in the table below:

Table 26: HSUVs reported by Kosmas *et al.* (2015) ⁵⁷ (obtained from CS, Section 3.4.3)

Health state	Mean HSUV	Relative difference compared to PF on-treatment
PF on-treatment (oral treatment)	0.71	-
PF on-treatment (IV treatment)	0.67	-6%
PF off-treatment	0.82	15%
PD on-treatment	0.55	-23%
PD off-treatment	0.59	-16%

Abbreviations: HSUV: health state utility value; IV: intravenous; PD: progressed disease; PF: progression-free.

The company stated that in the base case analysis, the utility value for the PF health state was informed by the AMPLIFY trial. The company examined the possibility that PF patients on and off treatment would have different utility values by referencing the increase in utility off-treatment reported by Kosmas et al (2015), however this approach resulted in an over estimation of the PF off-treatment value, and thus it was assumed that PF patients and on and off-treatment would have the same utility values. However, an adjustment was included for patients receiving IV treatment, based on the decrement reported by Kosmas et al (2015) for PF patients receiving oral or IV treatments.

As pointed out by the company, disease progression is associated with worsening disease-related symptoms negatively impacting HRQoL. Consequently, for the PD health state in the base case, as AMPLIFY showed no disutility associated with progression, the company applied the HSUV decrement for PD versus PF informed by Kosmas to the PF HSUV value from the AMPLIFY trial.

Within the model the disease related health state utility values are scaled using the age-related utility value of the general population to ensure that the disease related values do not exceed those of the general population. This used a formula to calculate the age-related utility decrement for each age beyond the starting age applied in the model (59.90 years) described by the company in response to a clarification question as

$$\text{"Decrement"} = U(\text{age}) / (U(\text{base}))$$

The base HSUV values used in the base case economic analysis are shown in the table below:

Table 27: Summary of HSUVs used in the economic analysis (obtained from CS, Section 3.4.5)

Health state	Base case HSUVs (SE)	Source	Justification
PF on-treatment (oral treatment)	[REDACTED]	AMPLIFY trial (AstraZeneca 2024 AMPLIFY CSR)	AMPLIFY trial used for consistency with patient population and efficacy inputs
PF on-treatment (IV treatment)	[REDACTED]	AMPLIFY trial; Kosmas <i>et al.</i> (2015) ⁵⁷ (AstraZeneca 2024 AMPLIFY CSR)	Decrement associated with IV versus oral treatment applied, in line with accepted approach in previous NICE CLL evaluations ^{15, 58}
PF off-treatment	[REDACTED]	AMPLIFY trial (AstraZeneca 2024 AMPLIFY CSR)	AMPLIFY trial used for consistency with patient population and efficacy inputs
PD on-treatment	[REDACTED]	AMPLIFY trial; Kosmas <i>et al.</i> (2015) ⁵⁷ (AstraZeneca 2024 AMPLIFY CSR)	PD HSUV from AMPLIFY trial lacked face validity. Decrement associated with progression was applied to PF value, in line with accepted approach in previous NICE CLL evaluations ^{15, 59}
PD off-treatment	[REDACTED]	AMPLIFY trial; Kosmas <i>et al.</i> (2015) ⁵⁷ (AstraZeneca 2024 AMPLIFY CSR)	

AE disutility values were adopted in the economic analysis sourced from the literature and multiplied by the anticipated duration of each AE to obtain a decrement that was used to calculate the total disutility for each AE. The company assumed that all AEs would occur during the first four weeks of treatment and so the utility decrements were applied in the first model cycle of the analysis. Scenario analysis examined the impact of excluding AE disutilities. The disutility values along with their durations are shown in the table below. The company predominately used TA891 (Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia), making similar assumptions to those in TA891 in the case of absence of information.

Table 28: Summary of AEs disutilities included in the economic analysis (obtained from CS, Section 3.4.4)

AE	Disutility	Duration (days)	Source of disutility value and duration
Anaemia	−0.09	23.21	TA487 (sourced from TA891) ¹⁵
Atrial fibrillation	−0.22	14	TA891 (assumed to be the same as highest disutility [infection]) ¹⁵
Cardiac disorders	−0.22	14.00	TA891 (assumed to be the same as highest disutility [infection]) ¹⁵
Diarrhoea	−0.2	3	<u>Disutility:</u> TA359 (sourced from TA891) <u>Duration:</u> TA403 (sourced from TA891) ¹⁵
Febrile neutropenia	−0.16	15.09	TA487 (sourced from TA891) ¹⁵
Hypertension	−0.02	21	<u>Disutility:</u> Wehler <i>et al.</i> 2018 ⁶⁰ (sourced from TA689) ⁵⁹ <u>Duration:</u> TA931 (assumed) ⁶¹
Hyponatremia	−0.02	21	Assumed the same as hypertension ⁶¹
Infections and infestations	−0.22	14	<u>Disutility:</u> TA487 (sourced from TA891) ¹⁵ <u>Duration:</u> TA891 (assumed) ¹⁵
Infusion-related reaction	−0.2	3.5	TA487 (sourced from TA891) ¹⁵
Malignant neoplasm	−0.22	14	Same approach as TA891 (assumed to be the same as the highest disutility [infection]) ¹⁵
Neutropenia	−0.16	15.09	TA487 (sourced from TA891) ¹⁵
Neutrophil count decreased	−0.16	15.09	TA487 (sourced from TA891) ¹⁵
Thrombocytopenia	−0.11	23.21	TA487 (sourced from TA891) ¹⁵

Abbreviations: AE: adverse event.

4.2.6.1 EAG Concern 6: Plausibility and validity of HSUVs used in the model

- Company's approach and main rationale:** The company derived HSUVs primarily from EQ-5D-5L data collected in AMPLIFY, with measurements taken both during treatment and follow-up. Utilities were estimated through a MMRM. The AMPLIFY post-progression data were sparse and did not demonstrate a clear disutility relative to progression-free states, because of this the company applied the PD–PF decrement from Kosmas et al. (2015) to AMPLIFY PF utilities in the base case. The PF off-treatment values from Kosmas produced utility estimates greater than 1.0 when added to AMPLIFY values, so the

company assumed equal PF utilities for on- and off-treatment states. Additionally, a decrement from Kosmas et al. (2015) was applied to reflect lower quality of life associated with intravenous treatment, consistent with previous NICE appraisals in CLL.

- EAG critique, assumptions, and justification:** The EAG has concerns about the plausibility of the utility values generated from AMPLIFY. The PF on-treatment values exceed age-matched general population norms, which is unlikely to reflect the experience of patients with CLL. There is also a risk of bias when relying on AMPLIFY as the main source of utility estimates, as trial-based quality-of-life improvements observed during early treatment may be transient and may not represent stable health states over time. The assumption of equal PF utilities for on- and off-treatment states is also considered implausible, as off-treatment patients would typically experience improved quality of life once treatment-related toxicity resolves. Although the company provided outputs from the mixed-model analysis, key methodological elements remain unclear, such as the full covariate specification, the covariance structure, and how missing data were handled. Without greater transparency, it is uncertain whether the model appropriately adjusts for relevant baseline factors that influence HRQoL.

EAG assumption: Patients with CLL have lower quality of life than age-matched members of the general population, and modelled HSUVs should not exceed population norms under any circumstance.

- EAG proposed approach**

Base case: Use the HSUVs reported by Kosmas et al. (2015):

Table 29: HSUVs reported by Kosmas et al. (2015)

Health state	Mean HSUV
PF on-treatment (oral treatment)	0.71

PF on-treatment (IV treatment)	0.67
PF off-treatment	0.82
PD on-treatment	0.55
PD off-treatment	0.66

Abbreviations: PF: progression-free; PD: progressed disease; IV: intravenous; HSUV: health state utility value.

Scenario analysis:

- Use AMPLIFY-derived utilities capped at general population utility values for age.
- Apply the company's original AMPLIFY-based approach without capping.

4.2.7 Resources and costs

The company initially conducted an economic SLR in December 2024 that was updated in August 2025 to identify relevant cost and resource use studies in patients with untreated CLL, however no costs from the SLR were utilized within the economic analysis.

As noted by the company, the acquisition costs for the intervention and comparator therapies were calculated based on dosing regimens from the SmPC for each therapy (Table 30). The intervention and comparator acquisition and administration costs included in this economic analysis are presented in Table 31.

Table 30: Intervention and comparator dosing regimens included in the company economic analysis (obtained from CS, section 3.5.1)

Regimen	Drug	Administration method	Dose (mg)	Administrations per treatment cycle (first cycle) ^a	Administrations per treatment cycle (subsequent cycles) ^a	Maximum treatment cycles	RDI (%)	Source
AV	Acalabrutinib	Oral	100	56	56	14		SmPC ⁶² (AstraZeneca 2024 AMPLIFY CSR)
	Venetoclax	Oral	20	7	0	12		
			50	7	0			
			100	7	0			
			200	7	0			
			400	0	28			
VenI	Venetoclax	Oral	20	7	0	12	100	SmPCs ^{63, 64}
			50	7	0			
			100	7	0			
			200	7	0			
			400	0	28			
	Ibrutinib	Oral	420	28	28	15	100	
	VenO	Venetoclax	Oral	20	7	0	12	100
50				7	0			
100				7	0			
200				7	0			
400				0	28			
Obinutuzumab		IV	1,000	3	1	6	100	

^aThe model cycle and treatment cycle for all interventions and comparators is 28 days.

Abbreviations: AV: acalabrutinib with venetoclax; IV: intravenous; RDI: relative dose intensity; SmPC: summary of product characteristics; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 31: Intervention and comparator acquisition and administration costs included in the company economic analysis (obtained from CS, Section 3.5.1)

Regimen	Drug	Drug acquisition costs						Drug administration costs		
		Pack/vial size (mg)	Units per pack/vial	Cost per pack/vial (£)	Drug acquisition cost (first model cycle) (£)	Drug acquisition cost (subsequent model cycles) (£)	Source	Drug administration cost (first model cycle) (£)	Drug administration cost (subsequent model cycles) (£)	Source
AV	Acalabrutinib	100	60				AstraZeneca	0.00	0.00	N/A
	Venetoclax	10	14	59.87	54.83	0.00	BNF 2025 ⁶⁶	0.00	0.00	N/A
		50	7	149.67	137.06	0.00		0.00	0.00	
		100	7	299.34	274.13	0.00		0.00	0.00	
					548.25	0.00		0.00	0.00	
					0.00	4,386.03		0.00	0.00	
VenI	Venetoclax	10	14	59.87	59.87	0.00	BNF 2025 ⁶⁶	0.00	0.00	N/A
		50	7	149.67	149.67	0.00		0.00	0.00	
		100	7	299.34	299.34	0.00		0.00	0.00	
					598.68	0.00		0.00	0.00	
					0.00	4,789.44		0.00	0.00	
	Ibrutinib	420	28	4,292.40	4,292.40	4,292.40	BNF 2025 ⁶⁷	0.00	0.00	N/A
VenO	Venetoclax	10	14	59.87	59.87	0.00	BNF 2025 ⁶⁶	0.00	0.00	N/A
		50	7	149.67	149.67	0.00		0.00	0.00	
		100	7	299.34	299.34	0.00		0.00	0.00	
					598.68	0.00		0.00	0.00	

Regimen	Drug	Drug acquisition costs						Drug administration costs		
		Pack/vial size (mg)	Units per pack/vial	Cost per pack/vial (£)	Drug acquisition cost (first model cycle) (£)	Drug acquisition cost (subsequent model cycles) (£)	Source	Drug administration cost (first model cycle) (£)	Drug administration cost (subsequent model cycles) (£)	Source
					0.00	4,789.44		0.00	0.00	
	Obinutuzumab	1,000	1	3,312.00	9,936.00	3,312.00	BNF 2025 ⁶⁸	1,458.70	430.24	NHS reference costs 2023/24, deliver complex chemotherapy, including prolonged infusional treatment, at first attendance [SB14Z] & deliver subsequent elements of a chemotherapy cycle [SB15Z]

^aAcalabrutinib with-PAS price; list price for all other treatments.

Abbreviations: AV: acalabrutinib with venetoclax; BNF: British National Formulary; N/A: not applicable; NHS: National Health Service; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

4.2.7.1 Subsequent treatment costs

Subsequent treatment costs were applied by the company to patients in the PD health state (on-treatment) as a one-off cost at the time of progression. As noted by the company, due to the immaturity of data from the AMPLIFY trial, the overall proportion of patients who received subsequent treatments in the trial is lower than would be expected in clinical practice. Consequently, the subsequent treatment distributions applied by the company in the base case economic analysis were calculated from the average of individual estimates provided by clinical experts for each treatment arm.

The company provides a scenario analysis using the subsequent treatment distributions from the AMPLIFY trial with treatments not reimbursed by NICE being excluded (Table 32).

Table 32: Subsequent treatment distributions based on AMPLIFY trial (adjusted to exclude treatments not relevant to UK clinical practice) - scenario analysis (obtained from CS, section 3.5.2)

Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with		
	AV	VenI	VenO
Acalabrutinib monotherapy	■	■	■
Ibrutinib monotherapy	■	■	■
Venetoclax monotherapy	■	■	■
Venetoclax with rituximab	■	■	■
Zanubrutinib monotherapy	■	■	■

Abbreviations: AV: acalabrutinib with venetoclax; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab; UK: United Kingdom.

4.2.7.2 EAG Concern 7: Proportions and distribution of subsequent treatments

- Company's approach and main rationale:** The company applied subsequent treatment costs to all patients entering the post-progression (PD) health state, resulting in approximately ■% of patients receiving a second-line regimen. The distribution of subsequent treatments was based on estimates provided by UK clinical experts, with the company assuming that real-world proportions would

be higher than those observed in trial datasets due to trial immaturity. The company also assumed that the sequencing of subsequent therapies does not influence post-progression survival. The resulting distribution assigns substantial proportions of patients to acalabrutinib monotherapy, zanubrutinib monotherapy, and venetoclax-based regimens, with smaller allocations to ibrutinib and venetoclax monotherapy.

Table 33: Subsequent treatment distributions used in the company base case economic analysis based on estimates from UK clinical experts (obtained from CS, section 3.5.2)

Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with		
	AV	VenI	VenO
Acalabrutinib monotherapy	████	████	████
Ibrutinib monotherapy	████	████	████
Venetoclax monotherapy	████	████	████
Venetoclax with rituximab	████	████	████
Zanubrutinib monotherapy	████	████	████

Abbreviations: AV: acalabrutinib with venetoclax; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

- EAG critique, assumptions, and justification:** The EAG considers the company's assumed █████% rate of subsequent therapy uptake to be inconsistent with the trial evidence, which shows notably lower proportions across AMPLIFY (████%), GLOW (7.5%), and CLL14 (18.1%). Feedback from EAG clinical advisers indicated that while the company's assumed proportion is too high, the trial-derived proportions are likely too low due to limited follow-up, suggesting that a balanced, evidence-informed estimate is needed. Applying subsequent therapies from cycle 1 rather than cycle 2 further misaligns with the model structure and should be corrected so that initiation corresponds with the transition into the PD state.

Regarding the distribution of subsequent treatments, EAG clinical advisers raised several concerns. First, ibrutinib initiation is now rare in UK practice and should be assigned a minimal proportion. Second, acalabrutinib is expected to remain the most commonly prescribed second-generation BTK inhibitor due to clinician familiarity, while zanubrutinib use is expected to increase but not exceed that of acalabrutinib. Third, venetoclax monotherapy has been substantially overstated; advisers emphasised that venetoclax-rituximab (VenR) is generally preferred to achieve deeper responses, with venetoclax monotherapy reserved only for frail patients. On this basis, the company's distribution underrepresents VenR and overrepresents monotherapies, likely underestimating subsequent treatment costs.

- **EAG proposed approach**

Base case: Use the midpoint between the trial-reported proportion of patients receiving subsequent therapy (in each arm) and the proportion of patients who progressed to derive the overall proportion receiving subsequent treatment. For the distribution of subsequent treatments, adopt the revised allocation based on EAG clinical adviser feedback.

Table 34: Subsequent treatment distributions used in the EAG base case

Subsequent treatment	% of patients receiving treatment after	Rationale
Acalabrutinib monotherapy	35	Most common 2nd-gen BTKi
Ibrutinib monotherapy	0	Rarely initiated
Venetoclax monotherapy	3	For frail only
Venetoclax with rituximab	37	Preferred for deep response
Zanubrutinib monotherapy	25	Increasing use; complements Acalabrutinib

Scenario analysis:

- Apply the company's original approach without modification.

- Estimate the proportions of all patients who received subsequent treatments based on relayed trials values.

4.2.7.3 Acquisition costs

Acquisition costs for subsequent treatments were calculated based on the dosing regimens from the respective SmPC for each therapy. The costs of subsequent treatment were estimated as a weighted average of the total cost of each subsequent treatment regimen and the distribution of patients estimated to receive each one. The duration of treatment for each subsequent treatment was sourced from the literature and is presented in Table 35, with the acquisition costs shown in Table 36.

Table 35: Dosing regimens for subsequent treatments included in the company economic analysis (obtained from CS, section 3.5.2)

Subsequent treatment	Drug	Administration method	Dose (mg)	Per	Administrations per treatment cycle	Median treatment duration (months)	Source
Acalabrutinib monotherapy	Acalabrutinib	Oral	100	Flat dose	56	39.10	SmPC ⁶² Davids <i>et al.</i> (2024) ⁶⁹
Ibrutinib monotherapy	Ibrutinib	Oral	420	Flat dose	28	41.00	SmPC ⁶⁴ Munir <i>et al.</i> (2019) ⁷⁰
Venetoclax monotherapy	Venetoclax	Oral	20	Flat dose	7	24.84	SmPC ⁶³ Kater <i>et al.</i> (2024) ⁷¹
			50		7		
			100		7		
			200		7		
			400		28		
Venetoclax with rituximab	Venetoclax	Oral	20	Flat dose	7	22.10	SmPC ⁶³ Seymour <i>et al.</i> (2018) ⁷²
			50		7		
			100		7		
			200		7		
			400		28		
	Rituximab	IV	375 ^b	mg/m ²	1	5.52	SmPC ⁷³ Seymour <i>et al.</i> (2018) ⁷²
			500 ^b		1		
Zanubrutinib monotherapy	Zanubrutinib	Oral	160	Flat dose	56	41.20	SmPC ⁷⁴ Brown <i>et al.</i> (2024) ⁷⁵

^aTreatment cycle and model cycle length were 28 days for all subsequent treatments. ^bA dose of 375 mg/m² was used in Cycle 1, then 500mg/m² from Cycle 2 onwards.

Abbreviations: IV: intravenous; SmPC: summary of product characteristics.

Table 36: Acquisition costs for subsequent treatments included in the economic analysis (obtained from CS, section 3.5.2)

Subsequent treatment	Drug	Pack/vial size (mg)	Units per pack/vial	Cost per pack/vial (£)	Total drug acquisition cost (£)	Source
Acalabrutinib monotherapy	Acalabrutinib	100	60	■	■	AstraZeneca
Ibrutinib monotherapy	Ibrutinib	420	28	4,292.40	191,308.82	BNF 2025 ⁶⁷
Venetoclax monotherapy	Venetoclax	10	14	59.87	28,646.84	BNF 2025 ⁶⁶
		50	7	149.67		
		100	7	299.34		
Venetoclax with rituximab	Venetoclax	10	14	59.87	32,968.83	BNF 2025 ⁶⁶
		50	7	149.67		
		100	7	299.34		
	Rituximab	100	2	■		BNF 2025 ⁷⁶
Zanubrutinib monotherapy	Zanubrutinib	80	120	4,928.65	206,021.68	BNF 2025 ⁷⁷

Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; FCR: fludarabine with cyclophosphamide and rituximab

4.2.7.4 Health state follow-up and monitoring costs

The company reports that follow-up and monitoring costs were incorporated in the economic analysis separately for the PF and PD health states and due to a lack of data, were assumed to be the same for patients regardless of being on- or off-treatment. For the base case, follow-up and monitoring costs for both health states were derived using the NICE evaluation for VenI (TA891), adjusted based on clinical expert opinion to better reflect clinical practice. The resulting frequencies were multiplied by current unit costs (Table 37).

Table 37: Follow-up and monitoring – frequency and cost of resource use (obtained from CS, Section 3.5.3)

Resource use	Cost (£)	Source	Frequency of use per model cycle by health state		Source
			PF	PD	
Laboratory tests					
Full blood count	3.10	NHS reference costs 2023/24; DAPS05, Haematology; Weighted average of all unit costs.	0.39	0.92	TA891 and clinical expert feedback ¹⁵
Lactate dehydrogenase	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.16	0.23	
Blood glucose	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.31	0.31	
Bone marrow exam	740.05	NHS reference costs 2023/24; SA33Z, Diagnostic Bone Marrow Extraction.	0.00	0.07	
Biopsy	763.73	NHS reference costs 2023/24; YJ04Z, Core Needle Biopsy of Axillary Lymph Nodes.	0.00	0.08	
Renal – urea electrolytes test	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.30	0.92	
Liver function	1.53	NHS reference costs 2023/24; DAPS04, Clinical biochemistry, Weighted average of all unit costs.	0.30	0.92	
Immunoglobulin blood test	7.74	NHS reference costs 2023/24; DAPS06, Immunology; Weighted average of all unit costs.	0.07	0.15	
Imaging					
Chest X-Ray	83.79	NHS reference costs 2023/24; RD50Z, DEXA Scan; As per TA689.	0.07	0.07	TA891 and clinical expert feedback ¹⁵
CT scan	136.24	NHS reference costs 2023/24; RD27Z, Computerised Tomography Scan of more than Three Areas.	0.04	0.16	
Hospital visits					

Resource use	Cost (£)	Source	Frequency of use per model cycle by health state		Source
			PF	PD	
Haematologist visit	184.09	NHS reference costs 2023/24; Outpatient Care, 303, Clinical haematology, Weighted average of all unit costs.	0.30	0.39	TA891 and clinical expert feedback ¹⁵
Other specialist visit	176.17	NHS reference costs 2023/24; Outpatient Attendances; 370, Medical Oncology Service, 800, Clinical Oncology Service; Weighted average of all units costs.	0.07	0.16	
Community visits					
General practitioner (GP) visit	45.00	PSSRU 2024, Table 9.4.2: Unit costs for a GP, per surgery consultation lasting 10 minutes including direct staff costs with qualification costs.	0.08	0.15	TA891 and clinical expert feedback ¹⁵
Transfusions					
Full blood transfusion	398.79	NHS reference costs 2023/24; Outpatient attendances: 303, Clinical Haematology: SA44A Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over.	0.00	0.07	TA891 and clinical expert feedback ¹⁵
Platelet transfusion	398.79	NHS reference costs 2023/24; Outpatient attendances: 303, Clinical Haematology: SA44A Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over.	0.15	0.08	

Abbreviations: CC: Complication and Comorbidity; CT: computed tomography; GP: general practitioner; NHS: National Health Service; PD: progressed disease; PF: progression-free; PSSRU: Personal Social Services Research Unit

Total follow-up and monitoring costs for the PF and PD health states used by the company in the base case economic analysis are summarised in Table 38.

Table 38: Total health state follow-up and monitoring costs per model cycle (obtained from CS, Section 3.5.3)

Health states	Sub-state	Total cost (£)
PF	On-treatment	148.33
	Off-treatment	
PD	On-treatment	313.85
	Off -treatment	

Abbreviations: PD: progressed disease; PF: progression-free

4.2.7.5 Adverse event management costs

The company also included the costs of managing AEs in the base case economic analysis. Only patients who experienced Grade ≥ 3 TEAEs with an incidence of $\geq 5\%$ in the intervention of interest (i.e., any incidence $< 5\%$ was considered as 0%) were considered. The key clinical trials for AV (AMPLIFY trial), VenI (GLOW trial), and VenO (CLL14 trial) were used as sources of information. It was assumed that the included TEAEs in the analysis required hospitalisation. Costs were estimated based on the weighted average of the individual TEAE costs and the proportion of patients that experienced these TEAEs for each treatment.

Table 39: Incidence of Grade ≥ 3 TEAEs occurring in $\geq 5\%$ of patients for AV, VenI and VenO and the associated hospitalisation costs included in the economic analysis (Obtained from CS, Section 3.5.4)

AE	Proportion of patients (%)			Cost (£)	Source
	AV (AMPLIFY) 21	VenI (GLOW) 36	VenO (CLL14) 34		
Anaemia	0.00	0.00	8.00	603.91	NHS reference costs 2023/24; SA09L, K, Other Red Blood Cell Disorders with CC Score 0-5, Non-Elective Inpatient Short Stay; As per NICE TA931.
Atrial fibrillation	0.00	6.60	0.00	1,333.98	NHS reference costs 2023/24; EB07A, B, C, D, E, Arrhythmia or Conduction Disorders; Weighted average of all unit costs.

AE	Proportion of patients (%)			Cost (£)	Source
	AV (AMPLIFY) 21	VenI (GLOW) 36	VenO (CLL14) 34		
Cardiac disorders	0.00	0.00	6.10	2,772.36	NHS reference cost 2023/24; EB03A, B, C, D, E; Heart Failure or Shock; Weighted average of all unit costs.
Diarrhoea	0.00	10.38	0.00	509.69	NHS reference costs 2023/24; FD10M; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; Non-elective inpatient short stay.
Febrile neutropenia	0.00	0.00	5.20	2,522.56	NHS reference costs 2023/24; SA35A, B, C, D, E, Agranulocytosis, Non-elective inpatient short stay and long stay; as per NICE TA931.
Hypertension	0.00	7.55	0.00	404.67	NHS reference costs 2023/24; EB04Z, Hypertension, Non-elective inpatient short stay; As per NICE TA931.
Hyponatremia	■	5.66	0.00	419.47	NHS reference costs 2023/24; KC04B, Inborn Errors of Metabolism with CC Score 0-2, Non-elective inpatient short stay; As per NICE TA931.
Infections and infestations	■	16.98	19.40	1,937.90	NHS reference costs 2023/24; WJ03A, B, C, D, E, F, G, Standard Infectious Diseases; Weighted average of all unit costs.
Infusion-related reaction	0.00	0.00	9.00	600.40	NHS reference costs 2023/24; JD07K; Skin Disorders without Interventions, with CC Score 0-1; Weighted average of all unit costs.
Malignant neoplasm	■	0.00	7.00	3,477.25	NHS reference costs 2023/24; WH14A, B,

AE	Proportion of patients (%)			Cost (£)	Source
	AV (AMPLIFY) 21	VenI (GLOW) 36	VenO (CLL14) 34		
					C, D, Other or Unspecified Neoplasm; Weighted average of all unit costs.
Neutropenia	26.80	34.91	52.80	695.84	NHS reference costs 2023/24; SA35A, B, C, D, E, Agranulocytosis, Non-elective inpatient short stay; As per NICE TA931.
Neutrophil count decreased	5.50	0.00	0.00	695.84	Assumed same as neutropenia.
Thrombocytopenia	5.50	0.00	0.00	752.52	NHS reference costs 2023/24; SA12G, H, J, K, Thrombocytopenia, Non-elective inpatient short stay; As per NICE TA931.

