NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **AstraZeneca**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Leukaemia Care
   b. Chronic Lymphocytic Leukaemia Support Association-Lymphoma Action
   c. UK Chronic Lymphocytic Leukaemia Forum- British Society for Haematology- Royal College of Pathologists

4. **Expert personal perspectives** from:
   a. Adrian Bloor – clinical expert, nominated by UK Chronic Lymphocytic Leukaemia Forum-Royal College of Pathologists
   b. Anna Schuh – clinical expert, nominated by National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
   c. Jackie Martin – patient expert, nominated by Chronic Lymphocytic Leukaemia Support Association-Lymphoma Action
   d. Nick York – patient expert, nominated by Leukaemia Care

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

6. **Evidence Review Group – factual accuracy check**

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 for untreated and treated chronic lymphocytic leukaemia (ID1613)

Document B

Company evidence submission

August 2020

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ID1613_Acalabrutinib_ Document B_[REDACTED]	**2**	**Yes**	**10th August 2020**

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Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse events
BCL	B-cell lymphoma
BCR	B-cell receptor
BCRI	B-cell receptor inhibitor
BFI	Brief Fatigue Inventory
BNF	British National Formulary
BR	Bendamustine plus rituximab
BSH	British Society of Haematology
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	Chronic lymphocytic leukaemia
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EPAR	European Public Assessment Report
EQ-5D	5-dimension EuroQol questionnaire
ESMO	European Society for Medical Oncology
FACIT	Functional Assessment of Cancer Therapy
FCR	Fludarabine, cyclophosphamide and rituximab-based
HR	Hazard ratio
HSUV	Health state utility values
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
IR	Idelalisib plus rituximab
IRC	Independent Review Committee
ITK	Interleukin-2–inducible kinase
ITT	Intention-to-treat
iWCLL	International Workshop on CLL
KEE	Key
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PICOS	population, intervention, comparators, outcomes, study design
PPS	post-progression survival
PR	partial response
PRL	partial response with lymphocytosis

PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
R/R	Relapse/refractory
SAE	Serious adverse events
SLR	Systematic literature review
TEAEs	Treatment-emergent adverse events
TLS	Tumour lysis syndrome
TTDeath	Time to pre-progression death
TTNT	Time to next treatment
TTP	Time to progression.
UK	United Kingdom
USA	United States of America

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

B.1.1 Decision problem

The objective of this single technology appraisal is to evaluate the clinical- and cost-effectiveness of acalabrutinib monotherapy for patients with untreated and treated chronic lymphocytic leukaemia (CLL) within its anticipated marketing authorisation for untreated and treated CLL.

The submission focuses on part of the technology's anticipated marketing authorisation and is in line with the scope issued by the National Institute for Health and Care Excellence (NICE) (Table 2). Aligned with its expected use in UK clinical practice, AstraZeneca are seeking reimbursement in the following patient populations:

A. Previously untreated adults with CLL who are ineligible for fludarabine, cyclophosphamide and rituximab-based (FCR) therapy

B. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable, and

C. Adults with relapsed or refractory (R/R) CLL who have had at least one previous therapy

The indication wording proposed by AstraZeneca is as follows:

[redacted]

The submission presents data for the following outcomes: progression-free survival (PFS), overall survival (OS), time to next treatment, adverse events (AEs), and health-related quality of life (HRQoL), which is consistent with the decision problem outlined by NICE. The economic analysis follows the NICE reference case and therefore ensures alignment with the NICE decision problem for acalabrutinib.

B.1.1.1 Comparators

A number of potential comparators are listed within the decision problem. However, only a proportion of these are routinely used in clinical practice for the patient populations relevant to this appraisal. Treatment options in CLL are guided by patient characteristics including their fitness level (usually assessed based on age, comorbidities, organ function), their performance status (PS) as defined by the Eastern Cooperative Oncology Group (ECOG), the presence of high-risk features (cytogenetic abnormalities), patient preference and social factors, such as caregiver stress and ease of transport.[1]

There are no standard criteria for diagnosing a patient's fitness level, however a few measures are commonly used. The combination of a patient's Cumulative Illness Rating

Scale (CIRS) score[2] (in clinical trials) and creatinine clearance (CrCL) have been used to assess the fitness level and organ function of patients able to tolerate intensive chemoimmunotherapy treatments. The CIRS is composed of 14 comorbidity categories with up to four points in each category. Patients who have a good ECOG PS (ECOG <2), a CIRS ≤6 and creatinine clearance ≥70 mL/min are generally categorised as "fit" and able to tolerate aggressive treatment, with the majority of patients aged ≤65 years. However, many patients are not able to tolerate such aggressive treatment regimens, and therefore are ineligible for treatments such as FCR therapy ('unfit patients').

A. Previously untreated adults with CLL who are ineligible for FCR therapy

The British Society of Haematology (BSH) guidelines (2018) recommends that **chlorambucil in combination with obinutuzumab** is the main-stay treatment option for patients with untreated newly diagnosed CLL whom are considered unfit for chemo-immunotherapy (e.g. FCR). In addition, outputs from a UK clinical advisory board comprising of 9 practicing haematologists advised that chlorambucil in combination with obinutuzumab is the most relevant comparator for this appraisal.[3,4]

FCR therapy, and **bendamustine with or without rituximab (BR)** are not suitable comparators as these treatments are considered unsuitable for 'unfit' patients. Whilst, for patients who are treatment-naïve, young and have no comorbidities (i.e. young, 'fit' patients), the combination of FCR is the recommended standard of care.[5] For bendamustine plus rituximab (BR) therapy, the BSH guidelines on CLL (2018) recommends BR as an alternative for fit patients only in whom FCR is contra-indicated due to specific comorbid conditions.[4] Furthermore, a group of nine UK-practicing haematologists advised that the use of BR therapy has diminished over recent years, and BR therapy is more commonly used in clinical trial settings only.[3]

Additionally, the pivotal Phase 3 randomised controlled trial (RCT) ELEVATE-TN study comparing acalabrutinib, acalabrutinib plus obinutuzumab, and chlorambucil plus obinutuzumab, excludes patients who would otherwise receive FCR-therapy. This pivotal study has been used to inform the clinical and pharmaco-economic evaluation of acalabrutinib in previously untreated patients.

Chlorambucil with or without rituximab is not routinely used in UK clinical practice and therefore it does not represent NHS standard care. NICE has not previously published guidance on the use of chlorambucil monotherapy or in combination with rituximab, and the BSH guidelines on CLL (2018) states that "*Chlorambucil in combination with rituximab is not routinely recommended"*.[4] Therefore, chlorambucil with or without rituximab is not a relevant comparator for this appraisal.

We note that **venetoclax with obinutuzumab** for untreated CLL is included in the decision problem and is subject to the ongoing NICE appraisal (ID1402). However, at the time of submission to NICE, the appraisal is still ongoing, and therefore venetoclax with obinutuzumab is not routinely commissioned by NHS England, nor does it reflect established NHS clinical practice. Therefore, AstraZeneca do not consider venetoclax with obinutuzumab a relevant comparator for this appraisal.

B. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable

Ibrutinib was recommended by NICE in TA429 for patients who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable.[6] Since its recommendation, ibrutinib has become established NHS care for this patient population, and is therefore a relevant comparator for this appraisal.[3] However, **idelalisib with rituximab** is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab.[6] BSH guidelines highlights that the higher risk of infection and death associated with idelalisib therapy has led to the European Medicines Agency (EMA) amending the licence to "first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies".[4,7] Therefore, idelalisib with rituximab is not considered a relevant comparator for this appraisal.

C. Adults with R/R CLL who have had at least one previous therapy

Following an initial response to treatment, most patients with CLL relapse and need additional therapy.[8] In addition, a proportion of patients have disease which is refractory to initial treatment. Collectively, these patients are referred to as having R/R CLL. Treatment for R/R CLL requires the evaluation of both the number and intensity of the previous therapies, the duration of response to those therapies, the presence of high-risk features [del(17p)/*TP53* mutations], and patient comorbidities.[4] In patients who have R/R disease, the BSH guidelines recommend repeat testing for the presence of TP53 disruption by FISH and DNA sequencing. Chemoimmunotherapy is not advised in patients who have not responded to prior chemoimmunotherapy, relapsed within 24–36 months of intensive chemoimmunotherapy or have acquired TP53 disruption.[4]

Ibrutinib represents established NHS practice and is therefore a relevant comparator to this appraisal in patients with R/R CLL who had at least one previous therapy.[3] This position is widely accepted with UK clinicians and is supported by nine UK-practicing haematologists who attended a recent advisory board meeting.[3]

Since the introduction of ibrutinib in the clinical care pathway for patients with R/R CLL, the utilisation of **FCR** therapy has become low, and therefore no longer represents established NHS clinical practice. FCR therapy is further complicated since current recommendations state that it is not advised in patients who have failed to responded to prior chemoimmunotherapy, or relapsed within 24–36 months of intensive chemoimmunotherapy. Therefore, the utilisation of FCR in R/R patients is low and so does not represent established NHS practice.[3,9]

As per the conclusions in NICE TA561, people with CLL whose disease has relapsed after 1 previous chemo-immunotherapy would be eligible for a B-cell receptor (BCR) pathway inhibitor, such as ibrutinib or idelalisib. However, most people receive treatment with ibrutinib rather than **idelalisib plus rituximab (IR)** in NHS clinical practice because IR has a more intensive dosing regimen than ibrutinib and is associated with an increased risk of infection.[10] Therefore, idelalisib with rituximab is not a relevant comparator.

Venetoclax with rituximab is not established NHS clinical practice. Whilst venetoclax with rituximab is recommended by NICE (TA561), only a small proportion of patients currently receive treatment with venetoclax in combination with rituximab after first relapse; representing only 3—7% patients in NHS practice.[9] Most commonly, venetoclax with rituximab is used in patients with a cardiac history, in whom Bruton's tyrosine kinase inhibitor (BTKi) is not a suitable treatment option. In contrast, ibrutinib represents the mainstay treatment option for treating patients with R/R CLL; estimated to account for between ~70% and 80% of NHS clinical practice.[9] Furthermore, feedback from nine UK-practicing haematologists from a recent advisory board noted that a BTKi, such as ibrutinib, is preferred vs venetoclax with rituximab in elderly and comorbid patients, and in patients with reduced renal function (defined as a CrCL <80 mL/min) who are at a particular risk from developing tumour lysis syndrome (TLS). This is particularly relevant as venetoclax has a complex dosing regimen (dose ramp up for 5 weeks), and additional TLS monitoring is required. Therefore, clinicians concluded that overall, there was a preference for treating with a BTKi prior to treating with venetoclax with rituximab.[3]

A summary of the comparators considered relevant for this appraisal is presented in Table 1.

Table 1. Comparators considered relevant for this appraisal

Comparator listed in the final scope	Relevance to this appraisal
Patients with previously untreated CLL	
Chlorambucil with or without rituximab	×
Obinutuzumab with chlorambucil	✓
Bendamustine with or without rituximab	×
Rituximab with fludarabine and cyclophosphamide	×
Venetoclax with obinutuzumab (subject to NICE appraisal)	×
Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable	
Ibrutinib	✓
Idelalisib with rituximab	×
Adults with R/R CLL who have had at least one previous therapy	
Bendamustine with or without rituximab	×
Venetoclax with rituximab	×
Ibrutinib	✓
Rituximab with fludarabine and cyclophosphamide	×
Idelalisib with rituximab	×

BTKI, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; R/R, relapsed refractory.

Table 2. 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 CLL (includes untreated and treated)	As per scope	N/A
Intervention	Acalabrutinib alone or with obinutuzumab	Acalabrutinib monotherapy in: • Previously untreated adults with CLL who are ineligible for FCR therapy, or • Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable, or Adults with R/R CLL who have had at least one previous therapy	Efficacy and safety data are available for acalabrutinib monotherapy in both untreated and, R/R patients from the pivotal Phase 3 RCTs ELEVATE-TN and ASCEND, respectively, and in patients receiving treatment with acalabrutinib in combination with obinutuzumab in the untreated patients only. However, feedback from UK clinical experts noted that acalabrutinib monotherapy is preferred due to the AEs associated with obinutuzumab.[3] Therefore, based on clinical feedback and the feasibility of demonstrating a cost-effective case, AstraZeneca is seeking for reimbursement for acalabrutinib monotherapy only.
Comparator(s)	For untreated CLL, including (but not limited to): • ibrutinib (17p deletion or TP53 mutation) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab	Previously untreated patients with CLL who are ineligible for FCR therapy: • obinutuzumab with chlorambucil Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable:	Previously untreated patients with CLL who are ineligible for FCR therapy: • Data informing the clinical and pharmaco-economic evaluation of patients with previously untreated CLL is taken from the ELEVATE-TN study, which only includes patients who are ineligible for FCR-based therapy. Therefore, patients who are eligible, or fit enough to receive FCR therapy are not considered in this appraisal.[11]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• rituximab with fludarabine and cyclophosphamide • venetoclax with obinutuzumab (subject to NICE appraisal) For treated CLL, including (but not limited to): • bendamustine with or without rituximab • venetoclax with rituximab • ibrutinib • rituximab with fludarabine and cyclophosphamide • idelalisib with rituximab	• ibrutinib Adults with R/R CLL who have had at least one previous therapy: • ibrutinib	• BR therapy is generally only considered for fitter patients in whom FCR is contra-indicated due to specific comorbid conditions.[4] • UK clinical experts concluded that the use of BR therapy has diminished in UK clinical practice, and it's use is more often seen in clinical trials.[3] • Chlorambucil with or without rituximab is not routinely used in UK clinical practice, and the BSH guidelines states that its use is not routinely recommended.[4] • Venetoclax with obinutuzumab is not considered a relevant comparator as at the time of submission, the appraisal is ongoing.[12] Therefore, venetoclax with obinutuzumab is not routinely commissioned by NHS England, and it does not represented established NHS practice. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation in whom chemo-immunotherapy is unsuitable: • Patients typically receive treatment with ibrutinib, in-line with the recommendations in TA429.[6] • UK clinical experts, and NICE have previously concluded that, idelalisib with rituximab is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab.[3]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• The licence for idelalisib therapy has been amended to "first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies".[7] Therefore, idelalisib therapy is not a relevant comparator. Adults with R/R CLL who have had at least one previous therapy: • Patients often receive treatment with ibrutinib as second-line therapy. • Since the introduction of ibrutinib in UK clinical practice, the use of FCR-based therapy, or idelalisib plus rituximab has diminished and no longer reflect established NHS practice.[3,6] • As previously discussed, FCR-therapy is typically reserved for younger, fitter patients, and its use is not advised in patients who have not responded to prior chemoimmunotherapy, relapsed within 24–36 months of intensive chemoimmunotherapy, whilst idelalisib plus rituximab is associated with significant AEs.[4,6]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• Venetoclax with rituximab does not currently represent established NHS clinical practice as its utilisation is low, with only 1—7% patients currently treated with this regimen. UK clinicians advised that the 5-week ramp-up dosing regimen and the requirements for monitoring of TLS has resulted in clinicians typically preferring to use ibrutinib as 2L therapy, whilst venetoclax with rituximab is more often used following subsequent[3] or in patients with a cardiac history who cannot tolerate ibrutinib. Further information is available in Section B.1.1.1.
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • time to next treatment • adverse effects of treatment • health-related quality of life.	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-minimisation analysis may be carried out. 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 perspective. The availability and cost of biosimilar products should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Cost-effectiveness of acalabrutinib vs obinutuzumab with chlorambucil in previously untreated patients with CLL: • Cost-minimisation analysis of acalabrutinib vs ibrutinib in previously untreated adults with CLL who have a 17p deletion or TP53 mutation: • Cost-minimisation analysis of acalabrutinib vs ibrutinib in adults with R/R CLL	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people with a 17p deletion or TP53 mutation • people untreated • people treated	Subgroups considered: • people with a 17p deletion or TP 53 mutation • people untreated • people treated	The pharmaco-economic evaluation of acalabrutinib is informed from the pivotal Phase 3 RCT evidence from the ELEVATE-TN and ASCEND trials, in patients either previously untreated or treated, respectively. Data from the ELEVATE-TN trial only includes patients in whom FCR-based therapy is unsuitable.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable • People with IgHV unmutated disease	• people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable	A proxy for the comparative efficacy of high-risk patients, defined as having a 17p deletion or TP53 mutation, are considered using the ITT data from the ASCEND trial, and compared with the current standard of care, ibrutinib via a MAIC. As per the approach adopted in NICE TA429, in the absence of any direct head-to-head data in previously untreated patients with a 17p deletion of TP53 mutation, we have compared the efficacy and safety of acalabrutinib vs ibrutinib via a MAIC using data from previously treated patients in the ASCEND and RESONATE trials as a proxy for previously untreated patients.[6] In NICE TA429, the committee accepted that in the absence of any evidence, the data from previously treated patients could be taken into account and led to a positive recommendation in first line high-risk patients.[6]

AEs, adverse events; BR, bendamustine plus rituximab; BSH, British Society of Haematology; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab-based; IgHV, immunoglobulin heavy chain variable region; MAIC, matching-adjusted indirect comparison; QALY, quality-adjusted life year; RCT, randomised controlled trial; R/R , relapsed or refractory; TLS, tumour lysis syndrome

B.1.2 Description of the technology being appraised

The summary of product characteristics (SmPC) and European public assessment report (EPAR) for acalabrutinib will be provided as soon as they become available .

Table 3. Technology being appraised

UK approved name and brand name	UK approved name: Acalabrutinib Brand name: CALQUENCE®
Mechanism of action	Acalabrutinib is a selective small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue (Cys481) in the BTK active site, leading to inhibition of BTK enzymatic activity.[13] BTK is a signalling molecule of the BCR and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. BTK is an essential element of the BCR-mediated signalling pathway, which is critical in the pathology of CLL.[13] Acalabrutinib is a second generation BTKi, with BTK with minimal off-target activity compared to 1st generation inhibitors such as ibrutinib (see Figure 2), thus potentially minimising off-target related adverse events.[13]
Marketing authorisation/CE mark status	Acalabrutinib is awaiting UK/EMA marketing authorisation for the indication described in this submission and a decision is anticipated in [redacted]. On 23rd July 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for acalabrutinib.[14] The anticipated wording of the Marketing Authorisation is: [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The SmPC is not available at this time. A copy will be provided as soon as possible.
Method of administration and dosage	The expected recommended dose of acalabrutinib is 100 mg taken orally twice daily. Patients are advised to swallow the capsule whole with water (with or without food) and wait 12 hours between doses. When acalabrutinib is administered in combination with obinutuzumab, it should be administered prior to obinutuzumab when given on the same day.
Additional tests or investigations	No

List price and average cost of a course of treatment	At the time of submission, the list price of acalabrutinib had not been confirmed [redacted]
Patient access scheme (if applicable)	[redacted]

BCR, B cell antigen receptor; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CHMP, Committee for Medicinal Products for Human Use; CLL, chronic lymphocytic leukaemia; EMA, European Medicines Authority; MCL, mantle cell lymphoma; SCL, small lymphocytic leukaemia; SmPC, summary of product characteristics.

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

B.1.3.1 Disease overview

CLL is the most common type of leukaemia and is more common in men than women.[15] CLL is characterised by the abnormal clonal proliferation and accumulation of mature and typically CD5-positive B-lymphocytes within the blood, bone marrow, lymph nodes, and spleen.[16] CLL has a unique disease trajectory, as most patients with CLL may not present with any symptoms at diagnosis. When present, typical cancer related symptoms or B symptoms, such as fever, chills, night sweats and weight loss may occur. Common clinical signs may include: enlarged lymph nodes, liver, spleen or bruising. Blood counts are often the most common abnormality with an increase in monoclonal lymphocytes and with progression over time, decreased haemoglobin and platelets.[17,18]

B 1.3.1.1 Clinical presentation, staging and diagnosis

In the UK, and based on the International Workshop on CLL (iwCLL), a diagnosis of CLL requires the presence of ≥ 5 × 10^9/L monoclonal B lymphocytes (5000/μL) in the peripheral blood for at least 3 months.[19,20]

Patients with CLL are often asymptomatic at presentation, with most (>70%) currently being diagnosed at an early stage.[21] Many of these patients will have indolent CLL for years and usually do not require treatment until the onset of symptoms.[22,23] Once a patient is diagnosed, clinical staging of CLL is established based on a physical examination and complete blood counts.

There are two widely used clinical staging systems in CLL — the Rai classification system,[24] which is primarily used in North America, and the Binet staging system,[25] which is mainly used in the UK and Europe.[19,22,23,26] The Rai classification system has five stages and is based on the number of lymphocytes, red blood cells and platelets and whether the lymph nodes, spleen or liver are enlarged. The Binet staging system has three stages based on the number of red blood cells and platelets and the number of areas of the lymphatic system that are enlarged, see Table 1.[24,25] Both clinical staging systems have been described due to their relevance to the acalabrutinib clinical trials.

Clinical staging does not accurately identify patients who may have indolent disease, nor does it predict response to treatment; however, it has clear prognostic implications for survival. With both staging systems, high-risk or advanced-stage (i.e., Rai stage III-IV; Binet stage C) patients have a median survival of one to two years, whereas low-risk or early-stage (i.e., Rai stage 0; Binet stage A) patients have a median survival time of more than 10 years.[22,23,26]

The highly heterogeneous disease course of CLL is also driven by an increasing number of patient and cytogenetic factors. High-risk cytogenetic factors typically predict an aggressive disease course and particularly poor prognosis. Such alterations have also been shown to impact treatment responses, including TP53 disruption (defined by either deletion of chromosome 17p or mutation of the TP53 gene) and IGHV mutation status. Additional

alterations, including del(11q), del(13q) and complex karyotype, have also been noted and further understanding of how these impact treatment outcomes is emerging.

In addition to high-risk cytogenetics, elderly patients (≥ 65 years old) are typically less fit than younger patients and commonly present with a combination of comorbidities, polypharmacy and impaired organ function that may impact their ability to tolerate treatment and are therefore typically ineligible for FCR regimens.

Typically, survival ranges from 5 to 10 years depending on disease stage (Rai 0: > 10 years; Rai I–II: > 8 years; Rai III–IV: 6.5 years). Treatment is usually not advocated for asymptomatic patients with early-stage CLL (i.e. Binet stage A or B or Rai stage 0–II; Table 4). Indeed, it is much more common for patients to be monitored for signs of increasing disease activity, often over several years.[27]

Table 4. Summary of Rai and Binet CLL staging systems

Stage	Description	Predicted median survival[a]
Rai system		
Low risk		
0	Lymphocytosis: lymphocytes in blood > 5 × 10^9/L, clonal B cells and > 40% lymphocytes in the bone marrow	> 10 years
Intermediate risk		
I	Lymphocytosis and lymphadenopathy	> 8 years
II	Lymphocytosis and hepatomegaly and/or splenomegaly with or without lymphadenopathy	
High risk		
III	Lymphocytosis and haemoglobin < 11.0 g/dL with or without lymphadenopathy or organomegaly	6.5 years
IV	Lymphocytosis and thrombocytes < 100 × 10^9/L with or without lymphadenopathy or organomegaly	
Binet system		
Binet A	Haemoglobin ≥ 10.0 g/dL, thrombocytes ≥ 100 × 10^9/L, < 3 lymph nodes involved	> 10 years
Binet B	Haemoglobin ≥ 10.0 g/dL, thrombocytes ≥ 100 × 10^9/L, ≥ 3 lymph nodes involved	> 8 years
Binet C	Haemoglobin < 10.0 g/dL, thrombocytes < 100 × 10^9/L	6.5 years

a Survival data are from Pflug et al. 2014,[28] as described by Eichorst et al. 2015[5]
CLL, chronic lymphocytic leukaemia.

B 1.3.1.2 Epidemiology

CLL is the most common type of leukaemia[15] and is more common in men than in women (Table 5). CLL accounts for 1% of total cancer cases in the UK (2015–2017) with 3,824 new cases diagnosed every year equating to 10 new cases a day. Since the early 1990s, the incident rate of CLL in the UK has risen by 17% with 37% of cases in females, and 63% in males. CLL is widely classified as an orphan disease, with an incidence rate of 5.7 per 100,000 population in the UK (Table 5). Every year, there are approximately 990 CLL deaths in the UK every year equating to nearly 3 every day (2015-2017).[29]

Table 5. CLL incidence rates in England and Wales (2017)

Data for leukaemia code C91.1.	England	Wales	UK
Number of new cases	3,157	124	3,541
European age-standardised incidence rates			
Persons	6.1 per 100,000	3.9 per 100,000	5.7 per 100,000
Male	8.4 per 100,000	4.6 per 100,000	7.9 per 100,000
Female	4.2 per 100,000	3.3 per 100,000	3.9 per 100,000

CLL, chronic lymphocytic leukaemia.
Source: Cancer Research UK[29]

B.1.3.2 Burden of CLL

CLL is a chronic disease associated with high disease morbidity and quality of life detriments; as such, maintaining or improving the quality of life of CLL patients with more advanced or progressive disease is important.

B1.3.2.1 Symptom burden

The most widely used tool to assess the symptom burden in patients with CLL is the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30).

Patients with CLL experience worse HRQoL than the general population across several domains, including symptoms (e.g. fatigue and sleep disturbances), as well as physical and mental functioning with fatigue being the most notable clinical symptom of CLL.[30,31]

A longitudinal study in patients with CLL (n=76) compared EORTC QLQ-C30 scores for patients who were not receiving anti-cancer therapy at the time of the study but could have received previous chemotherapy (n = 33) or no previous chemotherapy (n = 43). Data showed that overall, patients with CLL have substantially worse HRQoL than the general population.[30] The most troublesome symptoms (> 35) were fatigue and sleep disturbances in both groups, while scores of > 20 were seen for pain and constipation in both groups, dyspnoea in the previous chemotherapy group and appetite loss in the chemotherapy-naïve group (Table 6).[30]

Table 6. Comparison of HRQoL in patients with CLL who had or had not received chemotherapy versus the general population

	Mean score (SD)				*p* value CLL vs healthy controls	Effect-size
	Patients with CLL			Healthy controls (N = 152)		
	Prior chemotherapy (n = 33)	No prior chemotherapy (n = 43)	Total (N = 76)			
EORTC QLQ-C30 Symptom Scales[a]						
Fatigue	47.2 (29.2)	44.2 (29.9)	45.5 (29.4)	25.3 (24.8)	< 0.001	0.81
Nausea/vomiting	12.0 (20.4)	11.6 (17.6)	11.8 (18.7)	3.5 (12.0)	< 0.001	0.69
Pain	26.6 (31.1)	33.3 (33.3)	30.4 (32.3)	25.7 (30.3)	NS	0.16
Dyspnoea	28.3 (36.4)	19.0 (25.7)	23.1 (31.0)	12.9 (23.2)	< 0.01	0.44
Sleep disturbance	41.7 (36.9)	35.7 (32.8)	38.2 (34.5)	31.0 (33.3)	NS	0.22
Appetite loss	16.2 (29.0)	21.7 (29.0)	19.3 (28.9)	6.8 (18.4)	< 0.001	0.68
Constipation	21.9 (33.5)	24.4 (34.2)	23.3 (33.6)	8.7 (21.1)	< 0.001	0.69

	Mean score (SD)				*p* value CLL vs healthy controls	Effect-size
	Patients with CLL			Healthy controls (N = 152)		
	Prior chemotherapy (n = 33)	No prior chemotherapy (n = 43)	Total (N = 76)			
Diarrhoea	9.1 (19.1)	13.5 (26.6)	11.6 (23.6)	10.5 (22.0)	NS	0.05
Financial impact	10.1 (19.5)	16.7 (27.8)	13.8 (24.6)	12.7 (24.0)	NS	0.05

[a]Higher values indicate higher severity.

CLL, chronic lymphocytic leukaemia; CT, chemotherapy; EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, health-related quality of life; NS, not significant; QLQ-C30, 30-item core quality of life questionnaire; SD, standard deviation.

Source: Holzner et al. 2004[30]

A significantly higher rate of fatigue in CLL patients compared to the general population has been further demonstrated in a large international study (n=1,482). In this study 80% of respondents reported statistically significantly higher levels of fatigue than the general population (mean Brief Fatigue Inventory [BFI] scores of 2.8 vs 2.2; $p < 0.001$). Fatigue increased in-line with disease stage: mean BFI scores were 2.2, 2.6 and 3.6 for low-risk, intermediate-risk and high-risk CLL cases, respectively. In a multivariate analysis, female sex, extent of comorbid health conditions, current disease stage, emotional well-being score, social well-being score, and both current and previous treatments for CLL were associated with higher fatigue scores.[31]

In addition to the symptom burden of CLL, AEs associated with treatment add to the clinical burden of CLL. The following AEs are the most frequently reported according to a review of 1,168 patients receiving BR, FCR, rituximab monotherapy or ibrutinib monotherapy: anaemia (32–37%), neutropenia (58–72% of patients receiving BR or FCR), dyspnoea (19–28%), infection (21–38%) and nausea/vomiting (32–34% of patients receiving BR or FCR).[32]

B1.3.2.3 Impact on quality of life

The symptoms associated with CLL and treatment adversely affect patients' HRQoL.

Due to the chronic incurable relapsing remitting nature of CLL, many patients experience emotional and mental distress due to their condition including depression (22.6%), anxiety (40.3%) and have difficulty sleeping (34.7%).[10]

In the UK, a large number of patients with CLL are on 'Watch and Wait'. This is a process whereby patients with CLL are regularly monitored to track disease progression with treatment only initiated once intervention is required. During the "Watch and Wait" period patients are monitored and face constant uncertainly and emotional strain which has often been described as "Watch and Worry". In the UK there are approximately 13,000 people living with CLL who are on 'Watch and Wait'. Just over half of these patients (53%) express feeling more concerned or anxious since diagnosis, with 1 in 8 feeling constantly depressed or anxious.[33]

Patients with CLL live with significant emotional, psychological and physical issues that negatively impact on their quality of life.

B.1.3.3 Life expectancy

Although CLL is not curable, it often develops very slowly and treatment can keep it under control for many years with the majority of patients being alive at five years. The five-year survival rates for patients with CLL in England and Wales are similar to the average across Europe (Table 7).

Table 7. Five-year survival rates for CLL

Gender	England	Wales	European average
Male	67%	65%	68%
Women	73%	71%	74%

Source: Cancer Research UK[34]

OS ranges from 5 to ≥ 10 years, depending on patient age, disease stage and the presence or absence of high-risk mutation, with many 'fit' CLL patients expected to live out their normal lifespan (Table 8). Survival however is reduced in older/less fit and high-risk patients.[5]

Table 8. Median survival by stage

Stage	Median survival
Binet A	> 10 years
Binet B	> 8 years
Binet C	6.5 years

Source: Cancer Research UK[35]

B.1.3.4 Clinical pathway of care and acalabrutinib place in therapy

Most CLL patients (>70%) start off asymptomatic (Binet stage A or B or Rai stage 0–II), at which point the best approach is "Watch and Wait" or "active observation" until symptoms arise.[21] The majority of these patients may never require treatment during their lifetime.[21] 'Watch and Wait' generally includes periodic assessments of blood cell counts and clinical examination so that treatment can be initiated on development of symptomatic active disease.[20,36]

In patients who develop symptoms and require treatment, CLL remains an incurable disease. The UK clinical pathway is shaped by decisions made by the NICE, guidance from the BSH, and international bodies including the iwCLL, the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN). Guidance from NICE for these patients is summarised in Table 9.

The therapeutic landscape and available treatment options in CLL has constantly been evolving. The goal of treatment is to achieve effective and durable disease control while maintaining quality of life by minimizing the adverse events and toxicities of treatment. As such, the optimal first-line treatment strategy is largely dependent on the individual patient's characteristics, including age/fitness level, PS, and the presence of high-risk cytogenetics; as well as patient preference and social factors.[1,37]

Table 9. Current NICE guidance

Therapy line	Regimen (NICE TA)	Conditions of use
Untreated CLL[a]	**For patients without a 17p deletion or TP53 mutation**	
	Rituximab in combination with fludarabine and cyclophosphamide (TA174)[b38]	For whom fludarabine in combination with cyclophosphamide is considered appropriate
	Bendamustine +/- rituximab (TA216)[39]	For those who cannot have fludarabine combination chemotherapy
	Chlorambucil + rituximab (no TA published)[c]	
	Obinutuzumab + Chlorambucil (TA343)[40]	For whom fludarabine-based therapy and bendamustine based therapy is unsuitable
	For patients with a 17p deletion or TP53 mutation	
	Ibrutinib monotherapy (TA429)[6]	For whom chemoimmunotherapy is unsuitable
	Idelalisib with rituximab (TA359)[41]	For those with a 17p deletion or TP53 mutation
	Venetoclax (TA487)[42]	With a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, funded by CDF
Treated CLL	Venetoclax with rituximab (TA561)[10]	For people who have had at least 1 previous therapy
	Rituximab in combination with fludarabine and cyclophosphamide (TA193)[43]	For people not refractory to fludarabine and who have not been previously treated with rituximab[d]
	Idelalisib with rituximab (TA359)[41]	For people whose disease has been treated but has relapsed within 24 months
	Ibrutinib (TA429)[6]	For people who have had at least 1 previous therapy
	Venetoclax (TA487)[42]	With a 17p deletion or TP53 mutation whose disease has progressed after a B-cell receptor pathway inhibitor *OR* without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor, funded by CDF

a ID1613 (acalabrutinib), ID2708 (ibrutinib) and ID1401 (venetoclax) in progress.
b Fludarabine monotherapy (TA119) not recommended.
c use of chlorambucil, with or without rituximab, is detailed in TA343.
d unless treated within the context of a clinical trial either at a lower dose than licensed or in combination with chemotherapy other than fludarabine and cyclophosphamide.
BCR, B-cell receptor; DP, disease progression; CDF, cancer drugs fund; FCR, fludarabine, cyclophosphamide and rituximab.

B1.3.4.1 Current treatments in untreated and unfit CLL

Active treatment is only considered for patients with active disease. Initial treatment choice depends on patient characteristics, including age, comorbidities and high-risk disease features as well as patient preference.

Once a patient becomes symptomatic with active disease (Binet stage C or Rai stages III and IV) or meets iwCLL criteria for treatment, the optimal treatment for CLL in the first-line setting largely depends on the patient's characteristics – their fitness level and ability to tolerate toxicities associated with certain treatment regimens, and the presence of high-risk features.[1,37] Elderly patients (≥ 65 years old) are typically less fit than younger patients and commonly present with a combination of comorbidities, poly-medication and impaired organ function; in addition, some younger patients have comorbidities that have an impact on their ability to tolerate treatment, therefore are considered unfit.[44]

The majority of patients considered unfit, without any high-risk mutations, are treated with a combination of chlorambucil plus obinutuzumab (Figure 1). The BSH guidelines (2018) recommends that **chlorambucil in combination with obinutuzumab** is the main-stay treatment option for patients with untreated newly diagnosed CLL whom are considered unfit for chemo-immunotherapy (e.g. FCR). Regimens that combine chlorambucil with an anti-CD20 antibody (rituximab, ofatumumab or obinutuzumab) are associated with fewer AEs than FCR, making them more suitable for use in elderly and 'unfit' patients.[45]

Current treatments in untreated, high-risk CLL;

Most CLL cases are associated with the loss or acquisition of genetic material.[46] The common cytogenetic changes are:

- deletion of chromosome 13q region (del[13q]) in approximately 55% of cases
- acquisition of chromosome 12 (trisomy 12) in a further 10–20% of cases
- deletion of chromosome 11q region (del[11q]) in about 10% of cases
- deletion of chromosome 17p region (del[17p]) in about 5–8% of cases.

These are of clinical significance, as some cytogenetic changes are associated with a particularly poor prognosis. A patient's prognosis and treatment are also guided by the presence of these genetic abnormalities.

The most relevant prognostic parameters that render a patient as high-risk are the presence of del(17p) and/or TP53 mutations, and IGHV mutational status. The presence of a del(17p) chromosomal aberration or mutations of the tumour suppressor gene TP53 are predictive of both an aggressive disease course and a poor response to chemoimmunotherapy.[37,47-49] In addition, CLL with unmutated IGHV is associated with a more aggressive disease course than CLL with mutated IGHV.[37,50]

CLL having a complex karyotype, defined as the presence of at least three chromosomal aberrations, has been shown to be associated with a shorter time to first treatment, as well as shorter PFS and OS.[51]

Since its recommendation, **ibrutinib** has become established NHS care for this patient population, and is therefore a relevant comparator for this appraisal (Figure 1).[3]
In contrast, idelalisib with rituximab is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab.[6] The BSH guidelines on CLL (2018) highlights that the higher risk of infection and death associated with idelalisib therapy has led to the EMA amending the licence to "first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies.[4] Thus the use of IR is primarily limited to those patients who are unable to tolerate ibrutinib.[7]

Acalabrutinib place in therapy in untreated CLL:

A. Previously untreated adults with CLL who are ineligible for FCR therapy

B. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable, and

The proposed positioning of acalabrutinib in the CLL clinical pathway is shown in Figure 1. It is anticipated that acalabrutinib will be used as first line treatment in patients for whom chemoimmunotherapy is unsuitable i.e. patients considered 'unfit', in line with the pivotal phase 3 RCT ELEVATE-TN study presented in section B.2a. As such, acalabrutinib would be expected to displace obinutuzumab plus chlorambucil (TA343)[40] as a treatment option in these patients.
Due to the highly selective activity and minimal off-target activity, acalabrutinib is also anticipated to be used as an alternative to ibrutinib patients with a high-risk cytogenetic status (i.e. Del17p or TP53 disruption).

B1.3.3.2 Current treatments in treated, R/R CLL

Following an initial response to treatment, most patients with CLL relapse and need additional therapy.[8] In addition, a proportion of patients have disease which is refractory to initial treatment. Collectively, these patients are referred to as having R/R CLL. The decision to initiate therapy for relapsed CLL is based on the same considerations as for untreated patients; treatment for R/R CLL requires the evaluation of both the number and intensity of the previous therapies, the duration of response to those therapies, the presence of high-risk features [del(17p)/*TP53* mutations], and patient comorbidities.

Until the recent development of kinase inhibitors targeting B cell signalling pathways, treatment options in this population were of limited efficacy.[8] More often, targeted agents including ibrutinib and less often, IR or venetoclax plus rituximab (VenR), are the current treatment options in this setting. Ibrutinib is a simple oral regimen and is therefore the preferred treatment option. However, based on expert opinion, ibrutinib is not often used in patients with a history of cardiac co-morbidities. Given the different safety profiles of ibrutinib and idelalisib, in 2019, approximately 70% of patients receiving second-line treatment for CLL received ibrutinib with less than ~4% patients receiving idelalisib (Figure 1).[9]

The other treatment option for R/R CLL include venetoclax ± rituximab. As per TA561, VenR is recommended for treating CLL in patients who have had at least 1 previous therapy. In

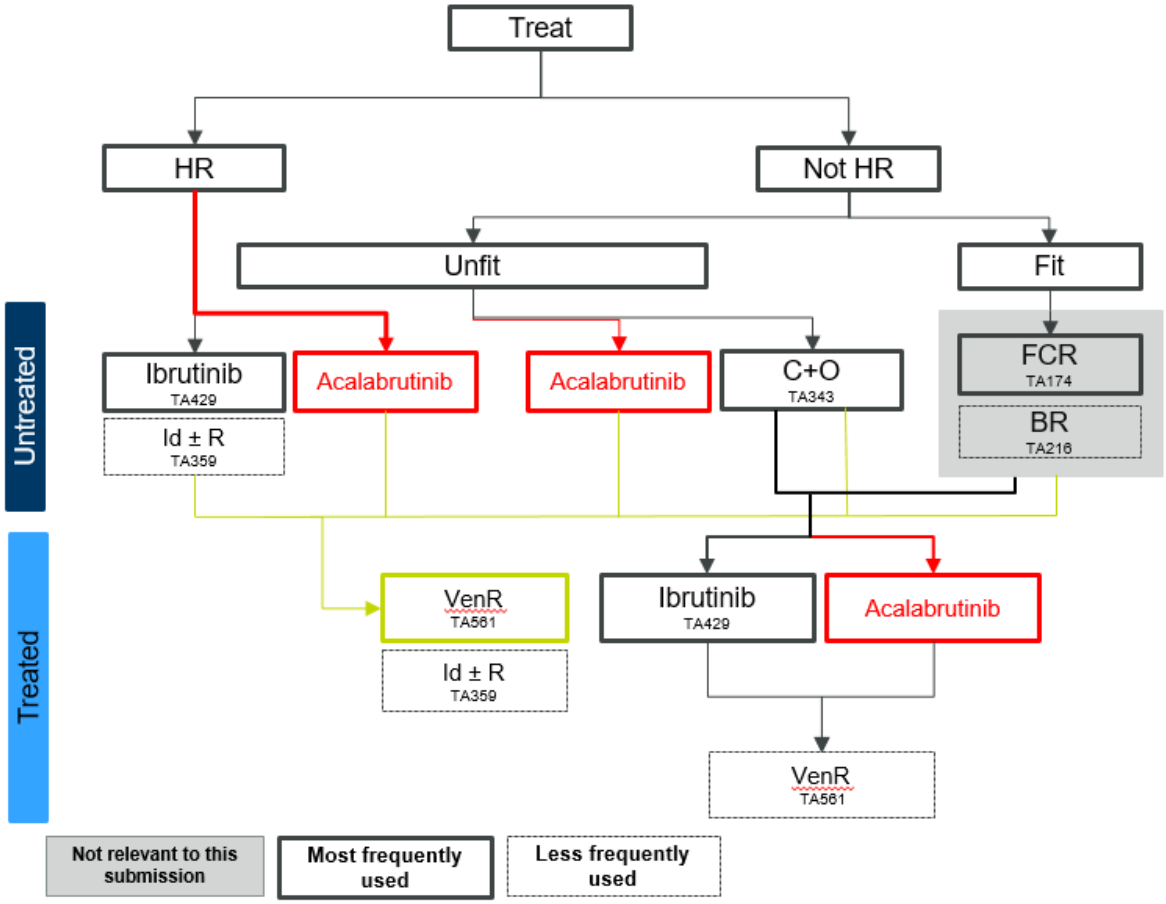
practice, VenR has been used as a second- line treatment option or third-line (or later) treatment option for patients previously treated with a BCR inhibitor (Figure 1), or for those who have cardiovascular disease, are receiving anticoagulant therapy or have a high risk of bleeding (and are thus unsuitable for ibrutinib therapy).[52] Increase use of VenR is hindered by its complex dosing regimen requiring a 5-week dose escalation regimen and frequent monitoring due to risk of TLS.[53,54] Recent market share estimates, suggest use of VenR is low with only ~7% of patients receiving VenR as second line therapy.[9]

Acalabrutinib place in therapy in treated CLL:

C. Adults with R/R CLL who have had at least one previous therapy

The proposed positioning of acalabrutinib in the CLL clinical pathway is shown in Figure 1, where it is anticipated to be used in R/R patients as second-line therapy and as alternative to ibrutinib due its favourable safety profile.

Figure 1. Clinical pathway of care and proposed position of acalabrutinib



BR, Bendamustine+rituximab; C+O, Chlorambucil+Obinutuzumab; FCR, fludarabine, cyclophosphamide, and rituximab; HR, High-risk, defined as mutation status of TP53 or Del17p; Id ± R, Idelalisib ± Rituximab; VenR, Venetoclax+rituximab.

Note: Excluded from algorithm - Venetoclax monotherapy currently in CDF in RR (TA487)

Sources: TA429,[6] TA359,[41] TA343,[40] TA174,[38] TA216,[39] TA561[10] and TA487[42]

B.1.3.5 Clinical guidelines

B1.3.5.1 UK and International guidelines – first-line treatment

Table 10 summarises guidance for the first line (untreated) management patients with CLL published by the UK's BSH, ESMO and the NCCN (USA).

Table 10. Summarised BSH 2018, ESMO 2017 and NCCN 2020 guidance

Patient category	ESMO 2017[5,55]	BSH 2018[4]	NCCN 2020 (preferred options only)[36]
Fit,[a] without TP53 disruption[b]	• Preferred: FCR • Alternative: BR	• Preferred: FCR • Alternative: BR	• Ibrutinib (category 1) • Acalabrutinib ± obinutuzumab • Venetoclax + obinutuzumab
Unfit[c] without TP53 disruption	• Chlorambucil + anti-CD20 (preferably obinutuzumab)	• Chlorambucil + anti-CD20 (obinutuzumab or ofatumumab) • BR • Ibrutinib	• Ibrutinib (category 1) • Acalabrutinib ± obinutuzumab • Venetoclax + obinutuzumab
TP53 disruption	• BCRi ± rituximab • Venetoclax if unable to receive BCRi	• Ibrutinib • Idelalisib + rituximab	• Ibrutinib • Acalabrutinib ± obinutuzumab • Venetoclax + obinutuzumab

a NCCN definition is patients aged under 65 years without significant comorbidities
b BSH only use TP53.
c NCCN definition is patients who are frail with significant comorbidities or patients aged over 65 years without significant comorbidities.
BCRi, B-cell receptor inhibitor; BR, bendamustine + rituximab; BSH, British Society of Haematology; CLL, chronic lymphocytic leukemia; ESMO, European Society for Medical Oncology; FCR, fludarabine, cyclophosphamide + rituximab; NCCN, National Comprehensive Cancer Network.

B.1.3.5.2 UK and International guidelines – R/R treatment

The treatment management of patients with R/R CLL is determined by the patient's level of fitness and the presence of any cytogenetic risk factors. These patients range from those who are relatively unfit and have limited treatment options, as well as much older frailer patients with comorbidities, who have experienced rapid relapse following chemotherapy, who have even fewer treatment options. The choice of treatment in R/R CLL considers the response to first-line treatment as well as comorbidities and the presence of TP53 disruption. A summary of relevant clinical guidelines is provided in Table 11.

Table 11. Guidelines for R/R CLL

Patient category	ESMO 2017[5,55]	BSH 2018[4]	NCCN 2020a (preferred options only)[36]
Patients with R/R CLL without	• Relapse occurs 24–36 months after CT:	• Idelalisib + rituximab • Ibrutinib	**Frail patients or aged > 65 years or younger with significant comorbidities**

Patient category	ESMO 2017[5,55]	BSH 2018[4]	NCCN 2020a (preferred options only)[36]
deletion of 17p or TP53 mutation	retreatment with first-line therapy • Ibrutinib/idelalisib + rituximab • Relapse occurs within 24–36 months after CT: venetoclax	• Venetoclax (patients who failed BCRi therapy) • Retreatment with CT (fit patients with CLL who relapse after a prolonged remission) • Allo-HSCT (patients who failed CT and BCRi therapy irrespective of TP53 status or harbour TP53 disruption and have not responded or lost response to BCRi)	• Acalabrutinib (cat 1)[b] • Ibrutinib (cat1) • Venetoclax + rituximab (cat 1) • Duvelsib (cat 2A) • Idelalisib + ibrutinib (cat2A) **Patients aged < 65 years without significant comorbidities** • Acalabrutinib (category 1)[b] • Ibrutinib (cat1) • Venetoclax + rituximab • Duvelsib (cat 2A) • Idelalisib + ibrutinib (cat 2A)
Patients with R/R CLL with deletion of 17p or TP53 mutation	• Allo-HSCT		• Acalabrutinib (cat1)[b] • Ibrutinib (cat 1) • Venetoclax + rituximab (category 1) • Duvelsib (cat 2A) • Idelalisib + rituximab (cat 2A) • Venetoclax (cat 2A)

a NCCN recommendations are classified into categories (1-3) based on the strength of evidence.
b Acalabrutinib has not been shown to be effective for ibrutinib-refractory CLL with BTK C481S mutations. Patients with ibrutinib intolerance have bene successfully treated with acalabrutinib without recurrence of symptoms.
Allo-HSCT, Allogeneic Hematopoietic Stem Cell Transplantation; BCRi, b-cell receptor inhibitor; cat, category; CLL, chronic lymphocytic leukaemia; CT, chemoimmunotherapy; TP53, tumour protein p53.

The BSH guidelines, published in 2018, recommend that for patients who are refractory to chemotherapy, have relapsed after chemo-immunotherapy or for whom re-treatment with chemo-immunotherapy is inappropriate, IR and ibrutinib monotherapy can be used and VenR might become an option for B-cell receptor inhibitor (BCRi) naïve patients. For patients who fail BCRi therapy, venetoclax is the treatment of choice.[4]

ESMO published a 2017 eUpdate for CLL treatment recommendations,[55] itself based on published 2015 guidelines.[5] These guidelines emphasise the priority given to the use of BCRis and venetoclax, e.g. the preferred treatment patients (fit or unfit) with a relapse 24–36 months from the start of initial chemotherapy (or refractory disease) consists of either a BCRi (+/- rituximab) or venetoclax (if failure to prior chemotherapy or BCRi or if del(17p) or TP53 mutation or unsuitable for BCRi). Allogeneic hematopoietic stem cell transplantation can be considered when patients are in remission.

The NCCN guidelines provide the most up to date guidance (2019),[36] which are classified into categories (1–3) based on the strength of evidence. For patients with R/R CLL, NCCN consistently recommends three preferred category 1 evidence therapies, independent of

age, comorbidities or del17p/TP53 mutation status, acalabrutinib monotherapy, ibrutinib monotherapy or venetoclax + rituximab.

The proposed placement of acalabrutinib in the treatment pathway is detailed previously in Figure 1.

B.1.3.6 Issues relating to current clinical practice

UK clinical advisory board

To help understand current UK clinical practice, AstraZeneca convened an advisory board on 24th January 2020, composed of nine active UK based haematologists working in CLL. Key findings are shown in Table 12.[3]

Table 12. Key statements on UK CLL treatment paradigm from advisory board

Due to a wider choice of safer, tolerable treatments, health care providers (HCPs) are now able to make personalised treatment decisions for patients with CLL rather than basing decisions on benefit/risk profiles.[3]

Overall, there is not one factor alone which drives therapy choice in patients with CLL, factors vary depending on individual patient considerations, in the first-line setting:[3]

- Fitness is the main consideration for treatment choice (age [< or > 65 years], CrCl, walk speed/distance. Toxicity and mutational status also considerations.
    - IGHV status and presence of TP53/del(17p) are important biomarkers for treatment choice. A Del(11q) may also be considered.
    - Young, fit, IGHV mutated less likely to receive BTKi
    - Ibrutinib preferred for TP53/del17p but this option less likely with cardiac comorbidity
    - patient eligibility for FCR can be assessed (fitness, IGHV status)

- Once advised by their HCP, patient choice is the driving factor for the final therapy choice
    - discuss efficacy (appropriate therapy recommendations based on fitness, mutational status), risks (toxicities, comorbidities), FDT versus continuous preference

a Outside of a clinical trial setting, del(17p)/TP53 aberration and IGHV status are not routinely tested; however, del(17p)/TP53 aberration is being tested more frequently than before, driven by the availability of treatments in this subset of patients.
CrCl, creatinine clearance; CLL, chronic lymphocytic leukaemia; FDT, fixed duration of treatment; IGHV, immunoglobulin heavy chain; MRD minimal residual disease; PFS, progression-free survival.
Source: AstraZeneca. CLL Advisory Board. 2020[3]

B.1.3.6.1 Unmet need

CLL remains an incurable disease;[5] patients in the UK have a median OS (from diagnosis) of 9 years,[56] although this is shorter in older/less fit and high-risk patients. Following an initial response to treatment, most patients with CLL eventually relapse (due to the presence of residual disease) and need additional therapy; prognosis after relapse remains poor.[8] In addition, a proportion of patients have disease that is refractory to initial treatment. Therefore, therapies, such as acalabrutinib, that can delay relapse are desirable.

Unmet need in untreated and unfit CLL

Newly diagnosed patients are restricted to older chemoimmunotherapy regimens with a lower efficacy, especially as patient age and fitness decreases.[57] Chlorambucil in combination with obinutuzumab is the mainstay treatment option for patients with untreated newly diagnosed CLL whom are considered unfit for chemo-immunotherapy (e.g. FCR) based on the BSH guidelines (2018) and the NICE recommendation (TA343).

Unmet need in untreated, high-risk CLL and in treated, R/R CLL

Tolerability issues with ibrutinib are likely linked to poorer than expected patient outcomes

Patients with untreated, high risk cytogenetic factors (TP53 mutation and 17p deletion) have poorer prognosis and do not respond well to chemoimmunotherapy therapy. Patients who have relapsed or are refractory to initial therapies are often older with additional comorbidities and have a worse prognosis. Further, at the time of relapse, some patients may develop genetic abnormalities [i.e., del(17p) or *TP53* mutations] due to clonal evolution. Compared to patients on front-line therapy who can experience a PFS of anywhere from 36-60 months with current therapies, the duration of response in second- and third-line CLL is usually much shorter, with PFS of only 12-24 months.

The introduction of ibrutinib came with a shift in clinical practice from time limited therapy to continuous monotherapy in untreated high risk and treated, R/R patients, following the NICE recommendation (TA429).[6] However, ibrutinib is associated with a substantial adverse event burden that negatively affects the morbidity of patients. While ibrutinib has demonstrated to be an effective, generally well tolerated drug in various haematological malignancies, published real-world datasets suggest a significantly higher overall treatment-related discontinuation rates in routine clinical practice to those reported in clinical trials. The type and frequency of toxicities with ibrutinib in patients with CLL reported in clinical trials with those reported in a real-world setting were reviewed.[58]

Toxicity with ibrutinib is also seen in real world settings, with a recent UK ibrutinib real world study reporting that 44% of patients experienced a dose reduction, interruption or discontinuation in the first 12 months compared with 4% in the RESONATE study[27] and more patients receiving discontinue due to adverse events (AEs; UK/Sweden: 24–26% at 10–12 months) compared with RCTs (33% at 36 months).[59]

Reasons for adverse events noted with ibrutinib are due to its mode of action: In addition to inhibiting Bruton's tyrosine kinase (BTK), ibrutinib is a potent covalent inhibitor of other kinases, including B-lymphoid tyrosine kinase, epidermal growth factor receptor, interleukin-2-inducible T-cell kinase and tyrosine-protein kinase.[60] As such, the off-target activity of ibrutinib is believed to be responsible for some of the adverse events and tolerability issues associated with its treatment.

These off-target actions are associated with unwanted effects on T helper and regulatory T cells differentiation, CD8+ T cell viability and cytotoxicity, and antibody-dependent cell-mediated cytotoxicity (ADCC) as well as adverse events such as major haemorrhage, rash, diarrhoea, atrial fibrillation/flutter, and sudden death. Specifically:

- The kinases interleukin-2–inducible kinase (ITK), TEC, and TXK play an important role in T cell receptor activation and development.[61]

- ITK is required for natural killer (NK) cell function and overall ADCC.[61,62] Inhibition of ITK results in inhibition of ADCC.[62] Inhibition of ITK can affect T and natural killer cell function, resulting in an increased susceptibility to infections.

- Inhibition of epidermal growth factor receptor is associated with diarrhoea, skin rash, cardiomyocyte dysfunction, and reduced cardiac contractile efficiency.[60,61,63-66]

- Inhibition of BTK and TEC is associated with defects in aggregation of platelets and increased bleeding risk.[67-70] This is due to alternations in signalling of the certain platelet receptors mediated via BTK and TEC.[68,71]

Outcomes are generally poor for patients who discontinue ibrutinib. Maddocks et al. 2015 reported that the median OS in patients with R/R CLL who discontinued other than for disease progression was 8 days, reflecting the fact that many patients discontinued ibrutinib owing to infection and died shortly after stopping therapy.[72] Median OS for those who discontinued owing to disease progression was 17.6 months from the time of relapse. Although ibrutinib may avoid some of the toxic effects associated with chemoimmunotherapy, the low rates of undetectable minimal residual disease with ibrutinib suggests that treatment must be continued indefinitely.[73]

Acalabrutinib addresses the significant unmet need for novel therapies with lower toxicity and durable efficacy

Acalabrutinib was designed as a more selective BTK inhibitor to mitigate some of the off-target toxicities associated with ibrutinib, by minimising off-target activity to kinases that are structurally similar to BTK (Table 13), the inhibition of which is associated with additional, often unwanted, effects, as described above.[71]

There is a significant unmet need for new therapies with lower toxicity and more durable (or at least equivalent) responses than currently available treatment options, particularly for patients considered ‘less fit’, such as older patients, or patients with significant comorbidities who may receive suboptimal treatment due to toxicity considerations.

Whilst targeted therapies (BTKi and B-cell lymphoma [Bcl-2i) have profoundly changed CLL management, with superior outcomes compared with chemo-immunotherapy, toxicity and patient discontinuation remains an issue.

Table 13. Comparison of kinase inhibition with acalabrutinib and ibrutinib

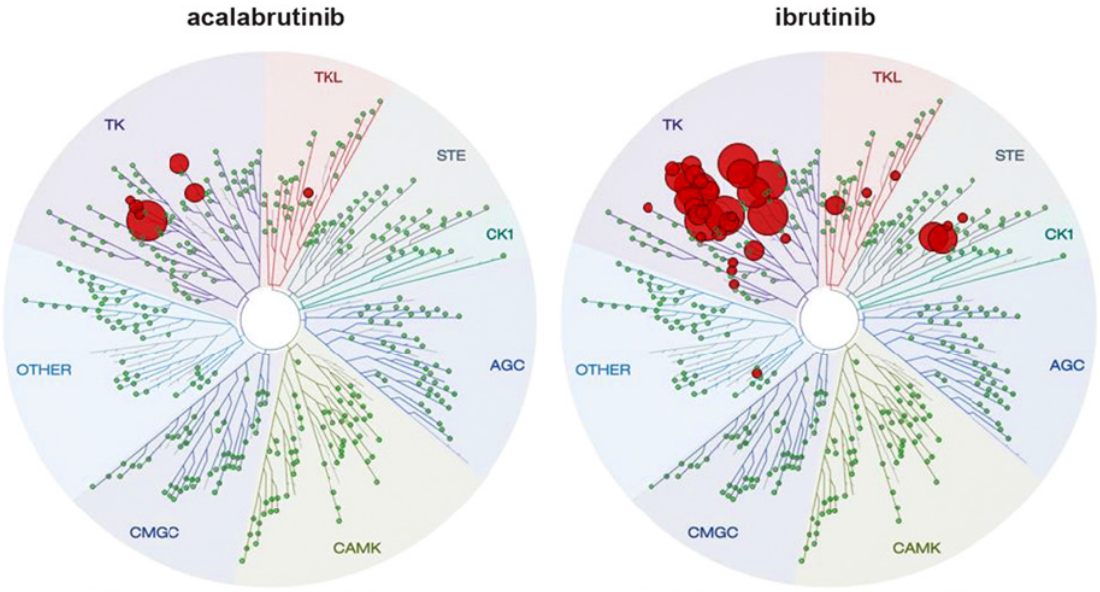
Kinase	IC_{50}, nmol/L	
	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10.0
ITK	> 1000	4.9
BMX	46.0	0.8

Kinase	IC_{50}, nmol/L	
	Acalabrutinib	Ibrutinib
TXK	368.0	2.0
EGFR	> 1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	> 1000	0.1
JAK3	> 1000	32.0

BLK: B-lymphoid tyrosine kinase; IC: Inhibitory concentration; ITK: Interleukin-2-inducible T-cell kinase; JAK3: Janus kinase 3; nmol: Nanomole; TEC: Tyrosine kinase expressed in hepatocellular carcinoma; TXK: T- and X-cell expressed kinase; EGFR: Epidermal growth factor receptor; ERBB2: Erythroblastosis oncogene B 2; ERBB4: Erythroblastosis oncogene B 4
Source: Barf et al. 2017[71]

The improved kinase selectivity of acalabrutinib compared to ibrutinib is shown below in Figure 2 and is believed to be responsible for the improved tolerability profile of acalabrutinib compared to ibrutinib.

Figure 2. Comparison of acalabrutinib and ibrutinib BTK selectivity



Note: Larger red circles represent stronger inhibition.
CAMK: Calmodulin-dependent protein kinase; CMGC: Cyclin-dependent kinases, mitogen-activated protein kinases, glycogen synthase kinase, and CDC-like kinases; TK: Thymidine kinase; TKL: Tyrosine-like kinase.
Source: Barf et al, 2017[71]

In addition to its high selectivity, the pharmacokinetic and pharmacodynamic profile of acalabrutinib may play a role in limiting exposure-related AEs. In a dose escalation study in healthy volunteers, acalabrutinib displayed rapid absorption (median time to maximum plasma concentration: 0.5–1.0 hours) and elimination (mean half-life: 0.9–2.1 hours).[71] As such, acalabrutinib's short plasma half-life and high selectivity toward BTK resulted in high median state occupancy of ≥ 95%. Taken together, the refined characteristics displayed by

acalabrutinib suggest that high dose intensity could be maintained for a longer duration than for ibrutinib, resulting in improved treatment outcomes.

Unmet need from a patient perspective

Treatment choice should be decided in discussion with the patient in consultation with a specialist physician and are based on the patient's wishes, comorbidities and potential side effects.[4] Within this context, there is a strong patient/physician preference for less toxic therapies, without loss of efficacy, that can keep patients out of hospital. As a secondary consideration, hospitalisation is also a major cost driver in first-line patients with CLL, especially those who are ineligible for fludarabine-based therapy.[74]

B.1.4 Equality considerations

There are no significant equality considerations associated with this appraisal.

Patients receiving chlorambucil plus obinutuzumab are typically older, less medically fit and chemotherapy-naïve. Administration of obinutuzumab require highly trained medical personnel and careful monitoring patients to avoid subsequent risk of infections. In contrast, acalabrutinib is suitable in patients regardless of PS or comorbidities coupled with an improved safety/tolerability profile. In addition, acalabrutinib is a simple oral regimen and does not require hospital visits with a reduced toxicity burden would likely be a desirable step toward improving outcomes for patients. Equality issues which may currently exist for older, frailer patient would be alleviated with the addition of ibrutinib to the current treatment landscape.

In patients currently receiving ibrutinib, due the highly-selective activity, acalabrutinib demonstrates minimal off-target activity that can maintain a median steady state BTK occupancy of ≥ 95%, and is therefore expected to have improved safety/tolerability profile compared with ibrutinib.

Therefore, we anticipate that acalabrutinib will result in a step-change in the treatment pathway for high risk (defined as having a 17p deletion or TP53 mutation) untreated patients, and is expected to offer better tolerability than current targeted therapies in patients with a cytogenetic mutation, and in patients with R/R CLL.

B.2a Clinical effectiveness: 1L (untreated) CLL patients

B.2a.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify RCTs previously conducted in first line CLL. The population, intervention, comparators, outcomes, study design (PICOS) criteria for study selection are presented in Appendix D.

The SLR conducted was broader than the scope of this submission. Therefore, studies were only extracted if they included ibrutinib or chlorambucil in combination with obinutuzumab, the comparators treatment of interest in the first-line setting (Section B1).

B.2a.2 List of relevant clinical effectiveness evidence

The SLR identified seven RCTs evaluating either ibrutinib or chlorambucil in combination with obinutuzumab. Table 14 presents details of these studies.

Table 14. Summary of study characteristics for RCTs identified in the SLR (1L setting)

Publication source (author_year)	Trial name (if any)	Treatment/Group	Publication type	Study setting	Study phase	Cross over
Goede 2014	CLL 11	• Obinutuzumab + Chlorambucil • Chlorambucil • Rituximab + Chlorambucil	Journal article	Multicenter international	III	NR
Burger 2015	RESONATE-2	• Ibrutinib • Chlorambucil	Journal article	Multicenter international	III	NR
Burger 2019	NR	• Ibrutinib • Ibrutinib + Rituximab	Journal article	Single center	II	NR
Fischer 2019	CLL 14	• Venetoclax + Obinutuzumab • Chlorambucil + Obinutuzumab	Journal article	Multicenter international	III	NR
Moreno 2019	ILLUMINATE	• Ibrutinib + Obinutuzumab • Chlorambucil + Obinutuzumab	Journal article	Multicenter international	III	Yes
Langerbeins 2019	CLL-12	• Ibrutinib • Placebo	Conference abstract	NR	III	NR
Woyach 2018	ALLIANCE	• Bendamustine + Rituximab • Ibrutinib	Journal article	Multicenter international	III	Yes

NR, not reported; RCT, randomised controlled trial; SLR, systematic literature review

Of the seven studies identified, six reported data on PFS in patients with untreated CLL. An estimate for OS was either not reached or not recorded in all the studies identified. Study characteristics, efficiency outcomes and safety outcomes retrieved for studies identified in the SLR are available in Appendix D.

Additionally, the ELEVATE-TN (NCT02475681) study,[11] was identified post completion of the SLR and provided comprehensive efficacy and safety data to evaluate acalabrutinib, acalabrutinib in combination with obinutuzumab, and chlorambucil in combination with obinutuzumab in previously untreated patients with CLL (Table 15).

Table 15. Clinical effectiveness evidence

Study number	NCT02475681 (ACE-CL-007)				
Study design	Randomised, multicentre, open-label, three-arm, phase 3 study				
Population	Patients with a diagnosis of CLL, no prior treatment, age ≥ 65 years, or age 19–64 years with a creatinine clearance of 30–69 mL/min and/or a score > 6 on the Cumulative Illness Rating Scale-Geriatric				
Intervention(s)	Acalabrutinib monotherapy and acalabrutinib plus obinutuzumab				
Comparator(s)	Chlorambucil plus obinutuzumab				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	Pivotal study used in the application for marketing authorisation				
Reported outcomes specified in the decision problem	PFS, OS, TTNT, AEs, HRQoL				
All other reported outcomes	ORR, ORR + PRL, healthcare resource utilization, pharmacokinetics, MRD				

AE, adverse event; HRQoL, health-related quality of life; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRL, partial response with lymphocytes; TTNT, time to next treatment.

B.2a.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2a.3.1 Study design

ELEVATE-TN is a global, randomised, open label, multi-centre, three-arm, phase 3 trial in patients with CLL who had not received any prior systemic therapy and were elderly or frail. Patients in ELEVATE-TN were randomised (1:1:1) to one of three treatment arms: chlorambucil plus obinutuzumab (arm A), acalabrutinib plus obinutuzumab (arm B) or acalabrutinib monotherapy (arm C). A total of 535 patients were randomised 1:1:1 between the three treatment arms. Participants in arm A who experienced Independent Review Committee (IRC)-confirmed disease progression were allowed to cross over to acalabrutinib monotherapy. Table 16 summarises the ELEVATE-TN trial methodology and the study design is presented in Figure 3. Note that whilst the clinical trial data are presented for all

treatment arms, a pharmacoeconomic evaluation has not been conducted for patients receiving treatment with acalabrutinib plus obinutuzumab (arm B).

The following stratification factors were applied at randomisation:

- 17p deletion (presence versus absence)
- ECOG PS (0, 1 versus 2)
- Geographic region (North America and Western Europe versus Other)

The primary endpoint in ELEVATE-TN was IRC-assessed PFS for acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab, and the key secondary endpoint was IRC-assessed PFS for acalabrutinib monotherapy vs chlorambucil plus obinutuzumab.

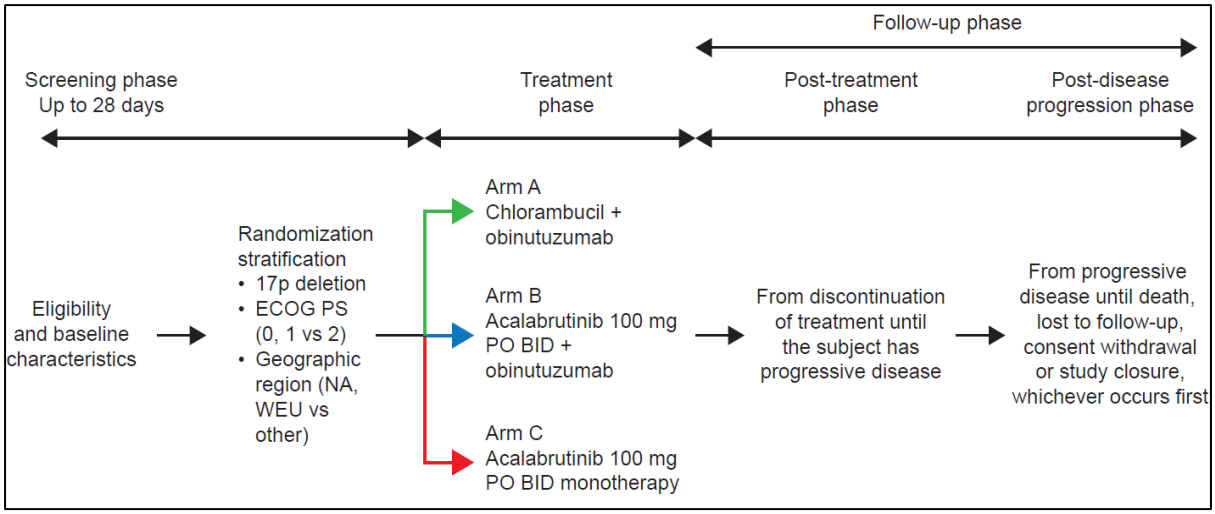
Table 16. Summary of trial methodology

Study details	ELEVATE-TN (ACE-CL-007; NCT02475681)
Location	Belgium, France, Germany, Israel, Italy, Spain, Sweden, UK, Brazil, Chile, Colombia, USA, Canada, Hungary, Lithuania, Poland, Australia, New Zealand
Design	Randomised, open label, multi-centre, three-arm, phase 3 trial in patients with CLL who had not received any prior systemic therapy and were elderly or frail
Randomization	Patients were randomised in a 1:1:1 ratio into the three treatment arms using an IWRS. Randomisation was stratified by: • 17p deletion (presence versus absence) • ECOG performance status (0, 1 versus 2) • Geographic region (North America and Western Europe versus Other)
Blinding	This was an open-label study, and neither the subjects nor the investigators were blinded to treatment.
Treatment	**Arm A (chlorambucil + obinutuzumab)** • Oral chlorambucil 0.5 mg/kg on days 1 and 15 of cycles[a] 1–6 • IV obinutuzumab over 6 cycles:[a] 100 mg on day 1 of cycle 1, 900 mg on day 2 of cycle 1, 1000 mg on days 8 and 15 of cycle 1 and 1000 mg on day 1 of cycles 2–6 **Arm B (acalabrutinib + obinutuzumab)** • Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity • IV obinutuzumab over 6 cycles,[a] 100 mg starting day 1 of cycle 2, 900 mg on day 2 of cycle 2, 1000 mg on days 8 and 15 of cycle 2, and 1000 mg on day 1 of cycles 3–7 **Arm C (acalabrutinib monotherapy)** • Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity **Crossover from arm A** • Oral acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity
Endpoints	**Primary endpoint:** • PFS (IRC), acalabrutinib + obinutuzumab vs chlorambucil + obinutuzumab **Key secondary endpoint:** • PFS (IRC), acalabrutinib monotherapy vs chlorambucil + obinutuzumab **Secondary endpoints:**

	• ORR (IRC) • TTNT • OS **Selected exploratory endpoints:** • PFS (investigator) • ORR (investigator) • ORR + PRL (investigator) • Medical resource use • FACIT-Fatigue, EORTC QLQ C30 and EQ-5D
Subgroup analyses	Presence of del(17p), ECOG PS at randomisation, geographic region, age group, sex, race, Rai stage at screening, Bulky disease, beta-2 microglobulin at baseline, presence of del(11q), TP53 mutation, *IGHV* mutation, complex karyotype

[a] Each cycle was 28 days.
ECOG PS, Eastern Cooperative Oncology Group Performance status; EORTC, European Platform of Cancer Research; EQ-5D, EuroQol five dimension; FACIT, Functional Assessment of Chronic Illness; IGHV, immunoglobulin heavy chain; IRC, independent review committee; IV, intravenous; ORR, overall response rate; PFS, progression-free survival; PRL, partial response with lymphocytes; TP53, tumour protein 53; TTNT, time to next treatment.

Figure 3. Study design



[a] Participants in arm A who experienced IRC-confirmed disease progression were allowed to cross over to acalabrutinib monotherapy.
BID, twice per day; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; NA, North America; IRC, Independent Review Committee; PO, oral; PS, Performance Status; WEU, Western Europe.
Source: ELEVATE-TN CSR[75]

B.2a.3.2 Eligibility criteria

Eligible patients were aged ≥65 years or, if younger than 65 years, had a CIRS-Geriatric score higher than 6 or renal dysfunction (creatinine clearance 30–70 mL/min), meaning that they would otherwise be unsuitable for FCR-based therapy. Before entering the study, patients were assessed to ensure that they met the eligibility criteria (Table 17).[75]

Table 17. Key eligibility criteria for ELEVATE-TN

Key inclusion criteria

• Age ≥ 65 years, or age 19–64 years with a creatinine clearance of 30–69 mL/min and/or a score > 6 on the Cumulative Illness Rating Scale-Geriatric • ECOG Performance Status of 0–2 • Diagnosis of CD20-positive CLL that meets published diagnostic criteria[19] • Active disease meeting ≥ 1 of the IWCLL 2008 criteria for requiring treatment[19] • Laboratory parameters: ANC ≥ 0.75 × 10^9/L;[a] platelet count ≥ 50 × 10^9/L;[b] AST and ALT ≤ 3.0 × ULN; total bilirubin ≤ 1.5 × ULN; estimated creatinine clearance of ≥ 30 mL/min
Key exclusion criteria
• Any previous systemic treatment for CLL • Significant cardiovascular disease • Required or received anticoagulation therapy with warfarin or other equivalent other vitamin K antagonists within 7 days of first dose of study drug

[a] ≥ 0.50 × 109/L in patients with bone marrow involvement.
[b] ≥ 30 × 109/L in patients with bone marrow involvement.
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukaemia; CSR, clinical study report. EC+OG, Eastern Cooperative Oncology Group; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; ULN, upper limit of normal.
Source: ELEVATE-TN CSR[75]

B.2a.3.3 Outcome measures

The definitions of the outcome measures available in the ELEVATE-TN study and whether they are used in the economic model are presented in Table 18.

Table 18. Outcome measures available form ELEVATE-TN and their inclusion into the economic model

Efficacy measures	Description	Data cut available	Used in economic model
Primary endpoint			
PFS (IRC)	IWCLL[19] Time from the date of randomisation to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first	08 February 2019[a]	Yes
Secondary			
ORR (IRC)	IWCLL[19] The proportion of patients achieving a best overall response (assessed by IRC) of CR, CRi, nPR or PR at or before initiation of subsequent anti-cancer therapy	08 February 2019[a]	No
TTNT	The time from date of randomisation to date of start of non-protocol-specified subsequent anti-cancer treatment for CLL or death due to any cause, whichever occurred first	08 February 2019[a]	Yes
OS	The time from date of randomisation to death due to any cause	08 February 2019[a]	No

Efficacy measures	Description	Data cut available	Used in economic model
Safety	AEs and SAEs as coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03)	08 February 2019[a]	Yes
Exploratory			
PFS (Inv)	IWCLL[19]	08 February 2019[a]	No
ORR (investigator)	The proportion of patients achieving a best overall response (assessed by the investigator) of CR, CRi, nPR or PR at or before initiation of subsequent anti-cancer therapy	08 February 2019[a]	No
ORR + PRL (investigator)	The proportion of patients achieving a best overall response (assessed by the investigator) of CR, CRi, nPR, PR or PRL at or before initiation of subsequent anti-cancer therapy	08 February 2019[a]	No
Medical resource use	Number of hospitalizations, emergency department visits, blood product transfusions and haematopoietic growth factor treatments, per patient per year	08 February 2019[a]	No
FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D	Change from baseline in FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D scores	08 February 2019[a]	Yes (EQ-5D-3L)

[a] interim analysis (see sections B.2.4 and B.2.6).
AE, adverse event; CLL, chronic lymphocytic leukaemia; CR, complete response; CRi, complete response with incomplete blood count recovery; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, 5-dimension EuroQol questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; IRC, Independent Review Committee; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; nPR, nodular partial remission; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRL, partial response with lymphocytosis; QLQ-C30, 30-item core quality of life questionnaire; SAE, serious adverse event; TTNT, time to next treatment.
Source: ELEVATE-TN CSR[75]

B.2a.3.4 Patient characteristics

In total 535 patients were randomised: 177 patients to the chlorambucil plus obinutuzumab arm (arm A), 179 patients to the acalabrutinib plus obinutuzumab arm (arm B) and 179 patients to the acalabrutinib monotherapy arm (arm C). The mean age of patients was 70 years and over half of patients were randomised at least 2 years after their initial diagnosis (median time from diagnosis to randomisation, 27.6 months).

Demographic and baseline characteristics were generally well balanced (Table 19). A slightly lower proportion of patients in the acalabrutinib plus obinutuzumab arm had unmutated immunoglobulin heavy chain variable gene (IGHV) or bulky disease (≥ 5 cm) than in the acalabrutinib monotherapy arm or the chlorambucil plus obinutuzumab arm.

Table 19. Baseline patient and disease characteristics in ELEVATE-TN

	Number (%) of patients			
	Arm B: acalabrutinib + obinutuzumab (n = 179)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)	Total (N = 535)
Age, years				
Mean (SD)	70.2 (8.02)	69.8 (7.57)	70.8 (7.56)	70.3 (7.72)
Median (range)	70 (41.0–88.0)	70 (44.0–87.0)	71 (46.0–91.0)	70 (41.0–91.0)
≥ 75	53 (29.6)	50 (27.9)	52 (29.4)	155 (29.0)
≥ 65	144 (80.4)	151 (84.4)	153 (86.4)	448 (83.7)
<65	35 (19·6%)	21 (11·7%)	15 (8·5%)	71 (13.2)
CIRS-G >6	30 (16·8%)	21 (11·7%)	15 (8·5%)	66 (12.3)
Time from initial diagnosis to randomization, months				
Mean (SD)	47.5 (51.93)	42.1 (45.10)	46.3 (48.67)	45.3 (48.61)
Median (range)	30.5 (0.4, 284.5)	24.4 (0.4, 242.6)	30.7 (0.3, 247.0)	27.6 (0.3, 284.5)
Sex (male)	111 (62.0)	111 (62.0)	106 (59.9)	328 (61.3)
Region				
North America	64 (35.8)	70 (39.1)	61 (34.5)	195 (36.4)
South America	5 (2.8)	8 (4.5)	7 (4.0)	20 (3.7)
Western Europe	49 (27.4)	42 (23.5)	52 (29.4)	143 (26.7)
Central and Eastern Europe	48 (26.8)	46 (25.7)	40 (22.6)	134 (25.0)
Australia, New Zealand	13 (7.3)	13 (7.3)	17 (9.6)	43 (8.0)
Disease characteristics				
ECOG PS				
0–1	169 (94.4)	165 (92.2)	167 (94.4)	501 (93.6)
2	10 (5.6)	14 (7.8)	10 (5.6)	34 (6.4)
Bulky disease (≥ 5 cm)	46 (25.7)	68 (38.0)	55 (31.1)	169 (31.6)
Rai stage				
0	3 (1.7)	0	1 (0.6)	4 (0.7)
I	54 (30.2)	48 (26.8)	50 (28.2)	152 (28.4)

	Number (%) of patients			
	Arm B: acalabrutinib + obinutuzumab (n = 179)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)	Total (N = 535)
II	36 (20.1)	44 (24.6)	48 (27.1)	128 (23.9)
III	48 (26.8)	50 (27.9)	40 (22.6)	138 (25.8)
IV	38 (21.2)	37 (20.7)	38 (21.5)	113 (21.1)
Beta-2 microglobulin >3.5 mg/L	132 (73.7)	140 (78.2)	132 (74.6)	404 (75.5)
Cytopenia	93 (52.0)	85 (47.5)	77 (43.5)	255 (47.7)
Constitutional symptoms	96 (53.6)	104 (58.1)	88 (49.7)	288 (53.8)
Genetic markers				
Del(17p)	17 (9.5)	16 (8.9)	16 (9.0)	49 (9.2)
Del(11q)	31 (17.3)	31 (17.3)	33 (18.6)	95 (17.8)
TP53 mutation	21 (11.7)	19 (10.6)	21 (11.9)	61 (11.4)
IGHV				
Mutated	74 (41.3)	58 (32.4)	59 (33.3)	191 (35.7)
Unmutated	103 (57.5)	119 (66.5)	116 (65.5)	338 (63.2)
Undetermined	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)
Del(17p), TP53 mutation, del(11q) or unmutated IGHV	117 (65.4)	129 (72.1)	129 (72.9)	375 (70.1)

Data are n (%) unless otherwise stated.

CSR, clinical study report; del(11q), deletion of chromosome 11q region; del(17p), deletion of chromosome 17p region; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain variable gene; SD, standard deviation; TP53, tumour protein 53 gene.

Source: ELEVATE-TN CSR[75]

B.2a.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2a.4.1 ELEVATE-TN sample size calculations (ITT population)

A sample size of 510 patients (approximately 170 subjects per treatment) was calculated to detect a hazard ratio (HR) of 0.60 for PFS for acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab at approximately 90% power.

The trial was powered by accrual of IRC-assessed PFS events, the primary endpoint. One final and one interim analysis were planned. The final analysis was planned when 167 IRC-assessed PFS events had been observed across the acalabrutinib plus obinutuzumab and chlorambucil plus obinutuzumab arms. The interim analysis was planned when approximately two-thirds (i.e. 111) of the required IRC-assessed PFS events for final analysis had occurred. If the required number of events had not been met by 24 months after the last patient was randomised, a time-based interim analysis was conducted.

B.2a.4.2 Statistical analysis

Table 20 summarises the statistical analyses used in ELEVATE-TN. All efficacy analyses were conducted based on the intention-to-treat population. The safety population included all patients who received at least one dose of study treatment.

Table 20. Summary of prespecified statistical analyses used in ELEVATE-TN

Endpoint	Analysis	Population[a]
Primary endpoint (acalabrutinib + obinutuzumab [arm B] vs chlorambucil + obinutuzumab [arm A])		
PFS (IRC)	• Summary of distribution of PFS for each treatment arm using median and 95% CI based on Kaplan–Meier estimates • HR and 95% CI estimated using a Cox proportional hazards model stratified by the randomization strata • Stratified log rank test comparing PFS, as assessed by IRC, between arm A and arm B	ITT population
PFS (sensitivity analyses)	• Inclusion of PFS without censoring for subsequent anti-cancer therapy • Inclusion of PFS events after ≥ 2 consecutively missed visits • Exclusion of subjects with important protocol deviations • Use of eCRF-recorded stratification factors	ITT population
PFS (subgroup analyses)	• Subgroups including: o age o sex (male vs female) o del(17p) (yes vs no) o *TP53* mutation (yes vs no) o del(11q) (yes vs no) o unmutated *IGHV* (yes vs no) o poor prognosis composite: o del (17p), *TP53* mutation, del(11q) or unmutated *IGHV* (yes vs no) o del (17p) and *TP53* mutation (yes vs no) o del (17p) or *TP53* mutation (yes vs no) o del(17p), *TP53* mutation or del(11q) (yes vs no) o complex karyotype (yes vs no) o Rai stage at screening (stage 0–II vs III–IV) o bulky disease (< 5 cm vs ≥ 5cm) o beta-2 microglobulin at baseline (≤ 3.5 mg/L vs > 3.5 mg/L) o ECOG status (0, 1 vs 2) o race (white vs non-white) o geographic region	ITT population subgroups
Key secondary endpoint (acalabrutinib monotherapy [arm C] vs chlorambucil + obinutuzumab [arm A])		
PFS (IRC)	Analysed with same approach used for primary endpoint	ITT population

Endpoint	Analysis	Population[a]
PFS (sensitivity analysis)	Same stratification factors as primary analysis	
Other secondary endpoints (acalabrutinib + obinutuzumab [arm B] or acalabrutinib monotherapy [arm C] vs chlorambucil + obinutuzumab [arm A])		
ORR (IRC)	• CMH test adjusting for randomization stratification factors • Summary of number and percentage of patients; 95% CI calculated based on normal approximation	ITT population
TTNT and OS	Analysed with same approach used for primary endpoint	ITT population
Exploratory endpoints (acalabrutinib + obinutuzumab [arm B] or acalabrutinib monotherapy [arm C] vs chlorambucil + obinutuzumab [arm A])		
PFS (investigator)	Analysed with same approach used for PFS (IRC)	ITT population
ORR (investigator)	Analysed with same approach used for ORR (IRC)	ITT population
ORR + PRL (IRC and investigator)	Analysed with same approach used for ORR (IRC)	ITT population
FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D	• Exploratory p values with no adjustment for multiple comparisons • Thresholds for clinically meaningful changes were based on 0.5 SD of the distribution of scores	SF population ITT population
Safety endpoints		
AEs and SAEs	Descriptive analyses by system organ class, preferred term, severity and relationship to study drug	Safety population

[a] For patients who crossed over from chlorambucil + obinutuzumab to acalabrutinib monotherapy, data before crossover were assessed for each endpoint except for OS; OS was assessed based on the ITT population during the whole study period, including the crossover period.

AE, adverse event; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; del(17p), deletion of chromosome 17p region; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, 5-dimension EuroQol questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; HR, hazard ratio; *IGHV*, immunoglobulin heavy chain variable gene; IRC, Independent Review Committee; ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QLQ-C30, 30-item core quality of life questionnaire; SAE, serious adverse event; SD, standard deviation; SF, severe fatigue; *TP53*, tumour protein 53 gene; TTNT, time to next treatment.

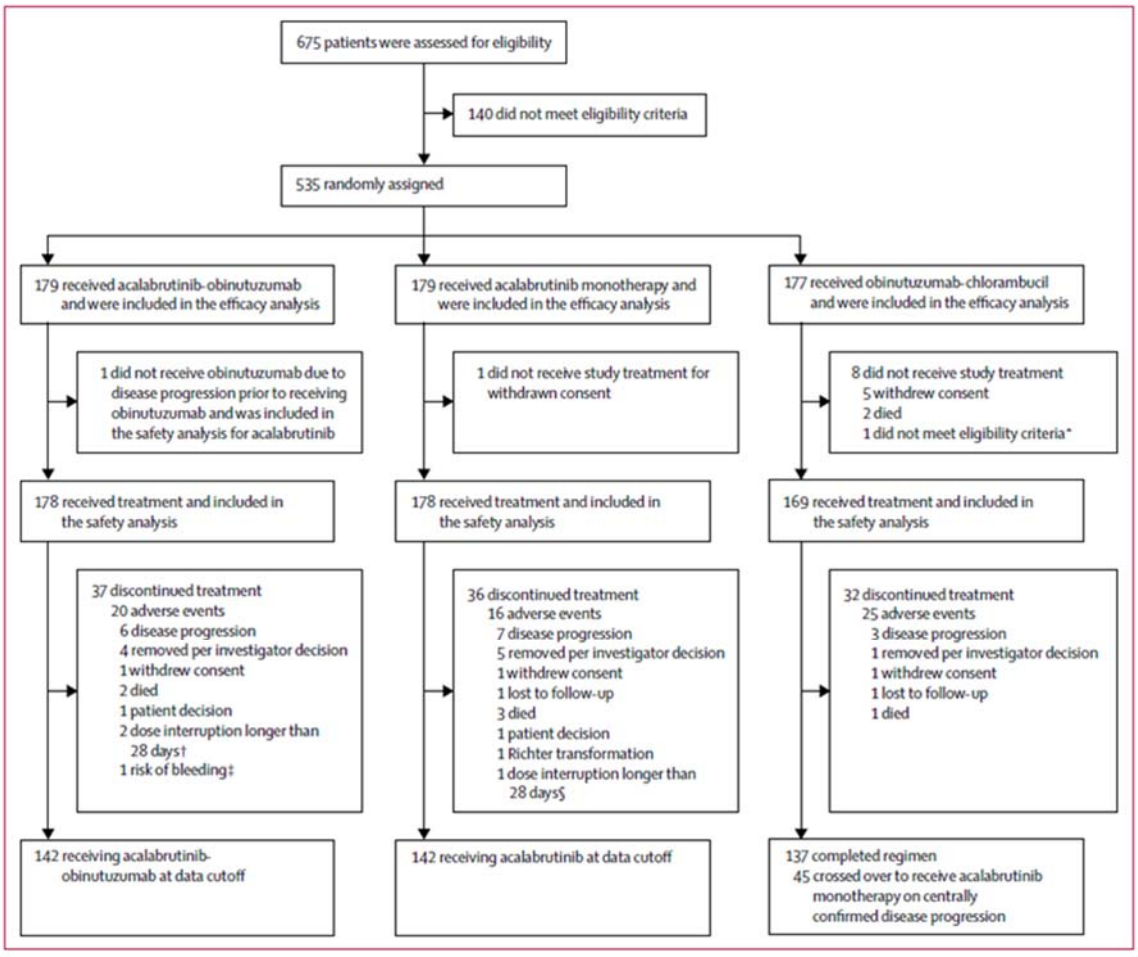
Source: ELEVATE-TN clinical study report[75]

B.2a.4.3 Participant flow in ELEVATE-TN

Of the 535 patients randomised, 526 patients received study treatment. As of the data cut-off date (8 February 2019), the median follow-up for acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab was 28.5, 28.4 and 28.0 months, respectively. In total, 33 patients (18.4%) receiving acalabrutinib plus obinutuzumab and 36 (20.1%) receiving acalabrutinib monotherapy discontinued treatment. In the chlorambucil plus obinutuzumab arm, no patients were receiving study drug at the time of data cut-off because most patients had completed their study regimen (chlorambucil: 77.4%; obinutuzumab: 85.9%).

In the chlorambucil plus obinutuzumab arm, 45 patients (25.4%) experienced disease progression and were eligible to cross over to acalabrutinib monotherapy.[11] In the crossover population, 91.1% of patients were continuing treatment with acalabrutinib and four patients had discontinued, owing to AEs (three patients) or progressive disease (one patient). The study participant flow is presented in Figure 4.

Figure 4. ELEVATE-TN CONSORT



Note: The safety population included all randomly assigned patients who received at least one dose of study medication with patients grouped according to the actual treatment received. In the safety population, 178 patients received acalabrutinib-obinutuzumab, 179 patients received acalabrutinib monotherapy, and 169 patients received obinutuzumab-chlorambucil. 12 patients did not meet eligibility criteria of being younger than 65 years and having a CIRS for Geriatrics score over 6 or CrCl of 30–69 mL/min.

*The patient was randomly assigned but subsequently found to have mantle cell lymphoma.
†Due to anaemia and pneumonia.
‡Risk of bleeding while taking aspirin and clopidogrel because of a non-ST myocardial infarction requiring a stent.
§ Due to grade 4 thrombocytopenia, followed by identification of an intestinal mass and subsequent intestinal perforation.
CIRS, Cumulative Illness Rating Scale; CrCl, creatine clearance; CONSORT,
Source: Sharman et al, 2020[11]

B.2a.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for the ELEVATE-TN trial is provided in Table 21. A full write up of the quality assessment can be found in Appendix D.

Table 21. Quality assessment results for ELEVATE-TN

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomly assigned (1:1:1) via a centralised interactive voice and web response system	Yes
Was the concealment of treatment allocation adequate?	Open-label study	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Baseline demographic and disease characteristics were similar between groups	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Patients and investigators were not masked to treatment. A masked independent review committee (IRC) assessed progression and response data.	No
Were there any unexpected imbalances in drop-outs between groups?	See Section B.2a.3.4	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

B.2a.6 Clinical effectiveness results of the relevant trials

The key efficacy outcomes for patients with untreated CLL from ELEVATE-TN are summarised in Table 22. All data are based on the interim data cut conducted on 08 February 2019.

Acalabrutinib (alone or in combination with obinutuzumab) produced statistically significant and clinically meaningful improvements in PFS, ORR and TTNT.

Median OS was not reached in any treatment arm; however, OS appeared to favour acalabrutinib monotherapy and acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab.