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; NHS: National Health Service; TEAE: treatment-emergent adverse event; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.
[Miscellaneous unit costs and resource use](#)

End-of-life costs

The company implemented end-of-life costs as a one-off cost for patients who transition to the death state. This is implemented in the model cycle before death. The cost of death was informed by the Health and Social Care 2024 manual (£11,278.00).

TLS management cost

The cost of TLS management an AE associated with venetoclax treatment was included by the company as a TLS management cost as a one-time cost of £2,612.40 informed by the NICE TA561.

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 explores decision modifiers, including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost-effectiveness results

5.1.1 Company's deterministic base case

The company reports both deterministic and probabilistic results as the base case. No severity modifier is incorporated into the analysis, with the company providing justification for this approach (see section 3.6 of the submission and *section 5.3* below). In the original submission, the company provided the deterministic base case results (Table 40). As part of the clarification process, the model was updated, and the final deterministic results are shown in Table 41 below, and indicate that AV dominates, being [REDACTED] costly and [REDACTED] effective in terms of QALYs gained than both VenI and VenO.

The company's probabilistic base case cost-effectiveness results are aligned with the deterministic results, again showing AV dominating VenI and VenO being [REDACTED] costly and [REDACTED] effective in terms of QALYs gained.

Table 40: Company's original submission deterministic base-case cost-effectiveness results - acalabrutinib with PAS price (Obtained from original CS, Section 3.10.1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) ^a	NMB at £30,000/QALY
AV	■	12.40	■	■	—	■	—	-
VenI	■	12.40	■	■	0.00	■	Dominant	■
VenO	■	12.40	■	■	0.00	■	Dominant	■

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 41: Company's deterministic base-case cost-effectiveness results- acalabrutinib with PAS price (Obtained from clarification response, appendix 1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) ^a	NMB at £30,000/QALY
AV	■	12.592	■	—	—	—	—	—
VenI	■	12.592	■	■	0.000	■	Dominant	■
VenO	■	12.592	■	■	0.000	■	Dominant	■

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

EAG comment

All the results are reported as a pair-wise comparison between either VenI and AV or VenO and AV, including the Net health benefit and net monetary benefit, which are labelled above as incremental NHB and incremental NMB.

5.1.2 Company's Sensitivity Analysis Results

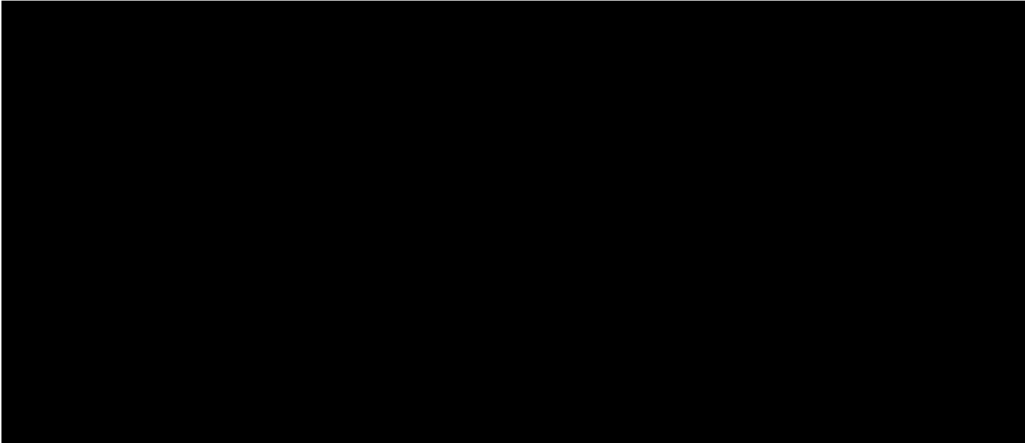
5.1.2.1 Company's Probabilistic Sensitivity Analysis Results

Probabilistic sensitivity analysis (PSA) was undertaken for the outcome of cost per QALY. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to key model input parameters. The PSA results were reported in tabular form (Table 42), and iterations presented on scatterplots.

Table 42: Company's probabilistic base-case cost-effectiveness results pairwise comparison- acalabrutinib with PAS price (Obtained from clarification response, appendix 1)

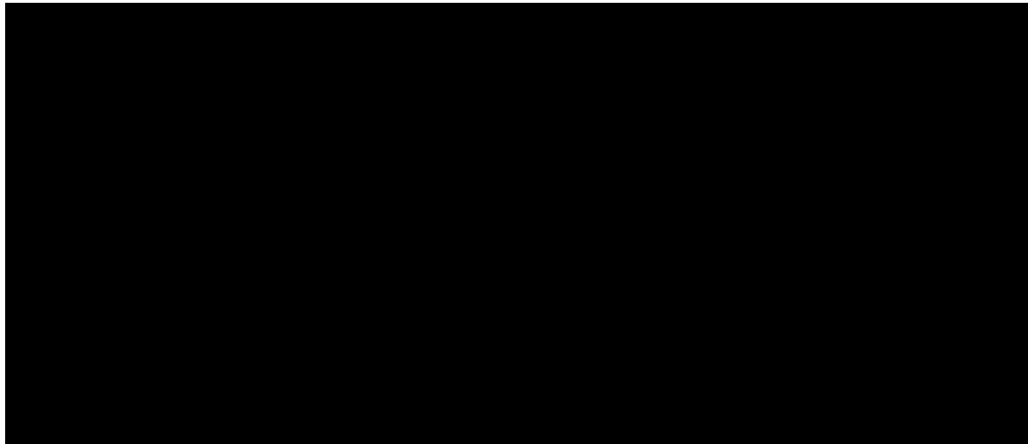
Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) ^a	NMB at £30,000/QALY
AV	████	12.591	████	████	-	████	-	-
VenI	████	12.591	████	████	0.000	████	Dominant	████
VenO	████	12.591	████	████	0.000	████	Dominant	████

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.



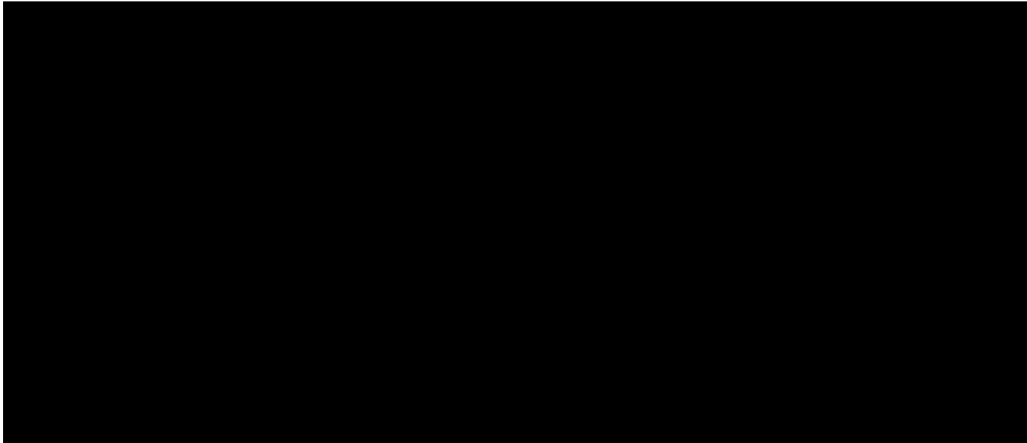
Abbreviations: AV: acalabrutinib with venetoclax; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay; VenI: venetoclax with ibrutinib.

**Figure 4: PSA Scatterplot for AV versus VenI (acalabrutinib with PAS price)
(Obtained from clarification response, appendix 1)**



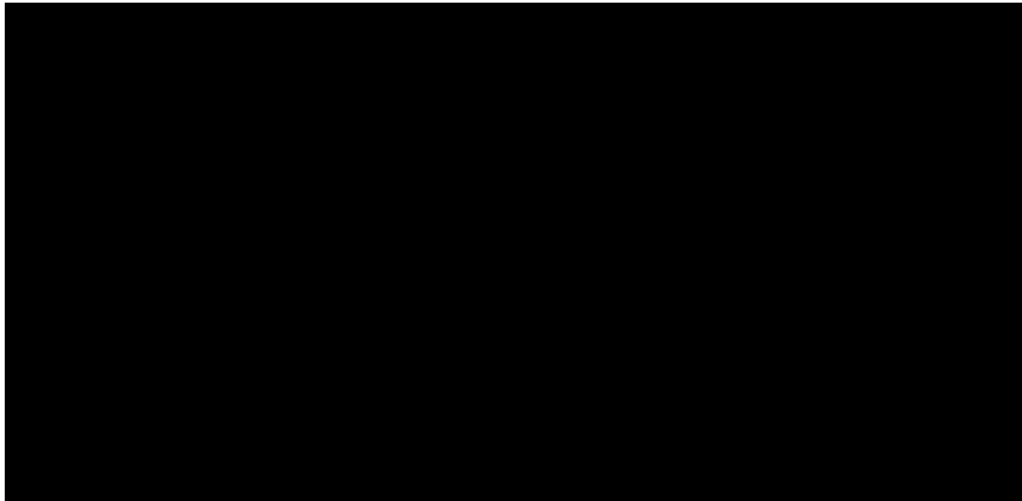
Abbreviations: AV: acalabrutinib with venetoclax; QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay; VenI: venetoclax with ibrutinib.

**Figure 5: Scatterplot of PSA iterations AV vs. VenO (acalabrutinib with PAS price)
(Obtained from clarification response, appendix 1)**



Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenI: venetoclax with ibrutinib.

Figure 6: Cost-effectiveness acceptability curve AV vs. VenI (Obtained from clarification response, appendix 1)



Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenO: venetoclax with obinutuzumab.

Figure 7: Cost-effectiveness acceptability curve AV vs. VenI (Obtained from clarification response, appendix 1)

EAG comment

As part of the PSA the survival curves for all three interventions are set to be equal in the model, because as noted by the company, an assumption that they are equal can be made. While it may be acceptable to set them equal in the deterministic analysis, it cannot be said that the survival curves will always be equal across all iterations of the PSA. Thus, it is necessary to describe the survival curves for each intervention separately, so that they can vary independently and the true impact of this independence be reflected in the results of the PSA.

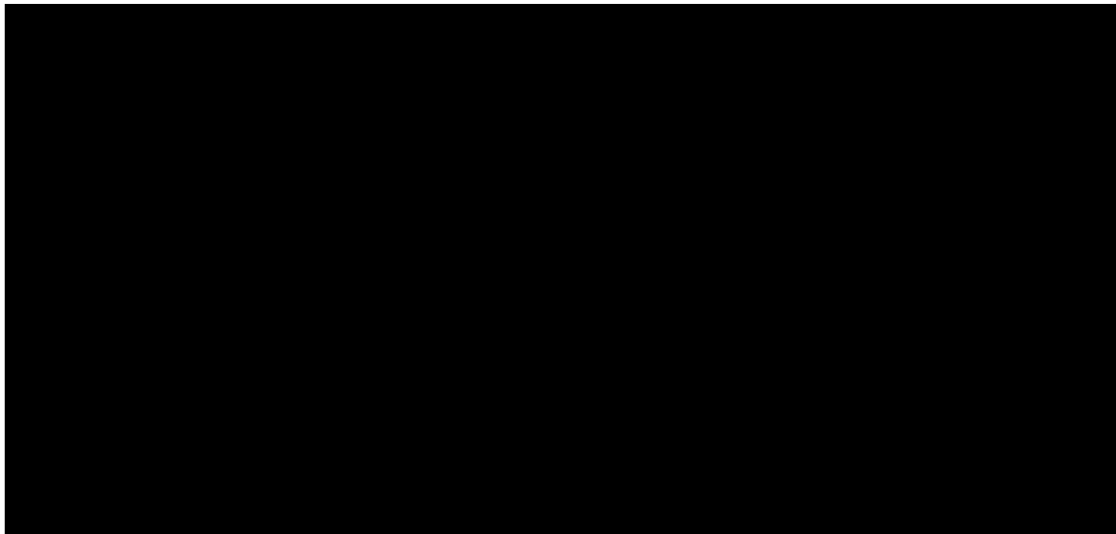
5.1.2.2 Company's deterministic sensitivity analysis

As reported by the company, deterministic sensitivity analysis (DSA) was undertaken to explore the impact of varying key model parameter values by +/- 10% on the NMB for each comparison. A tornado diagram showing the key drivers of the DSA in the base case economic analysis of AV versus VenI, and versus VenO, was presented, where a WTP of £30,000 per QALY was assumed. These tornado diagrams are shown in the figures below.

In both cases the company deterministic sensitivity analysis found that the most influential drivers in the base case economic analysis versus VenI and versus VenO were

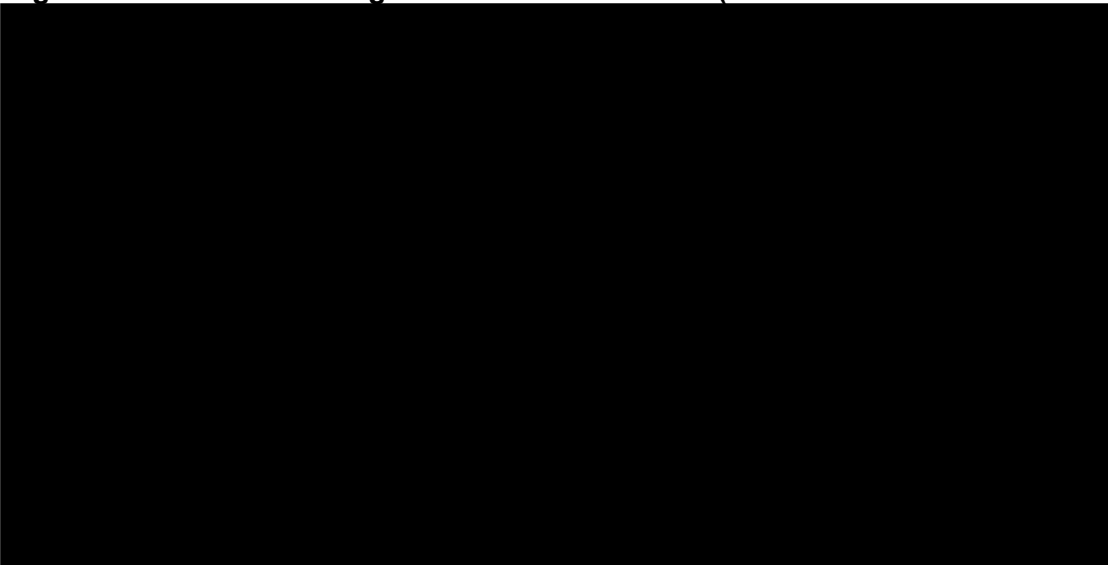
[REDACTED]

[REDACTED]



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; WTP: willingness-to-pay.

Figure 8: DSA tornado diagram for AV versus VenI (acalabrutinib with-PAS



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenO: venetoclax with obinutuzumab; WTP: willingness-to-pay.

Figure 9: DSA tornado diagram for AV versus VenO (acalabrutinib with-PAS price) using NMB (WTP threshold of £30,000 per QALY) (Obtained from clarification response, appendix 1)

5.1.2.3 Company's scenario analysis

The company conducted scenario analysis for AV vs VenI and AV vs VenO, the results are shown in the tables below. All scenarios found AV to be less

costly and more effective than the comparator with the exception of uncapped utilities and uncapped utility data collected from the AMPLIFY trial, which were found to lead to negative QALYs gained for AV vs VenI. In all cases AV was always the preferred option compared to either VenI or VenO.

Table 43: Scenario analysis results – AV versus VenI (acalabrutinib with-PAS price) (Obtained from clarification response, appendix 1)

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	NMB at £30,000/QALY (£)	ICER (£/QALY) ^a
Base case analysis					Dominant
TTP curve selection (log-logistic distribution)	Alternative TTP curve selection (gamma)				Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gen gamma)				Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gamma)				Dominant
Post-PS curve selection (exponential distribution)	Alternative post-PS curve selection (lognormal)				Dominant
Post-PS curve selection (exponential distribution)	Alternative post-PS curve selection (Weibull)				Dominant
Wastage assumed	Assume no wastage				Dominant
Subsequent treatment distribution based on clinician feedback	Subsequent treatment distributions from AMPLIFY				Dominant
Utility data collected from the AMPLIFY trial	Health state utilities from Kosmas <i>et al.</i> (2015)				Dominant
AE-related disutility applied	No AE-related disutility				Dominant
3.5% discount for costs and benefits	1.5% discount for costs and benefits				Dominant
100% RDI for VenI and VenO, AMPLIFY RDIs for AV	AV RDIs applied to VenI and VenO				Dominant

Uncapped utilities	General population capped utilities				
Uncapped utility data collected from the AMPLIFY trial	Health state utilities from Kosmas <i>et al.</i> (2015); capped by general population capped utilities				

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; incr: incremental; INHB: incremental net health benefit; N/A: not applicable; NMB: net monetary benefit; PAS: patient access scheme; post-PS: post-progression survival; QALY: quality-adjusted life year; WTP: willingness to pay; VenI: venetoclax with ibrutinib.

Table 44: Scenario analysis results – AV versus VenO (acalabrutinib with-PAS price) (Obtained from clarification response, appendix 1)

Base case	Scenario analysis	Incr. costs (£)	Incr. QALYs	NMB at £30,000/QALY (£)	ICER (£/QALY) ^a
Base case analysis					Dominant
TTP curve selection (log-logistic distribution)	Alternative TTP curve selection (gamma)				Dominant
Pre-PS curve selection (log-logistic distribution)	Alternative pre-PS curve selection (gen gamma)				Dominant
Pre-PS (log-logistic distribution)	Alternative pre-PS curve selection (gamma)				Dominant
Post-PS (exponential distribution)	Alternative post-PS curve selection (lognormal)				Dominant
Post-PS (exponential distribution)	Alternative post-PS curve selection (Weibull)				Dominant
Wastage assumed	Assume no wastage				Dominant
Subsequent treatment distribution based on clinician feedback	Subsequent treatment distributions from AMPLIFY				Dominant
Utility data collected	Health state utilities from				Dominant

from the AMPLIFY trial	Kosmas et al. (2015)				
AE-related disutility applied	No AE-related disutility	■	■	■	Dominant
3.5% discount for costs and benefits	1.5% discount for costs and benefits	■	■	■	Dominant
100% RDI for VenI and VenO, AMPLIFY RDIs for AV	AV RDIs applied to VenI and VenO	■	■	■	Dominant
Uncapped utilities	General population capped utilities	■	■	■	Dominant
Uncapped utility data collected from the AMPLIFY trial	Health state utilities from Kosmas et al. (2015); capped by general population capped utilities	■	■	■	Dominant

Abbreviations: AE: adverse event; AV: acalabrutinib with venetoclax; incr: incremental; INHB: incremental net health benefit; N/A: not applicable; NMB: net monetary benefit; PAS: patient access scheme; post-PS: post-progression survival; QALY: quality-adjusted life year; WTP: willingness to pay; VenI: venetoclax with ibrutinib.

5.2 EAG's additional analyses

5.2.1 Company's model validation and face validity check

The company reported that it considered the technical validity and clinical validity of the model. In the case of the technical validity, the company reported that the structure of the economic analysis was fully validated by an independent health economist prior to submission. In addition, quality control checks were conducted including technical cell by cell verification of all input data, calculations, data references, model interface and the Visual Basic used to implement the macros within the model. The results generated by the economic analysis were all checked by the company to ensure accuracy and consistency, and the correct functionality of the sensitivity and scenario analyses was also reviewed. For clinical validation the company reported that it obtained feedback from six UK clinical experts on the structure of the economic analysis obtained through validation exercises conducted between April and July 2025. Moreover, 15 Clinical experts reviewed and validated all key inputs and assumptions that were incorporated into the analysis,

EAG comment

The EAG reviewed the validation activities undertaken by the company and carried out its own independent verification of the economic model. During this process, several technical and structural issues were identified that required clarification and amendment. The EAG identified multiple modelling errors and inconsistencies in the company's submission, including:

- Incorrect implementation of discounting: No discounting was applied in the first two years, and subsequent discounting was applied at cycle-level, which did not comply with NICE requirements (resolved at clarification).
- Errors in time-to-treatment discontinuation (TTD): Venetoclax TTD was modelled incorrectly for AV, the model initiated at Cycle 0 (adding an artificial treatment cycle), and TTD curves were not capped at SmPC-defined treatment durations. This resulted in patients remaining on

treatment beyond permitted limits and inflated life-years and QALYs (corrected after clarification).

- Errors in the PSA implementation: The original PSA produced implausible survival extrapolations for the TTP, PrePS, and PPS curves. A corrected PSA with maximum 10,000 iterations was subsequently provided.
- Insufficient acknowledgement of the potential uncertainty associated with the equal-efficacy assumption: All TTP, PrePS and PPS curves referenced the same source calculations for both the deterministic and probabilistic analyses, preventing any variation in the curves between the interventions when running the PSA iterations. The EAG required these curves to vary independently within the PSA.

Additional concerns were raised based on model assumptions reviewed against company preferred inputs, including:

- Use of a starting age of 59.9 years rather than a more representative 71 years, which likely biases results in favour of longer survival gains.
- Use of unequal relative dose intensities across treatments, rather than applying a consistent 100% value as preferred by the EAG.
- Higher treatment completion proportions applied by the company compared with more conservative values preferred by the EAG.
- HSUVs for key health states appeared optimistic relative to alternative values applied by the EAG.
- Subsequent treatment was applied to almost all patients entering progressive disease, whereas the EAG used a more cautious proportion and adjusted initiation timing.

Each issue was raised with the company, and revised versions of the model were provided. The EAG reviewed the amended implementation and

confirmed that the previously identified errors had been addressed. Additional discussions were held with the team (including health economists, statistician, clinical reviewers) and the EAG clinical advisers to validate whether the revised assumptions and technical corrections were appropriate.

5.2.2 EAG's exploratory analyses using (preferred assumptions) company's base case

Table 45 highlights where the EAG considered more technically credible or evidence-based inputs might be used in the company's base case. Several of the company's assumptions introduced bias, either by relying on inputs that did not reflect the clinical data or by using modelling choices that appeared to inflate treatment benefit and mooted uncertainty. The EAG had concerns over the handling of baseline characteristics, treatment exposure, health-state utilities, subsequent treatments, survival modelling, and discounting. Some errors stemmed from the structure of the model itself, while others reflected selective or inconsistent application of evidence.

The EAG applied *alternative assumptions* to ensure the economic analysis reflected observed data, accepted modelling standards *as closely as possible*. Each *area of concern together* with the EAG's preferred approach and the relevant report sections, is presented in Table 45.

Table 45: Summary of EAG's exploratory analyses

Row	Variable	Company’s preferred approach			EAG’s preferred approach			Section in EAG report	
1	Starting age using in the model	59.9 years			71 years			Section 4.2.3.1	
2	Relative Dose Intensity (RDI)	█% for acalabrutinib, █% for venetoclax; RDI for VenI and VenO assumed 100%			Apply an RDI of 100% for all treatments			Section 4.2.4.2	
3	Proportion of Patients Completing Treatment	Regimen	Drugs	Completion (%)	Regimen	Drugs	Completion (%)	Section 4.2.4.1	
		Acalabrutinib + venetoclax	Acalabrutinib	█	Acalabrutinib + venetoclax	Acalabrutinib	█		
			Venetoclax	█		Venetoclax	█		
		Ibrutinib + venetoclax	Ibrutinib	█	Ibrutinib + venetoclax	Ibrutinib	85.0%		
			Venetoclax	█		Venetoclax	85.0%		
		Venetoclax + obinutuzumab	Obinutuzumab	█	Venetoclax + obinutuzumab	Obinutuzumab	84.9%		
			Venetoclax	█		Venetoclax	84.9%		
4	HSUVs Used in the Model	Health state		Base case HSUVs (SE)	Health state		Base case HSUVs (SE)	Section 4.2.6.1	
		PF on-treatment (oral treatment)		█	PF on-treatment (oral treatment)		0.71		
		PF on-treatment (IV treatment)		█	PF on-treatment (IV treatment)		0.67		
		PF off-treatment		█	PF off-treatment		0.82		
		PD on-treatment		█	PD on-treatment		0.55		
		PD off-treatment		█	PD off-treatment		0.66		

Row	Variable	Company's preferred approach	EAG's preferred approach	Section in EAG report																																													
5	Proportions and distribution of subsequent treatments	Applied to all patients progressing to PD (≈████%) <table><tr><th rowspan="2">Subsequent treatment</th><th colspan="3">Distribution of patients (%) after receiving first-line therapy with</th></tr><tr><th>AV</th><th>VenI</th><th>VenO</th></tr><tr><td>Acalabrutinib monotherapy</td><td>████</td><td>████</td><td>████</td></tr><tr><td>Ibrutinib monotherapy</td><td>████</td><td>████</td><td>████</td></tr><tr><td>Venetoclax monotherapy</td><td>████</td><td>████</td><td>████</td></tr><tr><td>Venetoclax with rituximab</td><td>████</td><td>████</td><td>████</td></tr><tr><td>Zanubrutinib monotherapy</td><td>████</td><td>████</td><td>████</td></tr></table> Modelling: subsequent treatment initiated from cycle 1.	Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with			AV	VenI	VenO	Acalabrutinib monotherapy	████	████	████	Ibrutinib monotherapy	████	████	████	Venetoclax monotherapy	████	████	████	Venetoclax with rituximab	████	████	████	Zanubrutinib monotherapy	████	████	████	Proportions of all patients who received subsequent treatments (Midpoint between trial value and proportion of patients who progressed) <table><tr><th>AV</th><th>VenI</th><th>VenO</th></tr><tr><td>≈████%</td><td>≈████%</td><td>≈████%</td></tr></table> Distribution of subsequent treatments <table><tr><th>Subsequent treatment</th><th>%</th></tr><tr><td>Acalabrutinib mono</td><td>35</td></tr><tr><td>Ibrutinib mono</td><td>0</td></tr><tr><td>Venetoclax mono</td><td>3</td></tr><tr><td>Ven + Rituximab</td><td>37</td></tr><tr><td>Zanubrutinib mono</td><td>25</td></tr></table> Modelling: subsequent treatment initiated from cycle 2.	AV	VenI	VenO	≈████%	≈████%	≈████%	Subsequent treatment	%	Acalabrutinib mono	35	Ibrutinib mono	0	Venetoclax mono	3	Ven + Rituximab	37	Zanubrutinib mono	25	Section 4.2.7.2
Subsequent treatment	Distribution of patients (%) after receiving first-line therapy with																																																
	AV	VenI	VenO																																														
Acalabrutinib monotherapy	████	████	████																																														
Ibrutinib monotherapy	████	████	████																																														
Venetoclax monotherapy	████	████	████																																														
Venetoclax with rituximab	████	████	████																																														
Zanubrutinib monotherapy	████	████	████																																														
AV	VenI	VenO																																															
≈████%	≈████%	≈████%																																															
Subsequent treatment	%																																																
Acalabrutinib mono	35																																																
Ibrutinib mono	0																																																
Venetoclax mono	3																																																
Ven + Rituximab	37																																																
Zanubrutinib mono	25																																																
6	Discount factor	No discount in the first two years, followed by a per-cycle discount factor	No discount in the first year, followed by an annual discount factor (resolved after clarification)	Section 4.2.2.1																																													
7	Error in modelling TTD beyond treatment duration in the PF health state	Some patients remained on treatment in the PF health state beyond the treatment duration.	No patients remained on treatment in the PF health state beyond treatment duration (resolved after clarification)	Section 4.2.5.3																																													
8	Modelling error in PSA performance due to probabilistic OS parameters	Modelling error in PSA	It was resolved by the company after the clarification stage.	Section 5.1.2.1																																													

Row	Variable	Company's preferred approach	EAG's preferred approach	Section in EAG report
9	The TTP, PrePS, and PPS survival curves for each intervention are assumed to be equal and so the Markov models are implemented in the model such that they refer to the same survival curve calculations.	By referring to the same survival curves calculations the TTP, PrePS, and PPS survival curves are the same for each intervention in the deterministic base case and for every iteration of the PSA, thereby underestimating the uncertainty associated with the assumption of equality.	Maintain the assumption that TTP, PrePS, and PPS curves are the same for each intervention, but allow them to vary independently for each iteration in the PSA analysis.	Section 5.1.2.1

Abbreviations: Acala: acalabrutinib; AV: acalabrutinib plus venetoclax; BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; FD: fixed-duration; GLOW: ibrutinib plus venetoclax Phase III trial; HRQoL: health-related quality of life; HSUV: health-state utility value; ITT: intention-to-treat; IV: intravenous; MMRM: mixed model for repeated measures; OS: overall survival; PD: progressive disease; PF: progression-free; PPS: post-progression survival; PrePS: pre-progression survival; PSA: probabilistic sensitivity analysis; QoL: quality of life; RDI: relative dose intensity; RWE: real-world evidence; SE: standard error; TTP: time to progression; TTD: time to discontinuation; Ven: venetoclax; VenI: ibrutinib plus venetoclax; VenO: venetoclax plus obinutuzumab; VenR: venetoclax plus rituximab; Zanu: zanubrutinib.

Table 46 and Table 47 present the effect of applying the EAG's preferred assumptions to the company's base case. For both comparisons between AV and VenI and VenO, the company's analysis characterises AV as dominant.

The EAG carried out several exploratory analyses to see how changes to key assumptions would affect the cost-effectiveness results. These changes included adjusting the starting age, applying full dose intensity, using alternative assumptions on treatment completion, applying different utility values and revising how subsequent treatments were modelled. Despite these adjustments, AV stayed dominant across all scenarios in both comparisons, although the size of the estimated benefit shifted depending on the assumption tested. The combined scenarios in each comparison showed noticeably [REDACTED], and the differences in QALYs across all analyses [REDACTED].

Table 46: Results of EAG's exploratory analyses using company's base case- AV versus Venl (acalabrutinib with-PAS price)

Changes applied to company's base case**		Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)***	ICER £/QALY
The company's base case (from the version after clarification stage)		████	████	████	Dominant
1	Using 71 years as starting age using in the model	████	████	████	Dominant
2	Apply an RDI of 100% for all treatments	████	████	████	Dominant
3	Using █████%, 85.0%, and 84.9% for AV, VenI, and VenO, respectively, as the proportion of patients completing treatment	████	████	████	Dominant
4	Using HSUVs reported by Kosmas <i>et al.</i> (2015)	████	████	████	Dominant
5	Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	████	████	████	Dominant
Combined 1-5 (EAG's base case)		████	████	████	Dominant

Key: AV: acalabrutinib plus venetoclax; VenI: ibrutinib plus venetoclax; VenO: venetoclax plus obinutuzumab; RDI: relative dose intensity; HSUV: health-state utility value; EAG: Evidence Assessment Group; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit.

*The severity modifier of 1 is applied for all exploratory analyses.

** The technical guidance related to the model changes can be found in the 'EAG-Technical report' worksheet and appendix 6.3 EAG Technical report in this report.

Changes applied to company's base case**		Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)***	ICER £/QALY
The company's base case (from the version after clarification stage)		████	████	████	Dominant
1	Using 71 years as starting age using in the model	████	████	████	Dominant
2	Apply an RDI of 100% for all treatments	████	████	████	Dominant
3	Using █████%, 85.0%, and 84.9% for AV, VenI, and VenO, respectively, as the proportion of patients completing treatment	████	████	████	Dominant
4	Using HSUVs reported by Kosmas <i>et al.</i> (2015)	████	████	████	Dominant
5	Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	████	████	████	Dominant
Combined 1-5 (EAG's base case)		████	████	████	Dominant

*The severity modifier of 1 is applied for all exploratory analyses.

** The technical guidance related to the model changes can be found in the 'EAG-Technical report' worksheet and appendix 6.3 EAG Technical report in this report.

5.2.3 EAG's deterministic and probabilistic base case and sensitivity analyses results

The following tables and figures summarise the EAG base-case cost-effectiveness results for acalabrutinib plus venetoclax (AV), compared with venetoclax plus ibrutinib (VenI) and venetoclax plus obinutuzumab (VenO), using the acalabrutinib PAS price. Deterministic and probabilistic results are presented as pairwise and fully incremental analyses, reporting total and incremental costs, life-years gained (LYG), quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and net monetary benefit (NMB) at a willingness-to-pay (WTP) threshold of £30,000 per QALY.

██████████. NMB converts QALY gains into monetary terms (incremental QALYs multiplied by the WTP threshold minus incremental costs), providing a single outcome measure where higher values indicate better value for money.

AV (at PAS price) is associated with [REDACTED] total costs than VenI in both deterministic and probabilistic analyses. The AV versus VenI PSA scatter plot shows that all samples are located in the [REDACTED] quadrants. The AV versus VenO PSA shows that majority of samples with [REDACTED] incremental costs, located in either the [REDACTED] quadrants.

The tornado plot describing the one-way deterministic sensitivity analysis indicates that subsequent treatment distributions and the progression-free-on-treatment utility parameters have the [REDACTED] impact on the NMB, although none of the parameters caused a change in the conclusions drawn from the analysis (NMB going from positive to negative or vice versa).

Table 48: EAG- Deterministic base case results for AV versus Venl and VenO (acalabrutinib with-PAS price)-pairwise comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs*	ICER (£/QALY) ^a	NMB at £30,000/QALY**
AV	■	10.61	■	-	-	-	-	-
Venl	■	10.61	■	■	-0.001	■	Dominant	■
VenO	■	10.61	■	■	0.000	■	Dominant	■

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

*The severity modifier of 1 is applied for analyses.

Table 49: EAG- Deterministic base case results for AV versus Venl and VenO (acalabrutinib with-PAS price)-Fully incremental analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs*	ICER (£/QALY) ^a	NMB at £30,000/QALY**
AV	■	10.61	■	-	-	-	-	-
VenO	■	10.61	■	■	0.000	■	Dominated	■
Venl	■	10.61	■	■	0.001	■	Dominated	■

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

*The severity modifier of 1 is applied for analyses.

Table 50: EAG- Probabilistic base case results for AV versus Venl and VenO (acalabrutinib with-PAS price)-pairwise comparison

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs*	ICER (£/QALY) ^a	NMB at £30,000/QALY**
AV	■	10.49	■	-	-	-	-	-
Venl	■	10.48	■	■	0.007	■	Dominant	■
VenO	■	10.50	■	■	-0.013	■	Dominant	■

Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

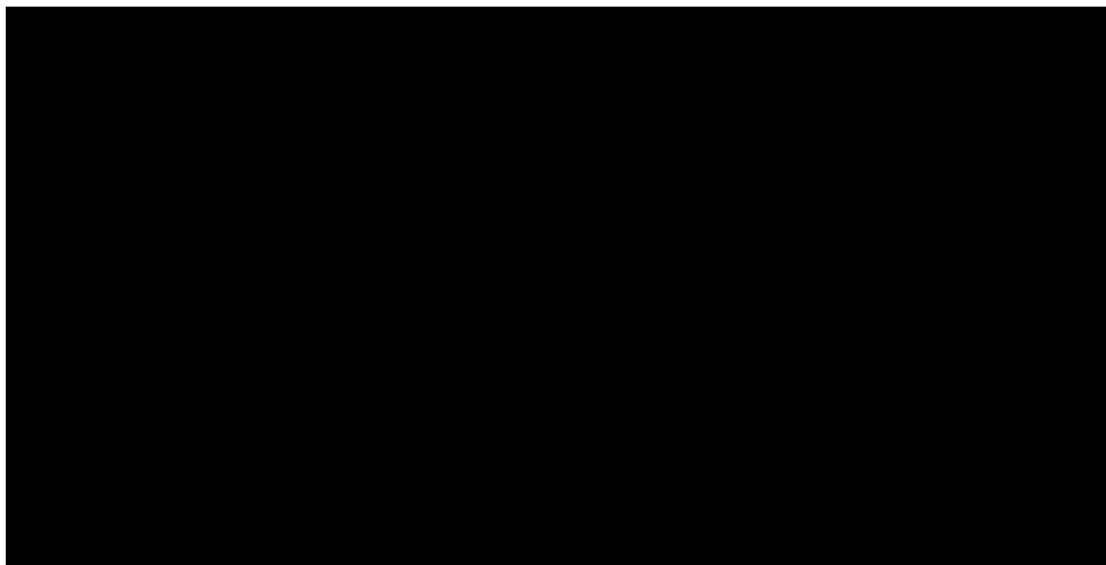
*The severity modifier of 1 is applied for analyses.

Table 51: EAG- Probabilistic base case results for AV versus VenI and VenO (acalabrutinib with-PAS price)-Fully incremental analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs*	ICER (£/QALY) ^a	NMB at £30,000/QALY**
AV	████	10.49	████	-	-	-	-	-
VenO	████	10.50	████	████	0.01	████	Dominated	████
VenI	████	10.48	████	████	-0.01	████	Dominated	████

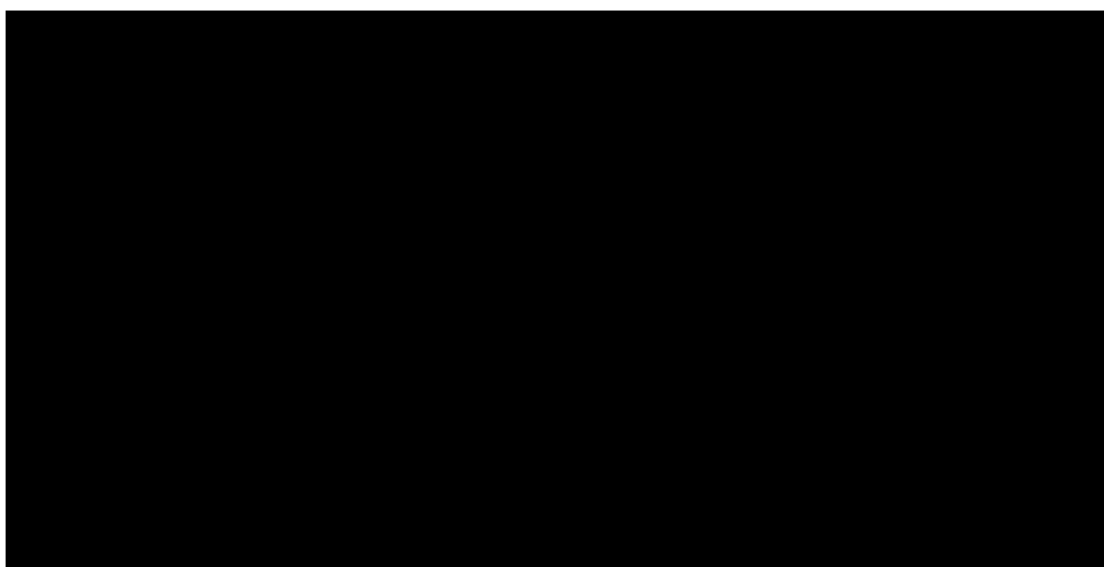
Abbreviations: AV: acalabrutinib with venetoclax; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gained; N/A: not applicable; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

*The severity modifier of 1 is applied for analyses.



Abbreviations: AV: acalabrutinib with venetoclax; CEAC: cost-effectiveness acceptability curve; PAS: patient access scheme; VenO: venetoclax with obinutuzumab.

Figure 12: CEAC for AV versus VenO (acalabrutinib with-PAS price)



Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenI: venetoclax with ibrutinib; WTP: willingness-to-pay.

Figure 13: EAG-NMB (WTP threshold of £30,000 per QALY) DSA tornado diagram for AV versus VenI (acalabrutinib with-PAS price)

Abbreviations: AV: acalabrutinib with venetoclax; DSA: deterministic sensitivity analysis; NmB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life year; VenO: venetoclax with obinutuzumab; WTP: willingness-to-pay.

Figure 14: EAG-NMB (WTP threshold of £30,000 per QALY) DSA tornado diagram for AV versus VenO (acalabrutinib with-PAS price)

5.2.4 Scenario analyses using EAG's preferred assumptions

Table 52 presents a structured set of scenario analyses undertaken using the EAG preferred assumptions for AV compared with VenI and VenO at the PAS price. These analyses assess the robustness of the economic conclusions to key structural and parameter uncertainties within the model. Each scenario varies one assumption relative to the EAG base case, allowing identification of parameters with the greatest potential to influence incremental outcomes. The scenarios cover demographic assumptions (starting age), treatment delivery assumptions (relative dose intensity and completion rates), health-related quality of life inputs (HSUV sources and capping), post-progression treatment pathways, and alternative parametric survival functions for time to progression and survival states.

Table 52: EAG's scenario analyses using EAG's preferred assumptions-AV versus VenI and VenO (acalabrutinib with-PAS price)

Variable/parameter	EAG's base-case assumption	EAG's scenario
Starting age using in the model	71 years	59.9 years
Relative Dose Intensity (RDI)	Apply an RDI of 100% for all treatments	Scenario 1: Apply an RDI of [REDACTED] % for venetoclax in all arms and an RDI of [REDACTED] % for ibrutinib and obinutuzumab Scenario 2: Apply the company's original assumption

Proportion of patients completing treatment	Using █%, 85.0%, and 84.9% for AV, VenI, and VenO, respectively, as the proportion of patients completing treatment	Scenario 1: Apply the company's approach. Scenario 2: Apply AV completion rates across all treatment arms. Scenario 3: Apply observed trial-based rates for VenI (GLOW) (77.40%) and VenO (CLL14) (76.40%).
Utility values	Using HSUVs reported by Kosmas <i>et al.</i> (2015)	Scenario 1: Company's approach (used in the base case) Scenario 2: Company's approach (used in the base case) capped at general population utility values for age.
Proportions and distributions of subsequent treatments	Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	Scenario 1: Apply the company's original approach Scenario 2: Estimate the proportions of all patients who received subsequent treatments based on relayed trials values.
TTP curve	Log-logistic	Scenario: Use Gamma for AV, but maintain log-logistic for comparators.
Pre Progression Survival curve	Log-logistic	Scenario: Use exponential for AV, but maintain log-logistic for comparators
Post Progression Survival	Exponential	Scenario: Use Gamma curve for AV, but maintain using exponential for comparators
TTP, PrePS, and PPS	Log-logistic (TTP), Log-logistic (PrePS), exponential (PPS)	Only in AV arm use exponential (TTP), Gamma (PrePS), Gamma (PPS)

Across the AV versus VenI analyses (Table 53), AV continued to be dominant when compared with VenI, although the size of the cost saving and the incremental QALY gain varied depending on the assumptions applied. Scenarios involving modified assumptions for survival modelling produced the █, with some leading to non-dominant outcomes and high ICERs. In contrast, adjustments relating to treatment completion, utilities and dose intensity produced █ and did not alter the overall conclusion.

For AV versus VenO (Table 53), in most cases, AV remained dominant, although the size of the incremental cost difference and the incremental QALY gain varied across scenarios. As observed previously, scenarios involving revised survival modelling had the █ in ICERs that were considerably █ than those produced under structural or parameter-based

adjustments. Changes relating to treatment completion, utility values and dose assumptions generally produced [REDACTED] in the results and did not alter the overall conclusion.

Table 53: Summary of EAG's scenario analyses using EAG's preferred assumptions- AV versus Venl (acalabrutinib with-PAS price)

EAG's base-case assumption	Scenario N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)**	ICER £/QALY
The EAG's base case (from the version after clarification stage)			██████	██████	██████	Dominant
71 years	1	59.9 years	██████	██████	██████	Dominant
Apply an RDI of 100% for all treatments	2	Scenario 1: Apply an RDI of █████% for venetoclax in all arms and an RDI of █████% for ibrutinib and obinutuzumab	██████	██████	██████	Dominant
	3	Scenario 2: Apply the company's base case approach	██████	██████	██████	Dominant
Using █████%, 85.0%, and 84.9% for AV, Venl, and VenO, respectively, as the proportion of patients completing treatment	4	Scenario 1: Apply the company's base case approach.	██████	██████	██████	Dominant
	5	Scenario 2: Apply AV completion rates across all treatment arms.	██████	██████	██████	Dominant
	6	Scenario 3: Apply observed trial-based rates for Venl (GLOW) (77.40%) and VenO (CLL14) (76.40%).	██████	██████	██████	Dominant
Using HSUVs reported by Kosmas <i>et al.</i> (2015)	7	Scenario 1: Company's approach (used in the base case)	██████	██████	██████	Dominant
	8	Scenario 2: Company's approach (used in the base case) capped at general population utility values for age.	██████	██████	██████	Dominant
Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	9	Scenario 1: Apply the company's original approach	██████	██████	██████	Dominant
	10	Scenario 2: Estimate the proportions of all patients who received subsequent treatments based on the relayed trial values.	██████	██████	██████	Dominant
Log-logistic (TTP curve)	11	Scenario: Use Gamma for AV but maintain log-logistic for comparators.	██████	██████	██████	██████

EAG's base-case assumption	Scenario N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)**	ICER £/QALY
Log-logistic (Pre Progression Survival curve)	12	Scenario: Use exponential for AV, but maintain log-logistic for comparators				Dominant
Exponential (Post Progression Survival)	13	Scenario: Use Gamma curve for AV, but maintain using exponential for comparators				
Log-logistic (TTP), Log-logistic (PrePS), exponential (PPS)	14	Scenario: Only in the AV arm use exponential (TTP), Gamma (PrePS), Gamma (PPS)				

EAG: External Assessment Group; N: Number; QALY/QALYs: Quality-adjusted life-year(s); NMB: Net monetary benefit; WTP: Willingness to pay; ICER: Incremental cost-effectiveness ratio; AV: Acalabrutinib plus venetoclax; VenI: Venetoclax plus ibrutinib; VenO: Venetoclax plus obinutuzumab; RDI: Relative dose intensity; HSUV/HSUVs: Health state utility value(s); TTP: Time to progression; PrePS: Pre-progression survival; PPS: Post-progression survival; GLOW: Clinical trial name; CLL14: Clinical trial name.

*The severity modifier of 1 is applied for all exploratory analyses.

Table 54: Summary of EAG's scenario analyses using EAG's preferred assumptions- AV versus VenO (acalabrutinib with-PAS price)

EAG's base-case assumption	Scenario N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)**	ICER £/QALY
The EAG's base case (from the version after clarification stage)						Dominant
71 years	1	59.9 years				Dominant
Apply an RDI of 100% for all treatments	2	Scenario 1: Apply an RDI of % for venetoclax in all arms and an RDI of % for ibrutinib and obinutuzumab				Dominant
	3	Scenario 2: Apply the company's base case approach				Dominant
Using %, 85.0%,	4	Scenario 1: Apply the company's base case approach.				Dominant

EAG's base-case assumption	Scenario N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)**	ICER £/QALY
and 84.9% for AV, VenI, and VenO, respectively, as the proportion of patients completing treatment	5	Scenario 2: Apply AV completion rates across all treatment arms.				Dominant
	6	Scenario 3: Apply observed trial-based rates for VenI(GLOW) (77.40%) and VenO(CLL14) (76.40%).				Dominant
Using HSUVs reported by Kosmas <i>et al.</i> (2015)	7	Scenario 1: Company's approach (used in the base case)				Dominant
	8	Scenario 2: Company's approach (used in the base case) capped at general population utility values for age.				Dominant
Proportions of subsequent treatments were taken as the midpoint between the trial values and the proportion of patients who progressed, with the distribution guided by the EAG's clinical advisers.	9	Scenario 1: Apply the company's original approach				Dominant
	10	Scenario 2: Estimate the proportions of all patients who received subsequent treatments based on relayed trials values.				Dominant
Log-logistic (TTP curve)	11	Scenario: Use Gamma for AV, but maintain log-logistic for comparators.				
Log-logistic (Pre Progression Survival curve)	12	Scenario: Use exponential for AV, but maintain log-logistic for comparators				Dominant
Exponential (Post Progression Survival)	13	Scenario: Use Gamma curve for AV, but maintain using exponential for comparators				
Log-logistic (TTP), Log-logistic (PrePS), exponential (PPS)	14	Scenario: Only in AV arm use exponential (TTP), Gamma (PrePS), Gamma(PPS)				

EAG: External Assessment Group; N: Number; QALY/QALYs: Quality-adjusted life-year(s); NMB: Net monetary benefit; WTP: Willingness to pay; ICER: Incremental cost-effectiveness ratio; AV: Acalabrutinib plus venetoclax; VenI: Venetoclax plus ibrutinib; VenO: Venetoclax plus obinutuzumab; RDI: Relative dose intensity; HSUV/HSUVs: Health state utility value(s); TTP: Time to progression; PrePS: Pre-progression survival; PPS: Post-progression survival; GLOW: Clinical trial name; CLL14: Clinical trial name.

EAG's base-case assumption	Scenario N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	NMB at £30,000 (£)**	ICER £/QALY

*The severity modifier of 1 is applied for all exploratory analyses.

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company estimates the expected quality-adjusted life expectancy (QALE) and the total life expectancy for the modelled population, quality-adjusted using UK population norm values for EQ-5D. The company utilises the total discounted QALYs for the current untreated non-high risk CLL in the UK, calculated in the base analysis for AV in this submission. The company concludes that *“as the absolute QALY shortfall and proportional QALY shortfall compared to the population receiving treatment with existing therapies were below the severity modifier threshold...no severity weights were used in the base case economic analysis.”*

The company stated that this approach is supported by the severity modifier weight definitions shown in Table 14, and the values shown in Tables 15 and 16.

Table 55: 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

Table 56: Summary of company's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in the EAG report
Proportion of female patients	36%	Section 3.3.1
Starting age (mean)	59.90 years	Section 3.3.1

Table 57: Summary of QALY shortfall analysis-based on the company's original base case

Comparator	QALE for general population	Total QALYs	Absolute QALY shortfall	Proportional QALY shortfall
VenI	12.46			
VenO				

EAG comment

The absolute QALY shortfall and the proportional QALY shortfall are both well below the threshold at which a severity modifier should be introduced into the analysis (Table 58 and Table 59). The EAG is therefore satisfied with the approach put forward by the company.

Table 58: Summary of EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Proportion of female patients	36%	Section 4.2.3
Starting age (mean)	71 years	Section 4.2.3

Table 59: Summary of QALY shortfall analysis-based on the EAG base case

Comparator	QALE for general population	Total QALYs	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
VenI	8.73				
VenO					

5.3.2 Uncaptured benefits

The company considers that the base-case economic analysis does not fully capture certain patient-centred benefits of AV compared with VenO and VenI. They argue that the all-oral administration of AV provides advantages in terms of patient convenience, avoidance of hospital attendance, reduced exposure to infusion-related risks, and no requirement for nursing or infusion capacity,

which they believe should translate into higher HRQoL gains. Although an IV-related utility decrement is applied for VenO, the company considers this insufficient to reflect the full burden of IV delivery on patients and NHS capacity. The company also stated that AV is associated with a more favourable safety and tolerability profile than VenI and VenO, supported by company-commissioned expert interviews and a modified Delphi panel conducted in 2025. They argue that QALY differences remain minimal because the modelled utility decrements for adverse events are small, and therefore the perceived benefits of better tolerability are not reflected in the final QALY outputs.

EAG comment

From an EAG perspective, these claims are not supported by robust, comparative empirical HRQoL or patient-reported outcome data, and rely mainly on expert opinion sourced through company-led processes, which is subject to potential bias. No alternative validated utility estimates, disutility values, or quantification of the claimed benefits were provided, limiting the ability to incorporate these factors into the model without risking speculative adjustment or double counting. Assertions regarding unmodelled advantage are therefore unsubstantiated, particularly given the very small incremental QALY differences under the equal-efficacy assumption. While the rationale for exploring oral vs IV impact and tolerability differences is reasonable in principle, the evidence presented is insufficient to justify model amendments or to materially influence the economic conclusion without further empirical data.

5.3.3 Health inequalities

No information is provided by the company with respect to health inequalities

5.4 Confidential comparator and subsequent treatment prices

This EAG report is accompanied by a cPAS appendix, which contains analyses using confidential pricing for comparator and subsequent treatments. Details on the affected treatments are provided in Table 60.

Table 60: Details of treatment prices affected in cPAS appendix

Name	Form	Dose per unit	Vial/Pack size	Source
Acalabrutinib	Oral	100	60	PAS
Venetoclax	Oral	10	14	PAS
		50	7	
		100	7	
Ibrutinib	Oral	420	28	PAS
Obinutuzumab	IV	1,000	1	PAS
Rituximab 100mg/10ml	IV	100	2	MPSC
Zanubrutinib	Oral	80	120	PAS

Abbreviations: PAS: Patient access scheme; CAA: Commercial access arrangement; MPSC: medicines procurement supply chain; IV: intravenous

5.5 Conclusions of the cost-effectiveness section

The company submitted a de novo model that largely follows the NICE reference case, but the comparator set is incomplete because licensed and commonly used monotherapies (acalabrutinib and zanubrutinib) were excluded. Clinical advisers considered these relevant, as AV is likely to widen the dual therapy eligible population rather than simply replace VenI or VenO. Without analyses against monotherapies, the submission does not fully answer the scope.

QALYs in the model are driven by assumed treatment duration and adverse event burden. Costs are driven by treatment duration, administration route, adverse events, acquisition prices, and assumptions about how many patients receive subsequent therapies and which drugs are used. The most influential assumptions for the ICER are equal efficacy across all dual therapies, treatment completion and time-on-treatment, and subsequent treatment proportions and mix.

Although the company report internal validation, the EAG identified errors affecting both costs and QALYs, including incorrect discounting, incorrect TTD implementation, PSA error, and suppressed survival uncertainty under the equal efficacy assumption. These were later corrected, but several core assumptions remained optimistic: an unrealistically young starting age, assumptions that inflate VenI and VenO utilisation, optimistic completion rates, utilities beyond plausible norms, and an unrepresentative distribution of subsequent therapies. All bias results in favour of AV.