Table 22. Key efficacy outcomes reported by ELEVATE-TN

	Arm B: acalabrutinib + obinutuzumab (n = 179)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)
IRC-assessed PFS			
Events	14 (7.8)	26 (14.5)	93 (52.5)
HR vs arm A (95% CI)	0.10 (0.06–0.17) *p* < 0.0001	0.20 (0.13–0.30) *p* < 0.0001	–
OS			
Events[a]	[redacted]	[redacted]	[redacted]
KM estimated OS[b], % (95% CI)			
12 months	96.1 (91.9–98.1)	98.3 (94.8–99.4)	96.5 (92.4–98.4)
24 months	94.9 (90.5–97.3)	94.7 (90.2–97.2)	91.7 (86.3–95.0)
36 months	94.9 (90.5–97.3)	93.5 (88.6–96.3)	88.1 (80.7–92.8)
Overall response rates			
ORR (CR + CRi + nPR + PR), n (%) [95% CI][a]	168 (93.9) [89.3–96.5]	153 (85.5) [79.6–89.9]	139 (78.5) [71.9–83.9]
p value[b]	< 0.0001	0.0763	
Time to next treatment			
Events	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Crossed over to acalabrutinib monotherapy	0	0	45 (25.4)
Subsequent anti-cancer therapy	5 (2.8)	11 (6.1)	10 (5.6)
Patients alive with no crossover or subsequent anti-cancer therapy, n (%)	166 (92.7)	158 (88.3)	107 (60.5)
HR vs arm A (95% CI)	0.14; 95% CI: 0.08–0.26; p < 0.0001	0.24; 95% CI: 0.15–0.40; p < 0.0001	

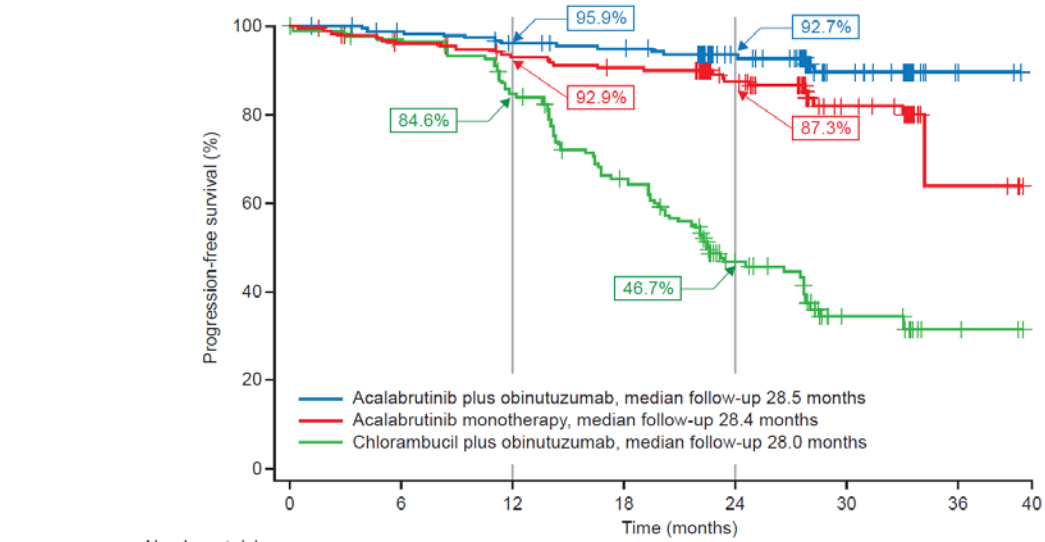
[a] 95% CI based on normal approximation (with use of Wilson's score).b Based on Cochran–Mantel–Haenzel test with adjustment for randomization stratification factors.
CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; CSR, clinical study report; IRC, Independent Review Committee; nPR, nodular partial remission; ORR, overall response rate; PD, progressive disease; PR, partial response
Source: ELEVATE-TN CSR[75]

B.2a.6.1 Primary and key secondary outcome (PFS)

The ELEVATE-TN trial met its primary endpoint, with acalabrutinib plus obinutuzumab treatment demonstrating a statistically significant improvement in IRC-assessed PFS, compared with chlorambucil plus obinutuzumab (Figure 5). Median PFS for acalabrutinib plus obinutuzumab was not reached and the median PFS with chlorambucil plus obinutuzumab was 22.6 months. This represented a 90% reduction in the risk of disease progression or death with acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab (HR: 0.10; 95% confidence interval [CI]: 0.6–0.17; p < 0.0001). The median follow-up in the acalabrutinib plus obinutuzumab and chlorambucil plus obinutuzumab arms were 28.5 months and 28.0 months, respectively.

The ELEVATE-TN trial also met its key secondary endpoint, with acalabrutinib monotherapy demonstrating a statistically significant and clinically meaningful improvement in IRC-assessed PFS, compared with chlorambucil plus obinutuzumab, after a median follow-up of 28 months. Treatment with acalabrutinib monotherapy resulted in an 80% reduction in the relative risk of disease progression or death versus chlorambucil plus obinutuzumab (HR: 0.20; 95% CI: 0.13–0.30; p < 0.0001). Median PFS for acalabrutinib monotherapy was not reached.

Figure 5. Kaplan–Meier plot for PFS (IRC assessment)



CSR, clinical study report; IRC, Independent Review Committee; PFS, progression-free survival.
Source: ELEVATE-TN CSR[75]

PFS results according to investigator assessment were consistent with those based on the IRC assessments. Acalabrutinib plus obinutuzumab and acalabrutinib monotherapy were both associated with significant improvements in investigator-assessed PFS compared with chlorambucil plus obinutuzumab (HR: 0.12; 95% CI: 0.07–0.21; p < 0.0001 and HR: 0.16; 95% CI: 0.10–0.27; p < 0.0001, respectively). The overall concordance rate of PFS between the IRC assessment and investigator assessment was 96.6%, 93.3% and 89.3% for

acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab, respectively (Table 23).[75]

Table 23. IRC- and investigator-assessed PFS and concordance

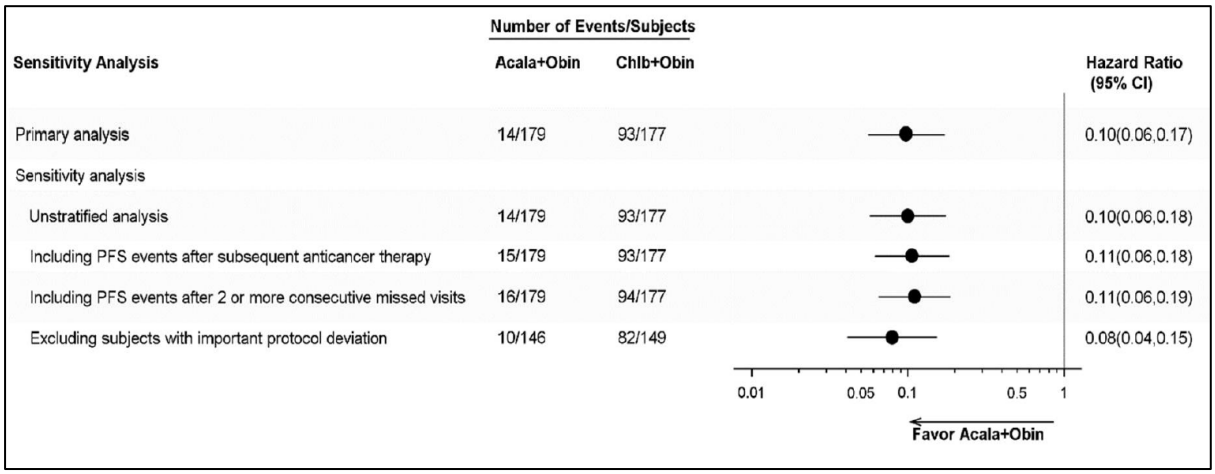
	Arm B: acalabrutinib + obinutuzumab (n = 179)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)
IRC-assessed PFS			
Events, n (%)			
Events	14 (7.8)	26 (14.5)	93 (52.5)
Death	5 (2.8)	6 (3.4)	11 (6.2)
Disease progression	9 (5.0)	20 (11.2)	82 (46.3)
KM-estimated PFS, % (95% CI)			
6-month PFS	98.9 (95.5–99.7)	95.9 (91.6–98.0)	97.0 (92.9–98.7)
12-month PFS	95.9 (91.7–98.0)	92.9 (87.8–95.9)	84.6 (78.0–89.3)
18-month PFS	94.8 (90.2–97.2)	90.5 (84.9–94.1)	65.6 (57.7–72.4)
24-month PFS	92.7 (87.4–95.8)	87.3 (80.9–91.7)	46.7 (38.5–54.6)
30-month PFS	89.6 (82.0–94.1)	81.9 (73.3–88.0)	34.2 (25.3–43.2)
36-month PFS	89.6 (82.0–94.1)	63.9 (29.4–84.9)	31.3 (21.8–41.3)
Investigator-assessed PFS			
Events, n (%)			
Events	15 (8.4)	19 (10.6)	86 (48.6)
Death	6 (3.4)	7 (3.9)	11 (6.2)
Disease progression	9 (5.0)	12 (6.7)	75 (42.4)
KM-estimated PFS, % (95% CI)			
6-month PFS	98.3 (94.8–99.5)	97.1 (93.2–98.8)	95.2 (90.7–97.6)
12-month PFS	95.4 (91.1–97.7)	94.7 (90.1–97.2)	85.5 (79.1–90.0)
18-month PFS	94.3 (89.6–96.9)	92.9 (87.8–95.9)	68.8 (61.0–75.3)
24-month PFS	91.9 (86.7–95.1)	90.4 (84.9–94.0)	54.7 (46.7–62.0)
30-month PFS	90.9 (85.3–94.5)	87.6 (81.0–92.1)	39.9 (30.6–49.1)
36-month PFS	90.9 (85.3–94.5)	87.6 (81.0–92.1)	36.9 (26.6–47.1)
Concordance between IRC- and investigator-assessed PFS			
Overall concordance rate	96.6	93.3	89.3

CI, confidence interval; CSR, clinical study report; IRC, Independent Review Committee; KM, Kaplan–Meier; PFS, progression-free survival.
Source: ELEVATE-TN CSR[75]

B.2a.6.2 Sensitivity analyses of primary endpoint

The results of all sensitivity analyses for the primary outcome, including the key analysis of PFS without censoring for subsequent anti-cancer therapy, were similar to those for the primary analysis, with HRs ranging from 0.08 to 0.11 (Figure 6), confirming the robustness of the primary analysis.

Figure 6. Forest plot showing the results of the sensitivity analysis for the primary endpoint: IRC-assessed PFS for acalabrutinib + obinutuzumab vs chlorambucil + obinutuzumab



CI, confidence interval; CO, chlorambucil + obinutuzumab; CSR, clinical study report; eCRF, electronic case report form; HR, hazard ratio; PFS, progression-free survival.
Source: ELEVATE-TN CSR[75]

B.2a.6.3 Secondary outcomes

Overall survival

The OS data are not mature and median OS was not reached in any treatment arm. However, the trend in OS favoured acalabrutinib plus obinutuzumab (HR: 0.47; 95% CI: 0.21–1.06; p = 0.0577) and acalabrutinib monotherapy (HR: 0.60; 95% CI: 0.28–1.27; p = 0.1556), compared with chlorambucil plus obinutuzumab (Table 24). After a median follow-up of 28.3 months, [redacted] receiving acalabrutinib plus obinutuzumab, [redacted] receiving acalabrutinib monotherapy and [redacted] receiving chlorambucil plus obinutuzumab had died.[75]

The Kaplan-Meier (KM)-estimated OS at 12 months was 96.1% (95% CI: 91.9–98.1) for acalabrutinib plus obinutuzumab, 98.3% (95% CI: 94.8–99.4) for acalabrutinib monotherapy and 96.5% (95% CI: 92.4–98.4) for chlorambucil plus obinutuzumab. At 36 months, the corresponding OS was 94.9% (95% CI: 90.5–97.3), 93.5% (95% CI: 88.6–96.3) and 88.1% (95% CI: 80.7–92.8), respectively.[75]

Table 24. Summary of overall survival outcomes in ELEVATE-TN

	Arm B: acalabrutinib + obinutuzumab (N = 179)	**Arm C: acalabrutinib monotherapy (N = 179)**	**Arm A: chlorambucil + obinutuzumab (N = 177)**
Events[a]	[redacted]	[redacted]	[redacted]
KM estimated OS[b], % (95% CI)			
6 months	98.3 (94.9–99.5)	98.9 (95.5–99.7)	97.1 (93.2–98.8)
12 months	96.1 (91.9–98.1)	98.3 (94.8–99.4)	96.5 (92.4–98.4)

	Arm B: acalabrutinib + obinutuzumab (N = 179)	Arm C: acalabrutinib monotherapy (N = 179)	Arm A: chlorambucil + obinutuzumab (N = 177)
18 months	94.9 (90.5–97.3)	97.1 (93.2–98.8)	94.7 (90.1–97.2)
24 months	94.9 (90.5–97.3)	94.7 (90.2–97.2)	91.7 (86.3–95.0)
30 months	94.9 (90.5–97.3)	93.5 (88.6–96.3)	89.9 (83.9–93.7)
36 months	94.9 (90.5–97.3)	93.5 (88.6–96.3)	88.1 (80.7–92.8)

[a] Included all deaths on study, including deaths after crossover for obinutuzumab + chlorambucil subjects who crossed over.
[b] KM estimate of proportion subjects who were alive at the timepoint.
CI, confidence interval; CSR, clinical study report; KM, Kaplan-Meier; OS, overall survival.
Source: ELEVATE-TN CSR[75]

Overall response rate (IRC-assessed)

In total, the IRC-assessed ORR with acalabrutinib plus obinutuzumab was 93.9% (95% CI: 89.3–96.5); this represents a statistically significant increase of 15.3% compared with those treated with chlorambucil plus obinutuzumab (ORR: 78.5%; 95% CI: 71.9–83.9; p < 0.0001). With acalabrutinib monotherapy, the IRC-assessed ORR was 85.5% (95% CI: 79.6–89.9); this represents an increase of 6.9% compared with chlorambucil plus obinutuzumab (p = 0.0763). Most patients in all treatment arms had a partial response (PR) to treatment (acalabrutinib plus obinutuzumab: 79.9%; acalabrutinib monotherapy: 83.8%; chlorambucil plus obinutuzumab: 72.3%; Table 25).

When including patients who had a partial response with lymphocytosis (PRL), IRC-assessed ORR plus PRL was significantly higher with acalabrutinib plus obinutuzumab (93.9%; 95% CI: 89.3–96.5; p < 0.0001) and acalabrutinib monotherapy (86.6%; 95% CI: 80.8–90.8; p = 0.0376) versus chlorambucil plus obinutuzumab (78.5%; 95% CI: 71.9–83.9).

Table 25. Treatment response rates (IRC-assessed)

	Arm B: acalabrutinib + obinutuzumab (n = 179)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 177)
Best overall response, n (%)			
CR	23 (12.8)	1 (0.6)	8 (4.5)
CRi	1 (0.6)	0	0
nPR	1 (0.6)	2 (1.1)	3 (1.7)
PR	143 (79.9)	150 (83.8)	128 (72.3)
PRL	0	2 (1.1)	0
Overall response rates			
ORR (CR + CRi + nPR + PR), n (%) [95% CI][a]	168 (93.9) [89.3–96.5]	153 (85.5) [79.6–89.9]	139 (78.5) [71.9–83.9]
p value[b]	< 0.0001	0.0763	
ORR + PRL, n (%) [95% CI][a]	168 (93.9) [89.3–96.5]	155 (86.6) [80.8–90.8]	139 (78.5) [71.9–83.9]
p value[b]	< 0.0001	0.0376	

[a] 95% CI based on normal approximation (with use of Wilson's score).
[b] Based on Cochran–Mantel–Haenzel test with adjustment for randomization stratification factors.
CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; CSR, clinical study report; IRC, Independent Review Committee; nPR, nodular partial remission; ORR, overall response rate; PD, progressive disease; PR, partial response; PRL, partial response with lymphocytosis.
Source: ELEVATE-TN CSR[75]

The ORRs according to investigator assessment were consistent with those based on IRC assessments (acalabrutinib plus obinutuzumab: 96.1% [95% CI: 92.1–98.1]; acalabrutinib monotherapy: 89.4% [95% CI: 84.0–93.1]; chlorambucil plus obinutuzumab: 82.5% [95% CI: 76.2–87.4]). ORR was significantly higher in the acalabrutinib plus obinutuzumab arm versus the chlorambucil plus obinutuzumab arm (13.6%; $p < 0.0001$) and numerically higher in the acalabrutinib monotherapy arm versus the chlorambucil plus obinutuzumab arm (6.9%; $p = 0.052$). When PRL was included in the investigator-assessed ORR, ORR was significantly higher with acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab (14.2%; $p < 0.0001$), and with acalabrutinib monotherapy versus chlorambucil plus obinutuzumab (9.7%, $p = 0.0048$).[75]

Time to next treatment (TTNT)

Acalabrutinib plus obinutuzumab and acalabrutinib monotherapy were each associated with a significantly higher TTNT, compared with chlorambucil plus obinutuzumab (HR: [redacted] and HR [redacted] respectively). In total, [redacted] patients ([redacted]), [redacted] patients ([redacted]) and [redacted] patients ([redacted]) switched to a subsequent anti-cancer treatment following acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab treatment, respectively. Additionally, [redacted] patients ([redacted]%) crossed over to acalabrutinib monotherapy from the chlorambucil plus obinutuzumab arm following IRC-confirmed disease progression.

B.2a.6.4 Exploratory outcomes

Patient reported outcomes

HRQoL was stable or improved from baseline over the study period in all treatment arms, as assessed using the 5-dimension EuroQol questionnaire (EQ-5D-3L). No statistically significant differences were observed between acalabrutinib plus obinutuzumab or acalabrutinib monotherapy and chlorambucil plus obinutuzumab. Similarly, when assessed using the EORTC QLQ-C30, all treatment arms were associated with improvements in HRQoL from baseline. Most domains of the EORTC QLQ-C30 were improved with acalabrutinib plus obinutuzumab and acalabrutinib monotherapy, including the global health status, fatigue, role functioning, emotional functioning, pain, dyspnoea, insomnia and appetite loss domains.

Fatigue was assessed using the Functional Assessment of Cancer Therapy (FACIT)-Fatigue questionnaire and acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab all improved fatigue scores from baseline. These improvements were greater in patients who had severe fatigue at baseline (FACIT-Fatigue score ≤ 34 at baseline).

B.2a.7 Subgroup analysis

B.2a.7.1 Patient subgroups of the primary and key secondary analyses

The PFS benefit of acalabrutinib plus obinutuzumab and acalabrutinib monotherapy versus chlorambucil plus obinutuzumab was consistent across all prespecified subgroups (Figure 7), including the following:

- Patients who had at least one chromosomal characteristic associated with poor prognosis (del[17p], TP53 mutation, del[11q] or unmutated IGHV) had a 92% reduction in the relative risk of disease progression or death with acalabrutinib plus obinutuzumab (HR: 0.08; 95% CI: 0.04–0.15) and an 87% reduction with acalabrutinib monotherapy (HR: 0.13; 95% CI: 0.08–0.21) versus chlorambucil plus obinutuzumab.

- Patients with a complex karyotype had a 91% reduction in the relative risk of disease progression or death with acalabrutinib plus obinutuzumab (HR: 0.09; 95% CI: 0.03–0.29) and a 90% reduction with acalabrutinib monotherapy (HR: 0.10; 95% CI: 0.03–0.33) versus chlorambucil plus obinutuzumab.

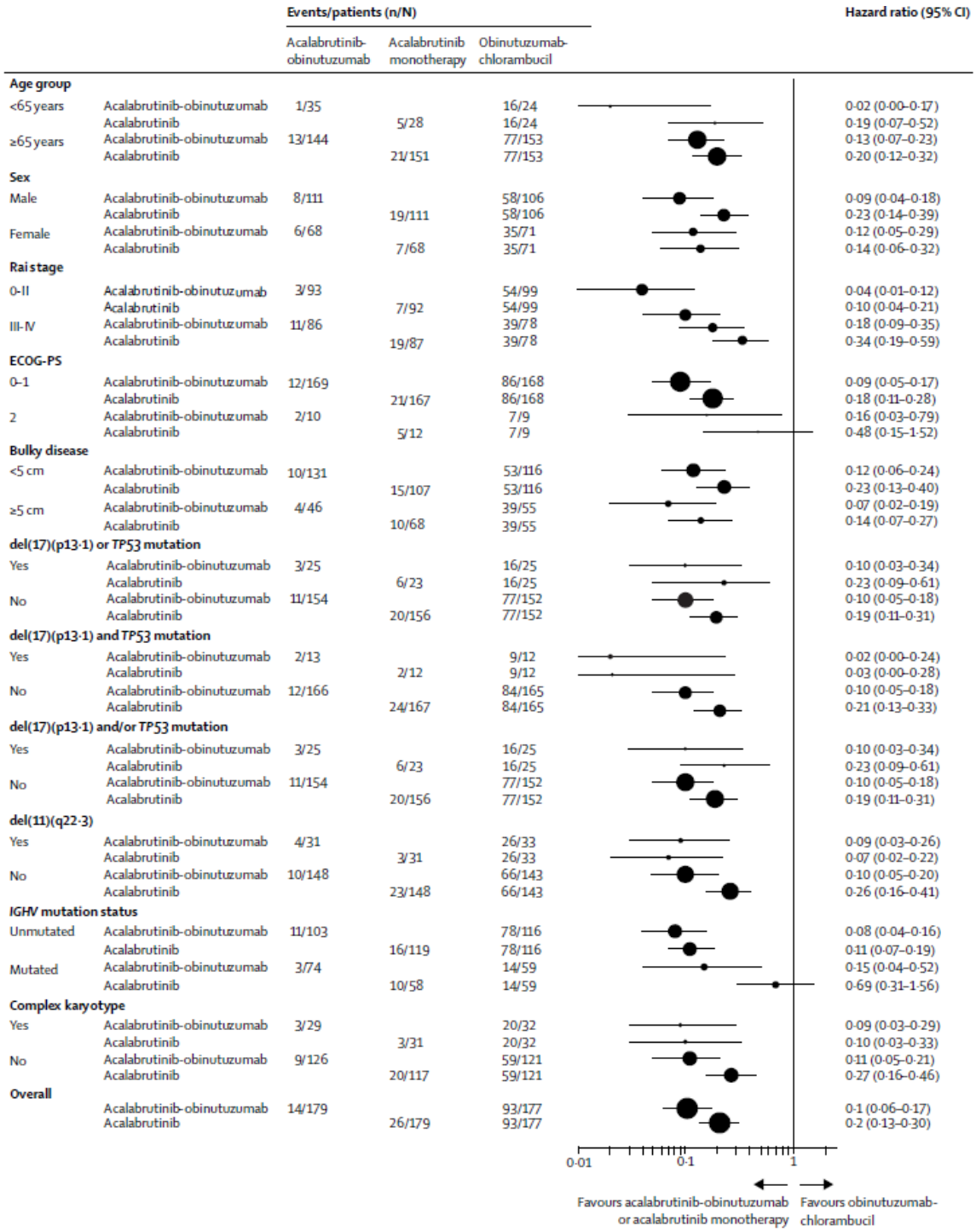
- Patients with non-chromosomal risk factors independently associated with reduced survival, including advanced stage disease (Rai stage), elevated beta-2 microglobulin or age 65 years or older, showed significant PFS benefit with acalabrutinib plus obinutuzumab and with acalabrutinib monotherapy, versus chlorambucil plus obinutuzumab.

- Acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: Rai stage III–IV, HR: 0.18 (95% CI: 0.09–0.35); beta-2 microglobulin greater than 3.5 mg/L at baseline, HR: 0.10 (95% CI: 0.05–0.18); and age 65 years or older, HR: 0.13 (95% CI: 0.07–0.23).

- Acalabrutinib monotherapy versus chlorambucil plus obinutuzumab: Rai stage III–IV, HR: 0.34 (95% CI: 0.19–0.59); beta-2 microglobulin greater than 3.5 mg/L at baseline, HR: 0.18 (95% CI: 0.11–0.30); and age 65 years or older, HR: 0.20 (95% CI: 0.12–0.32).

- In addition, patients with bulky disease 5 cm or greater showed significant PFS benefit with acalabrutinib plus obinutuzumab (HR: 0.07; 95% CI: 0.02–0.19) and with acalabrutinib monotherapy (HR: 0.14; 95% CI: 0.07–0.27) versus chlorambucil plus obinutuzumab.

Figure 7. Forest plot showing results from the prespecified subgroup of analysis of PFS



IGHV, immunoglobulin heavy chain variable gene; NE, not evaluable; TP53, cellular tumour antigen p53 gene; ECOG PS, Eastern Cooperative Oncology Group performance status.
Source: Sharman *et al.* 2020[11]

B.2a.8 Meta-analysis

All efficacy and safety data relevant to the decision problem are provided from one relevant RCT, ELEVATE-TN for acalabrutinib versus chlorambucil plus obinutuzumab. Therefore, it was not necessary to conduct a meta-analysis.

B.2a.9 Indirect and mixed treatment comparisons

Direct head-to-head evidence for acalabrutinib monotherapy versus chlorambucil plus obinutuzumab was available from the ELEVATE-TN study; therefore an indirect treatment comparison was not required.

B.2a.10 Adverse reactions

The safety results are presented across all patients who received at least one dose of study treatment.

B.2a.10.1 Acalabrutinib dose exposure

Exposure to acalabrutinib was similar across the two acalabrutinib treatment arms. The median duration of acalabrutinib treatment was 27.7 months (range: 0.7– 40.3 months) for the acalabrutinib plus obinutuzumab arm and 27.7 months for the acalabrutinib monotherapy arm (range: 0.3–40.2 months).

Because of the fixed number of treatment cycles for chlorambucil and obinutuzumab, the median duration of treatment was much shorter (chlorambucil: 5.5 months [range: 0.5–7.2 months]; obinutuzumab: 5.5 [range: 0.8—7.1] and 5.6 months [range: 0.9—7.4] in combination with acalabrutinib and chlorambucil, respectively) in the acalabrutinib plus obinutuzumab and the chlorambucil plus obinutuzumab arms.

Patients who crossed over from chlorambucil plus obinutuzumab to acalabrutinib monotherapy because of IRC-confirmed disease progression had a median duration of exposure to acalabrutinib of 11.0 months (range: 2.0–23.5 months).

B.2a.10.2 Treatment emergent adverse events

The proportions of patients who experienced treatment-emergent adverse events (TEAEs) were comparable between acalabrutinib plus obinutuzumab (96.1%), acalabrutinib monotherapy (95.0%) and chlorambucil plus obinutuzumab (98.8%).

The proportion of patients with grade ≥ 3 TEAEs was significantly lower with acalabrutinib monotherapy (49.7%) compared with acalabrutinib plus obinutuzumab (70.2%) and chlorambucil plus obinutuzumab (69.8%; Table 26). The most common TEAEs with acalabrutinib plus obinutuzumab were headache (39.9%), diarrhoea (38.8%) and neutropenia (31.5%), while headache (36.9%), diarrhoea (34.6%) and nausea (22.3%) were the most common TEAEs with acalabrutinib monotherapy. For chlorambucil plus obinutuzumab, the most common TEAEs were neutropenia (45.0%), infusion-related reaction (39.6%), and nausea (31.4%).

The most common grade ≥ 3 TEAEs with acalabrutinib plus obinutuzumab were neutropenia (29.8%), thrombocytopenia (8.4%), anaemia (5.6%) and pneumonia (5.6%). Similarly,

neutropenia (9.5%), anaemia (6.7%) and thrombocytopenia (2.8%) were the most common grade ≥ 3 TEAEs with acalabrutinib monotherapy. With chlorambucil plus obinutuzumab, neutropenia (41.4%), thrombocytopenia (11.8%) and TLS (7.7%) were the most common grade ≥ 3 TEAEs. A summary of Grade ≥3 TEAEs reported in ≥2% patients are presented in Table 27.

Discontinuation because of TEAEs was least common in the acalabrutinib monotherapy arm (9.5%), followed by the acalabrutinib plus obinutuzumab arm (10.7%) and then the chlorambucil plus obinutuzumab arm (14.2%).

Table 26. Summary of all treatment-emergent adverse events

Event	Number (%) of patients		
	Arm B: acalabrutinib + obinutuzumab (n = 178)	**Arm C: acalabrutinib monotherapy (n = 179)**	**Arm A: chlorambucil + obinutuzumab (n = 169)**
Any grade AE	171 (96.1)	170 (95.0)	167 (98.8)
Grade 1	7 (3.9)	14 (7.8)	4 (2.4)
Grade 2	39 (21.9)	67 (37.4)	45 (26.6)
Grade ≥ 3	125 (70.2)	89 (49.7)	118 (69.8)
Most common AEs (occurred in ≥ 10% of patients)			
Blood and lymphatic system disorders	80 (44.9)	56 (31.3)	92 (54.4)
Neutropenia	56 (31.5)	19 (10.6)	76 (45.0)
Thrombocytopenia	23 (12.9)	13 (7.3)	24 (14.2)
Anaemia	21 (11.8)	25 (14.0)	20 (11.8)
Gastrointestinal disorders	115 (64.6)	118 (65.9)	85 (50.3)
Diarrhoea	69 (38.8)	62 (34.6)	36 (21.3)
Nausea	36 (20.2)	40 (22.3)	53 (31.4)
Constipation	25 (14.0)	20 (11.2)	17 (10.1)
General disorders and administration site conditions	104 (58.4)	84 (46.9)	80 (47.3)
Fatigue	50 (28.1)	33 (18.4)	29 (17.2)
Pyrexia	23 (12.9)	12 (6.7)	35 (20.7)
Oedema peripheral	22 (12.4)	16 (8.9)	12 (7.1)
Chills	20 (11.2)	8 (4.5)	14 (8.3)
Infections and infestations	123 (69.1)	117 (65.4)	74 (43.8)
Upper respiratory tract infection	38 (21.3)	33 (18.4)	14 (8.3)
Urinary tract infection	22 (12.4)	22 (12.3)	8 (4.7)
Nasopharyngitis	20 (11.2)	17 (9.5)	7 (4.1)
Pneumonia	19 (10.7)	13 (7.3)	5 (3.0)
Injury, poisoning and procedural complications	80 (44.9)	52 (29.1)	73 (43.2)
Contusion	42 (23.6)	27 (15.1)	7 (4.1)
Infusion-related reaction	24 (13.5)	0	67 (39.6)
Metabolism and nutrition disorders	59 (33.1)	31 (17.3)	44 (26.0)
Decreased appetite	18 (10.1)	10 (5.6)	13 (7.7)
Musculoskeletal and connective tissue disorders	90 (50.6)	95 (53.1)	39 (23.1)

Event	Number (%) of patients		
	Arm B: acalabrutinib + obinutuzumab (n = 178)	**Arm C: acalabrutinib monotherapy (n = 179)**	**Arm A: chlorambucil + obinutuzumab (n = 169)**
Arthralgia	39 (21.9)	28 (15.6)	8 (4.7)
Back pain	25 (14.0)	25 (14.0)	14 (8.3)
Pain in extremity	22 (12.4)	11 (6.1)	7 (4.1)
Nervous system disorders	101 (56.7)	96 (53.6)	51 (30.2)
Headache	71 (39.9)	66 (36.9)	20 (11.8)
Dizziness	32 (18.0)	21 (11.7)	10 (5.9)
Respiratory, thoracic and mediastinal disorders	79 (44.4)	76 (42.5)	45 (26.6)
Cough	39 (21.9)	33 (18.4)	15 (8.9)
Dyspnoea	15 (8.4)	12 (6.7)	17 (10.1)
Skin and subcutaneous tissue disorders	89 (50.0)	76 (42.5)	45 (26.6)
Rash	21 (11.8)	25 (14.0)	8 (4.7)

AE, adverse event; CSR, clinical study report; SAE, serious adverse event.
Source: ELEVATE-TN CSR[75]

Table 27: Grade ≥ 3 adverse events reported in at least 2% of patients in any arm (safety population)

	Number (%) of patients		
	Arm B: acalabrutinib + obinutuzumab (n = 178)	Arm C: acalabrutinib monotherapy (n = 179)	Arm A: chlorambucil + obinutuzumab (n = 169)
Subjects with ≥ 1 grade ≥ 3 AE	125 (70.2)	89 (49.7)	118 (69.8)
Neutropenia	53 (29.8)	17 (9.5)	70 (41.4)
Thrombocytopenia	15 (8.4)	5 (2.8)	20 (11.8)
Anaemia	10 (5.6)	12 (6.7)	12 (7.1)
Febrile neutropenia	3 (1.7)	2 (1.1)	9 (5.3)
Diarrhoea	8 (4.5)	1 (0.6)	3 (1.8)
Upper respiratory tract infection	4 (2.2)	0	1 (0.6)
Pneumonia	10 (5.6)	4 (2.2)	3 (1.8)
Infusion-related reaction	4 (2.2)	0	9 (5.3)
Alanine aminotransferase increased	5 (2.8)	1 (0.6)	3 (1.8)
Neutrophil count decreased	2 (1.1)	0	5 (3.0)
Tumour lysis syndrome	2 (1.1)	0	13 (7.7)
Syncope	4 (2.2)	2 (1.1)	1 (0.6)
Hypertension	5 (2.8)	4 (2.2)	5 (3.0)

AE, adverse event.
Source: Source: ELEVATE-TN CSR[75]

B.2a.10.3 Serious AEs

A serious AE (SAE) was defined as any untoward medical occurrence that, at any dose, resulted in death, was life threatening, required hospitalization of more than 24 hours or prolongation of existing hospitalization, resulted in persistent or significant

disability/incapacity or was a congenital anomaly/birth defect. An event that did not meet these criteria was considered an SAE when, based upon appropriate medical judgement, the event may have jeopardized the patient or may have required intervention to prevent one of the other outcomes listed above.

SAEs, most of which were grade ≥ 3, occurred in 38.8%, 31.8% and 21.9% of patients who received acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab, respectively. Among patients treated with acalabrutinib, the most common SAE was pneumonia, which affected 12 patients (6.7%) receiving acalabrutinib plus obinutuzumab and five patients (2.8%) receiving acalabrutinib monotherapy. The most common SAE in patients treated with chlorambucil plus obinutuzumab was TLS, which occurred in eight patients (4.7%).

B.2a.10.4 Deaths

At the time of the data cut-off, eight patients (4.5%) in the acalabrutinib plus obinutuzumab arm, 12 patients (6.7%) in the acalabrutinib monotherapy arm and 13 patients (7.7%) in the chlorambucil plus obinutuzumab arm had died.

B.2a.10.5 Safety overview

The proportions of patients who experienced TEAEs were comparable between acalabrutinib plus obinutuzumab, acalabrutinib monotherapy and chlorambucil plus obinutuzumab (96.1% vs 95.0% vs 98.8%). The proportion of patients with grade ≥ 3 TEAEs was significantly lower with acalabrutinib monotherapy. A larger proportion of SAEs occurred in acalabrutinib plus obinutuzumab compared to acalabrutinib monotherapy and chlorambucil plus obinutuzumab, respectively. However, more deaths occurred in chlorambucil plus obinutuzumab compared to acalabrutinib plus obinutuzumab and acalabrutinib monotherapy. Therefore, the ELEVATE-TN study demonstrated that acalabrutinib is well tolerated and has an acceptable safety profile in patients with previously untreated CLL.

B.2b Clinical effectiveness: R/R CLL patients

B.2b.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify RCTs investigating treatments in patients with R/R CLL. The PICOS criteria for study selection are presented in Appendix D. The SLR conducted was broader than the scope of this submission therefore studies were only extracted if they included ibrutinib, the comparator treatment of interest in the R/R setting (see Section B1).

B.2b.2 List of relevant clinical effectiveness evidence

ASCEND was the only identified RCT evaluating the clinical efficacy and safety of acalabrutinib in patients with R/R CLL. The SLR identified five RCTs evaluating ibrutinib. Table 28 presents details of these studies.

Table 28. Summary of study characteristics for RCTs identified in the SLR (R/R setting)

Publication source (author_year)	Trial name (if any)	Treatments	Publication Type	Study setting	Phase	Cross over
Byrd 2014	RESONATE	• Ibrutinib • Ofatumumab	Journal article	Multicenter international	III	No
De Jong 2015	NR	• Ibrutinib (fasted/fed)	Journal article	Multicenter	NR	Yes
Sharman 2017	GENUINE	• Ibrutinib • Ibrutinib + Ublituximab	Conference abstract	Multicenter international	III	No
Huang 2018	NR	• Ibrutinib • Rituximab	Journal article	Multicenter international	III	Yes
Burger 2019	NR	• Ibrutinib • Ibrutinib + Rituximab	Journal article	Single center	II	No

NR, not reported; RCT, randomised controlled trial; R/R, relapsed/refractory; SLR, systematic literature review

Of the five studies identified, two report both efficacy and safety outcomes for ibrutinib in the R/R setting (Huang et al 2018 and RESONATE).

Huang et al. 2018 provides results in a single publication, whilst the RESONATE study evaluates the efficacy and safety of ibrutinib across multiple publications; as such extensive data from RESONATE could be collected and analysed. Study characteristics, efficiency outcomes and safety outcomes retrieved for the five studies identified in the SLR are available in Appendix D.

The clinical effectiveness of ibrutinib to inform this submission is based on the RESONATE trial on the basis that this trial represented the key clinical evidence informing the efficacy of ibrutinib in the NICE appraisal (TA429), and was determined to present data which were generalisable to clinical practice in England and Wales. Furthermore, extensive data could be collected and analysed from multiple publications identified in the SLR, to inform potential estimates for comparative effectiveness.

The ASCEND and RESONATE trials are presented in Table 29, with further details summarised in Table 30.

Table 29. Summary of pivotal trials for acalabrutinib and ibrutinib in the R/R setting

Author, year, study name	Intervention	Comparator
Ghia et al. 2019 [76] ASCEND	Acalabrutinib	IR/BR[a]
Byrd et al. 2014[77] RESONATE	Ibrutinib	Ofatumumab

[a] According to investigator's choice

BR, bendamustine plus rituximab; IR, Idelalisib plus rituximab

Table 30. Summary details for ASCEND and RESONATE

Study	ACE-CL-309 / ASCEND (NCT02970318)[76]	RESONATE (NCT01578707)[77]
Study design	Randomised, multicentre, open-label, phase 3 study	Randomised, multicentre, open-label, phase 3 study
Population	Patients with R/R CLL aged ≥ 18 years	Patients with CLL or SLL
Intervention(s)	Acalabrutinib	Ibrutinib
Comparator(s)	IR/BR[a]	Ofatumumab
Indicate if trial supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	PFS, OS, TTNT, AEs, HRQoL	PFS, OS, TTNT, AEs, HRQoL
All other reported outcomes	ORR, ORR + PRL, healthcare resource utilization, pharmacokinetics, MRD	ORR, rate of sustained haemoglobin and platelet improvement

[a] According to investigator's choice.

AE, adverse event; BR, bendamustine + rituximab; HRQoL, health-related quality of life; IR, Idelalisib plus rituximab; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRL, partial response with lymphocytosis; R/R CLL, relapsed/refractory chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; TTNT, time to next treatment.

B.2b.3 Summary of methodology of the relevant clinical effectiveness evidence – ASCEND and RESONATE

B.2b.3.1 Study design, methodology and eligibility criteria

Information for ASCEND was extracted from the CSR[75] and for RESONATE information was sourced from the primary publication.[77] Both ASCEND and RESONATE were multinational, open-label, RCTs, with enough similarities to enable matching in an indirect treatment comparison. A comparative summary of the trial methodology is presented in Table 31, and a summary of the study designs for the ASCEND and RESONATE studies are shown in Figure 8 and Figure 9, respectively.

Table 31: Comparative summary of trial methodology

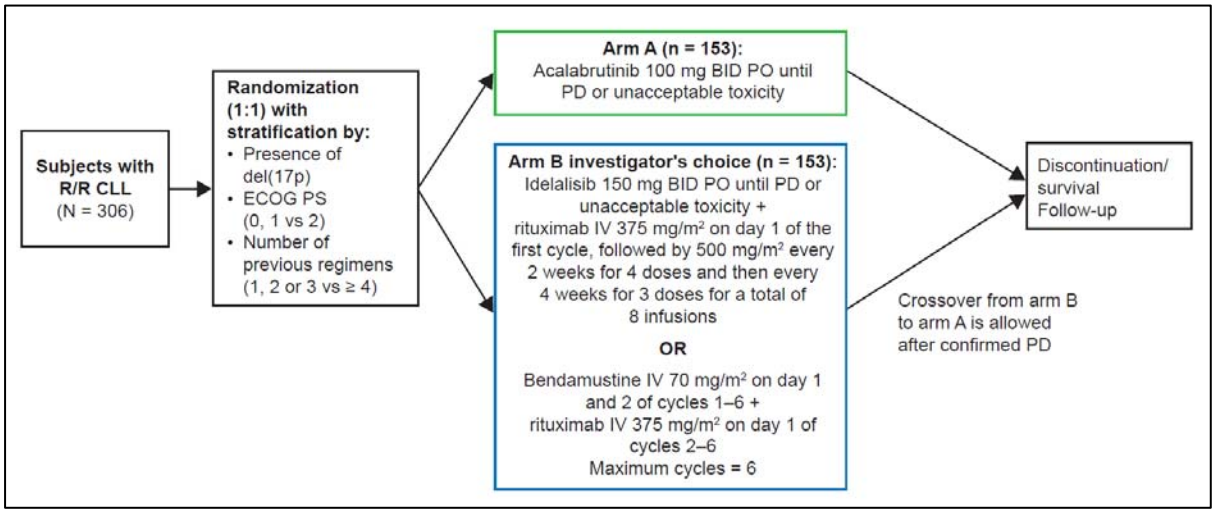
Trial reference	ASCEND (NCT02970318)[76]	RESONATE (NCT01578707)[77]
Location	102 sites across 25 countries: Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, France, Germany, Hong Kong, Hungary, Israel, Italy, Republic of Korea, New Zealand, Poland, Russia, Singapore, Slovakia, Spain, Sweden, Taiwan, Ukraine, UK and USA	67 sites across USA, Australia, and seven European countries
Trial design	Phase 3, multicentre, open-label randomised study	Phase 3, multicentre, open-label, randomised study
Randomisation	Patients were randomised in a 1:1 ratio into the three treatment arms using an IXRS. Randomisation was stratified by: • 17p deletion (presence versus absence) • ECOG performance status (0 or 1 versus 2) • Number of prior therapies (1, 2 or 3 vs ≥ 4)	Patients were randomised in a 1:1 ratio into the two treatment arms using an IWRS. Two randomisation schemes were generated: one for each geographical region (US vs. non-US). Under each scheme, patients were stratified according to resistance to purine analogue chemo-immunotherapy within 12 months of the last dose of a purine analogue and the presence/absence of 17p13
Blinding	Both trials were open-label studies, and neither the subjects nor the investigators were blinded to treatment.	
Eligibility criteria for participants	**Key inclusion criteria:** • Age ≥ 18 years • ECOG Performance Status of 0–2 • Diagnosis of CLL that meets published diagnostic criteria • Documented CD20-positive CLL • Active disease meeting ≥ 1 of the IWCLL 2008 criteria for requiring treatment • Laboratory parameters: ANC ≥ 0.75 × 109/L;[a] platelet count ≥ 50 × 109/L;[b] AST and ALT ≤ 2.0 × ULN; total bilirubin ≤ 1.5 × ULN; estimated creatinine clearance of ≥ 30 mL/min • ≥ 1 previous systemic therapy for CLL (excluding single-agent steroids or localized radiation)	**Key inclusion criteria:** • ≥ 1 previous systemic therapy for CLL/SLL • ECOG Performance Status of 0–1 • Diagnosis of CLL that meets published diagnostic criteria (CLL or SLL diagnosis)

Trial reference	ASCEND (NCT02970318)[76]	RESONATE (NCT01578707)[77]
	Key exclusion criteria: • Previous exposure to a BCL-2 inhibitor or a BCR inhibitor[c] • Significant cardiovascular disease • Required or received anticoagulation therapy with warfarin or other equivalent other vitamin K antagonists within 7 days of first dose of study drug	**Key exclusion criteria:** • Requirement for warfarin or strong CY3A4/5 inhibitors • Absolute neutrophil count of less than 750 cells/μl • Platelet count of less than 30,000 cells/μl
Settings and locations where data were collected	All data were collected on original source documents, and the investigator maintained detailed records for all patients. Patient data gathered during the study were captured electronically using eCRFs and from external (non-eCRF) data sources. An independent DMC periodically reviewed the safety data and also reviewed the planned interim efficacy analysis results.	The investigators and their research teams collected the data. An independent review committee, whose members were unaware of study-group assignments and lymphocyte counts, assessed progression and response. An independent data and safety monitoring committee evaluated safety and reviewed data from the protocol-specified interim analysis.
Study treatments	**Arm A (acalabrutinib):** • Oral 100mg twice per day until an unacceptable drug-related toxicity occurs or until disease progression **Arm B (IR):** • Idelalisib 150mg PO BID until disease progression or unacceptable toxicity + ≥ 8 IV infusions of rituximab **Arm C (BR):** • Bendamustine 70mg/m² IV (day 1 and 2 of each cycle) + 375mg/m² / 500mg/m² IV rituximab on day 1 of each cycle for up to 6 cycles	**Arm A (Ibrutinib):** • Oral 420mg once daily until disease progression or the occurrence of unacceptable toxic effects **Arm B (Ofatumumab):** • 300mg IV week 1, 2000mg weekly for 7 weeks and then every 4 weeks for 16 weeks
Primary outcomes	**PFS according to IRC assessment:** • The time from randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first	**PFS according to IRC assessment:** • Assessed in accordance with the criteria of the iwCLL. • Members of the committee were unaware of study-group assignment and lymphocyte counts

Trial reference	ASCEND (NCT02970318)[76]	RESONATE (NCT01578707)[77]
Pre-planned subgroups	To assess the consistency of efficacy in different subpopulations, subgroup analyses were performed based on: • Chromosomal characteristic (del[17p], *TP53* mutation, del[11q] or unmutated *IGHV*) • Non-chromosomal risk factors (advanced stage disease [Rai stage], elevated beta-2 microglobulin, age ≥ 65 years or bulky disease ≥ 5 cm) associated with poor prognosis	To assess the consistency of efficacy in different subpopulations, subgroups analyses were performed based on: • Baseline characteristics: resistance to purine analogues, sex, race or geographic region • Chromosomal characteristic (del[17p], *TP53* mutation, del[11q] or unmutated *IGHV*) • Non-chromosomal risk factors (advanced stage disease [Rai stage], ECOG score, elevated beta-2 microglobulin, age ≥ 65 years or bulky disease ≥ 5 cm) associated with poor prognosis

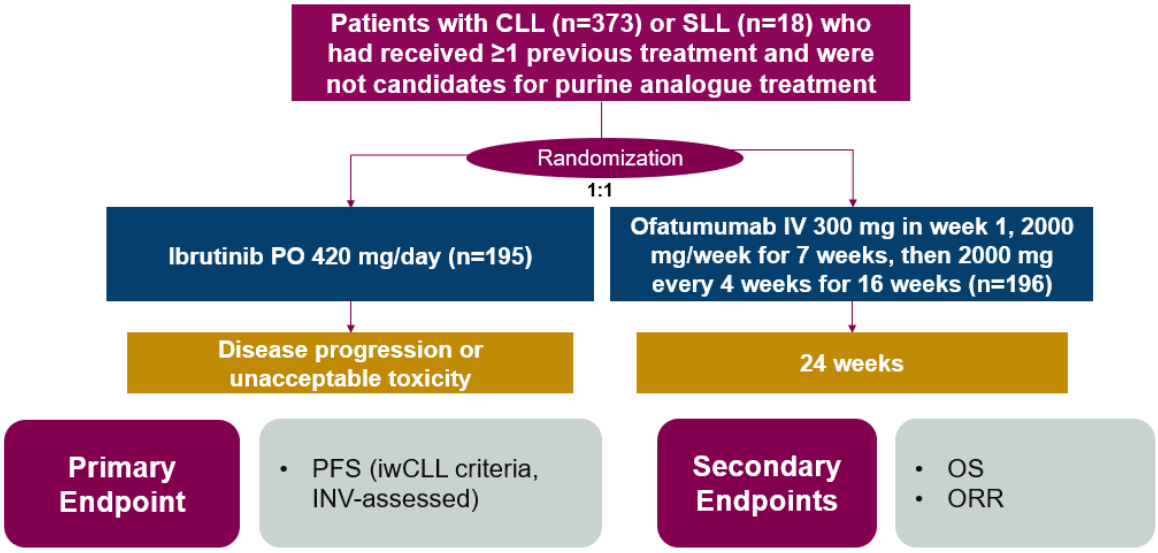
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate transaminase; BCR, B-cell receptor; BID, twice a day; CLL, chronic lymphocytic leukaemia; DMC, data monitoring committee; ECOG, Eastern Cooperative Oncology Group; eCRFs, electronic case report form; iwCLL, International Workshop on CLL; PO, orally; SLL, small lymphocytic lymphoma.

Figure 8. ASCEND study design



BID, twice per day; CLL, chronic lymphocytic leukaemia; del(17p), deletion of chromosome 17p region; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, progressive disease; PO, oral; PS, Performance Status; R/R, relapsed or refractory.
Source: ASCEND CSR[78]

Figure 9: RESONATE study design



CLL, Chronic lymphocytic leukaemia; INV, investigator; IV, intravenous; iwCLL, International Workshop on CLL; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; SLL, small lymphocytic lymphoma.
Source: ASCEND CSR[78]

B.2b.3.2.1 Outcome measures - ASCEND

The definitions of the outcome measures available in the ASCEND trial are presented in Table 32.

Table 32. Outcome measures available from ASCEND

Efficacy measures	Description

Primary endpoint	
PFS (IRC)	Time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first. KM curve was used to estimate the distribution of PFS.
Secondary	
Investigator assessed PFS	PFS, defined as the time from date of randomization to the date of first investigator assessed disease progression or death due to any cause, whichever comes first. KM curve was used to estimate the distribution of PFS.
OS	OS was defined as the time from date of randomization to death due to any cause.
PROs by FACIT-Fatigue	Change from baseline in GFS at Week 24 and Week 48, proportion of subjects with improvement / stable / deterioration in GFS, and time to first clinically meaningful improvement in GFS.
Investigator-assessed DOR	DOR determined by IRC and by investigators was analysed in the same fashion as PFS described above.
TTNT	TTNT was analysed in the same fashion as PFS described above.
Investigator and IRC-assessed ORR	Best overall response was defined as the best response as assessed by the investigator or IRC on or before the initiation of subsequent anticancer therapy.
Exploratory	
Improvement and/or resolution of disease-related symptoms	Disease-related symptoms (constitutional symptoms - weight loss, fever, night sweats, and fatigue) prior to subsequent anticancer therapy were summarized by timepoint.
Hematologic improvement in the subset of subjects with cytopenia(s) at baseline	Hematologic improvement was defined as follows for each parameter: ANC >1.5x10^9/L or increase ≥50% over baseline; haemoglobin >11 g/dL or increase ≥50% over baseline; platelet count >100x10^9/L or increase ≥50% over baseline.
PROs by EORTC QLQ-C30 and EQ-5D-5L	Change from baseline in GHS and other domains of EORTC QLQ-C30 and EQ-5D-5L VAS scores at Week 24 and Week 48, proportion of subjects with improvement/stable/deterioration in EORTC QLQ-C30 and EQ-5D-5L VAS scores, and time to first clinically meaningful improvement in EORTC QLQ-C30 and EQ-5D-5L VAS scores.
Medical resource use	Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use were collected for each treatment arm.

ANC, absolute neutrophil count; DoR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, 5-dimension EuroQol questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; GFS, global fatigue score; GHS, global health status; IRC, Independent Review Committee; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; KM, kaplan meier; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcomes; QLQ-C30, 30-item core quality of life questionnaire; TTNT, time to next treatment; VAS, visual analogue scale.
Source: ASCEND CSR[78]

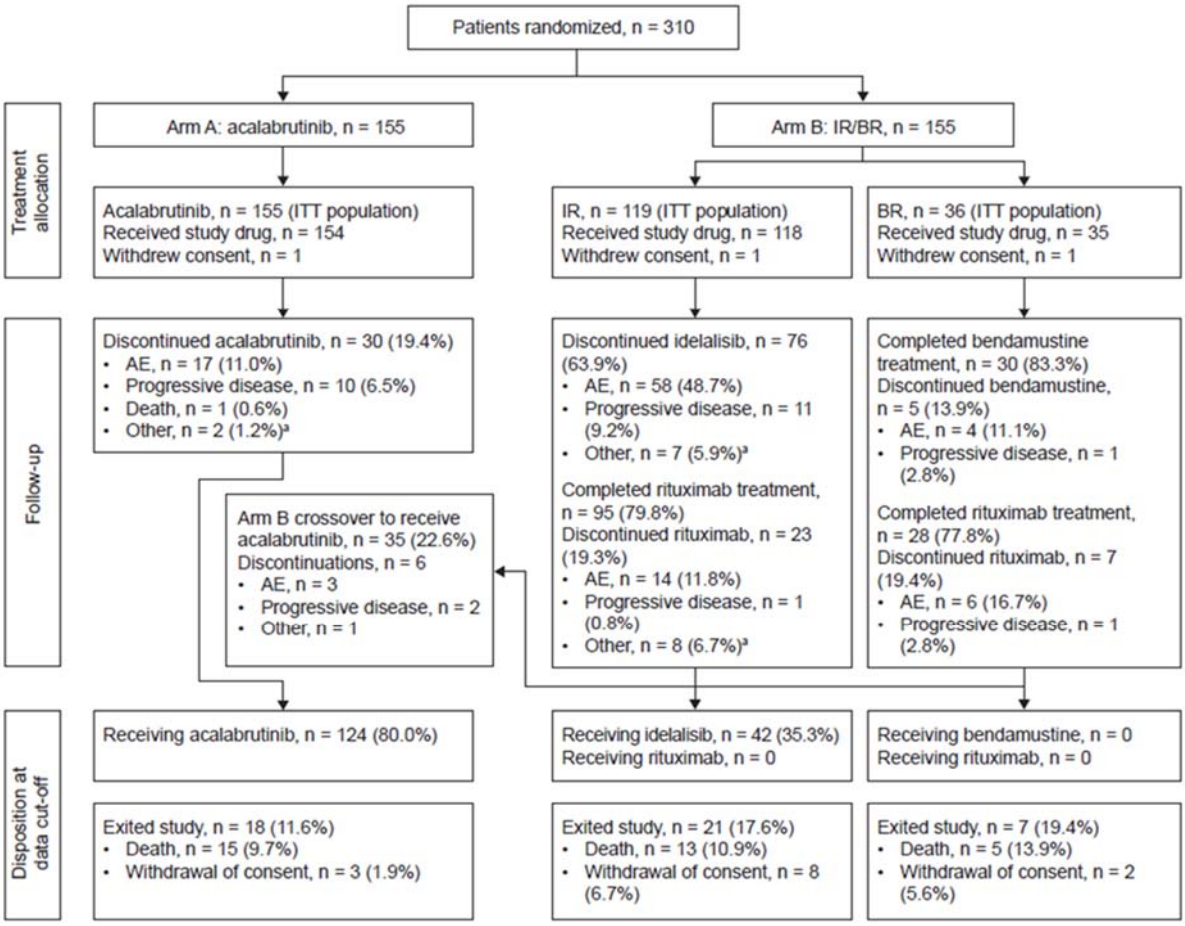
B.2b.3.2.2 Participant flow in ASCEND

Patient disposition and flow through the study are shown in Figure 10. In total 310 patients were randomised and 307 were treated. In the IR/BR arm, more patients were assigned by investigators to IR than to BR (119 vs 36, respectively). The median duration of follow-up was 16.10 months in the acalabrutinib arm and 15.74 months in the IR/BR arm.

As of the data cut-off date (15 January 2019), 30 patients (19.4%) in the acalabrutinib arm and 111 patients (71.6%) in the IR/BR arm had discontinued treatment. The primary reason for discontinuing acalabrutinib and idelalisib was AEs (17 patients [11.0%] and 58 patients [48.7%], the primary reason for discontinuing bendamustine and rituximab was completion of the treatment course (19.4% and 79.4%, respectively).

In total 35 patients in the IR/BR arm crossed over to acalabrutinib monotherapy (29 previously treated with IR and six previously treated with BR).

Figure 10. ASCEND patient flow at data cut-off date



[a]Discontinuation at patient's request, investigator's discretion, treatment interruption (idelalisib) or missed doses (rituximab).
AE, adverse event; BR, bendamustine + rituximab; IR, idelalisib + rituximab; ITT, intention-to-treat.
Source: ASCEND CSR[78]

B.2b.3.2.3 Patient characteristics - ASCEND

A total of 310 patients were randomised: 155 to acalabrutinib and 155 to IR/BR. Demographic and baseline characteristics were generally well balanced and there were no notable differences between treatment arms (Table 33).

Patients had an overall median age of 67 years, approximately two-thirds (67.1%) were male and 92.3% were white. The median number of previous therapies was lower in the acalabrutinib arm compared with the IR and BR arms. This was because more patients in

the acalabrutinib arm had only previously received one line of therapy (52.9%) compared to those who received IR (43.2%) or BR (48.1%). The majority of patients (87.7%) had at least one chromosomal characteristic associated with poor prognosis: del(17p), deletion of chromosome 11q region, unmutated immunoglobulin heavy chain variable gene (IGHV) or tumour protein 53 gene (TP53) mutation.

Table 33: Baseline demographics, disease characteristics and treatment history

	Number (%) of patients		
	Arm A: acalabrutinib (n = 155)	**Arm B: IR or BR (n = 155)**	**Total (n = 310)**
Age, years			
Mean (SD)	66.9 (9.9)	66.7 (9.6)	66.8 (9.7)
Median (range)	68 (32–89)	67 (34–90)	67 (32–90)
≥ 65	97 (62.6)	98 (63.2)	195 (62.9)
≥ 75	34 (21.9)	31 (20.0)	65 (21.0)
Sex (male)	108 (69.7)	100 (64.5)	208 (67.1)
Region			
North America	8 (5.2)	9 (5.8)	17 (5.5)
Australia, New Zealand	9 (5.8)	7 (4.5)	16 (5.2)
Western Europe	32 (20.6)	33 (21.3)	65 (21.0)
Central and Eastern Europe	99 (63.9)	99 (63.9)	198 (63.9)
Asia	7 (4.5)	7 (4.5)	14 (4.5)
Disease characteristics			
ECOG Performance Status			
0	58 (37.4)	55 (35.5)	113 (36.5)
1	78 (50.3)	79 (51.0)	157 (50.6)
2	19 (12.3)	21 (13.5)	40 (12.9)
Time from diagnosis to randomization, months			
Mean (SD)	88.5 (54.5)	87.1 (51.6)	87.8 (53.0)
Median (range)	85.3 (3.1–314.4)	79.0 (5.0–254.2)	79.0 (3.1–314.4)
Bulky disease (≥ 5 cm)	76 (49.0)	75 (48.4)	151 (48.7)
Rai stage			
0	2 (1.3)	4 (2.6)	6 (1.9)
I	39 (25.2)	32 (20.6)	71 (22.9)
II	49 (31.6)	54 (34.8)	103 (33.2)
III	21 (13.5)	18 (11.6)	39 (12.6)
IV	44 (28.4)	46 (29.7)	90 (29.0)
Beta-2 microglobulin > 3.5 mg/L	120 (77.4)	126 (81.3)	246 (79.4)
Cytopenia	85 (54.8)	80 (51.6)	165 (53.2)
Constitutional symptoms	91 (58.7)	97 (62.6)	188 (60.6)
Genetic markers			
Del(17p)	28 (18.1)	21 (13.5)	49 (15.8)
Del(11q)	39 (25.2)	44 (28.4)	83 (26.8)
TP53 mutation	39 (25.2)	34 (21.9)	73 (23.5)
IGHV			
Mutated	33 (21.3)	26 (16.8)	59 (19.0)
Unmutated	118 (76.1)	125 (80.6)	243 (78.4)
Undetermined	3 (1.9)	2 (1.3)	5 (1.6)

	Number (%) of patients		
	Arm A: acalabrutinib (n = 155)	Arm B: IR or BR (n = 155)	Total (n = 310)
Del(17p) or *TP53* mutation	22 (14.2%)	13 (8.4%)	35 (11.3%)
Del(17p), *TP53* mutation, del(11q) or unmutated *IGHV*	135 (87.1)	137 (88.4)	272 (87.7)
Previous treatment			
Time since last previous CLL therapy to first dose, months[a]			
Mean (SD)	31.5 (28.0)	29.7 (27.2)	30.6 (27.5)
Median (range)	26.4 (1.0–158.9)	22.7 (1.1–156.2)	24.1 (1.0–158.9)
Number of previous therapies			
1	82 (52.9%)	67 (43.2%)	149 (48.1%)
2	40 (25.8%)	46 (29.7%)	86 (27.7%)
3	17 (11.0%)	24 (15.5%)	41 (13.2%)
≥ 4	16 (10.3%)	18 (11.6%)	34 (11.0%)
Median (range)	1 (1–8)	2 (1–10)	2 (1–10)
Type of previous therapy			
Purine analogues	109 (70.3)	104 (67.1)	213 (68.7)
Alkylators (not bendamustine)	133 (85.8)	131 (84.5)	264 (85.2)
Bendamustine	47 (30.3)	48 (31.0)	95 (30.6)
Anti-CD20 mAbs	130 (83.9)	119 (76.8)	249 (80.3)
Stem cell transplant	1 (0.6)	1 (0.6)	2 (0.6)
Other	9 (5.8)	6 (3.9)	15 (4.8)

CLL, chronic lymphocytic leukemia; BR, bendamustine + rituximab; ECOG, Eastern Cooperative Oncology Group; IR, idelalisib + rituximab; SD, standard deviation.

B.2b.3.3.1 Outcome measures - RESONATE

The definitions of the outcome measures available in the RESONATE trial are presented in Table 34 below.

Table 34. Outcome measures available from RESONATE trial

Efficacy measures	Description
Primary endpoint	
PFS (IRC)	Time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first.
Secondary	
Investigator-assessed PFS	Investigator-assessed PFS is defined as time from randomization until disease progression (assessed by the Investigator per IWCLL 2008 criteria) or death from any cause, whichever occurs first.
IRC- and investigator-assessed ORR	Overall response rate (ORR) is defined as the proportion of patients who achieve a CR, CRi, nPR, or PR over the course of the study as evaluated by the IRC. Patients who do not have any post-baseline response assessment will be considered as non-responders
OS	OS is defined as the time from date of randomization until date of death due to any cause.
Rate of Sustained Hemoglobin and Platelet Improvement	Sustained hematological improvement is defined as improvement in cytopenia by ≥50%, or Hgb ≥11 g/dL, ANC ≥ 1500 cells/μL, platelets ≥100,000 with the duration of improvement lasting for ≥ 60 days without blood transfusion or growth factors.

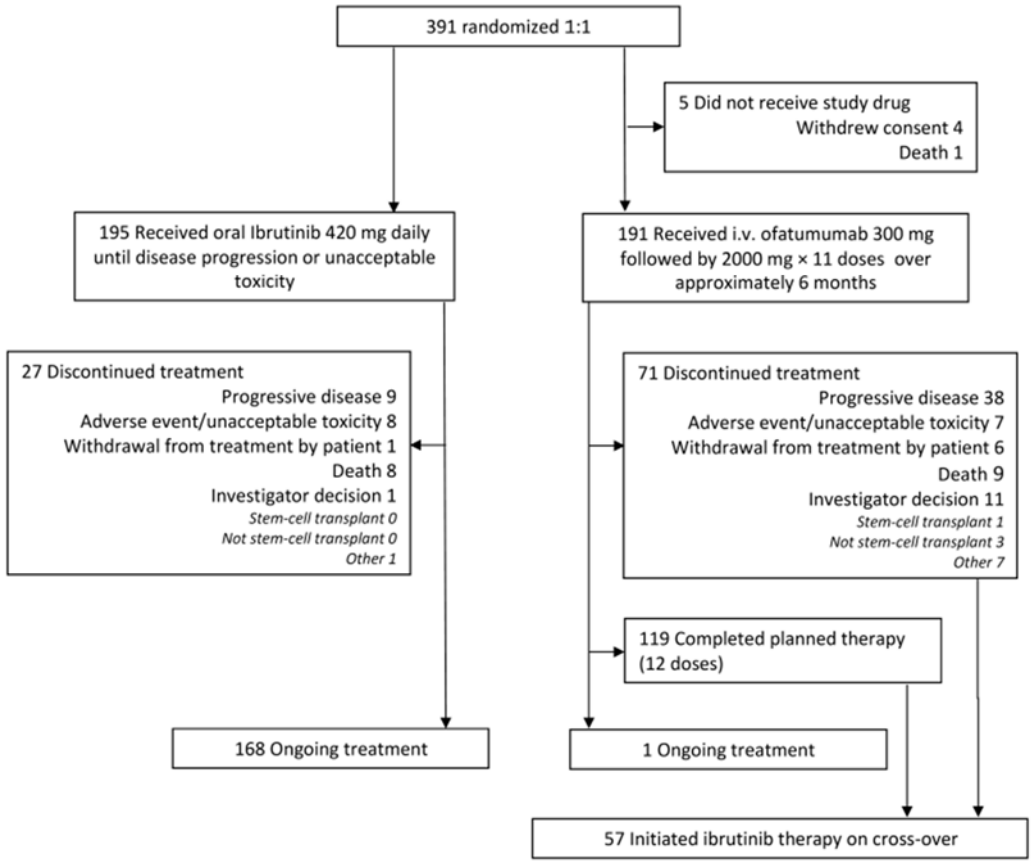
Exploratory	
Medical resource utilisation	Parameters collected for MRU associated with the therapy include number of hospitalizations, number of emergency department visits, number of blood product transfusions, and number of use of hematopoietic growth factors. Those parameters will be summarized with descriptive statistics by treatment arm.
Improvement of Disease-Related Symptoms	Disease-related symptoms including fatigue, night sweats, weight loss, fever, and symptoms of splenomegaly (abdominal pain/discomfort) will be assessed by at each assessment compared to baseline.
PK characteristics	The plasma concentration data for ibrutinib will be summarized using descriptive statistics at each timepoint.
Potential predictive biomarkers and/or disease-related mechanisms of resistance for the disease	Associations of biomarkers with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance [ANOVA], categorical, or survival model), depending on the endpoint. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups.

ANC, absolute neutrophil count; CR, complete response, CRi, Complete Remission with Incomplete Hematologic Recovery; DoR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, 5-dimension EuroQol questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; GFS, global fatigue score; GHS, global health status; IRC, Independent Review Committee; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; KM, kaplan meier; nPR, nodular partial remission; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient reported outcomes; QLQ-C30, 30-item core quality of life questionnaire; TTNT, time to next treatment; VAS, visual analogue scale.
Source: Byrd et al. 2014 (study protocol) [77]

B.2b.3.3.2 Participant flow in RESONATE

Patient disposition and flow through the study are shown in Figure 11

Figure 11: RESONATE patient flow at data cut-off date



Source: Byrd et al. 2014[77]

B.2b.3.3.3 Patient characteristics - RESONATE

A summary of the demographics and patient characteristics for the RESONATE trial can found in Table 35Table 35 below.

Table 35: Baseline demographics and disease characteristics - RESONATE

Characteristic	Ibrutinib (n=195)	Ofatumumab (n=196)
Age, years, median (range)	67 (30–86)	67 (37–88)
Male sex, n (%)	129 (66)	137 (70)
Prior therapies, median (range)	3 (1–12)	2 (1–13)
Time since initial diagnosis, months, median (range)	92 (5–329)	91 (6–346)
Histology at diagnosis, n (%)		
CLL	185 (95)	188 (96)
SLL	10 (5)	8 (4)
Genomic abnormalities, n (%)		
Unmutated *IGHV*	98/134 (73)	84/133 (63)
del(17p)(13.1)	63/195 (32)	64/196 (33)
del(11q)(22.3)	63/190 (33)	59/191 (31)

Characteristic	Ibrutinib (n=195)	Ofatumumab (n=196)
TP53 mutation	79/154 (51)	68/149 (46)
Complex karyotype	39/153 (25)	33/147 (22)

CLL, chronic lymphocytic leukaemia; del(17p), chromosome 17p deletion; del(11q), chromosome 11q deletion; IGHV, immunoglobulin heavy-chain variable region gene; SLL, small lymphoma leukaemia; TP53, tumour protein 53.

Source: Byrd et al. 2014[77]

B.2b.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the statistical analysis and study groups in the ASCEND and RESONATE trials are presented in Table 36.

Table 36. Summary of statistical analyses

Trial reference	Statistical analysis	Sample size, power calculation	Data management, patient withdrawal
ASCEND[76]	**Primary PFS analysis:** • Stratified 2-sided log rank test comparing PFS, as assessed by the IRC, between arm A and arm B • Summary of distribution of PFS for each treatment arm using median and 95% CI based on Kaplan–Meier estimates • HR and 95% CI estimated using a Cox proportional hazards model stratified by the randomization strata **Sensitivity analyses:** • Inclusion of PFS without censoring for subsequent anti-cancer therapy • Inclusion of PFS events after ≥ 2 consecutively missed visits • Exclusion of subjects with important protocol deviations • Use of eCRF-recorded stratification factors Same analyses were conducted for OS comparisons	Sample size of 306 patients to detect a hazard ratio of 0.55 for PFS at approximately 90% power	Other than partial dates, missing data for survival and response analyses were not imputed
RESONATE[77]	**Primary PFS analysis:** • The primary analysis was a two-sided log-rank test stratified according to the presence or absence of the chromosome 17p13.1 deletion and the disease refractory status at randomization.	The number of required events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90%.	NR

CI, confidence interval; eCRF, electronic case report form; HR, hazard ratio; IRC, independent research committee; NR, not recorded; OS, overall survival; PFS, progression-free survival.

B.2b.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment for the ASCEND and RESONATE studies is provided in Table 37 and Table 38, respectively. A full quality assessment of ASCEND and RESONATE is provided in Appendix D.

Table 37. Quality assessment results for ASCEND

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Patients were randomly assigned via a centralized procedure in a 1:1 ratio to receive acalabrutinib monotherapy or investigator's choice.	Yes
Was the concealment of treatment allocation adequate?	Open-label study – this study compared an oral monotherapy with (one of 2) combination therapies.	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	See Table 31	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants were unblinded to treatment allocation. Progression and responses were assessed centrally by the independent review committee (IRC), which was blinded to treatment-group assignments.	No
Were there any unexpected imbalances in drop-outs between groups?	See Table 31	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Table 38: Quality assessment results for RESONATE

	How is the question addressed?	Grade (yes/no/unclear/NA)
Was randomisation carried out appropriately?	Details not provided in paper.	Unclear
Was the concealment of treatment allocation adequate?	Open-label study – all patients and clinicians were aware of the treatment received.	No
Were the groups similar at the outset of the study in terms of prognostic factors?	See Table 31	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants were unblinded to treatment allocation. Primary outcome was PFS assessed by independent committee.	No
Were there any unexpected imbalances in drop-outs between groups?	See Table 31	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	From assessment of the publications and NICE guidance available.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

B.2b.6 Clinical effectiveness results of the relevant trials

B.2b.6.1 ASCEND

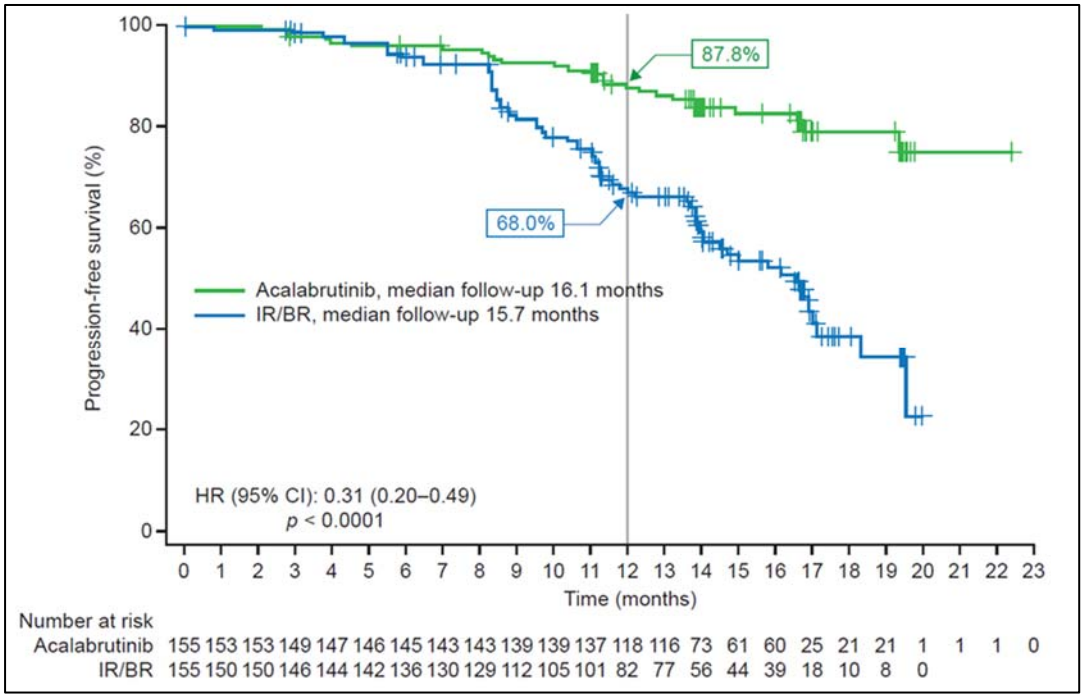
Primary endpoint: Progression-free survival

The primary endpoint of the ASCEND study was PFS, as assessed by IRC assessment using the iwCLL 2008 criteria.[19]

The ASCEND trial met its primary endpoint, with acalabrutinib treatment demonstrating a statistically significant and clinically meaningful improvement in IRC-assessed PFS, compared with investigator's choice of BR or IR, after a median follow-up of 16 months.[75,76] There was a 69% reduction in relative risk of disease progression or death (HR: 0.31; 95% CI: 0.20–0.49; $p < 0.0001$) with acalabrutinib compared with IR/BR (Figure 12). Median PFS for acalabrutinib was not reached and was 16.5 months (95% CI: 14.0–17.1) with IR/BR.

At the data cut-off, 82.6% of patients in the acalabrutinib arm were alive and did not have disease progression (median follow-up of 16.10 months) versus 56.1% of patients in the IR/BR arm (median follow-up of 15.7 months). The KM estimate of the proportion of subjects without a PFS event was higher with acalabrutinib versus IR/BR at 6, 12 and 18 months (Table 39).

Figure 12. Kaplan-Meier plot for PFS in ASCEND



CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee.
Source: ASCEND CSR[75,78]

Table 39. Primary PFS analysis (IRC assessment)

	Arm A: acalabrutinib (n = 155)	Arm B: IR or BR (n = 155)
Events, n (%)		
Death	8 (5.2)	9 (5.8)
Disease progression	19 (12.3)	59 (38.1)
KM-estimated PFS, % (95% CI)[a]		
6-month PFS	96.1 (91.5–98.2)	93.9 (88.6–96.8)
9-month PFS	92.7 (87.3–95.9)	82.4 (75.0–87.7)
12-month PFS	87.8 (81.3–92.1)	68.0 (59.4–75.1)

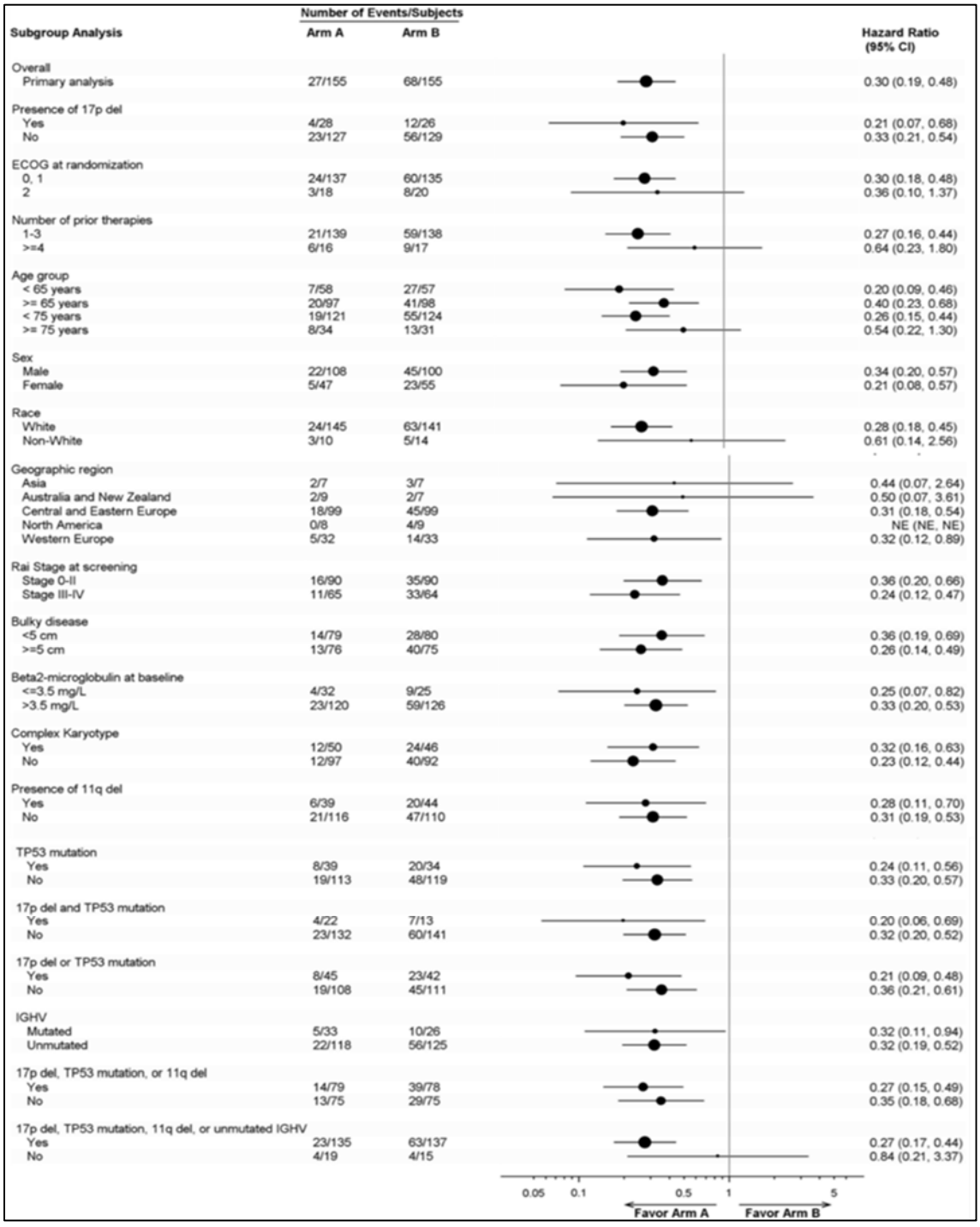
[a]Assessed by IRC.
BR, bendamustine + rituximab; CI, confidence interval; IR, idelalisib + rituximab; IRC, Independent Review Committee; KM, Kaplan–Meier; PFS, progression-free survival.
Source: ASCEND CSR[78]

Patient subgroups

The benefit of acalabrutinib on IRC-assessed PFS was statistically significant and clinically meaningful compared with IR or BR across most predefined subgroups, with HRs ranging from 0.20 to 0.84. This included patients with chromosomal characteristic (del[17p], TP53 mutation, del[11q] or unmutated IGHV) and non-chromosomal risk factors (advanced stage

disease [Rai stage], elevated beta-2 microglobulin, age ≥ 65 years or bulky disease ≥ 5 cm) associated with poor prognosis (Figure 13).

Figure 13. PFS subgroup analysis (IRC assessment)



11q del, deletion of chromosome 11q region; 17p del, deletion of chromosome 17p region; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain variable gene; IRC, Independent Review Committee; PFS, progression-free survival; TP53, tumour protein 53 gene.
Source: ASCEND CSR[78]

Key secondary outcomes

Overall survival

The OS data are not mature and median OS was not reached in either treatment arm. However, the OS trend favoured acalabrutinib, with a HR of 0.84 (95% CI: 0.42–1.66; p = 0.6089). After a median follow-up of 16.1 months in the acalabrutinib arm and 15.7 months in the IR/BR arm, 15 patients (9.7%) receiving acalabrutinib and 18 patients (11.6%) receiving IR/BR had died.

The KM-estimated OS at 12 months was 94.1% (95% CI: 89.0–96.9) for patients treated with acalabrutinib, and 90.6% (95% CI: 84.6–94.3) for those receiving IR/BR. OS results censoring at crossover were consistent with the main OS analysis.

Treatment response

The ORR with acalabrutinib was 81.3% (95% CI: 74.4–86.6) and 75.5% (95% CI: 68.1–81.6) with IR/BR, as assessed by IRC (Table 40). Most patients had a PR to treatment (acalabrutinib: 81.3%; IR/BR: 74.2%). Including patients who had a PRL increased the IRC-assessed ORR to 88.4% (95% CI: 82.4–92.5) with acalabrutinib and 77.4% (95% CI: 70.2–83.3) with IR/BR, and the difference was statistically significant (p = 0.011).

Response rates by investigator assessment were 79.4% (95% CI: 72.3–85.0) with acalabrutinib and 83.2% (95% CI: 76.6–88.3) with IR/BR. The overall concordance rate between the IRC-assessed and investigator-assessed ORRs for acalabrutinib and IR/BR was 86.5% and 80.0%, respectively. When PRL was included, the ORR was 92.9% (95% CI: 87.7–96.0) with acalabrutinib and 87.1% (95% CI: 80.9–91.5) with IR/BR.

Table 40. Overall response in ASCEND

	IRC assessment		**Investigator assessment**	
	Arm A: acalabrutinib (n = 155)	**Arm B: IR or BR (n = 155)**	**Arm A: acalabrutinib (n = 155)**	**Arm B: IR or BR (n = 155)**
Best overall response, n (%)				
CR	0	2 (1.3)	2 (1.3)	5 (3.2)
CRi	0	0	1 (0.6)	1 (0.6)
nPR	0	0	4 (2.6)	0
PR	126 (81.3)	115 (74.2)	116 (74.8)	123 (79.4)
PRL	11 (7.1)	3 (1.9)	21 (13.5)	6 (3.9)
Overall response rates				
ORR (CR + CRi + nPR + PR), n (%) [95% CI][a]	126 (81.3) [74.4–86.6]	117 (75.5) [68.1–81.6]	123 (79.4) [72.3–85.0]	129 (83.2) [76.6–88.3]
p value[b]	0.2248		0.3453	
ORR + PRL, n (%) [95% CI][a]	137 (88.4) [82.4–92.5]	120 (77.4) [70.2–83.3]	144 (92.9) [87.7–96.0]	135 (87.1) [80.9–91.5]
p value[b]	0.0110		0.0849	

[a] 95% CI based on normal approximation (with use of Wilson's score).

[b] Based on Cochran–Mantel–Haenzel test with adjustment for randomization stratification factors.
BR, bendamustine + rituximab; CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; CSR, clinical study report; IR, idelalisib + rituximab; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PRL, partial response with lymphocytosis.
Source: ASCEND CSR[75,78]

Time to next treatment

Acalabrutinib was associated with a significant increase in TTNT compared with IR/BR (HR: 0.35; 95% CI: 0.21–0.58; p < 0.0001). In the acalabrutinib arm, 13 patients (8.4%) switched to a subsequent anti-cancer therapy; in the IR/BR arm, eight patients (5.2%) switched to a subsequent anti-cancer therapy and 35 patients (22.6%) crossed over to acalabrutinib monotherapy (Table 41).

Table 41. Time to next treatment

	Arm A: acalabrutinib (n = 155)	Arm B: IR or BR (n = 155)
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Crossed over to acalabrutinib monotherapy	0	35 (22.6)
Subsequent anti-cancer therapy	13 (8.4)	8 (5.2)
Patients alive with no crossover or subsequent anti-cancer therapy, n (%)	133 (85.8)	102 (65.8)

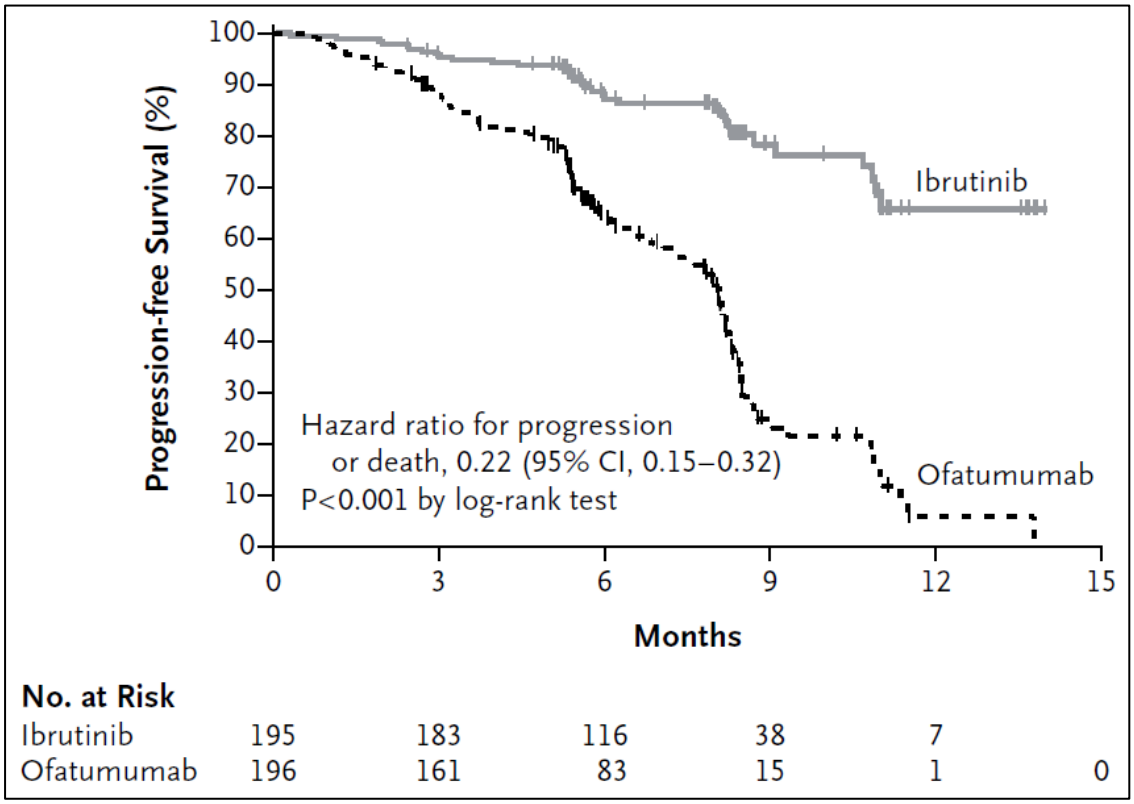
BR, bendamustine + rituximab; IR, idelalisib + rituximab.
Source: ASCEND CSR[75,78]

B.2b.6.2 RESONATE

Primary endpoint: Progression-free survival

Ibrutinib significantly prolonged the duration of PFS, with median PFS not reached after a median follow-up of 9.4 months, compared with median PFS of 8.1 months with ofatumumab (HR: 0.22 [95% CI: 0.15–0.32]; p < 0.001; Figure 14). This represents a 78% reduction in the risk of progression or death among patients treated with ibrutinib, as compared with ofatumumab. At 6 months, 88% of patients in the ibrutinib group were still alive with no disease progression, as compared with 65% in the ofatumumab group.

Figure 14. Kaplan-Meier plot for PFS in RESONATE



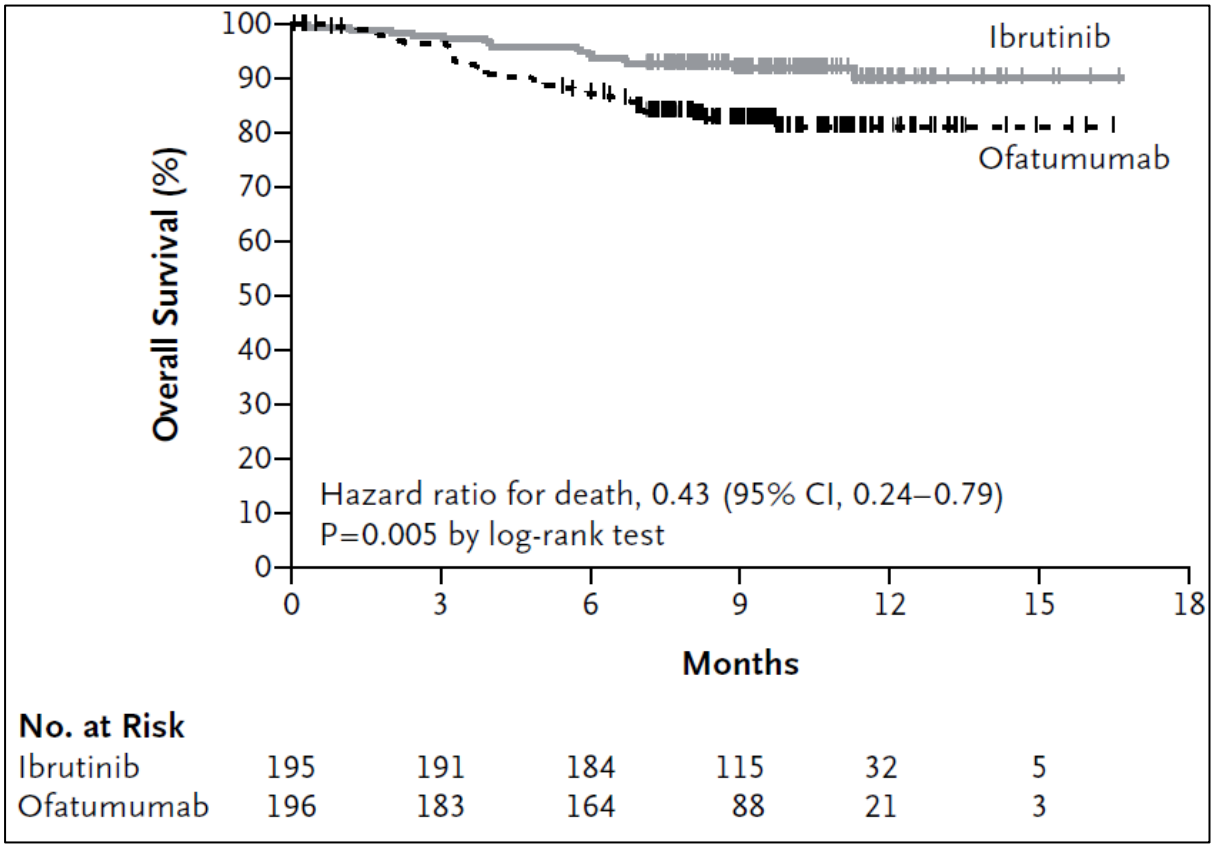
CI, confidence interval; PFS progression-free survival.
Source: Byrd et al. 2014[77]

Key secondary outcomes

Overall survival

Ibrutinib also significantly improved OS, as compared with ofatumumab (HR: 0.43 [95% CI: 0.24–0.79]; p = 0.005; Figure 15), with the risk of death reduced by 57%. At 12 months, OS was 90% in the ibrutinib arm and 81% in the ofatumumab arm.

Figure 15. Kaplan-Meier plot for OS in RESONATE

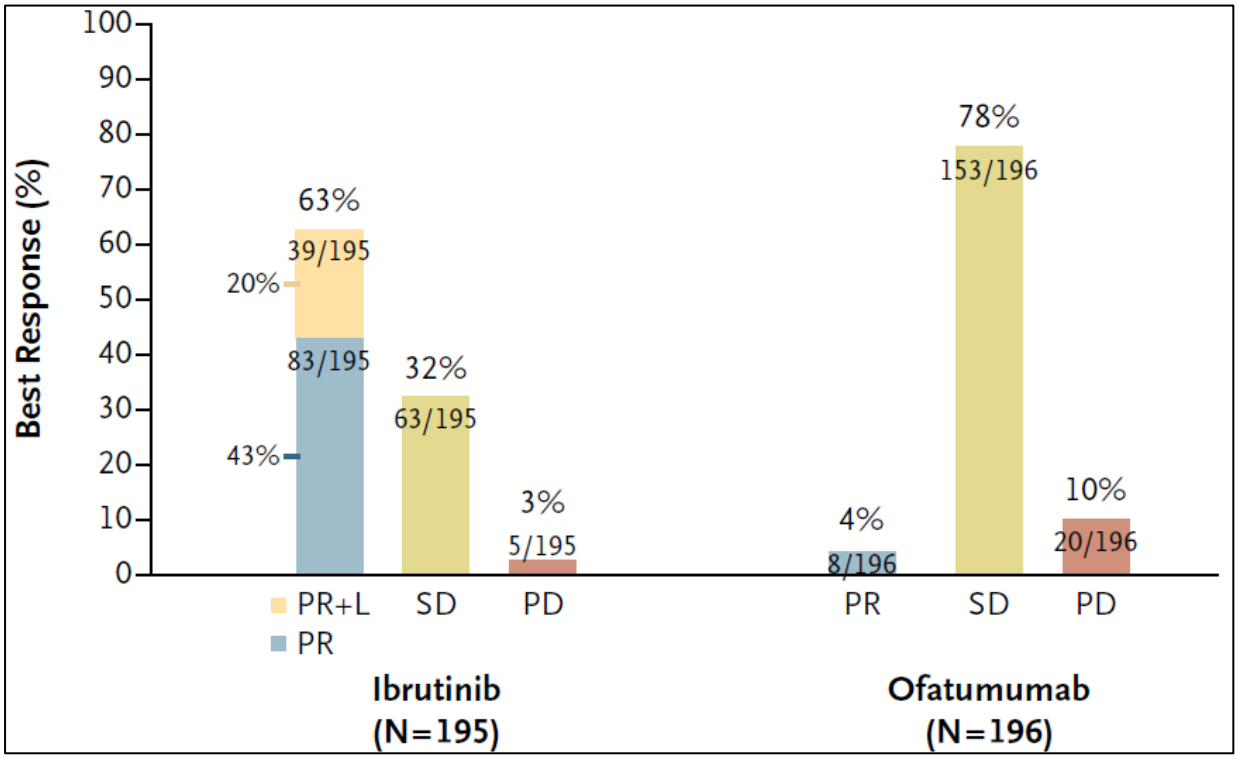


CI, confidence interval; OS, overall survival.
Source: Byrd et al. 2014[77]

Treatment response

The response rate was significantly higher in the ibrutinib group than in the ofatumumab group (Figure 16). Overall, 43% of the patients in the ibrutinib group had a PR, compared with 4% in the ofatumumab group (odds ratio, 17.4; 95% CI, 8.1 to 37.3; $p < 0.001$). In addition, 20% of the patients receiving ibrutinib had a PRL (resulting in a 63% response rate). Lymphocytosis was observed in 69% of the patients who were treated with ibrutinib and was not considered to be disease progression. The condition resolved in 77% of these patients during follow-up.