Using a corrected model and PAS price only for Acalabrutinib and based on the EAG's preferred assumptions, AV [REDACTED]. Fully incremental analysis identifies AV [REDACTED]. Uncertainty remains high because the equal efficacy assumption is weak and contradicted by alternative evidence, and results are sensitive to [REDACTED]. It appears that the AMPLIFY population is also [REDACTED] and [REDACTED] than the NHS population, so [REDACTED].

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7 Appendices

7.1 EAG assessment of risks of bias of the CS systematic review about the scope of the appraisal (modified ROBIS)

Table 61: EAG ROBIS evaluation of the company's SLR

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably no	Although the company outlined eligibility criteria in Section 3.2 of the Appendices and initially aligned with NICE's decision problem, the review introduced post hoc modifications, such as stratifying the population into low- and high-risk groups and restricting the analysis to fixed-duration regimens. These changes were not pre-specified in the protocol and resulted in the exclusion of relevant evidence, including continuous treatment regimens and comparators like zanubrutinib and acalabrutinib monotherapy.
1.2 Were the eligibility criteria appropriate for the review question?	Probably no	
1.3 Were eligibility criteria unambiguous?	Probably no	The rationale for excluding continuous treatments and certain comparators is not clearly defined, and the criteria do not sufficiently explain the basis for stratifying the population or focusing solely on fixed-duration regimens.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably no	It remains unclear whether the restrictions of the study design, particularly those related to conference abstracts, have been adequately articulated. Additionally, post hoc exclusion of comparators by narrowing down the population under evaluation may not have been supported.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably yes	The review applied language restrictions that were not pre-specified in the protocol. However, these exclusions may be justifiable.
Concerns regarding specification of study eligibility criteria	Some concerns	Studies that would have been important and relevant to answering the review question are likely to have been excluded from the review, either due to the lack of pre-specified objectives and eligibility criteria, or because inappropriate restrictions were imposed.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic	Yes	Searches in an appropriate set of bibliographic databases and other sources, were undertaken

sources for published and unpublished reports?		in October 2024 and recently updated in June 2025.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	Abstracts for the most recent two years of relevant conferences were sought and other additional searches undertaken (checking trial registers and the references of 15 identified reviews).
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably yes	Suitable terms, including thesaurus and free text variations, for the broad population (CLL) and the intervention or comparators were included in the bibliographic database searches. A clinical trials filter was appropriately added for MEDLINE and Embase. Searches were suitably broad for retrieving studies for an internationally relevant indirect treatment comparison (ITC). The EAG identified an error in the INAHTA search (combining CLL thesaurus and free-text terms with an 'AND' rather than an 'OR' in lines 1 and 2), which effectively restricted the search to records indexed as CLL. However, the majority of relevant records in this database are likely to still have been retrieved. Additionally, hand-searching of five HTA organisations was reported in the cost-effectiveness SLR searches, which would have helped identify any other HTAs from those organisations (see CS appendix E, tables 28 and 29).
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes	No date or language limits were applied. Case studies were excluded.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Two reviewers independently reviewed titles and abstracts against pre-defined eligibility criteria, resolved discrepancies through consensus, with a third independent reviewer making the final decision if necessary. The same approach was used for full text screening stage
Concerns regarding methods used to identify and/or select studies	No concerns	
3: Data collection and study appraisal sections		
3.1 Were efforts made to minimise error in data collection?	Probably no	Section B.3 of the Appendices document states that two independent reviewers completed the title/abstract and full-text screening. However, the processes for data extraction and risk of bias assessment were not reported and remain unclear.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably no	This may encounter certain challenges, as some studies pertinent to the decision problem and aligned with the eligibility criteria appear to have been excluded without adequate justification.

3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	Section B.5.3 of the Appendices outlines the reported effect estimates and corresponding 95% confidence intervals. However, these results are also presented throughout submission document B and appendices.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes	The company conducted risk of bias assessments using the RoB 2 tool for randomised controlled trials and the JBI checklist for non-randomised studies (Appendices, section B.5.2). However, detailed assessments for each individual study would have been preferable to clarify ambiguities surrounding the decisions made.
3.5 Were efforts made to minimise error in risk of bias assessment?	Probably no	Given the lack of reported information, the possibility of bias remains and cannot be ruled out.
Concerns regarding methods used to collect data and appraise studies	Some concerns	Given the limited information and exclusion of potentially relevant studies, the presence of bias remains a concern and cannot be conclusively dismissed.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	No	Section B.3.1 of the Appendices indicates that Flinn et al. (2019) was included and referenced in Table 8; however, it is absent from Table 10 without justifications. The EAG is not convinced by the exclusion of both continuous comparators (i.e., treatment-to-progression) and TP53 mutation-related studies. These exclusions appear inconsistent with the EMA EPAR Assessment Report Variation (Section 3.7.1), ¹ which states: “ <i>While patients with del(17p) or TP53 mutations were excluded from the AMPLIFY study due to an unsuitable comparator, the efficacy of acalabrutinib and venetoclax in the claimed indication has been characterised in other studies (ELEVATE-TN, CLL14, and SAT NCT03580928). Therefore, beneficial effects of the proposed new treatment regimens may be extrapolated to these patients as well.</i> ”
4.2 Were all predefined analyses followed or departures explained?	Yes	The systematic literature review has followed the guidelines of the Cochrane, NICE, and PRISMA.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes	Regression-based approaches, such as STCs, appear to have been used to mitigate the reduction in effective sample size (CS, Appendix B, Section 2.10).
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Probably no	Homogeneity across trials is reported in Section 2.10.2.1. However, no formal methods (such as forest plots, Cochran’s χ^2 or Q test, τ^2 , or I^2) were used to assess heterogeneity.

4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably no	A sensitivity analysis for the ITC is reported in Appendix section B.5.6. However, a sensitivity analysis assessing all covariates and their impact has not been reported.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably no	The risk of bias was assessed, but its conclusions were not incorporated into the SLR findings. No sensitivity analysis was conducted to evaluate the impact of study-level risk of bias.
Concerns regarding the synthesis and findings	Some concerns	
Risk of bias	Some concerns	

7.2 Summary of comparator studies

The EAG has reproduced and updated Tables 15 and 16 from the CS, section 2.10. Additionally, the most recent follow-up data have been used to report OS and PFS for relevant comparators

Table 62: Study characteristics and key inclusion criteria for the studies included in the company SLR

Study	Study enrolment period	Median follow-up period as of the latest DCO (months)	Latest DCO	Study inclusion criteria					Treatment arm	N
				Cytogenetics	Age	ECOG PS	CIRS	Creatinine clearance (mL/min)		
AMPLIFY Brown et al. (2024) ²¹ (AstraZeneca 2024 AMPLIFY CSR and TLF [Tables, Listings, and Figures]) (Open-label phase III RCT)	2019–24	40.8 (range 0–59)	30th April 2024	Without del(17p) or <i>TP53</i> mutation	≥18	≤2	<6	≥50	AV	291
									AVO	286
									FCR/BR	290
ELEVATE-TN ²⁵⁻²⁷ (Open-label phase III RCT)	2015–17	74.5 (range: 0–89)	3 March 2023	Not restricted	≥65, or ≥18 with comorbidities	≤2	>6	30–69	Acalabrutinib-Obinutuzumab	179
									Acalabrutinib	179
									OC1b	177
CLL13 ²⁹⁻³² (Open-label phase III RCT)	2016–19	63.8 (NR)	February 2024 ⁺	Without del(17p) or <i>TP53</i> mutation	≥18	≤2	<6	≥ 70	FCR/BR	229
									Venetoclax-Rituximab	237
									VenO	229

Study	Study enrolment period	Median follow-up period as of the latest DCO (months)	Latest DCO	Study inclusion criteria					Treatment arm	N
				Cytogenetics	Age	ECOG PS	CIRS	Creatinine clearance (mL/min)		
									Venetoclax-Obinutuzumab-Ibrutinib	231
CLL14 ³³⁻³⁵ (Open-label phase III RCT)	2014–18	76.4 (52.5,80.5)	May 2025 ⁺	Not restricted	≥18	-	>6	<70	VenO	216
									OC1b	216
GLOW ³⁶⁻³⁸ (Open-label phase III RCT)	2018–19	64 (range: NR)	NR	Without del(17p) or TP53 mutation	≥65, or ≥18 with comorbidities	≤2	>6	<70	VenI	106
									OC1b	105
Change ^{78, 79} (Open-label phase III RCT)	2020–24	23.5 (NR-47.5)	January 2024	Without del(17p) or TP53 mutation	≥65, or ≥18 with comorbidities	-	>6	30–69	Acalabrutinib	77
									Rituximab-Chlorambucil	78
CRISTALLO ⁸⁰ (Open-label phase III RCT)	2020–23	32 (NR)	Mar 19, 2024	without del(17p) or TP53 mutations	≥18	-	≤6	≥ 70	VenO	80
									FCR/BR	86
FLAIR ⁸¹⁻⁸³ (Open-label phase III RCT)	2017-2021	62.2	November 2024	Without <i>TP53</i> abnormalities	≥18 to ≤75	WHO ≤2	-	-	VenI (MRD guided)	260
									FCR	263

Study	Study enrolment period	Median follow-up period as of the latest DCO (months)	Latest DCO	Study inclusion criteria					Treatment arm	N
				Cytogenetics	Age	ECOG PS	CIRS	Creatinine clearance (mL/min)		
CAPTIVATE FD ³⁹⁻⁴² (Open-label, phase II single-arm trial)	2016–20	69.0 (range: NR)	NR	Not restricted	≥18 to <70	≤2	-	Adequate renal function	Venl	159
Jain <i>et al.</i> (2019) ^{84, 85} (Open-label, phase II single-arm trial)	2016–18	38.5 (range, 5.6-51.1)	NR	Not restricted	≥65, or ≥18 with >1 high-risk genetic feature	≤2	-	>50	Venl	80
SEQUOIA ⁸⁶⁻⁸⁹ (Open-label phase III RCT)	2017-2019	61.2 months (range 0–78.0)	April 30, 2024	Patients with and without del(17p); del(17p) patients assigned to non-randomized zanubrutinib arm (Group C)	≥65 years, or ≥18 years with comorbidities	≤2	>6 for FCR unsuitability	<70 mL/min (for FCR unsuitability)	Zanubrutinib	241
									Bendamustine + Rituximab	238
									Zanubrutinib (Group C – del(17p))	111

*Study completion date

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; ITC: indirect treatment comparison; OC1b: obinutuzumab with chlorambucil; NR, not reported; RCT; randomised controlled trial; WHO: World Health Organization performance status; Venl: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 63: Baseline characteristics of the studies included in the company's SLR

Study	Treatment arm	N	Age (median)	Age >65 years (%)	Age >75 years (%)	Male sex (%)	ECOG PS 0–1 (%)	ECOG PS 2 (%)	Rai stage III/IV (%)	Bulky disease ≥5cm (%)	CIRS >6 (%)	Creatinine clearance mL/min (median)	Beta-2 microglobulin > 3.5 mg/L (%)	TP53 mutation (%)	Del(17p) (%)	Unmutated IgHV (%)
AMPLIFY Brown et al. (2024) ²¹ (AstraZeneca 2024 AMPLIFY CSR and TLF [Tables	AV	291	61	27.1	■	61.2	90.0	9.6	47.1	38.8	2.1	-	58.1	0.0	0.0	57.4
	AVO	286	61	26.6	■	69.2	95.1	4.9	40.6	35.0	0.3	-	52.8	0.0	0.0	59.1
ELEVATE-TN ²⁵⁻²⁷	Acalabrutinib	179	70	84.4	27.9	62	92.2	7.8	48.6	38.0	11.7	75.0	78.2	10.6	8.9	66.5
CLL13 ²⁹⁻³¹	VenO	229	62	35.8	-	74.7	-	-	40.8	-	-	86.3	59.9	0.0	0.0	57.0
CLL14 ^{33, 34}	VenO	216	72	-	33.3	67.6	87.0	13.0	43.1 ^a	-	86.1	65.2	59.4	11.1	8.5	60.5
GLOW ³⁶⁻³⁸	VenI	106	71	84.9	33.0	55.7	87.7	12.3	57.3	39.0	69.8	66.5	69.8	6.6	0.0	51.9
Change ^{78, 79}	Acalabrutinib	77	64	-	-	55.8	-	-	-	-	-	-	-	0.0	0.0	-
CRISTALLO ⁸⁰	VenO	80	62	33.8	-	68.8	-	-	34.4 ^a	-	0.0	-	-	0.0	0.0	43.7
FLAIR ⁸¹⁻⁸³	VenI (MRD guided)	260	62	31.2	-	71.5	96.1 ^b (WHO)	3.1	41.9 ^a	-	-	83.0	-	0.4	0.0	47.3
CAPTIVATE FD ³⁹⁻⁴²	VenI	159	60	28.0	-	67.0	100.0	-	28.0	30.0	-	-	-	10.0	13.0	56.0
Jain et al. (2019) ^{84, 85}	VenI	80	65	54.0	-	71.0	-	-	51.0	-	-	-	-	14.0	18.0	83.0
SEQUOIA ⁸⁶⁻⁸⁹	Zanubrutinib	241	70	82.0	27.0	64.0	94.0	6.0	29.0 ^a	29.0	-	-	57.0	6.0	1.0	53.0

^aBinet stage C.

^bSummed percentages from reported categories.

^cReported as mean.

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; ITC: indirect treatment comparison; OC1b: obinutuzumab with chlorambucil; RCT: randomised controlled trial; WHO: World Health Organization performance status; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 64: Safety outcomes of the included studies in the company's SLR

Study	Treatment arm ^c	AE of Special Interest ^a									
		Atrial fibrillation (%)	Cardiac event (%)	Anaemia (%)	Infections (%)	Hemorrhage (%)	Major hemorrhage (%)	Hypertension (%)	SPM (%)	Diarrhea	TLS (%)
AMPLIFY (CS, Table 29)	AV (n=291)	0.7	9.3	6.9	50.9	32.3	1.0	4.1	2.7	32.6	0.3
ELEVATE-TN ²⁷	Acalabrutinib (n=179)	8.9	23.5	-	80.4	45.3	5.6	11.2	19.6	42.5 ^a	-
CLL13 ²⁹⁻³²	VenO (n=229)	0.9	1.3**	8.3	10.5***	NR	NR	10.1	5.7	32.9	11.4
CLL14 ³³⁻³⁵	VenO (n=216)	0.5	2.4	16.5	8.9	NR	NR	6.6%	14.2	27.8	0.5
GLOW ³⁶⁻³⁸	VenI (n=106)	14.2	2.8	17.9	12.3	NR	NR	13.2	7.5	50.9	0
ChangeE ^{78, 79}	Acalabrutinib (n=77)	0	3.9	15.6 ^s	81.82 ^s	NR	2.6	0	1.3	15.6 ^s	0
CRISTALLO ^{80, 90}	VenO (n=80)	0	6.49 ^s	16.88 ^s	79.23 ^s	NR	NR	9.09	1.3	35.1	10.4
FLAIR ⁸¹⁻⁸³	VenI (MRD guided) (n=260)	4.8	10.7	10.3	22.2***	NR	1.9	4.8	2.4	23.8	0.4
CAPTIVATE FD ³⁹⁻⁴³	VenI (n=159)	4.4 ^s	18.24 ^s	6.92 ^s	67	NR	2	16	6.3	62	0
Jain et al. (2019) ^{84, 85}	VenI (n=80)	15	NR	NR	NR	NR	NR	14	NR	41	0
SEQUOIA ⁸⁶⁻⁸⁹	Zanubrutinib (n=240)	7.1	15.0	9.2	79.6	52.1	5.0	22.9	12.9	20.8	0

^cITT population

^aWhere AEs of special interest list was not provided, AEs of any Grade has been reported. Longer follow up publications has been preferred. Preference has been as longer follow up, AEs of special interest. Then if not applicable, any AEs of most updated FUP and then if not, Grade 3 and above or serious AEs have been reported.

*AEs with frequency of occurrence >15%

Study	Treatment arm ^c	AE of Special Interest ^a									
		Atrial fibrillation (%)	Cardiac event (%)	Anaemia (%)	Infections (%)	Hemorrhage (%)	Major hemorrhage (%)	Hypertension (%)	SPM (%)	Diarrhea	TLS (%)

^aSum of cardiac arrest, cardiac failure, and cardiac failure congestive

^bTreatment-emergent serious adverse events

%Category includes hypertension and hypotension, each occurring in less than 3% of patients in each group.

^cSum of serious AEs and other adverse events

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; ITC: indirect treatment comparison; OClb: obinutuzumab with chlorambucil; NR, not reported; RCT: randomised controlled trial; WHO: World Health Organization performance status; VenI: venetoclax with ibrutinib; VenO: venetoclax with obinutuzumab.

Table 65: OS and PFS outcomes of the included studies in the company's SLR

Study	Treatment arm	Overall survival	Progression-free survival
AMPLIFY (CS, Table 11-12; CSR TLF, Table 14.2.1.1, 14.2.1.6, and 14.2.6.1)	AV	Median OS: 57.8 54 months (investigator): █ (95% CI, █ 48 months (investigator): █ (95% CI, █ 36 months (investigator): 94.1% (95% CI █ 24 months (investigator): █ (95% CI, █	Median PFS*: Not reached 54 months (investigator): █ (95% CI, █; IRC: █ (95% CI, █ 48 months (investigator): █ (95% CI, █; IRC: █ (95% CI, █ 36 months (investigator): 78.9% (95% CI █ IRC: 76.5% (95% CI, █ 24 months (investigator): █ (95% CI, █; IRC: █ (95% CI, █
ELEVATE-TN ²⁷	Acalabrutinib	Median OS*: Not reached	Median PFS*: Not reached 72 months (investigator): 61.5% (95% CI, 53.4-68.7)

Study	Treatment arm	Overall survival	Progression-free survival
		72 months (investigator): 75.5% (95% CI, 68.1-81.4) 60 months (investigator): 84% (95% CI, NR) 48 months (investigator): 87.6% (95% CI, NR)	60 months (investigator): 72% (95% CI, NR) 48 months (investigator): 77.9% (95% CI, NR)
CLL13 ²⁹⁻³²	VenO	Median OS*: Not reached 60 months (investigator): 93.6% (97.5% CI, NR) 48 months (investigator): 95.1% (97.5% CI, 91.9-98.3)	Median PFS*: Not reached 60 months (investigator): 69.8% (97.5% CI, NR) 48 months PFS rates (investigator): 81.8% (97.5% CI, 75.8-87.8)
CLL14 ³³⁻³⁵	VenO	Median OS*: NR 72 months (investigator): 78.7% (95% CI, NR) 24 months (investigator): 91.8% (95% CI, 88.1-95.5)	Median PFS: 76.2 months 72 months (investigator): 53.1% (95% CI, 45.9-60.3) 24 months (investigator): 88.2% (95% CI, 83.7-92.6)
GLOW ³⁶⁻³⁸	VenI	Median OS*: Not reached 60 months (investigator): 81.6% (95% CI, NR) 42 months (investigator): 87.5% (95% CI, 79.4-92.5) 30 months: NR 24 months: NR	Median PFS*: Not reached 60 months (investigator): 59.9% (95% CI, NR) 42 months (IRC): 74.6% (95% CI, 65.0-82.0) 30 months (IRC): 80.5% (95% CI, NR) 24 months (IRC): 84.4% (95% CI, NR)
ChangeE ^{78, 79}	Acalabrutinib	Median OS*: Not reached	Median PFS*: Not reached 24 months (IRC): 92% (95% CI, NR)
CRISTALLO ^{80, 90}	VenO	NR	Median PFS*: Not reached 24 months: 95.7% (95% CI, NR)
FLAIR ⁸¹⁻⁸³	VenI (MRD guided)	Median OS*: Not reached 60 months (investigator): 96.2% (95% CI, NR) 36 months (investigator): 98.0% (95% CI, 95.2-99.2)	Median PFS*: Not reached 60 months (investigator): 94.2% (95% CI, NR) 36 months (investigator): 97.2% (95% CI, 94.1-98.6)

Study	Treatment arm	Overall survival	Progression-free survival
CAPTIVATE FD ³⁹⁻⁴³	Venl	Median OS*: Not reached 66 months (investigator): 96.1% (95% CI, 91.4-98.2) 48 months (investigator): 98% (95% CI, 94-99) 24 months (investigator): 98% (95% CI, 94-99)	Median PFS*: Not reached 66 months (investigator): 60.2% (95% CI, 51.7 to 67.7) 48 months (investigator): 79% (95% CI, 71-84) 24 months (investigator): 95% (95% CI: 90-97); IRC: 89% (95% CI: 83-93)
Jain et al. (2019) ^{84, 85}	Venl	Median OS*: Not reached 36 months (investigator): 96% (95% CI, 92-100%) 12 months (investigator): 99% (95% CI, 96-100)	Median PFS*: Not reached 36 months (investigator): 93% (95% CI, 88-99%) 12 months (investigator): 98% (95% CI, 94-100)
SEQUOIA ⁸⁶⁻⁸⁹	Zanubrutinib	Median OS*: Not reached 60 months (investigator): 85.8% (95% CI, NR) 24 months (IRC): 94.3% (95% CI, 90.4-96.7)	Median PFS*: Not reached 60 months (investigator): 75.8% (95% CI, NR) 24 months (investigator): 87.0% (95% CI, 79.0-92.1); IRC: 85.5% (95% CI, 80.1-89.6)

*Median OS and PFS has been reported for the latest follow ups.

<ITT population

+Where AEs of special interest list was not provided, AEs of any Grade has been reported. Longer follow up publications has been preferred. Preference has been as longer follow up, AEs of special interest. Then if not applicable, any AEs of most updated FUP and then if not, Grade 3 and above or serious AEs have been reported.

*AEs with frequency of occurrence >15%

**Sum of cardiac arrest, cardiac failure, and cardiac failure congestive

***Treatment-emergent serious adverse events

%Category includes hypertension and hypotension, each occurring in less than 3% of patients in each group.

\$Sum of serious AEs and other adverse events (not including serious)

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CIRS: Cumulative Illness Rating Scale; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group performance status; FCR: fludarabine with cyclophosphamide and rituximab; ITC: indirect treatment comparison; OC1b: obinutuzumab

Study	Treatment arm	Overall survival	Progression-free survival

with chlorambucil; NR, not reported; RCT; randomised controlled trial; WHO: World Health Organization performance status; VenI: venetoclax with ibrutinib; VenO: venetoclax with Obinutuzumab.

7.3 EAG Technical report

Table 66: EAG Technical report

Row	Issue title	Worksheet	cell(s)	Details
1	Starting age	EAG-Results	D42	List with two options : Company base case, EAG base case, name: Starting_age_approach
2	Starting age	EAG-list	C3	71 , name: EAG_starting_age
3	Starting age	Model_Parameters	Z40	IF(Starting_age_approach="EAG base case",EAG_starting_age,59.9)
4	Discrepancies in Relative Dose Intensity (RDI)	Lists	C99	EAG base case
5	Discrepancies in Relative Dose Intensity (RDI)	Lists	D97	MATCH(Model_Parameters!J61,C97:C99,0)
6	Discrepancies in Relative Dose Intensity (RDI)	Treatment costs	L53	
7	Discrepancies in Relative Dose Intensity (RDI)	Treatment costs	L55:L59	
8	Discrepancies in Relative Dose Intensity (RDI)	Treatment costs	L60	
9	Discrepancies in Relative Dose Intensity (RDI)	Treatment costs	L62:L66	
10	Discrepancies in Relative Dose Intensity (RDI)	Treatment costs	L68:L72	
11	Discrepancies in Relative Dose Intensity (RDI)	Treatment costs	L73	
12	Discrepancies in Relative Dose Intensity (RDI)	Model_Parameters	L61	Lists!\$C\$97:\$C\$99

Row	Issue title	Worksheet	cell(s)	Details
13	Proportion of Patients Completing Treatment	EAG-Results		List with 3 options: Company base case, EAG base case, EAG scenario
14	Proportion of Patients Completing Treatment	EAG-list	B8:E15	EAG base case
15	Proportion of Patients Completing Treatment	EAG-list	M8:P15	EAG Scenario
16	Proportion of Patients Completing Treatment	EAG-list	C19:C34	Cycles 1-16
17	Proportion of Patients Completing Treatment	EAG-list	D19:D34	$\text{IF}(\text{C19} \leq \$\text{E\$10}, 100\% - (\text{C19} - 1) * ((100\% - \$\text{D\$10})) / (\$ \text{E\$10} - 1), 0)$
18	Proportion of Patients Completing Treatment	EAG-list	E19:E34	E19 AND E20 =0, E21=D21 ...
19	Proportion of Patients Completing Treatment	EAG-list	F19:F34	$\text{IF}(\text{C19} \leq \$\text{E\$12}, 100\% - (\text{C19} - 1) * ((100\% - \$\text{D\$12})) / (\$ \text{E\$12} - 1), 0)$
20	Proportion of Patients Completing Treatment	EAG-list	G19:G34	G19, G20 AND G21 =0, G22=F22 ...
21	Proportion of Patients Completing Treatment	EAG-list	H19:H34	$\text{IF}(\text{C19} \leq \$\text{E\$14}, 100\% - (\text{C19} - 1) * ((100\% - \$\text{D\$14})) / (\$ \text{E\$14} - 1), 0)$
22	Proportion of Patients Completing Treatment	EAG-list	I19:I34	$\text{IF}(\text{C19} \leq \$\text{E\$15}, 100\% - (\text{C19} - 1) * ((100\% - \$\text{D\$15})) / (\$ \text{E\$15} - 1), 0)$
23	Proportion of Patients Completing Treatment	EAG-list	N19:N34	Cycles 1-16
24	Proportion of Patients Completing Treatment	EAG-list	O19:O34	$\text{IF}(\text{N19} \leq \$\text{P\$10}, 100\% - (\text{N19} - 1) * ((100\% - \$\text{O\$10})) / (\$ \text{P\$10} - 1), 0)$
25	Proportion of Patients Completing Treatment	EAG-list	P19:P34	P19 AND P20 =0, P21=O21 ...
26	Proportion of Patients Completing Treatment	EAG-list	Q19:Q34	$\text{IF}(\text{N19} \leq \$\text{P\$12}, 100\% - (\text{N19} - 1) * ((100\% - \$\text{O\$12})) / (\$ \text{P\$12} - 1), 0)$

Row	Issue title	Worksheet	cell(s)	Details
27	Proportion of Patients Completing Treatment	EAG-list	R19:R34	R19 AND R20, AND R21 =0, R22=Q22 ...
28	Proportion of Patients Completing Treatment	EAG-list	S19:S34	IF(N19<=\$P\$14,100%-(N19-1)*((100%-\$O\$14))/(\$P\$14-1),0)
29	Proportion of Patients Completing Treatment	EAG-list	T19:T34	IF(N19<=\$P\$15,100%-(N19-1)*((100%-\$O\$15))/(\$P\$15-1),0)
30	Proportion of Patients Completing Treatment	Aca_Ven_mode I	Column J	LET(r, ROW()-ROW(\$C\$24)+1, IF(treatment_proportion_approach="company base case", INDEX(AV_TTD, r), IFERROR(IF(treatment_proportion_approach="EAG base case", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$D\$19:\$D\$34), IF(treatment_proportion_approach="EAG scenario", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$O\$19:\$O\$34), 0),), 0)))