Figure 16. Overall response rate in RESONATE



Note: Shown are best response to therapy as assessed by independent review.
CR, complete response; CRi, complete response with incomplete hematopoietic recovery; PR, partial response; PR+L, partial response with lymphocytosis; SD, stable disease; PD, progressive disease.
Data were unknown, missing, or could not be evaluated for 5 patients in the ibrutinib group and for 15 patients in the ofatumumab group.
Source: Byrd et al. 2014[77]

B.2b.7 Subgroup analysis

ASCEND

The benefit of acalabrutinib on PFS was clinically meaningful compared with IR or BR and similar across all pre-specified subgroups in the ASCEND trial (Figure 13). The benefit of acalabrutinib on IRC-assessed PFS was statistically significant and clinically meaningful compared with IR or BR across most predefined subgroups, with HRs ranging from 0.20 to 0.84. This included patients with chromosomal characteristic (del[17p], TP53 mutation, del[11q] or unmutated IGHV) and non-chromosomal risk factors (advanced stage disease [Rai stage], elevated beta-2 microglobulin, age ≥ 65 years or bulky disease ≥ 5 cm) associated with poor prognosis.

RESONATE

The benefit of ibrutinib on PFS was consistent regardless of baseline clinical characteristics or molecular features. The only significant test for heterogeneity was geographical region (p=0.02). In order to address this, a multivariate Cox proportional hazard analysis was employed, using a comprehensive list of baseline prognostic variables as covariates. After adjustment for the baseline covariates, the HR was 0.22 (0.085, 0.564) for USA and 0.20 (0.092, 0.451) for Europe/other. The selected covariates were considered clinically

appropriate and while acknowledging the caveats of the presented post-hoc analysis there is no reason to anticipate major differences between the regions. The consistent benefit in all subgroups was maintained after 16 month follow-up, rates of 12-month PFS were significantly better with ibrutinib than ofatumumab regardless of lymphocytosis, number of prior lines of therapy, presence of 17p deletion or other adverse cytogenetics. In line with PFS, the difference in OS was preserved in all subgroups.[6,77]

B.2b.8 Meta-analysis

All efficacy and safety data relevant to the decision problem are provided from two relevant RCTs, ASCEND for acalabrutinib and RESONATE for ibrutinib. Therefore, it was not necessary to conduct a meta-analysis.

B.2b.9 Indirect and mixed treatment comparisons

To date, there are no published head-to-head RCTs comparing the efficacy and safety of acalabrutinib and ibrutinib in patients R/R CLL. ELEVATE-RR, a non-inferiority trial comparing acalabrutinib with ibrutinib in patients with high-risk R/R CLL, is currently underway and is expected to complete in 2021.[79]

In the absence of head-to-head data, network meta-analysis (NMA) is usually performed to generate comparative data; however the NMA methodology has limitations where there are cross-trial differences, or a lack of a common comparator, such as in the case of ASCEND and RESONATE. To minimize bias, a matching-adjusted indirect comparison (MAIC) was carried out instead, in line with previous technology appraisals in this patient population (TA561).

B.2b.9.1 Methodology of matched-adjusted indirect comparison

The MAIC approach used individual patient-level data (IPD) from the ASCEND trial for acalabrutinib and adjusted the trial population to match average baseline characteristics reported in the RESONATE trial for patients receiving ibrutinib. Firstly, cross-trial similarities and differences were assessed and the feasibility of performing a MAIC was confirmed.

Table 42. ASCEND and RESONATE study design, inclusion and exclusion criteria

	ASCEND (ACE-CL-309) **N = 155**	**RESONATE** **N= 195**
Study design		
Patient population	CLL patients who received ≥ 1 treatment regimen	CLL or SLL if they received at least one previous treatment (inappropriate for purine analogue treatment)
Phase	Phase 3	Phase 3
Study design	Randomized, open-label, international multi-centre	Randomized, open-label, international multi-centre
Enrolment period	1st Dec 2016 – 17 Jan 2018	June 2012 – April 2013
Follow-up	16.1 months (median)	16.1 months (median) PFS31 19.0 months (median) OS26
Treatment exposure	15.7 months (median)	16.0 months (median) PFS

	ASCEND (ACE-CL-309) N = 155	RESONATE N= 195
AE assessment period	During treatment period and for 30 days prior to date of last dose	During treatment
Outcome definition		
Outcome assessment method	2008 iwCLL IRC PFS (primary); 2008 iwCLL investigator PFS, investigator ORR, IRC ORR, OS	2008 iwCLL IRC PFS (primary); ORR, OS
Definition of PFS	PFS is defined as the time from date of randomization to the date of first investigator-assessed disease progression or death due to any cause	
Definition of ORR	Achieving either a CR, Cri, nPR or PR (includes PR-L)	Achieving either a CR, CRi, nPR or PR (includes PR-L)
Inclusion criteria		
Demographics *Age* *Diagnosis*	 ≥ 18 years CD20-positive CLL	 ≥18 years CLL or SLL
Disease characteristics *ECOG (WHO) performance status* *Relapse or disease progression*	 ≤ 2 Relapsed or refractory disease	 0-1 Relapsed or refractory disease
Previous treatments *Number of prior therapies*	≥ 1 prior systemic therapy for CLL, single agent steroids or localized radiation not considered prior line of therapy. If single agent CD20 was given must have been ≥ 2 doses	≥ 1 prior therapy
Exclusion criteria		
Previous treatments *Chemotherapy* *Major surgery* *BCR/BCL inhibitors (e.g., BTK inhibitors)* *Other*	Any chemo within 30 days of first dose. Prior bendamustine allowed only if investigator's choice for treatment in arm B is idelalisib + rituximab Within 30 days of first dose Any Allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose	Within 3 weeks Ibrutinib Required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with a strong CYP3A4/5 inhibitor Previous treatment with ofatumumab Allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose
Prior conditions *Central nervous system lymphoma or leukaemia* *Stroke or intracranial haemorrhage* *Cardiovascular disease* *Bleeding*	Any 6 months before the 1st dose of the study drug Uncontrolled or untreated symptomatic arrhythmia, CHF, or MI within 6 months of screening or any class 3 or 4 cardiac disease as defined by NYHA classification (controlled asymptomatic AF during screening allowed to enrol)	Any 6 months before the 1st dose of the study drug

	ASCEND (ACE-CL-309) N = 155	RESONATE N= 195
	History of bleeding	

AE, adverse event; AF, atrial fibrillation; BCL, B-cell lymphoma; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CHF, congestive heart failure; CLL, chronic lymphocytic leukaemia; CR, complete response; CRi, complete response with incomplete haematopoietic recovery; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; iwCLL international workshop on Chronic lymphocytic leukaemia; IRC, Independent Review Committee; nPR, nodular partial response; MI, myocardial infarction; NYHA, New York Heart Association; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; SLL, small lymphocytic lymphoma; WHO, World Health Organization.

Data extraction: RESONATE trial

In addition to the aggregate baseline characteristics and study outcomes extracted in the SLR and from the publication, patient-level survival data (i.e., PFS and OS) were reconstructed from the published KM curves of RESONATE using NICE recommended methodology. The approach uses digitization software (e.g., Engauge digitization software[32]) to extract time points and survival probabilities from the published KM curve. Based on the extracted information, the number of patients at risk, the number of events, and the number of patients censored were calculated using the reconstruction algorithm.[33] As the KM curve does not include full information on the IPD, the reconstruction algorithm made reasonable assumptions on the distribution of the unavailable data. Proxy patient-level survival data was generated based on the reconstructed information and KM curves were reproduced and compared with the published KM curve to visually evaluate the level of agreement. When summary statistics (i.e., median time to progression, number of responders) were available in the comparator trial published paper, summary statistics from the reconstructed survival data was reproduced and compared with the published summary statistics to validate the reconstructed survival data.

Generating weights to balance average baseline characteristics

The baseline characteristics to be matched were selected based on data availability and input from clinical experts. Acalabrutinib arm IPD were assigned weights, such that weighted mean baseline characteristics in the ASCEND trial exactly matched those reported for patients in RESONATE. Weights were obtained from a logistic regression model (estimated odds [relative propensity] of being in the comparator trials relative to ASCEND). These weights were used to calculate the effective sample size, and then to recalculate clinical outcomes from ASCEND. The choice of matching parameters (Table 43) was made in consultation with clinical opinion and the NICE guidance on MAIC, and was subject to external validation.[80]

Table 43. Baseline characteristics matched in the MAICs

Baseline characteristic	ASCEND vs RESONATE
Age	✓
Sex	✓
Presence of bulky disease ≥ 5 cm	✓
Presence of del(17p)	✓
Presence of del(11q)	✓

TP53 status	–
ECOG PS 0	✓
ECOG PS 1	✓
ECOG PS 2	–
Beta-2 microglobulin > 3.5 mg/L	✓
Rai stage at screening (1 or 2, or 0–2)	✓
Rai stage 3 or 4 at screening	✓
One previous line of therapy	✓
Two previous lines of therapy	✓
≥ 3 previous lines of therapy	✓
Complex karyotype	✓
IGHV mutation status	✓
CrCl < 60 mL/min	✓

CrCl, creatinine clearance; del(11q), deletion of chromosome 11q region; del(17p), deletion of chromosome 17p region; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IGHV, immunoglobulin heavy chain variable gene; MAIC, matching-adjusted indirect comparison; TP53, tumour protein 53 gene.

For each comparison, comparative analyses were conducted both before and after weighting. Before matching, PFS and OS were summarised using KM curves and compared using the log-rank test and HRs estimated from Cox proportional hazards model. Binary outcomes (i.e., overall response rate [ORR] and safety outcomes) were summarized in proportions and compared using the Chi-square test. Risk differences and odds ratios (OR) with their 95% CI and p-values were reported.

After matching, PFS, OS and selected safety outcomes were compared between balanced trial populations using the weights generated in the MAIC. For PFS and OS, weighted survival curves based on the Nelson-Aalen estimator were generated. PFS and OS were compared using weighted log-rank test and HRs were estimated from a weighted Cox proportional hazards model. The proportional hazards assumption was tested both before and after matching. Binary outcomes were compared using weighted Chi-square test. Risk differences and odds ratios comparing acalabrutinib vs. comparator treatment were reported for ORR and selected safety outcomes. The 95% CI and p-values for the indirect comparisons were based on a robust estimate of the variance, based on a sandwich estimator, which accounted for the variability in the propensity score weights.

For each comparison, comparative analyses were conducted both before and after weighting. Before matching, binary outcomes (i.e., ORR and safety outcomes) were summarized in proportions and compared using the Chi-square test. Risk differences and odds ratios (OR) with their 95% CI and p-values were reported. PFS and OS were summarized using KM curves and compared using the log-rank test and HRs estimated from Cox proportional hazards model.

After matching, ORR, PFS, OS and selected safety outcomes were compared between balanced trial populations using the weights generated in the MAIC. Binary outcomes were compared using weighted Chi-square test. Risk differences and odds ratios comparing acalabrutinib vs. comparator treatment were reported for ORR and selected safety outcomes. The 95% CI and p-values for the indirect comparisons were based on a robust

estimate of the variance, based on a sandwich estimator, which accounted for the variability in the propensity score weights. For PFS and OS, weighted survival curves based on the Nelson-Aalen estimator were generated. PFS and OS were compared using weighted log-rank test and HRs were estimated from a weighted Cox proportional hazards model. The proportional hazards assumption was tested both before and after matching.

B.2b.9.2 Results

The comparison of baseline characteristics before and after matching between acalabrutinib and ibrutinib-treated patients is presented in Table 44. Patients in ASCEND who were ECOG PS 2 at baseline (n=19) were not included in the matching because RESONATE did not include patients with this PS. A further four patients were removed due to missing baseline characteristics therefore 132 acalabrutinib patients were matched.

Before matching:

- A significantly higher proportion of acalabrutinib-treated patients had a one prior therapy (51.5% vs. 18.0%, p < 0.0001).
- A significantly lower proportion of acalabrutinib-treated patients had tumour bulk < 5cm (50.0% vs. 64.0%, p = 0.02), 17p deletions (18.9% vs. 32.0%, p = 0.01) and Rai stage 3-4 (40.9% vs. 56.0%, p = 0.01).

After matching, all matched baseline characteristics were balanced (i.e. statistically equivalent) between the trials.

Table 44. ASCEND baseline characteristics before and after matching to RESONATE

	Before matching			After matching		
	Acalabrutinib N=132[a]	**Ibrutinib N=195**	**P-value**	**Acalabrutinib ESS=44**	**Ibrutinib N=195**	**P-value**
Age ≥70	48 (36.4%)	78 (40.0%)	0.58	[redacted]	[redacted]	[redacted]
Male	94 (71.2%)	129 (66.0%)	0.38	[redacted]	[redacted]	[redacted]
Bulky disease < 5 cm	66 (50.0%)	124 (64.0%)	< 0.05*	[redacted]	[redacted]	[redacted]
17p deletion	25 (18.9%)	63 (32.0%)	< 0.01*	[redacted]	[redacted]	[redacted]
11q deletion	30 (22.7%)	63 (32.0%)	0.09	[redacted]	[redacted]	[redacted]
ECOG PS 0	57 (43.2%)	79 (41.0%)	0.78	[redacted]	[redacted]	[redacted]
ECOG PS 1	75 (57.0%)	116 (59.0%)	0.93	[redacted]	[redacted]	[redacted]
β2-microglobulin	108 (81.8%)	153 (78.0%)	0.48	[redacted]	[redacted]	[redacted]
Rai stage 3-4	54 (40.9%)	109 (56.0%)	< 0.01*	[redacted]	[redacted]	[redacted]
Prior 1	68 (51.5%)	35 (18.0%)	< 0.0001*	[redacted]	[redacted]	[redacted]
Prior 2	36 (27.3%)	57 (29.0%)	0.83	[redacted]	[redacted]	[redacted]
Prior ≥ 3	13 (9.8%)	103 (53.0%)	< 0.0001*	[redacted]	[redacted]	[redacted]
Complex karyotype	40 (30.3%)	49 (25.0%)	0.35	[redacted]	[redacted]	[redacted]
IGHV unmutated	104 (78.8%)	142 (73.0%)	0.29	[redacted]	[redacted]	[redacted]
CrCl <60	35 (26.5%)	62 (32.0%)	0.35	[redacted]	[redacted]	[redacted]

* denotes p-value < 0.05

[a] this number (N=132) does not match the ASCEND acalabrutinib arm (N=155) due to incomplete baseline data recording for some patients in some outcomes.
CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IGHV, immunoglobulin heavy-chain variable.

PFS and OS were compared between ASCEND and RESONATE intervention arms (acalabrutinib and ibrutinib, respectively) before and after matching:

Differences in PFS between the two treatments were not statistically significant before matching (HR: [redacted] p=[redacted]), and remained so after matching, (HR: [redacted]), p=[redacted]), with a trend in favour of acalabrutinib. Differences in OS between the two treatments were not statistically significant before or after matching (HR: [redacted]), with a trend in favour of acalabrutinib.

Therefore, the results of the MAIC demonstrate that the efficacy of acalabrutinib in PFS and OS in patients with R/R CLL is <u>at least</u> equivalent to that of ibrutinib.

Table 45. Summary of MAIC results (<u>before</u> matching) for acalabrutinib versus ibrutinib for patients with R/R CLL

Median HR (95% CI)	PFS	OS
Acalabrutinib vs ibrutinib	[redacted]	[redacted]

CI, confidence interval; CLL, chronic lymphocytic leukaemia; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 46. Summary of MAIC results (<u>after</u> matching) for acalabrutinib versus ibrutinib for patients with R/R CLL

Median HR (95% CI)	PFS	OS
Acalabrutinib vs ibrutinib	[redacted]	[redacted]

CI, confidence interval; CLL, chronic lymphocytic leukaemia; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Sensitivity analyses

Sensitivity analyses were performed matching for different sets of baseline characteristics between the ASCEND study and the RESONATE study (for PFS and for OS). For PFS, before matching HR ranged [redacted] and after matching HR ranged from [redacted] but in all cases the difference was not statistically significant (Table 47). For OS, before matching HR ranged [redacted] and after matching HR ranged from [redacted] but in all cases the difference was not statistically significant (Table 47). The conclusions from the sensitivity analyses were in general consistent with those from the base case analyses.

Table 47: Sensitivity analyses for PFS and OS before and after matching in MAIC of acalabrutinib vs. Ibrutinib

Baseline characteristics	PFS				OS			
	Before matching		After matching		Before matching		After matching	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Base case (see **Table 6-1**) Age, gender, bulky, del 17p, del 11q, ECOG status, β2 microglobulin, Rai stage, no. prior lines, CrCl, complex karyotype, IGHV unmutated	[redacted]							
Sensitivity analysis 1 Removed rai, added binet, i.e. age, gender, bulky, del 17p, del 11q, ECOG status, β2 microglobulin, no. prior lines, binet score, CrCl, complex karyotype, IGHV unmutated	[redacted]							
Sensitivity analysis 2 All variables with complete data in RESONATE (Age, gender, bulky, del 17p, ECOG status, β2 microglobulin, Rai stage, no prior lines, binet score, CrCl) plus del11q	[redacted]							
Sensitivity analysis 3 All with complete data (i.e. sensitivity 2) plus del11q plus complex karyotype, IGHV unmutated	[redacted]							
Sensitivity analysis 4	[redacted]							

Baseline characteristics	PFS				OS			
	Before matching		After matching		Before matching		After matching	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All with complete data (i.e. sensitivity 2) plus del 11q plus IGHV unmutated								
Sensitivity analysis 5 All with complete data (i.e. sensitivity 2) plus del 11q plus complex karyotype	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval, CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression free survival.

The strengths of the MAIC include:

- Comprehensive evaluation of cross-trial heterogeneity and potential sources of bias
- Use of individual patient data for acalabrutinib to adjust for observed cross-trial differences in multiple patient characteristics versus the comparator trials using MAICs
- Consistency with methodological guidance issued by NICE[81]
- Creation of a "pseudo trial" between acalabrutinib and selected comparators that can potentially be used to link the single arm trial of acalabrutinib into the evidence network of an NMA.

B.2b.10 Adverse reactions

B.2b.10.1 ASCEND

Dose exposure

In arm A, the median duration of acalabrutinib treatment was 15.7 months, with 85.7% of patients receiving at least one year of therapy. This was longer than for patients in arm B treated with IR, for whom the median duration of idelalisib treatment was 11.5 months. The median duration of rituximab (IR/BR groups) and bendamustine treatment (BR group) was 5.5 and 5.6 months, respectively, both corresponding to completion of the planned treatment. Owing to the longer duration of treatment with acalabrutinib compared with IR/BR, the reporting period for AEs is longer with acalabrutinib.

Treatment emergent adverse events

In total, 93.5% of patients receiving acalabrutinib, 99.2% receiving IR and 80.0% receiving BR experienced TEAEs of any grade. Overall, patients treated with acalabrutinib were less likely to experience grade ≥ 3 TAEs than those receiving IR (49.4% vs 89.8%); the proportions of patients who had grade ≥ 3 TEAEs was similar in the BR (48.6%) and acalabrutinib groups (Table 48).

The most common TEAEs among patients treated with acalabrutinib were headache (22.1%), neutropenia (19.5%) and diarrhoea (18.2%). In the BR group, the most common TEAEs were diarrhoea (46.6%), neutropenia (44.9%), pyrexia (17.8%) and cough (15.3%) in the IR group, and neutropenia (34.3%), fatigue (22.9%), infusion-related reaction (22.9%), nausea (20.0%) and pyrexia (17.1%). Most TEAEs were grade 1 or 2; the most common grade ≥ 3 AE among patients treated with acalabrutinib was neutropenia (15.6%). There were no grade 5 TEAEs that occurred in more than one person.

Grade ≥ 3 TEAEs affecting at least 1% of patients in either arm are shown in Table 49. Grade ≥ 3 neutropenia was more common with IR/BR than with acalabrutinib, affecting 39.8% of patients treated with IR and 31.4% of those treated with BR, compared with 15.6%

in the acalabrutinib group. Diarrhoea was the next most common grade ≥ 3 TEAE in arm B, affecting 23.7% of patients receiving IR.

TEAEs led to fewer treatment discontinuations in the acalabrutinib group (16 patients [10.4%]) compared with the IR (62 [52.5%]) and BR (6 [17.1%]) groups.[20] Similarly, AEs that led to dose reductions occurred in proportionally fewer patients with acalabrutinib than with IR/BR: dose reductions were required to manage TEAEs for six patients (3.9%) receiving acalabrutinib, compared with 15 (12.7%) receiving idelalisib and five (14.3%) receiving bendamustine.

Table 48. Adverse events in ASCEND

Event	**Number (%) of patients**		
	Arm A	**Arm B**	
	Acalabrutinib (N = 154)	**IR (N = 118)**	**BR (N = 35)**
Any grade AE	144 (93.5)	117 (99.2)	28 (80.0)
Grade ≥ 3	76 (49.4)	106 (89.8)	17 (48.6)
Grade 5	6 (3.9)	5 (4.2)	2 (5.7)
Most common AEs (≥ 10% of patients)			
Headache	34 (22.1)	7 (5.9)	0
Neutropenia	30 (19.5)	53 (44.9)	12 (34.3)
Diarrhoea	28 (18.2)	55 (46.6)	5 (14.3)
Anaemia	23 (14.9)	10 (8.5)	4 (11.4)
Cough	23 (14.9)	18 (15.3)	2 (5.7)
Upper respiratory tract infection	22 (14.3)	17 (14.4)	4 (11.4)
Pyrexia	19 (12.3)	21 (17.8)	6 (17.1)
Thrombocytopenia	17 (11.0)	16 (13.6)	5 (14.3)
Pneumonia	16 (10.4)	14 (11.9)	2 (5.7)
Respiratory tract infection	16 (10.4)	8 (6.8)	0
Fatigue	15 (9.7)	10 (8.5)	8 (22.9)
Nausea	11 (7.1)	15 (12.7)	7 (20.0)
Constipation	10 (6.5)	9 (7.6)	5 (14.3)
Rash	10 (6.5)	16 (13.6)	2 (5.7)
Alanine aminotransferase increased	3 (1.9)	14 (11.9)	3 (8.6)
Infusion-related reaction	0	9 (7.6)	8 (22.9)

AE, adverse event; BR, bendamustine plus rituximab; CSR, clinical study report; IR, idelalisib plus rituximab.
Source: ASCEND CSR[75,78]

Table 49. Grade ≥ 3 adverse events reported in at least 2% of patients in either arm (safety population) in ASCEND

	Number (%) of patients		
	Arm A	**Arm B**	
	Acalabrutinib (n = 154)	**IR (n = 118)**	**BR (n = 35)**
Subjects with ≥ 1 grade ≥ 3 AE	76 (49.4)	106 (89.8)	17 (48.6)
Neutropenia	24 (15.6)	47 (39.8)	11 (31.4)
Anaemia	18 (11.7)	8 (6.8)	3 (8.6)
Pneumonia	8 (5.2)	10 (8.5)	1 (2.9)
Thrombocytopenia	6 (3.9)	9 (7.6)	1 (2.9)

Upper respiratory tract infection	3 (1.9)	4 (3.4)	1 (2.9)
Alanine aminotransferase increased	2 (1.3)	10 (8.5)	1 (2.9)
Diarrhoea	2 (1.3)	28 (23.7)	0
Neutrophil count decreased	2 (1.3)	9 (7.6)	1 (2.9)
Aspartate aminotransferase increased	1 (0.6)	6 (5.1)	1 (2.9)
Febrile neutropenia	1 (0.6)	3 (2.5)	1 (2.9)
Influenza	1 (0.6)	2 (1.7)	1 (2.9)
Pyrexia	1 (0.6)	8 (6.8)	1 (2.9)
Transaminases increased	0	6 (5.1)	0
Pneumonia pneumococcal	0	4 (3.4)	0
Rash	0	4 (3.4)	0
Colitis	0	3 (2.5)	0
Granulocytopenia	0	3 (2.5)	0

AE, adverse event; BR, bendamustine + rituximab; IR, idelalisib + rituximab.
Source: ASCEND CSR[78]

B.2b.10.2 Serious AEs

SAEs were defined as an AE that resulted in death, was life threatening, required or prolonged hospitalisation, resulted in persistent or significant disability/incapacity, resulted in a congenital anomality/birth defect in a neonate/infant born to a mother exposed to the investigational product, or was considered a significant medical event by the investigator based on their medical judgement.

SAEs, most of which were grade ≥ 3, occurred in 28.6%, 55.9% and 25.7% of patients who received acalabrutinib, IR and BR, respectively. Among patients treated with acalabrutinib, the most common SAE was pneumonia (5.2%). In the IR group, the most common SAE was diarrhoea (13.6%); no SAE affected more than one patient in the BR group.

Treatment-related SAEs were reported in 14 patients (9.1%) treated with acalabrutinib, compared with 46 (39.0%) treated with idelalisib, three (8.6%) with bendamustine, 15 (12.7%) with rituximab as part of the IR regimen and two (5.7%) with rituximab as part of the BR regimen. Among patients treated with acalabrutinib, two had a treatment-related SAE of atrial fibrillation; no other treatment-related SAE occurred in more than one patient. The main idelalisib-related SAE was diarrhoea, affecting 16 patients (13.6%).

B.2b.10.3 Deaths

At the time of this analysis, 15 patients (9.7%) in the acalabrutinib arm and 18 patients (11.8%) in the IR/BR arm had died as of the data cut-off date, including three patients initially treated with IR who died after crossing over to receive acalabrutinib. There were five deaths caused by disease progression, all of which occurred in the acalabrutinib arm. The most common cause of death was AEs. A total of five patients (one in the acalabrutinib arm and four in the IR/BR arm) died after Richter's transformation (a further three patients in the acalabrutinib arm and one in the IR/BR arm also had Richter's transformation, but were alive as of the data cut-off date). Only one death (a patient treated with IR who died of interstitial lung disease) was considered to be related to study treatment

B.2b.10.4 Safety overview

Acalabrutinib demonstrated a safety and tolerability profile in this study that was consistent with those previously observed in other acalabrutinib monotherapy haematological malignancy clinical trials, including in CLL. Compared with IR, acalabrutinib was associated with a lower incidence of grade ≥ 3 TEAEs (49.4% for acalabrutinib vs 89.8% for IR), as well as a lower incidence of SAEs (28.6% vs 55.9%) and TEAEs that led to treatment discontinuation (10.4% vs 52.5%). With BR, the incidences of grade ≥ 3 TEAEs and SAEs were similar (48.6% and 25.7%, respectively) and the incidence of TEAEs that led to treatment discontinuation was higher (17.1%) versus acalabrutinib. With a median acalabrutinib treatment duration of 15.7 months, compared with 11.5 months for idelalisib, 5.5 months for rituximab and 5.6 months for bendamustine, the data demonstrate that acalabrutinib monotherapy is well tolerated by patients with R/R CLL.

B.2b.10.5 RESONATE

Treatment exposure and adverse events

Treatment exposure was longer among patients receiving ibrutinib than among those receiving ofatumumab (median 8.6 months [range, 0.2–16.1] vs 5.3 months [range, 0–7.4]). The AEs that occurred in at least 10% of the patients are presented without adjustment for duration of exposure in Table 50. The most frequent non-haematologic AEs that occurred in at least 20% of the patients were diarrhoea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. Overall, 57% of the patients in the ibrutinib group and 47% of the patients in the ofatumumab group had at least one AE of grade 3 or higher.

Table 50. Adverse events in RESONATE

	Number (%) of patients			
	Ibrutinib (N = 195)		**Ofatumumab (N = 191)**	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any AE occurring during treatment	194 (99)	99 (51)	187 (98)	74 (39)
Diarrhoea	93 (48)	8 (4)	34 (18)	3 (2)
Fatigue	54 (28)	4 (2)	57 (30)	3 (2)
Nausea	51 (26)	3 (2)	35 (18)	0
Pyrexia	46 (24)	3 (2)	28 (15)	2 (1)
Anaemia	44 (23)	9 (5)	33 (17)	15 (8)
Neutropenia	42 (22)	32 (16)	28 (15)	26 (14)
Cough	38 (19)	0	44 (23)	2 (1)
Thrombocytopenia	33 (17)	11 (6)	22 (12)	8 (4)
Arthralgia	34 (17)	2 (1)	13 (7)	0
Upper respiratory tract infection	31 (16)	1 (1)	20 (10)	3 (2)
Constipation	30 (15)	0	18 (9)	0
Vomiting	28 (14)	0	12 (6)	1 (1)
Headache	27 (14)	2 (1)	11 (6)	0
Petechiae	27 (14)	0	2 (1)	0
Muscle spasm	25 (13)	0	16 (8)	0
Dyspnoea	23 (12)	4 (2)	20 (10)	1 (1)
Peripheral oedema	22 (11)	0	15 (8)	0

	Number (%) of patients			
	Ibrutinib (N = 195)		Ofatumumab (N = 191)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Back pain	22 (11)	2 (1)	12 (6)	1 (1)
Sinusitis	21 (11)	1 (1)	12 (6)	0
Dizziness	22 (11)	0	10 (5)	0
Contusion	21 (11)	0	6 (3)	0
Stomatitis	21 (11)	1 (1)	4 (2)	1 (1)
Pain in limb	20 (10)	1 (1)	8 (4)	0
Pneumonia	19 (10)	13 (7)	13 (7)	9 (5)
Urinary tract infection	19 (10)	7 (4)	10 (5)	1 (1)
Myalgia	19 (10)	1 (1)	7 (4)	0
Blurred vision	19 (10)	0	6 (3)	0
Night sweats	10 (5)	1 (1)	24 (13)	0
Peripheral sensory neuropathy	8 (4)	0	24 (13)	0
Infusion-related reaction	0	0	53 (28)	6 (3)

Listed are all AEs that occurred in at least 10% of the patients in either group. Five patients in the ofatumumab group did not receive a study drug.
AE, adverse event.
Source: Byrd et al. 2014[77]

B.2b.10.6 Indirect safety comparison

The MAIC also analysed AEs for acalabrutinib versus ibrutinib (Table 51) and the results demonstrate that the incidence of AEs (any grade and grade 3/4 AEs) was lower with acalabrutinib than with ibrutinib. Compared with ibrutinib, acalabrutinib was associated with significantly fewer SAEs (acalabrutinib: [redacted]; ibrutinib: [redacted]). In addition, compared with ibrutinib, acalabrutinib was associated with significantly lower incidences of grade 3/4 diarrhoea, infections, fatigue and hypertension, but a higher incidence of grade 3/4 anaemia. These results are in line with clinical expert opinion gathered in an UK advisory board in which members agreed that although acalabrutinib and ibrutinib have similar efficacy, the safety profile is a key differentiator, with less toxicities associated with acalabrutinib than ibrutinib.[3]

Table 51. Safety outcomes after matching for acalabrutinib versus ibrutinib

	Acalabrutinib	Ibrutinib	RD (%)		Odds ratio	
	ESS = 44 [A]	N = 195 [B]	Mean (95% CI) [A - B]	*P*-value	OR (95% CI)	*P*-value
Any grade AE						
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events						
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3–4 AEs						
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Acalabrutinib	Ibrutinib	RD (%)		Odds ratio	
	ESS = 44 [A]	N = 195 [B]	Mean (95% CI) [A - B]	*P*-value	OR (95% CI)	*P*-value
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* denotes p-value < 0.05

Note: Adverse events for acalabrutinib were defined by preferred terms. 'Any' refers to any grade 1-4

Note: Comparison of acalabrutinib v Ibrutinib at similar follow-up (Brown et al 2014,[82] Brown et al, 2018[83])

ACA, acalabrutinib; AE, adverse event; AF, atrial fibrillation; CI, confidence interval; IB, ibrutinib; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; PE, peripheral oedema; RD, rate difference; SAE, serious adverse event.

B.2.11 Ongoing studies in 1L and RR CLL patients

Both the ELEVATE-TN and ASCEND studies are ongoing, and are expected to complete in 2021 and 2020, respectively. Subsequent data cuts are expected to provide additional PFS and OS data, with ongoing follow-up expected post study completion to allow more mature OS data to be captured.

B.2.12 Innovation

Other than in patients with a cytogenetic mutation, such as a 17p deletion or TP53 mutation, there is a significant unmet need in first-line CLL, as there is currently no broad access for reimbursed BTK inhibitors or other novel agents in this setting. The standard of care for first-line CLL patients (excluding patients with a 17p-/ TP53m) is chemoimmunotherapy, which includes FCR therapy for fitter and younger patients, or chlorambucil in combination with obinutuzumab for patients in whom FCR therapy is unsuitable. Whilst chlorambucil plus obinutuzimab has been established clinical practice for many years, the anticipated survival benefit and reduction in disease progression offered by acalabrutinib has significant potential to represent a step-change in the treatment pathway.

[redacted]

In patients with a 17p deletion or TP53 mutation, and in patients with R/R CLL, acalabrutinib offers an alternative option to the first generation BTK inhibitor, ibrutinib. Due the highly-selective activity, acalabrutinib demonstrates minimal off-target activity that can maintain a median steady state BTK occupancy of ≥ 95%, and is therefore expected to have improved safety/tolerability profile compared with ibrutinib.

Therefore, we anticipate that acalabrutinib will result in a step-change in the treatment pathway for 1L (untreated) CLL patients without high-risk cytogenetic features (17p deletion or TP53 mutation), as well as offering better tolerability than current targeted therapies for patients with untreated CLL with high-risk cytogenetic features and in those with R/R CLL.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal interim findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The efficacy and safety of acalabrutinib in previously untreated patients and in patients with R/R CLL has been demonstrated in two large, multi-centre, international RCTs, ELEVATE-TN and ASCEND, respectively; both meeting their primary endpoints and demonstrating a consistent effect across all subgroups studied.

A) Previously untreated patients with CLL in whom FCR therapy is unsuitable

In patients with previously untreated CLL, acalabrutinib monotherapy demonstrated a statistically significant and clinically meaningful improvement in IRC-assessed PFS, compared with chlorambucil plus obinutuzumab, after a median follow-up of 28 months. Treatment with acalabrutinib monotherapy resulted in an 80% reduction in the relative risk of disease progression or death versus chlorambucil plus obinutuzumab (HR: 0.20; 95% CI: 0.13–0.30; p < 0.0001), with 87% patients remaining alive and progression-free (PF) at 24 months vs 47%. Median PFS for acalabrutinib monotherapy was not reached. Importantly, the PFS benefit was seen irrespective of the presence or absence of high-risk features, such as del(17p), del(11q) and unmutated IGHV, and irrespective of disease stage; demonstrating a significant clinical benefit across the entire patient population.

The secondary endpoint analyses support the favourable PFS results, namely:

- Although the OS data in ELEVATE-TN are still immature and median OS was not reached in any treatment arm, the OS trend favoured acalabrutinib monotherapy (HR: 0.60; 95% CI: 0.28–1.27; p = 0.1556), compared with chlorambucil plus obinutuzumab.
- The IRC-assessed ORR was 85.5% (95% CI: 79.6–89.9) with acalabrutinib monotherapy; representing an increase of 6.9% compared with chlorambucil plus obinutuzumab (p = 0.0763), and
- Acalabrutinib monotherapy was associated with a significantly higher TTNT, compared with chlorambucil plus obinutuzumab (HR: 0.24; 95% CI: 0.15–0.40; p < 0.0001).

Evidence from the ELEVATE-TN trial also demonstrated that the safety profile of acalabrutinib is considered acceptable, with the majority of AEs being Grade 1 or 2. The proportions of patients who experienced TEAEs were comparable between acalabrutinib monotherapy and chlorambucil plus obinutuzumab (95.0% vs 98.8%). SAEs, most of which were grade ≥ 3, occurred in 31.8% and 21.9% of patients who received acalabrutinib monotherapy and chlorambucil plus obinutuzumab, respectively. This is despite the duration of treatment with acalabrutinib being considerably longer than that of chlorambucil plus obinutuzumab, owing to the fixed number of cycles with chlorambucil plus obinutuzumab. Furthermore, few patients treated with acalabrutinib monotherapy discontinued treatment due to AEs compared with those receiving treatment with chlorambucil in combination with obinutuzumab (9.5% vs 14.2%, respectively).

Therefore, it can be concluded that acalabrutinib monotherapy represents an efficacious alternative to chlorambucil plus obinutuzumab, with an acceptable safety profile.

B) Adults with relapsed or refractory (R/R) CLL who have had at least one previous therapy

Acalabrutinib is the first CLL therapy to show a statistically and clinically meaningful improvement in PFS in a Phase 3 study compared with either a targeted therapy (idelalisib) or BR (88% vs. 68% and 69%, respectively, alive and progression free at 12 months), and a 69% reduction in the relative risk of disease progression or death (HR: 0.31; 95% CI: 0.20–0.49; p < 0.0001) (Figure 12). The benefits were observed cross all pre-specified subgroups,

with HR ranging from 0.20 to 0.64. In particular, when compared with IdR or BR, treatment with acalabrutinib results in a statistically significant improvement in patients with at least 1 high-risk feature associated with poor prognosis, such as a 17p deletion or p53 mutation (HR: 0.27, 95% CI: 0.17 –0.44; p<0.0001). Median PFS for acalabrutinib was not reached and was 16.5 months (95% CI: 14.0–17.1) with IR/BR.

The secondary endpoint analyses support the favourable PFS results, namely:

- Although the OS data in ASCEND are still immature and median OS was not reached in any treatment arm, OS numerically favoured acalabrutinib ([redacted]), compared with IR/BR.
- ORR was [redacted]) with acalabrutinib compared with [redacted]) with IR/BR.
- Acalabrutinib monotherapy was associated with a significantly higher TTNT, compared with IR/BR ([redacted]).

Evidence from the ASCEND trial also demonstrated that the safety profile of acalabrutinib is considered acceptable. Overall, patients treated with acalabrutinib were less likely to experience grade ≥ 3 AEs than those receiving IR (49.4% vs 89.8%); and the proportions of patients who had grade ≥ 3 AEs was similar between the BR (48.6%) and acalabrutinib groups. There were also fewer patients who discontinued treatment of acalabrutinib due to AE compared to patients treated with IR or BR (10.4% vs. 52.5% and 17.1%, respectively). Furthermore, fewer patients treated with acalabrutinib had dose reductions due to AEs compared with those treated with IR or BR (3.9% vs 12.7% and 14.3%, respectively)

Comparative efficacy and safety of acalabrutinib vs ibrutinib

In the absence of any published head-to-head RCTs, a MAIC was conducted to estimate the comparative efficacy and safety of acalabrutinib versus ibrutinib in patients previously treated with CLL. The results of the MAIC demonstrated a non-significant benefit associated with acalabrutinib vs ibrutinib in terms of PFS ([redacted]) and OS ([redacted]) before and after matching, respectively, and therefore clinical equivalence is assumed. Whilst it is likely that treatment with either acalabrutinib or ibrutinib results in similar clinical efficacy, it is anticipated that acalabrutinib will offer improved tolerability to patients due to its highly selective activity and minimal off-target activity.

The favourable safety profile observed for acalabrutinib is anticipated to provide an alternative option to clinicians when making treatment decisions based on efficacy and tolerability. This is a key consideration for a treatment given until disease progression or unacceptable toxicity.

To better understand the clinical efficacy of acalabrutinib relative to ibrutinib, key clinical expert opinion was sourced on the outputs of the clinical trial and MAIC.[84] Overall, the clinical experts agreed there was no efficacy difference (PFS, OS) between acalabrutinib and ibrutinib arms however, it was also noted that acalabrutinib had a more favourable safety profile specifically regarding other BTKi (ibrutinib) patient risk factors such as cardiovascular risk, bleeding, hypertension, arthralgia and sudden death. Therefore,

acalabrutinib would represent an important alternative to ibrutinib, particularly in patients with safety concerns regarding ibrutinib. Based on the results of the MAIC and the findings from the clinical experts, it was determined that a cost-minimisation analysis would be conducted for the comparison against ibrutinib in the R/R CLL.

Given the relative strength of the MAIC methodology in eliminating major cross-trial differences, its ability to utilise IPD to create a 'pseudo trial', coupled with robust NICE guidance on good practice, data from this comparison were incorporated into the cost-minimisation analysis, presented in section B.3b.

Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable

Patients with a cytogenetic mutation, such as those with a 17p deletion or a TP53 mutation are often defined as high-risk patients, and tend to have a worse prognosis than patients without a mutation. Despite this, data from the ELEVATE-TN trial demonstrated that patients who had at least one chromosomal characteristic associated with poor prognosis (del[17p], TP53 mutation, del[11q] or unmutated IGHV) had an 87% reduction with acalabrutinib monotherapy (HR: 0.13; 95% CI: 0.08–0.21) versus chlorambucil plus obinutuzumab; consistent with the intention-to-treat (ITT) population; and therefore acalabrutinib monotherapy in this high-risk population should be considered highly relevant. However, previously untreated high-risk patients typically receive treatment with ibrutinib, in-line with the recommendations in TA429.[6] Whilst idelalisib is also recommended for use, UK clinical experts and NICE have previously concluded that it is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab. Therefore, comparative evidence of acalabrutinib monotherapy vs ibrutinib should be considered in these patients.

Applicability of the evidence to the first-line setting

In appraisal TA429, NICE assessed ibrutinib for the treatment of untreated and previously treated patients with CLL, with evidence for ibrutinib based on the RESONATE study. The RESONATE trial was conducted in patients with previously treated CLL, and therefore did not contain any evidence of efficacy in the first-line setting. Despite this, the committee accepted that in the absence of any evidence, data from previously treated patients could be taken into account and NICE recommended ibrutinib as an option for treated CLL in people who have had at least one prior therapy as well as in patients who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable.

Therefore, in this context, evidence from the ASCEND trial (in previously treated patients with CLL) and MAIC (demonstrating equivalence with ibrutinib), can be generalised to the first-line high-risk setting. Data from the ASCEND trial is deemed to be the most relevant as a proxy for high-risk patients in the 1L setting, as the trial includes approx. 40% patients with a 17p and/or TP53 mutation, compared with approx. 20% in the ELEVATE-TN study.

B.2.13.2 Strengths and limitations in context to UK clinical practice

Acalabrutinib has been extensively studied across two large, international, randomised Phase 3 RCTs investigating the efficacy and safety of acalabrutinib in patients either previously untreated or treated CLL.

Data from the ELEVATE-TN trial showed that compared with current SoC; chlorambucil plus obinutuzumab, treatment with acalabrutinib monotherapy significantly improved PFS, with 87% vs 47% patients alive and PF at 24 months, and demonstrated an unprecedented risk reduction in disease progression or death by 80% (HR: 020; p<0.0001). Importantly, acalabrutinib offered consistent PFS improvements vs SoC across all pre-specified subgroups, including patients with high-risk cytogenetic mutations; such as a 17p deletion or TP53 mutation. This is important, as approximately 10% of untreated patients in routine practice have these high-risk mutations, and the prognosis for these patients is generally worse, and therefore it critical that highly efficacious and well-tolerated treatments are available for these patients. The trial also demonstrated that acalabrutinib monotherapy was generally well-tolerated, with fewer patients experiencing Grade 3 AEs, and discontinuations due to AEs in those treated with acalabrutinib monotherapy vs SoC.

In addition, data from the ASCEND trial also confirmed the efficacy and safety of acalabrutinib monotherapy in patients with R/R CLL compared with investigators choice of IR or BR. Whilst this is reassuring, and in the absence of head-to-head data, a MAIC was also conducted to assess the comparative efficacy of acalabrutinib vs current SoC, ibrutinib, where results indicated a non-statistically significant improvement in PFS and OS. Therefore, these results provide reassurance of at least clinical equivalence vs ibrutinib, whilst offering an improved safety profile.

Therefore, acalabrutinib monotherapy is likely to represent a step-change in the treatment for untreated, non-high-risk patients who are unsuitable for FCR-based therapy, and a well-tolerated, highly selective alternative treatment option to ibrutinib in untreated high-risk patients (with a 17p or TP53 mutation), and in patients with R/R CLL. Acalabrutinib monotherapy provides substantial clinical benefits as a first-line therapy in patients who are FCR-ineligible, regardless of the presence or absence of high-risk mutations.

Limitations of evidence base

Whilst the data from the ELEVATE-TN and ASCEND clinical trials provide statistically and clinically meaningful improvements in outcomes for patients with untreated or previously treated CLL, there are a number of potential limitations to consider.

At the time of the most recent data cut, the majority of patients were alive in the ELEVATE-TN trial ([redacted]% in the acalabrutinib monotherapy arm, and [redacted]% in the chlorambucil + obinutuzumab arm) and ASCEND trial ([redacted]% in the acalabrutinib arm and [redacted]% in the IR/BR).[75] However, the current OS data numerically favours acalabrutinib across all trials, and results from final analyses are expected for the ELEVATE-TN and ASCEND trials in 2021 and 2020, respectively.

[redacted]

In addition, there are no head-to-head data to inform the comparative efficacy of acalabrutinib vs ibrutinib in R/R patients, or in previously untreated patients with high-risk cytogenetic mutations. However, in the absence of head-to-head data, a MAIC was performed which demonstrated a non-significant improvement in PFS and OS. Nonetheless, clinical equivalence has been assumed. Therefore, given the relative strength of the MAIC methodology in eliminating major cross-trial differences, its ability to utilise IPD to create a 'pseudo trial', coupled with robust NICE guidance on good practice, data from this comparison were incorporated into a cost-minimisation analysis in the R/R setting.

B.2.13.3 End-of-life criteria

Acalabrutinib for the treatment of previously treated CLL is not expected to meet end-of-life criteria.

B.3a Cost effectiveness: 1L CLL patients

B.3a.1 Published cost-effectiveness studies

An SLR of studies reporting the economic evaluation, health state utility values (HSUV) and cost-of-illness of patients with previously untreated CLL, or R/R CLL was conducted from 1st January 2000 to the 12th February 2020. Full details of the cost effectiveness SLR are presented in Appendix G.

The review identified 12 NICE appraisals and 52 economic evaluations of different treatment options (25 journal publications and 27 conference abstracts). A summary of the economic evaluation studies is provided below (Table 52); only those studies which report results for the comparators of interest and a UK perspective are extracted.

Table 52. Summary list of published cost-effectiveness studies from a UK perspective in relevant comparators

Reference	Study design	Population	Comparators	Clinical data source	Resource use/costs data source	Utility data source	Results
First-line							
Sinha R, 2018 UK[85]	Cost utility 3-HS Markov with lifetime horizon and 4-week cycle length. (structure as Becker, 2016)	Untreated patients with CLL with comorbidities who cannot tolerate fludarabine-based therapy.	Ibrutinib compared with obinutuzumab + chlorambucil G-Clb	G-Cib from trial CLL11, other from Matching-adjusted indirect comparison (MAIC) NCT01010061	£UK at 2015/16 prices. Direct costs as per NICE guidelines. Costs related to medical management required during treatment and follow-up, treatment of adverse events, and end-of-life costs have been included.	Utility from the literature (Kosmas CE, 2015)[86] (Beusterien KM, 2010)[87] (Tolley K, 2013)[88]	An average gain of 1.49 quality-adjusted life-years (QALYs) estimated for ibrutinib at an average additional cost of £112,835 per patient. Ibrutinib is not cost-effective in the base case analysis without a price discount.
Becker U, 2016 UK[89]	Cost-effectiveness 3HS Markov model with lifetime (20 year) horizon and 1-week cycle length	Previously untreated patients with CLL who are unsuitable for fludarabine (F)	Range of treatment options for patients unsuitable for F-based therapies.	Clinical trial data from CLL11 and indirect treatment comparison Also, CLL5 and CLL8 CLL11: NCT01010061	£UK at 2013 prices. Res use from the CLL11 trial and UK sources	EORTC was collected in CLL11, but this study used utilities from a preference elicitation exercise (Kosmas, 2015)[86]	G-Clb was estimated to increase both quality-adjusted life expectancy and treatment costs compared with several commonly used therapies
TA343, 2015[40]	Clinical and cost-effectiveness of obinutuzumab in combination	Adults with untreated chronic lymphocytic leukemia who have	Obinutuzumab plus chlorambucil (GClib) compared with rituximab plus	The company used data from the CLL5 trial (a randomised controlled trial comparing fludarabine with	The company applied costs for drug acquisition, drug administration, health state and adverse events. It	EORTC QCQ-30 was collected in the CLL11 trial but was not	Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated chronic

Reference	Study design	Population	Comparators	Clinical data source	Resource use/costs data source	Utility data source	Results
	with chlorambucil for untreated CLL	comorbidities that make full-dose fludarabine-based therapy unsuitable for them,	chlorambucil (RClb), bendamustine plus rituximab (RBenda), bendamustine alone and chlorambucil alone	chlorambucil (FC) in untreated chronic lymphocytic leukemia) to model overall survival distribution, because the overall survival data from CLL11 were immature. The overall survival distribution in the model was validated using the Kaplan–Meier overall survival data that were available from CLL11.	assumed of no vial sharing for all intravenous drugs. Therefore, all calculations of price include drug wastage. The company did not map the EORTC-QL-C30 questionnaire to the EQ-5D. The ERG identified several mapping functions that could have been used. The ERG believed that a generic questionnaire such as the EQ-5D should have been used. Several assumptions in the company's model were queried: •The company used the incorrect utility value while on obinutuzumab treatment after the first cycle of	mapped to EQ-5D. The company carried out a utility elicitation study with a sample of 100 members of the UK general public (Kosmas, 2015).[86] PFS on oral treatment (chlorambucil): 0.71 PFS on IV treatment (rituximab and bendamustine): 0.67 PFS on initial therapy with increased hospital visits (obinutuzumab) :0.55 PFS after initial treatment was completed (all	lymphocytic leukemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: •bendamustine-based therapy is not suitable and •the company provides obinutuzumab with the discount agreed in the patient access scheme.

Reference	Study design	Population	Comparators	Clinical data source	Resource use/costs data source	Utility data source	Results
					obinutuzumab treatment. •The utility value for progression-free survival off treatment in the company's model was based on the utility elicitation study. •The company assumed a dose intensity of 100% for bendamustine and rituximab. •The company used its large network meta-analysis to estimate a hazard ratio of 0.40 for the comparison with bendamustine monotherapy. •The company used the estimated sample size from an ongoing trial to calibrate the correlation between the number of people who had a complete response and the progression-free	treatment arms):0.82 Progressed disease (all treatment arms): 0.60 ERG proposed certain changes in utility values and the final values used were: On obinutuzumab after first cycle of therapy: 0.67 PFS off treatment: 0.71	

Reference	Study design	Population	Comparators	Clinical data source	Resource use/costs data source	Utility data source	Results
					survival hazard ratio for treatment with RBenda and treatment with RClb		
Relapsed/refractory							
Vreman, 2019 UK[90]	Cost effectiveness analysis from the UK National Health System (NHS) perspective. 3-HS partitioned survival with lifetime (30 year) horizon and 28 days cycle length	Patients with relapsed CLL	Acalabrutinib compared to ibrutinib	RESONATE trial, NCT02029443	British National Formulary	Utility for acalabrutinib was not available and was therefore assumed equal to the ibrutinib utility of 0.799 reported in the RESONATE trial	The ICER for acalabrutinib versus ibrutinib was £61,941/QALY, with 3.44 incremental QALYs and incremental costs of £213,339.

BSC, best supportive care; CI, confidence interval; CAP, cyclophosphamide, doxorubicin and prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; CLL, chronic lymphocytic leukemia; DR, double refractory; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D, EuroQol 5-dimension; ERG, Evidence Review Group; FCR, fludarabine, cyclophosphamide and rituximab; G-Clb, obinutuzumab + chlorambucil; HS, health state; ICER, incremental cost-effectiveness ratio; ID, identifier; ISPOR, International Society of Pharmacoeconomics and Outcomes Research; KOL, key opinion leader; MAIC, matching-adjusted indirect comparison; miniR, low-dose rituximab; MRD, minimal residual disease; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSM, partitioned survival model; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-year; RCT, randomised controlled trial; STA, single technology appraisal; TA, technology appraisal; TP53, tumour protein 53; UK, United Kingdom; WTP, willingness to pay.

B.3a.2 Economic analysis

As the SLR did not identify an existing economic evaluation of acalabrutinib monotherapy in previously untreated CLL patients, a *de novo* economic model was built in Microsoft® Excel to estimate the incremental cost-effectiveness of acalabrutinib versus chlorambucil plus obinutuzumab in this setting. Key characteristics of the economic analysis are presented in Table 53; more detail is provided in subsequent sections.

Table 53. Summary of the economic analysis

Aspect	Details	Justification
Analytical methods	Semi-Markov model with 3 health states (PF, PD, Death)	Analytical technique that has been applied in several previous HTA submissions for anti-cancer treatments in CLL (TA487, TA343, TA359)[40-42] Markov framework allows flexibility to model PPS based on external data sources and more nuanced estimation of treatment costs Due to challenges associated with independently extrapolating PFS and OS, a semi-Markov model using PFS and PPS was selected
Patient population	Previously untreated patients	Aligned with anticipated license for acalabrutinib and population enrolled in the ELEVATE-TN trial (please refer to Section B1 for additional rationale)
Intervention	Acalabrutinib	In line with final NICE scope
Comparator	Chlorambucil + obinutuzumab	In line with final NICE scope (please refer to section B.1 Decision problem, description of the technology and clinical care pathway for additional rationale)
Perspective	NHS and PSS	Consistent with NICE reference case[91]
Time horizon	Lifetime (30 years)	Lifetime time horizon is required to capture all differences in treatment arms in the economic model; ~1% of patients still alive on acalabrutinib at 30 years
Cycle length	4 weeks (28 days)	Consistent with the study design of ELEVATE-TN which uses a period of 4 weeks for drug administration cycles
Half-cycle correction	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and end of each cycle
Discounting	Costs and health outcomes at 3.5%	Consistent with NICE reference case[91]
Clinical effectiveness: pre-progression	ELEVATE-TN	TTP and TTDeath were derived from PFS data from the ELEVATE-TN trial for acalabrutinib monotherapy and chlorambucil + obinutuzumab

Aspect	Details	Justification
Clinical effectiveness: post-progression	• RESONATE (1-2 prior therapies) • MURANO (1-2 prior therapies)	OS data from ELEVATE-TN were deemed too immature to provide robust parametric modelling estimates; therefore, PPS was informed by OS in R/R clinical studies in line with the treatment paradigm (see Section B1) PPS from the ibrutinib arm of RESONATE in R/R CLL was utilized used for the chlorambucil plus obinutuzumab base case as it represents survival in a population treated with a BTKi in second line, which is typical after treatment with chlorambucil plus obinutuzumab PPS from the venetoclax plus rituximab arm of MURANO in R/R CLL was used for the acalabrutinib monotherapy base cases. Patients progressing on a BTKi, would typically be ineligible for a BTKi in the second line. UK clinicians have indicated there is a preference for treating with a BTKi prior to treating with venetoclax with plus rituximab.
Safety	ELEVATE-TN	ELEVATE-TN was used to inform the safety profiles of acalabrutinib monotherapy and chlorambucil plus obinutuzumab
Measurement and valuation of health	• PF state: Based on EQ-5D data collected in the ELEVATE-TN trial • PD state: Alternative values sourced from published literature and previous CLL submissions • Disutilities associated with adverse events were sourced from published literature and previous CLL submissions • An age-related utility decrement was included, using methods described in Ara et al. 2010.[92]	HSUV were provided based on the societal preferences of the general population in the UK using the value sets developed for EQ-5D-3L
Costs	• Treatment acquisition • Treatment administration • Disease management costs • End of life	Costs included are consistent with standard practice. In the base case, disease management costs are derived from previous appraisals.

Aspect	Details	Justification
	• Management of grade 3 or above adverse events • Subsequent therapies	
Outcomes	• Total costs • Incremental costs • Disaggregated costs • Total QALYs • Incremental QALYs • Disaggregated QALYs • Total LYs • Incremental LYs • Disaggregated LYs • ICERs	Consistent with the final scope for this appraisal and the NICE reference case.[91]
Uncertainty	• Univariate sensitivity analysis • Scenario analysis • Probabilistic sensitivity analysis	Consistent with NICE reference case[91]

BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; EQ-5D; EuroQol 5-dimension; HSUV, health state utility values; LY, life years; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PPS, post-progression survival; PSS, Personal Social Services; QALYs, quality-adjusted life years; TTP, time to progression; TTD, time to death.

B.3a.2.1 Patient population

The *de novo* economic analysis evaluates the incremental cost-effectiveness of acalabrutinib monotherapy compared with chlorambucil in combination with obinutuzumab in the treatment of previously untreated CLL patients.

B.3a.2.2 Model structure

The cost-effectiveness model utilises a 3-health state semi-Markov structure, which includes three mutually exclusive health states: PF, progressed disease (PD), and death. Figure 17 describes the disease progression pathway in the model. Unlike a conventional Markov, the semi-Markov model captures and follows each cohort of patients entering the PD state in each cycle using tunnel states.

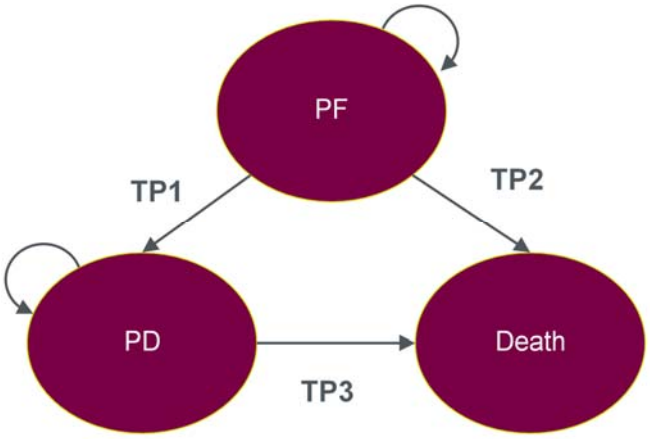
This technique allows the model to track the survival of each cohort entering the PD state which is vital, as upon progression to the R/R setting, patients experience deterioration in HRQoL arising from disease progression and its associated impact on anxiety and symptom burden. Furthermore, it ensures that the structural relationship between PFS and OS is maintained (i.e. logical inconsistencies arising from crossing curves due to extrapolating each outcome independently are negated). A cohort model approach was considered most appropriate as there is limited evidence of heterogenic effect of individual patient characteristics on future survival and disease course.

State occupancy was modelled at four-week intervals (28 days) over the course of the modelled time horizon (base case: 30 years). A four-week cycle length was used as it is the

common denominator between treatment cycle duration in ELEVATE-TN and the yearly time horizons required for the economic analysis.

The total costs and quality adjusted life years (QALYs) of treatments were estimated by combining the proportion of patients in each health state over time, with the costs and health utilities assigned to each state.

Figure 17. Health-state structure used in the economic model



PF, progression-free; PD, progressed disease; TP, transition probability.

The cohort in the model is initially assigned to the PF state, from which they can enter either the PD, or death states.

Health states

The health states included within the model describe the following disease stages:

- PF: All patients start in the PF state and receive first-line treatment until either progression or death.
- PD: The PD state captures patients who have progressed on their first line therapy prior to death and undergo subsequent lines of treatment
- Death: The death state is an absorbing state, meaning that patients transitioning to this health state are assumed to occupy it indefinitely.

Transitions

The transition probabilities (TPs), as shown in Figure 17, are time dependent. As disease progression and pre-progression death are competing mutually-exclusive events, TP1 and TP2 were modelled using competing risk equations. The TPs within the model are described in further detail below:

- TP1: TP1 governs transitions from the PF to PD state and is modelled using time to progression (TTP) data. TTP patient-level data from ELEVATE-TN was extrapolated (Section B.3a.3 Clinical parameters and variables) to derive TP1 for acalabrutinib monotherapy and chlorambucil plus obinutuzumab. In the trial, disease progression was defined in accordance with the iwCLL 2008 criteria[19] for CLL, with the modification that

treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression was not considered progressive disease.[93]

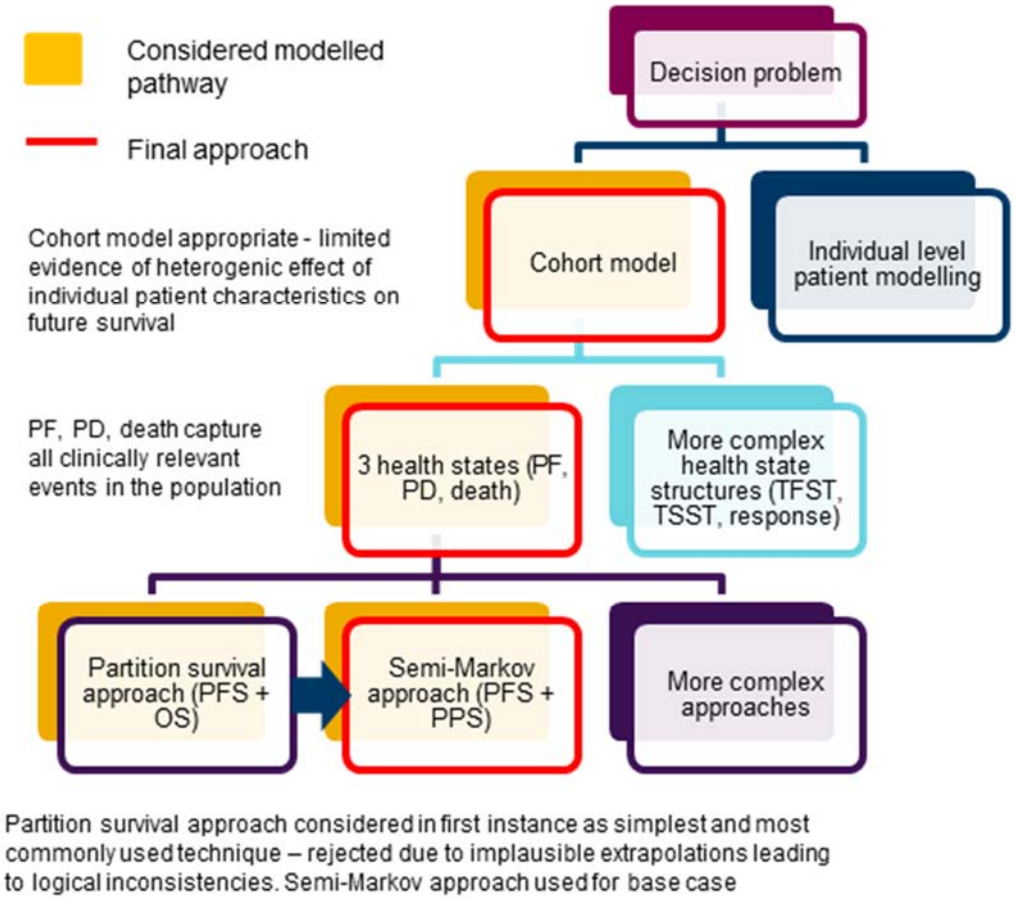
- TP2: The transition from PF to Death state (TP2) is modelled using time to pre-progression death (TTDeath) data. TTDeath patient-level data from ELEVATE-TN were extrapolated (Section B.3a.3 Clinical parameters and variables) to derive TP2 for acalabrutinib monotherapy and chlorambucil plus obinutuzumab. To ensure survival did not exceed that expected for the general population, TP2 was restricted by general population mortality which was applied as a competing risk.
- TP3: TP3 captures the risk of death at any time in patients with PD. TP3 was estimated using post-progression survival (PPS) data. PPS was modelled from RESONATE and MURANO OS data as described in Section B.3a.3 Clinical parameters and variables. As with TP2, general population mortality was applied as a competing risk to prevent survival exceeding that of the general population.

Model conceptualisation and justification for approach

The approach to selecting the final model methodology is shown in

Figure 18. At each step of the process, the most parsimonious approach was chosen and considered first, before moving on to more complex approaches. A partitioned survival approach was initially considered but rejected due to limitations in the analysis; specifically, direct extrapolation of the OS data from ELEVATE-TN using standard techniques produced logical inconsistencies when compared to the age-matched OS data from the UK population[94] (see Figure 19). OS data in ELEVATE-TN was very immature at data cut off (8 February 2019), with only [redacted] subjects in the acalabrutinib monotherapy arm and [redacted] subjects in the chlorambucil plus obinutuzumab arm having died.

Figure 18. Model conceptualisation



OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; TFST, time to first subsequent treatment or death; TSST, time to second subsequent treatment or death.

Figure 19. Extrapolation of OS data from ELEVATE-TN using standard parametric functions compared with age-matched OS from the UK general population (ONS)

KM, Kaplan-Meier; ONS, Office for National Statistics; OS, overall survival.

Features of the economic analysis are summarised and compared to previous NICE appraisals in CLL in Table 54.

Table 54. Features of the economic analysis

Feature	Previous NICE appraisals											Current appraisal	
	TA119[95]	TA174[38]	TA193[43]	TA202*[96]	TA216[39]	TA343[40]	TA344*[97]	TA359[41]	TA429[6]	TA487[42]	TA561[10]	Chosen values	Justification
Intervention	F	R	R	O	B	C+O	O+C/B	I+R	Ibr	V	V+R	A	NA
Date published	2007	2009	2009	2010	2011		2015	2015	2017	2017	2019	2020	NA
Indication	1L	1L	R/R CLL	R/R CLL	1L CLL	1L CLL	1L CLL	R/R CLL	1L and R/R CLL	BCRI-F CLL	R/R CLL	1L CLL	NA
Model structure	Markov	Markov	Markov	PSM	Markov	PSM	Semi-Markov model	Markov	PSM	PSM	PSM	Semi-Markov model	Independently fitting TTP/TTD and PPS curves produces logical inconsistencies
Time horizon	20 years	15 years	25 years	10 years	35 years	20 years	25 years	25 years	20 years	20 years	30 years	30 years	Dependent upon extrapolated OS, but 30 years was judged to sufficiently capture all relevant costs and benefits
Cycle length	4 weeks	1 month	1 month	1 day	3 months	Weekly	3 months	1 week	4 weeks	4 weeks	4 weeks	4 weeks	Aligns with the treatment cycle in ELEVATE-TN and used in

Feature	Previous NICE appraisals											Current appraisal	
	TA119[95]	TA174[38]	TA193[43]	TA202*[96]	TA216[39]	TA343[40]	TA344*[97]	TA359[41]	TA429[6]	TA487[42]	TA561[10]	Chosen values	Justification
													previous TAs of CLL
Starting age	NR	NR; assumed 59.5	NR	-	NR; assumed 63	71.7	-	71	NR; assumed 67	65.44; 66.25	64.18	70 years	Average age of ITT population of ELEVATE-TN
Half-cycle correction	NR	NR	NR	-	Yes	Yes	-	Yes	Yes	Yes	Yes	Yes	Prevents under- or over-estimation of costs and QALYs
Were health effects measured in QALYs; if not, what was used?	QALYs	QALYs	QALYs	-	QALYs	QALYs	-	QALYs	QALYs	QALYs	QALYs	QALYs	NICE reference case
Discount of 3.5% for utilities and costs	3.5%	3.5%	3.5%	-	3.5%	3.5%	-	3.5%	3.5%	3.5%	3.5%	3.5%	NICE reference case
Perspective (NHS/PSS)?	Yes	Yes	Yes	-	Yes	Yes	-	Yes	Yes	Yes	Yes	Yes	NICE reference case
Source of utilities	Utilities taken from Hancock et al 2002[98]	Utilities taken from Hancock et al 2002[98]	Utilities taken from Hancock et al 2002[98]	-	EQ-5D mapped from EORTC-C30 data from	TTO utility elicitation study with UK general population	-	EQ-5D from study 116 and literature-based values	EQ-5D from RESONATE	EQ-5D from M14-032 and M13-982 and literature-	Used utility values used in TA487[42] and TA359	EQ-5D-3L from ELEVATE-TN and literature-based values	NICE reference case and assumption

Feature	Previous NICE appraisals											Current appraisal	
	TA119[95]	TA174[38]	TA193[43]	TA202*[96]	TA216[39]	TA343[40]	TA344*[97]	TA359[41]	TA429[6]	TA487[42]	TA561[10]	Chosen values	Justification
					Study 02CLIII					based values			

1L, first line; A, acalabrutinib; B, bendamustine; BCRI-F, beta cell receptor inhibitor failure; C+O, chlorambucil + obinutuzumab; CLL, chronic lymphocytic leukemia; EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; F, fludarabine; Ibr, ibrutinib; I+R, idelalisib + rituximab; ITT, intention to treat; NICE, National Institute of Health and Care Excellence; NHS, National Health Service; NR, not reported; O, ofatumumab; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; PSS, personal social services; QALY, quality-adjusted life year; R, rituximab; R/R, relapsed/ refractory; TA, technology appraisal; TTO, time trade-off; UK, United Kingdom; V, venetoclax; V+R, venetoclax + rituximab.

*Guidance has been withdrawn because Novartis has discontinued ofatumumab.

Intervention technology and comparators

The intervention in the model is acalabrutinib monotherapy. The comparator in the model is obinutuzumab in combination with chlorambucil as, according to BSH guidelines,[4] this is the current standard of care in unfit patients (GRADE IB). Further rationale on choice of comparators can be found in section B.1 Decision problem, description of the technology and clinical care pathway. The details of the dosing used in the model can be found in Table 55.

Table 55. Treatment regimens used in the economic model

Drug	Administration	Dosing schedule	Treatment duration
Acalabrutinib	Oral (100mg capsules)	100 mg PO BID	Until disease progression or unacceptable toxicity
Obinutuzumab + chlorambucil	Obinutuzumab: IV Chlorambucil: oral	Obinutuzumab: Three doses of 1000 mg IV in the first 4-week period, one dose of 1000 mg IV every 4 weeks thereafter Chlorambucil: 0.5 mg/kg once every 2 weeks	Obinutuzumab: for a total of 6 cycles Chlorambucil: for a total of 6 cycles

BID, twice per day; IV, intravenous; PO, orally.

B.3a.3 Clinical parameters and variables

As a result of using a semi-Markov model, individual survival analyses were required for each possible transition (see Figure 17), and a competing risk analysis was used for this purpose. Given that trial data were in the form of OS and PFS, the necessary separate survival analyses were:

1. Time to progression (deaths considered censored events)
2. Time to pre-progression death (progression events considered censored events)
3. Time to death from progressed health state

The ELEVATE-TN study provided survival data up to a limited follow-up time. To apply a lifetime perspective in the cost-effectiveness analysis, extrapolation beyond the trial follow-up period was required. All data were taken from the latest 8 February 2019 data cut-off. At this time, in the acalabrutinib monotherapy and chlorambucil plus obinutuzumab arms, [redacted] and [redacted] of patients had experienced disease progression and [redacted] and [redacted] of patients had died before disease progression, respectively.

B3a.3.1 Parametric curve fitting

Survival curves for all endpoints were fitted using standard parametric models: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. None of the models included covariates for patient characteristics as demographics and baseline disease characteristics were well-balanced in the ITT population (Section B.2a Clinical effectiveness: 1L (untreated) CLL patients). Survival curves were fitted to patient level data from the ELEVATE-TN study, based on NICE Decision Support Unit (DSU) guidance.[99]

For all curves presented in the following sections, the following key criteria were applied:

- Clinical plausibility of long-term extrapolation compared to real world data
- Visual inspection of survival curve fit to KM data from the ELEVATE-TN trial
- Inspection of log-cumulative hazard plots (to assess the behaviour of the hazard over time)
- Statistical model fit, via measures such as Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC)

B3a.3.2 Pre-progression survival

The PFS endpoint from the trial were used to derive TTP and TTDeath curves by censoring death and progression events in the PFS dataset, respectively. In the model, the options listed in Table 56 are used to model TTP and TTDeath curves for acalabrutinib and relevant comparators.

Table 56. Methods used to estimate TTP and TTDeath curves for the model

Method	Description	Survival curves	Comparators
PLD from ELEVATE-TN	Direct comparison modelled using independent parametric models fitted to KM data from ELEVATE-TN	TTP TTDeath	Acalabrutinib monotherapy Chlorambucil plus obinutuzumab

KM, Kaplan-Meier; PLD, Patient-level data; TTDeath, Time to death (pre progression); TTP, Time to progression.

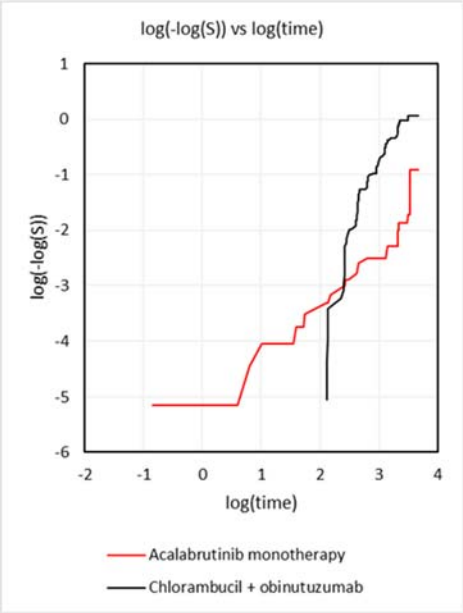
B3a.3.2.1 ELEVATE-TN

Survival data from the ELEVATE-TN trial were used to provide a head-to-head comparison between acalabrutinib monotherapy versus chlorambucil plus obinutuzumab. Survival analysis on patient level data provided the long-term extrapolations of TTP and TTDeath necessary to estimate transition probabilities over the time horizon of the model. The parametric models fitted to acalabrutinib monotherapy and chlorambucil plus obinutuzumab KM data are used to drive direct comparisons between these treatments.

Log-cumulative hazard plots were used to illustrate the spatial behaviour of hazard rate observed in ELEVATE-TN (non-monotonic hazard, monotonic hazard or constant hazards). The time trends in the log-cumulative hazard plot were used to help pre-specify the survival distributions that may be best suited to predicting hazard rates in the data, and to determine whether the assumption of proportional hazard, odds and/or accelerated failure time effects was reasonable.

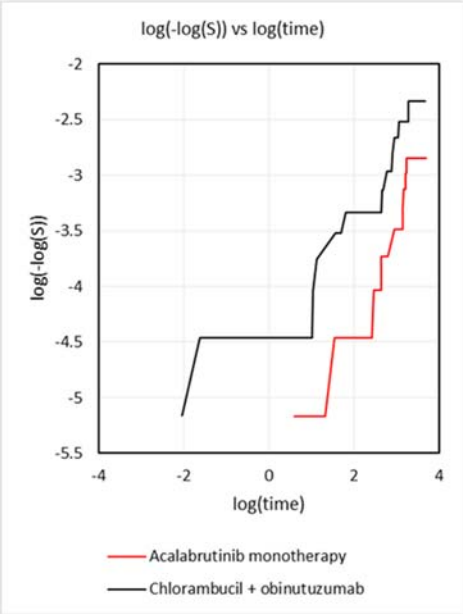
The log-cumulative hazard plots for TTP and TTDeath for acalabrutinib versus chlorambucil plus obinutuzumab are presented in Figure 20 and Figure 21, respectively. As demonstrated, a proportional treatment effect was deemed unreasonable and, as IPD were available, it was considered unnecessary to rely upon this assumption. Independent models were therefore used to generate TTP and TTDeath curves for each arm of the ELEVATE-TN study.

Figure 20. TTP log-cumulative hazard plots: acalabrutinib vs chlorambucil + obinutuzumab



S, survivor function.

Figure 21. TTDeath log-cumulative hazard plots: acalabrutinib vs chlorambucil + obinutuzumab



S, survivor function.

As the TTDeath curves for the treatments from the ELEVATE-TN trial are informed by a very low number of events (see Table 57*),* these curves are informed by general population mortality for most of the model time horizon. The TPs governing the transitions to the 'death' health state were thus implemented such that the mortality risk of the modelled population was never below the mortality risk observed in the age- and gender-matched general

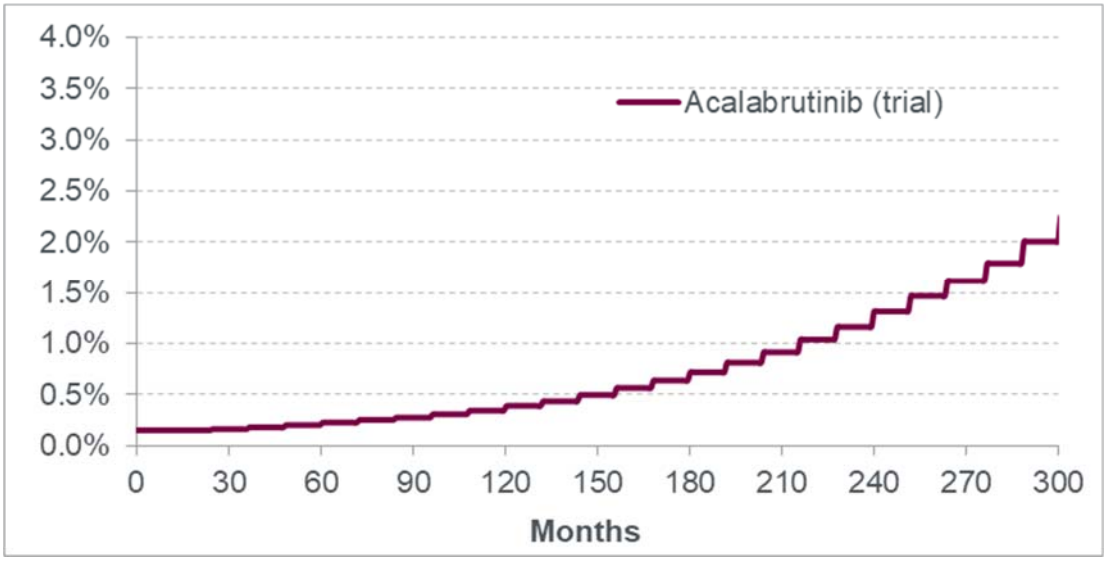
population. The mortality risks of the general population were derived from National Life Tables for the UK (q_x: death probability between age x and x+1) published by the Office for National Statistics and were applied as a competing risk for each cycle.[94] As shown in the illustrative example in Figure 22, general population mortality takes effect after ~48 months where there is a change from a smooth to stepwise increase in mortality risk.

Table 57. ELEVATE-TN OS data maturity

Arm of ELEVATE-TN	OS source	N	Number of deaths	Maturity
Acalabrutinib	ELEVATE-TN	179	[redacted]	[redacted]
Chlorambucil + obinutuzumab		177	[redacted]	[redacted]

OS, overall survival.

Figure 22. Illustrative risk of pre-progression death for acalabrutinib



B3a.3.3 Post progression survival

The model takes a cumulative approach to estimate the OS of the cohort. Initially, the cohort is assigned to the PF health state before transitioning to either the PD (using TTP), or death states (using TTDeath), and following progression, the period that patients stay alive is modelled using PPS data, which includes an adjustment for all-cause mortality. The sum of the time spent in the PF and PD health states gives the total time alive (i.e. OS) of the cohort. This approach was selected to avoid dependency on the OS endpoint from the ELEVATE-TN study as OS data were deemed too immature to provide informative long-term estimates.

The ELEVATE-TN trial was considered to inform PPS in the model. However, at the time of the latest data cut (8 February 2019), only [redacted] patients on acalabrutinib monotherapy and [redacted] on chlorambucil plus obinutuzumab had died post progression, respectively. To address the uncertainty around long-term survival of CLL patients and to reflect the subsequent treatment pathway and outcomes and costs that patients will accrue in UK clinical practice, two options to model PPS were included in the model: using OS data from RESONATE and MURANO, as described in Table 58. The OS data from the trials were extrapolated using the

methods described in Section B3a.3.1 Parametric curve fitting. For all treatments in the model, the PPS data source was chosen to align with the expected subsequent treatment.

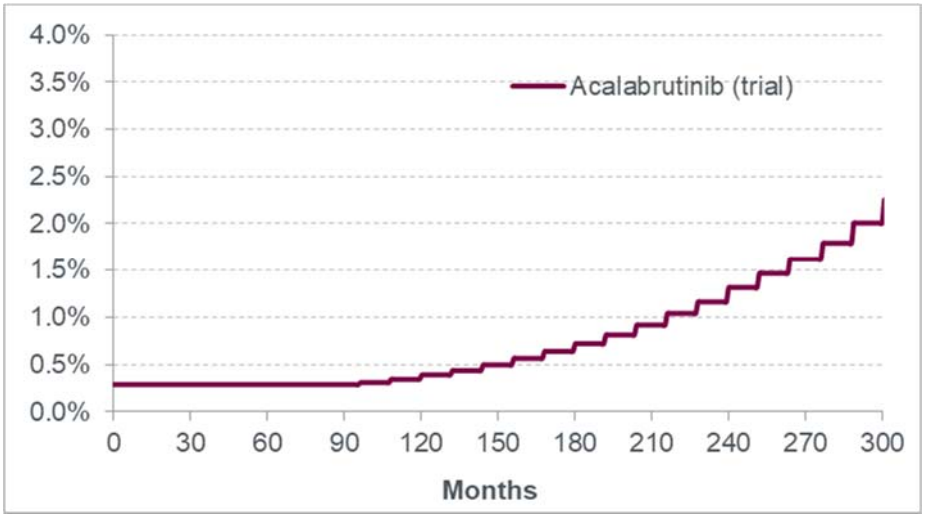
Table 58. Methods used to estimate PPS curves for the model

PPS Option	Description	Comment
RESONATE OS	PPS curves generated using published OS KM data from the RESONATE study (patients with 1-2 prior therapies only).	Assumes that patients who progress after first-line chemoimmunotherapy go on to receive ibrutinib as their subsequent therapy. Aligned with the treatment algorithm in Section B.1 Decision problem, description of the technology and clinical care pathway.
MURANO OS	PPS curves generated using published OS KM data for Venetoclax + rituximab from the MURANO study	Assumes progressed patients go on to receive venetoclax + rituximab as their subsequent therapy. Venetoclax + rituximab would only be suitable for patients who are not eligible for second line BTKi treatment. Aligned with the treatment algorithm in Section B.1 Decision problem, description of the technology and clinical care pathway.

BTKi, Bruton's tyrosine kinase inhibitor; KM, Kaplan-Meier; OS, overall survival; PPS, post-progression survival.

The PPS extrapolations are constrained by general population mortality for most of the model time horizon. As highlighted in the illustrated example in Figure 23, general population mortality risk takes effect during the time horizon of the model where the mortality risk changes from a smooth to stepwise increase.

Figure 23. Illustrative risk of pre-progression death for acalabrutinib



B3a.3.4 Base case selection: acalabrutinib vs chlorambucil + obinutuzumab

B3a.3.4.1 TTP/TTDeath

The ELEVATE-TN trial, as described in Section B.2, compared acalabrutinib monotherapy with chlorambucil plus obinutuzumab. PFS assessed by IRC was the primary endpoint in the ELEVATE-TN trial and was used to derive TTP and TTDeath curves by censoring death and progression events in the PFS dataset, respectively.

B3a.3.4.1.1 TTP (IRC): chlorambucil plus obinutuzumab

A summary of the goodness-of-fit statistics for the TTP IRC endpoint of chlorambucil plus obinutuzumab is presented in Table 59.

Table 59. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to TTP IRC data for chlorambucil + obinutuzumab

Distributions	AIC	BIC
Generalized gamma	**696.69289**	**706.22134**
Log-normal	702.0462	708.3985
Log-logistic	707.64354	713.99584
Gamma	708.21164	714.56394
Weibull	716.2533	722.6056
Gompertz	736.31625	742.66855
Exponential	773.25033	776.42648

AIC: Akaike information criterion; BIC: Bayesian information criterion; IRC, Independent review committee; TTP: Time to progression. **Best statistical fit.**

As shown in Figure 24, the statistically best fitting parametric model (generalized gamma) has a tail that is not observed in any of the other fitted curves of TTP data for chlorambucil

plus obinutuzumab. Most curves follow the KM closely for the observed period (~48 months), except for the exponential distribution. However, in the unobserved period, the exponential distribution provides the most optimistic extrapolation with more than 20% of patients predicted to be progression free at 5 years compared to <10% for all other distributions aside from the generalized gamma.

Figure 24. Parametric models overlaying the TTP IRC KM data for chlorambucil + obinutuzumab

B3a.3.4.1.2 TTDeath (IRC): chlorambucil plus obinutuzumab

A summary of the goodness-of-fit statistics for the TTDeath IRC endpoint of chlorambucil plus obinutuzumab is presented in Table 60.

Table 60. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to TTDeath IRC data for chlorambucil plus obinutuzumab

Distributions	AIC	BIC
Gamma	**163.49518**	169.84748
Weibull	163.54541	169.89771
Log-logistic	163.61865	169.97095
Exponential	164.01419	**167.19034**
Log-normal	164.23466	170.58696
Generalized gamma	165.47573	175.00418
Gompertz	165.54676	171.89906

AIC: Akaike information criterion; BIC: Bayesian information criterion; IRC, Independent review committee; TTDeath: Time to death (pre progression). **Best statistical fit.**

As shown in Figure 25, all parametric models exhibit tails with a plateau and the exponential distribution gave the most conservative estimates. In addition, visual inspection of the KM data showed little difference between the endpoints.

Figure 25. Parametric models overlaying the TTDeath IRC KM data for chlorambucil + obinutuzumab

B3a.3.4.1.3 TTP (IRC): acalabrutinib monotherapy

A summary of the goodness-of-fit statistics for the TTP IRC endpoint of acalabrutinib monotherapy is presented in Table 61.

Table 61. Statistical goodness-of-fit indicators (AIC/BIC) values for the parametric models fitted to TTP IRC of acalabrutinib monotherapy

Distributions	AIC	BIC
Exponential	**256.796706**	**259.984092**
Log-normal	257.99097	264.365742
Gompertz	258.646431	265.021203
Gamma	258.67943	265.054199
Log-logistic	258.875503	265.250275
Weibull	260.101931	266.476703
Generalized gamma	260.418569	269.980727

AIC: Akaike information criterion; BIC: Bayesian information criterion IRC, Independent review committee; TTP, Time to progression. **Best statistical fit.**

Figure 26 shows the KM and parametric survival distributions for acalabrutinib monotherapy. During the within-trial period (i.e. up to month 24), most of conventional distributions yielded an excellent fit to the KM data, but in the unobserved period (i.e. beyond month 30), the models generated different extrapolations for TTP. Landmark analysis shows that the different models predict a wide range in the percentage of patients remaining progression free after 20 years: from 0.0% for the Gompertz to 55.1% for the log-normal.

Figure 26. Parametric models overlaying the TTP IRC KM data for acalabrutinib monotherapy

B3a.3.4.1.4 TTDeath (IRC): acalabrutinib monotherapy

A summary of the goodness-of-fit statistics for the TTDeath IRC endpoint of acalabrutinib monotherapy is presented in Table 62.

Table 62. Statistical goodness-of-fit indicators (AIC/BIC) values for the parametric models fitted to TTDeath IRC of acalabrutinib monotherapy

Distributions	AIC	BIC
Exponential	**133.16834**	**136.35572**
Weibull	134.845	141.21977
Log-logistic	134.84863	141.2234
Gamma	134.84872	141.22349
Gompertz	134.88528	141.26005
Log-normal	135.01929	141.39406

AIC: Akaike information criterion; BIC: Bayesian information criterion; IRC, Independent review committee; TTDeath: Time to death (pre progression). **Best statistical fit.**

Due to the low number of death events to inform the curve, the generalised gamma did not provide a good fit for the data.

Figure 27 shows the KM and parametric survival distributions for acalabrutinib monotherapy. The Gompertz model provides the most conservative estimations, with the remaining parametric functions exhibiting tails which plateau.

Figure 27. Parametric models overlaying the TTDeath IRC KM data for acalabrutinib monotherapy

B3a.3.4.1.5 TTP/TTDeath curve selection: acalabrutinib monotherapy vs chlorambucil + obinutuzumab

The choice of baseline curves can have a large effect on the interpretability and clinical plausibility of the model and results. In order to identify the most plausible extrapolations, both the statistical fit and predicted long-term survival outputs from the model were assessed.

As mentioned earlier, in order to present a long-term PFS extrapolation, the distributions used to extrapolate TTP and TTDeath were aligned to provide a better representation of PFS. As the two distributions were aligned, it was not possible to use the generalised gamma distribution for the acalabrutinib monotherapy base case as no extrapolation was possible for TTDeath.

Statistical fit

When assessing the statistical fit of a model via AIC, a difference of less than two points is not considered meaningful.[100]

Acalabrutinib monotherapy

As shown in

Table 63, the exponential curve was the best fitting for both TTP and TTDeath and no distribution was outside of the two-AIC point threshold for both TTP and TTDeath.

Table 63. AIC values for the parametric models fitted to TTP and TTDeath for acalabrutinib monotherapy (PFS IRC)

Distributions	TTP	TTDeath
Exponential	**256.796706**	**133.16834**
Log-normal	257.99097	135.01929
Gompertz	258.646431	134.88528
Gamma	258.67943	134.84872
Log-logistic	258.875503	134.84863
Weibull	260.101931	134.845

AIC: Akaike information criterion; TTDeath: Time to death (pre progression). **Best statistical fit**

Chlorambucil plus obinutuzumab

As shown in Table 64, the best fitting TTP curve for chlorambucil plus obinutuzumab was the generalised gamma and the best fitting TTDeath curve was the gamma. The Gompertz distribution was outside of the two-AIC point threshold for both TTP and TTDeath and was not considered for the base case. As the exponential distribution and Weibull distributions were almost 80 and 20 AIC points away from the best fitting TTP curve, respectively, they were not considered to be suitable candidates to inform the base case.

Table 64: AIC values for the parametric models fitted to TTP and TTDeath for chlorambucil + obinutuzumab (PFS IRC)

Distributions	TTP	TTDeath
Generalized gamma	**696.69289**	165.47573
Log-normal	702.0462	164.23466
Log-logistic	707.64354	163.61865
Gamma	708.21164	**163.49518**
Weibull	716.2533	163.54541
Gompertz	736.31625	165.54676
Exponential	773.25033	164.01419

Abbreviations: AIC: Akaike information criterion; IRC, Independent review committee; PFS, Progression-free survival; TTDeath: Time to death (pre progression); TTP, Time to progression. **Best statistical fit.**

Clinical plausibility

Table 65 and Table 66 outline the landmark PFS and OS rates for acalabrutinib monotherapy and chlorambucil plus obinutuzumab.

Table 65. Acalabrutinib monotherapy and chlorambucil plus obinutuzumab landmark PFS rates (PFS IRC)

Function*	Treatment	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen gamma	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PPS: MURANO, exponential for acalabrutinib monotherapy

PPS: RESONATE, exponential for chlorambucil + obinutuzumab

*Same distributions modelled for TTP/TTD

IRC, Independent review committee; PFS, progression-free survival; PPS, post-progression survival

Table 66. Acalabrutinib monotherapy and chlorambucil plus obinutuzumab landmark OS rates

Function	Treatment	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen gamma	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chlo + Obin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS: MURANO, exponential for acalabrutinib monotherapy PPS: RESONATE, exponential for chlorambucil + obinutuzumab							

OS, Overall survival; PPS, post-progression survival

Acalabrutinib monotherapy

Following feedback from clinicians, it was expected that PFS with a first-line BTKi would be in line with that observed with ibrutinib in the RESONATE-2 trial where between 70-75% of patients were PF at 5 years.

Landmark PF rates are implausibly low for acalabrutinib monotherapy when using the Gompertz distribution, [redacted]. This is due to the TTP extrapolations (shown in Table 65) which predict more conservative results than the remaining curves. As the Gompertz TTP curves and PF extrapolations have little face validity, this distribution was rejected for use in the base case.

The exponential was selected for the base case following further discussions with clinical experts. The TTP extrapolations for the log-logistic and log-normal distributions were thought to be too high (optimistic), thus leaving the exponential, gamma and Weibull distributions for consideration. As the exponential distribution had the best statistical fit of the three and provided both the most stable and conservative cost-effectiveness estimates, it was selected for the base case. A scenario analysis was performed with the Weibull curve as it produced the most conservative PFS and OS extrapolations of the three curves.

Chlorambucil plus obinutuzumab

Only the log-normal, log-logistic, gamma and generalised gamma distributions were considered for the base case. While the generalised gamma was the statistically best fitting parametric model, the tail of the extrapolation was not observed in any of the other fitted curves of TTP data for chlorambucil plus obinutuzumab and lacked clinical validity: it is expected that all patients would progress on chlorambucil plus obinutuzumab during the time horizon of the analysis, and the percentage of patients progressing would not be expected to plateau.

The gamma, lognormal and log-logistic distributions produced similar survival extrapolations. As the lognormal distribution had the lower AIC value of the three options for TTP, it was selected to inform the base case. The log-logistic distribution was run as a scenario analysis.

B3a.3.4.2 PPS

Following disease progression, patients move onto subsequent therapies that are determined by the first-line treatment taken. In an advisory board, UK clinicians indicated high-risk or unfit patients on ibrutinib would commonly move on to a venetoclax-based regimen following disease progression.[3] Patients treated with acalabrutinib are expected to follow the same treatment sequence given that both ibrutinib and acalabrutinib are BTK inhibitors.

Patients treated with chlorambucil plus obinutuzumab would typically receive a BTKi post-progression (such as ibrutinib). As venetoclax-based regimens tend to be reserved for treatment post BTKi, patients that progress on second-line ibrutinib would then likely receive a venetoclax-based regimen in the third line. The majority of sequencing data supports the predominant use of venetoclax-based therapy following progression on ibrutinib.

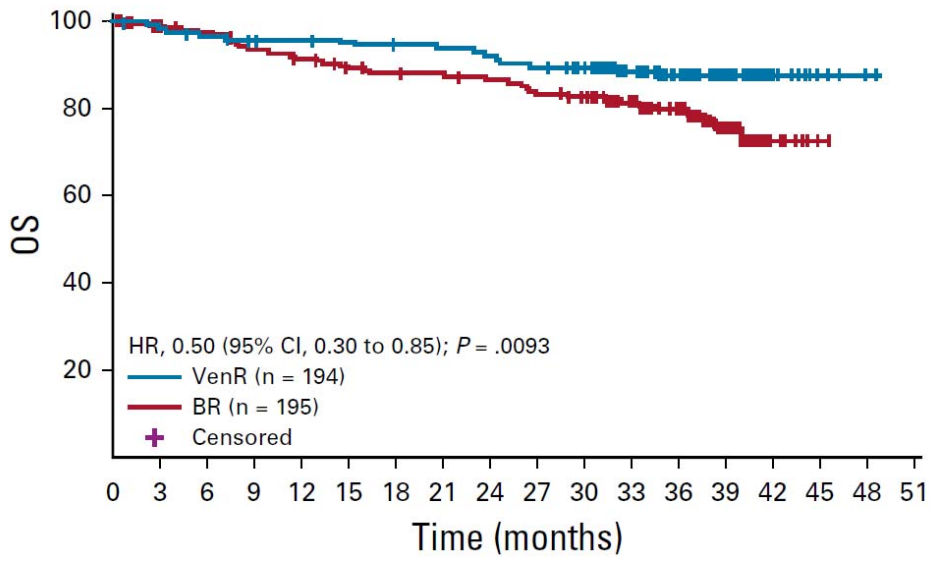
Furthermore, nine UK clinicians provided expert opinion on therapy options in the second line setting and there was group consensus that the preferred option following chlorambucil plus obinutuzumab would be either a BTKi or BCL-2i.[3]

In line with the anticipated treatment pathway for CLL patients based on clinical feedback, data from RESONATE (subsequent BTKi) and MURANO (subsequent venetoclax-based regimen) were selected to inform the PPS for chlorambucil plus obinutuzumab and acalabrutinib within the model, respectively.

B3a.3.4.2 MURANO OS (patients with 1-2 prior therapies only) for acalabrutinib

The randomised, open-label, phase 3 trial, MURANO, evaluated the efficacy of venetoclax plus rituximab therapy in the treatment of patients with R/R CLL. A total of 389 patients were randomly assigned to receive venetoclax for up to 2 years (from day 1 of cycle 1) plus rituximab for the first 6 months (venetoclax–rituximab group) or BR for 6 months (bendamustine–rituximab group).[53] MURANO OS data from the venetoclax-rituximab arm reported in Seymour from patients with 1-2 prior therapies were used as a proxy for PPS (Figure 28) for acalabrutinib. Among the 194 patients in the venetoclax + rituximab arm of the MURANO trial, 14 deaths were registered.

Figure 28. MURANO: OS with venetoclax + rituximab and bendamustine + rituximab[53]



CI, confidence interval; HR, hazard ratio; OS, overall survival.

A summary of the goodness-of-fit statistics for independent curves for the PPS endpoint is presented in Table 67.

Table 67. Statistical goodness-of-fit indicators (AIC/BIC) values for the parametric models fitted to MURANO venetoclax-rituximab arm

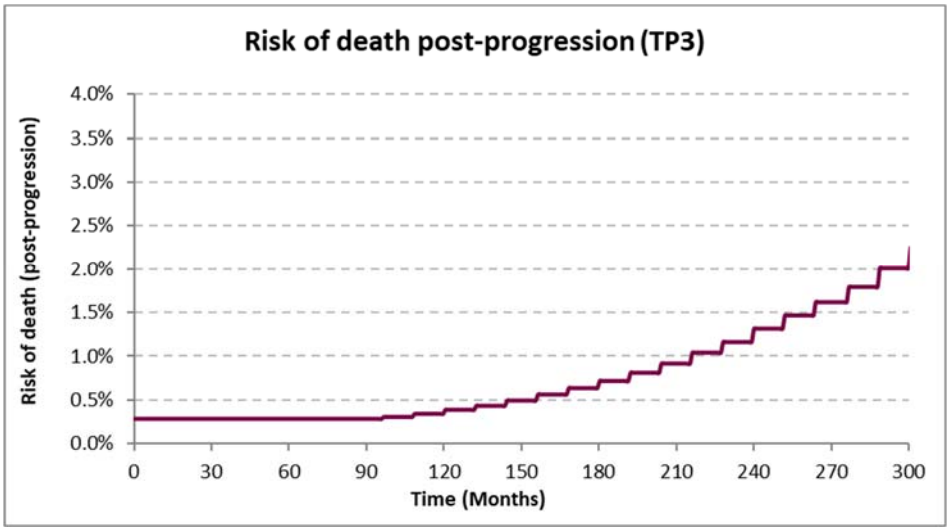
Distributions	AIC	BIC
Generalized gamma	**189.94865**	199.75223
Exponential	191.70934	**194.9772**
Log-normal	192.74138	199.2771
Gompertz	193.5885	200.12422
Log-logistic	193.62114	200.15686
Gamma	193.69103	200.22675
Weibull	193.69843	200.23415

AIC: Akaike information criterion; BIC: Bayesian information criterion. **Best statistical fit.**

The KM and parametric distributions can be seen in Figure 29. The exponential distribution was selected for the model's base case as it shows the lowest BIC (and second-lowest AIC after the generalised gamma, which was still within two AIC points).[100] The generalised gamma model was ruled out as the flat tail was deemed unrealistic. In addition, the exponential distribution was chosen for the base case as there is no strong evidence of an increasing risk before general population mortality is applied after ~90 months, as shown in Figure 30.

Figure 29. Parametric models overlaying the OS KM data for MURANO

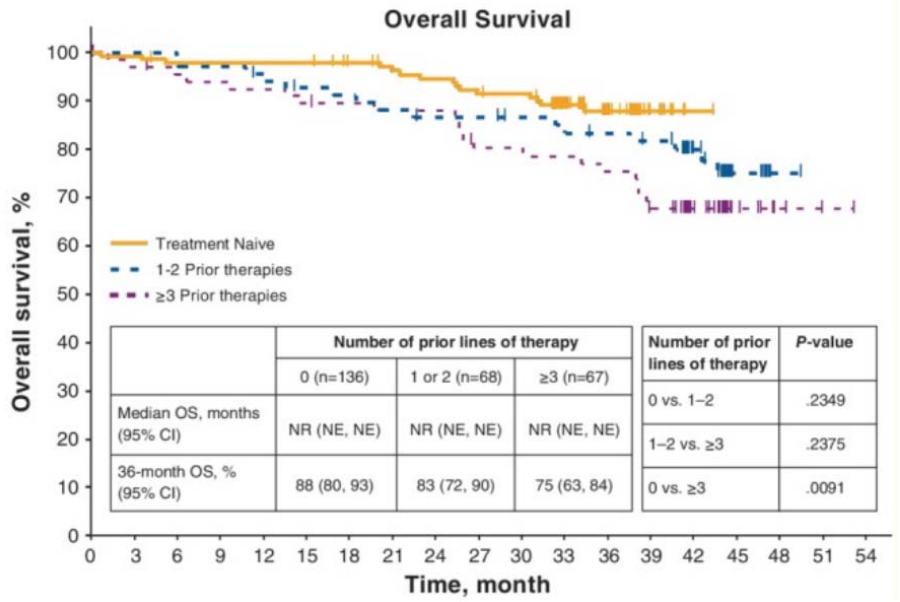
Figure 30. Risk of death post-progression with exponential curve and general population mortality as competing risks



B3a.3.4.2 RESONATE OS (patients with 1-2 prior therapies only) for chlorambucil + obinutuzumab

OS data from the ibrutinib arm of RESONATE reported in O'Brien et. al. (2019)[101] from patients with 1-2 prior therapies were used as a proxy for PPS for chlorambucil plus obinutuzumab (Figure 31). Among the 68 patients at risk, a total of 14 deaths were reported.

Figure 31. OS with ibrutinib by prior lines of therapy[101]



	Number of prior lines of therapy		
	0 (n=136)	1 or 2 (n=68)	≥3 (n=67)
Median OS, months (95% CI)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
36-month OS, % (95% CI)	88 (80, 93)	83 (72, 90)	75 (63, 84)

Number of prior lines of therapy	*P*-value
0 vs. 1–2	.2349
1–2 vs. ≥3	.2375
0 vs. ≥3	.0091

CI, confidence interval; NE, no event; NR, not reported; OS, overall survival.

A summary of the goodness-of-fit statistics for the parametric models fitted to the RESONATE OS KM data is presented in Table 68.

Table 68. Statistical goodness-of-fit indicators (AIC/BIC) values for the parametric models fitted to RESONATE (1-2 prior therapies only) ibrutinib arm

Distributions	AIC	BIC
Exponential	**175.56659**	**177.78609**
Gompertz	177.18722	181.62623
Weibull	177.28164	181.72065
Gamma	177.30062	181.73964
Log-logistic	177.3839	181.82292
Log-normal	178.00312	182.44213
Generalized gamma	179.20134	185.85986

AIC: Akaike information criterion; BIC: Bayesian information criterion. **Best statistical fit.**

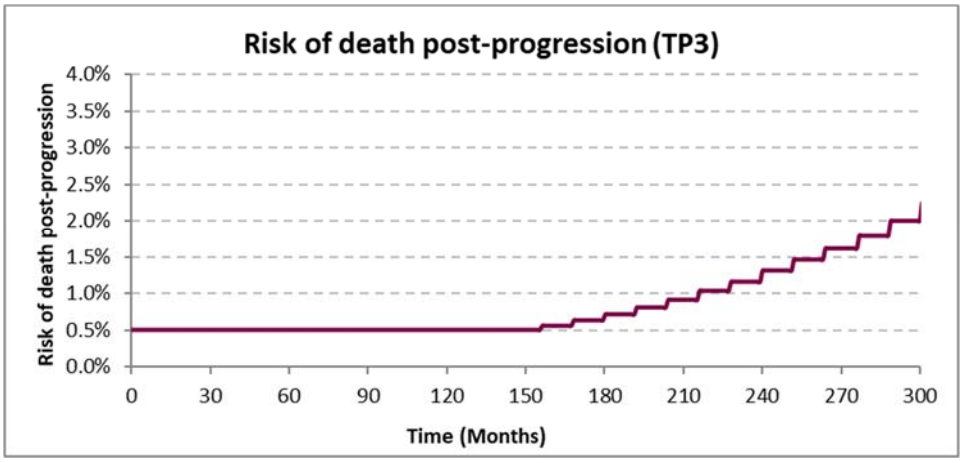
The KM and parametric distributions can be seen in Figure 32. The exponential was chosen for the base case as there is no evidence of an increasing risk before general population mortality is applied after ~150 months (Figure 33). In addition, it is the best statistically fitting distribution as it has the lowest AIC and lowest BIC.

Figure 32. Parametric models overlaying the OS KM data for RESONATE (1-2 prior therapies only)

KM, Kaplan Meier; OS, overall survival.

Figure 33 shows the risk of death post-progression implemented in the model using RESONATE PPS data.

Figure 33. Risk of death post-progression with exponential curve and general population mortality as competing risks



B3a.3.4.3 Summary of base case inputs

Table 69. Data sources and distributions used to inform base case clinical parameters

Arm	Clinical parameter	Data source	Chosen distribution
Acalabrutinib	TTP	ELEVATE-TN	Exponential
	TTDeath	ELEVATE-TN	Exponential
	PPS	MURANO OS (patients with 1-2 prior therapies only)	Exponential
Chlorambucil + obinutuzumab	TTP	ELEVATE-TN	Lognormal
	TTDeath	ELEVATE-TN	Lognormal
	PPS	RESONATE OS (patients with 1-2 prior therapies only)	Exponential

OS, Overall survival; PPS, post-progression survival; TTdeath; time to death (pre-progression); TTP, time to progression.

B.3a.4 Measurement and valuation of health effects

B.3a.4.1 Health-related quality-of-life data from clinical trials

The ELEVATE-TN study collected HRQoL data using the EQ-5D-3L. Data were collected at baseline, during the treatment phase, and during the post-treatment phase. The assessment schedule for data collection is provided in Table 70.

Table 70. PRO instruments assessment schedule until disease progression

	Screening	Treatment and Post-treatment Phase[a]		
Days		[redacted]	[redacted]	[redacted]
Study Windows	[redacted]		[redacted]	[redacted]
PRO assessments		[redacted]	[redacted]	[redacted]

PRO, patient-reported outcome; Q24W, every 24 weeks.

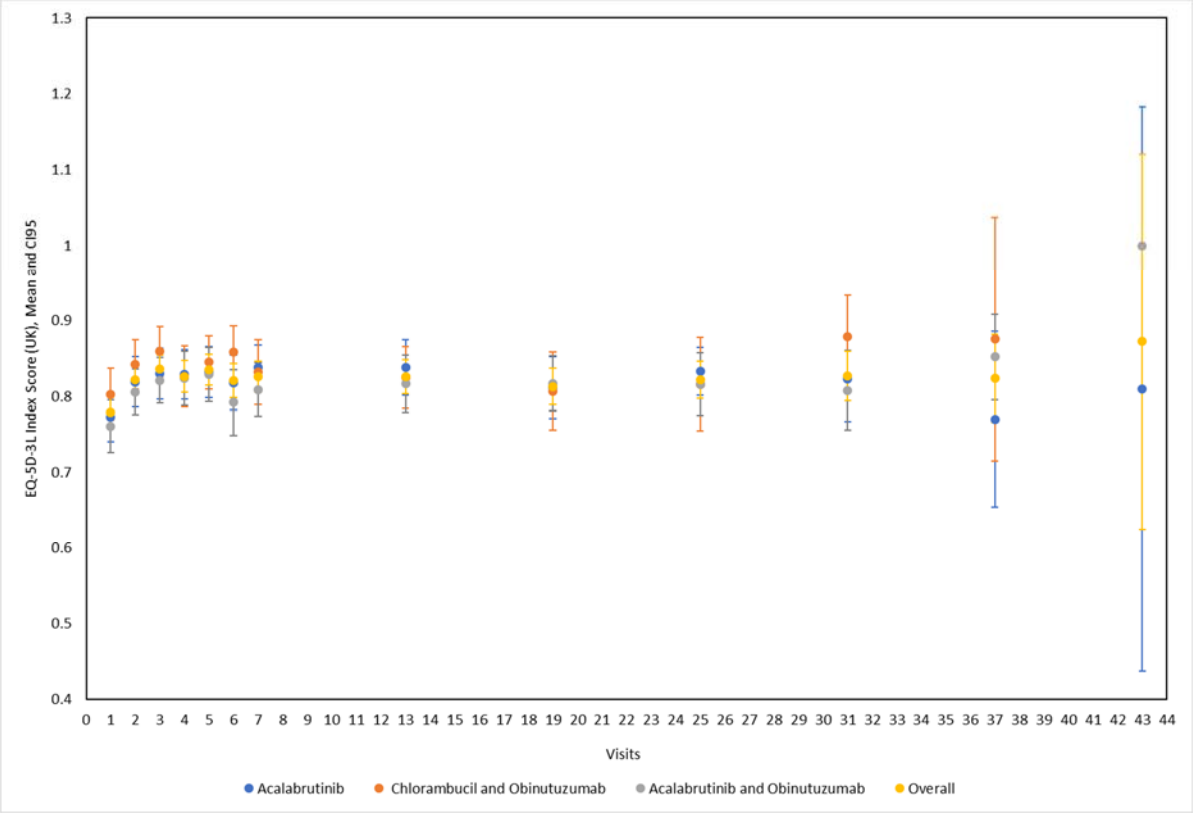
[a] There is no restriction on maximum treatment allowed with acalabrutinib. Patients who stop study treatment early because of an adverse event are to enter and early Post-treatment Phase.

[b] After Cycle 7 Day 1, PRO assessments should be collected every 24 weeks starting at Cycle 13.

The analysis of EQ-5D data was based on the ITT cohort of ELEVATE-TN. Records with a missing or invalid response on any EQ-5D domains were removed. HSUV were provided based on the societal preferences of the general population in the UK using the value sets developed for EQ-5D-3L.[102]

Descriptive statistics (number of observations, mean and standard deviation) based on observed data were calculated according to progression status, as assessed by IRC. There was no evidence of systematic differences in mean HSUV across study arms or by study visit, with overlapping 95% CI at all visits (see Figure 34). HSUV were therefore pooled across treatment groups to increase sample size in the analysis. The utility values from ELEVATE-TN are presented in Table 71.

Figure 34. EQ-5D-3L index (UK) per treatment and visit



CI, confidence interval; EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; UK, United Kingdom.

Table 71. Summary of utility values from ELEVATE-TN

Health state	Utility value: mean (SE)	95% CI
Progression free [redacted]	[redacted]	[redacted]
Progressed disease [redacted]	[redacted]	[redacted]

CI, confidence interval; SE, standard error.

The EQ-5D-3L utilities from ELEVATE-TN are within the 95% CI of the estimate for age-matched general population norm as reported in Ara and Brazier 2011 (see Table 72); the estimates for the PD health state are substantially higher than those estimated from clinical-trial-estimated HSUV used in models comparing CLL treatments (see Table 73) - potentially owing to the lack of data availability for patients with PD.

Table 72. Age/ health condition stratified mean EQ-5D scores for prevalent health conditions

Health state	Utility value: mean	95% CI
No history of health condition: 'cancer'; age band: 65 to ≤ 70	[redacted]	[redacted]

CI, confidence interval; EQ-5D, EuroQol 5-dimension.
Source: Ara et al. 2011(Table A4, supplementary appendix) [103]

B.3a.4.2 Mapping

No mapping techniques were used to estimate health-related quality-of-life data.

B.3a.4.3 Health-related quality-of-life studies

HRQoL estimates were extracted from the economic studies and health technology appraisals (HTA) appraisals on the treatment of previously untreated or R/R patients with CLL, identified in the SLR of cost-effectiveness studies. Details of the SLR are presented in Appendices G to I.

A summary of key published utility studies identified in the review and/ or included in previous HTA submissions is presented in Table 73.

Table 73. Key published utility studies identified in the review and/ or included in previous NICE technology appraisals

Health state	Value	Description	Population	NICE TA	Reference
PF	0.853	Based on clinical data from M14-032 study	R/R	487	NICE TA487[42]
	0.748	Based on clinical data from Study 119	R/R	561, 359	NICE TA359[41]
	0.800	Progression-free	R/R	359, 193	Hancock et al 2002[98]
	0.671	Progression-free; responding to treatment			Tolley et al 2013[88]
	0.394	Progression-free; not responding to treatment			
	0.820	PFS without therapy	1L	343	Kosmas et al 2015[86]
	0.710	PFS on initial therapy oral treatment	1L	343	
	0.670	PFS on initial therapy IV treatment	1L	343	
	0.799	PFS	R/R	429	NICE TA429[6]
	0.910	PFS with complete response	1L		Beusterien et al 2010[87]
	0.840	PFS with partial response	1L		
	0.780	PFS with no change	1L		
	0.710	Second-line treatment	R/R		
PD	0.680	Progressive disease	R/R	429	
	0.650	Third-line treatment	R/R		
	0.600	Progressive disease	1L and R/R	561, 487, 359, 193	Hancock et al 2002[98]

	0.214	Disease progression		NA	Tolley et al 2013[88]
	0.660	Progression after 1st line treatment	R/R	343	Kosmas et al 2015[86]
	0.550	PFS on 2nd line therapy	R/R		
	0.710	PFS without 2nd line therapy	R/R		
	0.590	Further progression	R/R		
	0.420	Relapsed treatment lines	R/R		

1L, first line; NICE, National Institute of Health and Care Excellence; PD, progressed disease; PF, progression free, PFS, progression-free survival; R/R, relapsed/ refractory; TA, technology appraisal.

B.3a.4.4 Age-related utility decrement

An age-related utility decrement was used in the model. The mean age in the ELEVATE-TN study, and so the mean age of patients starting the model, was around 70 years. As such, it is anticipated that a patient's quality of life will decline with age over the time horizon. The age-adjusted utility adjustment was implemented using the methods described in Ara et al. 2010.[92] In each model cycle, the health state utilities decrement was estimated based on the following equation:

$$HS_{utility} * (1 - (0.9508566 + 0.0212126 * (\%\, male) - 0.0002587 * age - 0.0000332 * age^2))$$

HS, health state.

The utility decrements were estimated for all patients alive (i.e. in PF and PD health states) in each model cycle and subtracted from the total QALYs accrued in a given cycle.

B.3a.4.5 Adverse reactions

The model accounts for the impact of all treatment related Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 AEs that occurred in at least 1% of patients treated with acalabrutinib monotherapy or chlorambucil + obinutuzumab. A summary of Grade ≥ 3 AEs included in the analysis is presented in

Table 74. AE incidence rates for acalabrutinib monotherapy and chlorambucil plus obinutuzumab were sourced from ELEVATE-TN.

AEs in the model have an impact on cost (patients accrue the costs associated with managing the AE) and the patient's quality of life (via utility decrements associated with each event). The costs and utility decrements resultant from AEs are applied to the proportion of patients experiencing the event in the first cycle of the model, assuming AEs would occur during the first four weeks of treatment.

Table 74. Summary of Grade ≥ 3 AEs included in the analysis

	Acalabrutinib	Chlorambucil + obinutuzumab
ALT/AST increased	0.56%	1.78%
Anaemia	6.70%	7.10%
Bleeding	1.70%	0.00%
Diarrhoea	0.56%	1.78%
Febrile Neutropenia	1.12%	5.33%
Infections and infestations	14.00%	8.30%
Infusion-related reaction	0.00%	5.33%
Neutropenia	9.50%	41.42%
Neutrophil Count Decreased	0.00%	2.96%
Thrombocytopenia	2.79%	11.83%
Tumour lysis syndrome	0.00%	7.69%
Source	**ELEVATE-TN**	**ELEVATE-TN**

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

The model accounts for quality of life loss resulting from AEs. The total decrement was estimated as incidence of each AE multiplied by the duration and disutility associated with each AE. Utility decrements associated with the AEs included in the model were sourced from previous NICE TAs and other published literature. All AE utility decrements were applied in cycle 1.

The disutility and duration estimates for AE used in the analysis is presented in Table 75.

Table 75. Disutility and duration estimates for AEs

AE	Disutility	Source	Duration (days)	Source	Comment
ALT/AST increased	-0.05	TA487[42]	20.99	TA487	
Anaemia	-0.09	TA487[42]	23.21	TA487	
Bleeding	-0.22	Wehler et al. 2018[104]	14.00	Assumption	Assumed the same as infections and infestations
Diarrhoea	-0.20	TA359[41]	3.00	TA403	Diarrhoea + Colitis disutility
Febrile Neutropenia	-0.20	TA359[41]	4.00	TA403	
Infections and infestations	-0.22	Wehler et al. 2018[104]	14.00	Assumption	Infection disutility
Infusion-related reaction	-0.20	TA487[42]	3.50	TA487	
Neutropenia	-0.16	TA487[42]	15.09	TA487	
Neutrophil Count Decreased	-0.16	TA487[42]	15.09	TA403	Assumed same as Neutropenia
Thrombocytopenia	-0.11	TA487[42]	23.21	TA487	
Tumour lysis syndrome	-0.22	Wehler et al. 2018[104]	14.00	Assumption	

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

B.3a.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

The base case analysis used the EQ-5D-3L utility value derived from the ELEVATE-TN study for the PF health state. This was considered the most robust and applicable source of utility data for this population, as they were directly collected in patients with previously untreated CLL, are aligned with age-matched general population norms as reported in Ara and Brazier 2011[103] and represent the fact that 94.4% of patients in ELEVATE-TN have a good PS (ECOG PS 0-1).

In ELEVATE-TN, the PD HSUVs were generated using a limited number of observations and hence lack face validity. As such, a PD utility value of 0.6 sourced from Holzner et al. was used in the base case. In this study, Holzner et al.[30] measured quality of life using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and the Functional Assessment of Cancer Therapy (FACIT): General questionnaire in 418 cancer patients, 81 of whom had CLL. The data were then used to give a general indication of reasonable utility values for CLL. This utility value was selected for the base case as it has been accepted in previous NICE submissions. [6] [41] The difference between the two health states represents the reduction in HRQoL related to disease progression, which leads to increased anxiety and symptom burden.

The utilities used in the base case analysis are presented in Table 76.

Table 76. Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% confidence interval
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

B.3a.5 Cost and healthcare resource use identification, measurement and valuation

Please refer to Appendix I for details on how relevant cost and healthcare resource data were identified for use in the model. The cost categories included in the model were:

- Treatment-related costs
    - Drug acquisition costs (including subsequent treatments)
    - Drug administration costs (including subsequent treatments)
    - Costs associated with treatment-related AEs
- Disease-management costs
- End-of-life costs

B.3a.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs were based on the dosing regimens presented in Table 77 and unit costs presented in Table 78. Acquisitions costs were applied in the model each cycle and for each treatment until either progression or the maximum number of administrations had been reached, whichever occurred first.

Table 77. Dosing information of therapies included in economic analysis

Treatment	Dosing regimen, administration method and number of cycles	Reference
Acalabrutinib	• Acalabrutinib: Dose of 100 mg administered orally twice daily until disease progression	AstraZeneca, ACE-CL-007 CSR[75]
Chlorambucil + obinutuzumab	• Chlorambucil: Dose of 0.5 mg/kg administered orally once every two weeks for a maximum of 6 cycles • Obinutuzumab: Three doses of 1000 mg IV in the first 4-week period, one dose of 1000 mg IV every 4 weeks for a further 5 administrations	
Ibrutinib *(Subsequent treatment)*	• Ibrutinib: 420 mg administered orally once daily until disease progression	Ibrutinib SmPC[105]
Venetoclax + rituximab *(Subsequent treatment)*	• Venetoclax: Dose of 400 mg administered orally once daily for a total of two years • Rituximab: first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 IV on day 1 of each cycle for a maximum of 6 cycles	Seymour et al 2018[53]

CSR, clinical study report; IV, intravenous; SmPC, summary of product characteristics.

Unit costs were sourced from the British National Formulary (BNF)[106] and drugs and pharmaceutical electronic market information tool (eMIT).[107] In instances where multiple pack prices were available, the pack price with the lowest cost per mg was used. The unit costs used in the analysis are presented in Table 78. The cost per cycle applied in the analysis for acalabrutinib and other therapies is presented in Table 79.

[redacted]

Table 78. Unit costs for therapies

Treatment	Formulation	Units per pack	Cost per pack / vial
Acalabrutinib	100 mg	60	[redacted]
Obinutuzumab	1000 mg	1	£3,312.00
Chlorambucil	2 mg	24	£42.87
Ibrutinib	420 mg	28	£4,292.40

Treatment	Formulation	Units per pack	Cost per pack / vial
Venetoclax	100	112	£4,798.47
Rituximab	500 mg	1	£785.84

Table 79. Drug acquisition costs

Treatment	Cost per cycle (28 days)
Acalabrutinib	[redacted] (Until progression)†
Chlorambucil + obinutuzumab	£10,003.73 (cycle 0) £3,397.73 (cycles 1-5)
Ibrutinib	£4,292.40 (Until progression)
Venetoclax + rituximab	£6,244.05 (For the first 6 cycles) £4,789.47 (cycles 7-12)

† [redacted] is equivalent to the acquisition cost for a 28-day cycle

Drug administration cost

Administration costs are applied for all treatments administered via IV; oral therapies were assumed to incur no administration costs. Unit costs for IV administration were based on NHS reference cost code SB12Z (total healthcare resource groups [HRGs], cost of administering simple chemotherapy;[108] this is aligned to assumptions made in previous NICE technology appraisals and accepted by the respective committees. A summary of the drug-related administration costs is presented in Table 80.

Table 80. Summary of drug-related administration costs

Treatment		Unit cost (per administration)	Administrations per cycle	Total cost per cycle
Acalabrutinib		£0.00	56	£0.00
Chlorambucil + obinutuzumab	Chlorambucil	£0.00	2	£228.29*
	Obinutuzumab	£228.29	3 in cycle 1 followed by 1 per cycle up to cycle 6	
Ibrutinib (subsequent treatment)		£0.00	28	£0.00
Venetoclax + rituximab (subsequent treatment)	Venetoclax	£0.00	28	£228.29*
	Rituximab	£228.29	1	

*For the first six cycles of the analysis.

Subsequent treatment costs

The analysis accounts for the costs of a subsequent treatment line after progression on a first-line therapy. These costs were estimated according to the distribution of progressed patients across different subsequent treatment options and considering the duration of each subsequent therapy.

As discussed in Section B3a.3.4.2 PPS, it was assumed that patients who receive acalabrutinib as their first-line treatment will receive venetoclax plus rituximab as their subsequent treatment. This is complemented with PPS survival from the MURANO trial. Patients who receive chlorambucil plus obinutuzumab as their first-line treatment will receive ibrutinib as their subsequent therapy, coupled with PPS survival from the RESONATE trial.

Table 81 presents a summary of the subsequent treatment regimens assumed in the base case analysis. The selection of subsequent therapies is aligned with the treatment pathway in the UK and has been validated by UK clinicians (see section B1).

Table 81: Subsequent treatment regimens by first-line treatment option

Subsequent treatment → **First-line treatment ↓**	**Ibrutinib**	**Venetoclax + rituximab**
Acalabrutinib monotherapy	0%	100%
Chlorambucil + obinutuzumab	100%	0%

The model tracks the survival of each cohort of patients entering the PD health state each cycle. Subsequent treatment costs were estimated as follows:

- Per cycle costs (and 1st cycle) for each subsequent treatment were estimated (see Table 79)
- The per cycle costs for fixed-duration subsequent treatment were applied for the defined duration or up until death, whichever occurred first. (Table 82)
- Total subsequent costs per cycle were calculated as a weighted average using the per cycle costs and the distribution of subsequent treatments (see Table 84)
- Using the tunnel states (i.e. survival for the cohort of progressed patients in each model cycle), the per cycle subsequent treatment costs were accrued by the proportion of patients alive in each cycle post progression (for the defined duration of each therapy)

To reflect the delay between disease progression and initiation of subsequent treatment, a treatment-free interval was incorporated into the model. The base case estimate was [redacted], which was estimated as the difference in median PFS (22.6 months) and median time to next treatment (TTNT) ([redacted]) in the chlorambucil plus obinutuzumab arm of ELEVATE-TN, rounded to the nearest integer. The data from the chlorambucil plus obinutuzumab arm was used for both acalabrutinib chlorambucil plus obinutuzumab, as the median was not reached in the acalabrutinib arm. This is judged to be a conservative assumption for the acalabrutinib arm, as the costs of subsequent therapy are likely to be incurred at a significantly later time than in the chlorambucil plus obinutuzumab arm. Median TTNT was not reached in the chlorambucil plus obinutuzumab arm; however, at [redacted] months, the KM estimate was [redacted] and was judged to provide an adequate proxy.

Subsequent treatment duration

The per cycle costs for each subsequent treatment were applied for the defined duration or up until death, whichever occurred first. The maximum defined duration for each subsequent therapy was either taken from the relevant SmPC or clinical expert opinion (see Table 82).

Table 82. Duration of subsequent treatments

		Treatment duration (cycles)	Comment
Ibrutinib		Maximum of 130 cycles (120 months)	UK clinical expert opinion
Venetoclax + rituximab	Venetoclax	26.0	SmPC
	Rituximab	6.0	SmPC

SmPC, summary of product characteristics

B.3.a.5.2 Health-state unit costs and resource use

The costs of disease management and patient follow-up in the model were calculated through a micro-costing approach where resource use (the number of occasions a component of care was accessed in a cycle) was multiplied by the unit cost for each resource item. The resource use data assigned to the PF and PD states were sourced from the recent NICE TA of venetoclax plus rituximab in the treatment of previously treated CLL (TA561). Unit costs were based on NHS reference costs.[108] Table 83 presents the resource use, unit costs and costs per cycle for the PF health state; Table 84 presents the equivalent information for the PD health state.

Table 83. PF health state costs and resource use

Resource	Use per cycle	Unit cost	NHS reference costs, year 2017-18 currency description	Cost per cycle
Full blood count	0.31	£2.51	DAPS05	£0.77
LDH	0.23	£1.11	DAPS04	£0.26
Haematologist visit	0.15	£159.65	Outpatient attendances: 303 – Clinical Haematology	£24.48
Total				**£25.50**

LDH, lactate dehydrogenase; NHS, National Health Service; PF, progression-free.

Table 84. PD health state costs and resource use

Resource	Use per cycle	Unit cost	NHS reference costs, year 2017-18 currency description	Cost per cycle
Full blood count	0.61	£2.51	DAPS05	£1.54
Chest X-ray	0.15	£77.48	Imaging: Direct Access – RD50Z	£11.88
Bone marrow exam	0.08	£495.98	Diagnostic Bone Marrow Extraction – SA33Z	£38.02
Haematologist visit	0.46	£159.65	Outpatient attendances: 303 – Clinical Haematology	£73.43
Inpatient visit (Non-surgical)	0.31	£432.93	Weighted average of day case SA32A, SA32B, SA32C and SA32D	£132.75
Full blood transfusion	0.84	£187.97	Outpatient attendances: 303 – Clinical Haematology: Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over – SA44A	£158.51
Total				**£416.13**

DAP, directly accessed pathology services; NHS, National Health Service; PD, progressed disease.

B.3a.5.3 Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the analysis and modelled via the incidence of Grade ≥ 3 AEs that occurred in at least 1% of patients. As outlined previously, the costs of AEs were included as one-off costs at the start of the model. The total cost was calculated as the product of the AE incidence (see

Table 74) and the respective unit cost. The unit costs for AE management are presented in Table 85. AE management costs were estimated using resource use and unit cost sources/estimates agreed to in previous NICE technology appraisals in CLL. If references are not available, the unit costs presented in the TA were inflated to 2019 values using the Hospital and Community Health Services Index.[109]

Table 85. Unit costs for AE management

Adverse event	Cost	Source	Comment
ALT/AST increased	£0.00	TA561[10]	Assumption of no cost based on TA561
Anaemia	£366.00	National schedule of reference costs (2017-18)	Currency code: SA04L. Resource use TA487[42]
Bleeding	£1,783.94	TA487[42]	Assumed to be the same as for infections
Diarrhoea	£149.00	National schedule of reference costs (2017-18)	Outpatient attendances: 301. Resource use from TA359[41]
Febrile Neutropenia	£6,623.14	TA487[42]	Reported cost inflated to 2019 (£)
Infections and infestations	£1,783.94	National schedule of reference costs (2017-18)	Activity weighted average (DZ11K – DZ11V) cost for pneumonia. Resource use from TA487
Infusion-related reaction	£0.00	TA487[42]	Assumption of no cost based on TA487[42]
Neutropenia	£136.34	TA487[42]	Reported cost inflated to 2019 (£)
Neutrophil Count Decreased	£136.34	TA487[42]	Assumed to be the same cost as for neutropenia
Thrombocytopenia	£640.09	National schedule of reference costs (2017-18)	Activity weighted average (SA12G – SA12K)
Tumour lysis syndrome	£1,226.80	TA487[42]	Reported cost inflated to 2019 (£)

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TA, technology appraisal.

B.3a.5.4 Miscellaneous unit costs and resource

End-of-life costs

The cost of end-of-life care are applied as a one-off cost to each death event in the model. The cost of end-of-life care was sourced from Round, Jones and Morris 2015[110], identified from the manufacturer submissions for TA429 and TA561, and estimated the direct and indirect cost for lung, breast, colorectal and prostate patients at the end of life in England and Wales. The end-of-life care cost applied in the analysis is £6,975.

B.3a.6 Summary of base-case analysis inputs and assumptions

B.3a.6.1 Summary of base-case analysis inputs

A summary of the key variables applied in the economic model (base case) is presented in Table 86.

Table 86. Summary of variables applied in the economic model

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Perspective	Payer	N/A	B.3a.2 Economic analysis
Time horizon	30	N/A	
Proportion females	38%	Not modelled	
Starting age in model (years)	70	Not modelled	
Body weight (kg)	79	Not modelled	
Body surface area (m^2)	1.93	Not modelled	
Discount rate (costs)	3.5%	N/A	
Discount rate (outcomes)	3.5%	N/A	
Clinical parameters			
Efficacy parameters			
TTdeath distribution – A	Exponential	Multivariate normal	B.3a.3 Clinical parameters and variables
TTdeath distribution – C+O	Log-normal	Multivariate normal	
TTP distribution – A	Exponential	Multivariate normal	
TTP distribution – C+O	Log-normal	Multivariate normal	
PPS data – A	MURANO	N/A	
PPS data – C+O	RESONATE	N/A	
PPS distribution – A	Exponential	Multivariate normal	
PPS distribution – C+O	Exponential	Multivariate normal	
Probability of adverse events – A			
ALT/AST increased	0.56%	SE: 0.0011 (beta)	B.3a.3 Clinical parameters and variables
Anaemia	6.70%	SE: 0.0134 (beta)	
Bleeding	1.70%	SE: 0.0034	
Diarrhoea	0.56%	SE: 0.0011 (beta)	
Febrile Neutropenia	1.12%	SE: 0.0022 (beta)	
Infections and infestations	14.00%	SE: 0.0280 (beta)	
Infusion-related reaction	0.00%	NA	
Neutropenia	9.50%	SE: 0.0190 (beta)	
Neutrophil Count Decreased	0.00%	NA	
Thrombocytopenia	2.79%	SE: 0.0056 (beta)	
Tumour lysis syndrome	0.00%	NA	
Probability of adverse events – C+O			

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
ALT/AST increased	1.78%	SE: 0.0036 (beta)	B.3a.3 Clinical parameters and variables
Anaemia	7.10%	SE: 0.0142 (beta)	
Bleeding	0.00%	NA	
Diarrhoea	1.78%	SE: 0.0036 (beta)	
Febrile Neutropenia	5.33%	SE: 0.0107 (beta)	
Infections and infestations	8.30%	SE: 0.0166 (beta)	
Infusion-related reaction	5.33%	SE: 0.0107 (beta)	
Neutropenia	41.42%	SE: 0.0828 (beta)	
Neutrophil Count Decreased	2.96%	SE: 0.0059 (beta)	
Thrombocytopenia	11.83%	SE: 0.0237 (beta)	
Tumour lysis syndrome	7.69%	SE: 0.0154 (beta)	
Duration of adverse events (days)			
ALT/AST increased	20.99	SE: 4.1975 (Gamma)	B.3a.4 Measurement and valuation of health effects
Anaemia	23.21	SE: 4.6416 (Gamma)	
Bleeding	14.00	SE: 2.8000 (Gamma)	
Diarrhoea	3.00	SE: 0.6000 (Gamma)	
Febrile Neutropenia	4.00	SE: 0.8000 (Gamma)	
Infections and infestations	14.00	SE: 2.8000 (Gamma)	
Infusion-related reaction	3.50	SE: 0.6996 (Gamma)	
Neutropenia	15.09	SE: 3.0173 (Gamma)	
Neutrophil Count Decreased	15.09	SE: 3.0173 (Gamma)	
Thrombocytopenia	23.21	SE: 4.6416 (Gamma)	
Tumour lysis syndrome	14.00	SE: 2.8000 (Gamma)	
Health-related quality of life			
Utility parameters			
PFS	[redacted]	[redacted]	B.3a.4 Measurement and valuation of health effects
PD	[redacted]	[redacted]	
Disutility parameters			
Age-related decrement	Incorporated from Ara et al. 2010	Not modelled	B.3a.4 Measurement and valuation of health effects
ALT/AST increased	-0.050	SE: 0.0100 (beta)	
Anaemia	-0.090	SE: 0.0180 (beta)	
Bleeding	-0.218	SE: 0.0436 (beta)	
Diarrhoea	-0.200	SE: 0.0400 (beta)	
Febrile Neutropenia	-0.200	SE: 0.0400 (beta)	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Infections and infestations	-0.218	SE: 0.0436 (beta)	
Infusion-related reaction	-0.200	SE: 0.0400 (beta)	
Neutropenia	-0.163	SE: 0.0326 (beta)	
Neutrophil Count Decreased	-0.163	SE: 0.0326 (beta)	
Thrombocytopenia	-0.108	SE: 0.0216 (beta)	
Tumour lysis syndrome	-0.218	SE: 0.0436 (beta)	
Costs			
Disease management costs and resource use			
PF: full blood count	0.31 per 28 days	SE: 0.0613 (beta)	B.3.a.5.2 Health-state unit costs and resource use
PF: LDH	0.23 per 28 days	SE: 0.0460 (beta)	
PF: haematologist visit	0.15 per 28 days	SE: 0.0307 (beta)	
PD: full blood count	0.61 per 28 days	SE: 0.1227 (beta)	
PD: chest X-Ray	0.15 per 28 days	SE: 0.0307 (beta)	
PD: bone marrow exam	0.08 per 28 days	SE: 0.0153 (beta)	
PD: haematologist visit	0.46 per 28 days	SE: 0.0920 (beta)	
PD: inpatient visit (non-surgical)	0.31 per 28 days	SE: 0.0613 (beta)	
PD: full blood transfusion	0.84 per 28 days	SE: 0.1687 (beta)	
Full blood count unit cost	£2.51	Fixed	
LDH unit cost	£1.11	Fixed	
Haematologist visit unit cost	£159.65	Fixed	
Chest X-Ray unit cost	£77.48	Fixed	
Bone marrow exam unit cost	£495.98	Fixed	
Inpatient visit (non-surgical) unit cost	£432.93	Fixed	
Full blood transfusion unit cost	£187.97	Fixed	
End of life care			
End of life care cost (one-off)	£6,975.00	Not modelled	B.3.a.5.2 Health-state unit costs and resource use
% patients who receive EoL care	100.00%	SE: 0.20000 (beta)	
Adverse event costs			
ALT/AST increased	£0.00	Fixed	B.3.a.5.2 Health-state unit costs and resource use
Anaemia	£366.00	Fixed	
Bleeding	£1,783.94	Fixed	
Diarrhoea	£149.00	Fixed	
Febrile Neutropenia	£6,623.14	Fixed	
Infections and infestations	£1,783.94	Fixed	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Infusion-related reaction	£0.00	Fixed	
Neutropenia	£136.34	Fixed	
Neutrophil Count Decreased	£136.34	Fixed	
Thrombocytopenia	£640.09	Fixed	
Tumour lysis syndrome	£1,226.80	Fixed	
Acquisition cost			
Acalabrutinib pack cost (60 x 100mg)	[redacted]	Fixed	B.3.a.5.2 Health-state unit costs and resource use
Obinutuzumab vial cost (1 x 1000mg)	£3,312.00	Fixed	
Chlorambucil pack cost (25 x 2mg)	£42.87	Fixed	
Subsequent treatment cost			
Ibrutinib pack cost (28 x 420mg)	£4,292.40	Fixed	B.3.a.5.2 Health-state unit costs and resource use
Rituximab vial cost (1 x 500mg/m^2)	£785.84	Fixed	
Venetoclax pack cost (100 x 112mg)	£4,789.47	Fixed	
Treatment administration and monitoring cost			
Administration (per infusion; IV)	£228.29	Fixed	B.3.a.5.2 Health-state unit costs and resource use
Subsequent treatment duration			
Ibrutinib subsequent treatment duration	RESONATE; capped to 130 cycles	Fixed	B.3.a.5.2 Health-state unit costs and resource use
Rituximab subsequent treatment duration	6.00 cycles	Fixed	
Venetoclax subsequent treatment duration	26.00 cycles	Fixed	
Distribution of subsequent treatments			
Acalabrutinib monotherapy			
Venetoclax + rituximab	100%	Fixed	
Chlorambucil + obinutuzumab			
Ibrutinib	100%	Fixed	B.3.a.5.2 Health-state unit costs and resource use

A, acalabrutinib; A+O, acalabrutinib + obinutuzumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BR, bendamustine + rituximab; C+O, chlorambucil + obinutuzumab; CI, confidence interval; EoL, end of life; IR, idelalisib + rituximab; ITT, intent to treat; IV, intravenous; LDH, lactate dehydrogenase; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; SE, standard error; TLS, tumour lysis syndrome; TTdeath, time to pre-progression death; TTP, time to progression.

B.3a.6.2 Assumptions

A summary of the model assumptions is presented in Table 87.

Table 87. Summary of key assumptions in the model

Model input	Assumption	Rationale
Time horizon	30 years	As per NICE guidance, a lifetime model (assumed to 30 years' time horizon given the age of the modelled cohort) was used.
PPS data source for acalabrutinib	MURANO venetoclax plus rituximab OS data (patients with 1-2 prior therapies only) was used to inform post-progression survival for patients in the acalabrutinib arm	Patients progressing on a BTKi, would typically be ineligible for a BTKi in the second line. UK clinicians have indicated there is a preference for treating with a BTKi prior to treating with venetoclax plus rituximab. See Section B1.
PPS data source for C+O	RESONATE ibrutinib OS data (patients with 1-2 prior therapies only) was used to inform post-progression survival for patients in the C+O arm	PPS from RESONATE was utilized for the chlorambucil + obinutuzumab as it represents survival in a population treated with a BTKi in second line, which is typical after treatment with chlorambucil + obinutuzumab. See Section B1.
Health state utility values	No difference in HSUVs by treatment arm Progressed disease health state was sourced from the literature	Based on the ELEVATE-TN study, the summary statistics showed no evidence of a meaningful difference in the HSUV scores of patients across treatment arms In ELEVATE-TN, the PD HSUVs were generated using a limited number of observations and hence lack face validity. As such, a PD utility value of 0.6 sourced from Holzner et al. was used, which has been previously accepted in NICE appraisals
Monitoring	Equivalent monitoring across treatment arms	Assumed that patients will be monitored in the same fashion regardless of treatment option
Treatment duration	Patients are treated until progression	Treatment duration is informed by PFS and hence patients are treated until progression
Administration costs	No administration costs for oral regimens	Regimens administered orally can be taken by patients at

Model input	Assumption	Rationale
		home. It is assumed that no costs are incurred
End of life care cost	Inclusion of end of life care cost	Reflects costs borne by the NHS/PSS. The model assumes that patients will receive end-of-life care within the NHS and accrue a one-off cost on each death event

C+O, chlorambucil + obinutuzumab; HSUV, health-state utility values; NICE, National Institute for Health and Clinical Care; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSS, Personal and Social Services; UK, United Kingdom.

B.3a.7 Base-case results

B.3a.7.1 Base-case incremental cost-effectiveness analysis results

Total costs, life years, QALYs, and incremental cost per QALY gained for acalabrutinib versus chlorambucil plus obinutuzumab are presented in Table 88. Acalabrutinib monotherapy was associated with [redacted] additional QALYs and [redacted] additional costs. As such, the incremental cost-effectiveness ratio for acalabrutinib monotherapy versus chlorambucil + obinutuzumab was [redacted].

Table 88. Base-case results (A vs C+O)

Technologies	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
C+O	[redacted]	[redacted]	[redacted]	-	-	-	-
A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A, acalabrutinib; C+O, chlorambucil + obinutuzumab; ICER, incremental cost-effectiveness ratio; LYs, life-years gained; QALY, quality-adjusted life-year.

B.3a.8 Sensitivity analyses

B.3a.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the parametric uncertainty associated with the base-case model results. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved.

The PSA was run for 1,000 iterations for the base-case analyses. Results from the PSA are presented in Table 89.

Table 89. Average results based on the probabilistic sensitivity analysis (1,000 iterations)

Technologies	Total			Incremental			ICER
	Costs	Lys	QALYs	Costs	LYs	QALYs	
C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A, acalabrutinib; C+O, chlorambucil + obinutuzumab; ICER, incremental cost-effectiveness ratio; LYs, life-years gained; QALY, quality-adjusted life-year.

The cost-effectiveness planes and acceptability curves for acalabrutinib versus chlorambucil + obinutuzumab are presented in Figure 35 and Figure 36 respectively.

Figure 35. Cost-effectiveness plane for A versus C+O

A, acalabrutinib; C+O, chlorambucil + obinutuzumab; PSA, probabilistic sensitivity analysis.

Figure 36. Cost-effectiveness acceptability curve for A vs C+O

A, acalabrutinib; C+O, chlorambucil + Obinutuzumab.

B.3a.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted by varying model parameters between the upper and lower 95% CIs of the expected values used in the deterministic base case, or by ±20% if a CI was not available.

The parameters included in the deterministic analyses are presented in Table 90. The results of the deterministic sensitivity analyses for the top ten parameters are presented in the figure below.

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Table 90. Parameters included in the DSA and respective lower and upper values

Parameter	Lower	Base case	Upper
Cost of adverse event – ALT/AST increased	0.00	0.00	0.00
Cost of adverse event – Anemia	292.80	366.00	439.20
Cost of adverse event – Bleeding	1427.15	1783.94	2140.73
Cost of adverse event – Diarrhea	119.20	149.00	178.80
Cost of adverse event – Febrile Neutropenia	5298.51	6623.14	7947.77
Cost of adverse event – Infections and infestations	1427.15	1783.94	2140.73
Cost of adverse event – Infusion-related reaction	0.00	0.00	0.00
Cost of adverse event – Neutropenia	109.07	136.34	163.60
Cost of adverse event – Neutrophil Count Decreased	109.07	136.34	163.60
Cost of adverse event – Thrombocytopenia	512.07	640.09	768.11
Cost of adverse event – Tumor lysis syndrome	981.44	1226.80	1472.16
ALT/AST increased - Acalabrutinib (trial)	0.00	0.01	0.01
Anemia – Acalabrutinib (trial)	5.4%	6.7%	8.0%
Bleeding – Acalabrutinib (trial)	1.4%	1.7%	2.0%
Diarrhea – Acalabrutinib (trial)	0.4%	0.6%	0.7%
Febrile Neutropenia – Acalabrutinib (trial)	0.9%	1.1%	1.3%
Infections and infestations – Acalabrutinib (trial)	11.2%	14.0%	16.8%
Infusion-related reaction – Acalabrutinib (trial)	0.0%	0.0%	0.0%
Neutropenia – Acalabrutinib (trial)	7.6%	9.5%	11.4%
Neutrophil Count Decreased – Acalabrutinib (trial)	0.0%	0.0%	0.0%
Thrombocytopenia – Acalabrutinib (trial)	2.2%	2.8%	3.4%
Tumor lysis syndrome – Acalabrutinib (trial)	0.0%	0.0%	0.0%
ALT/AST increased – Chlorambucil + Obinutuzumab	1.4%	1.8%	2.1%
Anemia – Chlorambucil + Obinutuzumab	5.7%	7.1%	8.5%
Bleeding – Chlorambucil + Obinutuzumab	0.0%	0.0%	0.0%
Diarrhea – Chlorambucil + Obinutuzumab	1.4%	1.8%	2.1%
Febrile Neutropenia – Chlorambucil + Obinutuzumab	4.3%	5.3%	6.4%

Parameter	Lower	Base case	Upper
Infections and infestations – Chlorambucil + Obinutuzumab	6.6%	8.3%	10.0%
Infusion-related reaction – Chlorambucil + Obinutuzumab	4.3%	5.3%	6.4%
Neutropenia – Chlorambucil + Obinutuzumab	33.1%	41.4%	49.7%
Neutrophil Count Decreased – Chlorambucil + Obinutuzumab	2.4%	3.0%	3.6%
Thrombocytopenia – Chlorambucil + Obinutuzumab	9.5%	11.8%	14.2%
Tumor lysis syndrome – Chlorambucil + Obinutuzumab	6.2%	7.7%	9.2%
Health state utilities – Progression free	[redacted]	[redacted]	[redacted]
Health state utilities – Progressed disease	[redacted]	[redacted]	[redacted]
Terminal care / end of life costs – SUM	5580.00	6975.00	8370.00
Drug free period between 1L progression and 2L (cycles):	11.20	14.00	16.80
Disutility from adverse event – ALT/AST increased	-0.04	-0.05	-0.06
Disutility from adverse event – Anemia	-0.07	-0.09	-0.11
Disutility from adverse event – Bleeding	-0.17	-0.22	-0.26
Disutility from adverse event – Diarrhea	-0.16	-0.20	-0.24
Disutility from adverse event – Febrile Neutropenia	-0.16	-0.20	-0.24
Disutility from adverse event – Infections and infestations	-0.17	-0.22	-0.26
Disutility from adverse event – Infusion-related reaction	-0.16	-0.20	-0.24
Disutility from adverse event – Neutropenia	-0.13	-0.16	-0.20
Disutility from adverse event – Neutrophil Count Decreased	-0.13	-0.16	-0.20
Disutility from adverse event – Thrombocytopenia	-0.09	-0.11	-0.13
Disutility from adverse event – Tumor lysis syndrome	-0.17	-0.22	-0.26
Duration of adverse event – ALT/AST increased	16.79	20.99	25.19
Duration of adverse event – Anemia	18.57	23.21	27.85
Duration of adverse event – Bleeding	11.20	14.00	16.80
Duration of adverse event – Diarrhea	2.40	3.00	3.60
Duration of adverse event – Febrile Neutropenia	3.20	4.00	4.80
Duration of adverse event – Infections and infestations	11.20	14.00	16.80
Duration of adverse event – Infusion-related reaction	2.80	3.50	4.20

Parameter	Lower	Base case	Upper
Duration of adverse event – Neutropenia	12.07	15.09	18.10
Duration of adverse event – Neutrophil Count Decreased	12.07	15.09	18.10
Duration of adverse event – Thrombocytopenia	18.57	23.21	27.85
Duration of adverse event – Tumor lysis syndrome	11.20	14.00	16.80
Micro-costing disease management costs – Progression-free - SUM	20.40	25.50	30.60
Micro-costing disease management costs – Progressed disease - SUM	332.91	416.13	499.36

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DSA, deterministic sensitivity analysis.

Figure 37.Tornado diagram: A vs C+O

A, acalabrutinib; C+O, chlorambucil + obinutuzumab.

The main drivers common to both comparisons are the health state utilities and PD disease management costs and drug free period between progression and initiation of a second line therapy.

B.3a.8.3 Scenario analysis

A list of scenario analyses ran in the model for acalabrutinib versus chlorambucil plus obinutuzumab are presented in Table 91 and results are presented in Table 92.

Table 91. List of scenario analyses conducted

Parameter	Base case	Scenario	Comment
Time horizon	30 years	25 years	Assess the impact of alternative time horizons
		20 years	
Discount rate for costs and outcomes	3%	6%	Assess the impact of discounting
		0%	
PF utility value	[redacted]	No history of health condition: 'cancer'; age band: 65 to ≤ 70: 0.8078	Assess the impact of capping PF utility to the general population norms
Age utility decrement	Apply	Do not apply	Assess impact of applying an age utility decrement
Acalabrutinib survival extrapolations (TTP and TTDeath)	Exponential	Weibull	Assess the impact of the next most viable alternative extrapolation of survival estimates
Chlorambucil + obinutuzumab survival extrapolations (TTP and TTDeath)	Log-normal	Log-logistic	Assess the impact of the next most viable alternative extrapolation of survival estimates

A, acalabrutinib; C+O, chlorambucil + obinutuzumab; OS, overall survival; PF, progression-free; PPS, post-progression survival; TTP, time to progression.

Table 92. Results of scenario analysis for acalabrutinib vs chlorambucil plus obinutuzumab

Parameter/ outcome	Scenario	Technology	Discounted total cost	Discounted total QALYs	Incremental costs	Incremental QALYs	ICER
Base case	**-**	**C+O**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25 years	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20 years	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and outcomes	6%	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	0%	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PF utility value	No history of health condition: ‘cancer’; age band: 65 to ≤ 70: 0.8078	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age utility decrement	Do not apply	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib survival extrapolations (TTP and TTDeath)	Weibull	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chlorambucil + obinutuzumab survival extrapolations (TTP and TTDeath)	Log-logistic	C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A, acalabrutinib; C+O, chlorambucil + obinutuzumab; ICER, incremental cost-effectiveness ratio; PF, progression-free; QALY, quality-adjusted life year; TTDeath, time to pre-progression death; TTP, time to progression.

B.3a.9 Subgroup analysis

Analysis of subgroups from ELEVATE-TN was not undertaken.

B.3a.10 Validation

B.3a.10.1 Validation of cost-effectiveness analysis

A review of existing NICE TAs in CLL was undertaken to determine the most appropriate modelling approaches and model structure, healthcare resource use, sources of costs, and utility and disutility values. Based on these reviews, a three-health state (PF, PD and death) modelling approach was chosen as it captures clinically important aspects of the disease. A partitioned survival approach was evaluated, but direct extrapolation of OS from ELEVATE-TN led to implausible long-term OS projections across all arms and for all but one of the distributions tested. For this reason, a semi-Markov model was chosen to inform the analysis; this approach has been used and validated in numerous previous NICE TAs.

The model was reviewed by health economists within AstraZeneca who were not involved with the project. The review included an assessment of the face validity of the model, and third-party validation of the calculations and data sources used. Clinical outcomes predicted by the model were compared to ELEVATE-TN outcomes and key external expert (KEE) opinion.[84] A range of extreme-value and logic tests were conducted to test the behaviour of the model and ensure the results were logical.

Long-term survival extrapolations were selected based on statistical, visual and clinical plausibility and all final curve choices were validated by UK clinicians. A cap on mortality was imposed such that the risk of death for the patient cohort could not be less than all-cause risk of death.

Unit costs were sourced from the most recent PSSRU, eMIT database, BNF and NHS reference costs to ensure that the results of the economic analysis are appropriate for decision making in the UK setting.

B.3a.11 Interpretation and conclusions of economic evidence

B.3a.11.1 Summary of results

A *de novo* economic analysis was developed to evaluate the incremental cost-effectiveness of acalabrutinib compared with chlorambucil plus obinutuzumab in the treatment of previously untreated CLL.

The three health states in the model were PF, PD, and death. This health state structure (i.e. 3-states) has been extensively validated and applied in previous technology assessments in CLL.

A semi-Markov approach was chosen to evaluate PFS and OS over the modelled time horizon. This approach was chosen as it provided both an excellent reflection of the clinical trial data and logical extrapolations of OS (direct extrapolation of the OS data from ELEVATE-TN produced logical inconsistencies when compared to age-matched OS data from the UK population).

Model data were sourced primarily from the ITT population in the ELEVATE-TN study, a well-designed, open-label, international Phase III RCT in the relevant patient population. Data from ELEVATE-TN were available up to approximately three years, however the economic analysis was conducted over a 30-year time horizon. Choice of extrapolations to inform the predicted long-term outcomes across all arms of ELEVATE-TN were based on the opinions of UK CLL KEEs.[84]

Aligned with the anticipated treatment pathway for patients with CLL, subsequent treatments were assumed to be venetoclax plus rituximab and ibrutinib for acalabrutinib and chlorambucil plus obinutuzumab treatment arms, respectively. PPS was modelled using OS data from the MURANO and RESONATE studies: well-designed, international Phase III RCTs that evaluated the efficacy of venetoclax plus rituximab and ibrutinib, respectively, in subjects with R/R CLL. PPS data sources were selected to appropriately reflect the modelled subsequent treatments. Both PPS and subsequent treatment regimens were validated by a UK clinician. The results of the trials and associated economic evaluation are considered generalisable to clinical practice in the UK.

B.3a.11.2 Summary of cost-effectiveness estimates

Results of the analysis showed that the incremental cost-effectiveness ratio (ICER) for acalabrutinib monotherapy versus chlorambucil plus obinutuzumab was [redacted]. Across the majority of sensitivity analyses explored, acalabrutinib continued to generate cost-effectiveness estimates versus chlorambucil with obinutuzumab. The probabilistic ICER and deterministic ICER are sufficiently close, highlighting the robustness of the model

Together, these analyses highlight that acalabrutinib is a cost-effective therapy that addresses significant unmet need and suggest that acalabrutinib-based therapy should be reimbursed for the treatment of previously untreated CLL for whom a fludarabine-based regimen is inappropriate.

B.3b Cost-minimisation analysis: patients with R/R CLL and high-risk patients with previously untreated CLL

This section presents a cost-minimisation analysis between acalabrutinib and ibrutinib for the treatment of patients with R/R CLL and high-risk patients with previously untreated CLL.

The efficacy and safety of acalabrutinib in previously treated patients with CLL has been demonstrated in the ASCEND trial: a large, international, Phase 3 study involving over 300 patients. Acalabrutinib for the treatment of R/R CLL met its primary and key secondary endpoints, demonstrating a significant improvement in efficacy, in comparison with IR/BR. In addition, acalabrutinib showed an acceptable safety and tolerability profile that was consistent with the other clinical trials of acalabrutinib.[75,76,111] See Section B2.

An MAIC was conducted to estimate the comparative efficacy and safety of acalabrutinib versus ibrutinib in patients with R/R CLL based on data from ASCEND and RESONATE. The results of the MAIC indicated that acalabrutinib is likely to provide at least equal efficacy benefits (in terms of PFS and OS) to those achieved with ibrutinib. This equivalent efficacy likely comes with a better safety profile, as shown by the MAIC analysis. See Section B2.

Based on the results of the MAIC and the findings from the clinical experts (See Section B2.), it was determined that a cost-minimisation analysis would be conducted for the comparison against ibrutinib in R/R CLL.

The RESONATE trial was conducted in patients with previously treated CLL, and therefore did not contain any evidence of efficacy in the first-line setting. Despite this, the committee for NICE TA429 accepted that in the absence of any evidence, data from previously treated patients could be taken into account when evaluating the use of ibrutinib in high-risk, previously untreated CLL patients, and recommended ibrutinib as an option for treated CLL in people who have had at least one prior therapy as well as in patients who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable.

Therefore, in this context, evidence from the ASCEND trial (in previously treated patients with CLL) and MAIC (demonstrating equivalence with ibrutinib), can be generalised to the first-line high-risk setting. Data from the ASCEND trial is deemed to be the most relevant as a proxy for high-risk patients in the 1L setting, as the trial includes approx. 40% patients with a 17p and/or TP53 mutation, compared with approx. 20% in the ELEVATE-TN study. On this basis, a cost-minimisation analysis between acalabrutinib and ibrutinib for the treatment of high-risk patients with previously untreated CLL was conducted to support reimbursement of acalabrutinib in the first-line setting for high-risk patients.

B.3b.1 Changes in service provision and management

Acalabrutinib is not anticipated to require any changes to current service provision and management. No differences in resource use are expected between acalabrutinib and ibrutinib.

Administration

Acalabrutinib is orally administered as a monotherapy twice daily at a patient's home. It does not require any associated administration and therefore has no administration costs.

Monitoring

Acalabrutinib requires no additional monitoring above that currently conducted for biologic therapies already recommended for use in R/R CLL.

Setting

The cost-minimisation analysis is conducted in NHS practice for patients with CLL who have been previously treated. Costs are considered from an NHS and PPS.

B.3b.2 Cost-minimisation analysis inputs and assumptions for R/R CLL

B.3b.2.1 Features of the cost-minimisation analysis

A cost-minimisation analysis was conducted to evaluate the expected cost to the NHS associated with the use of acalabrutinib versus ibrutinib in the treatment of previously treated patients with R/R CLL. The cost-minimisation analysis was calculated considering a full cost-effectiveness analysis, assuming equal efficacy, in order to properly estimate and account for the total costs associated with acalabrutinib and ibrutinib.

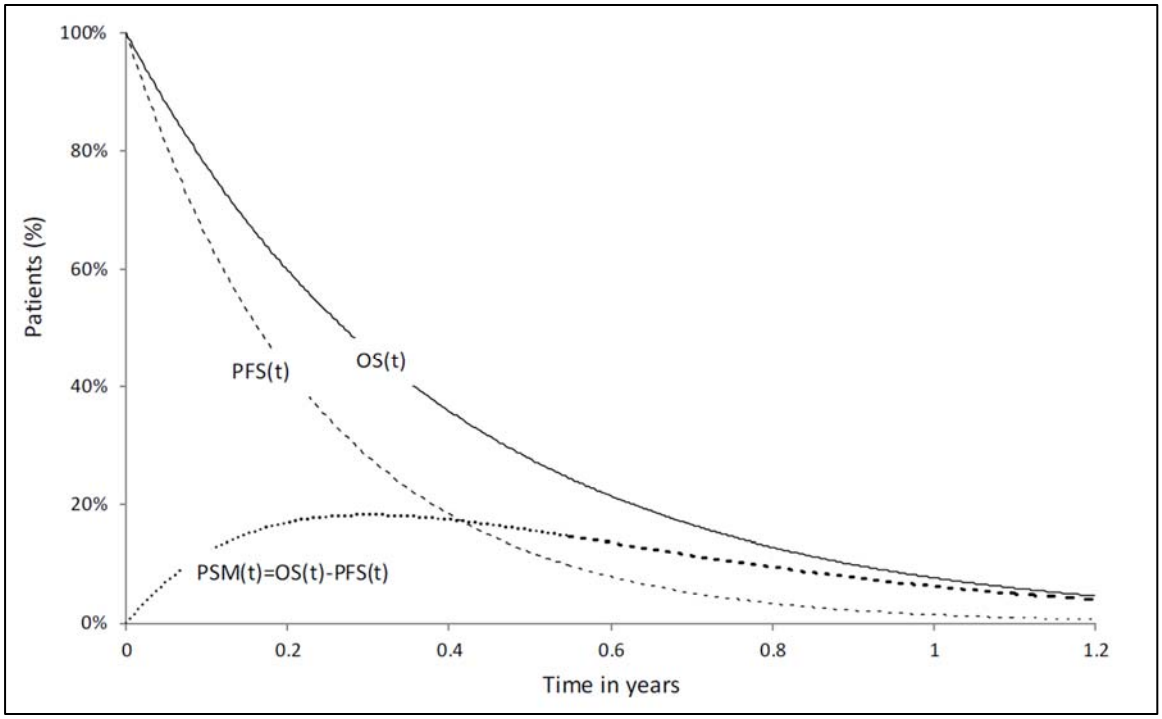
Model structure

The cost-effectiveness analysis was implemented using a partitioned survival model (PSM) with three mutually-exclusive health states: PF, PD, and death. The model was developed in MS Excel. In PSM, the state occupancy of the simulated cohort is estimated by extrapolating trial data for the cumulative probability of PFS and OS to a lifetime time horizon. The cycle length used in the model is 28 days.

The model structure is presented in Figure 38. In each cycle, the curves are used to estimate:

1. The proportion of patients who are alive and have not progressed, (area under the PFS(t) dotted line)
2. The proportion of patients who have progressed but have not yet died (Figure 38area between the PFS(t) and OS(t) lines)
3. The proportion of patients who have died (area under the PSM(t) solid line)

Figure 38. PFS and OS curves to estimate health state occupancy in the PSM



OS: Overall survival; PFS: Progression-free survival; PSM: Partitioned survival model
Source: NICE DSU 2017[112]

The PF and PD health states are associated with different costs. The costs captured in the model include drug costs (acquisition, administration and monitoring), disease monitoring costs (routine scans and patient follow-ups), terminal care costs, and AE costs. The total costs of treatments are estimated by combining the proportion of patients in each health state over time with the costs assigned to each state.

Model population

The target population for the model is aligned with the patient cohort enrolled in the ASCEND study, i.e. CLL symptomatic R/R patients (Section B.2). Table 93 provides an overview of the baseline characteristics of the model population.

Table 93. Baseline patient characteristics in the cost-minimisation analysis

Population characteristic	Input
Starting age (years)	67
Proportion female (%)	32.90
Body weight (kg)	77.50
Body surface area (m^2)	1.91

kg: kilogram; m: metre

Time horizon

A lifetime horizon was used in the model, as per NICE guidelines, to capture the total costs of acalabrutinib and ibrutinib. The time point used was 30 years, which corresponds to when less than 5% of the model population is alive. This time point was selected based on a

review of previous economic models and long-term survival for R/R CLL patients in the model.

Cycle length

The cycle length used in the model was 4 weeks (28 days). This is in line with the cycle length used in previous NICE submissions for CLL (TA429, TA487 and TA561).[6,10] Furthermore, this cycle length is also consistent with the ASCEND study design, which uses a period of 4 weeks for drug administration cycles.

Discounting

Discounting is not applied to costs in the base case, in line with NICE guidance on cost-minimisation analysis. However, the impact of discounting costs at 3.5% was explored in scenario analysis.

B.3b.2.2 Estimation of survival curves to inform treatment and disease costs

In order to estimate lifetime costs, it was necessary to extrapolate the PFS and OS data for acalabrutinib and ibrutinib. RESONATE was selected as the baseline trial due its longer follow-up, thus providing more certainty on the results. PFS and OS KM data from the 6-year follow-up of ibrutinib RESONATE trial published in Munir et al. 2019[113] (median PFS: 44.1 months) was extrapolated. In line with the argument of equal efficacy, as demonstrated by the MAIC between ASCEND and RESONATE (please refer to section B2), extrapolated PFS and OS for acalabrutinib were estimated by applying a HR=1 to the ibrutinib curves.

The results of the MAIC showed that differences in PFS between the two trials (acalabrutinib vs. ibrutinib) were not statistically significant before matching (HR: [redacted], p = [redacted]), and remained so after matching, (HR: [redacted], p = [redacted]). Differences in OS between the two trials were also not statistically significant before or after matching (HR: [redacted], p = [redacted] and HR: [redacted], p = [redacted], respectively). For the purpose of the cost-minimisation analysis, it was conservatively assumed that PFS and OS outcomes were no different between ibrutinib and acalabrutinib and therefore the HRs for OS and PFS were set to 1.

Reported PFS and OS KM curves from RESONATE were digitised using WebPlotDigitiser version 4.2 and the algorithm presented in Guyot et al. 2012[114] was run in the statistical package R to reconstruct IPD. Parametric survival modelling was conducted using standard methodologies as with the cost-utility analysis conducted in previously untreated CLL and recommended in NICE DSU guidance.[99]

Progression-free survival

The PFS survival curves and the within-trial goodness-of-fit statistics are presented in Figure 39 and Table 94, respectively. All parametric curves provide a good fit for the observed period. The log-logistic and log-normal distribution exhibit plateauing tails with the other models providing more consistent estimates. All six parametric distributions closely aligned with the 40% landmark survival rate at 5 years. However, clinical expert opinion regarded the log-logistic and log-normal curves as too optimistic at 10 and 15 years. Of the remaining curves, the Gompertz was deemed overly conservative given that less than 2% of patients

were estimated to be PF at 15 years. The Weibull distribution was the next-most reasonable curve and had the second-best statistical fit. As such, the Weibull distribution was selected as an appropriate curve for ibrutinib PFS.

Figure 39. Extrapolation of ibrutinib PFS (RESONATE; ITT population)

ITT, intention to treat; PFS, progression-free survival.

Table 94. Summary of goodness-of-fit statistics for the parametric survival analysis of PFS for ibrutinib (RESONATE; ITT population)

Distribution	Ibrutinib PFS (RESONATE; ITT population)	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention to treat; PFS, progression-free survival.
Note: bold and underlined values indicate the best-fit scores.

Overall survival

The PFS survival curves and the within-trial goodness-of-fit statistics are presented in Figure 40 and Table 95, respectively. All parametric curves provide a good fit for the observed period, with two groups of models separating in the beginning of the unobserved period. All survival extrapolations show a decline in OS as time increases with the log-logistic and log-normal distributions starting to plateau at approximately 165 months, therefore predicting too optimistic long-term OS extrapolation. The exponential distribution exhibited the lowest AIC and BIC statistics and was selected as the preferred curve to model OS in the R/R setting. To avoid unrealistic survival projections in the model, OS was constrained by age and gender adjusted general population mortality. At each model cycle, the highest mortality risk (from the OS curve or general population mortality) was used to estimate survival for the

next cycle. The mortality risks of the general population were sourced from UK National Statistics.[94]

Figure 40. Extrapolation of ibrutinib OS (RESONATE; ITT population)

KM: Kaplan-Meier; OS: Overall survival

Table 95. Summary of goodness-of-fit statistics for the parametric survival analysis of OS for ibrutinib (RESONATE; ITT population)

Distribution	Ibrutinib PFS (RESONATE; ITT population)	
	AIC	BIC
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention to treat; OS: Overall survival
Note: bold and underlined values indicate the best-fit scores.

B.3b.2.3 Costs

The costs captured in the model include drug costs (acquisition, administration and monitoring), disease monitoring costs (routine scans and patient follow-ups), terminal care costs, and AE costs. Subsequent treatment costs were not included in the analysis as subsequent treatment sequences are expected to be equivalent across primary treatment arms and both acalabrutinib and ibrutinib are administered until disease progression. Therefore, the inclusion of subsequent treatments would have minimal or no impact on the results.

Intervention and comparators' acquisition costs

Table 96 presents a summary of the key inputs, assumptions and acquisition costs included for acalabrutinib and ibrutinib.

Table 96. Acquisition costs of the intervention and comparator technologies

	Acalabrutinib	Ibrutinib
Pharmaceutical formulation	100 mg film-coated tablets (Pack of 60)	420 mg film-coated tablets (Pack of 28)
(Anticipated) care setting	Patient's home	
Acquisition cost (excluding VAT) *	List price: [redacted] PAS price: [redacted]	List price: £4,292.40
Method of administration	Oral administration	
Doses	Twice daily dose of 100mg	Once daily dose of 420 mg
Dosing frequency	Both treatments are administered daily until disease progression or intolerance	
Dose adjustments	N/A	
Average length of a course of treatment	[redacted]over a 30-year horizon (mean duration in PF state based on PFS extrapolation)	

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme or other nationally available price reduction. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

Abbreviations: N/A, not applicable; PAS: patient access scheme; VAT: Value added tax

Drug acquisition costs were based on the dosing regimen, cost per dose and the number of doses required each cycle. Dosing regimens for all treatments were sourced from the relevant pivotal studies where possible. Pack prices shown were sourced from the BNF.[115]

Acquisition costs were applied in each cycle until disease progression or until the maximum number of administrations had been reached. The base case analyses assumed all treatments had 100% relative dose intensity and usage.

Administration and monitoring costs

Since all the treatments included in the analysis were administered orally, no administration costs were included in this analysis. Acalabrutinib and ibrutinib do not require monitoring over and above disease-related monitoring, therefore no treatment monitoring costs were included in the analysis.

Table 97 displays the total cost per cycle for treatments included in the model, assuming 100% relative dose intensity and usage.

Table 97. Total treatment costs per cycle

Treatment	Total cost per cycle
Acalabrutinib	[redacted]
Ibrutinib	£4,292.40

Intervention and comparators' healthcare resource use and associated costs

Routine healthcare costs were applied in each model cycle to the proportion of patients in the PF and PD health states. These costs were independent of the treatment received and represented routine tests and visits associated with disease management in R/R CLL. Resource use estimates and costs for the PF and PD health states were sourced from the recent NICE appraisal for venetoclax in combination with rituximab in R/R CLL (NICE TA561).[10]

Routine costs were estimated by multiplying resource use (for each cycle) with the relevant unit cost. Unit costs for resource items were taken from NHS tariffs.

Table 98. Progression-free state costs and resource use

Resource use item	Resource use per cycle	Unit cost	Cost per cycle
Full blood count	0.31	£2.51	£0.77
LDH	0.23	£1.11	£0.26
Haematologist visit	0.15	£159.65	£24.48
Total			**£25.50**

LDH: lactate dehydrogenase

Table 99. Progressed disease state costs and resource use

Resource use item	Resource use per cycle	Unit cost	Cost per cycle
Full blood count	0.61	£2.51	£1.54
Chest X-Ray	0.15	£77.48	£11.88
Bone marrow exam	0.08	£495.98	£38.02
Haematologist visit	0.46	£159.65	£73.43
Inpatient visit (Non-surgical)	0.31	£432.93	£132.75
Full blood transfusion	0.84	£187.97	£158.51
Total			**£416.13**

Adverse reaction unit costs and resource use

In the base case, all treatment-related Grade ≥3 AEs that occurred in at least 1% of patients treated with acalabrutinib or ibrutinib were included in the cost-minimisation analysis. The AE incidence rates used in the base case were sourced from the respective trials and are presented in Table 100.

Scenario analysis was conducted where the incidence rates for Grade 3-4 AEs were sourced from the MAIC (Section B2). The AE incidence rates resulting from the MAIC are also presented in Table 100.

AEs are applied to the proportion of patients experiencing the event in the first cycle of the model, hence assuming that the majority of AEs occur during the first four weeks of treatment.

Table 100. Incidence of adverse events included in the model

Adverse event	Base case		Scenario analysis	
	Acalabrutinib	Ibrutinib	Acalabrutinib	Ibrutinib
Anaemia	11.70%	4.62%	16.50%	6.00%
Diarrhoea	1.30%	4.10%	0.30%	4.60%
Dyspnoea	0.00%	2.05%	--	--
Fatigue	0.00%	2.05%	0.50%	3.60%
Infections and infestations	14.90%	24.00%	11.10%	21.00%
Neutropenia	15.58%	16.41%	15.70%	18.00%
Atrial fibrillation	1.30%	3.00%	0.80%	3.60%
Thrombocytopenia	3.90%	5.64%	3.40%	6.00%
Bleeding	--	--	0.50%	3.00%
Source	ASCEND	RESONATE	MAIC	

The total AE costs were calculated as the product of the AE incidence and its respective unit cost. The unit costs for AE management used in the model are shown in Table 101. Whenever possible, AE management costs were estimated using resource use reported in previous NICE submissions and unit costs from the most recent UK national tariffs.

Alternatively, costs were estimated by inflating the reported cost to 2019 (£) using the hospital & community health services index.

Table 101. Unit costs of adverse events

AE	Cost	Source	Comment
Anaemia	£366.00	NHS tariffs[116]	Currency code: SA04L
Diarrhoea	£149.00	NHS tariffs[116]	Outpatient attendances: 301
Dyspnoea	£0.00	NICE TA561[10]	Assumption of no cost based on TA561
Fatigue	£636.67	NHS tariffs[116]	Activity weighted average (AA31C-AA31E)
Infections and infestations	£1,783.94	NHS tariffs[116]	Activity weighted average (DZ11K - DZ11V) cost for pneumonia
Neutropenia	£136.34	NHS tariffs[116]	Reported cost inflated to £2019
Atrial fibrillation	£1,783.94	NHS tariffs[116]	Assumed same as infections
Thrombocytopenia	£640.09	NHS tariffs[116]	Activity weighted average (SA12G - SA12K)
Bleeding	£1,783.94	NHS tariffs[116]	Assumed same as infections

Miscellaneous unit costs and resource use

The cost of terminal care was applied to all patients upon death, regardless of the health state in which the event occurred. In two recent NICE submissions, the costs of terminal care were based on a published study of end of life care for solid tumour cancer patients. The terminal care costs reported in the NICE appraisal for venetoclax in combination with rituximab (TA561)[10] was inflated to 2019 (£) and applied to all patients in the cycle before death (£6,975).

B.3b.2.4 Model inputs and assumptions

A summary of the inputs used in the cost-minimisation analysis is presented in Table 102 and all of the key assumptions are presented in Table 103.

Table 102. Summary of model base case inputs

Input	Value	Reference
Time horizon (years)	30	NICE FTA user guide[91]
Discount rate	0%	NICE FTA user guide[91]
Average age (years)	67.00	Pooled ITT analysis of ASCEND
Percent female	32.90	Pooled ITT analysis of ASCEND
Body weight (kg)	77.50	Pooled ITT analysis of ASCEND
Body surface area (m^2)	1.91	Pooled ITT analysis of ASCEND
PFS HR for acalabrutinib vs. ibrutinib	1	

Input	Value	Reference
OS HR for acalabrutinib vs. ibrutinib	1	Assumption of equal efficacy between acalabrutinib and ibrutinib
Acquisition costs per cycle	Acalabrutinib (list): [redacted] Acalabrutinib (PAS): [redacted] Ibrutinib (list): £4,292.40	BNF, Company data
Administration cost per cycle	Acalabrutinib: £0 Ibrutinib: £0	Assumption
Routine resource use costs per cycle	PF health state: £25.50 PD health state: £416.13	NICE TA561[10]
End of life cost	£6,975	NICE TA561[10]

BNF: British national formulary; FTA: fast track appraisal; ITT: intention-to-treat; OS: overall survival; PAS: patient access scheme; PF: progression-free; PFS: progression-free survival, PD: progressed disease

Table 103. Key assumptions in the base case

Assumption	Rationale for assumption
PFS and OS are assumed to be identical between acalabrutinib and ibrutinib	Cost-minimisation analysis is accepted for treatments that demonstrate similar efficacy. Given the results of the MAIC, acalabrutinib is associated with at least similar efficacy compared with ibrutinib, therefore assuming equal efficacy in the base case is conservative.
Incidence of adverse events are assumed to differ between acalabrutinib and ibrutinib	The results of the MAIC for acalabrutinib and ibrutinib suggested a significant difference in AEs between acalabrutinib and ibrutinib.

AE, adverse events; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression free survival

B.3b.3 Cost-minimisation analysis inputs and assumptions for high risk untreated CLL

B.3b.3.1 Features of the cost-minimisation analysis

A cost-minimisation analysis was conducted to evaluate the expected cost to the NHS associated with the use of acalabrutinib versus ibrutinib in the treatment of high-risk patients (adults with CLL who have a 17p deletion or TP53 mutation) with previously untreated CLL. The cost-minimisation analysis was calculated considering a full cost-effectiveness analysis, assuming equal efficacy, in order to properly estimate and account for the total costs associated with acalabrutinib and ibrutinib.

Model structure

The cost effectiveness analysis was implemented using the same semi-Markov model used for the assessment of acalabrutinib monotherapy compared with chlorambucil in combination with obinutuzumab in the treatment of previously untreated CLL patients. For a description of the model structure please refer to Section B.3a.2.2 Model structure.

PF and PD health states are associated with different costs. The costs captured in the model include drug costs (acquisition, administration and monitoring), disease monitoring costs (routine scans and patient follow-ups), terminal care costs, and AE costs. The total costs of treatments are estimated by combining the proportion of patients in each health state over time with the costs assigned to each state.

Model population

The target population for the model is aligned with the high-risk 17p del / TP53 mutation previously untreated patient cohort enrolled in the ELEVATE-TN study. Table 104 provides an overview of the baseline characteristics of the model population based on the ITT dataset.

Table 104. Baseline patient characteristics in the cost-minimisation analysis

Population characteristic	Input
Starting age (years)	70
Proportion female (%)	38.00
Body weight (kg)	79.00
Body surface area (m^2)	1.93

kg: kilogram; m: metre

Time horizon

A lifetime time horizon was used in the model, as per NICE guidelines, to capture the total costs of acalabrutinib and ibrutinib. The time point used was 30 years, which corresponds to when less than 1% of the model population is alive. This time point was selected based on a review of previous economic models and long-term survival for previously untreated CLL patients. An equivalent time horizon is applied in the cost-utility analyses for previously untreated CLL patients (see Section B.3a.2.2 Model structure).

Cycle length

The cycle length used in the model was 4 weeks (28 days). This is in line with the cycle length used in previous NICE submissions for CLL (TA429, TA487 and TA561),[6,10,42] and is consistent with the ELEVATE-TN study design, which uses a period of 4 weeks for drug administration cycles.

Discounting

Discounting is not applied to costs in the base case, in line with NICE guidance on cost-minimisation analysis. However, the impact of discounting costs at 3.5% was explored in a scenario analysis.

B.3b.3.2 Estimation of survival curves to inform treatment and disease costs

In order to estimate lifetime costs, it was necessary to extrapolate the PFS and OS data for acalabrutinib and ibrutinib. ELEVATE-TN was selected as the baseline trial. In line with the argument of equal efficacy, as demonstrated by the MAIC between ASCEND and RESONATE in R/R CLL (please refer to section B.2b.9), extrapolated PFS and OS for ibrutinib were estimated by applying a HR=1 to the acalabrutinib curves based on the ITT dataset.

Parametric survival modelling was conducted using standard methodologies as recommended in NICE DSU guidance.[99] Survival analysis on patient level data provided the long-term extrapolations of TTP and TTDeath to estimate transition probabilities over the time horizon of the model. The parametric models fitted to acalabrutinib were used as reference curves, to which HRs were applied, to estimate TTP and TTDeath for ibrutinib. As the HRs from the MAIC were for PFS, they are not aligned with the endpoints used in the model, i.e. TTP and TTDeath. The PFS HRs are applied to TTP and TTDeath and hence the same relative risk applies to both endpoints. This assumption was necessary as TTP and TTDeath endpoints are not usually reported in the literature, thus making an indirect treatment comparison on these endpoints unfeasible.

The model takes a cumulative approach to estimate the OS of the cohort. Initially, the cohort is assigned to the PF health state before transitioning to either the PD (using TTP), or death states (using TTDeath) and following progression, the period that patients stay alive is modelled using PPS data, which includes an adjustment for all-cause mortality. The sum of the time spent in the PF and PD health states give the total time alive (i.e. OS) of the cohort. This approach was selected to avoid dependency on the OS endpoint from the ELEVATE-TN study as OS data were deemed too immature to provide informative long-term estimates. To address the uncertainty around long-term survival of PU CLL patients, data from the MURANO study for venetoclax plus rituximab was used. The PPS data source was chosen to align with the expected subsequent treatment as informed by UK clinicians. The PPS extrapolations however are constrained by general population mortality for most of the model time horizon.

The curves used in the analysis are presented in full in Section B3a.3.4 Base case selection: acalabrutinib vs chlorambucil + obinutuzumab. The exponential distribution was selected to extrapolate ELEVATE-TN TTP and TTD for acalabrutinib. A HR of 1 was applied to the

curves to estimate TTP/TTD curves for ibrutinib. PPS was informed by data from the MURANO for venetoclax plus rituximab to align with the anticipated treatment pathway for CLL patients based on clinical feedback. The exponential distribution was selected to extrapolate PPS based on MURANO OS data. Curves were selected based on statistical and visual fit, and were subsequently validated by UK clinicians. PPS is assumed equal across acalabrutinib and ibrutinib.

B.3b.3.3 Costs

The costs captured in the model include drug costs (acquisition, administration and monitoring), disease monitoring costs (routine scans and patient follow-ups), terminal care costs, and AE costs. Subsequent treatment costs were not included in the analysis as subsequent treatment sequences are expected to be equivalent across primary treatment arms and both acalabrutinib and ibrutinib are administered until disease progression. Therefore, the inclusion of subsequent treatments would have minimal or no impact on the results.

Intervention and comparators' acquisition costs

Table 105 presents a summary of the key inputs, assumptions and acquisition costs included for acalabrutinib and ibrutinib.

Table 105. Acquisition costs of the intervention and comparator technologies

	Acalabrutinib	**Ibrutinib**
Pharmaceutical formulation	100 mg film-coated tablets (Pack of 60)	420 mg film-coated tablets (Pack of 28)
(Anticipated) care setting	Patient's home	
Acquisition cost (excluding VAT) *	List price: [redacted] PAS price: [redacted]	List price: £4,292.40
Method of administration	Oral administration	
Doses	Twice daily dose of 100mg	Once daily dose of 420 mg
Dosing frequency	Both treatments are administered daily until disease progression or intolerance	
Dose adjustments	N/A	
Average length of a course of treatment	[redacted] over a 30-year horizon (mean duration in PF state based on PFS extrapolation)	

Drug acquisition costs were based on the dosing regimen, cost per dose and the number of doses required each cycle. Dosing regimens for all treatments were sourced from the relevant pivotal studies where possible. Pack prices shown in Table 96 were sourced from the BNF.

Acquisition costs were applied in each cycle until disease progression or until the maximum number of administrations had been reached. The base case analyses assumed all treatments had 100% relative dose intensity and usage.

Administration and monitoring costs

Since all the treatments included in the analysis were administered orally, no administration costs were included in this analysis. Acalabrutinib and ibrutinib do not require monitoring over and above disease related monitoring, therefore no treatment monitoring costs were included in the analysis.

Table 106 displays the total cost per cycle for treatments included in the model, assuming 100% relative dose intensity and usage.

Table 106. Total treatment costs per cycle

Treatment	Total cost per cycle
Acalabrutinib	[redacted]
Ibrutinib	£4,292.40

Intervention and comparators' healthcare resource use and associated costs

Routine healthcare costs were applied in each model cycle to the proportion of patients in the PF and PD health states. These costs were independent of the treatment received and represented routine tests and visits associated with disease management in untreated CLL. Resource use estimates and costs for the PF and PD health states were sourced from the recent NICE appraisal for in venetoclax in combination with rituximab in R/R CLL (NICE TA561).[10]

Routine costs were estimated by multiplying resource use (for each cycle) with the relevant unit cost. Unit costs for resource items were taken from NHS tariffs.

Table 107. Progression-free state costs and resource use

Resource use item	Resource use per cycle	Unit cost	Cost per cycle
Full blood count	0.31	£2.51	£0.77
LDH	0.23	£1.11	£0.26
Haematologist visit	0.15	£159.65	£24.48
Total			**£25.50**

LDH: lactate dehydrogenase

Table 108. Progressed disease state costs and resource use

Resource use item	Resource use per cycle	Unit cost	Cost per cycle
Full blood count	0.61	£2.51	£1.54
Chest X-Ray	0.15	£77.48	£11.88
Bone marrow exam	0.08	£495.98	£38.02
Haematologist visit	0.46	£159.65	£73.43
Inpatient visit (Non-surgical)	0.31	£432.93	£132.75
Full blood transfusion	0.84	£187.97	£158.51
Total			**£416.13**

Adverse reaction unit costs and resource use

In the base case, all treatment-related Grade ≥3 AEs that occurred in at least 1% of patients treated with acalabrutinib or ibrutinib were included in the cost-minimisation analysis. The AE incidence rates used in the base case were sourced from the respective trials and are presented in Table 109.

AEs are applied to the proportion of patients experiencing the event in the first cycle of the model, hence assuming that the majority of AEs occur during the first four weeks of treatment.

Table 109. Incidence of adverse events included in the model

Adverse event	Acalabrutinib	Ibrutinib
Abdominal pain	0.00%	2.96%
Anaemia	6.70%	5.93%
Atrial fibrillation	0.00%	4.00%
Bleeding	1.70%	6.00%
Diarrhoea	0.56%	3.70%
Febrile neutropenia	1.12%	2.22%
Hypo/ hypertension	0.00%	4.44%
Infections and infestations	14.00%	25.00%
Neutropenia	9.50%	10.37%
Platelet count decreased	0.00%	2.96%
Rash	0.00%	2.96%
Thrombocytopenia	2.79%	2.22%
Source	ELEVATE-TN	RESONATE-2

The total AE costs were calculated as the product of the AE incidence and its respective unit cost. The unit costs for AE management used in the model are shown in Table 110. Whenever possible, AE management costs were estimated using resource use reported in previous NICE submissions and unit costs from the most recent UK national tariffs. Alternatively, costs were estimated by inflating the reported cost to 2019 (£) using the hospital & community health services index.

Table 110. Unit costs of adverse events

AE	Cost	Source	Comment
Abdominal pain	£802.83	TA487[42]	Reported cost inflated to £2019
Anaemia	£366.00	National schedule of reference costs (2017-18)[117]	Currency code: SA04L. Resource use TA487[42]
Atrial fibrillation	£1,783.94	TA487[42]	Assumed to be the same as for infections
Bleeding	£1,783.94	TA487[42]	Assumed to be the same as for infections
Diarrhoea	£149.00	National schedule of reference costs (2017-18)[117]	Outpatient attendances: 301. Resource use from TA359[42]
Febrile neutropenia	£6,623.14	TA487[42]	Reported cost inflated to 2019 (£)
Hypo/ hypertension	£658.95	National schedule of reference costs (2017-18)[117]	Currency code: EB04Z
Infections and infestations	£1,783.94	National schedule of reference costs (2017-18)[117]	Activity weighted average (DZ11K – DZ11V) cost for pneumonia. Resource use from TA487
Neutropenia	£136.34	TA487[42]	Reported cost inflated to 2019 (£)
Platelet count decreased	--	-	Assumed £0
Rash	--	-	Assumed £0
Thrombocytopenia	£640.09	National schedule of reference costs (2017-18)[117]	Activity weighted average (SA12G – SA12K)

Miscellaneous unit costs and resource use

The cost of terminal care was applied to all patients upon death, regardless of the health state in which the event occurred. In two recent NICE submissions, the costs of terminal care were based on a published study of end of life care for solid tumour cancer patients. The terminal care costs reported in the NICE appraisal for venetoclax in combination with rituximab (TA561)[10] was inflated to 2019 (£) and applied to all patients in the cycle before death (£6,975).

B.3b.3.4 Model inputs and assumptions

A summary of the inputs used in the cost-minimisation analysis is presented in Table 111 and all of the key assumptions are presented in Table 112.