Row	Issue title	Worksheet	cell(s)	Details
31	Proportion of Patients Completing Treatment	Aca_Ven_model	Column I	<pre> LET(r, ROW()-ROW(\$C\$24)+1, IF(treatment_proportion_approach="company base case", INDEX(AV_TTD, r), IFERROR(IF(treatment_proportion_approach="EAG base case", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$E\$19:\$E\$34), IF(treatment_proportion_approach="EAG scenario", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$P\$19:\$P\$34), 0)), 0))) </pre>
32	Proportion of Patients Completing Treatment	Aca_Ven_model	Column AR from AR25	<pre> IF(treatment_proportion_approach="company base case",(AD24+AD25)/2, IF(C25>'EAG-list'!\$E\$10,0,(AD24+AD25)/2)) </pre>
33	Proportion of Patients Completing Treatment	Aca_Ven_model	Column AZ24	<pre> IF(treatment_proportion_approach="company base case", AR24*(AcaVen_Aca_txcost_cyc1*\$A24+AcaVen_Ven_txcost_subscyc*\$B24), (AR24*AcaVen_Aca_txcost_cyc1)+(I24*AcaVen_Ven_txcost_subscyc)) </pre>
34	Proportion of Patients Completing Treatment	Aca_Ven_model	Column AZ25	<pre> IF(treatment_proportion_approach="company base case", AR25*(AcaVen_Aca_txcost_subscyc*\$A25+AcaVen_Ven_txcost_subscyc*\$B25), (AR25*AcaVen_Aca_txcost_subscyc)+(I25*AcaVen_Ven_txcost_subscyc)) </pre>

Row	Issue title	Worksheet	cell(s)	Details
35	Proportion of Patients Completing Treatment	Aca_Ven_model	Column AZ26	IF(treatment_proportion_approach="company base case", AR26*(AcaVen_Aca_txcost_subscyc*\$A26+AcaVen_Ven_txcost_cyc1*\$B26), (AR26*AcaVen_Aca_txcost_subscyc)+(I26*AcaVen_Ven_txcost_cyc1))
36	Proportion of Patients Completing Treatment	Aca_Ven_model	Column AZ27 and beyond	IF(treatment_proportion_approach="company base case",AR27*(AcaVen_Aca_txcost_subscyc*\$A27+AcaVen_Ven_txcost_subscyc*\$B27), (AR27*AcaVen_Aca_txcost_subscyc)+(I27*AcaVen_Ven_txcost_subscyc))
37	Proportion of Patients Completing Treatment	Ibru_Ven_model	Column P	IFERROR(IF(treatment_proportion_approach="EAG base case", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$F\$19:\$F\$34), IF(treatment_proportion_approach="EAG scenario", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$Q\$19:\$Q\$34), IF(C24 <= AV_aca_maxadmin, Aca_Ven_model!J24,IF(C24>MAX(\$BB\$10:\$BC\$11),0, P23*(P23/P22))))),0)
38	Proportion of Patients Completing Treatment	Ibru_Ven_model	Column I	IFERROR(IF(treatment_proportion_approach="EAG base case", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$G\$19:\$G\$34), IF(treatment_proportion_approach="EAG scenario", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$R\$19:\$R\$34), IF(C24 <= AV_aca_maxadmin, Aca_Ven_model!J24,IF(C24>MAX(\$BB\$10:\$BC\$11),0, P23*(P23/P22))))),0)
39	Proportion of Patients Completing Treatment	Ibru_Ven_model	Column AX25 and ...	IF(treatment_proportion_approach="company base case", (AJ24+AJ25)/2, IF(C25>'EAG-list'!\$E\$12,0,(AJ24+AJ25)/2))

Row	Issue title	Worksheet	cell(s)	Details
40	Proportion of Patients Completing Treatment	Ibru_Ven_model	BF24	IF(treatment_proportion_approach="company base case", AX24*(IbruVen_ibu_txcost_cyc1*\$A24+IbruVen_Ven_txcost_subscyc*\$B24), (AX24*IbruVen_ibu_txcost_cyc1)+(I24*IbruVen_Ven_txcost_subscyc))
41	Proportion of Patients Completing Treatment	Ibru_Ven_model	BF 25 and bf26	IF(treatment_proportion_approach="company base case", AX25*(IbruVen_ibu_txcost_subscyc*\$A25+IbruVen_Ven_txcost_subscyc*\$B25), (AX25*IbruVen_ibu_txcost_subscyc)+(I25*IbruVen_Ven_txcost_subscyc))
42	Proportion of Patients Completing Treatment	Ibru_Ven_model	BF27	IF(treatment_proportion_approach="company base case", AX27*(IbruVen_ibu_txcost_subscyc*\$A27+IbruVen_Ven_txcost_cyc1*\$B27), (AX27*IbruVen_ibu_txcost_subscyc)+(I27*IbruVen_Ven_txcost_cyc1))
43	Proportion of Patients Completing Treatment	Ibru_Ven_model	BF28 and ...	IF(treatment_proportion_approach="company base case", AX27*(IbruVen_ibu_txcost_subscyc*\$A27+IbruVen_Ven_txcost_cyc1*\$B27), (AX27*IbruVen_ibu_txcost_subscyc)+(IbruVen_Ven_txcost_subscyc))
44	Proportion of Patients Completing Treatment	VenO_model	Column P	IFERROR(IF(treatment_proportion_approach="EAG base case", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$I\$19:\$I\$34), IF(treatment_proportion_approach="EAG scenario", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$T\$19:\$T\$34),IF(C24>MAX(\$BB\$10:\$BC\$11), 0, Aca_Ven_model!I24))),0)
45	Proportion of Patients Completing Treatment	VenO_model	Column I	IFERROR(IF(treatment_proportion_approach="EAG base case", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$H\$19:\$H\$34), IF(treatment_proportion_approach="EAG scenario", XLOOKUP(C24,'EAG-list'!\$C\$19:\$C\$34,'EAG-list'!\$S\$19:\$S\$34),IF(C24>MAX(\$BB\$10:\$BC\$11), 0, Aca_Ven_model!I24))),0)

Row	Issue title	Worksheet	cell(s)	Details			
46	Proportion of Patients Completing Treatment	VenO_model	Column AX25 and ...	IF(treatment_proportion_approach="company base case",(AJ24+AJ25)/2,IF(C25>'EAG-list'!\$E\$15,0,(AJ24+AJ25)/2))			
47	Proportion of Patients Completing Treatment	VenO_model	BF24	IF(treatment_proportion_approach="company base case", AX24*(VenO_ven_txcost_cyc1*\$A24+VenO_Obi_txcost_cyc1*\$B24), (AX24*VenO_ven_txcost_cyc1)+(I24*VenO_Obi_txcost_cyc1))			
48	Proportion of Patients Completing Treatment	VenO_model	BF 25 and ...	IF(treatment_proportion_approach="company base case", AX25*(VenO_ven_txcost_subcyc*\$A25+VenO_Obi_txcost_subcyc*\$B25), (AX25*VenO_ven_txcost_subcyc)+(I25*VenO_Obi_txcost_subcyc))			
49	HSUVs Used in the Model	Utilities	AC18:AC22	Health state		Mean	
				Progression-free on treatment (oral treatment)		0.71	
				Progression-free on treatment (IV treatment)		0.67	
				Progression-free off treatment		0.82	
				Progressed disease on treatment		0.55	
				Progressed disease off treatment		0.66	
50	Proportions and distribution of subsequent treatments	EAG-list	C43:F49	Regimen	% of patients receiving treatment after		
					Acalabrutinib + venetoclax	Ibrutinib + venetoclax	Venetoclax + obinutuzumab
				Acalabrutinib	35.00%	35.00%	35.00%
				Ibrutinib	0.00%	0.00%	0.00%
				Zanubrutinib	3.00%	3.00%	3.00%
				Venetoclax-rituximab	37.00%	37.00%	37.00%

Row	Issue title	Worksheet	cell(s)	Details				
				Venetoclax monotherapy	25.00%	25.00%	25.00%	
51	Proportions and distribution of subsequent treatments	EAG-list	I43:K44	Acalabrutinib + venetoclax	Ibrutinib + venetoclax	Venetoclax + obinutuzumab		
					6.90%	15.30%		
52	Proportions and distribution of subsequent treatments		P44	(Aca_Ven_model!AX22+I44)/2				
53	Proportions and distribution of subsequent treatments		Q44	(Ibru_Ven_model!BD22+J44)/2				
54	Proportions and distribution of subsequent treatments	EAG-list	R44	(VenO_model!BD22+K44)/2				
55	Proportions and distribution of subsequent treatments	Lists	C42	EAG clinical advosers (EAG base case)				
56	Proportions and distribution of subsequent treatments	Lists	D39	MATCH('Subsequent treatment'!F11,Lists!C40:C42,0)				
57	Proportions and distribution of subsequent treatments	Subsequent	F11	LIST: =Lists!\$C\$40:\$C\$42				

Row	Issue title	Worksheet	cell(s)	Details
		treatment		
58	Proportions and distribution of subsequent treatments	Subsequent treatment	E17:E21	CHOOSE(SubsqTx_source,V17:V21,AA17:AA21,'EAG-list'!D45:D49)
59	Proportions and distribution of subsequent treatments	Subsequent treatment	F17:F21	CHOOSE(SubsqTx_source,W17:W21,AB17:AB21,'EAG-list'!E45:E49)
60	Proportions and distribution of subsequent treatments	Subsequent treatment	G17:G21	CHOOSE(SubsqTx_source,X17:X21,AC17:AC21,'EAG-list'!F45:F49)
61	Proportions and distribution of subsequent treatments	EAG-Results	D74	LIST: Company base case, EAG base case, EAG scenario
62	Proportions and distribution of subsequent treatments	Aca_Ven_model	AX24 AND ..	Y24*AC24
63	Proportions and distribution of subsequent treatments	Aca_Ven_model	AX22	SUM(AX24:AX546)
64	Proportions and distribution of subsequent treatments	Aca_Ven_model	BH24 AND ..	(IF(AND(C24=1,OR(Proportion_ST_approach="EAG base case",Proportion_ST_approach="EAG scenario")),0,IF(Proportion_ST_approach="EAG base case",('EAG-list'!\$P\$44/\$AX\$22)*(Y24*AC24)*INDEX(SecondLine_TxCost,MATCH(InterventionA,TxNames_AE_Subsq_Cost,0)),IF(Proportion_ST_approach="EAG scenario",('EAG-list'!\$I\$44/\$AX\$22)*(Y24*AC24)*INDEX(SecondLine_TxCost,MATCH(InterventionA,TxN

Row	Issue title	Worksheet	cell(s)	Details
				ames_AE_Subseq_Cost,0)),(Y24*AC24)*INDEX(SecondLine_TxCost,MATCH(InterventionA,TxNames_AE_Subseq_Cost,0)))))*AY24
65	Proportions and distribution of subsequent treatments	lbru_Ven_model	BD24 AND ...	AE24*AI24
66	Proportions and distribution of subsequent treatments	lbru_Ven_model	BD22	SUM(BD24:BD546)
67	Proportions and distribution of subsequent treatments	lbru_Ven_model	BN24 AND ..	BE24*(IF(AND(C24=1,OR(Proportion_ST_approach="EAG base case",Proportion_ST_approach="EAG scenario")),0,IF(Proportion_ST_approach="EAG base case",('EAG-list'!\$Q\$44/\$BD\$22)*(AE24*AI24)*INDEX(SecondLine_TxCost,MATCH(InterventionA,TxNames_AE_Subseq_Cost,0)),IF(Proportion_ST_approach="EAG scenario",('EAG-list'!\$J\$44/\$BD\$22)*(AE24*AI24)*INDEX(SecondLine_TxCost,MATCH(InterventionA,TxNames_AE_Subseq_Cost,0)),(AE24*AI24)*INDEX(SecondLine_TxCost,MATCH(Compa2,TxNames_AE_Subseq_Cost,0),1))))))
68	Proportions and distribution of subsequent treatments	VenO_model	BD24 AND ...	AE24*AI24
69	Proportions and distribution of subsequent treatments	VenO_model	BD22	SUM(BD24:BD546)

Row	Issue title	Worksheet	cell(s)	Details
70	Proportions and distribution of subsequent treatments	VenO_model	BN24 AND ..	BE24*(IF(AND(C24=1,OR(Proportion_ST_approach="EAG base case",Proportion_ST_approach="EAG scenario")),0,IF(Proportion_ST_approach="EAG base case",('EAG-list'!\$R\$44/\$BD\$22)*(AE24*AI24)*INDEX(SecondLine_TxCost,MATCH(Compas3,TxNames_AE_Subseq_Cost,0),1),IF(Proportion_ST_approach="EAG scenario",('EAG-list'!\$K\$44/\$BD\$22)*(AE24*AI24)*INDEX(SecondLine_TxCost,MATCH(Compas3,TxNames_AE_Subseq_Cost,0),1),(AE24*AI24)*INDEX(SecondLine_TxCost,MATCH(Compas3,TxNames_AE_Subseq_Cost,0),1))))))
71	TTP-Scenario: Use Gamma for AV, but maintain log-logistic for comparators.	EAG-Results	D83	List: Original approach, Gamma for AV --- NAME TTP_scenario
72	TTP-Scenario: Use Gamma for AV, but maintain log-logistic for comparators.	Aca_Ven_model	R24 AND ...	IF(K24:K546<=0,0,-LN(K24:K546))
73	TTP-Scenario: Use Gamma for AV, but maintain log-logistic for comparators.	Aca_Ven_model	K24 AND ...	IF(TTP_scenario="Original approach", Survival_Calc!W60,Survival_Calc!Q60)
74	PrePS-Scenario: Use exponential for AV, but maintain log-logistic for comparators.*	EAG-Results	D88	Original approach, Exponential for AV ---- NAME:PrePS_scenario
75	PrePS-Scenario: Use exponential for AV, but maintain log-logistic for comparators.*	Aca_Ven_model	L24 AND ..	IF(PrePS_scenario="Original approach", Survival_Calc!AN60, Survival_Calc!AG60)
76	Post Progression Survival- Use Gamma curve for AV, but maintain using exponential for comparators.	EAG-Results	D93	Original approach, Gamma for AV ----> PPS_scenario

Row	Issue title	Worksheet	cell(s)	Details
77	Post Progression Survival- Use Gamma curve for AV, but maintain using exponential for comparators.	Aca_Ven_model	M24 AND ...	IF(PPS_scenario="Original approach",Survival_Calc!BE60, Survival_Calc!AY60)
78	Capturing uncertainty around the assumption of equal efficacy	Survival_Calc		Create two additional identical sets of parameters and curves for each arm: AV, VenI, and VenO.
79	Capturing uncertainty around the assumption of equal efficacy	EAG-Results	D84	List: Company approach, EAG approach name: PSA_approach
80	Capturing uncertainty around the assumption of equal efficacy	Ibru_Ven_model	J24	IF(PSA_approach="company approach",Survival_Calc!W60,Survival_Calc!CG60)
81	Capturing uncertainty around the assumption of equal efficacy	Ibru_Ven_model	K24	IF(PSA_approach="company approach",Survival_Calc!AN60,Survival_Calc!CX60)
82	Capturing uncertainty around the assumption of equal efficacy	Ibru_Ven_model	L24	IF(PSA_approach="company approach",Survival_Calc!BE60,Survival_Calc!DO60)
83	Capturing uncertainty around the assumption of equal efficacy	VenO_model	J24	IF(PSA_approach="company approach",Survival_Calc!W60,Survival_Calc!FA60)
84	Capturing uncertainty around the assumption of equal efficacy	VenO_model	K24	IF(PSA_approach="company approach",Survival_Calc!AN60, Survival_Calc!FR60)
85	Capturing uncertainty around the assumption of equal efficacy	VenO_model	L24	IF(PSA_approach="company approach",Survival_Calc!BE60, Survival_Calc!GI60)



External Assessment Group (EAG) Addendum: Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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Declared competing interests of the authors

None.

Rider on responsibility for report

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1 Introduction

Prior to submitting the final report, the EAG requested access to the systemic anti-cancer therapy (SACT) dataset to better understand current clinical practice for untreated chronic lymphocytic leukaemia. After the submission of the final report, the EAG received the SACT dataset consisting of two cohorts:

Cohort 1: Adults with untreated chronic lymphocytic leukaemia who have received venetoclax with obinutuzumab (VenO).

Cohort 2: Adults with untreated chronic lymphocytic leukaemia who have received venetoclax with ibrutinib (VenI).

The EAG has summarised and assessed both cohorts in this addendum.

2 SACT data

The SACT data provided for this report, which includes approximately 90% of submitted data up to 31 March 2025, is considered complete. The dataset was extracted on 7 December 2025. The information includes patient age, Kaplan–Meier estimates of overall survival (OS), and OS parametric model fits with extrapolations covering 10 years following treatment initiation. At the most recent date on which patients' vital status was confirmed (5 October 2025), individuals without a recorded death were censored.

2.1 Eligibility criteria

Data were collected for untreated adults (aged ≥ 18 years) diagnosed with CLL in England between 1 April 2018 and 31 December 2023. Treatment with venetoclax plus obinutuzumab (VenO; cohort 1) and venetoclax plus ibrutinib (VenI; cohort 2) was initiated on or after 9 December 2020 (NICE TA663 publication date) and 31 May 2023 (NICE TA891 publication date), respectively. A caveat applies to this analysis: treatment identification relied solely on the regimen-level SACT table, and the detailed drug administration records in the drug detail table were not reviewed. As a result, some eligible patients may have been missed, potentially leading to a potential underestimation of the sample size.

The population included in the SACT VenO and VenI cohorts are more closely aligned with the European Medicines Agency's European Public Assessment Report (EPAR, Section 3.7.1),¹ and the marketing authorisation for acalabrutinib plus venetoclax (AV), as it reflects a broad real-world population. In contrast, the AMPLIFY trial² applied more restrictive eligibility criteria and therefore represents a narrower and potentially fitter patient group.

2.2 Cohort 1: Venetoclax plus obinutuzumab

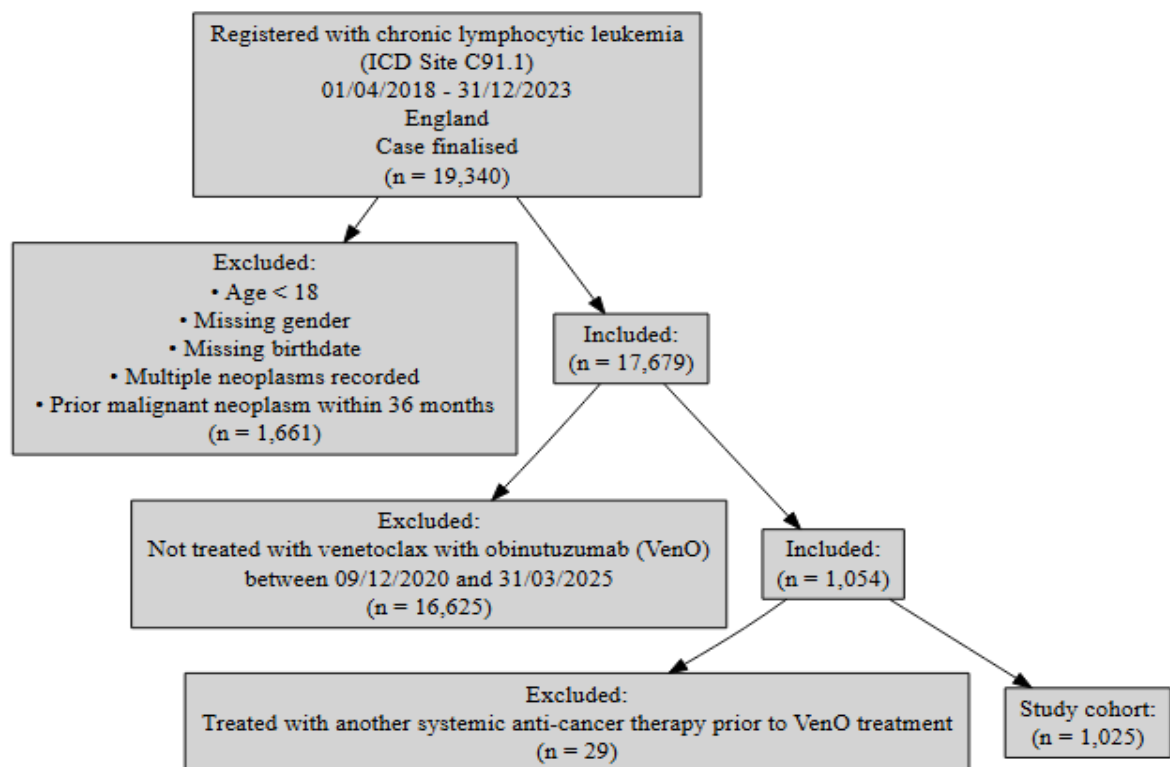


Figure 1: Inclusion/exclusion flow chart

The median age in the SACT VenO cohort was approximately 65 years, which is higher than the median age reported for the AV arm in AMPLIFY (61 years). The SACT VenO cohort also included a higher proportion of male patients

(70%) compared with the AMPLIFY AV arm (61.2%). No additional baseline characteristics were available within the SACT dataset.

Table 1: Mean age, standard deviation, median age and IQR of patients who have received venetoclax with obinutuzumab, split by gender

Characteristics	Female (N=310)	Male (N=715)
Mean age at start of regimen (SD)	64 (10)	65 (10)
Median age at start of regimen (Q1,Q3)	65 (57, 73)	65 (58, 72)

2.2.1 Overall survival

With a median follow-up of 30.3 months (range 0.1 to 57.8), the restricted mean survival over the full observed curve was 54.38 months, while the median survival was not reached.

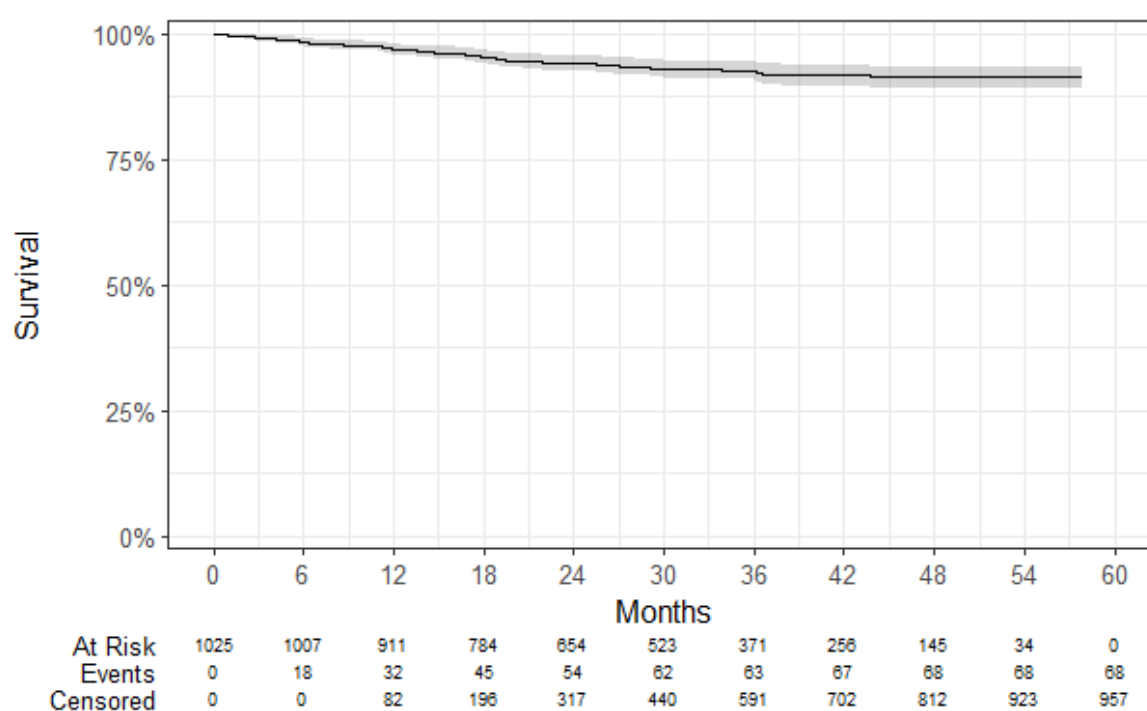


Figure 2: Overall survival for patients who have received VenO

2.3 Cohort 2: VenI

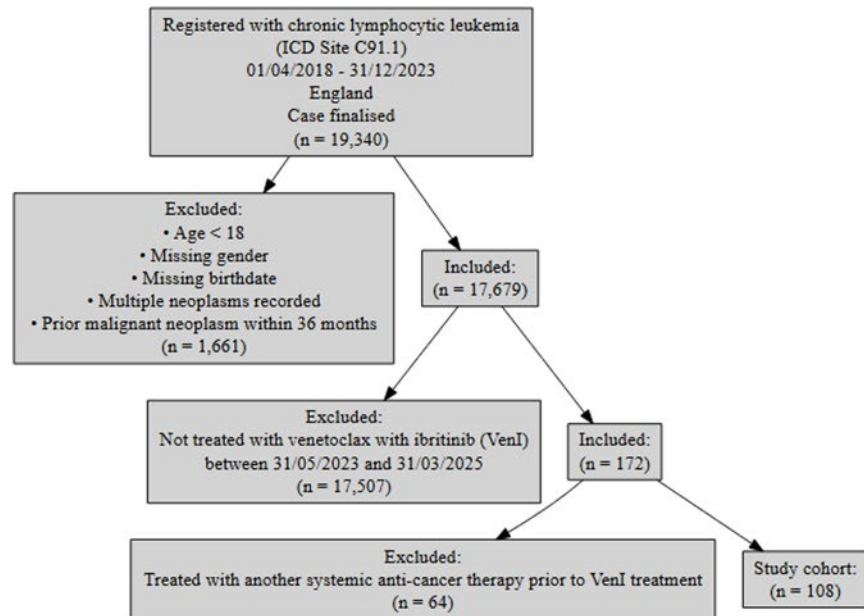


Figure 3. Inclusion/exclusion flow chart

The median age in the SACT VenI cohort was approximately 64 years, which is higher than the median age reported for the AV arm in the AMPLIFY trial (61 years). Most patients included in the SACT VenI cohort were male (81%) which is higher than the proportion of male participants in AV arm of the AMPLIFY trial (61.2%). No additional baseline characteristics were available within the SACT dataset.

Table 2. Mean age, standard deviation, median age and IQR of patients who have received VenI, split by gender

Characteristics	Female (N=33)	Male (N=75)
Mean age at start of regimen (SD)	66 (9)	62 (10)
Median age at start of regimen (Q1,Q3)	67 (59, 71)	63 (57, 68)

2.3.1 Overall survival

With a median follow-up of 19.4 months (range 4.3 to 28 months), the restricted mean survival over the whole curve was 27.26 months. The median survival was not reached.

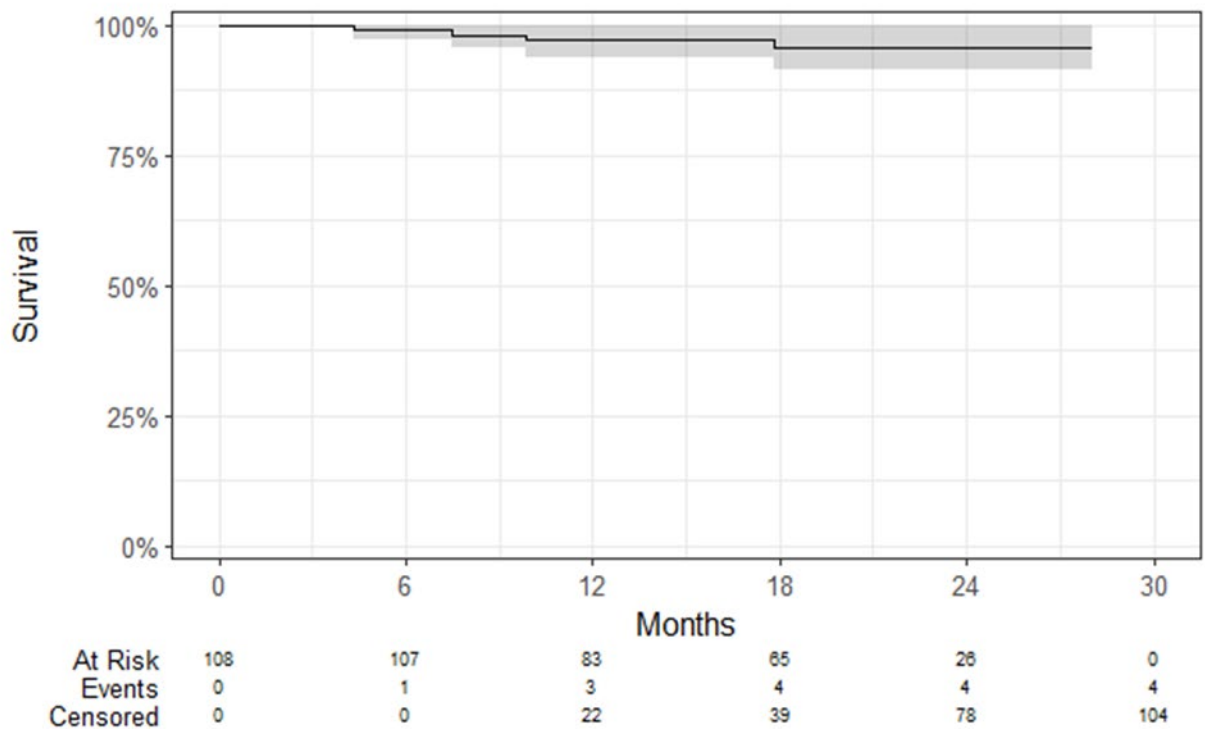


Figure 4. Overall survival amongst patients who have received VenI

2.4 Overall survival comparison

The EAG has digitally recreated the datasets from the presented Kaplan Meier (KM) plots, and presents a comparison of the KM functions of the two SACT datasets (VenI and VenO) and the AV arm of AMPLIFY.

Note that the VenI and VenO information reflects real-world datasets which are on average a slightly older population, and include people with del(17p)/TP53 mutation. The EAG anticipates that these differences introduce bias in favour of AV. However, a comparison of the KM functions shows little difference between the KM estimators (Figure 5). Hazard ratios from a Cox model did not find a significant difference between VenI and VenO versus AV: 1.11 (95% CI: 0.37, 3.37); 1.49 (95% CI: 0.86, 2.58), respectively).

The follow-up for VenI is too immature to give conclusive evidence, however the EAG still considers the assumption of equal efficacy between VenI and AV may be biased in favour of AV.

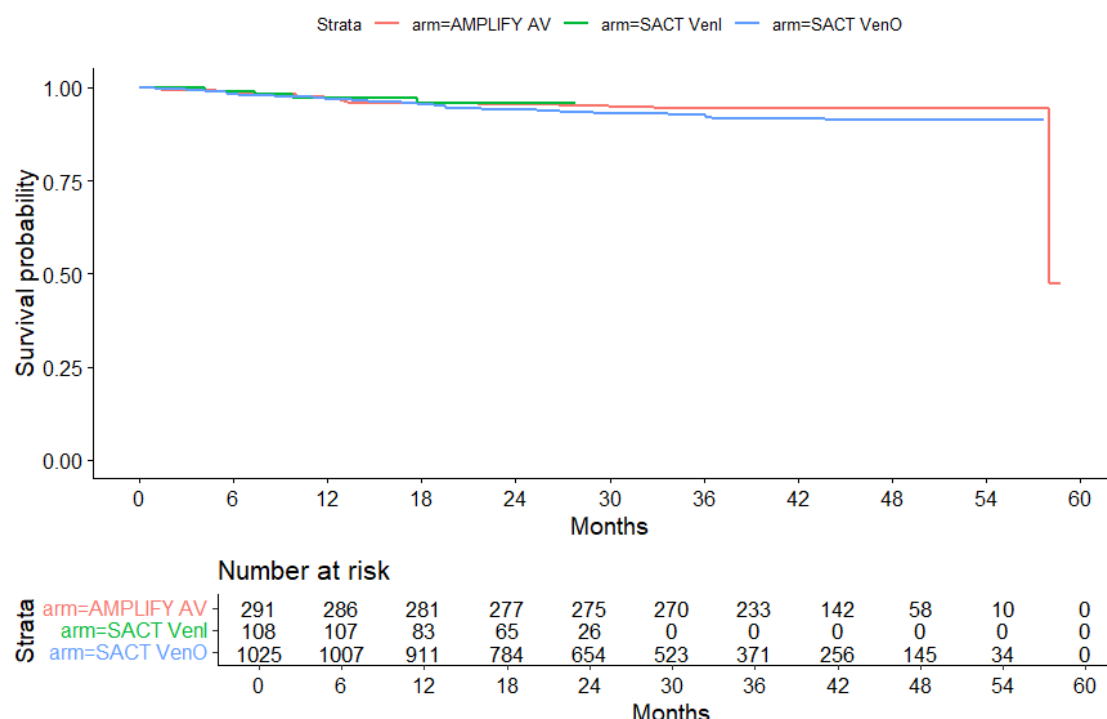


Figure 5: Comparison of overall survival Kaplan-Meier functions for VenI (SACT), VenO (SACT) and AV (AMPLIFY)

The EAG has not been able to apply the overall survival information from the SACT dataset into the economic model, as the model does not use OS as an input, but instead uses post-progression survival.

The EAG has not presented additional analyses using the ages reported in the SACT report for three reasons. Firstly, the reports do not present a single age for each population, but give one for each sex subgroup, meaning there is uncertainty in the population average. Secondly, we anticipate that AV will not directly displace VenI or VenO, and the recipient population is likely to have a slightly older average age. Hence the age in the SACT report is not necessarily an improvement over current modelling assumptions. Thirdly, the impact will be negligible given the assumption of equal efficacy. Existing EAG scenario analyses already explored the impact of changing the starting age.

References

1. European Medicines Agency (EMA) - Committee for Medicinal Products for Human Use (CHMP). *Calquence: EPAR - Assessment report - Variation*. 2025. URL: https://www.ema.europa.eu/en/documents/variation-report/calquence-h-c-005299-ii-0028-epar-assessment-report-variation_en.pdf (Accessed 30 January 2026).
2. Brown JR, Seymour JF, Jurczak W, Aw A, Wach M, Illes A, *et al*. Fixed-Duration Acalabrutinib Combinations in Untreated Chronic Lymphocytic Leukemia. *N Engl J Med* 2025;**392**(8):748-62. <http://dx.doi.org/10.1056/NEJMoa2409804>

Single Technology Appraisal

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

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 1 December 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.

Principal factual inaccuracies

Issue 1 Inaccurate interpretation of the target reimbursement population and the implications of this on EAG conclusions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the report, the External Assessment Group (EAG) have argued that the target population for whom AV would be reimbursed should be aligned with the overall licensed population for AV (patients with untreated CLL). However, the Company Submission (CS) clearly outlines that the target population for reimbursement is: 1. Patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation 2. Aligned with the AMPLIFY trial, which forms the evidence base supporting this submission 3. Narrower than the overall licensed population for acalabrutinib, which is all patients with untreated CLL This population was selected as it	In all instances where the licensed population of AV is mentioned, the report should specify that the Company are seeking reimbursement for a narrower population than the licensed population, and that the reason for this is to ensure alignment with the patient population in the AMPLIFY trial: patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation (i.e., non-high risk disease). In addition, the report should be updated to focus on the target population (i.e., patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation) within the context of AV being a fixed-duration treatment when discussing the generalisability of the AMPLIFY trial and key modelling assumptions.	In this evaluation, the target population for reimbursement is narrower than the overall licensed population. It is critical for any reader to understand the target reimbursement population, as it has implications for the generalisability of the trial, and the assumptions made throughout the evaluation and the economic analysis. As such, any discussions of the generalisability of the trial, and the key assumptions in the Company's evaluation, should be made in the context of the target population, rather than the licensed population. By not focusing on the Company's target reimbursement population, the EAG report's assessment of this evaluation is inaccurate. In addition, if the Company's target population is not made clear throughout the EAG report, this	This is not a factual inaccuracy. The EAG acknowledged the company's preference for a narrower population aligned with the AMPLIFY trial. However, recommendations must reflect the marketing authorisation and NICE's decision problem to avoid excluding eligible NHS patients. The EMA- and MHRA-licensed population represents NHS practice, whereas the AMPLIFY population is only a subset, limiting generalisability. The EAG was not persuaded by the company's rationale for imposing restrictions that exclude clinically eligible patients. Clinical experts, consistent with BSH 2025 guidance, emphasised that NHS practice supports shared decision-making, where both fixed-duration and continuous

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
aligns with the population in the AMPLIFY trial and is the most clinically relevant population for this fixed-duration treatment. This incorrect interpretation of the decision problem target population has led to further issues (outlined below).		could lead to misinterpretation of the Company base case.	options are discussed, considering disease characteristics, patient preference, safety, co-morbidities, concurrent medication, and the potential benefit of a treatment-free interval. BSH guidance does not impose strict eligibility or age-based limitations; both regimens are considered for all age groups, reinforcing that decisions should be individualised rather than constrained by arbitrary criteria. For patients with 17p deletion or TP53 mutations, acalabrutinib and venetoclax have each demonstrated efficacy, and the AV combination is licensed to include this subgroup. Both drugs are independently recommended by NICE for these patients. Broadening the population would provide additional options, simplify decision-making, and is low-risk for the NHS, affecting only a small proportion of patients (5–10%) who may otherwise never access this combination. This approach avoids a repeated NICE appraisal and represents an

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			efficient use of resources.
Issue 2, Section 1.3, page 21, states that: “<i>AV is licensed for all patients with untreated CLL, however the population of AMPLIFY is not representative of this group</i>”. This sentence does not make clear that the Company’s target reimbursement population in this submission is narrower than the licensed population and is in line with the AMPLIFY trial population. The target reimbursement population is patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation (i.e., non-high risk disease) which is aligned with the evidence-base from the pivotal AMPLIFY trial.	The first sentence of Key Issue 2 should be removed or updated to accurately describe the distinction between the licensed population and the target reimbursement population, and clarify that the target population is aligned with the AMPLIFY trial.	It is misleading and irrelevant to discuss the generalisability of the AMPLIFY trial to the licensed population, as this is not the Company’s target reimbursement population in this evaluation. The Company have previously clarified the target population for this evaluation in detail, as part the response to Clarification Question A11. The generalisability of the AMPLIFY trial should be discussed in the context of the Company’s target reimbursement population. The target population in this evaluation is patients with untreated CLL without a 17p deletion or <i>TP53</i> mutation, which is aligned with the AMPLIFY trial. In addition, as a fixed-duration treatment, AV will be received by patients for whom fixed-duration therapies would be considered suitable in UK clinical practice. When considering this target	Not a factual error. Please refer to the first comment above for details.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		population, the AMPLIFY trial is generalisable to patients who would receive AV in UK clinical practice, as confirmed by UK clinical experts.	
Issue 2, Section 1.3, page 21 states that <i>“The mean age of patients included in the AMPLIFY trial (59.9 years) is significantly lower than mean age of UK patients at presentation in clinical practice (around 70 years) as confirmed by our clinical experts. This raises concerns about the generalisability of trial findings, and it is difficult to gauge whether treatment benefit extends to older patients.”</i> Similarly, Section 4.2.3.1, page 83 states that <i>“The EAG clinical advisers report that the mean age at treatment in the UK is around 70 years”</i>. In both instances here, the exact population being referred to when discussing the ‘age of UK patients at presentation in clinical practice’ and the ‘mean age at treatment in	The Company requests that more details are provided about the exact population the EAG’s clinical advisers are referring to, and how this relates to the target reimbursement population in this evaluation. If the clinical experts are referring to a population that is not aligned with the target reimbursement population (e.g., the overall untreated CLL population), this should be acknowledged in these sentences, and the conclusions should be updated accordingly. If the EAG clinical experts are referring to the age of patients in the overall untreated CLL population, the sentence highlighting the concerns raised about the generalisability of the trial findings should be removed as it is not valid to compare the	The target population in this evaluation is narrower than the licensed population (the overall untreated CLL population). Any comments on the AMPLIFY trial and its generalisability to UK clinical practice should be made with reference to the target reimbursement population, rather than the overall CLL population. In addition, when discussing feedback from UK clinical experts, clarity should be provided on the exact patient population that the clinical experts were asked to comment on. Without this clarity, the clinical expert feedback may be inaccurately portrayed within the EAG report and misinterpreted. Considering age specifically, the age of patients within the target reimbursement population and the	Not a factual inaccuracy. Please refer to the first comment above for details.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the UK' is not clearly defined.	AMPLIFY trial with the overall CLL population.	overall CLL population will differ, as confirmed by clinical experts. Patients for whom fixed-duration therapies are deemed suitable are expected to be generally younger than the wider untreated CLL population. Therefore, it is misleading to discuss the generalisability of the AMPLIFY trial with regards to age without focusing on the specific target population in this evaluation.	
The EAG report describes the average age reported across different publications in Section 4.2.3.1, page 83: <i>“Some UK real-world evidence places the median age at diagnosis at 71.3 years, with similar estimates seen internationally (70.4 years in Finland and 72 in the CORE study).”</i> However, the EAG report does not provide any details on the populations included within these publications.	When comparing the AMPLIFY trial population to international real-world evidence, the Company requests that the EAG report specifies the populations included in the UK real-world evidence study (overall untreated CLL population), Finland-based study (overall untreated CLL/SLL population), and the CORE study (CLL/SLL; treatment line unclear from referenced publication). The EAG report should acknowledge any limitations when comparing the AMPLIFY population to these publications, specifically differences between the	To ensure any assessment of the generalisability of the AMPLIFY trial population is interpreted appropriately. If the AMPLIFY population is not being compared with the relevant patient population (i.e., patients with untreated, non-high risk CLL), this should be acknowledged to aid interpretation.	Not a factual error; however, the additional details are provided for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	populations.		
In Issue 2, Section 1.3, page 21, and in Section 4.2.3.1, page 83, the EAG report states that “<i>The EAG considers the company’s assumed starting age to be substantially lower than would be expected in routine UK practice</i>” and “<i>a starting age of 59.9 years is not representative of UK clinical practice.</i>”	The Company request that the EAG report specifies the specific CLL population being discussed when stating that the Company’s assumed starting age is lower than would be expected in routine UK practice. The Company also requests that the EAG reconsider the conclusions stated in the EAG report around how representative the starting age in the Company’s economic analysis is of the UK patient population expected to receive AV, considering that patients with non-high risk untreated CLL who are suitable for fixed-duration therapies are typically younger and fitter compared with patients deemed more suitable for treat-to-progression therapies.	It is misleading to compare the age of the AMPLIFY trial with the overall population of patients with untreated CLL, as this is not the target population for this submission. Patients expected to be eligible for AV are those for whom fixed-duration therapies are deemed suitable. Based on input from UK clinical experts obtained by the Company, which aligns with the NICE evaluation for zanubrutinib monotherapy in CLL (TA931), these patients are expected to be generally younger than those eligible for treat-to-progression therapies, and therefore the wider untreated CLL population.	Not a factual inaccuracy. Please refer to the first comment above for details.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Issue 2 Incorrect calculation of VenI treatment costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Total treatment costs of VenI are incorrectly calculated in the EAG's model: 'Ibru_Ven_model' sheet, cells BF28:BF546 These errors substantially impact results of the economic analysis and, as such, impact the interpretation of the cost-effectiveness of AV in the EAG report. Further errors relating to this issue are identified under 'EAG modelling	The formula calculating treatment costs for VenI incorrectly applies the 'IbruVen_Ven_txcost_cyc1' named range for the remaining time horizon, rather than 'IbruVen_Ven_txcost_subcyc' in line with the preceding parts of the formula. Range referencing should be amended accordingly. The current formula reads as follows for all cycles of venetoclax: =IF(treatment_proportion_approach="company base case", AX27*(IbruVen_ibru_txcost_subcyc*\$A27+IbruVen_Ven_txcost_cyc1*\$B27), (AX27*IbruVen_ibru_txcost_subcyc)+(I27*IbruVen_Ven_txcost_cyc1)) Following the first cycle of venetoclax this formula should be updated to: =IF(treatment_proportion_approach="company base case", AX28*(IbruVen_ibru_txcost_subcyc*\$A28+IbruVen_Ven_txcost_subcyc*\$B28), (AX28*IbruVen_ibru_txcost_subcyc)+(I28*IbruVen_Ven_txcost_subcyc)) This captures the difference in cost of venetoclax in the ramp up period in cycle 1 vs the fixed does given in subsequent cycles. Additionally, the Company requests that any results which are changed once this correction has been implemented are updated in the EAG report. Any interpretation or conclusions of the cost-effectiveness analysis should also be	The treatment costs of VenI are incorrectly calculated. As a result, the total treatment costs of VenI are underestimated in the EAG model. This greatly impacts the results of the cost-effectiveness analysis. Following correction of this error, all results and conclusions in the EAG report should be updated to ensure the results of the cost-effectiveness analysis are accurately presented.	The EAG confirm that there was an error in the part of the formula used when applying the new TTD for VenI. The formula has been amended, and all analyses have been rerun using the corrected version.

inaccuracies’.	updated, as required.		

Issue 3 Incorrect statement on the starting age used in the Venl evaluation (TA891)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 2, Section 1.3, page 21 states that “ <i>The EAG has amended the starting age in the economic model to 71 years, matching the age used in the appraisal of Venl (TA891), which has the same license as AV.</i> ”	The Company requests that the EAG: - Clarify that the starting age of 71 years used in the EAG base case was taken from the FCR-unsuitable/high-risk population, derived from the GLOW trial, in the evaluation for Venl (TA891) - Acknowledge that the evaluation for Venl (TA891) also used a starting age of 58 years for the FCR-suitable population, derived from the CAPTIVATE FD cohort, which more closely aligns with the target reimbursement population for this evaluation - Removes mention of Venl having the same license as AV	The Company’s target reimbursement population of this evaluation is narrower than the overall licensed population. It is therefore not relevant to reference that Venl has the same license to AV when referring to the starting age in the economic analysis. The EAG has not accurately outlined the starting ages used in the Venl evaluation (TA891). The starting age of 71 years was solely for patients who were in the FCR-unsuitable/high-risk population. A starting age of 58 years was also used in this evaluation for the FCR-suitable population. It is misleading to simply state that the starting age in the evaluation for Venl (TA891) was 71 years, without acknowledging the younger age also used in another portion of the population.	Not a factual error. The EAG acknowledges the age thresholds cited by the company. However, recent BSH guideline (2025) and expert opinion confirm that fitness is no longer a key factor in treatment choice because targeted therapies are generally well tolerated across all fitness levels, and age groups. Furthermore, the company has suggested in submission section 1.2.3 that fitness based on FCR or BR should not be considered, and this was supported by the EAG’s clinical experts. Removing fitness criteria, as proposed, means all age groups and fitness levels should be included, which the company has indirectly done by using GLOW as one of the main

			trials for indirect treatment comparison to support assumed equal efficacy. This approach reflects the company's perspective on treatment pathways as outlined in its submission. The EAG considered the GLOW population relevant for this appraisal because its mean age of 71 closely aligns with NHS patients, as highlighted by real-world evidence and the EAG's clinical experts. However, for clarity, the EAG has made minor text edits to reflect the approach taken in TA891.

Issue 4 Misleading discussion of ITC methodologies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.5 of the EAG report, the EAG present a critique of the ITC approach used by the Company. As part of this, they discuss alternative ITC methodologies, namely NMA, MAIC and ML-NMR. The EAG present a biased and misleading discussion of	The EAG report should be amended to also acknowledge the limitations associated with conducting their proposed alternative ITC methodologies.	The EAG present a biased and misleading discussion of the alternative ITC methodologies, without sufficient acknowledgement or discussion of the significant limitations that would be associated with conducting their proposed	Not a factual error. It is appropriate for the EAG to critique the company's approach rather than restate their arguments in detail. Where applicable, the EAG has addressed and

the alternative ITC methodologies, without acknowledging the limitations that would be associated with them.		alternatives.	summarized the company's main justification for not conducting alternative ITCs.
Section 3.5.1, page 61 of the EAG report describes why the Company did not consider an NMA to be feasible, but notes that <i>"The EAG considers that heterogeneity between studies does not inherently preclude the conduct of an NMA and maintains that the output may be helpful for decision-making. To explore their concerns, the company could have explored excluding studies that most strongly violate NMA assumptions"</i> .	The sentence stating that the Company could have excluded studies that most strongly violate the NMA assumptions should be removed.	Excluding studies that most strongly violate the NMA assumptions would result in the network becoming disconnected. As such, it would not be feasible to conduct the analysis suggested by the EAG. It is inaccurate to state that the Company could have explored this. Moreover, this suggested approach would not resolve the uncertain validity of the shared TEM assumption. This should therefore be acknowledged when suggesting that an NMA could be conducted.	Not a factual error. The information has not been clearly presented to the EAG. The EAG has acknowledged the limitations in Section 3.5.1 and suggested that uncertainties around the network, as noted by the company in its submission and response to Clarification Question A8, could have been explored through exclusion and sensitivity analyses.
Section 3.5.1, page 62, of the EAG report states that <i>"While not all TEMs are consistently reported across published trials, a MAIC may still have been feasible, given that the company did not provide any estimate of ESSs. Instead, the company opted to use a STC. The EAG notes that a STC is subject to a similar assumption relating to the extent of overlapping data in that whilst extrapolation beyond the range of patient-level data is</i>	This text should be amended so that it is not implied that a MAIC and an STC are subject to the same exact limitations. The text should acknowledge the differences between MAIC and STC methodology and how these impact the bias introduced, noting that an STC fundamentally avoids the inherent instability associated with reweighting, unlike a MAIC.	It is inaccurate to describe the assumptions of an STC as "similar" to that of a MAIC. This blurs an important distinction between MAICs and STCs as a MAIC's sensitivity to overlap is operational (extreme weights and effective sample size loss), whereas an STC's is primarily about model validity and extrapolation. Overall, an STC avoids the inherent instability associated with reweighting with a	Not a factual error. The EAG's note is clear in addressing the violation of the overlapping assumption in both methodologies (Table 11).

<i>possible, it is necessary for the relationships to be consistent with those within the observed data. When populations overlap, this extrapolation is of much lower concern, but in this instance, it remains a potential source of bias.”</i>		MAIC. The EAG wording is an inaccurate interpretation of the Company’s justification for an STC being the most appropriate ITC methodology and fails to give a balanced distinction compared to an MAIC.	
Table 11, Section 3.5.1, page 62–63 of the EAG report presents the key strengths, limitations or assumptions associated with potential ITC approaches. The table only states “<i>Requires all effect modifiers and prognostic factors to be adjusted for</i>” as the key limitation or assumption. However, the Company provided an overview of the assumptions underlying an NMA, MAIC and ML-NMR, and accompanying rationale on why these assumptions would not hold.	The table should be amended to include a more comprehensive list of the key limitations and assumptions associated with alternative methods, as detailed in the Company submission (Section 2.10.2) and response to Clarification Question A8.	NMA: It is incorrect to only include the assumption that effect modifiers are balanced across studies as the requirement for an NMA. An NMA in this context also requires equivalence of FCR/BR, FCR only and BR only arms, equivalence of MRD-guided VenI and fixed-duration VenI, and differences in eligibility criteria across trials did not affect treatment outcomes, and that treatment switching did not affect comparative treatment estimates. MAIC: It is incorrect to only include adjustment for all effect modifiers and prognostic factors as the only key assumption required for an unanchored MAIC. The positivity assumption also needs to be met, and there needs to be sufficient overlap in patient characteristics. ML-NMR: It is incorrect to only include adjustment for all effect	Not a factual error. The EAG has cited the company’s ITC discussions at the start of section 3.5.1, thus, has not restated them. As reflected in Table 11’s title, it provides a high-level overview of potential indirect treatment comparison approaches, summarizing their key strengths and limitations.

		modifiers and prognostic factors as the only key assumption required for ML-NMR. As provided in the Company's response to Clarification Question A8, there are additional assumptions required for ML-NMR. For example, there is a lack of evidence on covariate correlation between VenI and VenO, covariate reporting was inconsistent across studies, evidence supporting assumption of shared TEMs for treatments within the same class was not available, and IPD were not available for comparator studies. These limitations are not fully reflected in the EAG report.	

Issue 5 Incomplete explanation of Company evidence supporting equal efficacy of AV, VenI and VenO

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
When describing the evidence provided by the Company in support of the assumption of equal efficacy for AV versus VenI and VenO in Issue 3, Section 1.3, page 22 of the EAG report, it is stated that <i>"The supporting analyses provided by the company are based on a limited presentation of STCs and a Bucher</i>	The Company requests that the wording is amended to acknowledge that, in addition to the STCs and Bucher ITC, the Company's assumption of equal efficacy between AV, VenI and VenO was based on extensive clinical expert validation, through interviews with 6 UK clinical experts and a modified Delphi panel which	The full evidence base provided by the Company in support of the assumption of equal efficacy applied in the economic analysis is currently not accurately portrayed in the EAG report.	The EAG has critiqued the statistical approach in support of equal efficacy in section 3.5.5 and discussed the Delphi panel separately in section 3.5.6. However, minor changes were applied in the text for clarity. The EAG has amended to

ITC”. Similarly, in Section 3.5.5, page 67–68, the EAG report describes the ITC evidence included in the Company’s submission, then states <i>“The conclusion of equal efficacy is based on highly uncertain analyses, which are likely to be overestimating the benefits of AV and are not supported by external analyses (see section 3.6). The company has not provided comprehensive analyses or justification for not providing these analyses.”</i> These statements do not acknowledge the feedback from UK clinical experts obtained from interviews conducted by the Company, or results of the modified Delphi panel conducted with 22 clinical experts, both of which supported the assumption of equal efficacy.	included 22 UK clinical experts.		clarify the company's suggestion.
In Section 3.5.6, page 69, the EAG report states <i>“While the panel offers useful clinical insights, it cannot substitute for empirical validation of assumptions underpinning indirect treatment comparisons. Expert elicitation should complement, not replace, robust statistical methods</i>	The Company requests that the wording is updated to indicate that the expert elicitation was provided to complement the robust statistical analyses conducted by the Company (i.e., STCs and a Bucher ITC).	The current wording suggests that the Delphi panel was provided in place of any ITCs, which is an inaccurate representation of the evidence provided by the Company.	The EAG has revised the text.