Table 111. Summary of model base case inputs

Input	Value	Reference
Time horizon (years)	30	NICE FTA user guide[91]
Discount rate	0%	NICE FTA user guide[91]
Average age (years)	70	High risk - 17p del / TP53 mutation patients of ELEVATE-TN
Percent female	38.00	High risk - 17p del / TP53 mutation patients of ELEVATE-TN
Body weight (kg)	79.00	High risk - 17p del / TP53 mutation patients of ELEVATE-TN
Body surface area (m^2)	1.93	High risk - 17p del / TP53 mutation patients of ELEVATE-TN
PFS (applied to TTP/TTD curves) HR for acalabrutinib vs. ibrutinib	1	Assumption of equal efficacy between acalabrutinib and ibrutinib
OS HR for acalabrutinib vs. ibrutinib (assumed PPS is equivalent across treatment arms)	1	
Acquisition costs per cycle	Acalabrutinib (list): [redacted] Acalabrutinib (PAS): [redacted] Ibrutinib (list): £4,292.40	BNF, Company data
Administration cost per cycle	Acalabrutinib: £0 Ibrutinib: £0	Assumption
Routine resource use costs per cycle	PF health state: £25.50 PD health state: £416.13	NICE TA561[10]
End of life cost	£6,975	NICE TA561[10]

BNF: British national formulary; FTA: fast track appraisal; ITT: intention-to-treat; OS: overall survival; PAS: patient access scheme; PF: progression-free; PFS: progression-free survival, PD: progressed disease

Table 112. Key assumptions in the base case

Assumption	Rationale for assumption
PFS and OS are assumed to be identical between acalabrutinib and ibrutinib	Cost-minimisation analysis is accepted for treatments that demonstrate similar efficacy. Aligned with the NICE appraisal of ibrutinib (TA429) and given the results of the MAIC, acalabrutinib is associated with at least a similar efficacy compared with ibrutinib, therefore assuming equal efficacy in the base case is conservative.
Incidence of adverse events are assumed to differ between acalabrutinib and ibrutinib	The results of the MAIC for acalabrutinib and ibrutinib suggested a significant difference in AEs between acalabrutinib and ibrutinib.

B.3b.4 Clinical expert validation

Key clinical expert opinion was sourced on the outputs of the clinical trial and MAIC (Section B.2b).[84] Overall, the clinical experts agreed there was no efficacy difference (PFS, OS) between acalabrutinib and ibrutinib arms. It was also noted that acalabrutinib had a more favourable safety profile specifically regarding other BTKi (ibrutinib) patient risk factors such as cardiovascular risk, bleeding, hypertension, arthralgia and sudden death.

B.3b.5 Results in R/R CLL

Base-case results

The results of the cost-minimisation analysis of acalabrutinib and ibrutinib in patients with R/R CLL are presented in Table 113. The estimated total costs over the lifetime horizon were [redacted] for acalabrutinib and [redacted] for ibrutinib. The difference was driven by acquisition costs and AE costs, with equal resource costs for both treatments due to the same duration of treatment (time in PF) for acalabrutinib and ibrutinib.

Table 113. Base case results for cost-minimisation analysis against ibrutinib

	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	TOTAL COSTS (£)
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]

In the base case, acalabrutinib provided the same health benefits as ibrutinib at a lower incremental cost of [redacted]. Therefore, acalabrutinib can be considered a cost-effective option for the treatment of R/R CLL compared to ibrutinib.

Scenario analysis

Scenario analyses are presented in Table 114. These assessed the impact on the results of using AEs from the MAIC and applying a discount rate of 3.5% per annum. Across these scenarios, the lower incremental costs for acalabrutinib ranged from [redacted] to [redacted].

Table 114. Scenario analysis for cost-minimisation analysis against ibrutinib

	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	TOTAL COSTS (£)
Base case				
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
AEs sourced from MAIC				
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate: 3.5%				
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]

AEs, adverse events; MAIC, matching-adjusted indirect comparison.

B.3b.6 Results in high-risk previously untreated CLL

Base-case results

The results of the cost-minimisation analysis of acalabrutinib and ibrutinib in high risk patients with previously untreated CLL are presented in Table 113. The estimated total costs over the lifetime horizon were [redacted] for acalabrutinib and [redacted] for ibrutinib. The difference was driven by acquisition costs and AE costs, with equal resource costs for both treatments due to the same duration of treatment (time in PF) for acalabrutinib and ibrutinib.

Table 115. Base case results for cost-minimisation analysis against ibrutinib

	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	TOTAL COSTS (£)
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]

In the base case, acalabrutinib provided the same health benefits as ibrutinib at a lower incremental cost of [redacted]. Therefore, acalabrutinib can be considered a cost-effective option for the treatment of high-risk previously untreated patients compared to ibrutinib.

Scenario analysis

Scenario analyses are presented in Table 114. These assessed the impact on the results of applying a discount rate of 3.5% per annum. Across these scenarios, the lower incremental costs for acalabrutinib ranged from [redacted] to [redacted].

Table 116. Scenario analysis for cost-minimisation analysis against ibrutinib

	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	TOTAL COSTS (£)
Base case				
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate: 3.5%				
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]

	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	TOTAL COSTS (£)
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]

B.3b.7 Interpretation and conclusions of economic evidence

Costs comparison were undertaken for acalabrutinib and ibrutinib in patients with R/R CLL and in high-risk patients with previously untreated CLL. The analyses were informed by a PSM and a semi-Markov model with mutually exclusive health states for PF, PD and death. The economic analyses were conducted over a 30-year time horizon.

Model data were sourced from the pivotal trials for acalabrutinib and ibrutinib in the R/R and first-line settings. The trials informing the analyses were representative of patients in UK clinical practice. PFS and OS extrapolation was required to fully capture treatment and disease related costs. A MAIC between acalabrutinib and ibrutinib in R/R patients demonstrated equal efficacy between the treatments can be assumed. Both trials informing the MAIC (ASCEND and RESONATE) had a significant proportion of patients identified as high risk.

B.3a.11.1 Summary of results

Results of the cost-minimisation analyses for acalabrutinib and ibrutinib showed that acalabrutinib provides the same health benefits as ibrutinib at a lower incremental cost both in the R/R and first-line settings. Therefore, acalabrutinib can be considered a cost-effective option for the treatment of patients with R/R CLL and high-risk patients with previously untreated CLL compared to ibrutinib.

B.4 References

1. Shanafelt T. Treatment of older patients with chronic lymphocytic leukemia: key questions and current answers. *Hematology Am Soc Hematol Educ Program.* 2013;2013:158-167.
2. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res.* 1992;41(3):237-248.
3. AstraZeneca. CLL Advisory Board. 2020. In.
4. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. *Br J Haematol.* 2018;182(3):344-359.
5. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v78-84.
6. National Institute for Health and Care Excellence. TA429 Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. 2017. Available at: https://www.nice.org.uk/guidance/ta429 (accessed February 2020). In.
7. Electronic Medicines Compendium. SmPC: Zydelig 150 mg Film-coated Tablets. April 2019. Available at: https://www.medicines.org.uk/emc/product/3329/smpc (accessed February 2020). In.
8. Shustik C, Bence-Bruckler I, Delage R, Owen CJ, Toze CL, Coutre S. Advances in the treatment of relapsed/refractory chronic lymphocytic leukemia. *Ann Hematol.* 2017;96(7):1185-1196.
9. AstraZeneca. IPSOS Healthcare Cancer Therapy Monitor. 2020. In.
10. National Institute for Health and Care Excellence. TA561 Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. 2019. Available at: https://www.nice.org.uk/search?q=Venetoclax+with+rituximab+for+previously+treated+chronic+lymphocytic+leukaemia (accessed February 2020). In.
11. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.
12. National Institute for Health and Care Excellence. ID1402 Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. 2020. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10328 (accessed June 2020). In.
13. Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. *Nat Rev Cancer.* 2014;14(4):219-232.
14. European Medicines Agency. Calquence. 2020. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/calquence (accessed July 2020). In.
15. Bhayat F, Das-Gupta E, Smith C, McKeever T, Hubbard R. The incidence of and mortality from leukaemias in the UK: a general population-based study. *BMC Cancer.* 2009;9:252.
16. Rozman C, Montserrat E. Chronic lymphocytic leukemia. *N Engl J Med.* 1995;333(16):1052-1057.
17. Leukemia & Lymphoma Society. Chronic Lymphocytic Leukemia. 2017:1-52. In.
18. Awan F, Byrd J. Chronic Lymphocytic Leukemia. In: Hoffman R, Benz EJ Jr., Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Philadelphia, PA: Elsevier, Inc.; 2018:1244-1264. In.
19. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood.* 2008;111(12):5446-5456.
20. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;131(25):2745-2760.

21. Parry HM, Damery S, Mudondo NP, et al. Primary care management of early stage chronic lymphocytic leukaemia is safe and effective. *QJM.* 2015;108(10):789-794.
22. Sagatys EM, Zhang L. Clinical and laboratory prognostic indicators in chronic lymphocytic leukemia. *Cancer Control.* 2012;19(1):18-25.
23. Van Bockstaele F, Verhasselt B, Philippe J. Prognostic markers in chronic lymphocytic leukemia: a comprehensive review. *Blood Rev.* 2009;23(1):25-47.
24. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood.* 1975;46(2):219-234.
25. Binet JL. [New data on the prognosis of chronic lymphoid leukemia ; anatomo-clinical classification]. *Acquis Med Recent.* 1981;198:191-200.
26. Desai S, Pinilla-Ibarz J. Front-line therapy for chronic lymphocytic leukemia. *Cancer Control.* 2012;19(1):26-36.
27. Milne K, Sturrock B, Chevassut T. Chronic Lymphocytic Leukaemia in 2020: the Future Has Arrived. *Curr Oncol Rep.* 2020;22(4):36.
28. Pflug N, Bahlo J, Shanafelt TD, et al. Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. *Blood.* 2014;124(1):49-62.
29. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) incidence statistics. 2020. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence (accessed July 2020). In.
30. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur J Haematol.* 2004;72(6):381-389.
31. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol.* 2007;139(2):255-264.
32. Kabadi SM, Goyal RK, Nagar SP, Kaye JA, Davis KL. Treatment patterns, adverse events, and economic burden in a privately insured population of patients with chronic lymphocytic leukemia in the United States. *Cancer Med.* 2019;8(8):3803-3810.
33. Leukaemia Care. The experience of Chronic Lymphocytic Leukaemia (CLL) patients living on Watch and Wait. Available at: https://media.leukaemiacare.org.uk/wp-content/uploads/FINAL-Watch-and-Wait-report-Leukaemia-Care-EMBARGOED-16-APRIL.pdf (accessed July 2020). In.
34. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) survival statistics. 2020. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/survival#heading-Zero (accessed July 2020). In.
35. Cancer Research UK. Chronic lymphocytic leukaemia (CLL): Survival. 2020. Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/survival#:~:text=Survival%20for%20all%20stages%20of%20CLL&text=They%20are%20from%20the%20National,or%20more%20after%20being%20diagnosed (accessed July 2020).
36. National Comprehensive Cancer Network (NCCN).Chronic Lymphocytic Leukemia Clinical Guidelines. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf (accessed July 2020). In.
37. International CLLIPIwg. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 2016;17(6):779-790.
38. National Institute for Health and Care Excellence. TA174 Rituximab for the first-line treatment of chronic lymphocytic leukaemia. 2009. Available at: https://www.nice.org.uk/guidance/ta174 (accessed February 2020). In.
39. National Institute for Health and Care Excellence. TA216 Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. 2011. Available at: https://www.nice.org.uk/guidance/ta216 (accessed February 2020). In.
40. National Institute for Health and Care Excellence. TA343 Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. 2015. Available at: https://www.nice.org.uk/guidance/ta343 (accessed February 2020). In.
41. National Institute for Health and Care Excellence. TA359 Idelalisib for treating chronic lymphocytic leukaemia. 2015. Available at: https://www.nice.org.uk/guidance/ta359 (accessed February 2020). In.

42. National Institute for Health and Care Excellence. TA487 Venetoclax for treating chronic lymphocytic leukaemia. Technology appraisal guidance. 2017. Available at: https://www.nice.org.uk/guidance/ta487 (accessed February 2020). In.
43. National Institute for Health and Care Excellence. TA193 Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia. 2010. Available at: https://www.nice.org.uk/guidance/ta193 (accessed February 2020). In.
44. Robak T, Stilgenbauer S, Tedeschi A. Front-line treatment of CLL in the era of novel agents. *Cancer Treat Rev.* 2017;53:70-78.
45. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014;370(12):1101-1110.
46. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. *Lancet.* 2018;391(10129):1524-1537.
47. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet.* 2010;376(9747):1164-1174.
48. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. *J Clin Oncol.* 2010;28(29):4473-4479.
49. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* 2000;343(26):1910-1916.
50. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood.* 1999;94(6):1840-1847.
51. Cavallari M, Cavazzini F, Bardi A, et al. Biological significance and prognostic/predictive impact of complex karyotype in chronic lymphocytic leukemia. *Oncotarget.* 2018;9(76):34398-34412.
52. Parikh SA. Chronic lymphocytic leukemia treatment algorithm 2018. *Blood Cancer J.* 2018;8(10):93.
53. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med.* 2018;378(12):1107-1120.
54. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *N Engl J Med.* 2019;380(23):2225-2236.
55. ESMO. eUpdate – Chronic Lymphocytic Leukaemia Treatment Recommendations. June 2017. Available at: https://www.esmo.org/guidelines/haematological-malignancies/chronic-lymphocytic-leukaemia/eupdate-chronic-lymphocytic-leukaemia-treatment-recommendations (accessed July 2020). In.
56. Pfeil AM, Imfeld P, Pettengell R, et al. Trends in incidence and medical resource utilisation in patients with chronic lymphocytic leukaemia: insights from the UK Clinical Practice Research Datalink (CPRD). *Ann Hematol.* 2015;94(3):421-429.
57. Leblond V, Aktan M, Ferra Coll CM, et al. Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study. *Haematologica.* 2018;103(11):1889-1898.
58. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica.* 2018;103(5):874-879.
59. Ghia P, Cuneo A. Ibrutinib in the real world patient: many lights and some shades. *Haematologica.* 2016;101(12):1448-1450.
60. Berglof A, Hamasy A, Meinke S, et al. Targets for Ibrutinib Beyond B Cell Malignancies. *Scand J Immunol.* 2015;82(3):208-217.
61. Harrington B, Gulrajani M, Covey T. ACP-196 is a second generation inhibitor of Bruton tyrosine kinase (BTK) with enhanced target specificity [abstract 2908]. Presented at the American Society of Hematology (ASH) 2015 Annual Scientific Meeting; December 5-8, 2015; Orlando FL.
62. Rajasekaran N, Sadaram M, Hebb J, et al. Three BTK-Specific Inhibitors, in Contrast to Ibrutinib, Do Not Antagonize Rituximab-Dependent NK-Cell Mediated Cytotoxicity. *Blood.* 2014;124(21):3118-3118.
63. Balagula Y, Garbe C, Myskowski PL, et al. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. *Int J Dermatol.* 2011;50(2):129-146.

64. Lynch TJ, Jr., Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist.* 2007;12(5):610-621.
65. Li J, Gu J. Diarrhea with epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients: A meta-analysis of randomized controlled trials. *Crit Rev Oncol Hematol.* 2019;134:31-38.
66. Hirsh V, Blais N, Burkes R, Verma S, Croitoru K. Management of diarrhea induced by epidermal growth factor receptor tyrosine kinase inhibitors. *Curr Oncol.* 2014;21(6):329-336.
67. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. *J Thromb Haemost.* 2017;15(5):835-847.
68. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. *Blood.* 2014;124(26):3991-3995.
69. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med.* 2016;374(4):323-332.
70. Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia.* 2015;29(4):783-787.
71. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): A Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
72. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. *JAMA Oncol.* 2015;1(1):80-87.
73. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med.* 2018;379(26):2517-2528.
74. Delgado J, Rossi D, Forconi F, et al. Characterising the burden of chronic lymphocytic leukemia in fludarabine-ineligible patients in spain, italy, and the united kingdom (UK): A retrospective observational study. *Blood.* 2014;124(21).
75. Acerta Pharma. ELEVATE-TN (ACE-CL-007) Clinical Study Report. 2019. In.
76. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2020:JCO1903355.
77. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.
78. AstraZeneca. ASCEND (ACE-CL-309) Clinical Study Report. 2019. In.
79. ClinicalTrials.gov. Study of Acalabrutinib (ACP-196) Versus Ibrutinib in Previously Treated Subjects With High Risk CLL. Available at: https://clinicaltrials.gov/ct2/show/NCT02477696?term=NCT02477696&draw=2&rank=1 (accessed July 2020). In.
80. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Med Decis Making.* 2018;38(2):200-211.
81. National Institute for Health and Care Excellence Decision Support Unit. Technical Support Document 18: Population-adjusted indirect comparisons (MAIC and STC). 2016. Available at: http://nicedsu.org.uk/technical-support-documents/population-adjusted-indirect-comparisons-maic-and-stc/ (accessed August 2020). In.
82. Brown JR, Hillmen P, O'Brien S, et al. Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATETM Trial of Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *Blood.* 2014;124 (21)(3331).
83. Brown JR, Davids M, Chang J, et al. Outcomes of Ibrutinib (Ibr) Therapy in Ibr-Naïve Patients (pts) with Chronic Lymphocytic Leukemia (CLL) Progressing after Venetoclax (Ven). . *Blood.* 2019;134 (Supplement_1): 4320.
84. AstraZeneca. KoL/KEE key insights. 2020. In.
85. Sinha R, Redekop WK. Cost-Effectiveness of Ibrutinib Compared With Obinutuzumab With Chlorambucil in Untreated Chronic Lymphocytic Leukemia Patients With Comorbidities in the United Kingdom. *Clin Lymphoma Myeloma Leuk.* 2018;18(2):e131-e142.

86. Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. *Leuk Lymphoma.* 2015;56(5):1320-1326.
87. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes.* 2010;8:50.
88. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ.* 2013;14(5):749-759.
89. Becker U, Briggs AH, Moreno SG, Ray JA, Ngo P, Samanta K. Cost-Effectiveness Model for Chemoimmunotherapy Options in Patients with Previously Untreated Chronic Lymphocytic Leukemia Unsuitable for Full-Dose Fludarabine-Based Therapy. *Value Health.* 2016;19(4):374-382.
90. Vreman RA, Geenen JW, Hovels AM, Goettsch WG, Leufkens HGM, Al MJ. Phase I/II Clinical Trial-Based Early Economic Evaluation of Acalabrutinib for Relapsed Chronic Lymphocytic Leukaemia. *Appl Health Econ Health Policy.* 2019;17(6):883-893.
91. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal (Updated: April 2013). Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword (accessed February 2020). In.
92. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health.* 2010;13(5):509-518.
93. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol.* 2012;30(23):2820-2822.
94. Office for National Statistics. National life tables: UK. 2019; https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
95. National Institute for Health and Care Excellence. TA119 Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. 2007. Available at: https://www.nice.org.uk/guidance/ta119 (accessed February 2020). In.
96. National Institute for Health and Care Excellence. TA202 Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. 2010 Available at: https://www.nice.org.uk/guidance/ta202 (accessed February 2020). In.
97. National Institute for Health and Care Excellence. TA344 Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. 2015. Available at: https://www.nice.org.uk/guidance/ta344 (accessed February 2020). In.
98. Hancock S, Wake B, Hyde C. Fludarabine as first line therapy for chronic lymphocytic leukemia 42. 2002. Birmingham, West Midlands Health Technology Assessment Collaboration. Ref Type: Report 1.
99. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making.* 2013;33(6):743-754.
100. Burnham, Kenneth P. and David R. Anderson . 2002. Model Selection and Multimodel Inference: A Practical Information-Theoretical Approach. 2d ed. New York: Springer-Verlag.
101. O'Brien SM, Byrd JC, Hillmen P, et al. Outcomes with ibrutinib by line of therapy and post-ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. *Am J Hematol.* 2019;94(5):554-562.
102. Dolan P. Modeling valuations for EuroQol health states. *Med Care.* 1997;35(11):1095-1108.
103. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health.* 2011;14(4):539-545.
104. Wehler E, Storm M, Kowal S, Caresse C, Boscoe B. A health state utility model estimating the impact of ivosidenib on quality of life in patients with relapsed/refractory acute myeloid leukemia. 2018; https://library.ehaweb.org/eha/2018/stockholm/215730/michael.storm.a.health.state.utility.model.estimating.the.impact.of.ivosidenib.html. Accessed April, 2020.
105. Electronic Medicines Compendium. SmPC: Imbruvica 140mg Film-Coated Tablets. April 2020. Available at: https://www.medicines.org.uk/emc/product/10025/smpc (accessed February 2020). In.

106. British National Formulary. British National Formulary. 2020; https://bnf.nice.org.uk/.
107. Gov.uk. Drugs and pharmaceutical electronic market information tool (eMIT). March 2020. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (accessed March 2020). In.
108. NHS improvement. Reference Cost Collection: National Schedule of Reference Costs - Year 2017-18 - NHS trust and NHS foundation trusts. https://improvement.nhs.uk/resources/reference-costs/.
109. Curtis, A. L, and Burns, Amanda. Unit Costs of Health and Social Care 2018. Unit Costs of Health and Social Care . PSSRU, Kent, UK, 176 pp. ISBN 978-1-911353-10-2. 2018.
110. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med.* 2015;29(10):899-907.
111. AstraZeneca. A randomised, multicentre, 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.
112. National Institute for Health and Care Excellence Decision Support Unit. Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: A critical review. 2017. Available at: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf (accessed August 2020). In.
113. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94(12):1353-1363.
114. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol.* 2012;12:9.
115. British National Formulary. Available: https://www.bnf.org/.
116. NHS England. National Tariff. Available at: https://www.england.nhs.uk/pay-syst/national-tariff/ (accessed August 2020).
117. NHS improvement. Reference Cost Collection: National Schedule of Reference Costs - Year 2017-18 - NHS trust and NHS foundation trusts. Available at: https://improvement.nhs.uk/resources/reference-costs/ (accessed August 2020).

B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

An SmPC and EPAR will be provided as soon as they become available.

Appendix D: Identification, selection and synthesis of clinical evidence

The details of the methods and results of the SLR of CLL are in the report provided separately in a standalone appendix D.

Appendix E: Subgroup analysis

No additional data to provide.

Appendix F: Adverse reactions

No additional data to provide.

Appendix G: Published cost-effectiveness studies

The details of the methods and results of the SLR of CLL are in the report provided separately in a standalone Appendix G.

Appendix H: Health-related quality-of-life studies

The details of the methods and results of the SLR of CLL are in the report provided separately in a standalone Appendix H.

Appendix I: Cost and healthcare resource identification, measurement and valuation

The details of the methods and results of the SLR of CLL are in the report provided separately in a standalone Appendix I.

(ID1613_BOI SLR in CLL_Report_v6).

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Please see confidential information checklist documents for details of data marked AIC or CIC.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Clarification questions

[August 2020]

File name	Version	Contains confidential information	Date
ID1613 acalabrutinib ERG clarification letter for company to PM Company response_[Redacted]	V1.0	Yes	8th September 2020

Notes for company

Highlighting in the template

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

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

SUNDEE

Section A: Clarification on effectiveness data

Additional references requested

A1. Please provide the Appendix for Sharman *et al*. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020;395(10232):1278-1291.

The appendix for Sharman *et al.* is included in the zipped folder as part of the reference pack for this set of responses to ERG questions.

A2. Please provide the full Clinical Study Report (CSR) for ELEVATE-TN.

The full CSR for ELEVATE-TN is included in the zipped folder as part of the reference pack for this set of responses to ERG questions.

A3. Please provide the full CSR for ASCEND.

The full CSR for ASCEND is included in the zipped folder as part of the reference pack for this set of responses to ERG questions.

A4. Please provide a list of all publications for ELEVATE-TN and ASCEND, including conference abstracts.

Table 1 presents a full publication list for ELEVATE-TN and ASCEND.

Table 1. Full publication list for ELEVATE-TN and ASCEND

ELEVATE-TN	ASCEND
Sharman J, Banerji V, Fogliatto LM *et al.* ELEVATE-TN: phase 3 study of acalabrutinib combined with obinutuzumab (O) or alone vs O plus chlorambucil (Clb) in patients (pts) with treatment-naïve chronic lymphocytic lukaemia (CLL). *Blood* 2019;134(Suppl 1):31.	Ghia, P., Pluta, A., Wach, M *et al.* ASCEND phase 3 study of acalabrutinib vs. investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic lukemia. European Hematology Association Library. 16 June 2019; 273529; LB2606
Sharman JP, Miklos E, Jurczak W *et al.* Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020;395:1278-91.	Ghia, P., Pluta, A., Wach, M *et al.* Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results. *J Clin Oncol* 2020; 38(Suppl):Abstr 8015.

ELEVATE-TN	ASCEND
-	Ghia, P., Pluta, A., Wach, M *et al.* ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol* 2020: doi: 10.1200/JCO.19.03355

Literature searching

A5. CS Appendix D.1.1., page 2. Please update the searches from 19th August 2019 and confirm that no further recent and eligible studies have been published.

The searches have been updated from 19th August 2019 to 10th February 2020. The objective of the SLR was to identify RCT publications for relevant comparators to the intervention (acalabrutinib monotherapy). Following the updated search, one RCT publication for a relevant comparator was extracted in the treatment-naïve chronic lymphocytic leukaemia (CLL) population, Sharman et al. 2019 (ELEVATE-TN), which included an obinutuzumab plus chlorambucil arm.[1] Sharman et al. 2019 does not present any additional information to the CSR used in the company submission. In the relapsed/refractory (R/R) CLL population, no additional RCT publications for relevant comparators were identified which were relevant to the decision problem. At second stage screening, no intervention (acalabrutinib monotherapy) trials were identified in addition to ELEVATE-TN and ASCEND. Full details of the SLR update including methodology and results are provided in Appendix A.

A6. CS Appendix D.1.1., page 2. Please confirm whether trials registers have been searched? If so, please provide the search strategy.

The Cochrane Database of Systematic Reviews (CDSR) and Cochrane Controlled Register of Trials (CENTRAL) were searched using the Cochrane Library interface. The search strategy for the Cochrane Library interface, with search timeframe from database inception to 10th February 2020, is provided in Appendix A, Table 48 of this document**.**

Ongoing studies

A7. CS, Section B.2.11, page 104. Please provide details of other ongoing studies of acalabrutinib in CLL (other than ELEVATE-TN and ASCEND) including comparators and expected primary completion dates.

Other than ELEVATE-TN and ASCEND, there are a total of 21 ongoing clinical trials in CLL with acalabrutinib as a study treatment. Table 2 presents the treatments and expected primary completion date for each ongoing trial.

Table 2. Ongoing trials for acalabrutinib in CLL

Trial name	Treatments	Expected primary completion date
Ace-Cl-311[2]	• Acalabrutinib + venetoclax • Acalabrutinib + venetoclax + obinutuzumab • Chemoimmunotherapy	March 2024
Ace-Cl-110[3]	• Acalabrutinib + ceralasertib	February 2022
Avo[4]	• Acalabrutinib + venetoclax + obinutuzumab	January 2022
Ace-Cl-006[5]	• Acalabrutinib • Ibrutinib	March 2021
Ace-Cl-002[6]	• Acalabrutinib followed by ACP-319 • ACP-319 followed by acalabrutinib	July 2020
ACE-CL-003[7]	• Acalabrutinib + obinutuzumab	January 2022
CLL2-BAAG[8]	• Bendamustine followed by obinutuzumab, acalabrutinib and venetoclax	May 2021
Ace-Cl-001[9]	• Acalabrutinib	January 2021
NCT03516617[10]	• Acalabrutinib • Acalabrutinib + obinutuzumab • Observational	March 2025
NCT04169737[11]	• Acalabrutinib (ACA) + venetoclax (VEN) +/- early obinutuzumab	July 2023
NCT03580928[12]	• Acalabrutinib, venetoclax, and O • obinutuzumab	January 2026
NCT03516617[13]	• Acalabrutinib • Acalabrutinib + obinutuzumab	March 2025
NCT03868722[14]	• Acalabrutinib + venetoclax • Placebo	July 2030
NCT04178798[15]	• Acalabrutinib • Wait and watch	February 2023
NCT04075292[16]	• Acalabrutinib • Chlorambucil + rituximab	February 2023
NCT04189952[17]	• Acalabrutinib in combination with R-ICE	March 2022

Trial name	Treatments	Expected primary completion date
NCT03932331[18]	• Acalabrutinib	October 2022
Ace-Cl-208[19]	• Acalabrutinib	February 2020
NCT02337829[20]	• Acalabrutinib	July 2021
Ace-Cl-003[21]	• Acalabrutinib + obinutuzumab • Acalabrutinib + venetoclax + rituximab • Acalabrutinib + obinutuzumab + venetoclax	January 2022
NCT03788291[22]	• Acalabrutinib + rituximab	February 2023

Included studies

A8. CS, Section B.2a.3, page 41. For ELEVATE-TN, please provide the following additional information:

(a) How many centres/patients were from the UK?

(b) Which concomitant medications were allowed, required or prohibited?

(c) Which subsequent treatments were received?

(a) In ELEVATE-TN, [redacted] trial sites were based in the UK with [redacted] patients enrolled in total. Information by site and treatment arm is presented in Table 3 (CSR, Table 14.1.1.1).

Table 3. Enrolment of patients in United Kingdom sites, ELEVATE-TN

	Acala + Obin (N=179)	Acala (N-=179)	Chlb +Obin (N=177)	Total (N=535)
United Kingdom	[redacted]	[redacted]	[redacted]	[redacted]
269 -Leicester Royal Infirmary	[redacted]	[redacted]	[redacted]	[redacted]
295 -Leeds Teaching Hospitals NHS Trust	[redacted]	[redacted]	[redacted]	[redacted]
331 -Southampton University Hospital	[redacted]	[redacted]	[redacted]	[redacted]
464 -Addenbrooke's Hospital	[redacted]	[redacted]	[redacted]	[redacted]
482 -Royal Bournemouth Hospital	[redacted]	[redacted]	[redacted]	[redacted]
617 -Kings College Hospital	[redacted]	[redacted]	[redacted]	[redacted]
622 -Royal Cornwall Hospital	[redacted]	[redacted]	[redacted]	[redacted]
637 -New Cross Hospital	[redacted]	[redacted]	[redacted]	[redacted]

	Acala + Obin (N=179)	Acala (N-=179)	Chlb +Obin (N=177)	Total (N=535)
941 -Derriford Hospital	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: NHS, National Health Service				

(b) In ELEVATE-TN the following concomitant medications were permitted (CSR, Section 9.4.6.1):

- Antiemetics, if clinically indicated
- Standard supportive care medications
- Hematopoietic growth factors
- Short course use of steroids for premedication use, or to manage obinutuzumab infusion-related reactions or to manage other inflammatory reactions, such as asthma exacerbations

In ELEVATE-TN the following concomitant medications were prohibited (CSR, Section 9.4.6.2):

- Any chemotherapy, anti-cancer immunotherapy, experimental therapy, or radiotherapy for treating CLL if being used to treat the disease initially under study.
- High-dose corticosteroids used to treat the underlying CLL.
- Warfarin and equivalent vitamin K antagonists (e.g. phenprocoumon)

In ELEVATE-TN the following concomitant medications were not recommended or had restrictions on use (CSR, Sections 9.4.6.3 and 9.4.6.4):

- Use of strong CYP3A inhibitors/inducers to be avoided when possible as acalabrutinib is metabolized by CYP3A
- Subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. This is based on the results of a study (ACE-HV-005) that evaluated the effect of agents that reduce gastric acidity (antacids or proton-pump inhibitors) on acalabrutinib absorption.

- Use of omeprazole, esomeprazole, lansoprazole, or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in exposure to acalabrutinib.
- Treatment with an H2-receptor antagonist is to be taken approximately 2 hours after an acalabrutinib dose.

(c) Table 4 presents the subsequent treatments received by subjects in ELEVATE-TN (CSR, Table 14.1.3.3).

Table 4. Subsequent anticancer therapy for CLL (ITT population)

Type of subsequent anticancer therapy - n (%)	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
Bendamustine	[redacted]	[redacted]	[redacted]
Anti-CD20 monoclonal antibodies	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]
Venetoclax	[redacted]	[redacted]	[redacted]
Immunosuppressives	[redacted]	[redacted]	[redacted]
RCHOP	[redacted]	[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]
CVP	[redacted]	[redacted]	[redacted]
Investigational drugs	[redacted]	[redacted]	[redacted]
Steroids	[redacted]	[redacted]	[redacted]
Obinutuzumab and chlorambucil	[redacted]	[redacted]	[redacted]
PI3K	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Vindesine	[redacted]	[redacted]	[redacted]

Abbreviations: CLL, Chronic lymphocytic leukaemia; CVP, Cyclophosphamide, vincristine sulfate, prednisone; FCR, Fludarabine, cyclophosphamide, rituximab; ITT, Intent-to-treat;; PI3K, Phosphoinositide 3-kinase; RCHOP, Rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone.

A9. CS, Section B.2b.3, page 67. For ASCEND, please provide the following additional information:

(a) How many centres/patients were from the UK?

(b) Which concomitant medications were allowed, required or prohibited?

(c) Which subsequent treatments were received?

(a) In ASCEND there were [redacted] patients in total from the United Kingdom (treated at the clinical trial service unit, University of Oxford), [redacted] patients in the acalabrutinib arm and [redacted] patient in the idelalisib plus rituximab arm (CSR, Table 14.1.1.1).

(b) In ASCEND, for subjects on idelalisib, prophylaxis for pneumocystis jirovecii pneumonia (PJP) was required for all patients throughout idelalisib treatment and for a period of 2-6 months after discontinuation of the drug (CSR, Section 9.4.6.1).

In ASCEND the following concomitant medications were permitted (CSR, Section 9.4.6.2):

- Anti-emetics if clinically indicated
- Standard supportive care medications, including hematopoietic growth factors
- Subjects considered at risk for tumour lysis syndrome received appropriate hydration and allopurinol or rasburicase.
- Subjects at risk for pneumonitis anti-infectious prevention was considered.
- Antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone)
- Prophylaxis with intravenous immunoglobulin (IVIG) in subjects with low immunoglobulin levels.
- For subjects at risk for infections, bacterial/viral/fungal prophylaxis was allowed per institutional standards.
- Short course use of steroids (≤2 weeks) >20 mg/day for premedication. Corticosteroids could be administered for longer than 2 weeks to treat idelalisib-related AEs (e.g., pneumonitis and colitis).
- Localised, short courses of radiotherapy were allowed for the treatment of lesions unrelated to the disease under study, if approved by the medical monitor. If a subject developed a second primary malignancy during the study,

continuation on study medication after curative treatment of the second primary malignancy could be considered after discussion with the medical monitor.

- Steroids to premedicate or manage rituximab infusion-related reactions.

In ASCEND the following concomitant medications were prohibited (CSR, Section 9.4.6.3):

- Any chemotherapy, anticancer immunotherapy, experiment therapy, radiotherapy for treating CLL if being used to treat the disease initially under study.
- High-dose corticosteroids used to treat the underlying CLL.
- Warfarin and equivalent vitamin K antagonists (e.g. phenprocoumon)

(c) Table 5 presents the subsequent treatments received by subjects in ASCEND (CSR, Table 14.1.3.4):

Table 5. Subsequent anticancer therapy for CLL (ITT population)

Type of subsequent anticancer therapy - n (%)	Arm A (Acalabrutinib) (N=155)	Arm B (IR/BR) (N=155)	Total (N=310)
Purine analogues	[redacted]	[redacted]	[redacted]
Alkylators other than Bendamustine	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	[redacted]
Anti-CD20 monoclonal antibodies	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]
Venetoclax	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Abbreviations: BR, Bendamustine/ rituximab; CLL, Chronic lymphocytic leukaemia; CD20, B-lymphocyte antigen CD20; IR, Idelalisib/ rituximab; ITT, Intent-to-treat;

A10. CS, Section B.2b.3, Table 32, page 72. In ASCEND, please clarify if TTNT was defined in the same way as ELEVATE-TN – *"The time from date of randomisation to date of start of non-protocol-specified subsequent anti-cancer treatment for CLL or*

death due to any cause, whichever occurred first". Was crossover to acalabrutinib monotherapy counted as the start of non-protocol treatment?

In the ASCEND trial, TTNT was defined as the time from date of randomisation to date of institution of non-protocol specified treatment for CLL (or first dose date of acalabrutinib for Arm B subjects who crossed over to receive acalabrutinib) or death due to any cause, whichever occurred first. Subjects who did not have the above specified events prior to the data cut-off date were censored at the date of last visit. TTNT was calculated as (earlier date of institution of non-protocol specified treatment for CLL or death due to any cause) - date of randomisation + 1. For censored subjects, the date of last visit replaced the earlier date of institution of non-protocol specified treatment for CLL or death due to any cause in the calculation (CSR, page 78).

Patients in Arm B who crossed over to acalabrutinib were included in the calculation of TTNT. Details are presented in Table 6 (CSR, Table 27). [redacted] subjects in the IR/BR arm ([redacted] subjects on IR and [redacted] subjects on BR) crossed over to acalabrutinib monotherapy. [redacted] of these crossover subjects discontinued acalabrutinib treatment as of the data cut-off date, including [redacted] subjects who discontinued due to an AE, [redacted] subjects who discontinued treatment due to PD, and [redacted] subject who discontinued for another reason (CSR, page 102).

Table 6. Time to next treatment (ITT Population)

	Arm A Acalabrutinib (N=155)	**Arm B IR or BR (N=155)**
Subject Status		
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Start of crossover therapy	[redacted]	[redacted]
Start of subsequent anticancer therapy	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: BR, Bendamustine/ rituximab; IR, Idelalisib/ rituximab; ITT, Intent-to-treat

A11. CS, Section B.2a.4.3, Figure 4, page 51. Within ELEVATE-TN, please confirm that 179 patients were included in the safety analysis for acalabrutinib monotherapy (178 allocated and n=1 switched treatment group).

In ELEVATE-TN there were 179 subjects included in both the ITT population and the safety population for the acalabrutinib arm (CSR, Table 11).

A12. PRIORITY. CS, Section B.2a.10.4, page 65. With respect to ELEVATE-TN, please clarify:

(a) The number of deaths in the ITT and safety populations. Deaths from any cause in the obinutuzumab plus chlorambucil group are stated as 13 in CS Section B.2a.10.4, whilst 15 deaths are reported in the Lancet publication.

(b) The number and causes of deaths due to AEs (number and type of AE).

(c) The number of discontinuations due to AEs (number and type of AE).

(a) The Lancet publication and CS Section B2a.10.4, taken from the ELEVATE-TN CSR, Table 41 report different number of deaths from any cause in the obinutuzumab plus chlorambucil group because one includes two additional patients from the crossover period. 13 deaths from CSR Table 41 are based on source Table 14.3.3.2 which only included death during the randomisation period while 15 deaths are based on source Table 14.3.3.1 which included both the randomisation and crossover periods.

(b) Table 7 presents the breakdown of the number and causes of death due to AE in ELEVATE-TN (CSR, Table 14.3.3.3). In total, there were [redacted] deaths due to AEs in the safety population: [redacted] in the acalabrutinib plus obinutuzumab group, [redacted] in the acalabrutinib monotherapy group, and [redacted] in the obinutuzumab plus chlorambucil group.

Table 7. Treatment emergent adverse events with a fatal outcome (Grade 5) in the safety population of the ELEVATE-TN study

Preferred term	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
Subjects with a Grade 5 TEAE- n (%)	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Gastric cancer stage IV	[redacted]	[redacted]	[redacted]

Preferred term	Acala + Obin (N=179)	Acala (N=179)	Chlb + Obin (N=177)
Metastases to bone	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Acute myelomonocytic leukaemia	[redacted]	[redacted]	[redacted]
Bacterial sepsis	[redacted]	[redacted]	[redacted]
Bronchopulmonary aspergillosis	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Goitre	[redacted]	[redacted]	[redacted]
Lung adenocarcinoma	[redacted]	[redacted]	[redacted]
Myositis	[redacted]	[redacted]	[redacted]
Parkinson's disease	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]
Abbreviations: TEAE, Treatment-emergent adverse event			

(c) Sharman et al. 2020 (Supplementary materials, Table S7) shows the AEs of any grade leading to treatment discontinuation. In total, 19 subjects in the acalabrutinib plus obinutuzumab arm and 17 subjects in the acalabrutinib monotherapy arm discontinued acalabrutinib treatment due to AEs. In total, 11 subjects in the acalabrutinib plus obinutuzumab arm and 10 subjects in the obinutuzumab plus chlorambucil arm discontinued obinutuzumab due to AEs. In total, 24 subjects in the obinutuzumab plus chlorambucil arm discontinued chlorambucil due to AEs.

Table 8 presents the number discontinuations due to TEAEs and type of TEAEs in ELEVATE-TN (CSR, Table 14.3.5.5).

Table 8. Adverse events leading to discontinuation of study treatment in ≥2 subjects in any treatment arm (Safety population), ELEVATE-TN

Preferred term	N (%) of subjects					
	Arm B Acalabrutinib + Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N= 179)		Arm A Obinutuzumab + Chlorambucil (N=169)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with ≥1 TEAE leading to discontinuation of **acalabrutinib**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	N (%) of subjects					
	Arm B Acalabrutinib + Obinutuzumab (N=178)		Arm C Acalabrutinib Monotherapy (N= 179)		Arm A Obinutuzumab + Chlorambucil (N=169)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hepatitis B reactivation	[redacted]					
Sepsis						
Subjects with ≥1 TEAE leading to discontinuation of **obinutuzumab**						
Infusion related reaction						
Neutropenia						
Subjects with ≥1 TEAE leading to discontinuation of **chlorambucil**						
Neutropenia						
Thrombocytopenia						
Upper respiratory tract infection						
Abbreviations: TEAE, Treatment-emergent adverse event						

A13. PRIORITY. CS, Section B.2b.10.1, page 97. With respect to ASCEND, please clarify:

(a) The number of deaths due to AEs

(b) The reasons for discontinuations due to AEs (number and type of AE)

(c) Discontinuations due to AEs in acalabrutinib monotherapy group n=16 (CS Figure 10) or n=17 (CS B.2b.10.1).

(a) In the acalabrutinib monotherapy group of ASCEND, 8 subjects (5.2%) died due to AEs; [redacted] In the IR group, 9 subjects (7.6%) died due to AEs; [redacted] In the BR group, 4 subjects (11.4%) died due to AEs (CSR, Table 40).

(b) Table 9 provides a summary of discontinuations due to TEAEs (CSR, Table 34). Among the subjects who had TEAEs, 16 (10.4%) from the acalabrutinib arm,

[redacted] from the IR arm and [redacted] from the BR arm discontinued treatment. In the acalabrutinib arm, [redacted] and there were no TEAEs that led to discontinuation by more than 1 subject. There were [redacted] leading to discontinuation related to acalabrutinib, including [redacted]

In subjects who received IR, 59 (50.0%) subjects had TEAEs that led to discontinuation of idelalisib, of which [redacted] had Grade ≥3 events. Among the most common TEAEs leading to discontinuation, were: diarrhoea (14 [11.9%] subjects), increased alanine aminotransferase (5 [4.2%] subjects), pneumonia and increased transaminases (4 [3.4%] subjects each), and increased aspartate aminotransferase, colitis, interstitial lung disease, and pneumonitis (3 [2.5%] subjects each).

In subjects who received BR, 4 (11.4%) subjects had TEAEs leading to discontinuation of bendamustine, of which [redacted] subjects had Grade ≥3 events.

In subjects who received IR or BR, 21 (13.7%) subjects with TEAEs that led to discontinuation of rituximab included [redacted] subjects with Grade ≥3 events. Pneumonia was the most commonly reported TEAE that led to rituximab discontinuation (3 [2.0%] subjects), followed by infusion-related reaction (2 [1.3%] subjects). All other events occurred in 1 subject each.

In the crossover period, there were a total of [redacted] subjects who discontinued due to TEAEs [redacted]

Table 9. TEAEs leading to drug discontinuation in ASCEND (safety population)

	N (%) of Subjects		
	Arm A	Arm B	
	Acalabrutinib (N=154)	IR (N=118)	BR (N=35)
TEAE leading to drug discontinuation	16 (10.4%)	[redacted]	[redacted]

Acalabrutinib only	16 (10.4%)	N/A	N/A
Rituximab only	N/A	[redacted]	[redacted]
Bendamustine only	N/A	N/A	[redacted]
Idelalisib only	N/A	[redacted]	N/A
Bendamustine and rituximab	N/A	N/A	[redacted]
Idelalisib and rituximab	N/A	[redacted]	N/A
Abbreviations: BR, Bendamustine/ rituximab; IR, Idelalisib/ rituximab N/A, not available; TEAE, Treatment-emergent adverse event			

(c) The discrepancies between the two sections of the CS were due to differences in patient numbers between the ITT and safety population. The 17 subjects in Figure 10 of the CS (CSR, Table 12) relate to the ITT population. The 16 subjects in B.2b.10.1 (CSR, Table 34) relate to the safety population.

A14. CS, Section B.2a.6, page 53. Please present a summary of the HRQoL outcomes in ELEVATE-TN and provide the PRO CSR.

The PRO CSR for ELEVATE-TN is included in the zipped folder as part of the reference pack for this set of responses to ERG questions. The FACIT-Fatigue, European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EuroQoL five-dimension three-levels (EQ-5D 3L) instruments were administered in ELEVATE-TN. Based on the results of the literature review from the PRO CSR and patient interviews, the FACIT-Fatigue and EORTC Global Health Status (GHS) were used as primary PRO-endpoints.

A summary of the baseline scores of all the PRO instruments for the ITT and safety populations can be found in Figure 31 and Figure 32 of Appendix B. During the period subjects were progression free and remained in the study, subjects show improvement in symptoms that are relevant to the CLL. Specifically, with changes from baseline of 3.77 points (acalabrutinib plus obinutuzumab) and 4.66 points (acalabrutinib monotherapy) in the ITT population and 9.98 points (acalabrutinib plus obinutuzumab) and 11.79 (acalabrutinib monotherapy) in the safety population on a 0-52 scale over 96 weeks and improvement in overall HRQoL (as measured by the EORTC QLQ-C30 GHS) with changes from baseline of 5.88 points (acalabrutinib plus obinutuzumab) and 7.72 points (acalabrutinib monotherapy) in the ITT population and 14.50 points (acalabrutinib plus obinutuzumab) and 12.83 points (acalabrutinib monotherapy) in the safety population on a 0–100 scale over 96

weeks. In subjects who received acalabrutinib compared with the combination of obinutuzumab plus chlorambucil, time to progression was prolonged and improvements in fatigue and overall HRQoL were observed. Specifically, among subjects receiving acalabrutinib plus obinutuzumab, improvements in fatigue and overall HRQoL of 3.77 points (GFS) and 5.88 points (GHS) were observed at Week 96. For subjects receiving acalabrutinib monotherapy, improvements in fatigue and overall HRQoL of 4.66 points (GFS) and 7.72 points (GHS) were observed at Week 96.

A15. CS, Section B.2b.6, page 81. Please present a summary of the HRQoL outcomes in ASCEND and provide the PRO CSR.

The PRO CSR for ASCEND is included in the zipped folder as part of the reference pack for this set of responses to ERG questions. Both FACIT-Fatigue and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 were administered in ASCEND and were used as primary PRO-endpoints.

During this period, subjects showed improvement in symptoms that are relevant to the CLL. Specifically, subjects showed improvement in fatigue (as measured by the FACIT-Fatigue Global Fatigue Scale) with increased scores of 3.61 points in the total population and 10.32 points in the safety population on a 0–52 scale over 48 weeks and improvement in overall HRQoL (as measured by the EORTC QLQ-C30 Global Health Scale) with increased scores of 7.21 points in the total population and 14.74 points in the safety population on a 0–100 scale over 48 weeks.

In subjects receiving acalabrutinib, compared with IR/BR, time to progression or death was prolonged, the proportion of subjects experiencing side effects was lower, and equal improvements in symptoms and impacts that are relevant to the subjects were observed. Specifically, among subjects receiving acalabrutinib, improvement in fatigue and overall HRQoL of 3.61 points (GFS) and 7.21 points (GHS) were observed at Week 48.

A16. CS, Section B.2a.3.3., page 44. For ELEVATE-TN, please clarify the frequency of outcome measurement assessment (i.e. please provide the schedule of assessments).

The full schedule of assessments in ELEVATE-TN is included in the zipped folder as part of the reference pack for this set of responses to ERG questions.

The frequency of outcome measurement assessment for all treatment arms was as follows (a cycle=28 days):

- PRO: on Day 1 of Cycles 1-7, then every 24 weeks from Cycle 7 Day 1.
- Overall response assessment: every 12 weeks (+/- 14 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on-treatment scan on Cycle 7 Day 1, and so on through Cycle 24, and then every 24 weeks (+/- 14 days) thereafter.
- Adverse events: Day 1, 2, 8, 15 and 22 of Cycle 1; Day 1, 8 and 15 of Cycle 2; Day 1 and 15 of Cycles 3 to 6; Day 1 of Cycle 7; then every 12 weeks starting at Cycle 10 (e.g. Cycles 10, 13, 16). For patients who permanently discontinued the study drug early for any reason, a safety follow-up visit was conducted after 30 (+7) days after the last dose of study drug.

Inclusion criteria

A17. CS Appendix D, Table 5, page 9. The eligibility criteria presented in Table 5 are for a systematic review that was conducted by the company. However, eligibility criteria for the review presented in the CS were more restrictive – the comparator was restricted to chlorambucil plus obinutuzumab or ibrutinib for treatment-naive CLL patients, and to ibrutinib only for previously treated CLL patients. Also, the CS appears to be restricted to RCTs, unlike the inclusion criterion for the review in Appendix D Table 5. Please provide the eligibility criteria for the review presented in the CS.

To clarify, the original SLR performed by the company (up until 19th August 2019) was performed with eligibility criteria as per CS (Appendix D, Table 5). This SLR identified a broad range of comparators. In line with the comparators considered

appropriate to the decision problem, CS Section B.1.1.1, restrictions were applied such that data on the following comparators only was extracted:

- Treatment naïve CLL
    - obinutuzumab with chlorambucil
    - ibrutinib
- R/R CLL
    - ibrutinib

Given the availability of RCT evidence, only RCTs were included and extracted as they are considered the gold standard for the measure of efficacy and safety to inform healthcare decision making and enable ITCs.[23] At second stage screening, no acalabrutinib monotherapy trials were identified in addition to the pivotal studies, ELEVATE-TN and ASCEND.

A18. CS Appendix D, Table 5, page 9. Please clarify the age cut-off used to define adult patients.

Age was not specified as an inclusion criterion for the SLR in CS Appendix D. The term “adult patients” was defined as patients who are ≥18 years old. After reviewing all publications included and extracted from the SLR, we can confirm that all studies included adult patients defined as ≥18 years old with an average age of 65+ years old.

A19. CS Appendix D, Table 5, page 9. Please clarify if any restrictions were applied with respect to the dose of the interventions.

In the SLR, no restrictions were applied based on dose of interventions.

A20. CS Appendix D, Table 5, page 9. The NICE scope included idelalisib with rituximab as a comparator for treatment-naïve CLL. However, this comparator is not listed in Table 5 for this population. Please clarify why this option was not included as a comparator in the review.

Ibrutinib was recommended by NICE in TA429 for patients who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable.[24] However, since the introduction of ibrutinib, idelalisib with rituximab is no longer routinely used

in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab.[24] This position was supported by UK clinical experts at an advisory board who stated that idelalisib with rituximab is rarely used in clinical practice due to safety concerns and that ibrutinib has replaced idelalisib with rituximab as standard of care (SoC) because idelalisib with rituximab has a higher risk of infection and death.[25]

Furthermore, the BSH guidelines highlight that the higher risk of infection and death associated with idelalisib therapy has led to the European Medicines Agency (EMA) amending the licence to "first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies".[26,27] Therefore, idelalisib with rituximab is not considered a relevant comparator for this appraisal as idelalisib would only be appropriate for patients in whom a BTK inhibitor is unsuitable.

A21. CS, Appendix D, page 11. ASCEND was not identified in the SLR. Please clarify how this study was identified.

ASCEND was identified in the original SLR (timeframe: database inception to 19th August 2019) through Ghia et al. 2019.[28] The CSR contains all information for ASCEND data analyses that are contained in Ghia et al. 2019. No additional ASCEND publications were identified in the SLR update (timeframe: August 2019 to 10th February 2020) as no further data from the clinical trial had been published up to this date cut-off.

A22. CS, Appendix D, page 38. Please confirm if quality assessment in the CS was conducted by one reviewer and checked by another, as was done for data extraction.

The quality assessment in the CS was performed by one reviewer.

A23. CS Section B.2b.2 page 65. The SLR identified 5 RCTS evaluating ibrutinib. Clinical effectiveness evidence for ibrutinib to inform the CS was taken from RESONATE alone, since this was used in a previous appraisal (TA429). Please

provide further justification of why the additional trials (particularly those published after TA429) were not considered to be informative to the current appraisal.

Byrd 2014 relates to RESONATE, the pivotal Phase III trial evaluating the efficacy and safety of ibrutinib in patients with R/R CLL.[29] The remaining four RCTs in the CS Section B2b.2, page 65, were not considered informative to the current appraisal because:

- De Jong 2015 reported phase 1 and 2 single-arm trials assessing ibrutinib pharmacokinetics under fasted and fed condition, impact of food-intake timing, and the safety and tolerability, and thus not relevant to the current appraisal.[30]
- Sharman 2017 (abstract) reported results for the GENUINE study which assessed ibrutinib alone or in combination with ublituximab. The publication did not report PFS or OS, the key outcomes of interest for the comparison of acalabrutinib versus ibrutinib, and was therefore not informative to the current appraisal.[31]
- Huang 2018 reported results of a study evaluating the efficacy and safety of ibrutinib compared with rituximab in predominantly Asian patients from China, Australia, Taiwan, and Malaysia. Overall, 85.6% (137/160) of patients were Asian. The RESONATE study included patients from UK/European centres and therefore is more relevant to the current submission.[32]
- Burger 2019 reported results of a single-centre, open label, Phase II study conducted in the US to evaluate the benefits of adding rituximab to treatment with ibrutinib only. Given that this was a single-centre and earlier phase study, the RESONATE study remained the preferred source of evidence to inform the current submission.[33]

Matching-adjusted indirect comparison

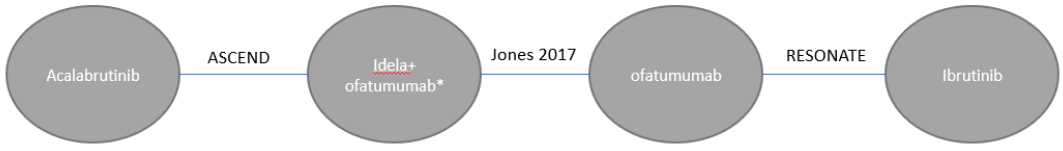
A24. PRIORITY. CS, Section B.2b.9, page 89. The CS states that *"NMA methodology has limitations ..."* and so in the absence of head-to-head studies of acalabrutinib and ibrutinib, a MAIC was performed instead. The early submission to NICE also presented an NMA. Please provide further details on why this NMA was

not included in the final submission, providing limitations of the specific analysis rather than NMA methodology in general.

In the R/R setting, ibrutinib represents established NHS practice and is therefore the relevant comparator to this appraisal in patients with previously treated CLL. In the absence of head-to-head data for acalabrutinib and ibrutinib, a network meta-analysis (NMA) was explored. This NMA was not included in the final submission, and instead AstraZeneca submitted a matched-adjusted indirect comparison (MAIC). AstraZeneca believes that the MAIC in R/R setting is appropriate for decision making as cross-trial heterogeneity was more adequately addressed. The reasons why the NMA was excluded from the final submission are explained below.

1. **Unanchored and open network and the need to further assume equal efficacy between comparators to derive a common comparator**
   - The most frequently used comparator in the ASCEND trial was idelalisib plus rituximab (IR). However, no studies were identified that compared IR vs. ibrutinib in the SLR. No common comparator could be identified with bendamustine plus rituximab (BR) either.
   - Figure 1 illustrates a potential unanchored network between the ASCEND and RESONATE studies for acalabrutinib and ibrutinib, respectively. The network would have relied on a study comparing idelalisib plus ofatumumab vs ofatumumab (Jones 2017). In order to allow a comparison to ibrutinib, based on the RESONATE trial, only one study potentially allowed for a connected network (Figure 1).

Figure 1. Path to connect acalabrutinib and ibrutinib in the RR population using the equivalence of idelalisib plus rituximab and idelalisib plus ofatumumab



   - This network would have required to assume equivalence of idelalisib plus ofatumumab (IdO) and IR, whereby ofatumumab or rituximab in combination with idelalisib were considered equivalent. This assumption was accepted by

the NICE committee in the appraisal of ibrutinib in the R/R setting (TA429). The equivalence of the combinations could be observed through the overlaying of the KM curves from the ASCEND and the study by Jones and colleagues.[34]

- Assuming equivalence of IdO and IR, acalabrutinib and ibrutinib could potentially be connected through IdO and ofatumumab based on Jones 2017 and RESONATE. [34,35]

2. **Concerns over the relevance of studies informing the network**
   - IR is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with IR.[24]
   - The combination of IdO is not routinely commissioned in UK practice as it was not reviewed by NICE and is not used in clinical practice.

3. **Unable to control for cross-trial heterogeneity**

   Certain factors were identified as prognostic through the analysis of individual patient level (IPD) data in ASCEND or through literature. These included age, gender, CIRS score, number of prior therapies, ECOG score, bulky disease, Rai/Binet stage, complex karyotype, 17p del, 11q del, TP53 mutation, IGHV mutation and level of β2-microglobulin.
   - Difference in inclusion criteria: ASCEND allowed patients with an ECOG score of 2 in the R/R population based on the inclusion and exclusion criteria, unlike the RESONATE trial.
   - Differences in patient population between ASCEND and RESONATE, included different proportion of patients with 17p deletion or TP53 mutation, bulky disease, prior therapies, RAI staging or complex karyotype that cannot be controlled for in an NMA (further detail provided in CS Document B, Table 44).

A25. CS, Section B.2b.9, page 91. The CS states *"The approach uses digitization software (e.g., Engauge digitization software[32])…. using the reconstruction algorithm.[33] ".* Please clarify which digitization software was used, and which

reconstruction algorithm was used. CS references #32 and #33 do not relate to digitisation software or reconstruction algorithms.

To confirm, the Engauge digitization software was used. CS reference #32 was unlinked to the reference list and the correct reference is:

- Engauge Digitizer. Available at, http://markummitchell.github.io/engauge-digitizer/ (accessed, 20th September 2019).

The reconstruction algorithm was based on the Guyot algorithm. CS reference #33 was unlinked to the reference list and the correct reference is:

- Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

A26. CS, Section B.2b.9, page 89. Please clarify the software used to perform the MAIC.

The software used to perform the MAIC was R version 3.6.2.

A27. CS Section B.2b.9.2, page 93. Please clarify how the final selection of variables for the MAIC was made. Why was the base-case favoured over the models presented in the sensitivity analysis (Table 47)?

The following baseline characteristics were considered to be matched between ASCEND and RESONATE in the MAIC based on the preliminary feasibility assessment and discussions with clinical experts:

- Age
- Sex
- Presence of bulky disease (≥ 5 cm)
- Presence of del (17p)
- Presence of del (11q)
- ECOG PS
- β2 microglobulin at baseline (> 3.5 mg/litre)
- Rai stage

- Number of prior therapy lines (1, 2 or ≥ 3)
- Complex Karyotype
- Immunoglobulin heavy-chain variable (IGHV) gene mutation status
- TP53 mutational status
- Binet stage
- CrCl < 60 per min (note: subgroup analysis did not use CrCl, instead TP53 mutational status and race were used)

After performing the MAIC, all baseline characteristics above were balanced (i.e. statistically equivalent) between the acalabrutinib and ibrutinib-treated patients except for TP53 status, Binet stage and ECOG PS 2 (CS, Section B.2b.9.2, Table 44). TP53 status was only available for 62% of the patients; however, as this is correlated with del17p, the base-case included del17p only. Furthermore, del 11q, complex karyotype and IGHV were only available for 97%, 78% and 69% of the ibrutinib population in RESONATE. Due to the overlap on Rai and binet staging, Rai stage only was included in the base case. Patients in ASCEND who were ECOG PS 2 at baseline (n=19) were not included in the matching because RESONATE did not include patients with this performance status. A further 4 patients were removed due to missing baseline characteristics therefore 132 acalabrutinib patients were matched.

The selection of variables for the base case followed NICE DSU TSD 18 guidance, and was based on a mix of clinical opinion and statistical analysis.[36] For the economic models, the base case was selected as key baseline and disease characteristics aligned with the CLL International Prognostic Index[37] (CLL IPI), and the effective sample size (ESS=44) was larger than with any of the sensitivity analyses (please see A29, Table 11).

A28. In all MAIC analyses, age was included as a binary covariate (Age > 70). Please justify the use of this cut-off and comment on the likely impact on MAIC weights. Why was age not included as a continuous covariate? The background section of the CS (page 23) mentions increased risk for elderly patients over 65.

The age cut-off was driven by the data reported for the RESONATE study in Brown et al 2014.[38] The data was retrieved from this as it provided follow-up length

corresponding to the ASCEND dataset. Age as a continuous variable could thus not be used in the MAIC.

The likely impact on the MAIC weights is unknown; however, the distribution of patients by age was similar in ASCEND (acalabrutinib: median=68; min=32; max:89) and RESONATE (ibrutinib: median=67; min=30; max: 86), therefore the impact of using a different approach to matching age is likely to be minimal.

A29. PRIORITY. Please provide the following additional results and details for the MAIC, that were described in the methods but not included in the CS:

(a) Assessment of the distribution of the produced weights (histogram and summary statistics for the base-case MAIC)

(b) Weighted KM curves (base-case MAIC)

(c) Assessment of proportional hazards (base-case MAIC)

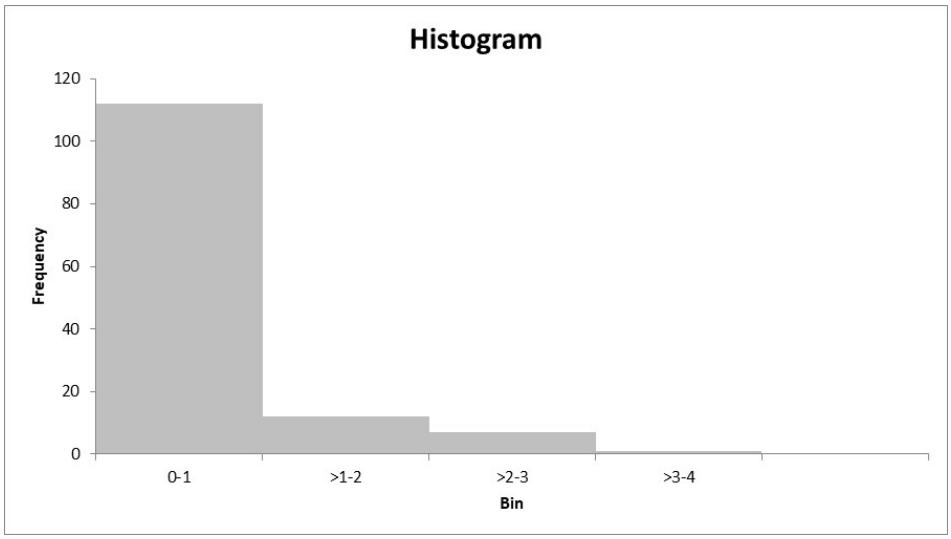
(d) Effective sample size (ESS) for sensitivity analyses 1-5.

(a) The mean and median MAIC weights in the base case were 0.49 and 0.19, respectively. Table 9 presents the distribution of the produced MAIC weights and Figure 2 presents MAIC weights' histogram.

Table 9. Distribution of the produced MAIC weights

Bin	#	Frequency (%)
0-1	112	85%
>1-2	12	9%
>2-3	7	5%
>3-4	1	1%
Abbreviations: MAIC, Matched adjusted indirect comparison		

Figure 2. Histogram representing the distribution of the produced MAIC weights



(b) Figure 3 and Figure 4 present weighted KM curves (base case MAIC) for PFS and OS.

Figure 3. PFS before and after matching in the MAIC analysis of acalabrutinib vs. ibrutinib in the R/R setting

Figure 4. OS before and after matching in the MAIC analysis of acalabrutinib vs. ibrutinib in the R/R setting

(c) Schoenfeld residuals were used to test the proportional hazard (PH) assumption. If PH holds, the plot of the residuals against time should show a linear trend with slope (rho coefficient)=0. A p-value was also output as the result of a test of non-negative slope (Therneau and Grambsch), where a p-value<0.05 would imply a violation of PH. [39]

Various reasons suggest that proportional hazard assumption held in the MAIC analysis (Table 10):

- Results of the rho coefficient suggest a linear trend
- Test for non-negative slope was not significant (p-value > 0.05)

Table 10. Results of test for proportionality in the R/R MAIC

	Outcome	Rho coefficient	p-value
Acalabrutinib vs. ibrutinib	PFS	-0.00355	0.97
	OS	0.101	0.464
Abbreviations: OS, Overall survival; PFS, Progression-free survival; PH, Proportional hazards			

(d) Table 11 presents the ESS for sensitivity analyses 1-5.

Table 11. ESS for sensitivity analyses 1-5

Sensitivity analyses number	ESS for acalabrutinib
1	34.7
2	42.4
3	34.8
4	41.8
5	35.1
Abbreviations: ESS, effective sample size	

Section B: Clarification on cost-effectiveness data

For clarification, AstraZeneca would like to highlight that a cost included in the 1L CUA was not written up in the CS, Document B.

The model accounts for one-time monitoring costs for venetoclax at treatment initiation. These were included to account for the costs associated with laboratory TLS prophylaxis required for all patients before initiation of venetoclax treatment. Accordingly, TLS prophylaxis costs (£1,975.46) sourced from a NICE submission of venetoclax plus rituximab were applied in the 1st cycle to all patients starting venetoclax.[40] This cost was included in the submitted CUA presented and is also included for all other analyses presented in the ERG response (including the updated base case and the two new CUAs).

The updated base case for the CUA based on the correction of errors identified by the ERG in B1, B15, B16, B17 and B18 is presented in Table 12. The base case ICER has reduced from [redacted] to [redacted]

Table 12. Base-case results (A vs C+O)

Technologies	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
C+O	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A, acalabrutinib; C+O, chlorambucil + obinutuzumab; ICER, incremental cost-effectiveness ratio; LYs, life-years gained; QALY, quality-adjusted life-year.

General questions – applicable to all models

B1. All three CLL models. Please clarify which year of NHS Reference Costs was applied in the three economic analyses.

The 2017/2018 NHS reference costs were used across all three models.[41] AstraZeneca recognise there are updated 2018/2019 NHS reference costs available and have updated these in all analyses provided in this response document. Table 13 shows the updated costs used in the analyses.

In the CUA comparison against chlorambucil plus obinutuzumab, the impact of this change on the cost-effectiveness of acalabrutinib is minimal, with the base case

ICER decreasing from [redacted] to [redacted] per QALY. In the 1L cost-minimisation analysis, the cost saving for acalabrutinib reduced from [redacted] to [redacted] and in the R/R cost-minimisation analysis, the cost saving remained at [redacted]. The updated costs were also used in the two additional CUAs (ERG clarification questions C1 and C2).

Table 13. NHS reference costs utilised in CUA for acalabrutinib vs chlorambucil plus obinutuzumab

Resource	2017/2018 unit cost	2018/2019 unit cost	NHS reference cost description
Disease management costs			
Full blood count	£2.51	£2.79	DAPS05
LDH	£1.11	£1.10	DAPS04
Haematologist visit	£159.65	£166.51	Outpatient attendances: 303 – Clinical Haematology
Chest X-ray	£77.48	£71.92	Imaging: Direct Access – RD50Z
Bone marrow exam	£495.98	£558.16	Diagnostic Bone Marrow Extraction – SA33Z
Inpatient visit (Non-surgical)	£432.93	£433.17	Weighted average of day case SA32A, SA32B, SA32C and SA32D
Full blood transfusion	£187.97	£253.13	OPROC Outpatient attendances: 303 – Clinical Haematology: Single Plasma Exchange and Other Intravenous Blood Transfusion, 19 years and over – SA44A
Administration costs			
Deliver Simple Parenteral Chemotherapy at First Attendance	£228.29	£241.06	SB12Z
Adverse event costs			
Anaemia	£366.00	£341.86	Currency code: SA04L
Atrial fibrillation	£1,783.94	£1,770.38	Assumed to be the same as for infections
Bleeding	£1,783.94	£1,770.38	Assumed to be the same as for infections
Diarrhoea	£149.00	£140.89	Outpatient attendances: 301
Fatigue	£636.67	£603.34	Activity weighted average (AA31C-AA31E)
Hypo/Hypertension	£658.95	£598.58	EB04Z
Infections and infestations	£1,783.94	£1,770.38	Activity weighted average (DZ11K – DZ11V) cost for pneumonia.
Thrombocytopenia	£640.09	£674.07	Activity weighted average (SA12G – SA12K)

Abbreviations: LDH, lactate dehydrogenase; NHS, National Health Service

B2. CS, Section B.3b, page 173. The CS states *"Acalabrutinib requires no additional monitoring above that currently conducted for biologic therapies already*

recommended for use in R/R CLL". Please justify the exclusion of these monitoring costs for all therapies.

It is not anticipated that acalabrutinib will require any additional monitoring requirements above those already implemented in routine clinical practice for other biological therapies. This includes the current standard of care chlorambucil plus obinutuzumab for patients in the first-line setting who are ineligible for FCR therapy, or ibrutinib in previously untreated high-risk patients, and R/R patients.

B3. All three CLL models. The models assume that all adverse events (AEs) are resolved in less than 1 month. Please comment on the clinical plausibility of this assumption.

AEs were incorporated as a one-off decrement on cost and quality of life and applied in the first cycle of the model. This approach was taken under the assumption that AEs are likely to occur very soon after treatment initiation and will only require acute care. It is expected that AEs are managed quickly with either dose reductions or dose interruptions and this approach towards adverse event modelling is commonplace in previous technology appraisals in CLL (e.g. NICE TA429 and NICE TA561). Given that the expected duration of each of the listed AEs is less than 28 days, the assumption that all AEs are resolved in less than a month is considered appropriate.

A small proportion of patients may experience an AE lasting longer than a month; however, these are typically limited to bruising, arthralgia and/or headaches which are often < Grade 3, self-limiting in nature and are most often managed via OTC analgesics.

B4. PRIORITY. All three CLL models. The models estimate drug costs assuming 100% relative dose intensity (RDI).

(a) Please explain why this assumption was made.

(b) Please provide details of mean RDI for acalabrutinib and obinatuzumab plus chlorambucil in ELEVATE, ibrutinib in RESONATE and venetoclax plus rituximab in MURANO.

(a) The relative dose intensity (RDI) for acalabrutinib, chlorambucil plus obinutuzumab and the subsequent treatments included in the analysis were high and consistently above 94% (Table 14). The models thus assumed a 100% RDI across all treatments. Using actual RDI is anticipated to have a small impact on the results.

(b) A summary of the mean RDI for acalabrutinib and chlorambucil plus obinutuzumab in ELEVATE-TN, ibrutinib in RESONATE, and venetoclax plus rituximab in MURANO is presented in Table 14.

Table 14. Mean relative dose intensity for acalabrutinib and comparators

Treatment	Mean relative dose intensity (RDI)	Reference
Acalabrutinib	96.8%	ELEVATE-TN CSR, Table 14.3.1.1.
Chlorambucil plus obinutuzumab	93.8%	ELEVATE-TN CSR, Table 14.3.1.2.
Ibrutinib (RESONATE)	94.8%	ID749 Committee papers – Ibrutinib
Venetoclax plus rituximab (MURANO)	Median dose intensity – 97% (mean not reported)	ID1097 Committee papers – Ven+R
Abbreviations: CSR, clinical study review.		

B5. All three CLL models. The models do not include administration costs for acalabrutinib or ibrutinib. Please confirm that pharmacy preparation and dispensing costs are not relevant for either of these drugs.

Further engagement with UK clinical experts confirmed that there are no additional pharmacy preparation or dispensing costs associated with oral cytogenetic therapies, such as BTKi's compared with non-cytogenetic medicines. Given that both medications are presented in tablet formulations and the dispensing processes are the same, pharmacy preparation and dispensing costs can be assumed to be equivalent between acalabrutinib and ibrutinib. As such, inclusion of such costs would not bear any impact on the relative cost-effectiveness of either of these drugs.

Untreated CLL model - acalabrutinib versus obinatuzumab plus chlorambucil

B6. CS, Section B.3a.2, page 115. This model includes a proportion of patients with high-risk cytogenetic factors ((del)17p and TP53). The CS states that these patients would be treated with ibrutinib and a separate cost-minimisation analysis is presented for this subgroup. Why have these patients been included in the untreated CLL cost-utility model?

Patients with a high-risk cytogenetic factor ((del)17p or TP53) represented a relatively small proportion in both arms of the ELEVATE-TN study, which informs the untreated CLL model for acalabrutinib versus obinutuzumab plus chlorambucil. In ELEVATE-TN the proportions of patients with high-risk cytogenetic factors were (del)17p= 16/179 (8.9%) and TP53=19/179 (10.6%) for acalabrutinib and (del)17p=16/177 (9.0%) and TP53=21/177 (11.9%) for obinutuzumab plus chlorambucil (CSR, Table 13).

Due to the small sample size, it was considered more appropriate to inform the untreated CLL model for acalabrutinib versus obinutuzumab plus chlorambucil based on the overall population, rather than a small post-hoc subgroup representing ~10% of the ELEVATE-TN study.

Furthermore, in ELEVATE-TN the efficacy of acalabrutinib compared to obinutuzumab plus chlorambucil as represented by the IRC-PFS HR was 0.23 (95% CI: 0.09; 0.61) in patients with a del(17p) or TP53 mutation and 0.19 (95% CI: 0.11; 0.31) in patients without a del(17p) or TP53 mutation. Thus, although the data is still immature, the efficacy of acalabrutinib in both groups of patients was similar at data cut-off.

B7. CS, Section B3a.3.2.1, page 126 *"Log-cumulative hazard plots were used to illustrate the spatial behaviour of hazard rate observed in ELEVATE-TN (non-monotonic hazard, monotonic hazard or constant hazards). "* Can a cumulative

hazard ever be non-monotonic? Does the company mean the hazard? Please provide these plots.

The wording relates to the hazards, not cumulative hazards. Variations on the log-cumulative hazard plot to assess the suitability of the log-logistic and log-normal distributions and assumptions of the proportional odds and/or acceleration failure time effects are presented for time to progression and time to pre-progression death in Figure 5 and Figure 6. The hazard plots are presented in Figure 7 and Figure 8 for time to progression and time to pre-progression death, respectively.

Figure 5. Time to progression in ELEVATE-TN

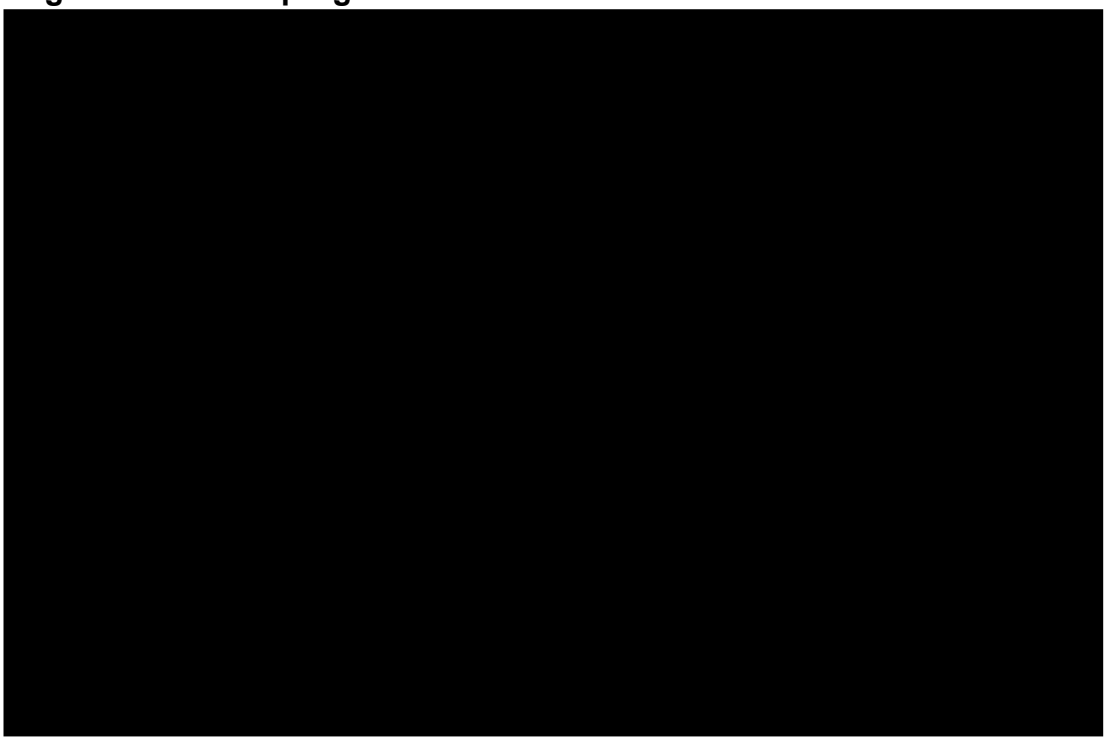
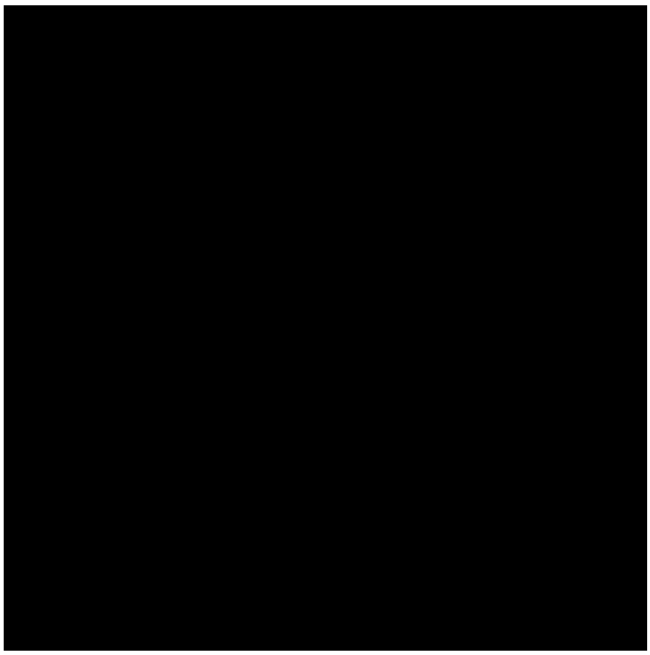


Figure 6. Time to pre-progression death in ELEVATE-TN

Figure 7. Time to progression (hazard plots)

a) Acalabrutinib



b) Chlorambucil plus obinutuzumab

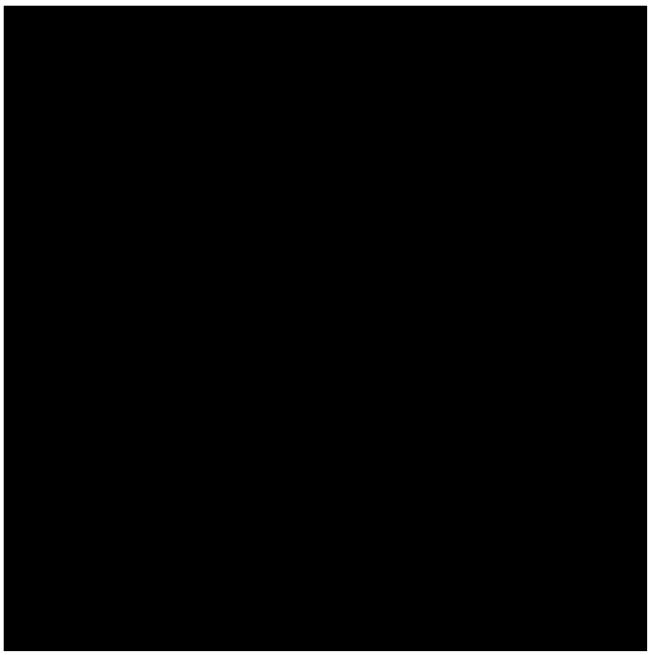
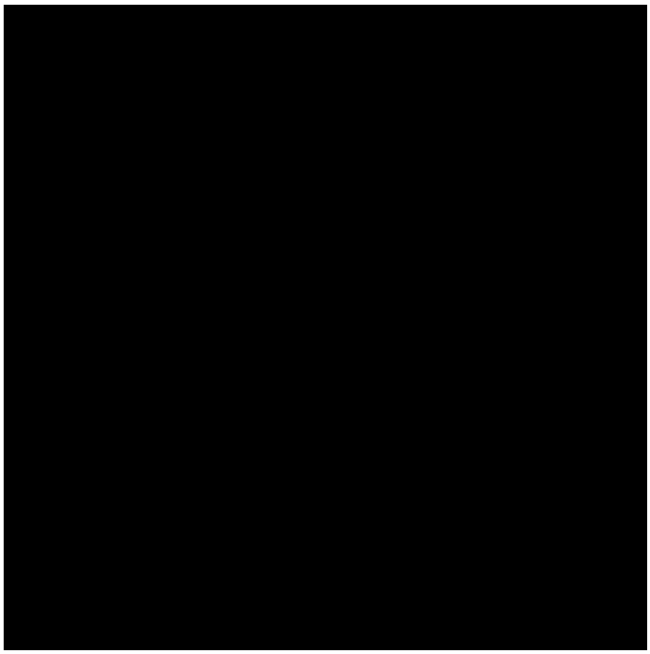
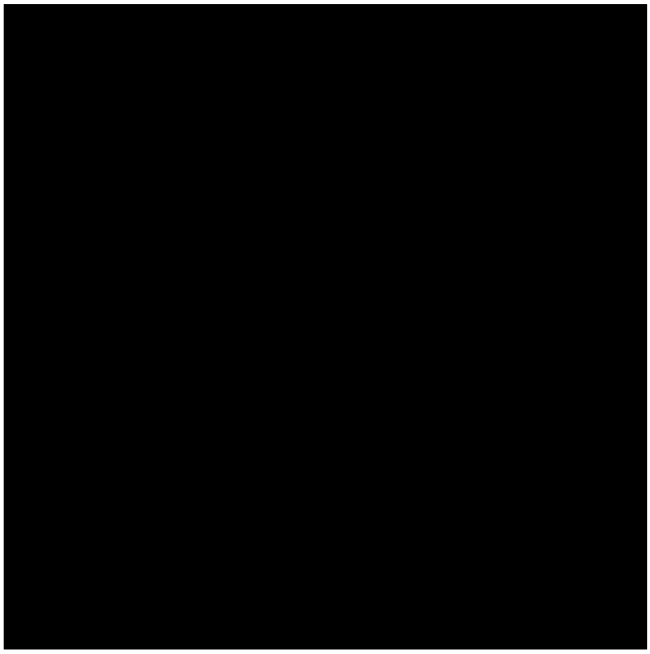


Figure 8. Time to pre-progression death (hazard plots)

a) Acalabrutinib



b) Chlorambucil plus obinutuzumab



B8. CS, Section B.3a.3.4.1.5, Figure 27, page 134. The generalised gamma model for pre-progression mortality is not shown in Figure 27. Please include this model in the figure.

The generalised gamma model for pre-progression mortality was excluded from Figure 27 as the model produced clinically implausible results for the acalabrutinib TTDeath extrapolations (IRC PFS). Due to an extremely small-scale coefficient, the distribution returned values of 0 for all time points.

B9. PRIORITY. CS, Section B.3a.3.1, page 125. Please justify the use of different parametric models for pre-progression mortality and time to progression between the treatment groups. What is the clinical reasoning for assuming that progression and death risks are constant for acalabrutinib but not constant for obinatuzumab plus chlorambucil?

The parametric models for TTP and TTDeath were selected independently for each treatment based on the statistical fit and the clinical plausibility of the long-term extrapolations. This approach was deemed to hold more clinical relevance than the use of consistent extrapolations across the two treatment arms.

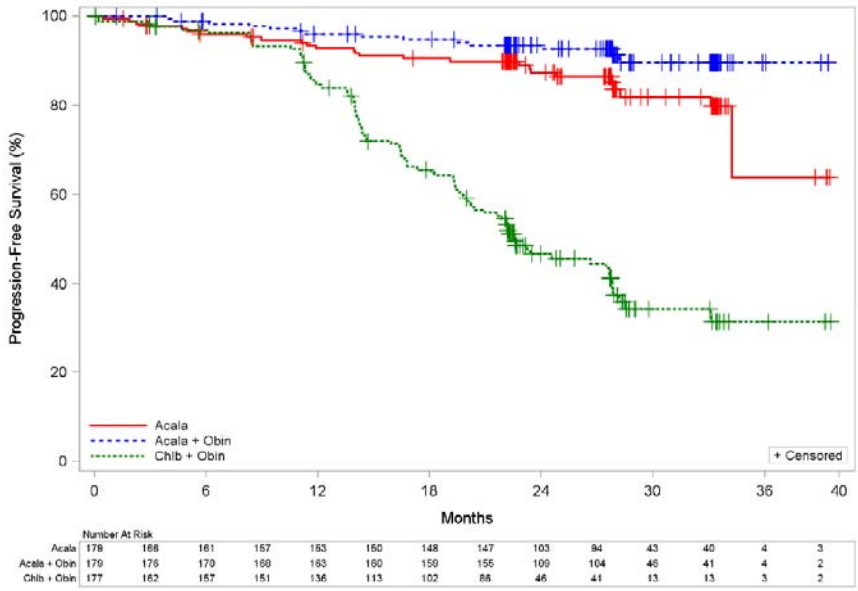
As described in CS Section B3a.3.4.1.5, page 134, the exponential distribution was selected for the acalabrutinib extrapolations as it was the best statistically fitting curve for both TTP and TTDeath and provided the most plausible long-term extrapolations based on clinical feedback (i.e. 67.6% of patients PF at 5 years compared to the 70-75% observed in RESONATE-2 without overestimating the longer term PFS benefit). The exponential distribution was also in line with the representation of the TTP hazards (Figure 7a) which show a relative constant hazard up to approximately 20-25 months, after which the plot is uninformative due to small number of patients at risk (Figure 9). The TTDeath hazards (Figure 8a) are increasing but within a narrow range of 0 to 0.0015.

For chlorambucil plus obinutuzumab the TTP hazards were not constant (Figure 7b), and the log-normal provided the second best statistically fitting curve for TTP. The generalised gamma provided the best statistical fit but was deemed inappropriate as the tail of the extrapolation plateaued. This behaviour was not observed with any of the other fitted curves and lacked clinical plausibility. In addition, the log-normal

distribution provided the most optimistic long-term survival extrapolation for chlorambucil plus obinutuzumab.

Therefore, acalabrutinib and chlorambucil plus obinutuzumab had different hazard functions, and required different parametric curves fitted. These curves were validated by UK clinicians.

Figure 9. Kaplan-Meier plot for progression-free survival by IRC assessment (ITT population)



Abbreviations: IRC, independent review committee; ITT, intention-to-treat.

B10. CS, Section B3a.3.4.1.5, page 137. The CS states *"As the exponential distribution had the best statistical fit of the three and provided both the most stable and conservative cost-effectiveness estimates, it was selected for the base case."* Please clarify what is meant by *"stable"* in this context.

The inclusion of 'stability' can be removed, and the sentence should read "As the exponential distribution had the best statistical fit of the three and provided the most conservative cost-effectiveness estimates, it was selected for the base case."

B11. PRIORITY. CS, Section B3a.3.4.1.5, page 137. The CS states *"Only the log-normal, log-logistic, gamma and generalised gamma distributions were considered*

for the base case." Why were the other survival models in the Generalised F family not considered?

Seven distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma, and gamma) were fitted to the data. The exponential, Weibull and Gompertz distributions were considered for the base case but were excluded due to poor statistical fit (CS page 135). When assessing the statistical fit of the models via AIC, distributions that were outside of the two-AIC point threshold for both TTP and TTDeath were excluded as this difference was considered meaningful.[42]

B12. PRIORITY. CS, Section B.3a.3.3, page 128. The model uses data from MURANO (venetoclax plus rituximab) and RESONATE (ibrutinib) for post-progression survival. This assumes that a patient who receives acalabrutinib first-line and then progresses have a more favourable prognosis compared with a patient who receives obinatuzumab plus chlorambucil first-line and then progresses. Please clarify:

(a) Whether you are assuming that this survival benefit is related to acalabrutinib versus obinatuzumab plus chlorambucil or the treatments received in each arm after disease progression

(b) What evidence is available to support this assumption

(c) Why the data from MURANO and RESONATE were not adjusted to account for potential confounders between the studies

(d) Whether clinical opinion was sought to support this assumption of a survival benefit after progression.

(e) Given the limited evidence of a survival advantage from ELEVATE-TN, please justify the assumption of any survival gain for acalabrutinib versus obinatuzumab plus chlorambucil.

a) UK clinical experts engaged by AstraZeneca confirmed that intuitively, the most efficacious regimen given earlier in the treatment pathway is most likely to translate into an improved long-term survival/prognosis for patients.

UK clinicians also felt that by providing a non-DNA damaging agent in the front-line setting, such as acalabrutinib vs immuno-chemotherapy, the disease is likely to be

more genetically stable in the longer-term, and therefore result in improved outcomes. Furthermore, by improving the duration of PFS in the front-line setting, it is more likely that patients will achieve a 'functional cure' and reach their natural life expectancy and therefore receive fewer lines of subsequent therapy. Clinicians therefore believed that by receiving fewer lines of therapy, the disease will be biologically easier to treat and patients are more likely to achieve a response.

Further supporting this, a multicentre, retrospective analysis of 683 patients with CLL demonstrated that patients who received treatment with a BTKi as front-line therapy compared with idelalisib-based therapy experienced a significantly better PFS in all settings [front line HR: 2.8 (95% CI: 1.3,6.3; p=0.01) and R/R HR: 2.8 (95% CI: 1.9, 4.1; p<0.001)].[43] Whilst idelalisib therapy is not frequently used in UK clinical practice and has been superseded by ibrutinib therapy, this further supports the conclusion that earlier treatment with efficacious therapies is likely to translate into improvements in response to subsequent therapies.

UK clinicians also stated that it would be implausible to assume that overall benefit would be worse than that offered by ibrutinib therapy; particularly given the improved tolerability profile and the higher selectivity and occupancy associated with acalabrutinib therapy vs ibrutinib.[44]

b) Please see the response to (a) for the clinical plausibility and rationale for this assumption.

c) AstraZeneca does not have access to the patient-level data for either the RESONATE or the MURANO trial, and therefore adjusting for potential confounders between the trials is not possible.

However, in UK clinical practice, patients are often treated with a BTKi followed by a BCL2i, such as venetoclax.[25] Therefore, the use of the MURANO trial to inform the PPS for patients who receive acalabrutinib as front-line therapy, and the RESONATE trial to inform PPS for patients who receive a BTKi as second-line therapy is reflective of the anticipated treatment sequencing in UK clinical practice.

However, whilst the assumption that patients who receive acalabrutinib as front-line therapy are likely to have a favourable prognosis relative to patients receiving front-line therapy with chlorambucil plus obinutuzumab is biologically and clinically plausible (see response to B12a), AstraZeneca acknowledges there may be a degree of residual confounding between the two studies.

Therefore, an exploratory analysis has been conducted where both acalabrutinib and chlorambucil plus obinutuzumab receive ibrutinib post-progression (RESONATE PPS data). The impact of the ICER is minimal, with the updated base case ICER for the comparison against chlorambucil plus obinutuzumab increasing from [redacted] to [redacted] per QALY.

d) Yes, UK clinical input was obtained to understand the biological and clinical plausibility of this approach. Please see response (a) for further information.

e) Overall survival data from the ELEVATE-TN trial is immature, with median OS not reached in any treatment group (acalabrutinib monotherapy vs chlorambucil plus obinutuzumab HR: 0.60; 95% CI: 0.28, 1.27; p=0.16), with estimated OS at 24 months of 95% and 92% in the acalabrutinib monotherapy and chlorambucil plus obinutuzumab treatment arms, respectively.

However, despite the immaturity of the survival data, after a median follow-up of 28.3 months, median PFS was significantly longer with acalabrutinib monotherapy vs chlorambucil plus obinutuzumab (HR: 0.20; 95% CI: 0.13, 0.30; p<0.0001), with an estimated PFS at 24 months of 87% and 47% in the acalabrutinib and chlorambucil plus obinutuzumab treatment arms, respectively.

Despite the relatively short follow-up, there is already a separation of the curves. At the time of the trial, patients who progress on chlorambucil plus obinutuzumab already have access to novel agents including cross-over to acalabrutinib or other novel agents. Despite this, the survival curve in the chlorambucil plus obinutuzumab arm appears to be worse than the acalabrutinib monotherapy arm.

Furthermore, analysis from other novel agents, such as ibrutinib or venetoclax plus rituximab clearly demonstrate that the early PFS benefit does indeed translate into a

long-term survival benefit. For example, final analysis from the RESONATE trial including up to 6 years follow-up demonstrated a PFS benefit for ibrutinib vs ofatumumab in R/R patients (HR 0.148; 95% CI: 0.113, 0.196; p<0.001) which translated in an OS benefit, with an approximately 36% reduction in the risk of death (HR: 0.639; 95% CI: 0.418, 0.975).[45] This was further demonstrated in the MURANO trial which demonstrated a PFS benefit for venetoclax plus rituximab vs bendamustine plus rituximab in R/R patients (HR 0.17; 95% CI: 0.11, 0.25; p<0.001) which also translated into a longer-term OS benefit with a 62% reduction in the risk of death (HR 0.48; 95% CI: 0.25, 0.90).[46]

Therefore, given the vast improvement in PFS, the historical evidence from other novel agents, and evidence that use of more efficacious treatment regimens used as front-line therapy translating into improved outcomes, it is clinically plausible that the ELEVATE-TN trial will demonstrate a robust improvement in survival with the availability of more mature date.