<i>such as NMA, MAIC, or ML-NMR.”</i>			

Issue 6 Inaccurate discussion of unanchored MAIC by Munir et al. (2025)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 3, Section 1.3, page 22 the EAG describe that <i>“In addition, a recent unanchored MAIC suggests superiority of VenI over AV”</i>. Section 3.6.2, page 72, states that <i>“An unanchored MAIC comparing AV and VenI by Munir et al. (2025) reported significantly superior for individual patient-level data (IPD) of VenI (pooled GLOW and CAPTIVATE FD) compared to AV in the AMPLIFY.”</i>	When discussing the results of the unanchored MAIC by Munir et al. (2025), the EAG report should state that the MAIC showed superiority of VenI over AV in terms of PFS only.	It should be specified that the MAIC was conducted for uMRD and PFS only, so findings do not inform the comparative efficacy of AV and VenI in terms of OS. It is inaccurate to just state that the MAIC showed superiority of VenI versus AV without specifying the outcomes.	The EAG has revised the text with minor changes.
The EAG report describes the unanchored MAIC by Munir et al. (2025) in Section 3.6.2, page 72. However, the EAG report provides limited details on this analysis and does not discuss any limitations associated with the unanchored MAIC by Munir et al. (2025) and implications on interpretation of the results.	The Company requests that the report: - Includes details on the limitations associated with the unanchored MAIC by Munir et al. (2025) - Notes that the unanchored MAIC was only reported in a conference abstract, not in a full journal article - Acknowledges that OS was not explored in the analysis	Inherent limitations associated with an unanchored MAIC have not been acknowledged in the EAG report, such as reductions in the effective sample size and the assumption that all prognostic factors/treatment effect modifiers have been adjusted for. These limitations introduce uncertainty and potential bias into the results. The current wording implies that an unanchored MAIC would not be associated with any	Not a factual error. The EAG has already addressed the main limitations in the EAG report, section 3.6.2. However, the EAG added the conference abstract study design.

	Amends the wording around differences in follow-up biasing results in favour of AV	limitations, which is a biased and misleading presentation of this analysis. The EAG report should note that the results are from a conference abstract and not a peer-reviewed publication. The Company also suggests that the statement about follow-up duration biasing results is removed, as there is insubstantial evidence to indicate which direction results are biased in favour of. It is misleading to conclude that this bias would likely be in favour of AV.	

Issue 7 Reference to issues resolved at clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG refer to several issues as being key areas of concern, despite these being resolved by the Company at clarification questions stage. Page 81, Section 4.2.2.1 states “EAG concern 1: Inappropriate incorporation of discount factors into the model. Company’s Approach:	The Company requests that issues resolved after clarifications be removed from the report. Alternatively, they should be acknowledged but not framed as key issues or notable modelling errors. Any wording suggesting that errors included in the Company’s original	The issues which the Company accepted and addressed after clarification questions should not be relevant to the Committee, as they have already been resolved. It is misleading to include these as modelling errors in the Executive Summary, as this suggests they are outstanding errors.	Not a factual error. From the EAG side, this evaluation started with the receipt of the first submission, and the EAG believed that all stages and changes should be documented. The EAG is not aware of the source of the rationale behind the

<i>The company applies discounting starting from year three, with values remaining undiscounted for the first two years. In addition, discounting is implemented for each 28-day cycle rather than on an annual basis.</i>" This section does not reflect that this error was addressed at clarification questions.			
Section 5.2.1, page 131 states "<i>The EAG identified multiple modelling errors and inconsistencies in the company's submission, including:</i> • <i>Incorrect implementation of discounting: No discounting was applied in the first two years, and subsequent discounting was applied at cycle-level, which did not comply with NICE requirements (resolved at clarification).</i> • <i>Errors in time-to-treatment discontinuation (TTD): Venetoclax TTD was modelled incorrectly for AV, the model initiated at Cycle 0 (adding an artificial treatment cycle), and TTD curves were not capped at SmPC-defined treatment durations. This resulted in patients remaining on treatment</i>	model were the "Company's preferred approach" should be removed, as these were errors that have all since been corrected.	Including them as the Company's 'preferred' approach is a misrepresentation of the Company's position. These were errors that have since been corrected by the Company, rather than a preferred approach, and should be portrayed as such if included in the EAG report.	company's statement that issues resolved after clarifications should be removed. In any case, for all items considered by the company and resolved in the updated model after the clarification stage, the EAG clearly indicated that they were resolved at clarification.

<i>beyond permitted limits and inflated life-years and QALYs (corrected after clarification).</i> <i>Errors in the PSA implementation: The original PSA produced implausible survival extrapolations for the TTP, PrePS, and PPS curves. A corrected PSA with maximum 10,000 iterations was subsequently provided.”</i>			
Section 5.2.2, page 135 of the EAG report includes the following under the header “<i>Company’s preferred approach: No discount in the first two years, followed by a per-cycle discount factor</i>”.			

Issue 8 Representation of time to treatment discontinuation data from AMPLIFY

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5.3, page 97 of the EAG report describes the EAG’s preferred approach to calculating TTD: “<i>To improve on the company’s approach and obtain a more balanced approach to modelling duration of treatment, the EAG utilises the completion rate</i>	The Company requests that the EAG acknowledge the limitations of their TTD approach and explicitly note the constraints associated with using completion rates from heterogeneous trials to inform TTD inputs. This should include recognising the limitations of naïve	The discussion of the EAG’s preferred approach to calculating TTD is imbalanced and misleading as it does not acknowledge the limitations of this approach. The EAG’s method uses completion data from AMPLIFY for AV, GLOW	The EAG accepts that completion rates and time on treatment measure different things, but sees them as broadly aligned. Because comparable TTD data were not available for VenI and VenO, the EAG used a single

<i>information available for all three first line regimens. For VenI, for example, the EAG takes the midpoint of two reported values for treatment completion at 84.7% after 15 cycles. The EAG assumes a linearly decreasing time on treatment to estimate proportions for each cycle up to cycle 15. For VenO and AV, the EAG undertake the same approach, based on the reported trial information.”</i> However, the discussion of the EAG’s preferred approach does not acknowledge its limitations.	cross-trial comparisons and the clinical implausibility of assuming a linear pattern of discontinuation for FD regimens in the absence of data. The Company request that the EAG remove the “<i>more balanced</i>” wording.	and CAPTIVATE for VenI, and CLL14 and CLL13 for VenO to inform the completion rates for each treatment. The heterogeneity between the populations of these trials could materially affect treatment completion rates, which the EAG does not acknowledge. For example, several of the comparator trials include older patients than those enrolled in the AMPLIFY, which would be expected to result in higher rates of treatment discontinuation. The EAG approach also conflates time on treatment with completion rates, which the company understands to be two conceptually distinct measures. Completion rates reflect the proportion of patients reaching the maximum planned cycles and does not equate to the duration of treatment received by those who discontinue treatment early. The Company request that the EAG remove the “<i>more balanced</i>” wording as there is no evidence to suggest that this approach is more balanced than the Company’s preferred approach.	approach across all treatments rather than extending the non-linear AMPLIFY curve to settings where it was not supported by evidence. The method applies a gradual linear decline from cycle 1 to the respective observed completion values, including AV. The company’s use of the AMPLIFY TTD trajectory for all treatments created unnecessary bias by benefitting longer regimens over shorter fixed-duration options such as obinutuzumab.

Section 4.2.4.1, page 87 of the EAG report states “ <i>The EAG also questions the abrupt drop in completion between cycles 13 and 14 for AV (from ■% to ■%), which appears clinically implausible, as patients on fixed-duration regimens are generally encouraged to complete a treatment if they can tolerate it.</i> ”	The Company requests that wording which questions the validity of this drop in patients on treatment is removed, given that these data were taken directly from the AMPLIFY trial. Alternatively, the sentence should explicitly state that the time to treatment discontinuation data in the model are taken directly from the AMPLIFY trial.	Data informing time to treatment discontinuation in the economic analysis were derived directly from the AMPLIFY trial. As such, the rate of patients discontinuing treatment between Cycles 13 and 14 in the model is an accurate reflection of the discontinuation rate in AMPLIFY. Given the appropriateness of the data source used, it is misleading to suggest that the treatment completion rates applied for AV are implausible, particularly without acknowledge that these data came from the AMPLIFY trial.	
Section 4.2.4.1, page 88 of the EAG report states the EAG proposed approach to incorporating TTD from different sources to calculate proportions of patients completing each treatment. The Company was unable to verify the source of the figures provided within the referenced publications.	The Company request that the EAG provide exact calculations and sources used to derive the completion rates for VenI (85%) and VenO (84.9%) within the EAG report and/or economic model.	Greater transparency on the EAG-performed calculations would allow for an independent verification of these.	No factual error. To enhance transparency, the EAG added some text.

Issue 9 Misleading representation of the EAG’s proposed approach to the model starting age

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.3.1, page 83–84 of the	The Company requests that the	It is misleading to use a starting age	Not a factual error.

EAG report describes the EAG's preferred starting age: "Base case: <i>Apply the mean age reported in TA891 (Venl): 71.0 years (SD 8.02).</i>" Whilst the EAG report details the change in the EAG's base case starting age from the Company's base case, it does not acknowledge the limitations and implications of this change. Changing the starting age means that the age in the model is inconsistent with the AMPLIFY trial data used in the model.	EAG report includes a statement to acknowledge that using a starting age from the Venl evaluation (i.e., the GLOW trial) is associated with limitations as it does not align with the AMPLIFY trial, which was used to inform other baseline characteristics data and clinical inputs in the Company's economic analysis. The EAG report should acknowledge that increasing the starting age without adjusting associated clinical inputs does not account for the potential impact of older age on treatment efficacy, prognosis and TTD. As age is a potential prognostic factor and TEM, applying an older starting age from a different trial source may impact outcomes.	from a different trial source without acknowledging the limitations associated with this approach, and the uncertainty this introduces in modelled outcomes. Assuming an older starting age, based on the GLOW trial, whilst maintaining consistent clinical outcomes, predominantly from the AMPLIFY trial (i.e., TTP, pre-PS and post-PS), is not a valid assumption, given that age is a potential prognostic factor/treatment effective modifier. This limitation should be acknowledged in the EAG report. The company's key concern with this approach is that increasing the age of patients without acknowledging the potential impact this may have on outcomes, such as TTD and survival, is misleading. Acknowledging these limitations is important to ensure these factors are taken into account when interpreting results of the EAG's base case economic analysis.	The EAG assessments concluded that the starting age used in the company's model is lower than what is seen in UK practice. The mean age used in GLOW was more in line with UK practice. For more details, please refer to the EAG responses to Issues 1 and 3 in this document. Furthermore, given the assumption of equal efficacy, and current reliance on background mortality to inform overall survival, it is unlikely that any changes in absolute efficacy linked to changing the starting age will have any meaningful effect on the economic model. Furthermore, no information is available to explore this uncertainty.

Minor factual inaccuracies

Issue 10 Inaccurate description of AV tolerability profile

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that AV is associated with a “<i>gentler profile</i>” than VenI and VenO. For example, Issue 1, Section 1.3, page 20 states that “<i>The EAG clinical experts state that the gentler profile of AV compared to VenI and VenO means it is likely to broaden the potential patient pool for dual therapies, beyond those currently considered for VenI or VenO.</i>” Similar wording is used on Section 1.4, page 21; Section 4.2.4, page 86 and Section 4.2.5.3, page 96 of the EAG report.	The Company requests that more accurate wording is used to describe the safety profile of AV versus VenI and VenO. Please can this text be amended as follows: “<i>The EAG clinical experts state that the more tolerable safety profile of AV compared to VenI and VenO means it is likely to broaden the potential patient pool for dual therapies, beyond those currently considered for VenI or VenO.</i>”	The wording “<i>gentler profile</i>” does not accurately reflect the expected difference in tolerability profiles of AV versus VenI and VenO. This wording is vague and therefore potentially misleading. This wording should be updated to more accurately and clearly state that AV is expected to be more tolerable than VenI and VenO.	The EAG has amended the wording for further clarity.

Issue 11 Treatment guidelines informing the current treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2, page 34 of the EAG report states that “<i>fitness should be viewed broadly, incorporating patient preferences (e.g., fixed vs.</i>	The Company requests that this sentence also includes the 2025 BSH guidelines alongside the ESMO guidelines, given that these	Both the BSH and the ESMO guidelines support that a key decision informing treatment choices is intention to use fixed	Not a factual error. The EAG has amended the

continuous treatment), socioeconomic factors, ECOG performance status, and more... The recent ESMO guideline supports this approach, recommending treatment decisions based on the intention to use fixed-duration venetoclax-based or continuous BTKi therapy."	also support the statement around the various factors informing treatment fitness. Please amend this text as follows: "fitness should be viewed broadly, incorporating patient preferences (e.g., fixed vs. continuous treatment), socioeconomic factors, ECOG performance status, and more... The recent ESMO guideline and the 2025 BSH guidelines support this approach, recommending treatment decisions based on the intention to use fixed-duration venetoclax-based or continuous BTKi therapy."	duration of continuous treatment. Both guidelines should be mentioned to accurately reflect all available guidelines informing UK clinical practice.	text as was recommended.

Issue 12 Inaccurate description of benefits of AV versus VenI in terms of cardiac toxicities

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5.2, page 63 of the EAG report states that "AV's improved cardiovascular safety profile is acknowledged, attributed to its more selective inhibition of Bruton's tyrosine kinase (BTK), but the clinical relevance of this advantage may be limited, as such events are generally manageable within NHS practice."	The Company requests that the wording stating that the advantage of AV's improved cardiovascular safety profile is limited is removed. Please can the following wording be included: "VenI is not typically offered to patients with cardiac comorbidities, so the availability of AV, which could be offered to these patients, would mean more patients	The EAG report does not accurately reflect the full of benefit AV related to its improved cardiac toxicity profile. VenI is often not offered to patients with cardiac comorbidities, so the availability of AV would mean treatment with venetoclax plus BTKi combination therapy is available to more patients. The full benefits associated with	Not a factual error. Regarding VenI, BSH 2025 guidance advises that "the use of V+I in older patients with comorbidities should be carefully weighed against the potential risk of cardiovascular complications." This indicates that its use requires careful consideration rather than being

	<i>could receive treatment with a venetoclax plus BTKi combination therapy”.</i>	AV’s improved safety profile are not currently included in the EAG report, creating an inaccurate portrayal of AV’s safety benefits.	contraindicated, meaning it remains a potential option for some patients with appropriate caveats. The EAG has amended the text for clarity.

Issue 13 Misleading reference to additional trials for acalabrutinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2, page 32 of the EAG report states that “<i>While patients with del(17p) or TP53 mutations were excluded from the AMPLIFY study due to an unsuitable comparator, the efficacy of acalabrutinib and venetoclax in the claimed indication has been characterised in other studies (ELEVATE-TN, CLL14, and SAT NCT03580928)</i>”. The current wording implies that AV has been studied in ELEVATE-TN, CLL14 and SAT NCT03580928 in the target population addressed for this evaluation, which is incorrect.	The Company requests that wording is added to specify that the only Phase III trial providing efficacy data for AV in untreated CLL comes from AMPLIFY. Additionally, the Company requests that context for the other trials listed in Section 2 of the EAG report is added, to highlight that these do not provide evidence for AV in patients with untreated CLL: • ELEVATE-TN provides data for acalabrutinib monotherapy or acalabrutinib with obinutuzumab as treat-to-progression options • CLL14 investigated the comparative efficacy of VenO and OC1b	AMPLIFY is the only trial available for AV in untreated CLL. All other trials highlighted by the EAG in this section investigated acalabrutinib monotherapy, AVO or other interventions, rather than AV. However, this is not clearly specified in the report. This should therefore be detailed in the EAG report for clarity, as the current wording suggests additional relevant data are available but not used in the Company’s evaluation, which is inaccurate and misleading.	Not a factual inaccuracy. The EAG has quoted the European Medicines Agency’s European Public Assessment Report. No further amendments are needed.

	SAT NCT03580928 provides data for AVO in patients with high-risk CLL		

Issue 14 Incorrect statement on the evidence for the safety profile of acalabrutinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4.2, page 57 of the EAG report states that <i>“AMPLIFY’s AV arm is showing low rates of atrial fibrillation, cardiac events, TLS, and hypertension. However, its interpretation is limited by the fact that it has only been studied in a single trial. Broader evaluation across diverse cohorts would be necessary to confirm its tolerability profile and assess generalisability”</i> .	The statement on the interpretation of the safety data from AMPLIFY should be removed. Alternatively, the statement should be amended to acknowledge that the tolerability of AV observed in AMPLIFY is supported by a broader evaluation of the safety profile of acalabrutinib in a number of trials, such as ELEVATE-TN.	It is misleading to suggest that there is only one trial or a lack of data available to support the safety profile of acalabrutinib. The tolerability of acalabrutinib has been well-established in numerous trials, such as ELEVATE-TN and ASCEND, and this should be acknowledged in the report. This statement on safety data for AV only being available from AMPLIFY is contradictory to other statements in the EAG report referring to additional efficacy data for acalabrutinib and venetoclax (in various combinations) being available in other studies (Section 2, page 32 of the EAG report).	The EAG amended to text to acknowledge the ELEVATE TN and ASCEND safety profile for acalabrutinib monotherapy.

Issue 15 Irrelevant reference to data from the ELEVATE-TN trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4.3, page 59 of the EAG report describes median PFS data from ELEVATE-TN alongside CLL14: <i>“Median PFS was reached only in CLL14 (76.2 months), although ELEVATE-TN reported higher PFS rates at 72 months than AV at 54 months, aligning with clinical expert expectations.”</i> ELEVATE-TN was not used in the Company’s ITC, so it is not relevant to include results from this trial given that the Section 3.4 is titled <i>“Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison.”</i> In addition, this whole section relies entirely on naïve comparisons of data which are inappropriate and should be caveated with the limitations to such comparisons.	Remove description of median PFS data for ELEVATE-TN. Ensure that any naïve comparison of data is caveated with the appropriate limitations.	To ensure the description is focused on studies included in the ITC. To ensure limitations of naïve comparisons are appropriately included.	The EAG has amended the text.

Issue 16 Inaccurate presentation of Company ITC methodology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4.3, page 59 of the EAG report states that <i>“the PH assessment does not appear to factor in unanchored comparisons.”</i>	Remove wording stating that an assessment of proportional hazards was not considered in the Company’s unanchored comparisons and appropriately reflect the Company’s feasibility assessment.	The current description of the Company’s ITC feasibility assessment is incorrect. As detailed in Section 2.10.2, page 66 of the Company Evidence Submission, proportional hazards were considered in the ITC feasibility assessment, with full details of the assessment provided in Appendix B. It is therefore inaccurate to state that proportional hazards were not considered.	Not a factual error. Section 2.10.2 only considers hazard proportionality in the context of a NMA, and appendix B only contains presents information of within trial comparisons, which irrelevant to an unanchored comparison.
Section 3.5.1, page 63 of the EAG report states that <i>“The company has not presented a clear assessment of the potential covariates”</i> .	This sentence should be removed. Alternatively, amend wording to reflect that the Company performed a comprehensive assessment of potential covariates which was reported in the Company Evidence Submission and accompanying Appendices.	The wording in the EAG report is an inaccurate reflection of the comprehensive feasibility assessment conducted by the Company, as a full assessment of covariate reporting was provided in Section 2.10.1–2.10.2 of the Company Evidence Submission, with further details in Appendix B.	Not a factual error. While the company provided a list of potential covariates in the report, the EAG’s comment refers specifically to the context of ML-NMR, for which the company did not present any clear assessment of covariates or their suitability for adjustment.

Issue 17 Incorrect statement on Delphi panel results for safety of AV versus VenI

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5.6, page 69 of the EAG	Please can this text be amended as	As per Table 26 of the Company’s	The text has been amended for

report states that “While AV was considered comparable to VenO in safety based on AMPLIFY data, this was not the case for VenI.”	follows: “Based on AMPLIFY data, AV was considered comparable to VenO in terms of safety, whilst consensus was reached that AV has a better safety profile than VenI”.	submission, there was consensus agreement that fixed-duration AV would have a more favourable safety profile versus fixed-duration VenI treatment. The wording in the EAG report currently implies that AV may have been deemed to have a worse safety profile than VenI.	clarity.

Issue 18 Inaccurate description of Company justification for model structure

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2, page 80 of the EAG report states: “The company highlighted that this approach is aligned with semi-Markov models accepted in recent NICE appraisals for CLL (TA689, TA891, TA931).” This description does not note that the model structure was selected in line with NICE TSD 19, as noted in the Company’s clarification question response B2.	Please can the text be amended as follows: “The company highlighted that this approach is aligned with guidance in NICE TSD 19 and semi-Markov models accepted in recent NICE appraisals for CLL (TA689, TA891, TA931).”	The report currently presents an incomplete description of the Company’s justification for the selected model structure, which may be misleading. The EAG report should state that the model structure chosen is in line with guidance from NICE TSD 19, as noted by the Company in the response to clarification question B2.	No factual error. The EAG amended the text.

Issue 19 Incomplete description of Company justification for RDI assumptions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Issue 4, Section 1.3, page 23, the EAG report states “ <i>The company assumes 100% RDI for VenI and VenO.</i> ”	Please can the text be amended as follows: “ <i>The company assumes 100% RDI for VenI and VenO, in the absence of publicly available RDI data and in line with the NICE evaluation for VenI (TA891)</i> ”.	As acknowledged in the EAG report, the Company assumed 100% RDI for VenI and VenO due to the absence of publicly available RDI data for these treatments, and in line with precedent from the NICE evaluation for VenI (TA891). For completeness, details on the Company’s justification for assuming 100% RDI for VenI and VenO should be included. This is already acknowledged in Section 4.2.4.2, page 89, of the EAG report, The Company requests that this justification is also noted in Section 1.3, page 23, for completeness.	Not a factual error. All related details have been provided in the related sections No amendments are required.

Issue 20 Inaccurate representation of modelling of subsequent treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.2, page 111 of the EAG report states that their clinical advisers raised several concerns with the subsequent treatment	Remove the second concern noted by the EAG’s clinical advisers. Alternatively, update wording as	The EAG report currently suggests that the Company’s base case approach for subsequent treatments is not aligned with this feedback	Not a factual error. The text the company referenced reflects a general

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
distributions applied in the Company economic analysis. One of the concerns was <i>“acalabrutinib is expected to remain the most commonly prescribed second-generation BTK inhibitor due to clinician familiarity, while zanubrutinib use is expected to increase but not exceed that of acalabrutinib.”</i>	follows: <i>“Second, acalabrutinib is expected to remain the most commonly prescribed second-generation BTK inhibitor due to clinician familiarity, while zanubrutinib use is expected to increase but not exceed that of acalabrutinib. The EAG acknowledges that this is reflected in the subsequent treatment distributions applied in the Company’s base case economic analysis.”</i>	from the EAG’s clinical experts, which is incorrect. The report should be amended to reflect where the feedback from the clinical adviser’s was aligned with the Company’s base case approach.	concern raised by the EAG clinical advisers. The EAG believes there is no need to amend the wording.
Section 1.3, page 25 of the EAG report states <i>“the EAG adopts a more plausible estimate of the proportion receiving subsequent therapy by using a midpoint between trial-reported proportions and the company’s assumptions for each arm”</i>.	Please amend the text as follows: <i>“the EAG adopts ~~a more plausible~~ an estimate of the proportion receiving subsequent therapy by using a midpoint between trial-reported proportions and the company’s assumptions for each arm”</i>.	The approach adopted by the EAG for estimating the proportion of patients receiving subsequent therapy is their preferred approach. No evidence is provided to support this being “a more plausible estimate” so this wording should be removed. It is an inaccurate statement on the EAG’s preferred methodology.	The requested amendment isn’t appropriate. The wording reflects the EAG’s rationale and was based on clinical adviser input. The phrase “more plausible estimate” is justified because the method uses observed trial data rather than relying solely on assumptions. No change is required.

Issue 21 Incorrect acquisition costs for subsequent treatment with venetoclax and rituximab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 36, Section 4.2.7.3, page 113, of the EAG report still refers to the use of subcutaneous rituximab, however this was an error that was updated within the Company clarification responses to reflect the use of IV rituximab.	Please can the following amendments be made in line with the updates made during clarification questions: • Change rituximab formulation from 1,400 mg to 100 mg. • Change the number of units per pack/vial of rituximab from 1 to 2. • Change the cost per pack/vial of rituximab from £1,344.65 to £314.33. • Change the total drug acquisition cost for venetoclax with rituximab from £32,968.83 to £34,325.25. • Update table caption from “Table 36: Acquisition costs for subsequent treatments included in the economic analysis (obtained from CS, section 3.5.2)” to “Table 36: Acquisition costs for subsequent treatments included in the economic analysis”	The use of subcutaneous rituximab was an error in the Company model that was corrected at clarification questions. This should all be updated within the EAG report, in line with the changes made to the Company base case at the clarification questions stage.	We apologise for this oversight. The EAG report has been updated for Rituximab to read: Pack/vial size (mg) – 100 Units per pack/vial - 2 Cost per pack/vial (mg) – [REDACTED]

Issue 22 Description of the handling of the equal-efficacy assumption

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.1, page 132 of the EAG report states: <i>“Incorrect handling of uncertainty under the equal-efficacy assumption”</i>	Remove the description of the approach as ‘incorrect’.	This is a misleading use of wording. This was the intended approach within the CS, rather than an error, as implied by the EAG’s use of the term ‘incorrect’. This is a subjective judgement from the EAG, and the wording should be updated accordingly.	In response to the company’s observation, we have updated the phrase to read: “Insufficient acknowledgement of the potential uncertainty associated with the equal-efficacy assumption”.