B13. CS, Section B.3a.3.3, page 128. The model assumes that patients can receive a maximum of two lines of therapy; third- and subsequent-line treatments are not included. Please justify this assumption.

Prior to the introduction of novel therapies, the use of third- and subsequent-line treatments was relatively common. However, since the introduction of novel therapies, such as ibrutinib, patients stay on treatment for longer; remaining in a progression-free state, and therefore often reach their natural life span when receiving second-line treatment.

Therefore, only a small minority of patients are alive and progress following second-line treatment, and of these, only a cohort of patients are likely to be eligible/fit-enough to tolerate 3L+ treatments. In the case where a patient does need further treatment, treatment options are often limited to the availability of clinical trials of novel investigational medicines at the time of progression.

Nine UK clinical experts at an advisory board agreed that almost all CLL patients treated in the UK would receive two lines of treatment. Second-line treatments were chosen to best align with the anticipated subsequent treatment as validated by UK

clinicians. However, the treatment pathway following second-line treatment complicates attempts at modelling post-progression survival based on the available data for acalabrutinib and the comparator treatments. For any further lines of treatment, there is a distinct lack of sequencing data available.

Further engagement with UK clinical experts following receipt of the clarification questions support this, and note that patients are often aged 70-72 years at the time of initial treatment, and therefore 3L+ treatment is uncommon.

B14. CS, Section B.3a.3.3, page 128. Please provide information on the actual subsequent-line treatments received in each arm in ELEVATE-TN. Why were these data not used to inform the model?

Table 15 presents the subsequent line of treatments received in ELEVATE-TN for acalabrutinib monotherapy and chlorambucil plus obinutuzumab.

Table 15. Subsequent anticancer therapy for patients with progressed CLL in ELEVATE-TN (ITT population)

	Patients in the acalabrutinib monotherapy arm of ELEVATE-TN receiving a subsequent anticancer therapy	Patients in chlorambucil + obinutuzumab arm of ELEVATE-TN receiving a subsequent anticancer therapy
	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]
Anti-CD20	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Venetoclax	[redacted]	[redacted]
RCHOP	[redacted]	[redacted]
FCR	[redacted]	[redacted]
CVP	[redacted]	[redacted]
Steroids	[redacted]	[redacted]
C+O	[redacted]	[redacted]
PI3K	[redacted]	[redacted]

Abbreviations: C+O, chlorambucil + obinutuzumab; CVP, cyclophosphamide vincristine sulphate prednisone; FCR, fludarabine, cyclophosphamide and rituximab; PI3K, phosphoinositide 3-kinase; RCHOP, rituximab cyclophosphamide hydroxydaunomycin oncovin prednisone

Due to the immaturity of the ELEVATE-TN trial, only [redacted] patients in the acalabrutinib monotherapy arm and [redacted] patients in the chlorambucil plus obinutuzumab arm received a subsequent treatment following disease progression. In order to use the subsequent treatment distribution from the ELEVATE-TN trial in the model, the PPS

data from ELEVATE-TN would need to be used for consistency. However, at the time of the latest data cut (8 February 2019), only [redacted] patients on acalabrutinib monotherapy and [redacted] on chlorambucil plus obinutuzumab had died post progression, respectively. Generating PPS curves based on such a small pool of patients would have introduced considerable uncertainty into the PPS modelling.

Furthermore, in an advisory board, UK clinicians indicated high-risk or unfit patients on ibrutinib would commonly move on to a venetoclax-based regimen following disease progression and front-line treatment with a BTKi.[25] Patients treated with chlorambucil plus obinutuzumab would typically receive a BTKi post-progression (such as ibrutinib) as venetoclax-based regimens tend to be reserved for treatment post BTKi. In ELEVATE-TN, of the 82 patients who had disease progression for the chlorambucil plus obinutuzumab arm, 45 patients subsequently received acalabrutinib. As such, the current approach is appropriate and is reflective of the current and anticipated treatment sequencing in UK clinical practice.

B15. Untreated CLL Model, worksheet "LifeTables", columns N and O. Please provide the exact source for the life tables used in the model.

The 2015-2017 National Life Tables for the UK were used in the model.[47] AstraZeneca recognise that these life tables have been updated to 2016-2018 National Life Tables and all analyses provided in this response document have been conducted with the updated life tables. The impact of this change on the cost-effectiveness of acalabrutinib is minimal, with the base case ICER for the comparison against chlorambucil plus obinutuzumab increasing from [redacted] per QALY.

B16. Untreated CLL Model, worksheet "LifeTables" column Q. This column appears to represent a weighted rate of general population mortality within a 28-day model cycle. However, (i) worksheet "Surv_calcs_MM" columns BH and BI treat this rate as a probability and (ii) the weighting approach applied in the model assumes that the proportionate split of men and women at age 70 will be maintained at all subsequent ages. Please confirm if these two assumptions were intended.

- The use of the rate instead of a probability was not intended and has now been corrected. All analyses provided in this response document have been

conducted with the correction in place. The impact of this change on the cost-effectiveness of acalabrutinib is minimal, with the base case ICER for the comparison against chlorambucil plus obinutuzumab increasing from [redacted] per QALY.

- The proportionate split of men and women at age 70 was intentionally maintained for all subsequent ages. Given that the TTP and TTDeath extrapolations are generated using data from the ELEVATE-TN trial and this data was affected by the split of men and women within the trial, it was considered more appropriate to maintain the proportional split of men and women at age 70 for all time rather than re-proportionalise based on mortality, which would have introduced further complexity in the model. The use of a constant split is anticipated to proportionally underestimate survival in both treatments and have a minimal impact on the cost-effectiveness results.

B17. Untreated CLL Model, worksheet “Cost_calcs” columns H and BB. The acquisition cost calculations use the health state occupancy at model entry in both the first and the second model cycles - the first calculation is not half-cycle corrected, whilst the second calculation is half-cycle corrected (the population in the first model cycle is counted 1.5 times). This appears to be an error. Please clarify.

AstraZeneca acknowledge that this was an error in the model. This has been corrected to remove the double counting of patients in the first cycle for all treatments in the model and all analyses provided in this response document have been conducted with the correction. The impact of this change is in favour of acalabrutinib, with the base case ICER for the comparison against chlorambucil plus obinutuzumab decreasing from [redacted] per QALY.

B18. Untreated CLL Model, worksheet “Outcome_calcs” columns G and Y. The QALY calculations in rows 14 and 15 use the health state occupancy at model entry in both the first and the second model cycles - the first calculation is not half-cycle corrected, whilst the second calculation is half-cycle corrected (the population in the first model cycle is counted 1.5 times). This appears to be an error. Please clarify.

AstraZeneca acknowledge that this was an error in the model. This has been corrected to remove the double counting of patients in the first cycle for all

treatments in the model and all analyses provided in this response document have been conducted with the correction. The impact of this change on the cost-effectiveness of acalabrutinib is minimal, with the base case ICER for the comparison against chlorambucil plus obinutuzumab decreasing from [redacted] per QALY.

B19. Untreated CLL Model, worksheet “Costs_Tx”. The model does not include any wastage for oral treatments given in first- or second-line. Please justify this assumption.

There is no clinical justification to assume wastage of oral treatments in first- or second-line treatment. Pharmacists often follow clear dispensing protocols to ensure that there is no wastage of oral cytotoxic medications, with dispensing of subsequent prescriptions limited until the existing supply is exhausted.

As the treatment cycles are continuous, in practice, patients receiving oral treatment would only incur the full cost of a pack of medication once the previous pack has been fully consumed. It is unrealistic to assume that a patient receiving a pack of medication sufficient for 30 days treatment would discard 2 days’ worth of medication following completion of a 28-day cycle.

B20. CS, Section B3a.5.1, page 151. The model assumes that following disease progression of first-line treatment, patients will have a period of time off treatment before starting second-line treatment. The model assumes: (a) a delay of 14 cycles, based on the difference between median time to next treatment and median PFS, and (b) that all surviving patients go on to receive second-line treatment. For patients who started second-line treatment, please provide the mean time since progression in ELEVATE and the number of patients contributing data on this. Please also comment on the assumption that all surviving patients receive subsequent-line treatment.

It was not possible to generate reliable estimates of the mean time from progression to initiation of a subsequent therapy due to data immaturity of events and the limited number of patients available which is why the difference between the median TTNT and median PFS was used to inform the model.

Long-term OS data from RESONATE and MURANO were used to inform PPS in the model and the subsequent treatments received were aligned with the choice of PPS data source. As the survival benefit from these trials is applied to all surviving patients in the cohort, it was considered appropriate that patients would accrue the associated costs of treatment. When using RESONATE, surviving patients were assumed to receive second line treatment with ibrutinib and when using MURANO, surviving patients were assumed to be treated with venetoclax plus rituximab, as per the current and anticipated treatment sequencing in UK clinical practice.

Whilst it is unlikely that all patients would receive a second line treatment in clinical practice, nine UK clinical experts at an advisory board agreed that almost all UK CLL patients receive two lines of therapy and estimated only 7-10% of patients would not receive a second line treatment. Therefore, the assumption that all surviving patients receive a second line treatment in the model is deemed reasonable and aligned with clinical practice. Moreover, modelling a survival benefit for progressed patients without additional costs could be interpreted as an unsubstantiated residual treatment effect which lacks supporting data and could be subject to criticism.

B21. PRIORITY. CS, Section B.3a.4, page 143. The utility value for the progression-free state in ELEVATE-TN is higher than the age- and sex-matched estimate for the general population at model entry (0.817 vs 0.78). Please comment on the reliability of this estimate. Please also provide details regarding how this utility estimate was derived - was a statistical model used and how were repeated observations from individual patients accounted for?.

Further engagement with UK clinical experts confirmed that it is not uncommon for patients to achieve a ‘functional cure’ when receiving treatment for CLL and therefore will reach their normal life expectancy and will die from causes unrelated to CLL.

As such, with the introduction of more efficacious treatment options in the front-line setting, it is not implausible for patients to at least achieve a utility estimate equivalent to the age- and sex-matched general population. Furthermore, clinicians supported that patients are often aged approximately 71 or 72 years at the time of diagnosis in UK clinical practice, and it is more likely that patients of this age will

achieve a utility equivalent to their peers, whilst younger patients may be less likely to achieve such outcomes. However, the median age of patients of in the ELEVATE-TN was 70-71 years and is therefore consistent with those patients routinely treated in UK clinical practice.

The utility estimate observed in the ELEVATE-TN clinical trial is considered achievable. Particularly given that this estimate was calculated from patients similar to the characteristics observed in UK practice and the calculation of the age- and sex-matched utility estimates may be considered out-dated and/or may not be entirely reflective of the current population today. For example, the HSUVs reported in the Ara and Brazier et al was published in 2011 and utilises pooled data from surveys conducted between 2003 and 2006 to estimate the HSUVs in the general population.[48] Therefore, this estimate is at least 14 years old and may underestimate the true utility estimates of the age- and sex-matched general population.

The utility value for PF was derived based on a two-stage mean approach, where the utility values for each patient across PF time points were first averaged, and then the average across all patients was computed. In a linear mixed effects model with covariate for disease progression, the intercept (representing the utility for PF) was [redacted], showing consistency with the two-stage mean approach used in the base case model.

A scenario analysis has been conducted where 0.78 PF health state utility was used. The impact of the ICER is minimal, with the updated base case ICER for the comparison against chlorambucil plus obinutuzumab increasing from [redacted] per QALY.

B22. CS, Section B.3a.8.3, page 168. Please explain why only two alternative survival models (Weibull and log-normal) were considered for TTP and pre-progression mortality. Please also explain why no sensitivity analyses were conducted for PPS.

As described in the CS Section B3a.3.4.1.5, page 134, the Weibull and log-logistic curves were presented as scenario analyses for acalabrutinib and chlorambucil plus

obinutuzumab, respectively, as they were deemed to be the next most viable curves to inform TTP and TTDeath.

For the acalabrutinib extrapolations, it was not possible to use the generalised gamma distribution to generate curves for TTDeath (CS page 134) because the scale parameter was very close to zero. Following feedback from UK clinicians, the Gompertz distribution produced too conservative extrapolations with no patients being progression-free at 15 years and the TTP extrapolations using the log-normal and log-logistic distributions were deemed to be overly optimistic, thus leaving the exponential, gamma and Weibull distributions for consideration. The exponential distribution produced the most conservative cost-effectiveness estimates for the three distributions and provided the best statistical fit. As such, it was selected for use in the base case. The Weibull distribution was considered to be the next best alternative as it produced the most conservative PFS and OS extrapolations for acalabrutinib (CS page 137).

For the chlorambucil plus obinutuzumab extrapolations, the exponential, Weibull and Gompertz distributions were excluded due to poor statistical fit (CS page 135; ERG clarification question B11). The tail of the generalised gamma extrapolation lacked clinical validity, meaning this curve was rejected for use in the base case, leaving the gamma, log-normal and log-logistic distributions. The log-normal was selected for use in the base case as it had the best statistical fit of the three options for TTP. The log-logistic produced the most optimistic PFS and OS extrapolations for chlorambucil plus obinutuzumab and so was considered the next best curve.

The impact of different distributions used for the PPS extrapolation had minimal impact on the ICER and deemed not a key driver of the results.

High-risk CLL model – acalabrutinib versus ibrutinib

B23. PRIORITY. CS, Section B.1.3.1.1, page 22. The CS states that patients with high-risk cytogenetic factors such as (del)17p and TP53 mutations have a poorer prognosis than patients without those features. However, the cost-minimisation analysis for this population uses the overall ELEVATE-TN cohort for both the acalabrutinib and ibrutinib groups (the same population as Model 1 for untreated

CLL). Please explain why the analysis is not based on the subgroup of patients with (del)17p and TP53 mutations

The KM curves in ELEVATE-TN were not derived specifically for the high-risk subgroups due to the relatively small number of patients with a 17p deletion and/or TP53 mutations in either the acalabrutinib monotherapy or chlorambucil-obinutuzumab treatment arms (n=23 [12.8%] and 25 [14.1%], respectively), meaning that a matched-adjusted comparison would not be appropriate nor informative.

Furthermore, the data from the ELEVATE-TN trial demonstrates that the PFS response is robust and consistent across all subgroups, irrespective of cytogenetic status (HR: 0.23; 95% CI: 0.09, 0.61 and HR: 0.19; 95% CI: 0.11, 0.31 for patients with and without a del(17p) and/or TP53 mutation, respectively).

Finally, KM curves derived excluding patients with a del(17p) and/or TP53 mutation are consistent with those from the ITT population further supporting the conclusion that, although the data is relatively immature for acalabrutinib, response to acalabrutinib is consistent across subgroups (see Figure 10 and Figure 11).

Despite the RESONATE trial only including patients in the R/R setting, the Committee in appraisal TA429 agreed that, in the absence of any further evidence, the data from the previously treated population could be taken into account, resulting in the Committee making a positive recommendation in previously untreated high-risk patients using R/R data as a proxy to inform the efficacy of ibrutinib in the front-line setting.

Since this recommendation, ibrutinib has become established clinical care for patients with a del(17p) and/or a TP53 mutation, and therefore it is appropriate to compare the efficacy of the acalabrutinib monotherapy arm indirectly to the ITT population from the RESONATE trial to make a fair comparison with the evidence previously made available to the committee which enabled NICE to make a positive recommendation in this patient population.

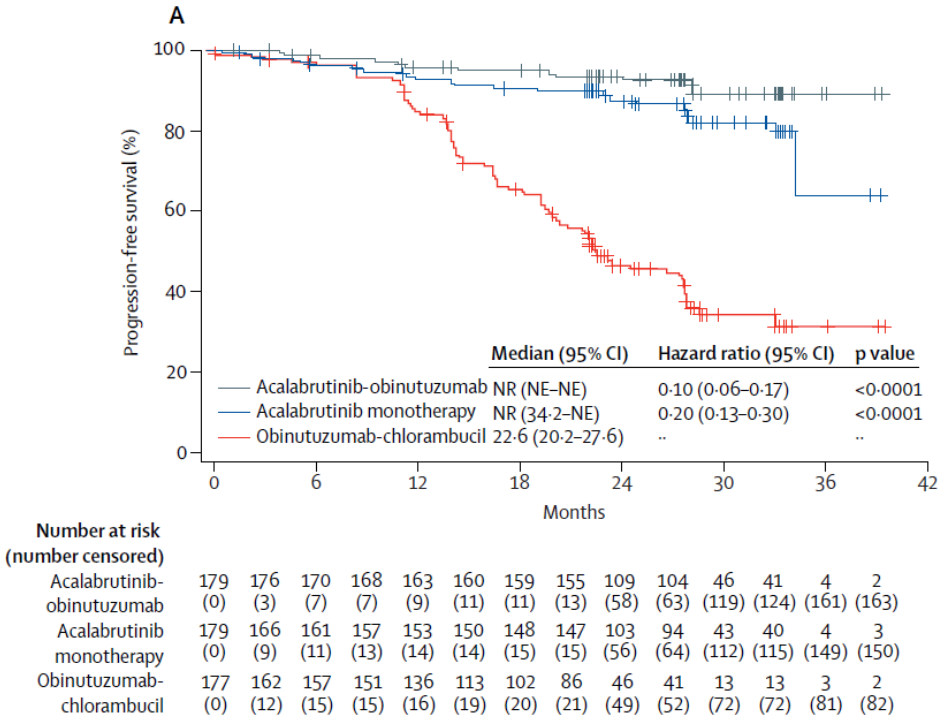
Since the recommendation for ibrutinib, data in the front-line setting has since become available from the RESONATE-2 trial.[49] However, this trial excluded patients with 17p deletion and only included 12 patients with a TP53 mutation. Therefore, it is

not appropriate to conduct a match-adjusted comparison vs the high-risk patients in the RESONATE trial due to the small sample size. However, a MAIC in the ITT population between the ELEVATE-TN and RESONATE-2 trials has since been conducted and demonstrated a consistent response and conclusion to those made from the MAIC between ASCEND and RESONATE (see the response to question B25 for further information).

Figure 10. PFS KM curve in patients with no 17p or TP53 mutations

Abbreviations: KM, Kaplan Meier; PFS, progression-free survival.

Figure 11. PFS KM curve in ITT population



Number at risk (number censored)														
Acalabrutinib-obinutuzumab	179 (0)	176 (3)	170 (7)	168 (7)	163 (9)	160 (11)	159 (11)	155 (13)	109 (58)	104 (63)	46 (119)	41 (124)	4 (161)	2 (163)
Acalabrutinib monotherapy	179 (0)	166 (9)	161 (11)	157 (13)	153 (14)	150 (14)	148 (15)	147 (15)	103 (56)	94 (64)	43 (112)	40 (115)	4 (149)	3 (150)
Obinutuzumab-chlorambucil	177 (0)	162 (12)	157 (15)	151 (15)	136 (16)	113 (19)	102 (20)	86 (21)	46 (49)	41 (52)	13 (72)	13 (72)	3 (81)	2 (82)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan Meier; NR, not reached; PFS, progression-free survival.

B24. CS, Section B.3a.5.1, Table 82, page 152. The CS states that according to clinical expert opinion obtained from the company, ibrutinib as a subsequent-line therapy would be given for a maximum of 130 cycles. However, in the high-risk CLL analysis, first-line ibrutinib is assumed to be given until disease progression and costs are accrued in every model cycle (including those beyond model cycle number 130). Please justify this assumption. In addition, please clarify whether your clinical experts indicated a maximum treatment time for acalabrutinib.

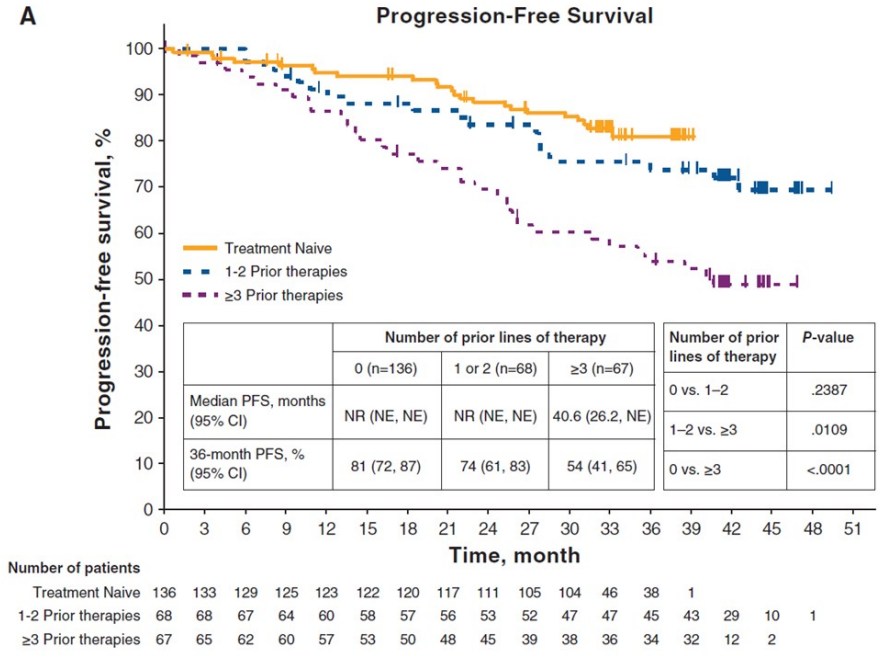
Following further UK clinical expert engagement, it was deemed plausible by clinicians that 1L high-risk patients treated with ibrutinib would have a longer maximum time on treatment than patients starting ibrutinib in the R/R setting.

In the 1L high-risk CLL analysis, 1L ibrutinib costs are accrued until disease progression or death, and the maximum time on treatment is determined by the choice of distributions used to extrapolate time to progression and pre-progression death (which are used in the model to estimate PFS) and were validated with UK clinical experts. As a result of the model structure, all subsequent-line therapies

require an explicit estimate (input) for their potential maximum duration. For the base case analysis, UK clinical expert opinion was sought to provide a plausible input and treatment duration was modelled for a maximum of 130 cycles (120 months).

A supporting analysis was conducted where PFS data from the ibrutinib arm of RESONATE reported in O'Brien et al. (2019)[50] from patients with 1-2 prior therapies were extrapolated to provide estimates of maximum time on treatment (Figure 12). Survival curves were fitted using standard parametric models: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. The fitted survival curves are presented in Figure 13. A cap on mortality was imposed such that the risk of progression or death for the patient cohort could not be less than all-cause risk of death. All curves presented in Figure 13. provide estimates of a maximum time on treatment of approximately 30 years. Based on this analysis, use of the UK clinical input was judged to be a conservative assumption.

Figure 12. PFS with ibrutinib by prior lines of therapy

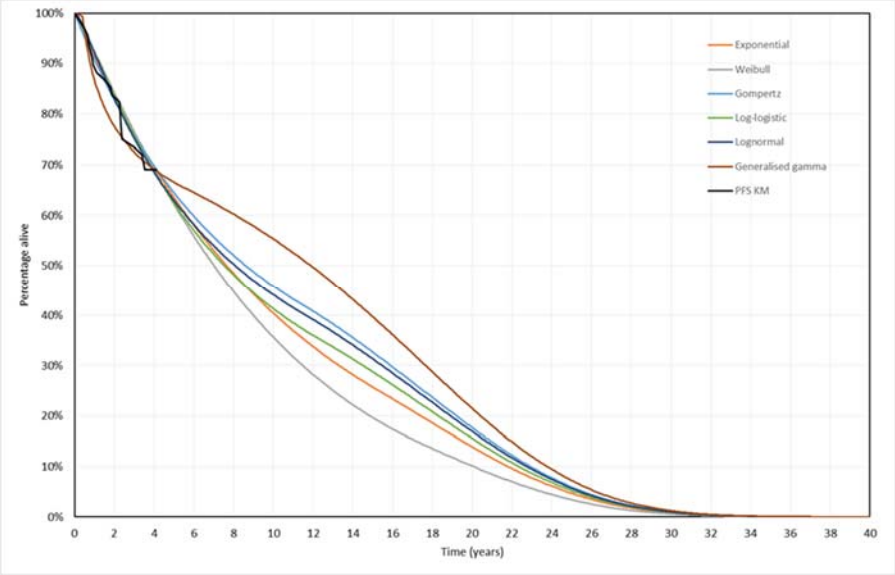


	Number of prior lines of therapy		
	0 (n=136)	1 or 2 (n=68)	≥3 (n=67)
Median PFS, months (95% CI)	NR (NE, NE)	NR (NE, NE)	40.6 (26.2, NE)
36-month PFS, % (95% CI)	81 (72, 87)	74 (61, 83)	54 (41, 65)

Number of prior lines of therapy	*P*-value
0 vs. 1–2	.2387
1–2 vs. ≥3	.0109
0 vs. ≥3	<.0001

Abbreviations: PFS, progression-free survival

Figure 13. Parametric models overlaying the PFS KM data for RESONATE (1-2 prior therapies only)



Abbreviations: KM, Kaplan Meier; PFS, progression-free survival.

B25. PRIORITY. CS, Section B.1.1, Table 1, page 19. The CS justifies the assumption of equivalence in efficacy between acalabrutinib and ibrutinib for untreated CLL patients with (del)17p or TP53 mutations from results of a MAIC using data from relapsed/refractory (R/R) CLL patients by stating that *"In NICE TA429, the committee accepted that in the absence of any evidence, the data from previously treated patients could be taken into account and led to a positive recommendation in first line high-risk patients"*. Please present evidence to support the assumption that the efficacy of acalabrutinib in patients with R/R CLL is transferable to treatment-naïve CLL patients with high risk cytogenetic factors.

NICE assessed ibrutinib in appraisal TA429 for the treatment of untreated and previously treated patients with CLL, with evidence for ibrutinib based on the RESONATE study. The RESONATE trial was conducted in patients with previously treated CLL, and therefore did not contain any evidence of efficacy in the first-line setting. Despite this, the Committee accepted that in the absence of any evidence, data from previously treated patients could be used as a proxy for the first-line high risk population. This resulted in a positive recommendation by NICE for ibrutinib in previously treated CLL patient as well as untreated patients who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable.

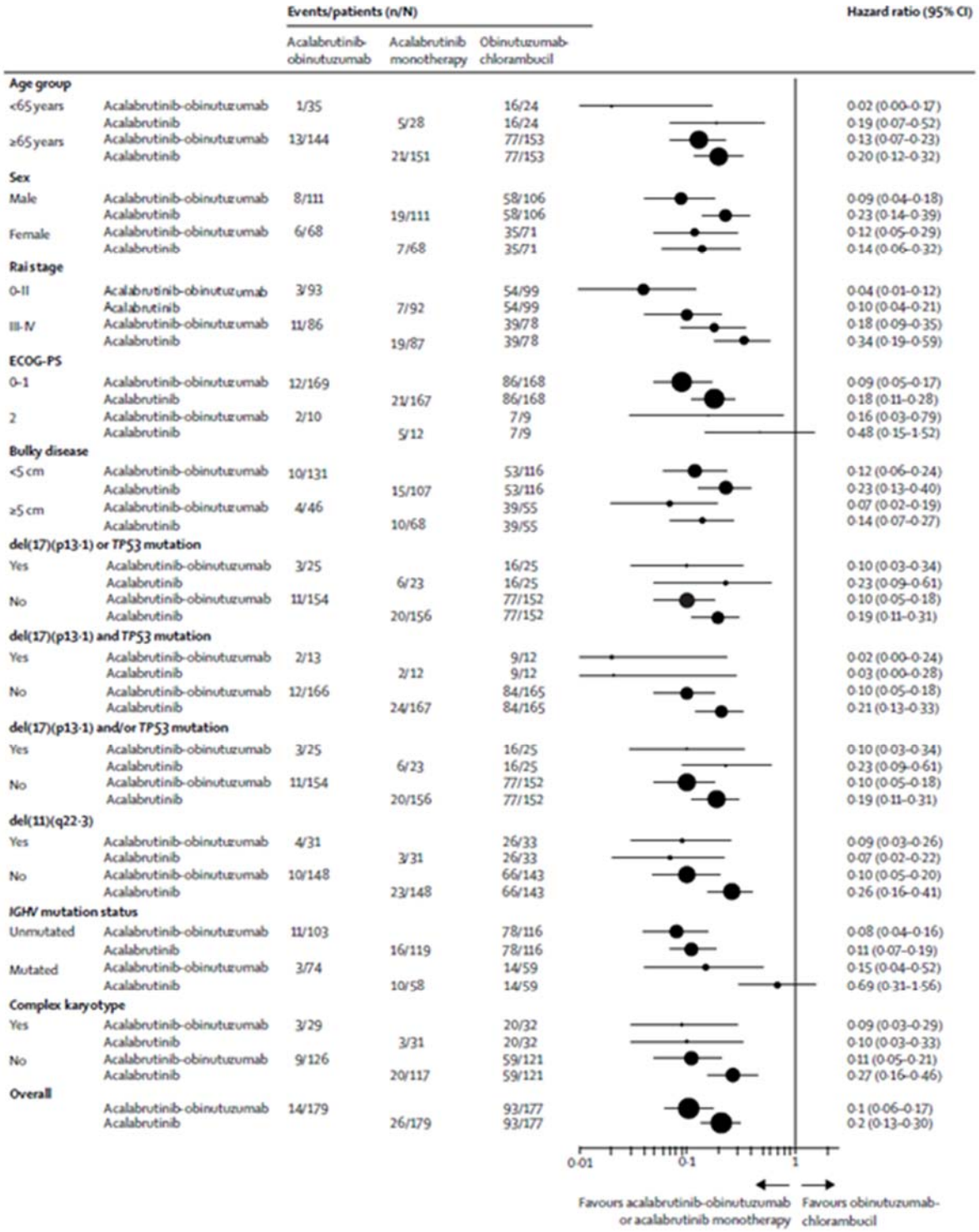
Additionally, when NICE assessed idelalisib in appraisal TA359 as a treatment option for untreated patients with high-risk cytogenetic factors (including TP53 mutation or 17p deletion), the positive recommendation that was issued for this subgroup was based on a dataset that included only nine patients who were treatment-naïve and had a 17p deletion. The EMA since issued a recommendation that idelalisib should not be administered to previously untreated CLL patients whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation), due to safety concerns. This leaves ibrutinib as the sole treatment option for this difficult to treat patient population.

In this submission, following the precedent set by TA429, evidence from the ASCEND trial (in previously treated patients with CLL) and MAIC (demonstrating equivalence with ibrutinib in previously treated patients) was generalised to the first-line high-risk setting. The ASCEND study was deemed to be the most relevant proxy for untreated high-risk patients as in contrast to the data sets used in TA359 and TA429, the majority of patients enrolled in ASCEND had complex cytogenetic risk factors (87.7%, n=272). Furthermore, the ASCEND trial included a total of 49 patients with 17p deletion which is greater than the number of patients with 17p deletion in RESONATE for TA429 (n=35) and in Study 101-08 used to inform TA359 (n=9).

In ASCEND, acalabrutinib showed a statistically and clinically meaningful improvement in PFS compared with either IR or BR. The clinical benefits were observed cross all pre-specified subgroups. In particular, when compared with IR or BR, treatment with acalabrutinib results in a statistically significant improvement in patients with at least 1 high-risk feature associated with poor prognosis, such as a 17p deletion or TP53 mutation (HR: [redacted]).

While the proportion of high-risk patients is smaller in the first-line study ELEVATE-TN, the statistically significant PFS benefit associated with acalabrutinib was seen irrespective of the presence or absence of high-risk features, such as del(17p), del(11q) and unmutated IGHV, and irrespective of disease stage; demonstrating a significant clinical benefit across the entire patient population.

Figure 14. Forest plot showing results from the prespecified subgroup of analysis of PFS in ELEVATE-TN



Abbreviations: IGHV, immunoglobulin heavy chain variable gene; NE, not evaluable; TP53, cellular tumour antigen p53 gene; ECOG PS, Eastern Cooperative Oncology Group performance status.
Source: Sharman *et al.* 2020

Ibrutinib was deemed to be the most relevant comparator in the untreated high-risk patient population. In the absence of head-to-head data comparing acalabrutinib to ibrutinib in this patient population, we sought to conduct an indirect treatment comparison. However, the Phase III RCT that evaluated ibrutinib in a treatment-naïve CLL population, RESONATE-2, explicitly excluded those who had the presence of a 17p deletion, which was regarded as a major limitation of the analysis. Furthermore, the study only enrolled 12 patients with TP53 mutation. Additionally, Kaplan-Meier curves or hazard ratios were not reported separately for those patients that had high-risk cytogenetic factors. This renders an ITC against ibrutinib in the untreated high-risk population impossible.

These challenges of conducting an indirect treatment comparison against ibrutinib in the untreated, high-risk population have also been recently recognised in the ongoing appraisal of venetoclax plus obinutuzumab (ID1402)

MAIC against ibrutinib in first-line CLL

To further strengthen the similarity in clinical efficacy between acalabrutinib and ibrutinib in the untreated, high-risk patient population, we conducted an exploratory MAIC. The comparison was informed by the ELEVATE-TN trial for acalabrutinib and the RESONATE-2 trial for ibrutinib.

The MAIC approach would use IPD from the ELEVATE-TN trial, and adjusted the trial population to match average baseline characteristics reported in the RESONATE-2 trial. RESONATE-2 was a randomised, open-label, Phase III study investigating the efficacy and safety of ibrutinib compared with chlorambucil in previously untreated patients with CLL.

Feasibility assessment

Firstly, cross-study heterogeneity in study populations, inclusion/exclusion criteria, study designs, sample sizes and outcome definitions and assessments were evaluated between ELEVATE-TN and RESONATE-2 to assess the feasibility of the MAIC comparison.

Specifically, the following study elements were assessed:

- Study design (i.e. phase, randomized, single-arm, blinded, treatment arms [drugs, doses], study year, treatment exposure, assessment period of safety outcomes, follow-up duration and crossovers).
- Sample sizes, including number of patients included in the baseline characteristics assessment and outcomes reporting.
- Inclusion and exclusion criteria.
- Baseline characteristics (e.g. demographics, disease characteristics, cytogenetics, ANC and platelet counts).
- Outcomes of interest (e.g. ORR, PFS, OS and safety outcomes) and detailed outcome definitions and assessment criteria (e.g. investigator assessment vs IRC assessment and use of consistent iwCLL28 response criteria).

Inputs from clinical experts were sought to inform a final assessment of feasibility for each comparison. A preliminary feasibility assessment was conducted to evaluate the overall relevance, availabilities and definitions of baseline characteristics and outcomes across all comparators. Then a comparator-specific feasibility assessment was carried out for ibrutinib. Finally, an external validation step was performed. It was concluded that a MAIC using these two studies would be feasible.

Table 16. Feasibility assessment of acalabrutinib versus ibrutinib in the untreated ITT population

	ELEVATE-TN	**RESONATE-2**
	N = 179, ACA + OB **N = 179 ACA**	**N = 136** **IB**
Study design		
Patient population	Aged ≤ 65 years *OR* 18–64 years with CrCl 30–69 mL/min or CIRS > 6	Previously untreated CLL or SLL (aged ≥ 65 years) with ≥ 1 comorbidity (CrCl < 70 mL/min, platelet count < 100,000 cells/μL, autoimmune cytopenia, ECOG PS 1–2)
Phase	Phase III	Phase III
Study design	Randomised, open- label, international multicentre	Randomised, open- label, international multicentre
Enrolment period	14 September 2015–08 February 2017	March 2013–May 2015
Follow-up	28.5 months (median) ACA + OB; 28.4 months (median) ACA	29 months (median)

Treatment exposure	27.7 months in both ACA + OB and ACA arms	28.5 months (median)
AE assessment period	During treatment period and for 30 days before date of last dose	During treatment
Crossover	Yes, from CH + OB to ACA + OB arm	Yes, from CH to IB arm
Outcome assessment method	2008 iwCLL IRC PFS CH + OB vs ACA + OB (primary); IRC PFS CH + OB vs ACA 2008 iwCLL INV PFS, ORR (IRC), TTNT, OS, AE, SAE, INV ORR, INV PFS	2008 iwCLL IRC PFS (primary), OS, ORR, Safety
Definition of PFS	Time from date of randomisation to date of first INV- assessed DP or death from any cause	Time from randomisation to first occurrence of DP, relapse or death from any cause
Definition of ORR	Achieving either a CR, CRi, nPR or PR (includes PR-L)	Achieving either a CR, CRi, nPR or PR (includes PR-L)
Inclusion criteria		
Demographics		
Age	≥ 18 years	≥ 65 years
Diagnosis	CLL	CLL or SLL
ECOG PS (WHO)	0–2	0–2
Unsuitable for FCR	Yes	Maybe: *'may preclude the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide or rituximab'*
CrCl	> 30 mL/min	> 30 mL/min
Exclusion criteria		
Previous treatments		
Major surgery	NR	Within 4 weeks before randomisation
Other	Any previous systemic treatment (previous localized radiotherapy allowed) Any live vaccine within 4 weeks of first dose of study drug Requires treatment with proton pump inhibitors	Any previous treatment (chemotherapy, radiotherapy and/or mAbs) intended to treat CLL/SLL Any immunotherapy, live vaccine or investigational drug within 4 weeks before randomization
Other medical conditions		
CNS lymphoma or leukaemia	Any	Any
Stroke or intracranial haemorrhage	History within 6 months before randomisation	History within 6 months before randomisation

CVD	Significant CVD e.g. uncontrolled or symptomatic arrhythmias, CHF or MI within 6 months of screening, or class 3 or 4 cardiac disease defined by the NYHA Functional Classification, or QTc > 480 ms at screening	Currently active, clinically significant CVD e.g. uncontrolled arrhythmia, or class 3 or 4 CHF as defined by the NYHA Functional Classification; or history of MI, UA or ACS within 6 months before randomisation
Bleeding	Warfarin or equivalent vitamin K antagonists within 7 days of first study drug Known history of bleeding	Treatment with warfarin
CrCl	< 30 mL/min	< 30 mL/min
Transformation of CLL to aggressive NHL-Richter's transformation	Prolymphocytic leukaemia or Richter's syndrome	Yes
del(17p)	Missing or incomplete documentation	Yes

Abbreviations: ACA, Acalabrutinib; ACS, acute coronary syndrome; AE, adverse event; CH, chlorambucil; CHF, congestive heart failure; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; CR, complete response; CRi, complete response with incomplete haematopoietic recovery; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IB, ibrutinib; INV, investigator; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MI, myocardial infarction; NHL, non-Hodgkin lymphoma; NR, not reported; NYHA, New York Heart Association; OB, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; PS, performance status; RI, rituximab; SAE, serious adverse event; SLL, small lymphocytic lymphoma; TTNT, time to next treatment; UA, unstable angina; WHO, World Health Organization.

Data extraction

Relevant patient-level data including baseline characteristics and outcomes of interest (i.e. PFS and OS) were extracted from the ELEVATE-TN trial datasets to create analytical datasets in preparation for the MAIC. Data validation against summary statistics reported in clinical study report was conducted to ensure the correct understanding and use of the data.

The following baseline characteristics were considered to be matched in MAIC based on the preliminary feasibility assessment and discussions with clinical experts:

- age
- sex
- presence of bulky disease (≥ 5 cm)
- presence of del(17p) mutation
- presence of TP53 mutation
- presence of del(11q) mutation
- ECOG PS

- β2-microglobulin at baseline (> 3.5 mg/L)
- Rai stage or Binet stage
- complex karyotype
- IGHV mutation status
- CrCl
- CIRS-G

In addition to the aggregate baseline characteristics and study outcomes extracted in the RESONATE-2 trial, patient-level survival data (i.e. PFS and OS) were reconstructed from the published Kaplan–Meier (KM) curves using the methods recommended by NICE. Digitisation software (Engauge Digitizer software) was used to extract time points and survival probabilities from the published KM curve. Based on the extracted information, the number of patients at risk, the number of events and the number of patients censored were calculated using the reconstruction algorithm. The reconstruction algorithm made reasonable assumptions on the distribution of the unavailable patient-level data. Proxy patient-level survival data were generated based on the reconstructed information and KM curves were reproduced and compared with the published KM curve to visually evaluate the level of agreement. Summary statistics from the reconstructed survival data were reproduced and compared with the published summary statistics to validate the reconstructed survival data.

Generating weights to balance average baseline characteristics

Patients from the ELEVATE-TN trial were selected based on the inclusion/exclusion criteria of RESONATE-2. In each comparison, patients with a missing value in the baseline characteristics to be matched were excluded from the analysis.

Individual patients in the acalabrutinib ELEVATE-TN trial were assigned weights such that:

- Weighted mean (standard deviation) baseline characteristics in ELEVATE-TN exactly matched all of those reported for patients in RESONATE-2.
- Each individual patient's weight was equal to their estimated odds (relative propensity) of being in RESONATE-2 versus ELEVATE-TN.

Weights meeting these conditions were obtained from a logistic regression model for the propensity of enrolment in RESONATE-2 versus ELEVATE-TN, with all matched-on baseline characteristics included as predictors.

Because only summary statistics for baseline characteristics were available for the comparator trials, the method of moments rather than the maximum likelihood approach was used for parameter estimation in the logistic regression. After matching, the baseline characteristics were compared between the acalabrutinib and comparator treatments trial populations to ensure the baseline means (standard deviations) were exactly matched. The distributions of weights were inspected to identify potential sensitivity to extreme weights. The weighted t-test for continuous variables and the weighted χ^2 test for categorical variables were used in the comparison.

Comparison of efficacy before and after matching

Comparative analyses were conducted both before and after weighting. Before matching, binary outcomes (i.e. ORR and safety outcomes) were summarized in proportions and compared using the χ^2 test. Risk differences and odds ratios (ORs) with their 95% CIs and p values were reported. PFS and OS were summarized using KM curves and compared using the log-rank test and HRs estimated from a Cox proportional hazards model.

After matching, PFS, OS were compared between balanced trial populations using the weights generated in the MAIC. Binary outcomes were compared using the weighted χ^2 test. The 95% CIs and p values for the indirect comparisons were based on a robust estimate of the variance, based on a sandwich estimator, which accounted for the variability in the propensity score weights. For PFS and OS, weighted survival curves based on the Nelson–Aalen estimator were generated. PFS and OS were compared using the weighted log-rank test and HRs were estimated from a weighted Cox proportional hazards model. The proportional hazards assumption was tested both before and after matching.

Results

The comparison of baseline characteristics before and after matching between acalabrutinib and ibrutinib-treated patients is shown in Table 17.

Table 17. Baseline characteristics before and after matching in MAIC of acalabrutinib vs. ibrutinib

Treatment (study)	Before matching			After matching		
	Acalabrutinib N = 136a	Ibrutinib N = 136	*p*	Acalabrutinib ESS=79	Ibrutinib N = 136	*p*
Age ≥ 73 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulky disease ≥ 5 cm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
del(11q)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
β2-microglobulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rai stage 3–4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGHV unmutated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CrCl < 60 mL/min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**$p < 0.05$.
aPre-match N does not necessarily match N of ELEVATE-TN owing to incomplete baseline data recording for some patients in some outcomes.
Abbreviations: CrCl, creatinine clearance; del(11q), deletion of chromosome 11q; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; *IGHV*, immunoglobulin G heavy-chain variable gene; MAIC, matching-adjusted indirect comparison; PS, performance status.

There was no statistically significant difference in PFS between acalabrutinib and ibrutinib (HR: [redacted]). Similarly, there no statistically significant difference in OS between acalabrutinib and ibrutinib (HR: [redacted]).

Table 18. PFS and OS before and after matching in MAIC of acalabrutinib monotherapy versus ibrutinib monotherapy

Treatment (study)	Outcome	Before matching		After matching	
		Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*

Acalabrutinib vs ibrutinib (RESONATE-2)	PFS	[redacted]	[redacted]	[redacted]	[redacted]
	OS	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CI, confidence interval; MAIC, Matched-adjusted indirect comparison; PFS, progression free survival; OS, overall survival					

After matching, PFS or OS KM curves for acalabrutinib overlapped considerably with the KM PFS or OS curves of ibrutinib, further suggesting equal efficacy between the two treatments, as per the conclusions made following the MAIC between the ASCEND and RESONATE study.

Figure 15. PFS before and after matching in MAIC of acalabrutinib monotherapy versus ibrutinib monotherapy

Figure 16. OS before and after matching in MAIC of acalabrutinib monotherapy versus ibrutinib monotherapy

Conclusion

The results of this MAIC, coupled with the results presented for the MAIC in the relapsed/refractory population and the sustained clinical benefit seen in untreated and previously treated patients with cytogenetic risk factors (ELEVATE-TN and ASCEND), strongly indicate that acalabrutinib is associated with at least similar clinical efficacy as ibrutinib in the untreated, high-risk patient population.

Therefore, whilst AstraZeneca believes that it is appropriate for the results of the MAIC in the previously-treated population to be considered generalisable to the high-risk patients in front-line setting (as per the approach adopted and accepted in appraisal TA429), the results of the MAIC performed in the front-line setting provide further reassurance of a consistent response between patients treated with either ibrutinib or acalabrutinib.

Furthermore, UK clinicians feel that it would be clinically implausible to assume a scenario where acalabrutinib offers a treatment effect less than that observed with ibrutinib due to the high selectivity toward BTK and high occupancy of >95% resulting in an expected improved safety/tolerability profile of acalabrutinib vs ibrutinib.

Relapsed/refractory CLL model – acalabrutinib versus ibrutinib

B26. PRIORITY. CS, Section B.3a.1, Table 52, page 114. The systematic review of existing economic evaluations of acalabrutinib identified a published study (Vreman *et al*, 2019) in R/R CLL which compared acalabrutinib versus ibrutinib without assuming clinical equivalence. Please explain why a full economic evaluation has not been undertaken for this population within the CS.

The early economic evaluation of acalabrutinib for relapsed chronic lymphocytic leukaemia (Vreman et al, 2019) is not affiliated with, nor represents, AstraZeneca's view on the relative efficacy of acalabrutinib when compared to ibrutinib.

The article states that '*preliminary efficacy of acalabrutinib was established in a multicentre, open-label, single-arm phase I/II tria*l' and that '*for acalabrutinib, efficacy compared with ibrutinib was established through an indirect treatment comparison based on the extracted individual patient data…*' which, given that the phase I/II trial for acalabrutinib is single-arm, we surmise to be a naïve comparison.

UK clinical expert opinion was sought regarding the plausibility of the results of the indirect treatment comparison presented in the publication where it was considered implausible and that the conclusions made in the report would not be supported by the UK clinical community. Clinicians cited the lack of direct head-to-head data to support such a strong claim, the use of early data which has been superseded with data from the Phase III clinical trials, distinct and significant differences in the patient population between the studies, and the differences in doses of the treatment received in the studies.

As reported previously, in the absence of published head-to-head RCTs, a MAIC was conducted to compare efficacy and safety of acalabrutinib versus ibrutinib in patients previously treated with CLL. Individual patient-level data from the confirmatory, Phase III, ASCEND RCT for acalabrutinib were adjusted so that the trial population matched average baseline characteristics reported in the RESONATE trial for patients receiving ibrutinib. The results of the MAIC demonstrated a non-significant benefit associated with acalabrutinib vs ibrutinib in terms of PFS ([redacted]) and OS

([redacted]) before and after matching, respectively. The MAIC-weighted time-to-event data (PFS and OS) are presented in Section C2 (Figure 23 and Figure 24). UK clinical expert opinion was sourced on the outputs of the clinical trials and MAIC, with the experts agreeing that there was no efficacy difference (PFS, OS) between acalabrutinib and ibrutinib.

Based on the results of the MAIC and UK clinical expert opinion, it was judged that treatment with either acalabrutinib or ibrutinib results in similar clinical efficacy, and therefore a cost-minimisation analysis was appropriate for the comparison against ibrutinib in the R/R CLL.

B27. PRIORITY. CS, page 175. Please clarify why the non-significant treatment effects on PFS and OS obtained from the MAIC should be interpreted as acalabrutinib being clinically equivalent to ibrutinib.

Whilst the MAIC showed that the differences in PFS and OS between ASCEND and RESONATE (acalabrutinib vs. ibrutinib) were not statistically significant, the hazard ratios for PFS and OS (HR: [redacted]; 95% CI: [redacted]; p = [redacted] and HR: [redacted]; 95% CI: [redacted]; p = [redacted], respectively) were in favour of acalabrutinib.

As such, a conservative assumption was made that acalabrutinib is at least of equal efficacy to ibrutinib.

This is further supported by the pharmacodynamic profiles of acalabrutinib and ibrutinib. Both drugs work by inhibiting BTK enzymatic activity. However, acalabrutinib is a second generation BTK inhibitor, with minimal off-target activity compared to first generation inhibitors such as ibrutinib thus potentially minimising off-target related adverse events. Therefore, whilst the common mechanism of action and the non-statistically significant hazard ratios suggest equivalent clinical efficacy, the improved kinase selectivity of acalabrutinib compared to ibrutinib is believed to be responsible for the improved tolerability profile of acalabrutinib compared to ibrutinib.

B28. PRIORITY. CS, Section B.3b.2.2, pages 175-177. Please clarify the criteria used to select the survival distributions for PFS and OS fitted to data from RESONATE (Weibull for PFS and exponential for OS).

Both the statistical fit and predicted long-term survival outputs from the model were assessed to identify the most plausible extrapolations.

PFS

The PFS investigator assessed (INV) parametric curves for ibrutinib are presented in Figure 17 and a summary of the goodness-of-fit statistics is presented in Table 19.

Figure 17. Parametric models overlaying the PFS KM data for ibrutinib from RESONATE

Abbreviations: HR: Hazard ratio; KM, Kaplan Meier; PFS: Progression-free survival
Source: [51]

Table 19. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to PFS data for ibrutinib

Distributions	AIC	BIC
Weibull	**1233.617563**	1240.163562
Exponential	1233.714717	**1236.987717**
Gompertz	1234.402728	1240.948727
Log-logistic	1235.297179	1241.843178
Generalised gamma	1235.456739	1245.275737
Log-normal	1239.647575	1246.193574

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: Progression-free survival. **Best statistical fit**

All parametric curves provide a good fit for the observed period, with two groups of models separating in the beginning of the unobserved period (Figure 17). The log-logistic and log-normal distribution exhibit plateauing tails with the other models providing more consistent estimates. UK clinical expect opinion indicated that at 5 years, approximately 40% of patients who had received ibrutinib as a treatment for R/R CLL would be expected to be progression-free. All six parametric distributions closely aligned with this 40% landmark survival rate at 5 years (Table 20). However, UK clinical expert opinion regarded the log-logistic and log-normal curves as too optimistic at 10 and 15 years. Of the remaining curves the Gompertz was deemed overly conservative given that less than 2% of patients were estimated to be alive at 15 years. The Weibull distribution was the next most conservative long-term PFS extrapolation curve and had the best statistical fit (Table 19). As such, the Weibull distribution was selected as an appropriate curve for ibrutinib PFS.

Table 20. Landmark PFS rates for ibrutinib by distribution

Function	1 year	2 years	3 years	4 years	5 years	10 years	15 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival

OS

The OS parametric curves for ibrutinib are presented in Figure 18 and a summary of the goodness-of-fit statistics is presented in Table 21.

Figure 18. Parametric models overlaying the OS KM data for ibrutinib from RESONATE

Abbreviations: KM, Kaplan Meier; OS, overall survival

Table 21. Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to OS data for ibrutinib

Distributions	AIC	BIC
Exponential	**978.4026617**	**981.6756612**
Gompertz	979.6444344	986.1904335
Weibull	979.7879252	986.3339243
Log-logistic	981.0798028	987.6258020
Generalised gamma	981.7177784	991.5367771
Log-normal	983.8368831	990.3828822

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival. **Best statistical fit**

All parametric curves provide a good fit for the observed period, with two groups of models separating in the beginning of the unobserved period. All survival extrapolations show a decline in OS as time increases with the log-logistic and log-normal distributions starting to plateau at approximately 165 months. UK clinical feedback indicated that the both the log-logistic and log-normal distributions predicted too optimistic long-term OS extrapolation (Table 22). Of the remaining four distributions the exponential distribution also exhibited the lowest AIC and BIC statistics. As such, the exponential distribution was selected as an appropriate curve for ibrutinib OS.

Table 22. Landmark OS rates for ibrutinib by distribution

Function	1 year	2 years	3 years	4 years	5 years	10 years	15 years	20 years	30 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: Overall survival. **Best statistical fit**

B29. R/R CLL Model, worksheet “cost_calcs” columns BY and ID. Please comment on the plausibility of the assumption that R/R patients will discontinue second-line treatment only if they progress or die.

Real-world studies in R/R CLL patients have shown that a proportion of patients receiving treat-to-progression treatments, such as ibrutinib, discontinue before disease progression due to experiencing drug toxicity and severe adverse events.[52,53] In the absence of time to treatment discontinuation data, progression-free survival data was used to model treatment costs. This assumed that patients remain on treatment (and incur associated costs and benefits) until they progress or die. While this assumption could potentially result in an overestimation of treatment costs in both arms, it is in line with the SmPCs for acalabrutinib and ibrutinib and has been previously accepted in NICE CLL appraisals.[24,39]

B30. CS, Table 100 and R/R CLL model, worksheets “Safety” and “Costs_AE”. Please clarify why the AEs "Neutrophil Count Decreased" and "Febrile Neutropenia" have not been included as AEs in Table 100 of the CS, whilst they are present in the model for R/R patients.

AstraZeneca have revised their AEs included in their analyses which means “Febrile Neutropenia” has been removed. The cost-minimisation analysis was intended to include AEs that occurred in at least 1% of patients treated with either acalabrutinib or ibrutinib. All AE rates with an incidence below 1% have now been completely removed from the model. To avoid further confusion, AEs that have no associated

utility decrement or cost have also been removed from the economic model. Please find below a table of all AEs that are applied in the R/R economic model.

Table 23. Adverse event rates applied in the revised R/R economic model

Adverse event	Base case	
	Acalabrutinib	**Ibrutinib**
Anaemia	11.70%	4.62%
Diarrhoea	1.30%	4.10%
Dyspnoea	0.00%	2.05%
Fatigue	0.00%	2.05%
Infections and infestations	14.90%	24.00%
Neutropenia	15.58%	16.41%
Neutrophil count decreased	1.3%	0%
Atrial fibrillation	1.30%	3.00%
Thrombocytopenia	3.90%	5.64%
Bleeding	1.9%	1.0%
Source	ASCEND	RESONATE

Section C: Additional analysis requests

C1. PRIORITY. Please present a full cost-utility analysis for the high-risk population using parametric models fitted to the MAIC-weighted time-to-event data (not assuming equivalence or proportional hazards).

Model structure

A probabilistic cost utility analysis was implemented using the same semi-Markov model used for the assessment of acalabrutinib monotherapy compared with chlorambucil in combination with obinutuzumab in the treatment of previously untreated CLL patients described in CS Section 3a.2.2, page 117. All corrections highlighted within B1, B15, B16, B17 and B18 of the ERG clarification questions have been addressed in this model.

Clinical parameters and variables – MAIC

A MAIC was conducted to compare acalabrutinib monotherapy versus ibrutinib as described in the response to clarification question B25. A single hazard ratio for PFS was calculated using the ELEVATE-TN and RESONATE-2 studies. In the model, the PFS hazard ratio is applied to both TTP and TTDeath and hence the same relative risk applies to both endpoints. This assumption was necessary as TTP and TTDeath endpoints are not usually reported in the literature, thus making an indirect treatment comparison on these endpoints unfeasible.

To estimate TTP and TTDeath curves for ibrutinib in the model, the adjusted hazard ratio from the MAIC was applied to the unadjusted TTP and TTDeath curves extrapolated for acalabrutinib monotherapy. Despite both the ELEVATE-TN and RESONATE-2 trial for acalabrutinib and ibrutinib defining IRC PFS as their primary endpoints, INV PFS was used in the MAIC to allow long-term data from ibrutinib to be captured. The data cut from Barr 2018[54] matched the scheduled follow-up in ELEVATE-TN study and only reported INV-assessed PFS.

As the hazard ratio was generated using the INV PFS endpoint, this endpoint was also used for the acalabrutinib monotherapy extrapolations to provide a fair comparison.

The hazard ratio for OS could not be used within the semi-Markov structure.

Clinical parameters and variables – Base case curve selection (INV)

TTP (INV): acalabrutinib monotherapy

A summary of the goodness-of-fit statistics for the TTP INV endpoint from ELEVATE-TN of acalabrutinib monotherapy is presented in Table 24.

Table 24. Statistical goodness-of-fit indicators (AIC/BIC) values for the parametric models fitted to TTP INV of acalabrutinib monotherapy

Distributions	AIC	BIC
Exponential	**168.73624**	**171.92362**
Log-normal	169.89132	176.26609
Gompertz	170.01881	176.39359
Log-logistic	170.45736	176.83213
Weibull	170.52265	176.89743
Gamma	170.54233	176.91710
Generalized gamma	171.41155	180.97371

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTP: Time to progression. **Best statistical fit**

As KM data were only available for the trial follow-up period, there is little information to inform the long-term extrapolation of TTP. Figure 19 demonstrates the uncertainty around the long-term extrapolations of TTP for acalabrutinib monotherapy. During the within trial period (i.e. up to month 24), most of conventional distributions yielded an excellent fit to KM data for acalabrutinib monotherapy but in the unobserved period (i.e. beyond month 30), the models generated differing extrapolations for TTP. These can be classed into two sets of clinical projections; one group with shallow survival curves (exponential, Weibull and gamma distributions), and another group with flat tails demonstrated by less shallow survival curves (Gompertz and generalized gamma distributions). Landmark analysis shows that the different models predict a wide range of patients that remain progression free after 20 years (from 53.5% [exponential] to 87.3% [Gompertz]); despite the wide range in extrapolated estimates, all options may predict unreasonably high 20-year PFS probabilities. Within the model, all-cause mortality would prevent optimistic PFS from leading to unrealistic OS estimates.

Figure 19. Parametric models overlaying the TTP INV KM data for acalabrutinib monotherapy

Abbreviations: INV, investigator-assessed; KM: Kaplan-Meier; TTP, time-to-progression

TTDeath (INV): acalabrutinib monotherapy

A summary of the goodness-of-fit statistics for the TTDeath INV endpoint of acalabrutinib monotherapy is presented in Table 25.

Table 25. Statistical goodness-of-fit indicators (AIC/BIC) values for the parametric models fitted to TTDeath INV of acalabrutinib monotherapy

Distributions	AIC	BIC
Exponential	**120.76854**	**123.95592**
Log-normal	122.68323	129.05801
Log-logistic	122.69063	129.0654
Gamma	122.69404	129.06882
Weibull	122.69535	129.07012
Gompertz	122.73642	129.11119
Generalized gamma	124.67161	134.23377

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTDeath: Time to death (pre progression). **Best statistical fit**

Similarly, to the TTP endpoints, KM data for TTDeath is relatively immature as few deaths occurred before progression in the acalabrutinib monotherapy arm of the ELEVATE-TN study. Figure 20 shows the KM and parametric survival distributions for acalabrutinib monotherapy. Beyond month 60, the curves start to separate with the Gompertz distribution providing considerably more conservative results than all the remaining parametric models.

Figure 20. Parametric models overlaying the TTDeath INV KM data for acalabrutinib monotherapy

Abbreviations: INV, investigator-assessed; KM: Kaplan-Meier; TTDeath: Time to death (pre progression)

TTP/TTDeath curve selection: acalabrutinib monotherapy vs ibrutinib

The choice of baseline curves can have a large effect on the interpretability and clinical plausibility of the model and results. In order to identify the most plausible extrapolations, both the statistical fit and predicted long-term survival outputs from the model were assessed.

As mentioned above, the hazard ratio in the MAIC was generated for PFS and so is not aligned with the TTP and TTDeath endpoints used in the model. In order to present a long-term PFS extrapolation, the distributions used to extrapolate TTP and

TTDeath were aligned as this would provide a better representation of PFS and the hazard ratio was applied to both sets of extrapolations.

Ibrutinib and acalabrutinib have the same mechanism of action; therefore, it was considered appropriate to use the same distribution for these treatments. In addition, the use of HRs to estimate relative a comparative curve mandates that the same distribution is applied.

Statistical fit

When assessing the statistical fit of a model via AIC, a difference of less than two points is not considered meaningful.[42] As shown in Table 26, the exponential curve was the best fitting for both TTP and TTDeath and only generalized gamma distribution was outside of the two AIC point threshold for both TTP and TTDeath. As such, the generalized gamma curve was not considered for use in the base case whilst all other curves were.

Table 26. AIC values for the parametric models fitted to TTP and TTDeath for acalabrutinib monotherapy (PFS INV)

Distributions	TTP	TTDeath
Exponential	**168.73624**	**120.76854**
Log-normal	169.89132	122.68323
Gompertz	170.01881	122.73642
Log-logistic	170.45736	122.69063
Weibull	170.52265	122.69535
Gamma	170.54233	122.69404
Generalized gamma	171.41155	124.67161
Abbreviations: AIC: Akaike information criterion; TTDeath: Time to death (pre progression). **Best statistical fit**		

Clinical plausibility

Table 27 and Table 28 outline the landmark PFS and OS rates for acalabrutinib monotherapy and ibrutinib. Following feedback from oncologists, it was expected that PFS in frontline ibrutinib would be in line with that observed in the RESONATE-2 trial where between 70-75% of patients were progression-free at 5 years. Of the five remaining curves being considered for the base case, the exponential distribution

provided the closest estimate with [redacted]% of patients alive at 5 years. As such, the exponential distribution was selected as the base case.

Furthermore, the exponential distribution has the lowest AIC scores for TTP and TTDeath and as such, provides the best fitting models for both extrapolations. Moreover, the exponential distribution provided the most conservative extrapolations for TTP, as shown in Figure 19. While the exponential distribution was only the fifth most conservative TTDeath curve (Figure 20), general population mortality surpasses TTDeath for the majority of the time horizon and as such, the effect of not using a more conservative distribution is minimal.

Table 27. Acalabrutinib monotherapy landmark progression-free survival rates (PFS INV)

Function	Treatment	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PPS: MURANO, exponential for acalabrutinib monotherapy and ibrutinib
Abbreviations: INV, investigator assessed; PFS, progression-free survival; PPS, post progression survival.

Table 28. Acalabrutinib monotherapy landmark overall survival rates (PFS INV)

Function	Treatment	1 year	5 years	10 years	15 years	20 years	30 years
Exponential	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Function	Treatment	1 year	5 years	10 years	15 years	20 years	30 years
Gompertz	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Acala mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PPS: MURANO, exponential for acalabrutinib monotherapy and ibrutinib
Abbreviations: INV, investigator assessed; PFS, progression-free survival; PPS, post progression survival.

Scenario analyses were conducted using the log-normal (second lowest AIC for TTP) and log-logistic distributions (lowest predicted survival at 20 years) for both TTP and TTDeath.

PPS

Following disease progression, patients move onto subsequent therapies that are determined by the first-line treatment taken. In an advisory board, UK clinicians indicated high-risk or unfit patients on ibrutinib would commonly move on to a venetoclax-based regimen following disease progression.[25] Patients treated with acalabrutinib are expected to follow the same treatment sequence given that both ibrutinib and acalabrutinib are BTK inhibitors. As such, PPS was informed by data from the MURANO for venetoclax plus rituximab (CS B3a.3.4.2, page 138) and the exponential distribution was selected to extrapolate PPS.

Measurement and valuation of health effects

With the exception of Section B.3a.4.5, the measurement and valuation of health effects is the same as in CS Section B.3a.4, page 143.

Adverse reactions

The model accounts for the impact of all treatment related Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 AEs that occurred in at least 1% of

patients treated with acalabrutinib monotherapy or ibrutinib. A summary of Grade ≥ 3 AEs included in the analysis is presented in Table 29. AE incidence rates for acalabrutinib monotherapy were sourced from ELEVATE-TN and from RESONATE-2 for ibrutinib.

AEs in the model have an impact on cost (patients accrue the costs associated with managing the AE) and the patient's quality of life (via utility decrements associated with each event). The costs and utility decrements resultant from AEs are applied to the proportion of patients experiencing the event in the first cycle of the model, assuming AEs would occur during the first four weeks of treatment

Table 29. Summary of Grade ≥ 3 adverse events included in the analysis

Adverse event	Acalabrutinib	Ibrutinib
Abdominal pain	0.00%	2.96%
Anaemia	6.70%	5.93%
Atrial fibrillation	0.00%	4.00%
Bleeding	1.70%	6.00%
Diarrhoea	0.56%	3.70%
Febrile neutropenia	1.12%	2.22%
Hypo/ hypertension	0.00%	4.44%
Infections and infestations	14.00%	25.00%
Neutropenia	9.50%	10.37%
Platelet count decreased	0.00%	2.96%
Rash	0.00%	2.96%
Thrombocytopenia	2.79%	2.22%
Source	ELEVATE-TN	RESONATE-2

The model accounts for quality of life loss resulting from AEs. The total decrement was estimated as incidence of each AE multiplied by the duration and disutility associated with each AE. Utility decrements associated with the AEs included in the model were sourced from previous NICE TAs and other published literature. All AE utility decrements were applied in cycle 1 only.

The disutility and duration estimates for AE used in the analysis is presented in Table 30.

Table 30. Disutility and duration estimates for adverse events

Adverse event	Disutility	Source	Duration (days)	Source	Comment
Abdominal pain	0.00		0.00		No data. Assume no disutility
Anaemia	-0.09	TA487[55]	23.21	TA487	
Atrial fibrillation	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Assumed the same as infections and infestations
Bleeding	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Assumed the same as infections and infestations
Diarrhoea	-0.20	TA359[57]	3.00	TA403	Diarrhoea + Colitis disutility
Febrile Neutropenia	-0.20	TA359[57]	4.00	TA403	
Hypo/hypertension	-0.02	Wehler et al. 2018[56]	21.00	TA403	Hypertension disutility
Infections and infestations	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Infection disutility
Neutropenia	-0.16	TA487[55]	15.09	TA487	
Platelet count decreased	-0.05	TA487[55]	20.99	TA487	Assumed the same as ALT/AST increased
Rash	-0.03	TA403[55]	21.00	TA403	
Thrombocytopenia	-0.11	TA487[55]	23.21	TA487	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TA, technology appraisal.

Cost and healthcare resource use identification, measurement and valuation

A full breakdown of the costs used in the model is presented in CS Section B.3b.3.3, page 186. The update of the NHS reference costs, as detailed in the response to clarification question B1, has been carried through. In addition to the costs stated in CS Section B.3b.3.3, subsequent treatment costs were reintroduced into the model. All acalabrutinib and ibrutinib patients were assumed to receive venetoclax plus rituximab as their second-line therapy to complement the use of MURANO PPS data. A breakdown of the subsequent treatment costs and duration used in the model can be found in CS Section B.3a.5.1 page 149.

Summary of base-case analysis inputs

A summary of the key variables applied in the economic model (base case) is presented in Table 31.

Table 31. Summary of variables applied in the economic model

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
Model settings		
Perspective	Payer	N/A
Time horizon	30	N/A
Proportion females	38%	Not modelled
Starting age in model (years)	70	Not modelled
Body weight (kg)	79	Not modelled
Body surface area (m^2)	1.93	Not modelled
Discount rate (costs)	3.5%	N/A
Discount rate (outcomes)	3.5%	N/A
Clinical parameters		
Efficacy parameters (INV)		
TTdeath distribution – acalabrutinib	Exponential	Multivariate normal
TTP distribution – acalabrutinib	Exponential	Multivariate normal
TTDeath HR – ibrutinib	[redacted]	SE: [redacted] (lognormal)
TTP HR – ibrutinib	[redacted]	SE: [redacted] (lognormal)
PPS data – acalabrutinib	MURANO	N/A
PPS data – ibrutinib	MURANO	N/A
PPS distribution – acalabrutinib	Exponential	Multivariate normal
PPS distribution – ibrutinib	Exponential	Multivariate normal
Probability of adverse events – acalabrutinib		
Abdominal pain	0.00%	NA
Anaemia	6.70%	SE: 0.0134 (beta)
Atrial fibrillation	0.00%	NA
Bleeding	1.70%	SE: 0.0034
Diarrhoea	0.56%	SE: 0.0011 (beta)
Febrile Neutropenia	1.12%	SE: 0.0022 (beta)
Hypo/ hypertension	0.00%	NA
Infections and infestations	14.00%	SE: 0.0280 (beta)
Neutropenia	9.50%	SE: 0.0190 (beta)
Platelet Count Decreased	0.00%	NA
Rash	0.00%	NA
Thrombocytopenia	2.79%	SE: 0.0056 (beta)
Probability of adverse events – ibrutinib		
Abdominal pain	2.96%	SE: 0.0059 (beta)
Anaemia	5.93%	SE: 0.0119 (beta)
Atrial fibrillation	4.00%	SE: 0.0080 (beta)
Bleeding	6.00%	SE: 0.0120 (beta)
Diarrhoea	3.70%	SE: 0.0074 (beta)
Febrile Neutropenia	2.22%	SE: 0.0044 (beta)
Hypo/ hypertension	4.44%	SE: 0.0089 (beta)
Infections and infestations	25.00%	SE: 0.0500 (beta)

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
Neutropenia	10.37%	SE: 0.0207 (beta)
Platelet Count Decreased	2.96%	SE: 0.0059 (beta)
Rash	2.96%	SE: 0.0059 (beta)
Thrombocytopenia	2.22%	SE: 0.0044 (beta)
Duration of adverse events (days)		
Abdominal pain	0.00	SE: 0.0000 (gamma)
Anaemia	23.21	SE: 4.6420 (gamma)
Atrial fibrillation	14.00	SE: 2.8000 (gamma)
Bleeding	14.00	SE: 2.8000 (gamma)
Diarrhoea	3.00	SE: 0.6000 (gamma)
Febrile Neutropenia	4.00	SE: 0.8000 (gamma)
Hypo/ hypertension	21.00	SE: 4.2000 (gamma)
Infections and infestations	14.00	SE: 2.8000 (gamma)
Neutropenia	15.09	SE: 3.0180 (gamma)
Platelet Count Decreased	20.99	SE: 4.1980 (gamma)
Rash	21.00	SE: 4.2000 (gamma)
Thrombocytopenia	23.21	SE: 4.6420 (gamma)
Health-related quality of life		
Utility parameters		
PFS	[redacted]	[redacted]
PD	[redacted]	[redacted]
Disutility parameters		
Age-related decrement	Incorporated from Ara et al. 2010	Not modelled
Abdominal pain	0.00	SE: 0.0000 (beta)
Anaemia	-0.09	SE: 0.0180 (beta)
Atrial fibrillation	-0.22	SE: 0.0440 (beta)
Bleeding	-0.22	SE: 0.0440 (beta)
Diarrhoea	-0.20	SE: 0.0400 (beta)
Febrile Neutropenia	-0.20	SE: 0.0400 (beta)
Hypo/ hypertension	-0.02	SE: 0.0040 (beta)
Infections and infestations	-0.22	SE: 0.0440 (beta)
Neutropenia	-0.16	SE: 0.0320 (beta)
Platelet Count Decreased	-0.05	SE: 0.0100 (beta)
Rash	-0.03	SE: 0.0060 (beta)
Thrombocytopenia	-0.11	SE: 0.0220 (beta)
Costs and resource use		
Disease management costs and resource use		
PF: full blood count	0.31 per 28 days	SE: 0.0613 (beta)
PF: LDH	0.23 per 28 days	SE: 0.0460 (beta)
PF: haematologist visit	0.15 per 28 days	SE: 0.0307 (beta)
PD: full blood count	0.61 per 28 days	SE: 0.1227 (beta)
PD: chest X-Ray	0.15 per 28 days	SE: 0.0307 (beta)

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
PD: bone marrow exam	0.08 per 28 days	SE: 0.0153 (beta)
PD: haematologist visit	0.46 per 28 days	SE: 0.0920 (beta)
PD: inpatient visit (non-surgical)	0.31 per 28 days	SE: 0.0613 (beta)
PD: full blood transfusion	0.84 per 28 days	SE: 0.1687 (beta)
Full blood count unit cost	£2.79	Fixed
LDH unit cost	£1.10	Fixed
Haematologist visit unit cost	£166.51	Fixed
Chest X-Ray unit cost	£71.92	Fixed
Bone marrow exam unit cost	£558.16	Fixed
Inpatient visit (non-surgical) unit cost	£433.17	Fixed
Full blood transfusion unit cost	£253.13	Fixed
End of life care		
End of life care cost (one-off)	£6,975.00	Not modelled
% patients who receive EoL care	100.00%	Not modelled
Adverse event costs		
Abdominal pain	£802.83	Fixed
Anaemia	£341.86	Fixed
Atrial fibrillation	£1,770.38	Fixed
Bleeding	£1,770.38	Fixed
Diarrhoea	£140.89	Fixed
Febrile neutropenia	£6,623.14	Fixed
Hypo/ hypertension	£598.58	Fixed
Infections and infestations	£1,770.38	Fixed
Neutropenia	£136.34	Fixed
Platelet count decreased	£136.34	Fixed
Rash	£0.00	Fixed
Thrombocytopenia	£674.07	Fixed
Acquisition cost		
Acalabrutinib pack cost (60 x 100mg)	[redacted]	Fixed
Ibrutinib pack cost (28 x 420mg)	£4,292.40	Fixed
Subsequent treatment cost		
Rituximab vial cost (1 x 500mg/m^2)	£785.84	Fixed
Venetoclax pack cost (100 x 112mg)	£4,789.47	Fixed
Treatment administration cost		
Administration (per infusion; IV)	£241.06	Fixed
One-time monitoring costs		
TLS Prophylaxis	£1,975.46	Fixed
Subsequent treatment duration		
Rituximab subsequent treatment duration	6.00 cycles	Fixed
Venetoclax subsequent treatment duration	26.00 cycles	Fixed
Distribution of subsequent treatments – acalabrutinib		
Venetoclax + rituximab	100%	Fixed
Distribution of subsequent treatments – ibrutinib		

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
Venetoclax + rituximab	100%	Fixed

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; EoL, end of life; ITT, intent to treat; IV, intravenous; LDH, lactate dehydrogenase; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; SE, standard error; TLS, tumour lysis syndrome; TTDeath: Time to death (pre progression); TTP, time to progression.

Assumptions

A list of model assumptions is presented in CS Section B.3a.6.2. Additional assumptions are presented in Table 32.

Table 32. Additional assumptions specific to comparisons against ibrutinib

Model input	Assumption	Rationale
MAIC hazard ratios	In the model, the PFS hazard ratio is applied to both TTP and TTDeath and hence the same relative risk applies to both endpoints	This assumption was necessary as TTP and TTDeath endpoints are not usually reported in the literature, thus making an indirect treatment comparison on these endpoints unfeasible
PPS data source for ibrutinib	MURANO venetoclax plus rituximab OS data (patients with 1-2 prior therapies only) was used to inform post-progression survival for patients in the ibrutinib arm	Patients progressing on a BTKi, would typically be ineligible for a BTKi in the second line. UK clinicians have indicated there is a preference for treating with a BTKi prior to treating with venetoclax plus rituximab. See CS Section B1

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CS, company submission; MAIC, matching adjusted indirect comparison; OS, overall survival PFS, progression-free survival; PPS, post-progression survival; TTDeath: Time to death (pre progression); TTP, time to progression; UK, United Kingdom.

Base case results

As previously discussed in CS doc B, a cost-minimisation analysis is justified in light of non-statistical differences observed in the MAIC, and UK clinical opinion.

However, AstraZeneca understand the need to assess the uncertainty of efficacy and have presented the probabilistic results of the cost-effectiveness analysis to show the uncertainty of the data. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters were

preserved. The PSA was run for 1,000 iterations for the base case and for all scenario analyses presented.

Total costs, life years, QALYs, and incremental cost per QALY gained for acalabrutinib versus ibrutinib are presented Table 33. Acalabrutinib monotherapy was associated with [redacted] additional QALYs and [redacted] additional costs. As such, acalabrutinib monotherapy dominated ibrutinib.

Table 33. Base-case results (acalabrutinib vs ibrutinib)

Technologies	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

The cost-effectiveness planes and acceptability curves for acalabrutinib versus chlorambucil plus obinutuzumab are presented in Figure 21 and Figure 22, respectively.

Figure 21. Cost-effectiveness plane for acalabrutinib versus ibrutinib

Abbreviations: A, acalabrutinib; I, ibrutinib; QALY, quality-adjusted life year.

Figure 22. Cost-effectiveness acceptability curve for acalabrutinib versus ibrutinib

Scenario analysis

A list of scenario analyses ran in the model for acalabrutinib versus chlorambucil plus obinutuzumab is presented in Table 34 and results are presented in Table 35.

Table 34. List of scenario analyses conducted

Parameter	Base case	Scenario	Comment
Time horizon	30 years	25 years	Assess the impact of alternative time horizons
		20 years	
Discount rate for costs and outcomes	3%	6%	Assess the impact of discounting
		0%	
PF utility value	[redacted]	No history of health condition: 'cancer'; age band: 65 to ≤ 70: 0.8078	Assess the impact of capping PF utility to the general population norms
Age utility decrement	Apply	Do not apply	Assess impact of applying an age utility decrement
Acalabrutinib survival extrapolations (TTP and TTDeath)	Exponential	Log-normal	Assess the impact of the next most viable alternative extrapolation of survival estimates. The log-normal presents the second lowest AIC for TTP
Acalabrutinib survival extrapolations (TTP and TTDeath)	Exponential	Log-logistic	Assess the impact of the next most viable alternative extrapolation of survival estimates. The log-logistic presented the lowest predicted survival at 20 years

Abbreviations: OS, overall survival; PF, progression-free; PPS, post-progression survival; TTDeath: Time to death (pre progression); TTP, time to progression.

Table 35. Results of scenario analysis for acalabrutinib vs ibrutinib

Parameter/ outcome	Scenario	Technology	Discounted total cost	Discounted total QALYs	Incremental costs	Incremental QALYs	ICER
Base case	-	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25 years	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20 years	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and outcomes	6%	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	0%	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PF utility value	No history of health condition: 'cancer'; age band: 65 to ≤ 70: 0.8078	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age utility decrement	Do not apply	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib survival extrapolations (TTP and TTDeath)	Lognormal	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib survival extrapolations (TTP and TTDeath)	Log-logistic	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PF, progression-free; QALY, quality-adjusted life year; TTDeath: Time to death (pre progression); TTP, time to progression.

Interpretation and conclusions of economic evidence

Results of the analysis showed that acalabrutinib monotherapy is less costly and more effective (QALYs) than ibrutinib across all scenarios. These analyses highlight that acalabrutinib is a cost-effective therapy that addresses significant unmet need and suggest that acalabrutinib-based therapy should be reimbursed for the treatment of previously untreated CLL in high-risk patients.

C2. PRIORITY. Please present a full cost-utility analysis for the R/R CLL population using parametric models fitted to the MAIC-weighted time-to-event data (not assuming equivalence or proportional hazards).

As described in Section B.2b.9, an MAIC was conducted to estimate the comparative efficacy and safety of acalabrutinib versus ibrutinib in patients with R/R CLL based on data from ASCEND and RESONATE.

For PFS and OS, weighted survival curves based on the Nelson-Aalen estimator were generated. PFS and OS were compared using weighted log-rank test and HRs were estimated from a weighted Cox proportional hazards model. The proportional hazards assumption was tested both before and after matching. Further details on testing for the proportional hazards assumption is provided in response to Question A29. The KM curves for PFS and OS before and after matching in the are shown in Figure 23 and Figure 24.

Figure 23. PFS before and after matching in MAIC of acalabrutinib vs. ibrutinib

Abbreviations: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival

Figure 24. OS before and after matching in MAIC of acalabrutinib vs. ibrutinib

Abbreviations: MAIC, matching-adjusted indirect comparison; NR, not reached; OS, overall survival.

Differences in PFS between the two treatments were not statistically significant before matching (HR: [redacted] p=[redacted]), or after matching, (HR: [redacted]), p=[redacted]), with a trend in favour of acalabrutinib.

Differences in OS between the two treatments were not statistically significant before or after matching (HR:

[redacted]), with a trend in favour of acalabrutinib.

Five sensitivity analyses were performed matching for different sets of baseline characteristics between the two studies and produced results consistent with the base case analysis. Across all sensitivity analyses, after matching, the HRs ranged from [redacted] for PFS and [redacted] for OS. However, in all cases the difference was not statistically significant.

These estimates, coupled with Figure 23 and Figure 24, demonstrate that the comparative clinical efficacy estimates of acalabrutinib and ibrutinib in the R/R CLL population are overlapping, statistically non-significant and therefore subject to uncertainty. While all the hazard ratios estimated by the MAIC favoured acalabrutinib, for the purposes of this appraisal we conservatively assumed there is no difference in clinical efficacy between acalabrutinib and ibrutinib in R/R CLL and conducted a cost-minimisation analysis. Hazard ratios of 1 were conservatively applied to the baseline PFS and OS estimated using the 6-year follow up of ibrutinib RESONATE trial.

Due to the high uncertainty surrounding the hazard ratios for OS and PFS, we undertook a probabilistic cost-utility analysis to assess how sensitive the ICER would be to differences in incremental effects. There is literature suggesting that even when a treatment effect does not reach statistical significance, it is appropriate to conduct cost-effectiveness sensitivity analyses.[58]

Cost-utility analysis in R/R CLL

Model structure

A probabilistic cost-utility analysis was conducted using the same partitioned-survival model used for the cost comparison analysis of acalabrutinib compared with ibrutinib for the treatment of relapsed and refractory CLL, as described in section B.3b.2.1 of the company submission. All updates to model inputs highlighted within B1 and B30 of the ERG clarification questions have been included in this economic model.

Clinical parameters and variables

The adjusted hazard ratios from the MAIC were applied to the unadjusted PFS and OS curves extrapolated for ibrutinib monotherapy from the RESONATE trial to estimate extrapolated OS and PFS for acalabrutinib.

The selections for the baseline PFS and OS parametric curves were as described in section B.3b.2.2 of the company submission and ERG clarification questions B28. A top-line summary is presented below

PFS

All parametric curves provided a good fit for the observed period. Based on clinicals expert opinion, the log-logistic and log-normal curves were deemed as too optimistic at 10 and 15 years, and of the remaining curves Gompertz was deemed overly conservative. The Weibull distribution was the next-most reasonable curve and had the second-best statistical fit. As such, the Weibull distribution was selected as an appropriate curve for ibrutinib PFS.

Figure 25. Extrapolation of ibrutinib PFS (RESONATE; ITT population)

Abbreviations: ITT, intention to treat; KM, Kaplan Meier; PFS, progression-free survival.

Table 36. Summary of goodness-of-fit statistics for the parametric survival analysis of PFS for ibrutinib (RESONATE; ITT population)

Distribution	Ibrutinib PFS (RESONATE; ITT population)	
	AIC	**BIC**
Weibull	**1233.62**	1240.16
Exponential	1233.71	**1236.99**
Gompertz	1234.40	1240.95
Log-logistic	1235.30	1241.84
Generalised gamma	1235.46	1245.28
Lognormal	1239.65	1246.19

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention to treat; PFS, progression-free survival. **Best statistical fit.**

OS

All parametric curves provide a good fit for the observed period. The log-logistic and log-normal distributions however starting to plateau at approximately 165 months, predicting too optimistic long-term OS extrapolation. The exponential distribution exhibited the lowest AIC and BIC statistics and was selected as the preferred curve to model OS in the R/R setting. To avoid unrealistic survival projections in the model, OS was constrained by age and gender adjusted general population mortality sourced from the Office of National Statistics. At each model cycle, the highest mortality risk (from the OS curve or general population mortality) was used to estimate survival for the next cycle.

Figure 26. Extrapolation of ibrutinib OS (RESONATE; ITT population)

Abbreviations: ITT, intention to treat; KM: Kaplan-Meier; OS: Overall survival

Table 37. Summary of goodness-of-fit statistics for the parametric survival analysis of OS for ibrutinib (RESONATE; ITT population)

Distribution	**Ibrutinib PFS (RESONATE; ITT population)**	
	AIC	**BIC**
Exponential	**978.40**	**981.68**
Gompertz	979.64	986.19
Weibull	979.79	986.34
Log-logistic	981.08	987.63
Generalised gamma	981.72	991.54
Lognormal	983.84	990.38

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention to treat; OS: Overall survival. **Best statistical fit.**

Measurement and valuation of health effects

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

The base case analysis used the EQ-5D-3L utility value derived from the ASCEND study for the PF health state. This was considered the most robust and applicable source of utility data for this population, as they were directly collected in patients

with previously treated CLL, are aligned with age-matched general population norms as reported in Ara and Brazier 2011.[48]

In ASCEND, the PD HSUVs were generated using a limited number of observations and hence lack face validity. As such, a PD utility value of 0.6 sourced from Holzner et al. was used in the base case. In this study, Holzner et al.[59] measured quality of life using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and the Functional Assessment of Cancer Therapy (FACIT): General questionnaire in 418 cancer patients, 81 of whom had CLL. The data were then used to give a general indication of reasonable utility values for CLL. This utility value was selected for the base case as it has been accepted in previous NICE submissions.[24,57] The difference between the two health states represents the reduction in HRQoL related to disease progression, which leads to increased anxiety and symptom burden.

The utilities used in the base case analysis are presented in Table 38.

Table 38. Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)
Progression free	[redacted] (0.012)
Progressed disease	0.600 (0.060)

Age-related utility decrement

An age-related utility decrement was used in the model. The mean age in the ASCEND study, and so the mean age of patients entering the model, was around 67 years. As such, it is anticipated that a patient's quality of life will decline with age over the time horizon. The age-adjusted utility adjustment was implemented using the methods described in Ara et al. 2010.[60] In each model cycle, the health state utilities decrement was estimated based on the following equation:

$$HS_{utility} * (1 - (0.9508566 + 0.0212126 * (\%\, male) - 0.0002587 * age - 0.0000332 * age^2))$$

HS, health state.

The utility decrements were estimated for all patients alive (i.e. in PF and PD health states) in each model cycle and subtracted from the total QALYs accrued in a given cycle.

Adverse reaction utility decrement

The model accounts for the impact of all treatment related Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 AEs that occurred in at least 1% of patients treated with acalabrutinib or ibrutinib in the respective R/R clinical trials. A summary of Grade ≥ 3 AEs included in the analysis is presented in response to B30 of the ERG questions.

The model accounts for quality of life loss resulting from AEs. The total decrement was estimated as incidence of each AE multiplied by the duration and disutility associated with each AE. Utility decrements associated with the AEs included in the model were sourced from previous NICE TAs and other published literature. All AE utility decrements were applied in cycle 1.

Table 39. Disutility and duration estimates for adverse events

Adverse event	Disutility	Source	Duration (days)	Source	Comment
ALT/AST increased	-0.05	TA487[55]	20.99	TA487	
Anaemia	-0.09	TA487[55]	23.21	TA487	
Atrial fibrillation	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Assumed the same as infections and infestations
Bleeding	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Assumed the same as infections and infestations
Diarrhoea	-0.20	TA359[57]	3.00	TA403	Diarrhoea + Colitis disutility
Dyspnoea	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Assumed the same as infections and infestations
Fatigue	-0.07	TA403[61]	21.00	TA403	
Infections and infestations	-0.22	Wehler et al. 2018[56]	14.00	Assumption	Infection disutility
Neutropenia	-0.16	TA487[55]	15.09	TA487	

Neutrophil Count Decreased	-0.16	TA487[55]	15.09	TA403	Assumed same as Neutropenia
Thrombocytopenia	-0.11	TA487[55]	23.21	TA487	
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TA, technology appraisal					

Cost and healthcare resource use identification, measurement and valuation

A full breakdown of the costs used in the model is presented in CS Section B.3b.2.3, page 177. The update of the NHS reference costs, as detailed in the response to clarification question B1, has been carried through. In addition to the costs stated in the CS, subsequent treatment costs were reintroduced into the model. All acalabrutinib and ibrutinib patients who progressed were assumed to receive venetoclax plus rituximab as their subsequent therapy. A summary of the dosing information is provided in Table 40 and unit and administration costs for venetoclax in combination with rituximab and Table 41.

Table 40. Dosing information for venetoclax plus rituximab

Dosing information	Reference
• Venetoclax: Dose of 400 mg administered orally once daily for a total of two years • Rituximab: first dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 intravenously on day 1 of each cycle for a maximum of 6 cycles	Seymour et al 2018[46]

Table 41. Costs associated with venetoclax plus rituximab

Treatment	Venetoclax	Rituximab
Formulation	100	500 mg
Units per pack	112	1
Cost per pack / vial	£4,798.47	£785.84
Unit cost (per administration)	£0	£241.06
Administrations per cycle	1	1
Total cost per cycle	£0	£241.06*
One-time monitoring	£1,975.46	£0
Cost for cycles 1-6	£6,244.05	
Cost for cycles 7-12	£4,789.47	

* For the first six cycles of the analysis.

Summary of base-case analysis inputs

A summary of the key variables applied in the economic model (base case) is presented in Table 42.

Table 42. Summary of variables applied in the R/R economic model

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
Model settings		
Perspective	Payer	N/A
Time horizon	30	N/A
Proportion females	33%	Not modelled
Starting age in model (years)	67	Not modelled
Body weight (kg)	77.5	Not modelled
Body surface area (m^2)	1.91	Not modelled
Discount rate (costs)	3.5%	N/A
Discount rate (outcomes)	3.5%	N/A
Clinical parameters		
Efficacy parameters		
PFS distribution – ibrutinib	Weibull	Multivariate normal
OS distribution – ibrutinib	Exponential	Multivariate normal
PFS hazard ratio – acalabrutinib	[redacted]	[redacted] (lognormal)
OS hazard ratio – acalabrutinib	[redacted]	[redacted] (lognormal)
Adverse event rates – acalabrutinib		
ALT/AST increased	1.95%	SE: 0.0039 (beta)
Anaemia	11.70%	SE: 0.0234 (beta)
Atrial fibrillation	1.30%	SE: 0.0026 (beta)
Bleeding	1.90%	SE: 0.0038 (beta)
Diarrhoea	1.30%	SE: 0.0026 (beta)
Dyspnoea	0.00%	NA
Fatigue	0.00%	NA
Infections and infestations	14.90%	SE: 0.0298 (beta)
Neutropenia	15.58%	SE: 0.0312 (beta)
Neutrophil count decreased	1.30%	SE: 0.0026 (beta)
Thrombocytopenia	3.90%	SE: 0.0078 (beta)
Adverse event rates – ibrutinib		
ALT/AST increased	0.00%	NA
Anaemia	4.62%	SE: 0.0092 (beta)
Atrial fibrillation	3.00%	SE: 0.0060 (beta)
Bleeding	1.00%	SE: 0.0020 (beta)
Diarrhoea	4.10%	SE: 0.0082 (beta)
Dyspnoea	2.05%	SE: 0.0041 (beta)

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
Fatigue	2.05%	SE: 0.0041 (beta)
Infections and infestations	24.00%	SE: 0.0480 (beta)
Neutropenia	16.41%	SE: 0.0328 (beta)
Neutrophil count decreased	0.00%	NA
Thrombocytopenia	5.64%	SE: 0.0113 (beta)
Duration of adverse event (days)		
ALT/AST increased	20.99	SE: 4.1980 (gamma)
Anaemia	23.21	SE: 4.6420 (gamma)
Atrial fibrillation	14.00	SE: 2.8000 (gamma)
Bleeding	14.00	SE: 2.8000 (gamma)
Diarrhoea	3.00	SE: 0.6000 (gamma)
Dyspnoea	14.00	SE: 2.8000 (gamma)
Fatigue	21.00	SE: 4.2000 (gamma)
Infections and infestations	14.00	SE: 2.8000 (gamma)
Neutropenia	15.09	SE: 3.0180 (gamma)
Neutrophil count decreased	15.09	SE: 3.0180 (gamma)
Thrombocytopenia	23.21	SE: 4.6420 (gamma)
Health-related quality of life		
Utility parameters		
Progression-free	[redacted]	SE: 0.0120 (beta)
Progressed disease	0.6	SE: 0.0600 (beta)
Disutility parameters		
Age-related decrement	Incorporated from Ara et al. 2010	Not modelled
ALT/AST increased	-0.05	SE: 0.0100 (beta)
Anaemia	-0.09	SE: 0.0180 (beta)
Atrial fibrillation	-0.22	SE: 0.0440 (beta)
Bleeding	-0.22	SE: 0.0440 (beta)
Diarrhoea	-0.20	SE: 0.0400 (beta)
Dyspnoea	-0.22	SE: 0.0440 (beta)
Fatigue	-0.07	SE: 0.0001 (beta)
Infections and infestations	-0.22	SE: 0.0440 (beta)
Neutropenia	-0.16	SE: 0.0320 (beta)
Neutrophil count decreased	-0.16	SE: 0.0320 (beta)
Thrombocytopenia	-0.11	SE: 0.0220 (beta)
Costs and resource use		
Disease management costs and resource use		
PF: full blood count	0.31 per 28 days	SE: 0.0613 (beta)
PF: LDH	0.23 per 28 days	SE: 0.0460 (beta)
PF: haematologist visit	0.15 per 28 days	SE: 0.0307 (beta)
PD: full blood count	0.61 per 28 days	SE: 0.1227 (beta)

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
PD: chest X-Ray	0.15 per 28 days	SE: 0.0307 (beta)
PD: bone marrow exam	0.08 per 28 days	SE: 0.0153 (beta)
PD: haematologist visit	0.46 per 28 days	SE: 0.0920 (beta)
PD: inpatient visit (non-surgical)	0.31 per 28 days	SE: 0.0613 (beta)
PD: full blood transfusion	0.84 per 28 days	SE: 0.1687 (beta)
Full blood count unit cost	£2.79	Fixed
LDH unit cost	£1.10	Fixed
Haematologist visit unit cost	£166.51	Fixed
Chest X-Ray unit cost	£71.92	Fixed
Bone marrow exam unit cost	£558.16	Fixed
Inpatient visit (non-surgical) unit cost	£433.17	Fixed
Full blood transfusion unit cost	£253.13	Fixed
End of life costs		
End of life care cost (one-off)	£6,975.00	Not modelled
% patients who receive EoL care	100.00%	Not modelled
Adverse event costs		
ALT/AST increased	£0.00	Fixed
Anaemia	£341.86	Fixed
Atrial fibrillation	£1770.38	Fixed
Bleeding	£1770.38	Fixed
Diarrhoea	£140.89	Fixed
Dyspnoea	£0.00	Fixed
Fatigue	£603.34	Fixed
Infections and infestations	£1770.38	Fixed
Neutropenia	£136.34	Fixed
Neutrophil count decreased	£136.34	Fixed
Thrombocytopenia	£674.07	Fixed
Acquisition cost		
Acalabrutinib pack cost (60 x 100mg)	[redacted]	Fixed
Ibrutinib pack cost (28 x 420mg)	£4,292.40	Fixed
Subsequent treatment costs		
Rituximab vial cost (1 x 500mg/m^2)	£785.84	Fixed
Venetoclax pack cost (100 x 112mg)	£4,789.47	Fixed
Treatment administration cost		
Administration (per infusion; IV)	£241.06	Fixed
One-time monitoring costs		
TLS Prophylaxis	£1,975.46	Fixed
Subsequent treatment duration		
Rituximab subsequent treatment duration	6.00 cycles	Fixed

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)
Venetoclax subsequent treatment duration	26.00 cycles	Fixed
Distribution of subsequent treatments – acalabrutinib and ibrutinib		
Venetoclax + rituximab	100%	Fixed
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; EoL, end of life; IV, intravenous; LDH, lactate dehydrogenase; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; SE, standard error; TLS, tumour lysis syndrome.		