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The starting age in the EAG's preferred base case is incorrectly stated as 70 years in the following tables. The correct starting age should be 71 years. - Table 2, Section 1.6, page 28 - Table 3, Section 1.6, page 29 - Table 46, Section 5.2.2, page 138 - Table 47, Section 5.2.2, page 139	Change the starting age from 70 to 71 years.	To accurately reflect the starting age in the EAG's preferred base case.	Error has been corrected
Page 53 of the EAG report includes a typographical error, as it incorrectly refers to the term HRQoL as "HRQo".	Correct the term "HRQo" to HRQoL.	Update the typographical error to ensure accuracy in abbreviations used.	Error has been corrected
Page 53 of the EAG report includes a typographical error, as it incorrectly refers to venetoclax as "venetoclaxc".	Correct the word "venetoclaxc" to venetoclax.	Update the typographical error to ensure accuracy in drug naming.	Error has been corrected
Paragraph 5, Section 3.3.2, page 53 of the EAG report includes an error in the proportion of patients in the chemoimmunotherapy arm who experienced a cardiac event. The EAG report states that 5.2% of patients receiving	Change the proportion of patients in the chemoimmunotherapy arm who experienced cardiac events from 5.2% to 3.5%	Update error in proportion of patients to ensure accuracy.	Error has been corrected

chemoimmunotherapy experienced cardiac events of any grade, whereas the correct proportion should be 3.5%			
- Paragraph 5, Section 3.3.2, page 53, of the EAG report does not specify in text that the proportion of patients with secondary primary malignancies presented excludes patients with non-melanoma skin cancer - The EAG report also incorrectly states that 0.8% of patients receiving chemoimmunotherapy experienced secondary primary cancers excluding non-melanoma skin cancer, whereas the correct proportion is 0.4%	The text relating to the proportion of patients with secondary primary malignancies excluding non-melanoma skin cancer should be updated from “Secondary primary cancers were also more common with AV treatment than with chemoimmunotherapy (2.7% vs 0.8%)” to “Secondary primary cancers excluding non-melanoma skin cancer were also more common with AV treatment than with chemoimmunotherapy (2.7% vs 0.4%)”.	Update errors in text and proportion of patients to ensure accuracy.	Error has been corrected
Paragraph 2, Section 3.4.3, page 58 of the EAG report states that “At 48 months, VenO (CLL13) reported 95.1% OS and 81.8% PFS, and VenI (CAPTIVATE FD) showed 98% OS and 79% PFS. In comparison, AV (AMPLIFY) reported █████% OS and █████% PFS, though differences in population may contribute”. While these values are indeed correct, the EAG should clarify that the PFS estimate presented is based on investigator assessment and not an	Update the text from “At 48 months, VenO (CLL13) reported 95.1% OS and 81.8% PFS, and VenI (CAPTIVATE FD) showed 98% OS and 79% PFS. In comparison, AV (AMPLIFY) reported █████% OS and █████% PFS, though differences in population may contribute” to “At 48 months, VenO (CLL13) reported 95.1% OS and 81.8% investigator-assessed PFS, and VenI (CAPTIVATE FD) showed 98% OS and 79% investigator-assessed PFS. In comparison, AV (AMPLIFY)	To ensure clarify and avoid confusion.	The text is updated.

IRC assessment.	<i>reported █████ % OS and █████ % investigator-assessed PFS, though differences in population may contribute”.</i>		
The EAG report refers to the Company Evidence Submission by its old name, Document B, in multiple instances, for example: - Table 7, Section 3.1.1, page 45,: “CS, appendix B, section B.3 and CS, doc B, section 2.5” - Table 7, Section 3.1.1, page 45,: “CS, appendix B, sections B.5.3, B.5.6, and CS, doc B, section 2.10” - Table 9, Section 3.4.2, page 57: “AMPLIFY (AV) (CS, doc B, Table 29)” - Table 10, Section 3.4.3, page 58: “AMPLIFY (AV)(CS, doc B, Table 11-12; CSR TLF, Table 14.2.1.1, 14.2.1.6, and 14.2.6.1)” - Paragraph 2, Section 3.5.1, page 60: “A feasibility assessment is provided in Document B, Section 2.10.2”	Update reference from Document B to Company Evidence Submission throughout.	To ensure the Company Evidence Submission Document is being referred to correctly.	Reference from Document B to Company Submission has been updated throughout.
Table 26, Section 4.2.6, page 99 of the EAG report includes a typographical	The table caption should be updated from “Table 26: HSUVs reported by	To ensure correct cross-	Table caption has been

error in the table caption. The current caption is “Table 26: HSUVs reported by Kosmas et al. (2015)⁵³ (obtained from CS, Section 3.4.1)”.	<i>Kosmas et al. (2015)⁵³ (obtained from CS, Section 3.4.1)” to “Table 26: HSUVs reported by Kosmas et al. (2015)⁵³ (obtained from CS, Section 3.4.3)”.</i>	referencing.	updated
Table 16, Section 16, page 73, incorrectly states the proportion of patients with CrCl <60 ml/min for AV as 58%. The correct value is 13.1%.	Update the proportion of patients with a CrCl <60 ml/min for AV from 58% to 13.1%.	Update error in proportion of patients to ensure accuracy.	The EAG amended the proportions.
Section 4.2.6, page 99, of the EAG report includes a typographical error, as it references an incorrect publication year for the Kosmas et al. (2015) study. The current EAG report states “The company examined the possibility that PF patients on and off treatment would have different utility values by referencing the increase in utility off-treatment reported by Kosmas et al (2025), however this approach resulted in an over estimation of the PF off-treatment value, and thus it was assumed that PF patients and on and off-treatment would have the same utility values.”	The publication year of the Kosmas et al. study should be updated from 2025 to 2015.	To ensure referencing to the correct study.	The publication year of the Kosmas et al. study has been updated
Section 5.2.1, page 131 of the EAG report includes a typographical error in the word model, as it incorrectly states	The word “mode” should be updated to model.	Update the typographical error for accuracy.	Error has been corrected

"mode".			

EAG modelling inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'Lists' sheet, cells C97:C99	The list of RDI scenarios should be renamed in line with the changes and additions made by the EAG (e.g. "EAG base case" now being the scenario based on assumed 100% RDI for all treatments).	The proposed amendment allows for scenarios relating to RDI to be correctly selected in the model.	This is not factual error and no impact on the results. The EAG simply wanted to retain the wording used by the company.
'Aca_Ven_model' sheet, column AZ; 'Ibru_Ven_model' sheet, column BF; 'VenO_model' sheet, column BF	It appears that by referring to the newly added columns on the respective sheets, the treatment cost calculations for ibrutinib/obinutuzumab are not being half-cycle corrected. This should be amended to apply half-cycle correction in line with the other treatment components.	Consistent application of half-cycle correction more accurately represents the individual treatment costs of each intervention.	We are still applying the half-cycle correction to the values relating to pre-progression (on treatment). The sum of that column has been used to estimate the proportions of all patients who received subsequent treatments. This means that, even with the half-cycle correction applied, the first three values remain unchanged, and the impact is approximately zero.
'Ibru_Ven_model' sheet, column BN;	The "EAG base case" and "EAG scenario" parts of the formula refer to the incorrect cells on the 'EAG list' sheet (P44 and I44, rather than the correct Q44 and J44); further, the InterventionA named range is incorrectly used (rather than the correct Compa2). All formulae	The proposed amendment results in more accurate calculations of subsequent treatment costs.	The EAG confirmed that there was an error in the part of the formula used when applying the source of subsequent treatment for VenI. The formula has been

	across column BN should be corrected accordingly.		amended, and all analyses have been rerun using the corrected version.
'VenO_model' sheet; column BN	The "EAG base case" and "EAG scenario" parts of the formula incorrectly refer to the InterventionA and Compa2 named ranges (rather than the correct Compa3). All formulae across column BN should be corrected accordingly.	The proposed amendment results in more accurate calculations of subsequent treatment costs.	The current formula refers to cell R44 for the EAG base case and to cell K44 for the scenario analyses. This means that both are correctly referencing VenO, and no amendment is needed.

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Paragraph 2, Section 3.3.1, page 52	The 95% CI of estimated OS at 36 months for AV and chemoimmunotherapy should be marked as confidential, as these data are not available in the public domain.	The estimated OS at 36 months was 94.1% (95% CI: ■■■, ■■■) with AV, and 85.9% (95% CI: ■■■, ■■■) with chemoimmunotherapy.	These data are available in the public domain (see AMPLIFY trial report). We have marked as confidential as requested.
Table 14, Section 3.5.3, Page 65	PFS rates at 30 and 48 months for the FCR/BR arm of the AMPLIFY trial should be marked as confidential, as these data are not available in the public domain.	PFS rate for the FCR/BR arm of the AMPLIFY trial was ~■■% at 30 months and ~■■% at 48 months	PFS rates at 30 and 48 months for the FCR/BR arm have been marked as confidential
Section 5.1.1, page 120	Qualitative description of the cost-effectiveness results should be marked as confidential, as model results are not intended to be published.	“indicate that AV dominates, being ■■■ costly and ■■■ effective in terms of QALYs gained than both VenI and VenO”	Qualitative description of the cost-effectiveness results has been marked as confidential
Table 45, Section 5.2.2, page 134,	RDI for acalabrutinib and venetoclax should be marked as confidential, as these data are not available in the public domain.	For acalabrutinib, RDI is ■■■%, and for venetoclax, it is ■■■%.	RDI for acalabrutinib and venetoclax has been marked as confidential
Paragraph 3, Section 5.2.4, page 147	Qualitative description of the NMB values should be marked as confidential, as model results are not intended to be published.	“The survival model structure (Scenarios 11 and 14) ■■■ incremental QALYs and ■■■ NMB values, showing high dependence on extrapolation choice rather than observed data.”	Text revised based on new analyses.
Table 63,	The proportions of patients in the AV and	AV arm	Confidential marking has been

Section 7.2, page 178,	AVO arms with an ECOG PS of 2 do not need to be marked as confidential. Similarly, the proportions of patients in the AV and AVO arms with unmutated <i>IgHV</i> do not need to be marked as confidential.	Patients with an ECOG PS of 2: 9.6% Patients with unmutated <i>IgHV</i> : 57.4% AVO arm Patients with an ECOG PS of 2: 4.9% Patients with unmutated <i>IgHV</i> : 59.1%	removed

Topic name: Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia

Topic ID: 6232

Managed Access Lead: Sarika Paul

Date of assessment(s): 23/12/2025

Feasibility of successful managed access	Comments / Rationale	
Committee judgement required	Rationale for rating	The company have submitted a managed access proposal including the final data cut of the trial in the company submission, and some additional data from SACT. This will address some uncertainties raised by the EAG, but not all. Therefore the committee will need to assess if managed access is appropriate to resolve the outstanding uncertainties following their decision on routine commissioning.
	Previous ratings and rationale for change	Previously there was no managed access proposal, however one was submitted on request.

Managed Access Proposal	Yes (on request)	
Managed Access Team input at Committee meeting	High	As there is a proposal managed access colleagues will attend committee meetings.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this.
Are there outstanding uncertainties that could be resolved with further data collection?	Medium	The company have submitted a managed access proposal which includes a further data cut from the AMPLIFY trial to provide further OS and PFS data. They also included the collection of SACT data for patient characteristics to address the uncertainty in the generalisability of the AMPLIFY trial to the NHS population. The NICE managed access team also consider it feasible to collect data on the proportion and distribution of subsequent treatments, from both the AMPLIFY trial and SACT.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Yes	There is a further data cut from the AMPLIFY trial, and SACT data available. However as discussed on the uncertainties tab, these would only help resolve some of the uncertainties identified.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	As a cancer topic, SACT data collection is feasible, and a proposal has been made to enable this.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	None identified.

Key questions for committee if Managed Access is considered	
1	
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6	
Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
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Commissioner Ops Briefing

Explanation

This page guides the discussion between the Managed Access Team and partner organisations at Managed Access Operational meetings. It provides a summary of the MAT's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. It is updated with key issues raised by either MAT or the other participants in those meetings. This page is not aimed at the Committee or other readers, and may make points that seem irrelevant outside of the target audience, but should contain no confidential information. As with the overall feasibility assessment, it does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, or use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:

Green - No key issues identified

Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)

Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation.

Topic name:

Topic ID:

Managed Access Lead:

Date of assessment(s):

Acalabrutinib with venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia

6232

Sarika Paul

23/12/2025

Feasibility of successful managed access		Comments / Rationale
Committee judgement required	Rationale for rating	The company have submitted a managed access proposal including the final data cut of the trial in the company submission, and some additional data from SACT. This will address some uncertainties raised by the EAG, but not all. Therefore the committee will need to assess if managed access is appropriate to resolve the outstanding uncertainties following their decision on routine commissioning.
	Previous ratings and rationale for change	Previously there was no managed access proposal, however one was submitted on request.

Managed Access Proposal	Yes (on request)	
Managed Access Team input at Committee meeting	High	As there is a proposal managed access colleagues will attend committee meetings.

Area	Rating	Comments / Rationale
Is this technology eligible for managed access through the CDF or IMF?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this.
What is the likelihood that further data collection could sufficiently resolve key uncertainties?	Medium	The company have submitted a managed access proposal which includes a further data cut from the AMPLIFY trial to provide further OS and PFS data. They also included the collection of SACT data for patient characteristics to address the uncertainty in the generalisability of the AMPLIFY trial to the NHS population. The NICE managed access team also consider it feasible to collect data on the proportion and distribution of subsequent treatments, from both the AMPLIFY trial and SACT.
Are data sources available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	Yes	There is a further data cut from the AMPLIFY trial, and SACT data available. However as discussed on the uncertainties tab, these would only help resolve some of the uncertainties identified.
Is RWE data collection within managed access feasible?	High	As a cancer topic, SACT data collection is feasible, and a proposal has been made to enable this.

Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	None identified.

Points raised by MAT	
1	
2	
3	
4	
5	
6	

Points raised by managed access Ops Group	
1	Following discussion at CMA ops, a proposal was requested from the company.
2	
3	
4	
5	
6	

Early Identification for Managed Access

Explanation on criteria

These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a ‘high’ rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for managed access.

Date agreed with NHSE	12/01/2026

Is this technology eligible for managed access through the CDF or IMF?	
Rating	Rationale
Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this.

Uncertainties

Explanation
This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team. The Managed Access Team will justify its decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating. Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

What is the likelihood that further data collection could sufficiently resolve key uncertainties?	
Rating	Rationale
Medium	The company have submitted a managed access proposal which includes a further data cut from the AMPLIFY trial to provide further OS and PFS data. They also included the collection of SACT data for patient characteristics to address the uncertainty in the generalisability of the AMPLIFY trial to the NHS population. The NICE managed access team also consider it feasible to collect data on the proportion and distribution of subsequent treatments, from both the AMPLIFY trial and SACT.

Key Uncertainties							
Number	Title	Summary of issue	Impact on ICER	Data available to resolve uncertainty	Data collection in company proposal	Resolvable with managed access	Managed Access Team view on feasibility
EAG1	Lack of comparison to acalabrutinib and zanubrutinib monotherapies (treat-to-progression therapies)	Based on guidelines and clinical expert feedback, the company include Venl and VenO as the only relevant comparators, which are the two dual therapies currently approved for untreated CLL. Whilst acalabrutinib and zanubrutinib monotherapies are approved as first line therapies, they are given to patients who are less fit, though there are no clear criteria for this assessment. The company consider that the availability of AV will not affect treatment selection criteria whether patients receive dual or mono therapy. The EAG clinical experts state that the gentler profile of AV compared to Venl and VenO means it is likely to broaden the potential patient pool for dual therapies, beyond those currently considered for Venl or VenO. This means that acalabrutinib and zanubrutinib monotherapies are relevant comparators to AV. The experts also highlighted that these monotherapies are often chosen in settings with limited access to hospitals able to provide the supporting services required for dual therapies. The EAG requested that the company undertake an analysis comparing to acalabrutinib and zanubrutinib monotherapies. The company did not provide the requested analysis. Alternatively, AV access could be restricted to people considered eligible for Venl or VenO, however this may require clear eligibility criteria to be established.	unknown	No	Uncertainty cannot be resolved via data collection in managed access	Low	This could be resolved with further analysis from the company, or by committee discussion
EAG2	Generalisability of AMPLIFY trials to target NHS population (age)	AV is licensed for all patients with untreated CLL, however the population of AMPLIFY is not representative of this group. The mean age of patients included in the AMPLIFY trial (59.9 years) is significantly lower than mean age of UK patients at presentation in clinical practice (around 70 years). The company conducted a subgroup analysis by age and an improvement in progression free survival (PFS) and overall survival (OS) in favour of treatment with AV compared with chemoimmunotherapy was observed. The EAG, however, notes that the sample size of most of the subgroups was small with few events in the subgroup of patients older than 65 years. As such, these analyses were not statistically powered to detect differences between subgroups and results should be interpreted with caution.	This has a small impact on the ICER in EAG scenario analysis, but the effect is dependent on assumptions around relative efficacy.	SACT data could provide information on patient age.	The company have submitted a managed access proposal which includes SACT data collection to help resolve this uncertainty.	High	
EAG3	Reliance on assumption of equal efficacy for AV, Venl and VenO	In the EAG report, they highlight that the company relies on the assumption of equal efficacy of AV to Venl and VenO to inform the cost-effectiveness modelling. This assumption is made across pre-progression survival, time-to-progression, and post-progression survival. This assumption remains highly uncertain and is not well supported with strong evidence. The EAG report states that the supporting analyses provided by the company are based on a limited presentation of STCs and a Bucher ITC, all of which the EAG consider likely to overestimate the benefits of AV due to clear biases. In addition, a recent unanchored MAIC suggests superiority of Venl over AV. The EAG maintains this assumption in the EAG base case but explores a range of scenarios modelling inferior efficacy outcomes for AV to assess the impact on the ICER. In the EAG PSA, the strict assumption of equivalence is relaxed, with each treatment's efficacy coming from the same distribution and parameters but being sampled independently across each iteration, meaning the impact of potential superiority/inferiority is captured.	unknown - but this assumption, and the small incremental QALY differences, means that the ICERs from scenario analyses are very variable	No	The MA proposal by the company only suggests data collection on efficacy of AV.	Low	Further analyses from the company would help resolve this uncertainty, or committee discussion will be needed. While MA would collect further data on AV efficacy, managed access does not typically collect data on comparator treatments. However NICE is increasingly using RWE for comparator drugs during appraisal, and so if managed access is deemed the most appropriate route by the committee, this could be explored.

EAG4	Modelling of time on-treatment and relative dose intensity for AV, VenI and VenO	For AV, the company use information from AMPLIFY to inform the usage of acalabrutinib and venetoclax, combining information on time-to-treatment discontinuation (TTD) and relative dose intensity (RDI). For VenI and VenO, as no TTD information is reported, the company uses the same TTD curve but adjusts it for the number of cycles. The company assumes 100% relative dose intensity for VenI and VenO. The EAG considers that the assumptions of equal TTD and 100% (RDI) are unrealistic, given that AV is considered more tolerable than VenI and VenO. The company approach is likely to be overestimating the usage of VenI and VenO, overestimating their costs. The EAG uses reported information for the treatment completion rates for AV, VenO and VenI, and assumes a linearly decreasing rate from 100% across the relevant number of cycles.	This has a large impact on the ICER and would impact decision making	Possibly	The company have submitted a managed access proposal which suggests collecting ToT for VenO and VenI - data collection for comparator drugs is not typically included within a managed access agreement.	Medium	Managed access agreements do not typically include comparator agreements, however NICE is increasingly using RWE for comparator drugs during appraisal, and so if managed access is deemed the most appropriate route by the committee, this could be explored.
EAG5	Choice of health state utility values used in the model	The company derived HSUVs from EQ-5D-5L data collected in AMPLIFY, mapped these to EQ-5D-3L, and estimated utilities using a mixed model for repeated measures. However, the resulting values appear implausible: PF on-treatment utilities exceed age-matched population norms, and the assumption of equal PF utilities for on- and off-treatment states conflicts with expected improvements once treatment-related toxicity resolves. The AMPLIFY post-progression data were sparse, requiring external adjustments that add further uncertainty. In addition, the company did not fully report key elements of the mixed-model specification, making it unclear whether the estimates are appropriately adjusted for baseline factors influencing HRQoL. The EAG therefore considers that the company's approach risks overstating quality of life and inflating QALY estimates.	This has a small impact on the ICER	No	No utilities data was proposed for collection in the managed access proposal	Low	Committee discussion should be sufficient to resolve this uncertainty.
EAG6	Proportion and distribution of subsequent treatments	The company assumes that almost all patients who progress receive subsequent therapy, applying this proportion equally across AV, VenI, and VenO. This exceeds what is observed in trial data (in all related trials), and the EAG's clinical advisers consider it unrealistic for UK practice. The EAG adopts a more plausible estimate of the proportion receiving subsequent therapy by using the midpoint between trial-reported proportions and the company's assumptions for each arm. For the distribution of specific treatments, the EAG applies a revised allocation based on clinical-adviser feedback, assuming the same distribution across AV, VenI, and VenO.	This has a moderate impact on the ICER	Further data cuts from the trial, or RWE from SACT could help resolve this uncertainty.	Data on subsequent treatments was not mentioned in the company managed access proposal, however it is feasible to collect this is the committee consider it to be a key uncertainty.	High	The AMPLIFY trial collects yearly follow up data for progressed patients who have not withdrawn consent, including data on subsequent treatments. SACT data could provide additional RWE to support the trial data.
COMPANY1	Long term overall survival	There is a further data-cut remaining for the AMPLIFY trial, and inclusion of this data in analysis following a period of managed access would increase the long term data for overall survival and for progression free survival.	Unknown	Further data cuts from the trial could help resolve this uncertainty	Yes the company managed access proposal includes a further data cut from the AMPLIFY trial, which would increase median follow up by several years.	High	

Data Collection

Explanation
This tab collects information on the data sources that could be available for further data collection during a period of managed access, including any ongoing clinical trials, NHS registry data sets, and non-registry data sets. Analysts should assess the availability of this data to answer key uncertainties.

Are data sources available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	
Rating	Rationale
Yes	There is a further data cut from the AMPLIFY trial, and SACT data available. However as discussed on the uncertainties tab, these would only help resolve some of the uncertainties identified.

Existing or proposed clinical trials	
Name and registry ID of trial	Study of Acalabrutinib (ACP-196) in Combination With Venetoclax (ABT-199), With and Without Obinutuzumab (GA101) Versus Chemoimmunotherapy for Previously Untreated CLL (AMPLIFY) NCT03836261
Is trial proposed for managed access?	Yes
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT03836261
Start date	Feb-19
Anticipated completion date	Jan-27
Data cut presented to committee	Apr-24
Data collection timeline	Data collection timelines for AMPLIFY are confidential in the managed access proposal
Description of trial	The purpose of this study is to evaluate the efficacy and safety of acalabrutinib in combination with venetoclax (AV), and AV with and without obinutuzumab compared to chemoimmunotherapy in subjects with previously untreated CLL. Patients were randomised 1:1:1 to a treatment arm, and following completion of treatment cycles, were followed up until progression, and a subsequent survival follow up process was initiated. Post-treatment follow-up was performed every 12 weeks for approximately three years (144 weeks), then every 24 weeks thereafter until disease progression, death, withdrawal of consent by patient, loss to follow-up, or study termination by sponsor, whichever occurred first. Patients who progressed (and had not withdrawn consent) were contacted approximately every year by clinic visit or telephone, to assess survival and subsequent anti-cancer therapy until death, withdrawal of consent, loss to follow-up, or study termination by sponsor, whichever occurred first. At the DCO date of the interim analysis (30th April 2024), and at a median follow-up of 40.8 months (range 0–59 months), 89 (30.6%) IRC-assessed PFS events were reported for AV and 95 (32.8%) for FCR/BR. AMPLIFY met its primary objective and treatment with AV was associated with a statistically significant improvement in IRC-assessed PFS compared with FCR/BR (HR: 0.65; 95% CI: 0.49, 0.87; p-value: 0.004 [p-value boundary: 0.0469]). OS, was a key secondary endpoint of the AMPLIFY trial. At the DCO date of the interim analysis (30th April 2024), 18 patients (6.2%) had died in the AV arm, and 42 patients (14.5%) had died in the FCR/BR arm (10% of maturity). The OS HR for AV versus FCR/BR was 0.33 (95% CI: 0.18, 0.56; nominal p-value: <0.001), representing a 67% reduction in the risk of death for patients who received AV versus FCR/BR.
Link(s) to published data	

Existing or proposed clinical trials	
Name and registry ID of trial	A Study of Acalabrutinib Plus Venetoclax Versus Venetoclax Plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (MAJIC) NCT05057494
Is trial proposed for managed access?	No
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT05057494
Start date	Sep-19
Anticipated completion date	Jul-27
Data cut presented to committee	Not presented in company submission.
Data collection timeline	
Description of trial	a phase III RCT investigating the safety and efficacy of AV versus VenO in untreated CLL or small lymphocytic lymphoma, is ongoing.
Link(s) to published data	

NHS registry data	
Name of registry	SACT
Is registry proposed for managed access?	Yes
Mandated data collection?	SACT is a mandated data set.
Available to use?	Yes
Data items already collected	Yes, the company have submitted a managed access proposal which includes collection of patient characteristics in SACT.
Issues raised by committee or stakeholders	
Data collection timeline	The timeline for data collection was not specified in the managed access proposal

Data collected in clinical practice

SACT

Explanation on criteria
This tab collects more detailed information on the data within registries, and on the registries themselves. It will only be important to fill these firelds in if a managed access agreement is likely to happen.

Is RWE data collection within managed access feasible?		
Overall Rating	Rationale/comments	
High		As a cancer topic, SACT data collection is feasible, and a proposal has been made to enable this.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS England's SACT dataset is an established mandatory dataset
Prior experience with managed access	High	NHS England's SACT Team have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	0
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	NHS England's SACT Team have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS England's SACT Teaml have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk

Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS England's SACT Team's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSE, SACT, blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	0
Analyses		
How easily could collected data be incorporated into an economic model	High	0
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	0
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	0
Security assurance	Yes	0
Existing relevant ethics/research approvals	Not applicable	0
Patient consent	Yes	No prior patient consent required
Funding		
Existing funding	Yes	Established partnership between NHS England's CDF team and SACT team (part of NDRS)
Additional funding required for MA	No	0
If yes, has additional funding been agreed in principle	Not applicable	0
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		

Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created
Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created
Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	0

Other issues

SACT

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	Rationale/comments
No	None identified.

Burden		Rating	Rationale / comments
	Expected overall additional patient burden from data collection?	Low	Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access
	Expected overall additional system burden from data collection?	Low	As above
	Do stakeholders consider any additional burden to be acceptable	Not applicable	0
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	0

Patient Safety		Rating	Rationale / comments
	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

Patient access after MAA		Rating	Rationale / comments
	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative Medicines Fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	0

Service implementation		Rating	Rationale / comments
	Is the technology disruptive to the service	No	0
	Will implementation subject the NHS to irrecoverable costs?	No	0
	Is there an existing service specification which will cover the new treatment?	Yes	0

Patient eligibility		Rating	Rationale / comments
	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	It is expected that the entire eligible patient population, as recommended by NICE, will be able to access the medicine. Detailed blueteq criteria will be developed by NHSE prior publication of any positive draft final NICE guidance
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	-

	Rating	Rationale / comments

Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?	
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes
	As above	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?	
	Will the technology be used differently to how it would be if it had been recommended for use?	No
	0	
	Any issues from registry specific questions	No
	0	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?	
	Any issues from registry specific questions	No
	0	
	Additional considerations for managed access	
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes
	0	
	Any issues from registry specific questions	No
	0	

Equality		Rating	Rationale / comments
	Are there any equality issues with a recommendation with managed access	No	There are not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

Timings		Rating	Rationale / comments
	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access