Base case results

As previously discussed in CS Document B, a cost-minimisation analysis is justified in light of non-statistical differences observed in the MAIC, and UK clinical opinion.

However, AstraZeneca understand the need to assess the uncertainty of efficacy and have presented the probabilistic results of the cost-effectiveness analysis to show the uncertainty of the data. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters were preserved. The PSA was run for 1,000 iterations for the base case and for all scenario analyses presented.

Total costs, life years, QALYs, and incremental cost per QALY gained for acalabrutinib versus ibrutinib are presented in Table 43. Acalabrutinib monotherapy was associated with [redacted] additional QALYs and [redacted] incremental costs. As such, acalabrutinib dominated ibrutinib.

Table 43. Average results based on the probabilistic sensitivity analysis (1,000 iterations)

Technologies	Mean probabilistic results						
	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

The cost-effectiveness planes and acceptability curves for acalabrutinib versus chlorambucil plus obinutuzumab are presented in Figure 27 and Figure 28, respectively.

Figure 27. Cost-effectiveness plane for acalabrutinib versus ibrutinib

Abbreviations: A, acalabrutinib; I, ibrutinib; QALY, quality-adjusted life year.

Figure 28. Cost-effectiveness acceptability curve for acalabrutinib versus ibrutinib

Scenario analysis

A list of scenario analyses ran in the model for acalabrutinib versus ibrutinib are presented in Table 44 and results are presented in Table 45.

Table 44. List of scenario analyses conducted

Parameter	Base case	Scenario	Comment
Time horizon	30 years	25 years	Assess the impact of alternative time horizons
		20 years	
Discount rate for costs and outcomes	3%	6%	Assess the impact of discounting
		0%	

Parameter	Base case	Scenario	Comment
Time horizon	30 years	25 years 20 years	Assess the impact of alternative time horizons
Age utility decrement	Apply	Do not apply	Assess impact of applying an age utility decrement
PFS and OS hazard ratios	PFS: [redacted] OS: [redacted]	PFS: [redacted] OS: [redacted]	Assess impact of applying alternative hazard ratios from the MAIC sensitivity analyses to baseline ibrutinib OS and PFS. Sensitivity analysis 3 was tested as a scenario as it adjusted for the highest number of covariates
Ibrutinib PFS extrapolations	Weibull	Exponential	Assess the impact of the next most viable alternative extrapolation of survival estimates.
Ibrutinib OS extrapolations	Exponential	Weibull	Assess the impact of the next most viable alternative extrapolation of survival estimates
Abbreviations: PFS, progression-free survival; OS, overall survival			

Table 45. Results of scenario analysis for acalabrutinib vs ibrutinib

Parameter/ outcome	Scenario	Technology	Discounted total cost	Discounted total QALYs	Incremental costs	Incremental QALYs	ICER
Base case	-	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25 years	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20 years	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and outcomes	6%	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	0%	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age utility decrement	Do not apply	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative PFS and OS Hazard ratios	PFS: 0.91 OS: 0.98	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib PFS extrapolations	Exponential	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib OS extrapolations	Weibull	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Interpretation and conclusions of economic evidence

Results of the cost-utility analysis showed that acalabrutinib monotherapy is less costly and more effective (QALYs) than ibrutinib in the base case probabilistic analysis and across all deterministic scenarios. These analyses highlight that acalabrutinib is a cost-effective therapy that addresses significant unmet need in this patient population, and suggests that acalabrutinib-based therapy should be reimbursed for the treatment of relapsed and refractory CLL.

References

1. Sharman JPB, V.; Fogliatto, L.M.; Herishanu, Y.; Munir, T.; Walewska, R.; Follows, G.; Karlsson, K.; Ghia, P.; Corbett, G.; Walker, P.; Egyed, M.; Jurczak, W.; Salles, G.; Janssens, A.; Cymbalista, F.; Wierda, W.G.; Coutre, S.; Pagel, J.M.; Skarbnik, A.; Kamdar, M.; Woyach, J.; Izumi, R.; Munugalavadla, V.; Patel, P.; Wang, M.H.; Wong, S.; Byrd, J.C. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL). *Blood.* 2019;134(31).
2. Study of Acalabrutinib (ACP-196) in Combination With Venetoclax (ABT-199), With and Without Obinutuzumab (GA101) Versus Chemoimmunotherapy for Previously Untreated CLL. https://www.clinicaltrials.gov/ct2/show/NCT03836261. Accessed September 2020.
3. A Study of AZD6738 and Acalabrutinib in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL). https://clinicaltrials.gov/ct2/show/NCT03328273. Accessed September 2020.
4. Acalabrutinib, Venetoclax, and Obinutuzumab for Initial Therapy of CLL (AVO). https://clinicaltrials.gov/ct2/show/NCT03580928. Accessed September 2020.
5. ClinicalTrials.gov. Study of Acalabrutinib (ACP-196) Versus Ibrutinib in Previously Treated Subjects With High Risk CLL. Available at: https://clinicaltrials.gov/ct2/show/NCT02477696?term=NCT02477696&draw=2&rank=1 (accessed July 2020). In.
6. Acalabrutinib in Combination With ACP-319, for Treatment of Chronic Lymphocytic Leukemia. https://clinicaltrials.gov/ct2/show/NCT02157324. Accessed September 2020.
7. Woyach JA, Blachly JS, Rogers KA, et al. Acalabrutinib plus Obinutuzumab in Treatment-Naive and Relapsed/Refractory Chronic Lymphocytic Leukemia. *Cancer Discov.* 2020;10(3):394-405.
8. Sequential Regimen of Bendamustin-Debulking Followed by Obinutuzumab, Acalabrutinib and Venetoclax in Patients With Relapsed/Refractory CLL (CLL2-BAAG). https://clinicaltrials.gov/ct2/show/NCT03787264. Accessed September 2020.
9. ACP-196 (Acalabrutinib), a Novel Bruton Tyrosine Kinase (Btk) Inhibitor, for Treatment of Chronic Lymphocytic Leukemia. https://clinicaltrials.gov/ct2/show/NCT02029443. Accessed September 2020.
10. Acalabrutinib With or Without Obinutuzumab in Treating Participants With Early-Stage Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. https://clinicaltrials.gov/ct2/show/NCT03516617. Accessed September 2020.
11. Acalabrutinib and Venetoclax With or Without Early Obinutuzumab for the Treatment of High Risk, Recurrent, or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. In.
12. Acalabrutinib, Venetoclax, and Obinutuzumab for Initial Therapy of CLL. In.
13. Acalabrutinib With or Without Obinutuzumab in Treating Participants With Early-Stage Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. In.
14. Acalabrutinib and Venetoclax Treatment of Newly Diagnosed Patients With CLL at High Risk of Infection or Early Treatment. In.

15. Study to Investigate the Use of Acalabrutinib in the Treatment of Patients With Chronic Lymphocytic Leukemia. In.
16. Study of Acalabrutinib Versus Chlorambucil Plus Rituximab in Adult Subjects With Previously Untreated Chronic Lymphocytic Leukemia. In.
17. Acalabrutinib in Combination With R-ICE For Relapsed or Refractory Lymphoma. In.
18. Study of Acalabrutinib in Chinese Adult Subjects With Relapsed or Refractory Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia or Other B-cell Malignancies. In.
19. A Study of ACP-196 (Acalabrutinib) in Subjects With Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy. https://www.clinicaltrials.gov/ct2/show/NCT02717611. Accessed September 2020.
20. Acalabrutinib in Patients With Relapsed/Refractory and Treatment naïve Deletion 17p CLL/SLL. https://www.clinicaltrials.gov/ct2/show/NCT02337829. Accessed September 2020.
21. Acalabrutinib in Combination With Anti-CD20 and Venetoclax in Relapsed/Refractory or Untreated CLL/SLL/PLL. https://www.clinicaltrials.gov/ct2/show/NCT02296918. Accessed September 2020.
22. Acalabrutinib and High Frequency Low Dose Subcutaneous Rituximab in Patients With Previously Untreated Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma. https://clinicaltrials.gov/ct2/show/NCT03788291. Accessed September 2020.
23. Jansen J.P.; Fleurence R.; Devine B.; Itzler RB, A.; Hawkins, N.; Lee, K.; Boersma, C.; Annemans, L.; Cappelleri, J.C. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health.* 2011;14(4):417-428.
24. National Institute for Health and Care Excellence. TA429 Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. 2017. Available at: https://www.nice.org.uk/guidance/ta429 (accessed February 2020). In.
25. AstraZeneca. CLL Advisory Board. 2020. In.
26. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. *Br J Haematol.* 2018;182(3):344-359.
27. Electronic Medicines Compendium. SmPC: Zydelig 150 mg Film-coated Tablets. https://www.medicines.org.uk/emc/product/3329/smpc. Published April 2019. Accessed February 2020.
28. Ghia PP, A.; Wach; M, Lysak, D.; Kozak, T.; Simkovic; M.; Kaplan, P.; Kraychok, I.; Illes, A.; De La Serna, J.; Dolan, S.; Campbell, P.; Musuraca, G.; Jacob, A.; Avery, E.J.; Lee, J.H.; Liang, W.; Patel, P.; Quah, C.; Jurczak, W. . ASCEND phase 3 study of acalabrutinib vs. investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). *European Hematology Association Library.* 2019;273259(LB2606).
29. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.

30. de Jong J, J. Sukbuntherng, D. Skee, J. Murphy, S. O'Brien, J. C. Byrd, D. James, P. Hellemans, D. J. Loury, J. Jiao, V. Chauhan, and E. Mannaert. . The effect of food on the pharmacokinetics of oral ibrutinib in healthy participants and patients with chronic lymphocytic leukemia. *Cancer Chemother Pharmacol.* 2015;75:907-916.
31. Sharman JPB, D.M.; Mato, A.; Kambhampati, S.; Burke, J.M.; Lansigan, F.; Schreeder, M.T. ; Lunin, S.D.; Ghosh, N.; Zweibach, A.; Shtivelband; M.I.; Travis; P.M.; Chandler, J.; Kolibaba, K.S.; Sporteli, P.; Miskin, H.P.; Weiss, M.S.; Flinn, I.W. . Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: Results of the GENUINE phase 3 study. *Journal of Clinical Oncology* 2017;35(1):7504-7504.
32. : Huang X, Qiu, L.; Jin, J.; Zhou, D.; Chen, X.; Hou, M.; Hu, J.; Hu, Y.; Ke, X.; Li, J.; Liang, Y.; Liu, T.; Lv, Y.; Ren, H.; Sun, A.; Wang, J.; Zhao, C.; Salman, M. ; Sun, S.; Howes, A.; Wang, J.; Wu, P. and Li, J. Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. *Cancer Med.* 2018;7(4):1043-1055.
33. Burger J.A.; Sivina M. JNKEKTEZN-GGMHXJJL. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood.* 2019;133(10):1011-1019.
34. Jones JA, Robak T, Brown JR, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. *Lancet Haematol.* 2017;4(3):e114-e126.
35. Brown J HP, O'brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. *Leukemia.* 2018;32(1):83-91.
36. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Med Decis Making.* 2018;38(2):200-211.
37. M.Á.; Marín K.; Hernández-Rivas J.M.; Hernández J.Á. M-NCP-SMG-GYMIH-SMR-VAEIMSHCF. The International Prognostic Index for Patients with Chronic Lymphocytic Leukemia Has the Higher Value in Predicting Overall Outcome Compared with the Barcelona-Brno Biomarkers Only Prognostic Model and the MD Anderson Cancer Center Prognostic Index. *Biomed Res Int.* 2018.
38. Brown J.R.; Hillmen POB, S.O.; Barrientos, J.C.; Reddy, N.M.; Coutre, S.; Tam, C.S.; Mulligan, S.P.; Jaeger, U.; Barr, P.M.; Furman R.R.; Kipps, T.J.; Cymbalista, F.; Thornton, P.; Caligaris- Cappio, F.; Delgado, J.; Montillo, M.; DeVos, S.; Moreno, C.; Pagel, J.; Burger, J.A.; Chung, D.; Lin, J.; Gau, L.; Chang, B.; McGreivy, J.; James, D.F.; Byrd, J.C. Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATE Trial of Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma. 2014.
39. Grambsch P, & Therneau, T. . Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. *Biometrika.* 1994;81(3):515-526.
40. NICE. TA561: Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia (In develpment). https://www.nice.org.uk/guidance/ta561/history. Published 2018. Accessed.

41. NHS improvement. Reference Cost Collection: National Schedule of Reference Costs - Year 2017-18 - NHS trust and NHS foundation trusts. https://improvement.nhs.uk/resources/reference-costs/. Accessed.
42. Burnham, Kenneth P. and David R. Anderson . 2002. Model Selection and Multimodel Inference: A Practical Information-Theoretical Approach. 2d ed. New York: Springer-Verlag.
43. Mato A.R.; Hill B.T.; Lamanna N.; Barr PMU, C.S.; Brander, D.M.; Howlett, C.; Skarbnik, A.P.; Cheson, B.D.; Zent, C.S.; Pu, J.J.; Kiselev, P., Foon, K., Lenhart, J., Henick Bachow, S.; Winter, A.M.; Cruz, A.L.; Claxton, D.F.; Goy, C.; Isaac, K.; Kennard, K.H.; Timlin, C.; Fanning, M.; Gashonia, L..; Yacur, M.; Svoboda, J.; Schuster, S.J.; Nabhan, C. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann Oncol.* 2017;28(5):1050-1056.
44. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): A Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
45. Paul M Barr, Talha Munir, Jennifer R Brown, et al. Final Analysis From RESONATE: 6-Year Follow-Up in Patients With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma on Ibrutinib. Poster #264. Presented at the 2019 ASCO Annual Meeting; May 31 - June 4, 2019; Chicago, IL, USA. Published 2019. Accessed.
46. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med.* 2018;378(12):1107-1120.
47. Office for National Statistics. National life tables: UK. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Published 2019. Accessed.
48. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health.* 2011;14(4):539-545.
49. Burger JA, Barr PM, Robak T, et al. 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.* 2020;34(3):787-798.
50. O'Brien SM, Byrd JC, Hillmen P, et al. Outcomes with ibrutinib by line of therapy and post-ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. *Am J Hematol.* 2019;94(5):554-562.
51. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94(12):1353-1363.
52. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica.* 2018;103(5):874-879.
53. Shadman M, Sail K, Manzoor BS, et al. Treatment Discontinuation Patterns for Patients with CLL in the Real-World Settings: Results from a Multi-Center Study. *Blood.* 2019;134(Supplement_1):3048-3048.

54. Barr PM, Robak T, Owen C, et al. 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.* 2018;103(9):1502-1510.
55. National Institute for Health and Care Excellence. TA487 Venetoclax for treating chronic lymphocytic leukaemia. Technology appraisal guidance. 2017. Available at: https://www.nice.org.uk/guidance/ta487 (accessed February 2020). In.
56. Wehler E, Storm M, Kowal S, Caresse C, Boscoe B. A health state utility model estimating the impact of ivosidenib on quality of life in patients with relapsed/refractory acute myeloid leukemia. https://library.ehaweb.org/eha/2018/stockholm/215730/michael.storm.a.health.state.utility.model.estimating.the.impact.of.ivosidenib.html. Published 2018. Accessed April, 2020.
57. National Institute for Health and Care Excellence. TA359 Idelalisib for treating chronic lymphocytic leukaemia. 2015. Available at: https://www.nice.org.uk/guidance/ta359 (accessed February 2020). In.
58. Dakin H, Wordsworth S. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. *Health Econ.* 2013;22(1):22-34.
59. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur J Haematol.* 2004;72(6):381-389.
60. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health.* 2010;13(5):509-518.
61. NICE. TA403: Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer. https://www.nice.org.uk/guidance/ta403. Published 2016. Accessed.
62. Sharman JP, Banerji V, Fogliatto LM, et al. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL). *Blood.* 2019;134(Supplement_1):31-31.

Appendix A. Identification, selection and synthesis of clinical evidence

The objective of the clinical systematic literature review (SLR) update was to summarise the clinical efficacy and safety of different pharmacological interventions for the treatment of treatment-naïve CLL and R/R CLL.

The search included studies published between August 2019 and 10th February 2020. The key biomedical literature databases searched are presented in Table 46.

Table 46. Electronic databases searched

Data source	Platform
Embase®	Embase.com; http://www.embase.com/
MEDLINE®	
MEDLINE® In-process	PubMed; http://www.ncbi.nlm.nih.gov/sites/entrez
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

Abbreviations: Embase, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online.

Strategies used to search electronic databases are presented in Table 47, Table 48 and Table 49.

Table 47. Search strategy Embase® using Embase.com platform for clinical review (search timeframe: August 2019 to 10th February 2020)

No.	Query	Facet	Hits
#1	'chronic lymphatic leukemia'/de	Disease	1,674
#2	'b cell leukemia'/exp		128
#3	lymphom* near/2 lymphocyt*		241
#4	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')		39,852
#5	(chronic OR cronic OR 'well differential')		74,286
#6	#4 AND #5		5,867
#7	#1 OR #2 OR #3 OR #6		6,186

#8	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR allocated NEAR/2 random OR random* NEAR/1 assign* OR random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	Study design	514,823
#9	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR 'case control study' OR (case* NEXT/1 control*):ab,ti		445,921
#10	#8 OR #9		683,208
#11	('rituximab'/syn OR 'chlorambucil'/syn OR 'cyclophosphamide'/syn OR 'fludarabine'/syn OR 'pentostatin'/syn OR 'prednisone'/syn OR 'prednisolone'/syn OR 'doxorubicin'/syn OR 'vincristine'/syn OR 'cytarabine'/syn OR 'bendamustine'/syn OR 'oxaliplatin'/syn OR 'lenalidomide'/syn OR 'corticosteroid'/syn OR 'ibrutinib'/syn OR 'alemtuzumab'/syn OR 'ofatumumab'/syn OR 'idelalisib'/syn OR 'obinutuzumab'/syn OR 'mechlorethamine'/syn OR 'venetoclax'/syn OR 'flavopirido' OR 'acalabrutinib'/syn)	Interventions	72,249
#12	'ublituximab'/syn OR 'umbralisib'/syn OR 'darbepoetin alfa'/syn OR 'BGB-3111'/syn OR 'dinaciclib'/syn OR 'duvelisib'/syn OR 'oblimersen'/syn		561
#13	(rchop OR 'r chop' OR 'rchop' OR fcr OR pcr OR cfar OR fr OR fc OR ofar) NEAR/2 regime*		120
#14	#11 OR #12 OR #13		72,573
#15	#7 AND #10 AND #14	Combination facet	1,722
#16	**#**15 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)	Limits	250
#17	#15 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)		124
#18	#16 OR #17		374
#19	#15 NOT #18		1,348

Table 48. Search strategy Cochrane using Cochrane library platform for clinical review (search timeframe: August 2019 to 10th February 2020)

No.	Query	Facet	Hits
#1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	Disease	18

#2	“b cell leukaemia” OR “b cell leukemia”		56
#3	lymphom* near/2 lymphocyt*		43
#4	(leuk?em* OR leu?em* OR lymph* near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR “b cell”))		2,521
#5	(chronic OR cronic OR “well differential”)		12,446
#6	#4 AND #5		519
#7	#1 or #2 or #3 or #6		536
#8	(rituximab or "idec c2b8" or mabthera or reditux or rituxan or rituxin):ab,ti,kw		542
#9	MeSH descriptor: [Cyclophosphamide] explode all trees		726
#10	(carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin or cycloblastine or “cyclofos amide” or cyclofosfamid or cyclofosfamide or cyclophar or cyclophosphamid or "cyclophosphamide isopac" or cyclophosphamides or cyclophosphan or cyclophosphane or "cyclostin n" or cycloxan or cyphos or cytophosphan or cytophosphane or cytoxan or "cytoxan lyophilized" or "endocyclo phosphate" or endoxan or "endoxan asta" or endoxana or "endoxon asta" or enduxan or genoxal or ledoxan or ledoxina or "lyophilized cytoxan" or mitoxan or neosan or neosar or noristan or "nsc 26271" or "nsc 2671" or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid):ab,ti,kw	Intervention	16
#11	(fludarabine OR fludara):ab,ti,kw or vidarabine		113
#12	(bendamustine OR “cimet 3393” OR cytostasan OR cytostasan r OR cytostasane OR “imet 3393” OR levact OR ribomustin OR treanda):ab,ti,kw		76
#13	MeSH descriptor: [Pentostatin] explode all trees		4
#14	(coforin or coformycin or covidarabine or deoxycoformycin or nipent or "nsc-21s321" or "nsc 218321" or nsc218321 or oncopent or pantostatin):ab,ti,kw		1
#15	MeSH descriptor: [Prednisone] explode all trees		617
#16	(ancortone or "apo prednisone" or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin? or decortisyl or dehydrocortisone or dekortin or delitisone or "dellacort a" or "delta dome" or "delta cortelan" or "delta cortisone" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or deltra or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or "me korti" or meprison or metacortandracin or meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen m" or prednicorm or prednicot or prednidib or prednison or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or "sterapred ds" or ultracorten or urtilone or winpred):ab,ti,kw		14
#17	MeSH descriptor: [Doxorubicin] explode all trees		484
#18	(adriablastin? or adriacin or adriamicin? or adriamycin? or adriblastin?		50

	or adrim or adrimedac or adrubicin or amminac or caelix or caelyx o r "caelyx/doxil" or carcinocin or dexorubicin or "dox sl" or doxil or doxolem or "doxor lyo" or rastocin or resmycin or "rp 25253" or rp25253 or rubex or rubidox or sarcodoxome or "tlc d 99"):ab,ti,kw		
#19	MeSH descriptor: [Vincristine] explode all trees		244
#20	("l 37231" or l37231 or "vin cristine" or vincristin or vincrisul):ab,ti,kw		236
#21	(chlorambucil or amboclorin or "cb 1348" or "cb1348" or chlorambacil or chloraminophene or chlorbutin or chloroambucil or chorambucil or ecloril or leuceran or leukeran or linfolysin or lymp holysin or "nsc 3088" or nsc3088)		45
#22	(alemtuzumab OR campath OR “ldp 103” OR “ldp103” OR lemtrada OR mabcamp ath):ab,ti,kw		54
#23	(BGB-3111):ab,ti,kw OR “corticosteroid”		902
#24	MeSH descriptor: [Cytarabine] explode all trees		231
#25	(bendamustine or "cimet 3393" or "cytostasan r" or cytostasane or "imet 3393" or levact or ribomustin or treanda)		77
#26	(lenalidomide or "cc 5013" or cc5013 or "cdc 501" or "cdc 5013" or cdc501 or cdc5013 or "enmd 0997" or enmd0997 or "imid 3" or imid3 or revimid or revlimid):ab,ti,kw		277
#27	(ibrutinib or "cra 032765" or cra032765 or imbruvica or "pci 32765" or "pci 32765-00" or "pci 32765 00" or pci32765 or pci3276500):ab,ti,kw		83
#28	(acalabrutinib or "acp 196" or acp196):ab,ti,kw		23
#29	(ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or "humac cd20" or "humax cd20" or humaxcd20):ab,ti,kw		33
#30	(obinutuzumab OR afutuzumab OR “ga 101” OR ga101 OR r 7159 OR r7159 OR “ro 5072759” OR ro5072759):ab,ti,kw		59
#31	(rchop OR "r chop" OR "rchop" OR fcr OR pcr OR cfar OR fr OR fc OR ofar) NEAR/2 regime*		21
#32	(ublituximab or "tg 1101" or "tg1101"):ab,ti,kw		2
#33	(umbralisib or "TGR-1202" or "TGR 1202"):ab,ti,kw		1
#34	(dinaciclib or "sch 727965" or sch727965):ab,ti,kw		1
#35	(duvelisib or "ink 1197" or ink1197 or "ipi 145" or ipi145):ab,ti,kw		9
#36	(“gs 1101” OR “cal 101” OR cal101 OR “gs 1101” OR gs1101 OR idelalisib):ab,ti,kw		17
#37	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #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		3,148
#38	#7 and #37 in Trials and Methods Studies (Word variations have been searched)		205

Table 49. Search strategy MEDLINE® In-Process using Pubmed.com platform for clinical review (search timeframe: August 2019 to 10th February 2020)

No.	Query	Facet	Hits

#1	"Chronic B-Cell Lymphocytic Leukemia" OR ("leukemia"[All Fields] AND "lymphocytic"[All Fields] AND "chronic"[All Fields] AND "b-cell"[All Fields])	Disease	1,018
#2	“b cell leukaemia” OR “b cell leukemia”		114
#3	lymphom* AND lymphocyt*		1,792
#4	(leukem* OR leukaem* OR leucem* OR leucaem*OR lymph*) AND (lymphocyt* OR lymphoblast* OR linfoid* OR “b cell”) AND (chronic OR cronic OR “well differential”)		5,534
#5	#1 or #2 or #3 or #4		6,652
#6	(rituximab or "idec c2b8" or mabthera or reditux or rituxan or rituxin)	Intervention	3,422
#7	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR “cyclofos amide” OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR “cyclophosphamide isopac” OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR “cytoxan lyophilized” OR “endocyclo phosphate” OR endoxan OR endoxan-asta OR “endoxan asta” OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR “lyophilized cytoxan” OR mitoxan OR neosan OR neosar OR noristan OR “nsc 26271” OR “nsc 2671” OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid)		300,804
#8	(fludarabine OR fludara)		439
#9	(bendamustine or "cimet 3393" or "cytostasan r" or cytostasane or "imet 3393" or levact or ribomustin or treanda)		242
#10	(Pentostatin or coforin or coformycin or covidarabine or deoxycoformycin or nipent or "nsc-21s321" or "nsc 218321" or nsc218321 or oncopent or pantostatin)		29
#11	(Prednisone or ancortone or "apo prednisone" or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin? or decortisyl or dehydrocortisone or dekortin or delitisone or "dellacort a" or "delta dome" or "delta cortelan" or "delta cortisone" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or deltra or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or "me korti" or meprison or metacortandracin or meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen m" or prednicorm or prednicot or prednidib or prednison or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or "sterapred ds" or ultracorten or urtilone or winpred)		16,126
#12	(Doxorubicin or adriablastin? or adriacin or adriamicin? or adriamycin? or adriblastin? or adrim or adrimedac or adrubicin or amminac or caelix or caelyx or "caelyx/doxil" or carcinocin or dexorubicin or "dox sl" or doxil or doxolem or "doxor lyo" or rastocin or resmycin or "rp 25253" or rp25253 or rubex or rubidox or sarcodoxome or "tlc d 99")		6,131
#13	(Vincristine or "l 37231" or l37231 or "vin cristine" or vincristin or vincrisul)		1,223
#14	(chlorambucil or amboclorin or "cb 1348" or "cb1348" or chlorambacil or chloraminoph		126

	ene or chlorbutin or chloroambucil or chorambucil or ecloril or leuceran o r leukeran or linfolysin or lympholysin or "nsc 3088" or nsc3088)		
#15	(alemtuzumab OR campath OR “ldp 103” OR “ldp103” OR lemtrada OR mabcampath)		390
#16	(“gs 1101” OR “cal 101” OR cal101 OR “gs 1101” OR gs1101 OR idelalisib)		151
#17	(cytarabine or alcysten or alexan or ara C or arabinocytosil or arabitin or aracytidine or aracytin or aracytine or "beta ara c" or citarabina or citarabine or cyclocide or cylocide or cytarabide or cytar abin or cytarbine or cytarine or "cytosa u" or cytosar or "cytosar 4" or "cytosar u" or "cytosar-u" or cytovis or depocyt or depocyte or "dtc 101" or dtc101 or iretin or laracit or novumtrax or "nsc 63878" or nsc63878 or tarabine or "tarabine pfs" or "u 19920 a" or "u 19920a" or u19920a or udicil)		69,488
#18	(lenalidomide or "cc 5013" or cc5013 or "cdc 501" or "cdc 5013" or cdc501 or cdc5013 or "enmd 0997" or enmd0997 or "imid 3" or imid3 or revimid or revlimid)		754
#19	(ibrutinib or "cra 032765" or cra032765 or imbruvica or "pci 32765" or "pci 32765-00" or "pci 32765 00" or pci32765 or pci3276500)		4,858
#20	(acalabrutinib or "acp 196" or acp196)		91
#21	(ofatumumab or arzerra or "gsk 1841157" or gsk1841157 or "humac cd20" or "humax cd20" or humaxcd20)		99
#22	(obinutuzumab OR afutuzumab OR “ga 101” OR ga101 OR r 7159 OR r7159 OR “ro 5072759” OR ro5072759)		159
#23	(ublituximab or "tg 1101" or "tg1101")		11
#24	(umbralisib or "TGR-1202" or "TGR 1202")		12
#25	(dinaciclib or "sch 727965" or sch727965)		38
#26	(duvelisib or "ink 1197" or ink1197 or "ipi 145" or ipi145)		41
#27	(BGB-3111) or corticosteroid		14,219
#28	(rchop OR "r chop" OR "rchop" OR fcr OR pcr OR cfar OR fr OR fc OR ofar)		94,481
#29	#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 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28		468,165
#30	#5 and #29	Combination facet	2,218
#31	(#30 AND (inprocess[sb] OR pubstatusaheadofprint))	Limits	367

Bibliography of the systematic reviews and meta-analysis identified through database searching were utilised for the identification of relevant studies. Also, references of the included studies were checked to identify any additional studies.

Additionally, the following conference proceedings were hand searched for relevant publications between 2019-2020:

- American Society of Clinical Oncology (ASCO)
- European Society of Medical Oncology (ESMO)
- American Society of Hematology (ASH)
- International Conference on Malignant Lymphoma (ICML)
- Academy of Managed Care Pharmacy (AMCP)

For inclusion in the review, studies had to meet the predefined eligibility criteria as presented in Table 50. Randomised controlled, non-randomised controlled, and single-arm trials were included as part of the clinical SLR. It should be noted that articles published in the English language only were included in the review.

Table 50. Eligibility criteria used in the clinical systematic review

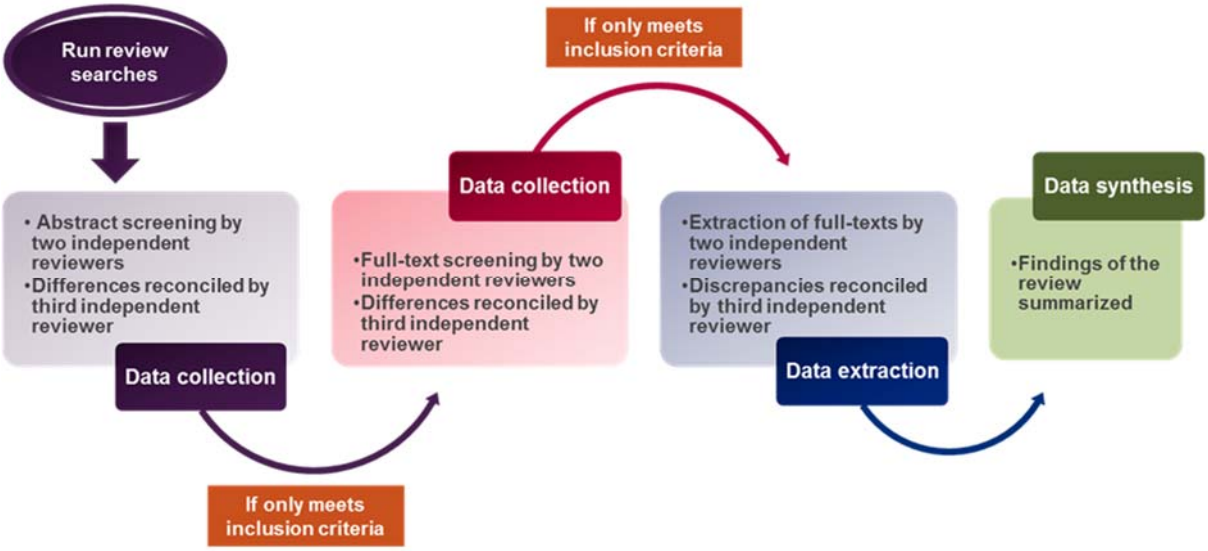
Clinical review	Inclusion criteria	Exclusion criteria
Patient population	• Adult patients with CLL irrespective of the gender, race, and/or ethnicity • CLL patients, both in previously untreated and relapsed/refractory setting	• Population does not consist of CLL patients, or no subgroup for CLL, or no outcomes separately for CLL • Mixed population with no subgroup outcome data for subtype of interest
Trial design	• RCTs, non-RCTs, and single arm trials	• Observational trials, case reports, case series, editorials, and review pieces
Language restrictions	• English	• Non-English
Publication year	• Studies have been published from August 2019 to 10th February 2020	• No restriction
Interventions of interest (The interventions will include at least one of the therapies, either as monotherapy or as part of a combination therapy)	**First-line treatment setting** • Acalabrutinib monotherapy • Acalabrutinib + Obinutuzumab • Obinutuzumab + Chlorambucil • Ofatumumab • Ibrutinib • Rituximab • Bendamustine • Venetoclax • Alemtuzumab • Chlorambucil • Lenalidomide • Pentostatin + Cyclophosphamide + Rituximab • Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone	• Studies do not include the drugs of interest

Clinical review	Inclusion criteria	Exclusion criteria
	• Bendamustine + Rituximab • Alemtuzumab ± Rituximab • Fludarabine + Cyclophosphamide + Rituximab • Dinaciclib • Duvelisib • Fludarabine + cyclophosphamide + oblimersen • Fludarabine/Pentostatin • Bendamustine + Obinutuzumab **Relapsed/refractory treatment setting** • Acalabrutinib monotherapy • Idelalisib + Rituximab • Bendamustine + Rituximab • Ibrutinib • Lenalidomide + Rituximab • Chlorambucil + Rituximab • Obinutuzumab + Chlorambucil • Idelalisib + Bendamustine + Rituximab • Ibrutinib + Bendamustine + Rituximab • Bendamustine + Ofatumumab • Rituximab + hyperCVAD • Ofatumumab + Chlorambucil • Corticosteroids ± Rituximab • Ibrutinib +/- Rituximab • Cladribine + Cyclophosphamide + Rituximab • Venetoclax + Rituximab • Venetoclax + Ibrutinib • Acalabrutinib • Ublituximab + Umbralisib (TGR-1202) • Fludarabine + Darbepoetin alfa • BGB-3111 • Ublituximab + Ibrutinib	
Outcomes	At least one of the following is reported: • Overall survival • Progression-free survival • Disease free survival • Duration of response • Time to response • Time to progression • Treatment free survival • Time to next treatment • Overall response and disease control rate • Minimal residual disease • Safety and withdrawals	• Studies do not report the outcomes of interest

Study selection

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into the HERON Systematic Review Database (SRDB), a bespoke, structured query language-based internet database. The systematic review was conducted according to the NICE guidelines. An outline of the systematic review process has been presented in Figure 29.

Figure 29. Project approach and methodology for the clinical review



First stage screening

All the citations were screened by two independent reviewers, followed with a quality check by a third independent reviewer. The first screening stage included reviewing citations based on their respective title and abstract. Citations that did not match the eligibility criteria were excluded at first-pass stage; where unclear, citations were included. Duplicates of citations (due to the overlap in the coverage of databases) were also excluded at the first-pass stage. Full-text copies of all the references that could potentially meet the eligibility criteria were obtained.

Second stage screening

After the completion of first stage screening, the full texts of relevant studies were examined in more detail to determine a final list of included studies. All the citations were screened by two independent reviewers, followed with a quality check by a third independent reviewer.

Data extraction

Data from the included studies were extracted into a pre-defined data extraction grid, ensuring that data are extracted uniformly and are comparable across the included studies. Data were extracted by a single reviewer, followed by quality check by a second independent reviewer. In cases where more than one publication describing a single trial was identified, the data were compiled into a single entry in the data extraction grid to avoid double counting of patients and studies.

Results

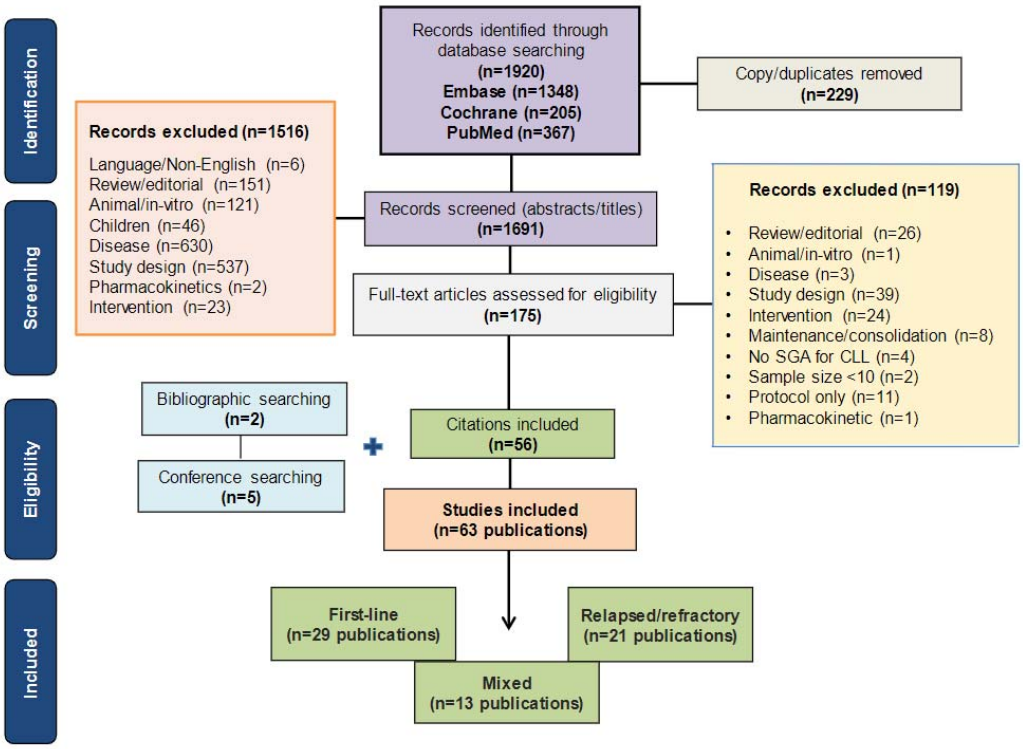
The search of the literature databases between August 2019 to 10th February 2020 yielded 1,920 references. The detailed screening of abstracts and full texts resulted in the final inclusion of 63 publications.

The scope of the clinical SLR was broader than the scope of this submission therefore results are only presented for RCTs which include relevant comparators:

- Treatment-naïve CLL (n=1 studies)
    - Chlorambucil plus obinutuzumab (C+O)
    - Ibrutinib
- R/R CLL (n=0 studies)
    - Ibrutinib

Randomised controlled trials were extracted only as these are considered the gold standard of study design. A PRISMA flow diagram of the search is presented in Figure 30.

Figure 30: Clinical PRISMA study flow diagram for SLR update (August 2019 to 10th February 2020)



Summary of findings in randomised controlled studies identified

Study characteristics

Treatment-naïve population

The study characteristics and eligibility criteria for the one relevant RCT, ELEVATE-TN, Sharman et al. 2019[62] in the treatment-naïve population identified are provided in Table 51 and Table 52 respectively.

Table 51. Summary of the study characteristics

Primary publication source (author_year)	Trial name (if any)	Treatment/Group	Publication type	Study setting	Study phase	Cross over
Sharman 2019	ELEVATE TN	• Acalabrutinib + Obinutuzumab • Acalabrutinib • Obinutuzumab + Chlorambucil	Conference abstract (ASH)	Multicenter	III	Yes

Table 52. Summary of inclusion and exclusion criteria across the included trials

Publication source (author_ year)	Trial name (if any)	Treatments	Age (yrs)	Prior malig -nant	ECOG 0-2	Lymph node (cm)	ANC (Units/L)	Hb (g/dL)	Platelet (Units/L)	CrCl (ml/min)	Renal fn	CIRS score	Del 17p	CNS pts	Active infec-tions	Prior trans-plant	LE >6 mts	Fdr In-eligible
Sharman 2019	ELEVATE -TN	• Acalabrutinib + Obinutuzumab • Acalabrutinib • Obinutuzumab + Chlorambucil	≥65, <65	NR	Incl	NR	NR	NR	NR	<70	NR	>6	Incl	NR	NR	NR	NR	NR

Abbreviations: Ade: Adequate; ANC: Absolute neutrophil count; CIRS: Cumulative illness rating score; CNS: Central nervous system; CrCl: Creatinine clearance; Del: Deletion; dL: Deciliter; Excl: Excluded; Fdr: Fludarabine; Hb: Haemoglobin; In. Ade: Inadequate; LE: Life expectancy; L: Liter; min: Minute; NR: Not reported

Efficacy outcomes

A summary of PFS and OS efficacy data is provided across Table 53 (median values), Table 54 (overall treatment naïve hazard ratios) and Table 55 (high risk subgroup hazard ratios). An additional efficacy outcome identified Sharman et al. 2019 was overall response rate (ORR).

Table 53. Summary of median PFS and OS reported across the included studies in a first-line treatment category

Publication source (author_year)	Trial name (if any)	Treatments	Median follow-up (years/months)	Median PFS, months (assessor)	Median OS, months
Sharman 2019	ELEVATE-TN	Acalabrutinib + Obinutuzumab	2.33/27.96	Not reached (IRC)	Not reached
		Acalabrutinib	2.33/27.96	Not reached (IRC)	Not reached
		Obinutuzumab + Chlorambucil	2.33/27.96	22.6 (IRC)	Not reached

Abbreviations: IRC: Independent review committee; NR: Not reported

Table 54. Summary of hazard ratios of PFS and OS reported across the included studies in a first-line treatment category

Publication source (author_ year)	Trial name (if any)	Hazard ratios reported for (comparison of treatments)	Median follow-up (years/ months)	Overall survival				Progression-free survival				Inv/IRC
				Hazard ratio	CI Min	CI Max	p vs. control	Hazard ratio	CI Min	CI Max	p vs. control	
Sharman 2019	ELEVATE-TN	Acalabrutinib + Obinutuzumab vs. Obinutuzumab + Chlorambucil	2.33/ 27.96	0.47	0.21	1.06	0.0577	0.1	0.06	0.18	<0.0001	IRC
		Acalabrutinib vs. Obinutuzumab + Chlorambucil	2.33/ 27.96	0.6	0.28	1.27	0.1556	0.2	0.13	0.31	<0.0001	IRC
Abbreviations: CI: Confidence interval; HR, hazard ratio; INV: Investigator; IRC: Independent review committee; MaX: maximum; Min: minimum; NR: Not reported												

Table 55. Hazard ratios of PFS reported across various high-risk CLL categories

Publication source (author_year)	Trial name (if any)	Treatment comparison	High-Risk subgroup	Hazard ratio	CI Min	CI Max	Assessor
Sharman 2019	ELEVATE-TN	Acalabrutinib + Obinutuzumab vs. Obinutuzumab + Chlorambucil	Del 17p	0.13	0.04	0.46	IRC
		Acalabrutinib vs. Obinutuzumab + Chlorambucil	Del 17p	0.2	0.06	0.64	IRC
Abbreviations: Del, deletion, CI, confidence interval: IRC; independent review committee: INV; investigator assessed: Max; maximum: Min; minimum: NR; Not reported: PFS; progression free survival							

Safety outcomes

Any grade adverse events

A summary of any grade AEs is provided across Table 56 and Table 57.

Table 56. Summary of any grade AEs - general adverse events, gastrointestinal symptoms, and respiratory tract infections

Publication source (author_ year)	Trial name (if any)	Treatments	N	Overall any grade	Headache	Fatigue	Arthralgia	Pyrexia	Diarrhea	Nausea	Abdominal pain	Respiratory tract infection	Pneumonia
Sharman 2019	ELEVATE- TN	Acalabrutinib + Obinutuzumab	178	171 (96%)	71 (40%)	NR	NR	NR	69 (39%)	36 (20%)	NR	NR	19 (11%)
		Acalabrutinib	179	170 (95%)	66 (37%)	NR	NR	NR	62 (35%)	40 (22%)	NR	NR	13 (7%)
		Obinutuzumab + Chlorambucil	169	167 (99%)	20 (12%)	NR	NR	NR	36 (21%)	53 (31%)	NR	NR	5 (3%)
Abbreviations: AE; adverse event;, NR: Not reported													

Table 57. Summary of any grade AEs – haematological adverse events and others

Publication source (author_year)	Trial name (if any)	Treatments	N	Major haemorrhage	Anaemia	Neutropenia	Febrile-Neutropenia	Bleeding	Peripheral oedema	Hypertension	Atrial fibrillation
Sharman 2019	ELEVATE-TN	Acalabrutinib + Obinutuzumab	178	NR	21 (12%)	56 (31%)	3 (2%)	77 (43%)	NR	NR	5 (3%)
		Acalabrutinib	179	NR	25 (14%)	19 (11%)	2 (1%)	70 (39%)	NR	NR	7 (4%)
		Obinutuzumab + Chlorambucil	169	NR	20 (12%)	76 (45%)	9 (5%)	21 (12%)	NR	NR	2 (1%)
Abbreviations: AE; adverse event;, NR: Not reported											

Grade 3-4 adverse events

A summary of any grade 3-4 AEs is provided across Table 58 and Table 59.

Table 58. Summary of grade 3-4 AEs - general adverse events, gastrointestinal symptoms, and respiratory tract infections

Publication source (author_year)	Study name (if any)	Treatments	N	Overall 3/4 grade	Headache	Fatigue	Arthralgia	Pyrexia	Diarrhea	Nausea	Abdominal pain	Respiratory tract infection	Pneumonia
Sharman 2019	ELEVATE -TN	Acalabrutinib + Obinutuzumab	178	125 (70%)	2 (1%)	NR	NR	NR	8 (4%)	0 (0%)	NR	NR	10 (6%)
		Acalabrutinib	179	89 (50%)	2 (1%)	NR	NR	NR	1 (1%)	0 (0%)	NR	NR	4 (2%)
		Obinutuzumab + Chlorambucil	169	118 (70%)	0 (0%)	NR	NR	NR	3 (2%)	0 (0%)	NR	NR	3 (2%)
Abbreviations: AE; adverse event; NR: Not reported													

Table 59. Summary of grade 3-4 AEs – haematological adverse events and others

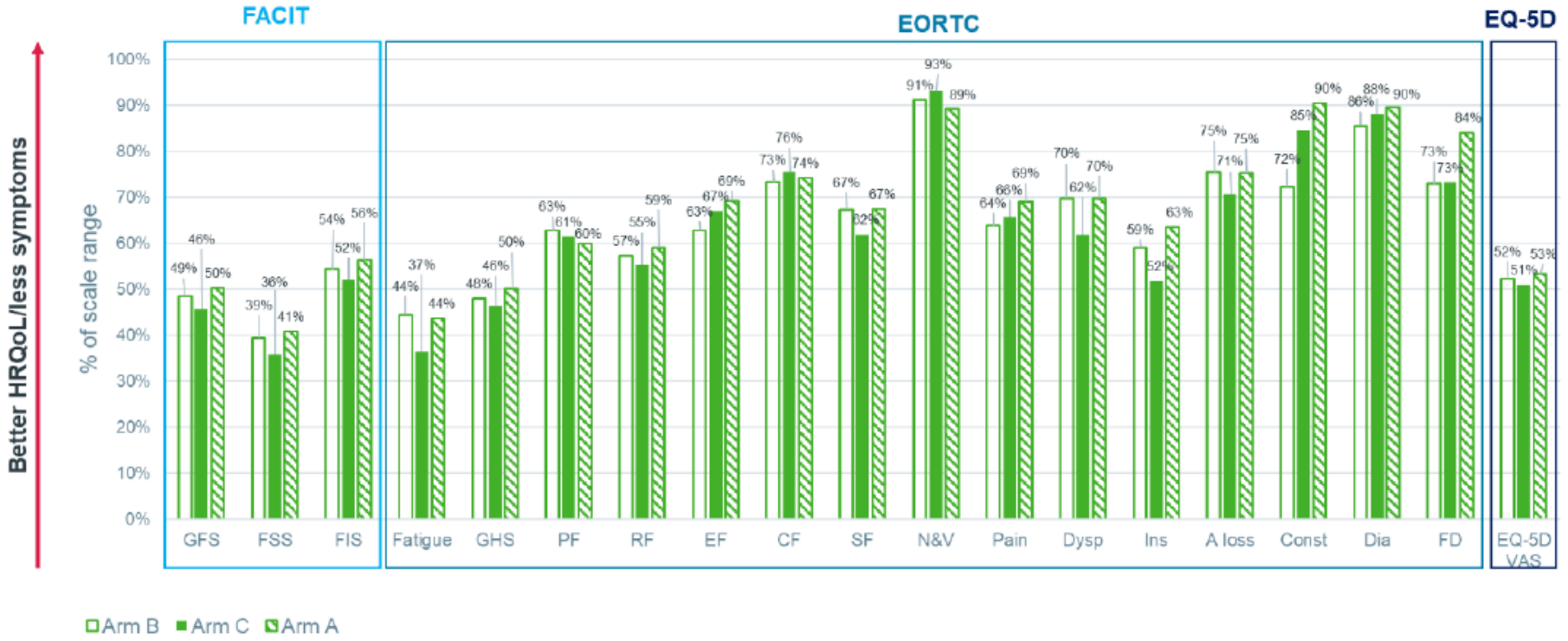
Publication source (author_year)	Trial name (if any)	Treatments	N	Anaemia	Neutropenia	Febrile-Neutropenia	Bleeding	Major haemorrhage	Peripheral oedema	Hypertension	Atrial fibrillation
Sharman 2019	ELEVATE-TN	Acalabrutinib + Obinutuzumab	178	10 (6%)	53 (30%)	3 (2%)	4 (2%)	NR	NR	5 (3%)	NR
		Acalabrutinib	179	12 (7%)	17 (9%)	2 (1%)	4 (2%)	NR	NR	4 (2%)	NR
		Obinutuzumab + Chlorambucil	169	12 (7%)	70 (41%)	9 (5%)	0 (0%)	NR	NR	5 (3%)	NR
Abbreviations: AE; adverse event; NR: Not reported											

Quality assessment of clinical trials

A quality assessment of ELEVATE-TN is provided in Section B.2a.5 of the CS, Table 21.

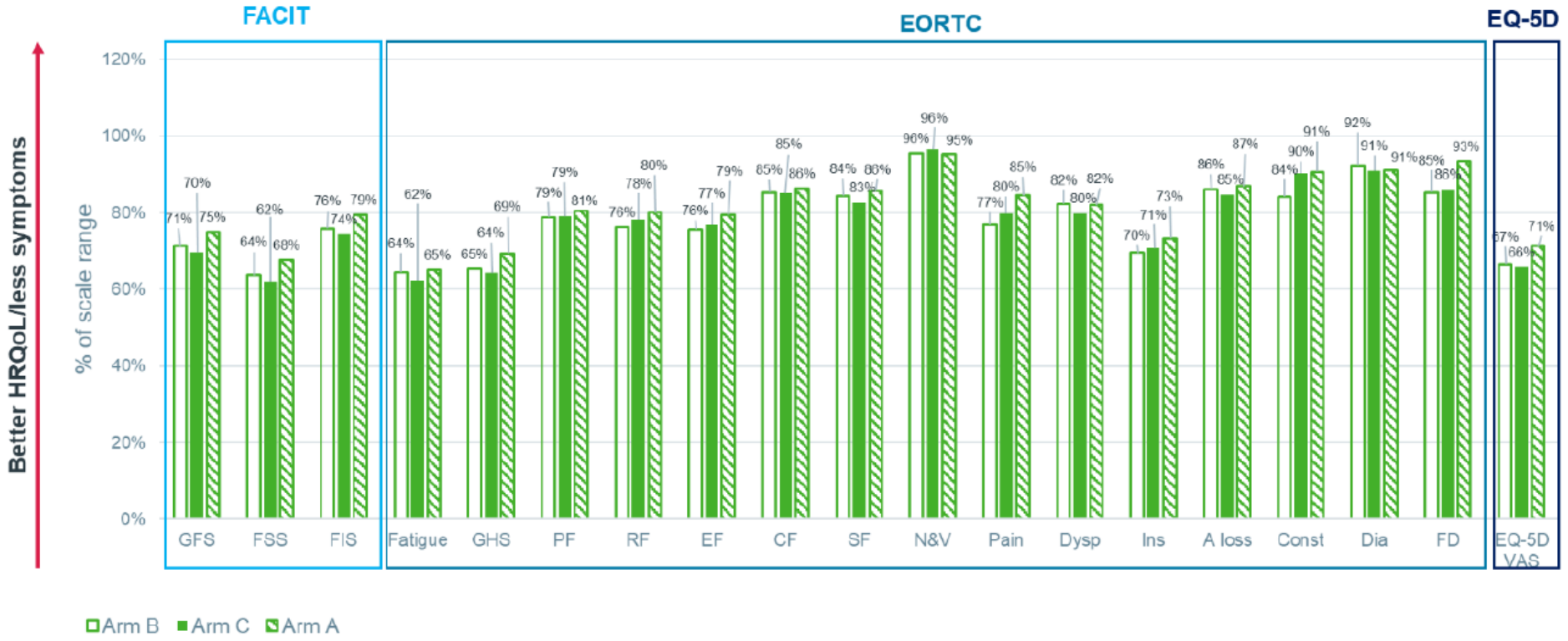
Appendix B. Integrated Patient Experience Report for ELEVATE-TN

Figure 31. Transformed Baseline PRO Scores- ITT Population



GFS = Global fatigue scale; FSS = Fatigue symptom scale; FIS = Fatigue impact scale; GHS = Global Health scale; PF = Physical functioning; RF = Role functioning; EF = Emotional functioning; CF = Cognitive functioning; SF = Social functioning; N&V= Nausea and vomiting; Dysp = Dyspnea; Ins = Insomnia; A loss = Appetite loss; Const = Constipation; Dia = Diarrhea; FD = Financial Difficulties

Figure 32. Transformed Baseline PRO Scores – Safety population



GFS = Global fatigue scale; FSS = Fatigue symptom scale; FIS = Fatigue impact scale; GHS = Global Health scale; PF = Physical functioning; RF = Role functioning; EF = Emotional functioning; CF = Cognitive functioning; SF = Social functioning; N&V= Nausea and vomiting; Dysp = Dyspnea; Ins = Insomnia; A loss = Appetite loss; Const = Constipation; Dia = Diarrhea; FD = Financial Difficulties

NICE National Institute for Health and Care Excellence

Patient organisation submission

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also received funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out at: http://www.leukaemiacare.org.uk/wp-content/uploads/2018/02/CODE-OF-PRACTICE.pdf
4b. 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.]	Abbvie: £10,000 grant, £240 grant, £23000 grant. £33,240 total. Gilead: £16,322.78 grant. Janssen: £1000 nurse conference, £650 grant, £15,000 grant, £21,890.19 grant. £38, 540.19 total

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was gathered through Leukaemia Care patient experience survey, 'Living with Leukaemia' (2017), included responses from 1152 CLL patients. Data and quotes also gathered from three Lymphoma Canada surveys, one in 2017 and another two in 2020. The 2020 survey included responses from 22 patients previously untreated patients who had taken acalabrutinib and 20 relapsed/refractory patients who had taken acalabrutinib. Additional information was also gathered through analysing patient stories and one to one discussion with patients.
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. The risk of developing CLL increases with age, it is most common in older adults, with a median age at diagnosis of between 67 and 72 years. Taking into consideration the physical, emotional, financial impact and further impact on carers a CLL diagnosis greatly affects the quality of life of CLL patients. **Diagnosis** There is evidence from several surveys that a CLL diagnosis can have a negative impact on the individual's mental health. The 2017 "Living with Leukaemia" Survey from Leukaemia Care reported 38% of CLL

	patients felt more anxious or depressed since diagnosis. Additionally, the Lymphoma Canada: Patient Experience survey further reported that CLL patients experience anxiety/worry (65%), stress (64%), difficulty sleeping (33%) and depression (27%). This is an ongoing issue some patients will continue to experience throughout the different phases of this disease. Around 75% of CLL patients have reported to be placed on watch and wait following diagnosis, according to the Leukaemia Care 2017 survey. For many, due to the long-term impact along with the un-certainties associated in terms of eventually requiring treatment once the watch and wait ends, can result in a substantial emotional and physical burden. ***"Having googled it, the reality of the diagnosis dawned on me: slow, unpredictable, incurable"***. **<u>Physical and emotional impact</u>** The most common symptoms reported at diagnosis, in the Leukaemia Care survey, include fatigue (43%), swollen lymph nodes (32%), fever/night sweats (27%), frequent and repeated infections (19%) and feeling weak or breathless (19%). Additionally, current treatments also report similar physical impact. Fatigue is reported to be the most common symptom experienced by CLL patients throughout their diagnosis and treatment pathway. For many, this is accompanied by emotional turmoil and has a profound impact on their lives, such as difficulty working, socialising or caring for themselves***. "So, for my colleagues at work, knowing the news of my chronic condition, it was business as usual after a while. I tried to make it for myself too. Of course, my body wouldn't have it and the fatigue got worse over time, so I eventually resigned"***. In CLL patients, the immune system is compromised and most patients suffer from infections. Infection risk can be worsened by treatment too. ***"During my treatment I suffered from many infections which results in admission to hospital. So, after my treatment I was very weak and could not walk very far and was always tired"***. These frequent and persistent infections can impact hugely on quality of life, as well as being a leading cause of death for CLL patients; this impact is being demonstrated by the COVID-19 situation, where CLL patients are at a greater risk of contracting and experiencing serious complications. Another result of this risk is need to self-isolate away from colleagues, family and friends in order to protect themselves from life-threatening infections.

	Effect on carers Through patient stories shared with Leukaemia Care, a theme that comes up is that some CLL patients may not always share their emotions and feeling with their loved ones, who most often are also their carer, as they feel they may "burden" them. This further adds on to the psychological wellbeing of the patient and maybe even the carer. ***"After being discharged from hospital I decided not to worry my family and kept things bottled up. Looking back now that was the wrong decisions".*** Living with CLL does not affect a patient in isolation, but instead creates a "ripple effect" impacting on the whole family. Family members/carers can be challenged with exhausting caretaking duties, in some cases this may reduce their own ability to maintain employment and contribute to society. 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. The stress and the physiological challenges associated with this can negatively impact the family members relationship and their mental well-being. ***"The insidious nature of the disease following my diagnosis caused persistent illness and side effects which over time contributed to our eventual break up".***
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The most common symptoms patients experienced on recent or current treatments include fatigue (59%), constipation or diarrhoea (35%), muscle, bone and joint pain (29%), infections (29%), neutropenia (26%) and nausea or vomiting (25%). Around 45% and 31% patients reported side effects had small impact and large impact respectively. Despite a few effective treatment options, CLL remains an incurable condition. Due to the heterogenous nature of CLL, treatment options vary by genetic markers(e.g. TP53 mutations or 17p deletions) age and fitness of the individual and stage of treatment. These factors may make the individual unsuitable for

	certain treatments, limiting their options. **<u>Treatments for untreated CLL</u>** Chemoimmunotherapies are the only treatment option available in the front-line setting for patients without the genetic markers (17p deletion or TP53 mutation). FCR (Fludarabine, cyclophosphamide and rituximab) for fit healthy patients, BR (bendamustine with rituximab) or chlorambucil, with or without rituximab, for patients with age-related comorbidities. If either treatments are not suitable then chlorambucil and obinutuzumab may be offered. Although most patients initially respond to chemoimmunotherapy, many may require additional therapy due to limited PFS. Additionally, there is myelotoxicity associated with chemoimmunotherapy administration, both in the short and long term. ***"I have chronic ITP because of having CLL and having treatment/chemo in the pasts. Currently, I am very mindful of avoiding infections or viruses".*** The current COVID-19 pandemic, further highlights the need for less immunosuppressive options in this sub-group of patients. The immunosuppression associated with these chemotherapy based treatments puts this group of patients in a very high risk of infection. Consequently, the need to take extra precaution and self-isolate from family and friends has a very negative impact on patient's quality of life. Patients with certain genetic markers, including 17p deletion,TP53 mutation or unmutated IGHV are unsuitable for chemo-immunotherapies, as these treatments are not effective in these patients. First-line treatment for patients with these genetic markers is limited to mainly ibrutinib or idelalisib with rituximab, although the latter is not as widely used. Some patients, in particular with heart conditions, may exhibit adverse events when taking ibrutinib, such as atrial fibrillation. ***"My husband has been on [ibrutinib] for a year now and suffers harsh bone pain, difficulty breathing and massive bruising with bleeding on arms. His illness has become our life. His blood counts have improved but the side effects are difficult. We wish there was an alternative therapy"***. There is a need for more selective and targeted inhibitors, with fewer and more tolerable side effects. In patients where ibrutinib is not a suitable option, the only other first-line therapy option is idelalisib with rituximab, which is not favoured due to the immune-related challenges some patients face and it is not as effective as ibrutinib. This emphasises the need for more treatment options in this set of patients, with very limited options. **<u>Treatments for relapsed/refractory CLL</u>**

	Treatments for relapsed/refractory patients become even more limited for patients with genetic markers (17p deletion or *TP53* mutations), venetoclax with rituximab and venetoclax monotherapy being the only treatment options available. The most severe risk associated with venetoclax treatment in initial stages is tumour lysis syndrome, which needs to be carefully monitored. Neutropenia is another key side effect experienced by majority of patients, which may negatively impact immunity. For those without the favourable genetic markers, idelalisib with rituximab and ibrutinib become available in the relapsed/refractory setting. Although there are a few options for patients with favourable genetic markers at the relapsed/refractory stages, but they do come with the associated side effects mentioned above. However, many patients have exhausted their options or are experiencing side effects that severely impact their quality of life, and in those patients even more treatment choices are needed. Our Leukaemia-Care Survey reported that 33% of patients have had a relapse following current treatment, of those 52% have relapsed once, 23% have relapsed twice, 13% have relapsed three times and 12% have relapsed four times of more. These patients relapsing from a prior therapy require access to more effective and tolerable treatment options. **Patient preference with treatments** Around 31% of the patients reported that the side effects they experienced with recent/current treatments had a large impact on their life (Leukaemia Care Survey). Additionally, patients reported that fatigue, nausea and frequency of infections were the most difficult side effects to tolerate (Lymphoma Canada: Patient Experience Survey). Taking this into consideration, newer treatments need to be more targeted so that fewer side effects are experienced by patients. CLL patients prefer oral-tablets as a method of treatment, with 59% reporting this preference in the Leukaemia Care Survey. Furthermore, the Lymphoma Canada survey results show that patients on oral therapies experienced less of an impact on their quality of life compared to patients on intravenous therapies; this took into consideration different factors including treatment-related fatigue, toleration of treatment, number and frequency of infections. Oral therapies limit hospital appointments too, as patients are able to take these treatments in the comfort of their home. This will benefit patients even more so now during the COVID-19 pandemic.

8. Is there an unmet need for patients with this condition?	The current COVID-19 situation highlights the need to move away from conventional chemotherapies and towards more targeted treatments. There is a need for treatments that provide longer duration of remission and fewer toxicities, both in the short and the long term, that are commonly associated with chemotherapies. Non-chemotherapeutic treatment options need to be available in the front-line settings for all CLL patients (unfit/fit populations). The immunosuppressive effects of chemotherapies, result in high risk of infections, making these patients extremely vulnerable to new viruses and other infections commonly reported by CLL patients. According to the Leukaemia-Care survey, majority (84%) of the CLL patients would like a choice of different treatment options Interestingly, when questioned about what patients consider to be the most important feature of a new treatment, most 76% answered improved/longer survival, followed by 68% that said improved quality of life and 56% that said tolerable side effects whilst on treatment. Overall, more effective treatment options with tolerable side effects are needed in all sub-sets of CLL patients, this will allow patients to make a choice.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Adverse events are one aspect of a treatment that can have an effect on quality of life for patients.Acalabrutinib is a second-generation inhibitor of the Bruton's tyrosine kinase protein (BTK). It is said to be highly selective compared to the other BTK inhibitor, ibrutinib, due to the mechanism by which it binds to BTK. This further prevents off-target inhibition activity, which may result in severe adverse events as seen in some patients on ibrutinib (e.g. atrial fibrillation). Ibrutinib, although has shown success in many CLL patients, most patients will discontinue ibrutinib treatment due to severe side effects. Both Phase 3 trials: EVEVATE TN and ASCEND for patients with untreated CLL and relapsed/refractory CLL respectively, reported improved PFS and tolerable safety profile. Due to its selectivity acalabrutinib is likely to benefit all categories of CLL patients, including fit/unfit and untreated/treated CLL. In addition to reduced adverse events, there are many other features of this treatment that patients feel

are of benefit.

- **Most patients are still taking acalabrutinib**

Twenty two patients responded to the Lymphoma Canada survey about treatment options. They had received acalabrutinib as a front-line treatment. Majority of these patients (95%) are still taking acalabrutinib, only 1 patient discontinued this therapy as their CLL progressed. This may be due to not only the effectiveness but also the tolerable side effects profile of this drug.

Twenty patients responded to the survey to share their experience of acalabrutinib in the treatment of relapsed or refractory CLL. Of those, 55% prior to this treatment had received ibrutinib, all of whom (100%) were not able to complete the full course of treatment due to intolerable side effects: "***Imbruvica caused me to have [atrial fibrillation]. Plus severe joint and leg pain off and on"***. Out of the 20 patients, 40% began acalabrutinib treatment less than 1-year ago, 25% began 1-2 years ago and 35% began more than 2 years ago. Most of these patients (90%) are still taking acalabrutinib, this includes 9/10 patients that previously discontinued ibrutinib treatment due to severe side effects. This suggests that patients are finding this new treatment more tolerable.

- **Many symptoms impacting quality of life are managed by acalabrutinib**

Many of the symptoms commonly reported by CLL patients (including fatigue, enlarged lymph nodes and frequent infections) are reduced by this new acalabrutinib treatment, as shown in the table below. This includes patients in both front-line and relapsed/refractory settings.

Symptom managed	Responses (%) (Frontline)	Responses (%) (Relapsed/Refractory)
Enlarged lymph nodes	82%	45%
Enlarged spleen	64%	15%
Increasing lymphocyte count	64%	60%
Fatigue, lack of energy	45%	45%
Frequent infections	36%	30%

Around 68% of frontline patients and 50% of the relapsed/refractory patients reported that acalabrutinib managed all their symptoms. This shows the effectiveness of this drug in terms of managing the symptoms that greatly impact the patient's quality of life in both settings. For patients where prior therapies have not been successful and in some cases have resulted in severe side effects, this drug provides an important option.

- **Tolerable side effects and impact on quality of life**

Around 36% of frontline patients and 20% of the relapsed refractory patients did not experience any side effects with acalabrutinib. Most patients reported diarrhoea, headache and muscle or joint pain as the most common side effects of this treatment in both settings. The table shows the impact of side effects on the quality of life, which took into consideration treatment-related fatigue, treatment-related headaches, number or frequency of infections and other side effects of treatment, summarised in the table below.

Side effects impact on quality of life	Average responses (%) (Front-line)	Average responses (%) (Relapsed/Refractory)
No impact	25%	48%
Some impact	23%	24%
Significant impact	8%	10%
Very significant impact	9%	3%

In particular, patients commented on the positive affect on quality of life due to the reduced number of infections in the relapsed/refractory settings. One patient commented by saying: ***"Big step up, dramatic improvements in fingernails; significantly reduced number of infection"*** and another said: ***"Fewer infections on treatment"***. Additionally, 90% of patients reported that acalabrutinib had a more positive impact on their quality of life than previous therapies.

- **Overall positive impact of acalabrutinib**

Majority of the patients (73% frontline and 60% for relapsed/refractory) reported that their health and well-being greatly improved following acalabrutinib as front-line and relapsed/refractory treatment respectively.

Furthermore, most patients had good-excellent experience with acalabrutinib in both settings.

Experience with acalabrutinib	Responses (%) Front-line	Responses (%) Relapsed/ Refractory
Poor	0%	5%
Satisfactory	5%	5%
Good	14%	10%
Very good	14%	40%
Excellent	68%	40%

Positive feedback from patients on acalabrutinib in untreated CLL:

- ***"it is so easy! no doctor visits, no prophylaxis, minor TLS risk, no infusions, no infusion reactions"***
- ***"Outstanding improvement. In fact, after taking just 4 pills, that is two days worth, my lymph nodes, one of which had measured 10cm, had decreased in size by 1/2!"***
- ***"I have del17p/tp53/unmutated, with a very poor prognosis. With this drug I am still alive 4 1/2 years later. I went from 97% neoplastic cells down to 3%."***

Positive feedback from patients on acalabrutinib as relapsed/refractory treatment of CLL

- ***"Easy. Oral. Initially had rapid affect"***
- ***"Excellent alternative for ibrutinib! Far fewer side effects, certainly less severe side effects. Yet seems to treat CLL equally as effectively as many other treatments"***

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Some patients may find twice a day tablet to be an inconvenience. It is also a continuous therapy. However these are not major issues when taking into consideration the overall benefits of the treatment, in particular the tolerable side effects profile.

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 groups will benefit from this technology. In the era of targeted non chemotherapies that are effective for all. There should not be distinctions made due to fitness in this era
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The psychological and physical impact of a CLL diagnosis can greatly affect the quality of life of a CLL patient.
- There is a need to move away from chemo-immunotherapies in the front-line settings and offer patients the choice of more tolerable and targeted therapies. This is because chemo-immunotherapies come with significant quality of life issues for all patients.
- Current treatments in the relapsed/refractory settings, although effective, can have variable patients' responses. Many experience severe side effects which can negatively impact their quality of life. In this group additional effective and more tolerable treatment options are needed.
- Patients on acalabrutinib have reported positive feedback in both front-line settings and relapsed/refractory settings, it manages many symptoms commonly reported by CLL patients, offers a tolerable side effects profile and overall, positively impacts the quality of life in these patients.
- Overall, acalabrutinib is a good alternative to other treatments, as is easily administered with limited hospital time and a lower risk of immunosuppression and infection.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Joint Submission on behalf of Chronic Lymphocytic Leukaemia Support (CLL Support) and Lymphoma Action (LA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Chronic Lymphocytic Leukaemia Support (CLL Support)** is a national patient led charity run by volunteers and was formed in 2005; it is the only UK Chronic Lymphocytic Leukaemia (CLL) specific support charity. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL, treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLLSA provides support to the UK CLL community and CLLSA membership of 3,000+ association members who live with CLL or are carers and the 13,000+ CLLSA on-line community members (not all UK based) on the Health Unlocked platform. CLLSA provides up to 6 patient conferences a year. CLLSA support patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and https://healthunlocked.com/cllsupport . The Association is funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from some pharmaceutical companies. **Lymphoma Action (LA)** is a national charity registered in England and Wales and in Scotland (see www.lymphoma-action.org.uk). Our primary aim and objective is to provide information, advice, support and training to everyone affected by lymphoma. We work throughout the UK, publishing leading, quality-assured written information on lymphoma,

	operating a clinical trials information service (Lymphoma Trials Link at www.lymphomas.org.uk/lymphoma-trialslink and providing a national helpline, a network of support groups and a buddy scheme. We have launched a well-being programme specifically designed for those with lymphoma (Live Your Life). We also provide education and training courses for healthcare professionals, as part of their CPD. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. Lymphoma Action is not a membership organization.
4b. 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.	**CLL Support** AbbVie (venetoclax) - £10, 000 Accord Healthcare (bendamustine, fludarabine) - NA Actavis UK (fludarabine) - NA AAH Pharmaceuticals (chlorambucil) - NA Aspen (chlorambucil) - NA Baxter healthcare (cyclophosphamide) - NA Dr Reddy's Laboratories (bendamustine) - NA Gilead Sciences (idelalisib) - £22,250 Janssen (Ibrutinib) - £10,000 medac (bendamustine) - NA Napp Pharmaceuticals (bendamustine, rituximab) - NA Roche (rituximab, obinutuzumab) - NA Sandoz (rituximab, cyclophosphamide, fludarabine) - NA Sanofi (fludarabine) - NA Seacross Pharmaceuticals (bendamustine) - NA Zentiva (bendamustine – NA **Lymphoma Action** AbbVie (venetoclax) - £10, 000

	Accord Healthcare (bendamustine, fludarabine) - NA Actavis UK (fludarabine) - NA AAH Pharmaceuticals (chlorambucil) - NA Aspen (chlorambucil) - NA Baxter healthcare (cyclophosphamide) - NA Dr Reddy's Laboratories (bendamustine) - NA Gilead Sciences (idelalisib) - £53, 938 Janssen (Ibrutinib) - £15,000 medac (bendamustine) - NA Napp Pharmaceuticals (bendamustine, rituximab) - NA Roche (rituximab, obinutuzumab) - £12, 000 Sandoz (rituximab, cyclophosphamide, fludarabine) - NA Sanofi (fludarabine) - NA Seacross Pharmaceuticals (bendamustine) - NA Zentiva (bendamustine - NA
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 gathered information about the patient experience with Acalabrutinib from the on line platform Health Unlocked which hosts the CLL Support community https://healthunlocked.com/cllsupport In addition, in February 2020 there was a worldwide on line survey undertaken by Lymphoma Canada and distributed on the HU CLL Support forum to enable UK participants to take part. https://www.surveymonkey.com/r/CLLCAN2020 and https://healthunlocked.com/cllsupport/posts/142606394/please-share-experience-of-venetoclax-plus-obinutuzimab-or-acalabrutinib-treatment-in-a-survey-that-may-help-others-gain-access The information obtained included patients that were in clinical trials and those outside clinical trials.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL is a complex disease to understand let alone diagnose. It takes an average of around 3 months from onset of symptoms (if the patient has any) to diagnosis and it can require repeated visits to healthcare professionals. This causes frustration and has a significant emotional impact; people affected know something is wrong but it can take a long time to confirm what that is. This impact continues throughout the treatment pathway for both patient and carers. In our surveys common issues reported at diagnosis include fatigue (51.6%), increased lymphocyte count (48%), enlarged lymph nodes (39.1%), frequent infections (21%), night sweats (19.4%), enlarged spleen or discomfort on upper left side of stomach (15.7%), shortness of breath (15.3%), anaemia (13.7%), thrombocytopenia (10.5%), pain (8.1%), fever (5.6%) and neutropenia (5.2%). In around 7 in 10 cases, CLL is discovered by chance during investigations for something else. This can be psychologically challenging for patients. Most people have not heard of CLL before their diagnosis. Once diagnosed, they are likely to focus on the 'leukaemia' aspect, as they understand this as a form of cancer. More often than not, there is not sufficient focus on the chronic, long-term nature of the disease. The most common approach to managing CLL is active monitoring. This is a challenge for people to understand and come to terms with. They have a cancer diagnosis but there is not any immediate treatment action. While approximately one third of patients experience few symptoms at diagnosis, almost all will develop increasing symptoms as their disease progresses. Two thirds will be monitored under "watch and wait" (active monitoring) until treatment is necessary because of an increasing and uncomfortable symptom burden. The other third will require treatment not long after or immediately after diagnosis. The negative emotional and psychological issues experienced at diagnosis remain high for the majority of patients during the watch and wait period: "stress" (75.8%), "anxiety" (59.3%), "difficulty sleeping" (38.7%) and "depression" (30.6%).

	For almost all patients, CLL is incurable. Any treatment usually ends in eventual relapse so patients live in a cycle of 'waiting, treatment then relapse', which is repeated and continues until death. Patients worry about relapse, knowing further toxic treatment is likely to impact negatively on their quality of life. Even after a period of successful treatment, patients can be left with a significant symptom burden and poor quality of life, uncertain as to what will happen next. It is psychologically challenging know that symptoms, quality of life and clinical assessments are likely to worsen and then further treatment be required. CLL tends to respond less well to each line of therapy, with shorter subsequent remissions. Around 85% of patients diagnosed are aged 65 or older and many also have comorbidities. This means the more toxic treatments are not well tolerated by the majority of patients. As CLL is a genetically evolving disease, many patients are also concerned that they could experience Richter's transformation to an acute form of lymphoma, which is a rapidly progressing and generally an 'end of life' event. This occurs in approximately 10% of patients although the risk of Richter's is influenced by the CLL genetics. Patients with CLL have an increased risk of infection, as their immune system is severely compromised by the disease even during the watch and wait phase. These frequent and persistent infections impact hugely on quality of life, as well as being a leading cause of death for CLL patients. During the winter, many patients, and their families, experience long periods of isolation to try to reduce the risk of infection. As outlined above, living with CLL is difficult and does not affect the patient alone, but creates a "ripple effect", impacting on the whole family and even friends and colleagues. Family members/carers can be challenged with exhausting caretaking duties when someone they know is diagnosed with CLL. Carers cited having to take on previously shared household duties. Many had to give up their own jobs, adding to the negative financial impact that living with CLL can cause. Patients' compromised immune systems and treatment side effects were cited by 20% of carers as a reason for reduced social contact with family and friends for both caregivers and patients. Some sacrificed

	holidays and non-essential social events because of it. Patients report: • *"It's so difficult to plan anything, especially holidays, as I have no idea if I'll be well enough to go.* • *Insurance is another expensive problem."* • *"I worry about catching flu as I can't make antibodies myself and so I tend to stay away from people during winter."* • *"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."* Living with CLL is living with uncertainty for both the patient and carer – uncertainty about disease progression, length of life, quality of life, possible infections and an inability to live a 'normal' life. **All of these comments were made before the current advice for shielding from COVID19 for CLL patients which has further restricted their opportunities for social and leisure activities.**
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	CLL is regarded as incurable and treatment goals and strategies need to be selected to suit individual needs. These depend on treatment history, overall health, fitness, co-morbidities risk, treatment goals and patient choice. The introduction of targeted therapies has provided treatment options that have improved survival and quality of life for the treatment-naive groups with high risk 17p deletions and TP53 aberrations. They would now be treated first line with Ibrutinib, Idelasilib or Venetoclax. Fitter patients who do not have the high risk 17p deletions and TP53 aberrations, irrespective of IGHV mutation status, are given more toxic chemo-immunotherapy regimens aimed at achieving durable remissions and, ideally, undetectable disease. However, patients with unmutated IGHV do poorly with chemo-immunotherapy and do not currently have access to newer targeted therapies. Chemo-immunotherapy treatment is often has a considerable impact on quality of life and may mean hospital

	admissions and cumulative toxicities over the patient's lifetime, including the risk of incomplete restoration of bone marrow function, future myelodysplasia and acute myeloid leukaemia. For less fit treatment-naïve patients without high-risk genetic features, irrespective of IGHV mutation status, the aim of treatment is to extend the 'time to next treatment' using better tolerated treatments. These are often less effective and do not give long remissions. CLL patients often require repeated treatments because CLL repeatedly relapses. Patients generally respond less well, with shorter remissions, to each subsequent line of therapy. All three targeted therapies are available for patients with relapsed or refractory CLL but the safety profile of each drug must be carefully matched to the patient's clinical condition and the co-morbities that are common in these patients which are generally older in age. For relapsed patients with access to Ibrutinib, the cardiac side effect of atrial fibrilation is a particular concern. They are aware that the reported adverse events of AF, hypertension, arthralgias and musculoskeletal pain appear to be much reduced with Acalabrutinib compared to Ibruitnib. Ibrutinib is contraindicated for some cardiac patients and those who need to take anticoagulants. It has been shown to induce hypertension, new or worsened, in 72% of patients, with a two-fold higher risk of other cardiovascular events such as heart failure, stroke and sudden cardiac death. Reference: https://ashpublications.org/blood/article-abstract/134/22/1919/375010/Hypertension-and-incident-cardiovascular-events Other side effects that can be severe enough for patients to stop treatment include arthralgia, musculoskeletal pain, cardiac events such as AF, diarrhoea and skin rashes. For many patients these diminish over time but not all. This patient's experience is not unusual: "*My own experience of Ibrutinib is of crippling joint pain, unbearable muscle cramps and hypertension, all ongoing after almost 5 years of treatment.*"

	Idelasilib has a toxicity profile that many doctors and patients find unacceptable. Venetoclax often requires multiple overnight stays in hospital because of the high risk of tumour lysis syndrome. Patients who experience disease progression or relapse after targeted therapies, or who have to discontinue due to side effects, have a dismal outlook because options are limited. For these patients an anti CD20 antibody therapy or best supportive care (BSC) may be the only options. Whilst BSC may treat symptoms or disease complications, it does not actively treat the CLL. As such, BSC leads to disease progression and ultimately death.
8. Is there an unmet need for patients with this condition?	Yes, there is clear and urgent unmet clinical need that Acalabrutinib would address. Because of the heterogeneous nature of CLL a wide range of treatment options is important. There is an unmet need for an effective, relatively non-toxic treatment that can produce durable remissions with few side effects. This is irrespective of patient co-morbidities, CLL genetics and IGHV mutation status. The unmet need is particularly urgent for treatment-naïve CLL patients of all ages without 17p and TP53 genetics as they do not have access to a targeted treatment for first line therapy. Within this group, those with complex genetics and unmutated IGHV have the greatest need as they do very poorly with chemo-immunotherapy. Early reports from clinical trials and real world surveys for both treatment-naïve and refractory patients indicate that Acalabrutinib offers a highly effective treatment similar to Ibrutinib but with a better safety profile which makes it suitable for patients with cardiovascular risk factors. The most common side effects that lead to discontinuation of Ibrutinib (arthralgias, worsening hypertension, cardiac events, musculoskeletal pain) are reported much less frequently with Acalabrutinib.

	The phase 3 studies, ASCEND and ELEVATE-TN, compared Acalabrutinib, alone or with Obinutuzumab, to standard of care treatments and demonstrated Acalabrutinib's improved efficacy and tolerability. Currently, a phase 3 study is ongoing to compare Acalabrutinib to Ibrutinib monotherapy (NCT02477696). In the setting of recent FDA approval, real-world evidence will help to elucidate the optimal use of acalabrutinib and its safety profile in the treatment of CLL. Acalabrutinib does have a unique AE profile of headaches which require careful monitoring and expertise in management. References: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7090151/ https://ashpublications.org/blood/article/134/Supplement_1/31/427832/ELEVATE-TN-Phase-3-Study-of-Acalabrutinib-Combined https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.7530 CLL patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a range of patients, including those who have poor prognostic factors and those of advanced age with existing co-morbidities. They also value new treatments with fewer and more tolerable side effects. We cannot overstate the importance and the need for a range of treatment options for patients with CLL given the heterogeneity of both the disease and patient population. Acalabrutinib would be a welcome and valuable addition for both treatment-naïve and relapsed/refractory patients, fulfilling a huge unmet need.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients are aware of Acalabrutinib from social media and on line CLL communities. Informed patients are asking questions about their 17p, TP53 and IGHV mutation status and they are aware of how that relates to their own clinical situation both in terms of treatment availability and its effectiveness. They are also aware of the effectiveness and safety profile benefits of Acalabrutinib compared to Ibrutinib, Idelasilib, Venetoclax.

	Patients are dissatisfied with the options available to treatment-naïve patients who do not have the 17p and TP53 genetic markers, especially those who have complex genetics or an unmutated IGHV status, because of the poor response to chemo-immunotherapy. Reports from patients who have experience of Acalabrutinib are overwhelmingly positive. These reports are from the on line Lymphoma Canada survey and the CLL HU community. The respondents were across a wide range of ages: 19% were age 40-59; 59% between 60-69 and 23% between 70-79 years. 68% of patients had accessed Acalabrutinib via a clinical trial, 23% via private insurance and 5% via a compassionate access programme. A small number of patients had switched from Ibrutinib to Acalabrutinib because of poor tolerability and were able to tolerate Acalabrutinib well. 90% of patients reported a positive experience of Acalabrutinib (either good, very good or excellent) and indicated that their health and wellbeing had "greatly improved" with Acalabrutinib treatment. 95% of patients were still taking Acalabrutinib at the time of the survey. The 5% who had stopped treatment, had stopped because of progression or Richter's transformation. Patients appreciate that the treatment is a tablet that is taken at home, albeit twice a day, reducing their need for hospital attendance. 68% of patients reported that Acalbrutinib managed all their CLL symptoms although 27% said they were still suffering from fatigue. 36% reported no side effects at all but 36% said they had headaches, 36% joint pains and 23% diarrhoea. Mouth sores were also reported but no skin rashes. Patient comments include: • *"It is so easy! No doctor visits, no prophylaxis, no infusions, no infusion reactions."*

	• *"This is a wonderful [treatment]...I am one 2.1cm node away from a complete remission… and I am thankful I was accepted into this trial. I feel like I have been given a gift of being part of finding a cure or at least a way to treat my CLL like any chronic condition."* • *"4 years on Acalabrutinib… I have experienced no side effects - none! My CLL is well controlled. I am so grateful and hope that others will be given the opportunity to benefit from what appears to be a superior BTK therapy for treatment-naive as well as R/R patients, especially for those who may not tolerate the side effects of ibrutinib."* • *"I feel so well, normal in fact. I've just had my 28 month follow up and it's all good."* • *"My quality of life is now much improved. I can now walk at a brisk pace for about a mile before needing to rest - a huge difference from just 3 months ago."* • *For the first time in 11 years I am able to relax about not having emergency admissions for IV antibiotics for febrile neutropenia or other serious infections."* • *"I was experiencing headaches until I resolved to drink at least a gallon of water a day. Poof. No more headaches. That has been my only negative side effect so far."* • *"It has been almost two years since I began the trial with Acalabrutinib, my fourth round of treatment. My counts are all within normal range and I am doing well. I have no side effects on it at apart from a headache just one day."* • *"Been on it for 18 months with phenomenal results. The only side effect were headaches for the first 2 weeks."* • *"I have been on Acalabrutinib for over 5 years. I have had no side effects."* • *"I'm so grateful to have this trial otherwise I would have had FCR chemo and I am unmutated, so not great."*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Twice a day dosage may be seen as a slight disadvantage. The ongoing nature of the treatment may be seen to be a disadvantage by some patients; however, others find it a comfort to continue treatment. Future studies may mean that treatment can be stopped or paused in patients with good remissions and then started again as necessary. Headaches in the early stages of treatment may deter patients who already suffer from migraine or headaches. Acalabrutinib may not be suitable for those who suffer with acid reflux treated with a proton pump inhibitor such as omeprazole, as it requires an acidic stomach for it pharmacokinetics.
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.	Because of the heterogeneous nature of CLL and the diverse population, with and without co-morbidities, who require an effective treatment, it is difficult to identify one population that would benefit more than others. However, treatment-naïve patients of all ages with complex genetics and/or unmutated IGHV status are likely to benefit more from this technology because they have a less favourable response to chemo-immunotherapy and targeted therapies are not available to them outside a clinical trial. Response to Acalabrutinib treatment is the same regardless of the patient's IGHV mutation status, genetic profile or prior treatment regimens, providing excellent responses for over 90% of patients.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We would prefer this treatment to be available to all CLL patients receiving their first treatment and any subsequent treatments. There are definitely equality issues if Acalabrutinib is only authorised for 'older' patients and not inclusive of all age groups. There are also equality issues for treatment-naïve patients who have complex genetics and/or an unmutated IGHV status as they do not have access to (targeted) treatments which will give them remissions of equal depth and length that other, IGHV mutated, patients experience. Targeted treatments are available effective for other patients who are recognised to have an equally poor prognositic profile (17p, TP53)
Other issues	
13. Are there any other issues that you would like the committee to consider?	We are presently, and for the immediate future, in the middle of the worldwide pandemic of COVID-19, a SARS-CoV-2 coronavirus which presents a real and immediate danger to the lives of CLL patients. The UK CLL Forum have posted a consensus document on their website. Their advice is the agreed view of a body of experts in CLL in current UK practice to mitigate the consequences of the COVID-19 pandemic. The advice presented is not part of routine practice but is hoping to mitigate against the risk of infection and hospitalisation in CLL patients. The document states, "*avoid Fludarabine and Bendamustine*," because of the risk of severe immunosuppression and risk of infection. For treatment-naïve patients needing to start treatment, "*consider Chlorambucil Obinutuzumab as alternative for all*." However, as patients we do not consider this an effective treatment and it could prejudice overall survival, progression free survival and response to future treatments.

	AstraZeneca have launched an Acalabrutinib CLL compassionate access programme for treatment-naïve patients and there are NHSE discussions ongoing with Prof Peter Clark regarding whether all patients needing treatment can have Ibrutinib as a safe and effective option. To have Acalabrutinib approved for treatment naïve patients would mean a safe, effective and well tolerated treatment for all CLL patients irrespective of genetics, IGHV mutation status and age. Approval of this treatment by NICE would provide a lifeline to especially vulnerable patients at this time. https://ukcllforum.org/wp-content/uploads/2020/04/UKCLL_COVID19_practical_b.pdf

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Access to multiple treatment options is important for ALL CLL patients, who often require many different lines of treatment for multiple relapses.
- Acalabrutinib addresses an unmet need for all CLL patients but especially for those who are treatment-naïve and who have complex genetics or an unmutated IGHV status as they do not have access to equally effective treatments as IGHV mutated patients at the present time.
- Acalabrutinib is an effective treatment that induces deep remissions, improving over time, with fewer off target side effects than Ibrutinib.
- Acalabrutinib can be suitable for patients with cardiovascular risk factors and those on anticoagulants.
- Acalabrutinib would offer an effective and relatively safe, non-toxic option for all CLL patients needing to start first or subsequent treatment, which is especially important during the current pandemic of COVID-19

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]/[redacted]/[redacted]/[redacted]/[redacted] **on behalf of UK CLL Forum/ British Society of Haematology (BSH)**
2. Name of organisation	**UK CLL Forum/ BSH/RCPath**

3. Job title or position	**Consultant Haematologists, UK CLL Forum [redacted] Members and members of the British Society of Haematology and Royal College of Pathologists**
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKCLL Forum is an umbrella organisation for CLL in the UK which aims to bridge the gap between the clinical and scientific aspects of the disease, encourages collaborative research and promotes education of healthcare professionals and patients. It provides a framework where the UK CLL community, can provide input towards national guidelines, good clinical practice and translational science. The forum facilitates communication between healthcare providers, patients and funding bodies. UK CLL Forum is a charity organisation and does receive support from interested Pharma companies. The British Society for Haematology (BSH) is the largest UK haematology organisation. Members work together to share ideas and knowledge, and to champion and strengthen haematology practice. It provides access to resources, events and education that support professional development, bridges the gap between research and practice, and produces guidelines to raise the standards of clinical and patient care.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12	Yes for CLL Forum: the funds are mainly used to organise educational meetings, provide travel grants for scientists Roche £10,000 Janssen £7000 Abbie £10,000 AZ £10,000

months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	CLL is currently considered an incurable cancer. It is a disease 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 with minimal toxicity in order to improve quality of life, progression free and overall survival.
7. What do you consider a clinically significant treatment	A clinically significant treatment response in CLL includes a sustained improvement in blood counts with resolution of lymphocytosis and lymphadenopathy, which subsequently translate into prolonged

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	progression free survival (PFS) and overall survival (OS). For certain treatments, minimal residual disease (MRD) can also be used as a surrogate for PFS and OS through specialised tests on blood and bone marrow. This is applicable to treatments such as chemo-immunotherapy (CIT) and venetoclax (a BCL2 inhibitor), but is generally not applicable to the BTK inhibitors (BTKi) such as Ibrutinib and Acalabrutinib because of the difference in their mechanism of action.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, especially for patients being treated in the frontline setting. **Front line treatment** Within the NHS, chemoimmunotherapy (CIT) continues to be the only funded frontline treatment for CLL patients for patients who have no evidence of *TP53* disruption (i.e. no mutation or deletion) – representing circa 90% of patients in total. This is despite multiple studies now showing that treatments with alternative agents, including both BTKi (ibrutinib and acalabrutinib with or without the addition of antibody) and BCL2 inhibitors (venetoclax, given with obinutuzumab in the frontline setting and rituximab in the relapse setting) result in improvement of both progression free survival and an improved tolerability profile. This effect appears to be most marked for those patients who have prognostic markers for poorer outcome (for example those patients with unmutated immunoglobulin heavy chain genes (*U-IGHV*)) Specifically, three phase 3 studies have now demonstrated that BTK inhibition with Ibrutinib is superior to CIT in terms of PFS in the frontline setting when compared to three standard frontline CIT regimens - FCR (1), BR (2) and Chl+O (3). Most importantly, an overall survival (OS) benefit was seen with Ibrutinib in comparison to FCR, originally reported and confirmed at a 4 year update of the trial presented at the American Society of Hematology meeting 2019. Additionally, a phase 3 study of Venetoclax and Obinutuzumab has shown a progression free survival benefit in comparison to chlorambucil obinutuzumab (4). Finally, ELEVATE CLL, a phase 3 study comparing acalabrutinib with or without obinutuzumab to obinutuzumab and chlorambucil (5) demonstrated improved PFS for both experimental arms over the comparator chemo-immunotherapy regimen of chlorambucil obinutuzumab. Despite these multiple Phase 3 studies, some with long follow up (>4 years), and out of keeping with European and US guidelines (see below), only chemo-immunotherapy remains funded within the NHS for the vast majority of frontline CLL patients. This exposes patients unnecessarily to the short and long term

	risk of chemotherapy based regimens (especially those of severe, life-threatening infections and secondary cancers) and utilises significant healthcare costs in terms of delivery and monitoring. Further, If we can deliver more effective, less toxic therapy and induce deeper remissions in CLL patients, the majority of whom are elderly, we will reduce hospital admissions and improve both quantity and quality of life. CLL treatment has significant impact on patients ability to work: the Leukaemia Care Living with Leukaemia survey reports that 43% of CLL patients had a temporary impact during treatment and 57% permanent (https://media.leukaemiacare.org.uk/wp-content/uploads/Living-with-Leukaemia-2018-Full-Report-Web-Version.pdf). If PFS is significantly prolonged we will reduce the number of patients who progress and require further therapy. **Relapsed therapy** Ibrutinib is NICE approved and has widely replaced CIT in the setting of *TP53* mutated/deleted CLL and in patients with relapsed CLL. While it is a highly effective therapy, it requires continuous treatment. In this context, toxicities such as infections, atrial fibrillation and arthralgia can significantly impact on the quality of life of patients particularly those with pre-existing co-morbidities. Venetoclax with or without rituximab is another highly effective therapy that is NICE approved for relapsed CLL. Venetoclax can be used as a 2 year time-limited treatment when used with rituximab and while it is not associated with cardiac toxicities or arthralgia, patients need close monitoring during the initial 5 week ramp up phase of treatment for tumour lysis monitoring, often requiring inpatient stays. Patients are also likely to need more hospital attendances Venetoclax and Rituximab and neutropenia is a relatively common toxicity with this combination. ASCEND CLL (Ghia P, et al. *European Hematology Association Library* 2019;273259:LB2606), which compared acalabrutinib to standard of care chemo-immunotherapy and an idelalsib containing regimen and showed a progression free survival over both comparators, and an improved tolerability profile to idelalaisib.

	It would be anticipated that acalabrutinib would provide an additional attractive option for patients in the relapsed setting because of the favourable side-effect profile reported. Results of a head-to-head trial comparison with Ibrutinib are likely to be reported next year (NCT02477696). 1. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381(5):432-43. 2. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379(26):2517-28. 3. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. 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 Oncol. 2019;20(1):43-56. 4. Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019;380(23):2225-36. 5. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020;395(10232):1278-91.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Frontline In the frontline setting patients with intact *TP53* are treated with CIT– FCR is the current standard for fit patients while Chlorambucil in combination with Obinutuzumab is used for less fit patients or those with co-morbidities. Patients with mutated/deleted TP53 CLL are treated with Ibrutinib in the frontline setting or with single agent venetoclax if a B-cell receptor pathway inhibitor is unsuitable. Idelalisib with Rituximab is also available for patients in this scenario. Currently Ibrutinib, Idelalisib and single agent Venetoclax are administered continuously until there is unacceptable toxicity or disease progression.

	Relapse In the relapsed setting CIT use has been replaced almost entirely by the availability of novel agents. There is currently a choice between Ibrutinib, single agent venetoclax and venetoclax+rituximab. The first 2 are continuous treatments while the third is 2 year fixed duration therapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH guidelines: https://b-s-h.org.uk/guidelines/guidelines/treatment-of-chronic-lymphocytic-leukaemia/ ESMO guidelines: https://www.esmo.org/guidelines/haematological-malignancies/chronic-lymphocytic-leukaemia/eupdate-chronic-lymphocytic-leukaemia-treatment-recommendations NCCN Guidelines: https://jnccn.org/view/journals/jnccn/18/2/article-p185.xml iwCLL guidelines: https://ashpublications.org/blood/article/131/25/2745/37141/iwCLL-guidelines-for-diagnosis-indications-for
• 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.)	Yes the pathway is reasonably well defined based on the accessibility of drugs on the NHS. Currently patients with intact *TP53* will be treated with either FCR CIT or entered into the FLAIR trial for frontline therapy. Older patients or those not fit for FCR due to co-morbidities are treated currently with, Bendamustine and Rituximab or NICE approved Chlorambucil and Obinutuzumab. Recently, an EAMS scheme has become available for frontline patients using acalabrutinib for patients who meet the same criteria as the ELEVATE CLL study. Patients with CLL harbouring a *TP53* deletion or mutation are currently eligible for Ibrutinib in the frontline setting or single agent venetoclax if a B-cell receptor pathway inhibitor is unsuitable. Idelalisib with Rituximab is also available. Patients relapsing after frontline CIT are treated with either Ibrutinib or Venetoclax+Rituximab. The choice is made based on assessment of individual patients by the treating physician and following discussion

	regarding patient preference. Single agent venetoclax is available for patients relapsing after both CIT and Ibrutinib but is used less often now with the availability of a time-limited option of Venetoclax+Rituximab .
• **What impact would the technology have on the current pathway of care?**	**Frontline** Patients would have a choice of receiving fixed duration chemo-immunotherapy compared to continuous oral acalabrutinib or acalabrutinib in combination with obinutuzumab. Both acalabrutinib monotherapy and the combination regimen results in improved PFS and a reduced side effect profile compared to the control arm; in subgroup analyses there is an indication that the combination regimen shows a further improvement in PFS even for patients with those with better prognosis disease (defined by those with mutated *IGHV* genes). **Relapsed** Patients would have an additional choice of receiving acalabrutinib compared to continuous ibrutinib or fixed duration venetoclax rituximab. Despite no head to head comparisons, the side effect profile of acalabrutinib is apparently less than that seen with ibrutinib- for example reduced incidence of atrial fibrillation and hypertension.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	In the frontline setting, treatment (if given without obinutuzumab) can be delivered entirely in the outpatient setting, not necessitating the need for a day unit or inpatient setting. In the relapse setting, patients would not require the intense monitoring needed for initial venetoclax administration.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Haematology Clinics, as per current standard of care in the frontline and relapsed setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal additional training would be needed, as clinics already deliver ibrutinib.
11. 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?	Yes. An additional effective agent in CLL would be expected to increase length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Acalabrutinib is reported to have an improved side effect profile, therefore resulting in less interventions for complications such as atrial fibrillation and hypertension.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Treatment is effective in all groups of patients regardless age and genetic characterisation
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 or additional tests or monitoring needed.)	The technology is an oral tablet that requires monitoring through an outpatient setting, similar to current technologies. Similarly to other types of BTKi therapy prophylaxis with co-trimoxazole is required

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No.
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?	Use of acalabrutinib would result in a higher QALY compared to CIT (significantly reduced risk of infections and anticipated reduction in secondary cancer, no need to attend day wards for infusions) and Ibrutinib (reduced incidence of cardiac complications such as atrial fibrillation (reported in up to 10% of individuals) and hypertension (reported in up to 50% of inidviduals).
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?	
• Is the technology a 'step-change' in the management of the condition?	Frontline: Cessation of chemo-immunotherapy in the frontline setting, which would be the consequence of introduction in the frontline setting, would be step change. Relapse: The technology is similar to current practice.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, frontline patients for whom CIT is not suitable
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?	Side effects are rare and easily manageable
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The control arms of the frontline ELEVATE study reflect current clinical practice in the UK. The treatment arm of the relapsed ASCEND study is more akin to current UK practice than the control arm.

• If not, how could the results be extrapolated to the UK setting?	Frontline: The current “FLAIR” clinical study is comparing ibrutinib containing regimes to chemo-immunotherapy and is widely adopted within the UK with >100 centres, and is similar in design to the treatment arm of ELEVATE
• What, in your view, are the most important outcomes, and were they measured in the trials?	OS, PFS, time to next treatment and treatment related complications are the most relevant outcomes when considering therapy with BTKi. All were measured in the studies. MRD is a further important endpoint, but more relevant for studies of CIT and BCL2 inhibition.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS and time to next treatment is widely used in a long term condition such as CLL and are recognised to predict long-term clinical outcomes.
• 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?	An EAMS scheme for acalabrutinib has commenced in the UK in April 2020.

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA174, TA216, TA343, TA359, TA429, TA452, TA469, TA487, TA561]?	No
21. How do data on real-world experience compare with the trial data?	There is limited data on the real world use of acalabrutinib due to lack of access to date; these data collections are in progress both as part of the UK EAMS scheme and elsewehere.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Access to acalabrutinib in the front line setting would be a step change for the vast majority of CLL patients in the frontline setting who currently only have access to inferior chemo-immunotherapy, both in terms of OS, PFS and side effects.
- Acalabrutinib in the relapsed setting would be an additional alternative to the currently available regimes
- Reduced healthcare costs in the frontline setting in terms of healthcare infrastructure needed.
- Anticipated reduced number of complications from BTKi related therapy if acalabrutinib replaced current standard of care ibrutinib in the relapsed setting.
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your 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 expert statement

- 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	**Professor Adrian Bloor**
2. Name of organisation	**Christie NHS Foundation Trust**

3. Job title or position	**Consultant Haematologist**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. 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.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition 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?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• 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 clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. 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?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. 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.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. 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?	
17. 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?	
• 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?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
19. 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?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance TA343 and TA429?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24.	

The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) is unsuitable. How is this FCR-unsuitable population clinically defined?	
25. Are the following (excluded as comparators in the company submission) considered to be established clinical practice in the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable? • idelalisib with rituximab (17p deletion or TP53 mutation)	

• chlorambucil with or without rituximab • bendamustine with or without rituximab • rituximab with fludarabine and cyclophosphamide	

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your 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.

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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 13 pages.

About you	
1. Your name	**Anna Schuh**
2. Name of organisation	**NCRI**

3. Job title or position	**Associate Professor and Consultant Haematologist, University of Oxford**
4. Are you (please tick all that apply):	☐ **X** an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? ☐**X** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
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 ☐ X other (they didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression and prevent complications; improve progression free survival and overall survival
8. 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.)	Untreated: Significant improvement in progression-free survival at 24 months: approx. 87% vs 47% with Chlorambucil-Obinutuzumab (ELEVATE) Relapsed: Prolonged progression free survival at 12 months: 88% with acalabrutinib versus 68% with physician's choice (ASCEND) Like other BTK inhibitors, acalabrutinib does not lead to minimal residual disease negativity and requires continuous therapy.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES. Untreated: acalabrutinib monotherapy should be considered as part of the new standard-of-care for all patients with treatment-naïve CLL alongside fixed-duration Venetoclax-Obinutuzumab Treated: Alongside ibrutinib as a better tolerated option for all patients with relapsed CLL who are either ibrutinib-naïve or intolerant to ibrutinib.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Untreated: Currently, there is no BTK-inhibitor treatment available for patients with CLL unless they have TP53 mutations/deletions. NICE approved SOC in the UK is chemoimmunotherapy with either FCR (fit patients) or Chlorambucil and Obinutuzumab (frail patients). This is obsolete as three independent randomised trials demonstrated superiority of the first-in-class BTK inhibitor ibrutinib compared to FCR (Shanafeldt T et al NEJM 2019), BR (Woyach J et al NEJM 2018) and Chlorambucil and Obinutuzumab (Moreno C et al Lancet 2018). with regards to PFS. Importantly, the ECOG study also compared ibrutinib to FCR and found an OS advantage for BTKi in fit patients (Shanafeldt et al NEJM 2019). However, Ibrutinib is not NICE approved. This is because Janssen decided against a NICE submission for pricing reasons. Ibrutinib is available in most EU countries and the US as frontline therapy for patients with CLL. There is no clinical reason to believe that acalabrutinib is inferior in terms of efficacy to ibrutinib. Venetoclax-Obinutuzumab is a fixed duration therapy that has been shown to be superior to Chlorambucil and Obinutuzumab in frail patients. Ven-Obinutuzumab is currently under review with NICE. There are no head-to-head comparisons against either Ibrutinib nor Acalabrutinib. Relapsed: Ibrutinib is available in the UK and NICE approved. Increasing evidence from long-term clinical trial follow-up and real-world data suggests that about one-thirds of patients have to discontinue Ibrutinib due to side-effects. In particular, cardiovascular side-effects are a potentially life-threatening toxicity. This was first recognised in a meta-analysis performed by the MHRA 2017. The highly selective acalabrutinib is much better tolerated and has equal efficacy. Data from the Phase 2 trial suggests that 80% of ibrutinib intolerant patients gain significant benefit from switching to acalabrutinib with resolution/decrease in previous toxicities (Awan F et al Blood Advances 2019). A head-to-head comparison between the two drugs in the relapse setting is closed to recruitment and is in follow-up. This study will give some idea of the differences in side-effects.
• Are any clinical guidelines used in the treatment of the	Schuh A et al. BSH guidelines 2018 (already out of date). Hallek M et al iwCLL guidelines 2018: already out of date, too.

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.)	The pathway is well defined. We know that chemo-immunotherapy is no longer the right treatment for treatment naïve patients. We also know that a significant number of patients with CLL does not tolerate Ibrutinib due to toxicity. Outstanding questions without evidence-base where clinical practice would vary: Untreated: Is Ven-Obi better than BTKi? This would require a direct comparison between fixed duration Ven-Obi followed by retreatment with Ven-Obi at disease recurrence versus continuous Ibrutinib or Acalabrutib; this head-to-head comparison will never happen. The opinion in the community is that continuous treatment with a BTKi is probably superior in terms of duration of response, but that fixed duration Ven-Obi is preferred by some patients thanks to the fixed duration and fewer side-effects compared to Ibrutinib. A better tolerated and still highly effective BTKi would be very popular with patients. Relapsed: We don't know whether Ibrutinib or Acalabrutinib should be followed by Ven-R or the other way around. An NCRI study proposal to address this question was rejected by HTA and CRUK, so this question will also remain unanswered.
• What impact would the technology have on the current pathway of care?	Untreated: It would finally provide access to a BTK inhibitor in frontline to patients in the UK. This approach has been shown to be superior with respect to progression free survival in all patients with CLL. For younger fit patients with CLL it is also superior with regards to overall survival (see above). It is therefore paramount that Acalabrutinib is made available as an option in frontline. Relapsed: two-thirds of patients with CLL are elderly and have co-morbidities, in particular hypertension, AF and ischemic heart disease. These patients are at significant risk of potentially life-threatening toxicity from ibrutinib. A better tolerated BTKi such as acalabrutinib would give these patients a long-term option BEFORE Venetoclax. Currently, these patients are given Venetoclax without prior BTKi and Venetoclax is then their last treatment option before supportive care.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is not available
• How does healthcare resource use differ between the technology and current care?	Untreated: patients currently receive intravenous chemoimmunotherapy. During the COVID19 pandemic, these treatments had to stop or were delayed. There is a huge backlog of patients waiting for treatment as there are not enough nurses or chair time, and curative treatments are being prioritised in line with the NICE recommendation for chemotherapy during COVID19. Even without COVID19, the routine administration of chemoimmunotherapy in a non-curative setting has significant resource implications that are never costed properly. In particular, there is the 25% admission rate for infections and requirement for intensive care with FCR. Ven-Obi (under review by NICE) is excellent treatment, but requires overnight admission of high-risk patients and close monitoring for tumourilysis over the initial five weeks of dose-escalation. This is difficult for some older patients and also younger patients in shielding. None of these resource implications are seen with BTK inhibitors. Relapsed: With Ibrutinib, the main implication is access to cardiology specialist testing. This will be far less of an issue with acalabrutinib.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics. Thanks to the tolerability of the drug, hospitals are also considering pharmacy and nurse-led clinics.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	For many patients, esp in frontline, care could be managed via specialists, but in the community with remote blood testing, postal service for drug supply and only 3-6 monthly reviews.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	See above
• Do you expect the technology to increase length of life more than current care?	Untreated: yes, there is no reason to believe that acalabrutinib will be less effective compared to ibrutinib, so the overall survival benefit seen with Ibrutinib compared to FCR will also apply to acalabrutinib.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Infection rates go down with BTK inhibitors with ongoing treatment and not up as with chemo. Most importantly, QoL correlates with remission duration. This is much longer with BTKi compared to FCR or chemoimmunotherapy.
13. Are there any groups of people for whom the technology would be more or	TP53 mutated/deleted patients, and they already have access to Ibrutinib in frontline.

less effective (or appropriate) than the general population?	
The use of the technology	
14. 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.)	Much easier than current SOC (See above): no need for intravenous treatment (FCR, Chlorambucil-Obinutuzumab); no tumourilysis prophylaxis (Ven-Obi); fewer cardiology appointments
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Treatment indications: iwCLL criteria Hallek et al Blood 2015 Definition of disease progression: iwCLL criteria Hallek et al Blood 2015

Do these include any additional testing?	
16. 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?	Yes: fewer hospital admissions and ITU admissions; fewer trips to hospital during the COVID pandemic (tablets can be posted to patients, therefore less infection risk and patients can continue to shield). Longer remission duration always translates into improved quality of life, but is never measured in clinical studies as patients come off study when they relapse. Lower rate of grade 1-2 infections has big impact on quality of life, but is also rarely measured.
17. 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?	See above

• Is the technology a 'step-change' in the management of the condition?	Yes, esp in frontline: from chemo to BTKi In relapse: from first in class "dirty" BTKi to second generation highly selective BTKi with significantly decreased toxicity compared to first-in-class Ibrutinib
• Does the use of the technology address any particular unmet need of the patient population?	Patients with CLL suffer from secondary immunodeficiency. It is important for patients to have access to a chemotherapy-free regimen that does not lead to further immunosuppression. This is particularly important because of COVID19. Many patients with CLL have cardiac comorbidities. To get access to a better tolerated drug with lower risk of cardiac arrhythmia, hypertension, failure and sudden cardiac death is important (see MHRA review of Ibrutinib toxicity 2017).
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Acalabrutinib is extremely well tolerated. The main adverse events are purple spots on the skin and headaches. Both are self-limiting and resolve spontaneously in the first few weeks of treatment. More serious side-effects are rare.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The trials under review reflect UK NICE guidance with respect to the comparator, clinical practice and patient populations
• 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?	PFS and tolerability are strong predictors for good quality of life. They were measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No, they were not used as MRD is not a surrogate marker for BTKi efficacy.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not yet. Watch the space. An early access programme in the real world during COVID19 is ongoing in the UK. It only includes frail patients with therapy-naïve CLL.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not yet
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA343 and TA429?	no
22. How do data on real-world experience compare with the trial data?	Not available yet
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

23b. Consider whether these issues are different from issues with current care and why.	no
Topic-specific questions	
24. The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) is unsuitable. How is this FCR-unsuitable population clinically defined?	Patients who are unsuitable for FCR are defined by CIRS score >6 in clinical trials. However, this scoring system is not applied in routine clinical practice. The most important risk factors for FCR complications are age >65; creat clearance >50mls/min; a history of recurrent infections (common in CLL) and cardiovascular comorbidities. In addition, there is a significant risk of bone marrow failure and second malignancy with FCR. These are age and co-morbidity independent. Therefore, one could argue that esp in younger and fit patients FCR should be contraindicated if a non-chemotherapy regimen is available (see Shanafeldt T et al NEJM 2019).
25. Are the following (excluded as comparators in the company submission) considered to be established clinical practice in	idelalisib with rituximab (17p deletion or TP53 mutation) is used for FCR unsuitable and ibrutinib-intolerant patients with relapsed CLL, although it has been almost completely replaced by venetoclax. This regimen is inferior compared to ibrutinib with regards to efficacy and has significant side-effects. It is therefore only used for patients with 17p deletion/TP53 mutations who really cannot tolerate ibrutinib or venetoclax.

the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable? • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • bendamustine with or without rituximab • rituximab with fludarabine and cyclophosphamide	chlorambucil with or without rituximab: strictly speaking, this is not NICE-approved, but it is still used occasionally for patients with treatment naïve CLL. Patients with relapsed CLL have access to ibrutinib or venetoclax in the UK. Bendamustine with or without rituximab: sometimes used in frontline and in relapsed setting Rituximab with fludarabine and cyclophosphamide: this is FCR. None of these regimens are SOC relapsed therapies. However, this the comparator choice for Ascend is completely irrelevant as the important message of the study is the tolerability of acalabrutinib (compared to ibrutinib in studies of patients with similar profile like Resonate).
Key messages	

26. In up to 5 bullet points, please summarise the key messages of your statement.

- It is critical for patients in the UK to gain access to a BTK inhibitor in frontline as this has been shown to be superior to chemoimmunotherapy with respect to PFS across all age groups.
- Specifically, for younger patients, BTK inhibition has been shown to improve overall survival compared to FCR. FCR has significant long-term risks of second cancer and bone marrow failure. BTK inhibitors should therefore be make available for young and fit patients.
- In the relapsed setting, Ibrutinib has transformed treatment of CLL. However, about one-third of patients, esp those with a cardiac history, cannot tolerate this first in class drug. A second generation BTKi that is better tolerated and equally effective should therefore become an option for all patients, esp those with cardiovascular risk factors.
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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you

1.Your name	Jackie Martin
2. Are you (please tick all that apply):	a patient with the condition? Yes a carer of a patient with the condition? No a patient organisation employee or volunteer? Yes, a patient advocate volunteer other (please specify):
3. Name of your nominating organisation	Chronic Lymphocytic Leukaemia Support (CLL Support) and also Lymphoma Action (LA)
4. Did your nominating organisation submit a submission?	yes, they did - Yes

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. Yes

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.)	
7. How did you gather the information included in your statement? (please tick all that apply)	I have personal experience of the condition and I am drawing on others' experiences. Please specify how this information was gathered: We gathered information about the patient experience with Acalabrutinib from the on line platform Health Unlocked which hosts the CLL Support on line community https://healthunlocked.com/cllsupport In addition, in February 2020 there was a worldwide on line survey undertaken by Lymphoma Canada and distributed on the HU CLL Support forum to enable UK participants to take part. https://www.surveymonkey.com/r/CLLCAN2020 and https://healthunlocked.com/cllsupport/posts/142606394/please-share-experience-of-venetoclax-plus-obinutuzimab-or-acalabrutinib-treatment-in-a-survey-that-may-help-others-gain-access The information obtained included patients that were in clinical trials and those outside clinical trials.

Living with the condition

8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL is a complex disease, generally of older people, in which almost all treatment ends in eventual relapse so patients live in a cycle of 'monitoring, treatment and then relapse', which is repeated and continues until death. Patients worry about relapse, knowing further toxic treatment is likely to impact negatively on their quality of life. Even after a period of successful treatment, patients can be left with a significant symptom burden and poor quality of life. It is psychologically challenging know that symptoms, quality of life and clinical assessments are likely to worsen and then further treatment be required. CLL tends to genetically evolve and respond less well to each line of therapy, with shorter subsequent remissions. Around 85% of patients diagnosed are aged 65 or older and many also have comorbidities. This means the more toxic treatments are not well tolerated by the majority of patients. The most common approach to managing CLL is an active monitoring phase. This is a challenge for people to understand and come to terms with. The negative emotional and psychological issues experienced at diagnosis remain high for the majority of patients during the monitoring period: "stress" (75.8%), "anxiety" (59.3%), "difficulty sleeping" (38.7%) and "depression" (30.6%). Patients report the difficulty of living with uncertainty both for them and their families/carers: "It's so difficult to plan anything, especially holidays, as I have no idea if I'll be well enough to go. Insurance is another expensive problem but my family would like a holiday." "I worry about catching flu as I can't make antibodies myself and so I tend to stay away from people during winter." 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." **All of these comments were made before the current advice for shielding from COVID19 for CLL**

	patients which has further restricted their opportunities for social and leisure.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	It's important that there are a range of treatment options because the safety profile of each drug must be carefully matched to the patient's clinical condition and the co-morbities that are common in these patients which are generally older in age. Patients are aware of targeted therapies and chemoimmunotherapy (CIT) is regarded as having many toxic side effects. Patients want to be able to move away from CIT. For relapsed patients with access to Ibrutinib, the cardiac side effect of atrial fibrilation and contraindication with anticoagulants is a particular concern. They are aware that the reported Ibrutinib adverse events of AF, hypertension, arthralgias and musculoskeletal pain appear more tolerable with Acalabrutinib.

10. Is there an unmet need for patients with this condition?	Yes, because of the heterogeneous nature of CLL a wide range of treatment options is important. There is an unmet need for an effective, relatively non-toxic treatment that can produce durable remissions with few side effects. With Acalabrutinib this is irrespective of patient co-morbidities, CLL genetics and IGHV mutation status. The unmet need is particularly urgent for treatment-naïve CLL patients of all fitness levels (inc those suitable for FCR) without 17p del and TP53 mutations as they do not have access to a targeted treatment for first line therapy. Within this group, all those with complex genetics and unmutated IGHV have the greatest need as they do very poorly with chemo- immunotherapy. Early reports from clinical trials and real world surveys for both treatment-naïve and refractory patients indicate that Acalabrutinib offers a highly effective treatment similar to Ibrutinib but with a better safety profile which makes it suitable for patients with cardiovascular risk factors. The most common side effects that lead to discontinuation of Ibrutinib (arthralgias, worsening hypertension, cardiac events, musculoskeletal pain) are reported much less frequently with Acalabrutinib. CLL patients want to transition from chemotherapy to an era of targeted therapy with proven efficacy in treating a wide range of patients, including those who have poor prognostic factors and those of advanced age with existing co-morbidities. They also value new treatments with fewer and more tolerable side effects.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Informed patients and carers are aware of Acalabrutinib from on line and social media. They are asking questions about their 17p, TP53 and IGHV mutation status and they are aware of how that relates to their own clinical situation both in terms of treatment availability and its effectiveness. They are also aware of the effectiveness and safety profile benefits of Acalabrutinib compared to Ibrutinib. Reports from patients who have experience of Acalabrutinib are overwhelmingly positive. A small number of patients had switched from Ibrutinib to Acalabrutinib because of poor tolerability to Ibrutinib and were able to tolerate Acalabrutinib well. 90% of patients reported a positive experience of Acalabrutinib (either good, very good or excellent) and indicated that their health and wellbeing had “greatly improved” with Acalabrutinib treatment. 95% of patients were still taking Acalabrutinib at the time of the survey. The 5% who had stopped treatment, had stopped because of progression or Richter’s transformation. Patients appreciate that the treatment is a tablet that is taken at home, albeit twice a day, and that reduces their need for hospital attendance (no iv treatment). In responses to out survey, 68% of patients reported that Acalbrutinib managed all their CLL symptoms although 27% said they were still suffering from fatigue. 36% reported no side effects at all but 36% said they had headaches, 36% joint pains and 23% diarrhoea. Mouth sores were also reported but no skin rashes. Patients are dissatisfied with the options available to treatment-naïve patients who do not have the 17p and TP53 genetic markers, especially those who have complex genetics or an unmutated IGHV status, because of the poor response to chemo-immunotherapy.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Twice a day dosage may be seen as a slight disadvantage The ongoing nature of the treatment may be seen to be a disadvantage by some patients; however, others find it a comfort to continue treatment. Future studies may mean that treatment can be stopped or paused in patients with good remissions and then started again as necessary. Headaches in the early stages of treatment may deter patients who already suffer from migraine or headaches. Acalabrutinib may not be suitable for those who suffer with acid reflux treated with a proton pump inhibitor such as omeprazole, as it requires an acidic stomach for it pharmacokinetics.
Patient population	
13. 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.	Because of the heterogeneous nature of CLL and the diverse population, with and without co-morbidities who require an effective treatment, it is difficult to identify one population that would benefit more than others. However, treatment-naïve patients **of all fitness levels** with complex genetics and/or unmutated IGHV status are likely to benefit most from this technology because they have a less favourable response to chemo- immunotherapy and targeted therapies are not available to them outside a clinical trial. Response to Acalabrutinib treatment is the same regardless of the patient's IGHV mutation status, genetic profile or prior treatment regimens, providing excellent responses for over 90% of patients.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are definitely health equality issues if Acalabrutinib is only authorised for 'older', less fit patients who are unsuitable for FCR and is not inclusive of all groups. There are health equality issues for treatment-naïve patients who have complex genetics and/or an unmutated IGHV status as they do not have access to effective (targeted) treatments which will give them remissions of equal depth and length that other, IGHV mutated, patients experience. Targeted treatments are available and effective for other patients who are recognised to have an equally poor prognositic profile (17p, TP53)
Other issues	
15. Are there any other issues that you would like the committee to consider?	We would prefer this treatment to be available to all CLL patients receiving their first treatment and any subsequent treatments. To have Acalabrutinib approved for treatment naïve patients would mean a safe, effective and well tolerated treatment for all CLL patients irrespective of genetics, IGHV mutation status and age. Approval of this treatment by NICE would provide a lifeline to especially vulnerable patients at this time.

Topic-specific questions	
16. The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) is unsuitable. How is this FCR-unsuitable population clinically defined?	The FCR unsuitable patient population is difficult to define in absolute terms and could include criteria outside fitness such as prognostic indicators of response to CIT such as unmutated IGHV status. Partly for this reason we fundamentally disagree with the company's position in this regard and feel the treatment should be available to all patients for whom it is suitable. This is for both treatment naive and relapsed/refractory patients.

17. Are the following (excluded as comparators in the company submission) considered to be established clinical practice in the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable? • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • bendamustine with or without rituximab • rituximab with fludarabine and cyclophosphamide	Idelasilib is not a treatment of choice by patients or doctors because of the adverse side effect profile. Chlorambucil +/- Rituximab is not often used in clinical practice. Bendamustine with Rituximab is occasionally used for patients who cannot tolerate FCR but do not qualify for a targeted treatment such as Ibrutinib. This is not an effective treatment for many patients and has toxic and, occasionally long lasting, side effects leading to further hospitalisations and morbidity.

Key messages
18. In up to 5 bullet points, please summarise the key messages of your statement: • Acalabrutinib addresses an unmet need for all CLL patients but especially for those who are treatment-naïve and who have complex genetics or an unmutated IGHV status as they do not have access to equally effective treatments as IGHV mutated patients at the present time. • Acalabrutinib is an effective treatment that induces deep remissions, improving over time, with fewer off target side effects than Ibrutinib and can be suitable for patients with cardiovascular risk factors and those on anticoagulants. • Acalabrutinib would offer an effective and relatively safe, non-toxic option for all CLL patients needing to start first or subsequent treatment, which is especially important during the current pandemic of COVID-19 • Access to multiple treatment options is important for ALL CLL patients, who often require many different lines of treatment for multiple relapses • To restrict the availability of Acalabrutinib to only those unfit for FCR is arbitrary and will introduce health inequalities for this group who do not have access to a non chemotherapy option for treatment.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nick York**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Leukaemia Care
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	*"Diagnosis was a difficult time for me Being told I had an incurable life limiting condition affected every aspect of my life. Learning to live on watch and wait (active monitoring) is hard to come to terms with. It seems counterintuitive until you have some understanding of how the disease is managed and treated. This exaggerated the high levels of anxiousness, fear and unknowing I felt at diagnosis."* 75% of people diagnosed with CLL are put onto watch and wait, this is a major issue experienced by the majority. High levels of anxiousness and emotional distress may be experienced during the entire time of watch and wait which can be many years before an intervention is required. It is very difficult to live with increasing symptoms and side effects and allow the disease to progress to an advanced level before intervention. Disease mediated acquired immune issues are likely to develop, which may be irreversible. Shared experiences gathered from focus groups attendance, patient meetings while supporting patients for 10 years has confirmed that this is a problem for many. This is further corroborated by evidence

	gathered during patient experience surveys carried out by Leukaemia Care, Lymphoma Canada and CLL support. CLL compromises the immune system and treatments may add to this. Patients may require additional prophylaxis and need to be vigilant and employ strategies to reduce risks of extreme side effects to common opportune infection. This negatively impacts on persons quality of life. A person diagnosed with CLL may experience repeated infection or isolation caused by the condition and their increased risk of opportune infection. CLL patients are not likely to respond to Immunisation and vaccination and may remain vulnerable at all times to new infection. Symptoms of the disease can be long term and an increasing and developing burden to cope with. Frequent periods of fatigue, infection, aching joints, bone pain, enlarging lymph nodes, extreme reactions to bites, or physical insults, can insidiously eat away at a person's ability to function or carry out activities of daily living.. Treatment may add new symptoms during and after treatment. Patients are aware of the potential for long term complication that may be caused by myelotoxic therapies or currently available continuous therapies. As CLL therapies are not curative there is often anxiety caused by fear of eventual relapse and transformation to a more aggressive form of the disease. This all adds to psychological and physiological burden a patient may experience. *"Living with CLL is a marathon and there are uncertainties caused by diagnosis of this disease at every corner. How long will I be on watch and wait? How do I manage to live with long term physical challenges? How do I avoid potential increased risk of infection? Will I always have to isolate to some degree? Will I need treatment? Will treatment work? Will I be able to tolerate treatment|? How long will my treatment last? How long will treatment side effects last? How long can I cope with side effects? How do I talk to my family, my children and friends? Will I be able to keep working, Will my partner be able to keep working? How can I reduce the burden on my family? Will I survive and for how long? How do we plan for the future as a family?"* As a CLL patient it may be difficult to share feelings with loved ones, who most often are also the carer. A patient is not diagnosed alone, the family are also diagnosed, which impacts on relationships and may

	restrict normal family activity, reduce income and burden a partner/carer.. This has been evidenced to a much greater extend during the COVID epidemic, where entire families are having to isolate or take on strategies to keep their loved ones living with CLL safe.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Treatments all come with side effects to varying degrees. CLL is essentially an incurable and heterogeneous disease that requires a range of treatment options to provide treatment choice to gain best outcomes for the individual. In an era of targeted therapy and novel effective therapies there is an opportunity to provide a more individualised approach to provide effective therapies to treat individual versions of CLL for patients at all levels of fitness and suitability to tolerate a treatment, *"I entered a clinical trial to access a BTKi but drew the arm for treatment with FCR. I reacted badly to treatment with this therapy and became pan cytopenic after two treatment cycles and the treatment had to be halted. During this brief spell on FCR I experienced two emergency admissions for suspected sepsis. My immunity is now further damaged than before treatment resulting in a need to self-infuse immunoglobulins every two weeks to give me some cover against opportune infection. I now am in treatment as a relapsed patient with Ibrutinib and have very few options remaining should I relapse. Access to a BTKi first line would have prevented early damage at the beginning of my treatment journey."* In the Leukaemia Care patient experience survey, around 31% patients reported that the side effects they experienced with recent/current treatments had a large impact on their life patients reported in the Lymphoma Canada survey that fatigue, nausea and frequency of infections were the most difficult side effects to tolerate. . These surveys report that CLL patients prefer oral-tablets as a method of treatment and that patients on oral therapies experienced reduced negative impacts on their quality of life compared to patients on intravenous therapies. With reductions in: treatment-related fatigue, number and frequency of infections and improvements in treatment tolerability.. Oral therapies administered in the home setting interfere less with activities of daily living and reduce opportunity of opportune infection.

	Currently available treatment therapies: Chemoimmunotherapy (CIT) is available in the 1st line setting to treat patients without TP53 aberrations: Fludarabine, cyclophosphamide and rituximab or bendamustine with rituximab for fitter patients. Chlorambucil, with or without a monoclonal antibody of rituximab or obinutuzimab, for less fit patients Although EMA licensed for treating all first line CLL patients the targeted Bruton's kinase inhibitor Ibrutinib is only available in England and Wales to treat TP53 aberrated patients. Idelalisib a PI3K inhibitor plus rituximab is also available to treat 1st line TP53 aberrated patients. Access to targeted therapies with a reduced toxicity footprint as an alternative to CIT is required to treat all first line patients .It has become increasing clear of this need for availability of less myelotoxic therapies and continuous therapies that help mitigate the increased infection risks of treatment.in the COVID pandemic. Acalabrutinib is currently available for treatment naive patients through an acalabrutinib CLL program provided by the company. It is not just the treatment naive population that require easy to administrate treatments with a reduced toxicity footprint to lessen the need for hospital attendance and reduce infection risk in the current COVID landscape. Acalabrutinib is a next generation BTKi and covalent and needed to add to limited therapies for relapsed patients, patients may also be unsuitable for Ibrutinib or venetoclax due to comorbidities. Patients may have to discontinue current therapies due to side effects of issues experienced following long term use, acalabrutinib is a proven alternative. Current recommendations from the UK CLL Forum - Practical guidelines for managing CLL in COVID pandemic post lockdown: https://ukcllforum.org/wp-content/uploads/2020/07/Practical_guidelines_managing_CLL_COVIDv3FINAL.pdf

10. Is there an unmet need for patients with this condition?	The developing move away from chemotherapies towards a more targeted treatment strategy has been accelerated in the light of the COVID pandemic. Although effective in some populations chemoimmunotherapy brings with it many serious treatment related side effects and the less fit population cannot tolerate the stronger more effective CIT and are treated with 'milder' CIT options that achieve less enduring responses . Therefore in the era of targeted therapies effective in all groups, there is a need for less myelotoxic treatment options as an alternative to CIT to reduce risk of long term side effects, improve quality of life and mitigate risks of serious infection complication in the COVID era TP53 aberrated and all relapsed CLL patients require further treatment options as comorbidities and AEs may make current options of ibrutinib, idelalisib or Venetoclax unsuitable. Acalabrutinib offers an effective alternative, an easy to administer single agent treatment with reduced toxicity footprint Patients want choice of effective treatment methods and tablet only administration in the home setting to reduce infection risk and negative impact on quality of life is preferred.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	• Ease of administration and convenience, minimal disruption to daily routine • Improvement to quality of life and ability to carry out activities. • Reduction and improvement of symptoms • Reduced hospital attendance and reliance on care team, very relevant during COVID pandemic. • Less negative impact on immune system and reduced risk of infection, very relevant during COVID pandemic

	• Reduced toxicity profile and easy to tolerate • Positive effects to health and wellbeing
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	A continuous therapy may be an inconvenience to some. However patients are excited by the potential benefits this treatment offers
Patient population	
13. 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.	Most patients may benefit from this technology. Effective treatment options are required for patients in all CLL settings. In the era of targeted therapies that are proving effective in all groups. Distinctions should not be made due to fitness or age
Equality	
14. Are there any potential equality issues that should be taken into account when	The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) is unsuitable. It is unusual to offer suggestions of equality issues that may prejudice younger fitter patients. But in this instance this appraisal prevents the younger FCR suitable group from access to a treatment as an alternative to a strong chemotherapy. All CLL patients live with protected characterises of age and disability and all may benefit from this treatment. This is especially relevant in the COVID era when less myelotoxic therapies are required

considering this condition and the technology?	options to protect life to reduce potential infection risk and potential extreme reactions to infection as a consequence of contracting COVID.. .
Other issues	
15. Are there any other issues that you would like the committee to consider?	A BTKi therapy is not currently available through routine commissioning for front line patients without TP53 aberrations, contrary to EMA licensing which has enabled access to a BTKi via private health care for several years. Acalabrutinib has been made available to NHS for first line treatment naive CLL patients ((fulfilling eligibility criteria for ELEVATE-TN population} during the COVID pandemic in an access program provided by the company. It is looking like the second surge of the COVID pandemic is now upon us. A less myelotoxic targeted alternative is required for all patients to mitigate risks and delivery of healthcare during COVID and into the future it is imperative that access to acalbrutinb continues after the companies access program ends.
Topic-specific questions	
16. The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) is unsuitable. How is this FCR-	

unsuitable population clinically defined?	
17. Are the following (excluded as comparators in the company submission) considered to be established clinical practice in the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable? • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • bendamustine with or without rituximab • rituximab with fludarabine and cyclophosphamide	Clinical expert answer

Key messages
18. In up to 5 bullet points, please summarise the key messages of your statement: • Patients confirm acalabrutinib significantly reduces and improves symptoms, offering an Improvement to quality of life and ability to carry out activities of daily living, with positive effects to health and wellbeing. • Acalabrutinib treatment is easy to administer and a convenient method of managing the disease with minimal disruption to daily routine, this treatment also reduces hospital attendance and reliance on care team, very relevant during COVID pandemic. • Acalabrutinib has a reduced toxicity profile, is easy to tolerate, reduces negative impact on immune system and subsequently reduces risk of infection, very relevant during COVID pandemic • There is a desire to move away from chemo-immunotherapies in front line settings and there is an unmet need of access to more tolerable and targeted treatments for both: the unfit and fit patient populations. • Additional treatment options are required for patients in the relapsed refractory setting , acalabrutinib offers a tolerable solution to complement currently available options to extend choice and survival

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Acalabrutinib for treating chronic lymphocytic leukaemia: A Single Technology Appraisal

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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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

Ruth Wong critiqued the company's search strategy. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Jean Hamilton critiqued the statistical aspects of the submission. Paul Tappenden and Aline Navega Biz critiqued the health economic analysis submitted by the company and undertook the ERG's exploratory analyses. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine plus rituximab
BSA	Body surface area
BSH	British Society of Haematology
BTK	Bruton's tyrosine kinase
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CLL	Chronic lymphocytic leukaemia
CLL IPI	CLL International Prognostic Index
Cm	Centimetre
CMA	Cost-minimisation analysis
cPAS	Comparator Patient Access Scheme
CR	Complete response
CrCl	Creatinine clearance
CRi	Complete response with incomplete bone marrow recovery
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine sulphate and prednisone
DARE	Database of Abstracts of Reviews of Effects
del(17p)	17p deletion
dL	Decilitre
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	European Cooperative Oncology Group
EF	Emotional functioning
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life
EQ-5D-3L	Euroqol 5-Dimensions 3-level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FACIT	Functional Assessment of Chronic Illness Therapy
FCR	Fludarabine, cyclophosphamide and rituximab
g	Gram
GClb	Obinutuzumab plus chlorambucil

GFS	Global Fatigue Score
GHS	Global Health Status
HCHS	Hospital and Community Health Services
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IgHV	Immunoglobulin heavy chain variable region
IPD	Individual patient data
IR	Idelalisib plus rituximab
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
iwCLL	International Workshop on CLL
IWRS	Interactive web response system
kg	Kilogram
KM	Kaplan-Meier
L	Litre
LDH	Lactate dehydrogenase
LS	Least squares
LYG	Life year gained
m^2	Metre squared
MAIC	Matching adjusted indirect comparison
mg	Milligram
mL	Millilitre
N	Number
N/a	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nPR	Nodular partial remission
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PF	Physical functioning
PFS	Progression-free survival
PH	Proportional hazards
PI3K	Phosphoinositide 3-kinase
PPM	Pre-progression mortality
PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcomes
PS	Performance status

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
R/R	Relapsed/refractory
RCHOP	Rituximab, cyclophosphamide, hydroxydaunomycin, oncovin and prednisone
RCT	Randomised controlled trial
RDI	Relative dose intensity
RF	Role functioning
SAE	Serious adverse event
SLL	Small lymphocytic leukaemia
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TLS	Tumour lysis syndrome
TP53	Tumour protein p53
TSD	Technical Support Document
TTNT	Time to next treatment
TTP	Time to progression
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VenR	Venetoclax plus rituximab
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, and do not necessarily reflect the opinion of NICE.

1.1 Overview of the ERG's key issues

The company's submission (CS) includes three economic analyses of acalabrutinib for the treatment of patients with chronic lymphocytic leukaemia (CLL):

- Model 1 - A cost-utility analysis of acalabrutinib versus obinutuzumab plus chlorambucil (GClb) in patients with untreated CLL (semi-Markov model)
- Model 2 – A cost-minimisation analysis (CMA) of acalabrutinib versus ibrutinib in patients with untreated high-risk CLL (del(17p) and TP53 mutations; semi-Markov model)
- Model 3 – A CMA of acalabrutinib versus ibrutinib in patients with relapsed/refractory (R/R) CLL (partitioned survival model).

The key issues identified by the ERG are summarised in Table 1.

Table 1: Overview of the ERG's key issues

Issue	Summary of issue	Population	Report sections
Issue 1	Restricted populations and comparators: Untreated CLL analyses restricted to patients in whom FCR/BR would be unsuitable. R/R CLL analyses restricted to patients who would otherwise be treated with ibrutinib	Untreated CLL and R/R CLL	Sections 3.1 and 3.3
Issue 2	Uncertainty surrounding clinical equivalence of acalabrutinib and ibrutinib in R/R CLL and high-risk CLL	High-risk and R/R CLL	Sections 4.4, 5.3.4 and 5.3.5
Issue 3	Inclusion of high-risk patients in untreated CLL model	Untreated CLL	Section 5.3.4
Issue 4	Costs of post-progression treatments overestimated	Untreated CLL	Section 5.3.4
Issue 5	Assumptions regarding fixed sequences of first- and second-line therapies for CLL	Untreated CLL	Section 5.3.4
Issue 6	Potentially pessimistic PFS model for GClb	Untreated CLL	Section 5.3.4
Issue 7	Highly optimistic assumptions regarding overall survival benefit for acalabrutinib	Untreated CLL	Section 5.3.4
Issue 8	Health utilities assumed to be better than those for the general population	Untreated CLL	Section 5.3.4
Issue 9	Absence of comparative evidence for acalabrutinib versus ibrutinib in patients with high-risk CLL	High-risk CLL	Section 5.3.4

CLL – chronic lymphocytic leukaemia; R/R – relapsed refractory; GClb – obinutuzumab plus chlorambucil; FCR - fludarabine, cyclophosphamide and rituximab; BR – bendamustine plus rituximab; PFS – progression-free survival

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.

Untreated CLL (Model 1)

Overall, acalabrutinib is assumed to affect QALYs by:

- Increasing the time that patients spend alive and progression-free
- Increasing the time that patients spend alive, including an additional relative survival benefit for second-line treatment after patients have discontinued acalabrutinib
- Reducing QALY losses resulting from adverse events (AEs).

Overall, acalabrutinib is assumed to affect costs by:

- Increasing first-line drug acquisition costs
- Reducing second-line drug acquisition costs
- Reducing health state resource use by increasing the time spent in the progression-free state and reducing the time spent in the post-progression state
- Reducing costs associated with managing adverse events.

The modelling assumptions that have the greatest effect on the ICER are:

- Assumptions regarding the duration for which second-line treatment is given.
- Assumptions regarding which second-line treatment regimen is given following GClb (ibrutinib or venetoclax plus rituximab [VenR]).
- Assumptions regarding the preferred parametric survival model for progression-free survival (PFS) in the GClb group
- Assumptions regarding the relative overall survival (OS) benefit for acalabrutinib compared with GClb. As the model uses a semi-Markov approach, OS is a function of all health state transitions included in the model.

High-risk CLL (Model 2) and R/R CLL (Model 3)

The company's CMAs for the high-risk CLL and R/R CLL populations assume that acalabrutinib is clinically equivalent to ibrutinib, hence QALY gains are not included in the analyses. Based on the assumptions applied in these CMAs, acalabrutinib is assumed to lead to cost-savings by:

- Reducing drug acquisition costs
- Reducing the costs associated with managing AEs.

1.3 The decision problem: Summary of the ERG's key issues

The ERG considers the company's description of the underlying health problem in the CS to be appropriate. The decision problem addressed in the CS is generally in line with the NICE scope. The target population in the CS is people with CLL (including both untreated and previously treated patients). The comparators included in the CS differ between the populations considered in the CS. In patients with untreated CLL (without high-risk cytogenetic features), the comparator is assumed to be GClb. In patients with high-risk CLL and patients with R/R CLL, the CS includes a single comparator – ibrutinib. Other comparators listed in the NICE scope are not included in the company's models.

Issue 1. Restricted populations and comparators: Untreated CLL analyses restricted to patients in whom FCR/BR would be unsuitable. R/R CLL analyses restricted to patients who would otherwise be treated with ibrutinib

Report section	Sections 3.1 and 3.3
Description of issue and why the ERG has identified it as important	Within the untreated CLL population (patients without high-risk cytogenetic features), the company has positioned acalabrutinib as a treatment for "unfit" patients who are ineligible for fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR). The CS notes that there are no standard criteria for determining fitness in UK clinical practice. The ELEVATE-TN trial enrolled patients who were aged ≥65 years, or aged 19–64 years with a creatinine clearance (CrCl) of 30–69 mL/min and/or a score > 6 on the Cumulative Illness Rating Scale-Geriatric. The CS states that these patients would not be suitable for FCR or BR. The CS does not include any clinical or economic comparisons of acalabrutinib versus FCR or BR in "fit" patients. Within the R/R CLL population, the company considers a single comparator - ibrutinib. Clinical advice received by the ERG suggests that this is generally appropriate; however, venetoclax plus rituximab (VenR) is also used as second-line treatment in a proportion of patients.
What alternative approach has the ERG suggested?	These restrictions have implications for the interpretation of the clinical evidence and the economic analyses presented in the CS: For the untreated CLL population (Model 1), the results of the company's cost-utility analysis relate specifically to treatment-naïve patients for whom treatment with FCR/BR is unsuitable. The clinical and cost-effectiveness of acalabrutinib versus FCR/BR in "fit" patients is unknown. For the R/R CLL population (Model 3), the results of the company's CMA are relevant only to patients who would otherwise receive ibrutinib. The incremental costs (and health outcomes) of acalabrutinib versus other second-line therapies, such as VenR, are not presented in the CS.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of acalabrutinib in patients who are fit enough to receive FCR/BR is unclear and the CS does not present any evidence for this population. It is likely that acalabrutinib is more expensive than VenR in the second-line setting, as acalabrutinib is not subject to a maximum fixed treatment duration (based on list prices for these regimens).
What additional evidence or analyses might help to resolve this key issue?	The CS does not present clinical or economic comparisons of acalabrutinib versus FCR or BR in treatment-naïve fit CLL patients. It is unclear whether robust evidence exists to allow a comparison of acalabrutinib versus VenR in patients with R/R CLL.

1.4 The clinical effectiveness evidence: Summary of the ERG's key issues

The clinical evidence for acalabrutinib in the CS is presented across two populations: (i) patients with untreated CLL, including a proportion of patients with del(17p)/TP53 mutations, and (ii) patients with previously-treated CLL.

Untreated CLL

The key evidence of the clinical effectiveness and safety of acalabrutinib in untreated CLL was derived from the ongoing ELEVATE-TN randomised controlled trial (RCT). ELEVATE-TN randomised adults with previously untreated CLL (either: age ≥65 years; or age 19–64 years with CrCl 30–69 mL/min and/or a score >6 on the Cumulative Illness Rating Scale-Geriatric) to acalabrutinib plus obinutuzumab (N=179), acalabrutinib monotherapy (N=179), or GClb (N=177). The acalabrutinib combination therapy arm is not included in the company's economic analyses and is not discussed further in this executive summary. There was a statistically significant treatment group difference for PFS favouring acalabrutinib monotherapy over GClb (hazard ratio [HR] 0.20, 95% confidence interval [CI]: 0.13–0.30; $p<0.0001$). At data cut-off, median PFS for the acalabrutinib monotherapy group had not been reached; median PFS for GClb was 22.6 months. There was no significant treatment group difference between acalabrutinib monotherapy and GClb for OS (HR 0.60, 95% CI: 0.28–1.27; $p=0.1556$). At data cut-off, median OS had not been reached in any treatment group. Fewer patients in the acalabrutinib monotherapy group experienced grade ≥3 adverse events compared with the GClb group (49.7% versus 69.8%).

Previously treated CLL

The key evidence of the clinical effectiveness and safety of acalabrutinib in previously treated (R/R) CLL was derived from the ongoing ASCEND RCT. ASCEND randomised adults with previously treated CLL to acalabrutinib monotherapy (N=155), or investigator's choice of therapy (N=155), which was either idelalisib plus rituximab (IR) or BR. There was a statistically significant treatment group difference for PFS favouring acalabrutinib monotherapy over IR/BR (HR 0.31, 95% CI: 0.20–0.49; $p<0.0001$). At data cut-off, median PFS was not reached in either study arm. At data cut-off, there was no significant treatment group difference in OS for acalabrutinib monotherapy compared against IR/BR (HR 0.84, 95% CI: 0.42–1.66; $p=0.6089$) and median OS had not been reached in either study arm. Grade ≥3 AEs were experienced by 49.4% of patients in the acalabrutinib arm, compared with 80.4% of the IR/BR arm.

In the absence of head-to-head evidence comparing acalabrutinib and ibrutinib, the company conducted an unanchored matching adjusted indirect comparison (MAIC) using data from the ASCEND and RESONATE RCTs. Weights were applied to individual patient data (IPD) from the acalabrutinib arm of ASCEND to balance the covariate distribution with that of the ibrutinib arm of RESONATE. Twelve covariates were included in the base-case MAIC. The HRs for acalabrutinib versus ibrutinib from a weighted Cox proportional hazards model were [redacted] (95% CI: [redacted]) for PFS and [redacted] (95% CI: [redacted]) for OS. The results of the MAIC were used to justify the assumption of equal efficacy between acalabrutinib and ibrutinib in the company's economic analyses in the high-risk CLL population (Model 2) and the R/R CLL population (Model 3).

The ERG does not believe that any relevant studies of acalabrutinib have been missed by the company's searches. The clinical advisors to the ERG considered that the populations of patients enrolled in ELEVATE-TN and ASCEND are representative of patients with CLL who would be considered for treatment with acalabrutinib in England.

The ERG considers that the available clinical evidence for acalabrutinib is subject to considerable uncertainty. This uncertainty arises from the immaturity of the available OS data, the absence of evidence relating specifically to the high-risk CLL population with del(17p)/TP53 mutations and the indirect comparison performed in the R/R CLL population. These clinical issues have direct implications for the cost-effectiveness of acalabrutinib and cannot be meaningfully delineated from them; as such, all key issues are presented together in Section 1.5.

1.5 The cost-effectiveness evidence: Summary of the ERG's key issues

Summary of company's economic analyses – untreated CLL (Model 1)

The company developed a semi-Markov model to assess the cost-effectiveness of acalabrutinib versus GClb for patients with untreated CLL. This model assumes fixed sequences of treatment, whereby patients who progress on first-line acalabrutinib are assumed to receive second-line VenR, whilst patients who progress on first-line GClb receive second-line ibrutinib. Model health states are defined in terms of progression and survival status. The cost-effectiveness of acalabrutinib was evaluated over a 30-year time horizon from the perspective of the NHS and PSS. The model uses data on time to progression (TTP) and pre-progression mortality (PPM) from ELEVATE-TN, with data on post-progression survival (PPS) drawn from external sources (the MURANO and RESONATE RCTs). A general population mortality constraint is applied to ensure that the mortality rate predicted by the parametric survival models never falls below that of the general population. Health state utility values were based on estimates derived from ELEVATE-TN, previous NICE appraisals and the literature. Information on the frequency of AEs was taken from ELEVATE-TN; associated disutilities and AE durations were taken from the literature, previous NICE TAs. and assumptions. Costs were taken from the BNF, previous NICE TAs and NHS Reference Costs. The company's updated model (received following the clarification round) suggests that the deterministic ICER for acalabrutinib versus GClb is £22,679 per QALY gained.

Summary of company's economic analyses – high-risk CLL (Model 2)

Based on the company's MAIC for R/R CLL patients, the company assumed that acalabrutinib is clinically equivalent to ibrutinib for patients with high-risk CLL. The CS presents a CMA for the high-risk CLL population based on the acalabrutinib arm from Model 1. The company's updated CMA for the high-risk CLL population suggests that acalabrutinib is cost-saving compared with ibrutinib (undiscounted cost savings = [redacted] per patient treated).

Summary of company's economic analyses – R/R CLL (Model 3)

Based on the conclusions of the MAIC for R/R CLL patients, the company also presented a CMA for patients with R/R CLL. The company's CMA for the R/R CLL population suggests that acalabrutinib is cost-saving compared with ibrutinib (cost savings = [redacted] per patient treated).

Additional information - PAS and cPAS discounts

The company has proposed a Patient Access Scheme (PAS) which takes the form of a simple price discount of [redacted]; the discounted cost per pack of acalabrutinib is [redacted]. This PAS discount is included in all results presented in this ERG report. Comparator Patient Access Scheme (cPAS) discounts are available for obinutuzumab, chlorambucil, and ibrutinib. In addition, cPAS discounts are available for venetoclax and rituximab, which are assumed to be given as second-line treatment following progression on acalabrutinib in the company's economic analysis in the untreated CLL population (Model 1). These discounts are confidential and cannot be reported here. The impact of these price discounts on the cost-effectiveness of acalabrutinib is presented in a separate confidential appendix to this ERG report.

The ERG's key issues are described in detail below.

Issue 2. Uncertainty surrounding clinical equivalence of acalabrutinib and ibrutinib in R/R CLL and high-risk CLL

Report section	Sections 4.4, 5.3.4 and 5.3.5 (Models 2 and 3)
Description of issue and why the ERG has identified it as important	There are no published head-to-head RCTs which compare acalabrutinib and ibrutinib in patients with R/R CLL. The company undertook an unanchored MAIC for PFS, OS and AEs using data from the acalabrutinib arm of the ASCEND trial and the ibrutinib arm of the RESONATE trial. These trials recruited patients with R/R CLL. The MAIC was used to estimate relative treatment effects (HRs for PFS and OS, and differences in AEs). The results of the MAIC were used to justify an assumption of clinical equivalence between acalabrutinib and ibrutinib which is assumed to be applicable to all populations. Unanchored MAICs require all treatment effect modifiers and prognostic variables to be known and accounted for in the adjustment model. The results of the indirect comparison may be biased due to unmeasured confounders and are associated with substantial uncertainty. The ERG considers that the company's conclusion that acalabrutinib and ibrutinib are clinically equivalent is likely to be reasonable within the R/R CLL population. This was supported by the ERG's clinical experts and additional information provided in the company's response to clarification questions. It is unclear whether the assumption of clinical equivalence between acalabrutinib and ibrutinib is appropriate in high-risk CLL as no direct or indirect comparison is presented using data for this specific patient population.

What alternative approach has the ERG suggested?	The ERG considers that the use of a MAIC was appropriate for the R/R CLL population. Whilst the ERG considers the company's conclusion of equivalent efficacy to be reasonable, this is subject to uncertainty. It is unclear whether the company could have undertaken a meaningful indirect comparison using the 35 patients with del(17p)/TP53 mutations in the acalabrutinib arm of ELEVATE-TN, or whether an equivalent dataset exists for high-risk CLL patients treated with ibrutinib.
What is the expected effect on the cost-effectiveness estimates?	This is unclear.
What additional evidence or analyses might help to resolve this key issue?	The ongoing ELEVATE-RR non-inferiority trial is comparing acalabrutinib versus ibrutinib in patients with R/R CLL. This trial is scheduled to complete in 2021. This study may resolve existing uncertainty in the R/R population. It is unclear whether a robust indirect comparison could be undertaken using existing data for the high-risk CLL patients in ELEVATE-TN and an external study of ibrutinib (in patients with high-risk CLL).

Issue 3. Inclusion of high-risk CLL patients in untreated CLL model

Report section	Section 5.3.4 (Models 1 and 2)
Description of issue and why the ERG has identified it as important	The company's economic analysis for the untreated CLL population (Model 1) uses data from the intention-to-treat (ITT) population of ELEVATE-TN. Thirty-five of 179 (19.55%) patients in the acalabrutinib arm and 37 of 177 (20.90%) patients in the GClb arm of this trial had del(17p)/TP53 mutations. According to the CS, current first-line treatment for these patients is ibrutinib and the company presents a separate economic comparison of acalabrutinib versus ibrutinib for this population (Model 2). Whilst the use of the ITT population in Model 1 preserves randomisation, it also contaminates the population included in the untreated CLL analysis and leads to an inconsistency whereby the same high-risk CLL patients are included in two models with different comparators.
What alternative approach has the ERG suggested?	It may be appropriate to remove high-risk CLL patients from the datasets used to inform PFS outcomes in Model 1. However, in ELEVATE-TN, randomisation was stratified according to del(17p) but not TP53 mutations; excluding these patients may lead to confounding. The extent of this potential confounding is unclear and has not been assessed by the company.
What is the expected effect on the cost-effectiveness estimates?	The potential confounding associated with excluding high-risk CLL patients from the ITT population of ELEVATE-TN is unclear. The associated impact on the cost-effectiveness of acalabrutinib is unclear.
What additional evidence or analyses might help to resolve this key issue?	Re-analysis of the untreated CLL model excluding patients with del(17p) and TP53 mutations.

Issue 4. Costs of post-progression treatments overestimated

Report section	Section 5.3.4 (Model 1)
Description of issue and why the ERG has identified it as important	In the company's model for the untreated CLL population, all patients who progress and survive an additional [redacted] years ([redacted] model cycles) are assumed to receive second-line VenR (following first-line acalabrutinib) or second-line ibrutinib (following first-line GClb). These costs are applied in the model on a cyclical basis to all patients who remain alive in the post-progression state, irrespective of whether they are still progression-free (from the point of initiating second-line therapy). The Summary of Product Characteristics (SmPC) for venetoclax, rituximab and ibrutinib indicate that these treatments should be discontinued at the point of disease progression. As such, the company's model overestimates the costs of second-line treatment. This error disadvantages the GClb group, because second-line ibrutinib is assumed to be given over a long time period than VenR.
What alternative approach has the ERG suggested?	The company's model structure does not include a second progression event, which makes the estimation of second-line costs difficult. In response to comments received from the company during the factual accuracy check, the ERG constructed a separate costing model which works in the same way as the company's original model, but which estimates costs according to PFS, rather than OS. The ERG's costing model is based on parametric survival models fitted to reconstructed IPD on PFS for ibrutinib-treated patients with 1-2 prior lines, constrained by OS and general population mortality risks. A Weibull model was selected for inclusion in the ERG's preferred analysis. The costs of second-line treatment for a given patient who has progressed on first-line therapy are assumed to be dependent on the time of disease progression, as this impacts on general population mortality risk, the maximum number of remaining treatment cycles and the appropriate discounting multipliers in each remaining treatment cycle.
What is the expected effect on the cost-effectiveness estimates?	Excluding other aspects of the ERG's preferred analysis, the ERG-corrected ICER for acalabrutinib versus GClb is £32,298 per QALY gained. The ERG's additional sensitivity analyses show that the ERG's preferred ICER is sensitive to the choice of second-line PFS model.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that the correction applied in the ERG's preferred analysis is appropriate. No further evidence or analysis is required to resolve this issue.

Issue 5. Assumptions regarding fixed sequences of first- and second-line therapies for CLL

Report section	Section 5.3.4 (Model 1)
Description of issue and why the ERG has identified it as important	The company's economic analysis for the untreated CLL population (Model 1) assumes fixed sequences of therapy. The company assumes that the comparator sequence for patients with untreated CLL (Model 1) is first-line GClb followed by second-line ibrutinib. The CS argues that patients receiving a Bruton's tyrosine kinase (BTK) inhibitor (i.e. acalabrutinib) as first-line therapy would typically be ineligible for a BTK inhibitor (i.e. ibrutinib) at second-line; hence the sequence assumed in the intervention group is first-line acalabrutinib followed

	by second-line VenR. These sequences are particularly important drivers of the cost-effectiveness of acalabrutinib, as in the company's base case model, more than 78% of the total treatment costs in the comparator group are attributable to the use of second-line ibrutinib. The ERG has several concerns regarding the sequences included in the model: (1) The second-line treatments included in the model do not reflect the second-line treatments received by patients in ELEVATE-TN. This introduces an inconsistency between the assumptions in the model and the experience of the ELEVATE-TN trial. (2) The evidence used to inform OS (via PPS) in the model does not relate to the assumed sequences included within it. (3) The model assumes that second-line VenR is more effective than second-line ibrutinib, based on unadjusted arm-based analyses of OS from MURANO and RESONATE. (4) The costs of second-line treatment, particularly for second-line ibrutinib in the comparator group, are erroneously inflated due to the error described in Issue [4] above. Taken together with point (2) above, the company's model is predisposed to disadvantage any sequence which includes ibrutinib rather than VenR in the second-line position of the sequence. (5) Clinical advisors to the ERG suggest that some patients currently receive second-line VenR following first-line GClb. At their list prices, second-line VenR is less expensive than ibrutinib per patient treated.
What alternative approach has the ERG suggested?	Amongst other model amendments, the ERG's preferred analysis: (i) uses the same PPS distribution for both treatment groups, (ii) corrects the error relating to post-progression treatment costs (see Issue [4]) and (iii) assumes that following progression on GClb, [redacted]% of patients will receive ibrutinib and the remaining [redacted]% of patients will receive VenR. An additional ERG sensitivity analysis is presented in which all progressed patients who receive first-line acalabrutinib or GClb receive second-line VenR.
What is the expected effect on the cost-effectiveness estimates?	Assuming that following progression on GClb, [redacted]% of patients receive second-line VenR and [redacted]% of patients receive second-line ibrutinib, the ICER for acalabrutinib versus GClb is estimated to be £41,653 per QALY gained. If all progressed patients in both groups receive second-line VenR, the ICER increases to £141,889 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The available OS data from ELEVATE-TN are immature. The ERG does not believe that there are any direct head-to-head studies which include the specific sequences of therapies included in the untreated CLL analysis (Model 1). Aside from conducting a new RCT which includes the sequences included in the company's model, it is unclear how this uncertainty could be resolved.

Issue 6. Potentially pessimistic PFS model for GClb

Report section	Section 5.3.4 (Model 1)
Description of issue and why the ERG has identified it as important	Within the economic analysis for the untreated CLL population (Model 1), the company selected log-normal distributions to represent TTP and PPM for the GClb group. This log-normal model suggests that approximately [redacted] of patients are alive and progression-free at 5 years. The minutes of the company's UK CLL advisory board meeting indicate that the company's clinical advisors preferred the generalised gamma model for PFS in both treatment groups. According to the CS, the company rejected this model for the acalabrutinib group because of model-fitting issues. The company rejected this model for the GClb group because *"the tail of the extrapolation was not observed in any of the other fitted curves of TTP data for chlorambucil plus obinutuzumab and lacked clinical validity."* The ERG agrees that it is reasonable to reject the use of generalised gamma within the acalabrutinib group. However, the ERG believes that the generalised gamma distribution for PFS may be appropriate in the GClb group because: (a) The company's clinical advisory board attendees appear to have preferred this model (b) The long-term analysis of the UK CLL11 trial suggests that 23% of patients in the GClb arm were still alive and progression-free at 5 years (54 patients still at risk at 5-years, median follow-up 59.4 months). This is considerably higher than the 5-year PFS probability indicated by the log-normal model ([redacted]). The generalised gamma PFS model indicates a 5-year PFS probability of approximately [redacted], which is less pessimistic than the company's selected model. (c) The ERG's clinical advisors supported the use of a less pessimistic PFS model for GClb.
What alternative approach has the ERG suggested?	Based on the set of parametric models considered, the ERG prefers the generalised gamma model for PFS in the GClb group. This is included in the ERG's preferred analysis.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of the generalised gamma PFS distribution for the GClb group in the ERG's corrected model increases the ICER for acalabrutinib from £32,298 to £45,921 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up from ELEVATE-TN will help to resolve this uncertainty. For the purposes of decision-making, further views regarding long-term expectations of PFS from independent clinical experts may be useful.

Issue 7. Highly optimistic assumptions regarding overall survival benefit for acalabrutinib

Report section	Section 5.3.4 (Model 1)
Description of issue and why the ERG has identified it as important	The available OS data from ELEVATE-TN are immature; less than [redacted] of patients died in any treatment arm. Any estimate of the relative survival advantage acalabrutinib over GClb, should it exist, is highly uncertain. The company's economic analysis for the untreated CLL

	population (Model 1) estimates OS as a function of TTP, PPM and PPS. TTP and PPM are modelled using parametric survival models fitted to data from ELEVATE-TN. In the acalabrutinib group, PPS is modelled using external OS data from the VenR arm of MURANO (applied as PPS in the acalabrutinib group) and the ibrutinib arm of RESONATE (applied as PPS in the GClb group). The ERG notes: • There is limited evidence to demonstrate an OS advantage for acalabrutinib versus GClb • As discussed in Issue [5], the CS does not present any randomised evidence to support estimates of OS relating to the specific sequences of treatments included in the model • Modelled OS is strongly influenced by general population mortality risks • Apparent differences between PPS for VenR and ibrutinib from MURANO and RESONATE may be a consequence of confounding resulting from unadjusted arm-based comparisons across trials • The company's model implies that a large proportion (at least [redacted]) of patients treated with acalabrutinib are cured. • Predicted OS for the acalabrutinib group is similar to that for the general population, with only a minimal loss of life expectancy (modelled acalabrutinib OS = [redacted] years; general population OS = 15.56 years). Given the limited evidence to support a survival advantage for acalabrutinib in untreated CLL, the ERG believes that the company's modelled results should be considered to be highly optimistic.
What alternative approach has the ERG suggested?	The ERG's preferred analysis uses the PPS function from RESONATE in both treatment groups as this leads to less favourable projections of OS. It is however unclear whether other more relevant sources exist.
What is the expected effect on the cost-effectiveness estimates?	Applying the same PPS function to both groups in the ERG's corrected model leads to an ICER for acalabrutinib versus GClb of £34,112 per QALY gained. Assuming zero incremental survival gain for acalabrutinib versus GClb increases the ICER to £92,985 per QALY gained. The ERG notes that given the observed PFS gain in ELEVATE-TN, the latter ICER is particularly pessimistic.
What additional evidence or analyses might help to resolve this key issue?	It is unclear whether the use of more flexible parametric models for all time-to-event outcomes would produce less optimistic OS estimates. Longer-term follow-up from ELEVATE-TN may provide evidence to suggest a survival advantage. However, as this trial does not include treatment arms which relate to the fixed sequences of first- and second-line therapies included in the model, this will not fully resolve the issue. Further clinical input on expected outcomes may be valuable.

Issue 8. Health utilities assumed to be better than those for the general population

Report section	Section 5.3.4 (Model 1)
Description of issue and why the ERG has	The utility value used in the progression-free state (utility=[redacted], from ELEVATE-TN) is higher than the mean EQ-5D score for the age- and

identified it as important	sex-matched population from Ara and Brazier (age 70 years, 38% female, estimated EQ-5D = 0.78). The ERG does not believe that patients with CLL have a better level of health-related quality of life (HRQoL) compared with the general population. The basis for estimating the post-progression utility value is unclear, as Holzner *et al* does not report preference-based utility values and the value of 0.60, which is assumed in the model, is not reported in the Holzner *et al* paper. Despite this, the ERG notes that this post-progression utility value has been used in several previous NICE technology appraisals in CLL.
What alternative approach has the ERG suggested?	The ERG believes that it would be more appropriate to use the utility value of 0.78 from Ara and Brazier for patients who are progression-free. Given earlier precedents, it may be reasonable to apply the post-progression utility value of 0.60. However, it should be noted that this is applied to all remaining survival time in the progressed disease state, irrespective of any additional progression-free benefit associated with second-line treatments. This is because the model structure includes only one progression event. The ERG's preferred analysis uses the EQ-5D estimate from Ara and Brazier in the progression-free health state. Owing to limitations in the model structure and the available evidence, no amendment was made to the utility value applied to the progressed disease state.
What is the expected effect on the cost-effectiveness estimates?	Applying the progression-free utility value from Ara and Brazier within the ERG's corrected model increases the ICER for acalabrutinib versus GClb to £35,153 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that the ERG's preferred analysis adequately addresses this issue.

Issue 9. Absence of comparative evidence for acalabrutinib versus ibrutinib high-risk CLL

Report section	Section 5.3.4 (Model 2)
Description of issue and why the ERG has identified it as important	The company's CMA for the high-risk CLL population (Model 2) is based on the findings of the MAIC undertaken using data from trials in patients with R/R CLL. The company's implemented CMA uses time-to-event data from the acalabrutinib arm of the untreated CLL analysis (Model 1), which relates to the ITT population of the ELEVATE-TN trial. The CS does not present any direct or indirect comparison of acalabrutinib versus ibrutinib specifically in patients with del(17p) or TP53 mutations.
What alternative approach has the ERG suggested?	The CS does not contain any comparative evidence for acalabrutinib versus ibrutinib in the high-risk CLL population. The results of the company's CMA (Model 2) should therefore be interpreted with caution.
What is the expected effect on the cost-effectiveness estimates?	This is unclear as no evidence is presented for this specific population. [redacted].
What additional	As noted in Issue [2], it is unclear whether the company could have

evidence or analyses might help to resolve this key issue?	undertaken a meaningful indirect comparison using the 35 patients with del(17p) and TP53 mutations in the acalabrutinib arm of ELEVATE-TN, or whether an equivalent dataset exists for high-risk CLL patients treated with ibrutinib.

1.6 Summary of ERG's preferred assumptions and resulting ICERs

The results of the ERG's exploratory analyses for the untreated CLL population are summarised in Table 2. Each analysis reflects individual model amendments relative to the ERG-corrected version of the model (EA1). The ERG's preferred analysis suggests that the ICER for acalabrutinib versus GClb is £61,702 per QALY gained. Additional sensitivity analyses indicate that the ICER for acalabrutinib may be markedly higher when second-line VenR is given following first-line GClb and when the model includes less optimistic assumptions regarding the incremental OS gains attributable to acalabrutinib.

Table 2: Summary of ERG preferred assumptions and ICER - Untreated CLL population

Exploratory analysis*	Incremental QALYs	Incremental cost	ICER (Change from company's base case)
Company's updated base case	[redacted]	[redacted]	**£22,679**
EA1: Correction of errors and outdated data sources	[redacted]	[redacted]	£32,298 (+£9,619)
EA2: Generalised gamma TTP and PPM for GClb	[redacted]	[redacted]	£45,921 (+23,242)
EA3: Use of RESONATE PPS in both groups	[redacted]	[redacted]	£34,112 (+£11,433)
EA4: Progression-free utility from Ara and Brazier	[redacted]	[redacted]	£35,153 (+12,474)
EA5: Inclusion of RDI	[redacted]	[redacted]	£28,448 (+£5,769)
EA6: Inclusion of wastage	[redacted]	[redacted]	£32,641 (+£9,962)
EA7: Second-line treatment mix for comparator ([redacted]% VenR; [redacted]% ibrutinib)	[redacted]	[redacted]	£41,653 (+£18,974)
EA8: ERG's preferred analysis	[redacted]	[redacted]	**£61,702 (+39,023)**
ASA1: Acalabrutinib followed by VenR versus GClb followed by VenR	[redacted]	[redacted]	£141,889 (+£119,210)
ASA2a: ERG's preferred analysis with 50% of incremental OS gain	[redacted]	[redacted]	£73,535 (+£50,856)
ASA2b: ERG's preferred analysis with zero incremental OS gain	[redacted]	[redacted]	£92,985 (+£70,306)
ASA3a: Second-line PFS (Gompertz)	[redacted]	[redacted]	£65,572 (+£3,870)
ASA3b: Second-line PFS (Log-normal)	[redacted]	[redacted]	£40,935 (-£20,767)

EA – exploratory analysis; ASA – additional sensitivity analysis (based on the ERG's preferred analysis); QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; VenR – venetoclax plus rituximab
**All exploratory analyses are based on the corrections applied in exploratory analysis 1.*

Table 3 and Table 4 present the results of the ERG's exploratory analyses using the company's CMAs for the high-risk CLL and R/R CLL populations, respectively. In both populations, the ERG's preferred analyses suggest that acalabrutinib is expected to generate cost-savings compared with ibrutinib. However, the ERG advises caution with respect to the high-risk CLL analysis, as the CS does not present any comparative evidence for this specific population and the time-to-event data included in the model are based on the overall ITT population of ELEVATE-TN.

Table 3: Summary of ERG preferred assumptions and cost difference – High-risk CLL population (Model 2)

Exploratory analysis	Incremental QALYs	Incremental cost	ICER (change from company base case)
Company's updated base case	0.00 (assumed)	[redacted]	N/a
EA8: ERG's preferred analysis	0.00 (assumed)	[redacted]	N/a

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; EA – exploratory analysis; ERG – Evidence Review Group

Table 4: Summary of ERG preferred assumptions and cost difference – R/R CLL population (Model 3)

Exploratory analysis	Incremental QALYs	Incremental cost	ICER (change from company base case)
Company's updated base case	0.00 (assumed)	[redacted]	N/a
EA8: ERG's preferred analysis	0.00 (assumed)	[redacted]	N/a

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; EA – exploratory analysis; ERG – Evidence Review Group

The ERG's full critique of the company's economic analyses and the ERG's exploratory analyses can be found in the main ERG report (Sections 5.3 and 5.4, respectively).

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease and the current treatment pathway for chronic lymphocytic leukaemia (CLL) in England.

2.1 Critique of the company's description of the underlying health problem

The company's submission (CS) contains a useful and accurate overview of CLL. CLL is the most common type of leukaemia and is characterised by the abnormal clonal proliferation and accumulation of mature and typically CD5-positive B-lymphocytes within the blood, bone marrow, lymph nodes, and spleen.[1] CLL is more common in men than in women; 3,157 new cases of CLL were diagnosed in England in 2017.[2] The incidence of CLL rises sharply from around age 45-49 years, with the highest rates in men aged 85-89 years and women aged 90+ years.[2]

CLL impacts both on patients' expected survival and health-related quality of life (HRQoL). Many patients with CLL are asymptomatic at the time of diagnosis and will have indolent disease which may not require treatment until the onset of symptoms many years later. The CS[1] highlights that disease stage at diagnosis has prognostic implications for survival. The two most widely-used staging systems are the Rai classification system and the Binet staging system[3, 4] (see Table 5). With both staging systems, patients with high-risk disease or advanced stage (i.e. Rai stage III-IV; Binet stage C) have a poorer survival prognosis, whereas low-risk or early-stage (i.e. Rai stage 0; Binet stage A) have a median survival time of more than 10 years. The presence of high-risk cytogenetic factors, particularly deletion of chromosome 17p (del(17p)) or mutation of the tumour protein p53 (TP53) gene, typically predict an aggressive disease course and a particularly poor prognosis.

The CS[1] also highlights that CLL places a significant emotional, psychological and physical burden on patients, leading to marked impacts on patients' HRQoL. The CS describes the impact associated with the symptom burden of the disease on patients' quality of life, particularly in terms of fatigue and sleep disturbance. In addition, the CS notes that further negative impacts on HRQoL may arise as a consequence of adverse events (AEs) associated with active treatments for CLL and anxiety and depression associated with having a positive diagnosis of the disease, including impacts on patients who are not currently receiving treatment.

Table 5: Summary of Rai and Binet CLL staging systems (reproduced from CS Table 4, based on Eichorst *et al*, 2015)

Stage	Description	Predicted median survival*
Rai system		
Low risk		
0	Lymphocytosis: lymphocytes in blood > 5×10^9/L, clonal B cells and > 40% lymphocytes in the bone marrow	> 10 years
Intermediate risk		
I	Lymphocytosis and lymphadenopathy	> 8 years
II	Lymphocytosis and hepatomegaly and/or splenomegaly with or without lymphadenopathy	
High risk		
III	Lymphocytosis and haemoglobin < 11.0 g/dL with or without lymphadenopathy or organomegaly	6.5 years
IV	Lymphocytosis and thrombocytes < 100×10^9/L with or without lymphadenopathy or organomegaly	
Binet system		
Binet A	Haemoglobin ≥ 10.0 g/dL, thrombocytes ≥ 100×10^9/L, < 3 lymph nodes involved	> 10 years
Binet B	Haemoglobin ≥ 10.0 g/dL, thrombocytes ≥ 100×10^9/L, ≥ 3 lymph nodes involved	> 8 years
Binet C	Haemoglobin < 10.0 g/dL, thrombocytes < 100×10^9/L	6.5 years

** Survival data are from Pflug et al. 2014,[3] based on Phase 3 trials conducted between 1997 and 2006 by the German CLL Study Group*
CLL - chronic lymphocytic leukaemia

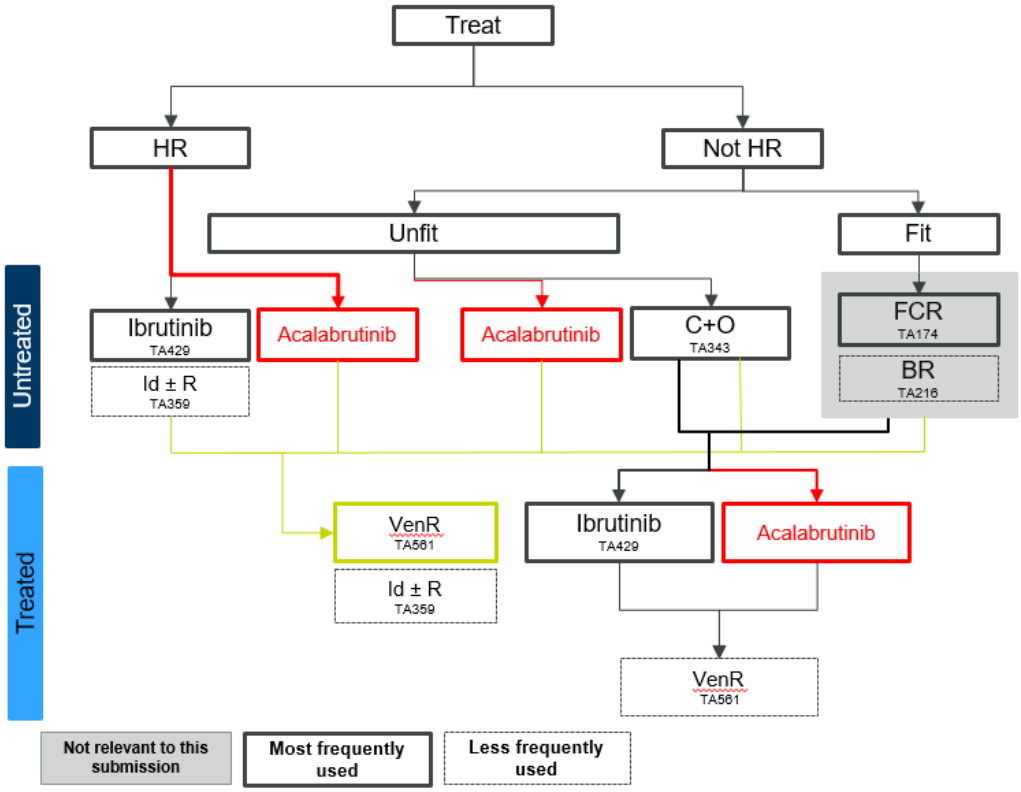
2.2 Critique of the company's overview of current service provision

As described in the CS,[1] the treatment pathway for CLL has evolved over time as a consequence of recommendations made by the National Institute for Health and Care Excellence (NICE), together with guidance from the British Society of Haematology (BSH) as well as international bodies including the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL), the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN). The current pathway for CLL is complex, with different options available according to whether patients have previously received treatment and according to the presence or absence of high-risk cytogenetic factors (del(17p) and TP53 mutations). The CS focusses on three populations, for whom treatment options are different: (1) patients with untreated CLL without high-risk cytogenetic features for whom treatment with fludarabine, cyclophosphamide and rituximab (FCR) and bendamustine plus rituximab (BR) are unsuitable; (2) patients with untreated CLL with high-risk cytogenetic features (del(17p) and TP53 mutations), and (iii) patients with previously treated (relapsed/refractory [R/R]) CLL. This latter group is not differentiated in terms of the presence or absence of high-risk cytogenetic features. The company's view of the current treatment pathway, including the proposed positioning of acalabrutinib in each of these three populations, is shown in Figure 1. The CS also summarises previous NICE technology appraisals (TAs) in CLL, as reproduced in Table 7.

Treatment options for CLL are guided by patient characteristics including: fitness, which is usually determined according to age; the presence of comorbidities and organ function; the presence of high-risk features (cytogenetic abnormalities such as del(17p) and TP53 mutations); patient choice and other social factors.[1] The CS notes that there are no standard criteria for determining patient fitness in current clinical practice. However, patients with a Cumulative Illness Rating Scale (CIRS) score of ≤6 and a creatinine clearance (CrCl) level of ≥70mL/min (usually aged ≤65 years) may be considered fit enough to tolerate aggressive regimens such as FCR. Within the untreated CLL population (without high-risk cytogenetic features), the CS focusses on unfit patients who do not meet these criteria and for whom aggressive treatments such as FCR would not be suitable.

The CS[1] states that for the untreated CLL population without high-risk cytogenetic features, current first-line treatment is obinutuzumab plus chlorambucil (GClb). For patients with untreated high-risk CLL (del(17p)/TP53 mutations) and patients with R/R CLL, the CS states that current practice is treatment with ibrutinib. The company's view regarding appropriate comparators is detailed further in Section 3.3. Clinical advisors to the ERG agreed with the company's view regarding current practice for the untreated CLL populations with and without high-risk cytogenetic features. For patients with R/R CLL, the clinical advisors noted that whilst ibrutinib is most commonly used, other treatment options are also available, including: venetoclax plus rituximab (VenR), venetoclax monotherapy (via the Cancer Drugs Fund [CDF]) and idelalisib plus rituximab (IR). The clinical advisors noted however that IR is rarely used due to increased risks of infection, morbidity and potentially death.

Figure 1: Clinical pathway of care and proposed position of acalabrutinib (reproduced from CS Figure 1)



BR – bendamustine plus rituximab; C+O – chlorambucil plus obinutuzumab; FCR - fludarabine, cyclophosphamide, and rituximab; HR - high-risk, defined as mutation status of TP53 or Del17p; Id ± R - idelalisib ± rituximab; VenR – venetoclax plus rituximab
Note: Excluded from algorithm - Venetoclax monotherapy currently in CDF in R/R CLL (TA487)
Sources: TA429,[5] TA359,[6] TA343,[7] TA174,[8] TA216,[9] TA561,[10] and TA487[11]

Table 6: Current NICE guidance in CLL (reproduced from CS Table 9)

Therapy line	Regimen (NICE TA)	Conditions of use
Untreated CLL[a]	**For patients without a 17p deletion or TP53 mutation**	
	Rituximab in combination with fludarabine and cyclophosphamide (TA174)[8b]	For whom fludarabine in combination with cyclophosphamide is considered appropriate
	Bendamustine +/- rituximab (TA216)[9]	For those who cannot have fludarabine combination chemotherapy
	Chlorambucil + rituximab (no TA published)[c]	
	Obinutuzumab + Chlorambucil (TA343)[7]	For whom fludarabine-based therapy and bendamustine based therapy is unsuitable
	For patients with a 17p deletion or TP53 mutation	
	Ibrutinib monotherapy (TA429)[5]	For whom chemoimmunotherapy is unsuitable
	Idelalisib with rituximab (TA359)[6]	For those with a 17p deletion or TP53 mutation
	Venetoclax (TA487)[11]	With a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, funded by CDF
Previously treated CLL	Venetoclax with rituximab (TA561)[10]	For people who have had at least 1 previous therapy
	Rituximab in combination with fludarabine and cyclophosphamide (TA193)[12]	For people not refractory to fludarabine and who have not been previously treated with rituximab[d]
	Idelalisib with rituximab (TA359)[6]	For people whose disease has been treated but has relapsed within 24 months
	Ibrutinib (TA429)[5]	For people who have had at least 1 previous therapy
	Venetoclax (TA487)[11]	With a 17p deletion or TP53 mutation whose disease has progressed after a B-cell receptor pathway inhibitor *OR* without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor, funded by CDF

a ID1613 (acalabrutinib), ID2708 (ibrutinib) and ID1401 (venetoclax) in progress.
b Fludarabine monotherapy (TA119) not recommended.
c Use of chlorambucil, with or without rituximab, is detailed in TA343.
d Unless treated within the context of a clinical trial either at a lower dose than licensed or in combination with chemotherapy other than fludarabine and cyclophosphamide.
CL – chronic lymphocytic leukaemia; NICE – National Institute for Health and Care Excellence; TA – technology appraisal; CDF – Cancer Drugs Fund

3. CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final scope issued by NICE[13] and addressed in the CS is presented in Table 7.

Table 7: Company's statement of the decision problem (reproduced from CS, Table 2)

	Final scope issued by NICE	Decision problem addressed in CS	Rationale if different from the final NICE scope
Population	People with CLL (includes untreated and treated)	As per scope	N/a
Intervention	Acalabrutinib alone or with obinutuzumab	Acalabrutinib monotherapy in: • Previously untreated adults with CLL who are ineligible for FCR therapy, or • Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable, or Adults with R/R CLL who have had at least one previous therapy	Efficacy and safety data are available for acalabrutinib monotherapy in both untreated and, R/R patients from the pivotal Phase 3 RCTs ELEVATE-TN and ASCEND, respectively, and in patients receiving treatment with acalabrutinib in combination with obinutuzumab in the untreated patients only. However, feedback from UK clinical experts noted that acalabrutinib monotherapy is preferred due to the AEs associated with obinutuzumab.[14] Therefore, based on clinical feedback and the feasibility of demonstrating a cost-effective case, AstraZeneca is seeking for reimbursement for acalabrutinib monotherapy only.
Comparator(s)	For untreated CLL, including (but not limited to): • ibrutinib (17p deletion or TP53 mutation) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab • obinutuzumab with chlorambucil • bendamustine with or without rituximab • rituximab with fludarabine and cyclophosphamide • venetoclax with obinutuzumab (subject to NICE appraisal)	Previously untreated patients with CLL who are ineligible for FCR therapy: • obinutuzumab with chlorambucil Previously untreated adults with CLL who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable: • ibrutinib Adults with R/R CLL who have had at least one previous therapy: • ibrutinib	Previously untreated patients with CLL who are ineligible for FCR therapy: • Data informing the clinical and pharmaco-economic evaluation of patients with previously untreated CLL is taken from the ELEVATE-TN study, which only includes patients who are ineligible for FCR-based therapy. Therefore, patients who are eligible, or fit enough to receive FCR therapy are not considered in this appraisal.[15] • BR therapy is generally only considered for fitter patients in whom FCR is contra-indicated due to specific comorbid conditions.[16] • UK clinical experts concluded that the use of BR therapy has diminished in UK clinical practice, and it's use is more often seen in clinical trials.[14]

	Final scope issued by NICE	Decision problem addressed in CS	Rationale if different from the final NICE scope
	For treated CLL, including (but not limited to): • bendamustine with or without rituximab • venetoclax with rituximab • ibrutinib • rituximab with fludarabine and cyclophosphamide • idelalisib with rituximab		• Chlorambucil with or without rituximab is not routinely used in UK clinical practice, and the BSH guidelines states that its use is not routinely recommended.[16] • Venetoclax with obinutuzumab is not considered a relevant comparator as at the time of submission, the appraisal is ongoing.[17] Therefore, venetoclax with obinutuzumab is not routinely commissioned by NHS England, and it does not represented established NHS practice. Previously untreated adults with CLL who have a 17p deletion or TP53 mutation in whom chemo-immunotherapy is unsuitable: • Patients typically receive treatment with ibrutinib, in line with the recommendations in TA429.[5] • UK clinical experts, and NICE have previously concluded that, idelalisib with rituximab is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab.[14] • The licence for idelalisib therapy has been amended to *"first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies"*[18] Therefore, idelalisib therapy is not a relevant comparator.

	Final scope issued by NICE	Decision problem addressed in CS	Rationale if different from the final NICE scope
			Adults with R/R CLL who have had at least one previous therapy: • Patients often receive treatment with ibrutinib as second-line therapy. • Since the introduction of ibrutinib in UK clinical practice, the use of FCR-based therapy, or idelalisib plus rituximab has diminished and no longer reflects established NHS practice.[5, 14] • As previously discussed, FCR therapy is typically reserved for younger, fitter patients, and its use is not advised in patients who have not responded to prior chemoimmunotherapy, relapsed within 24–36 months of intensive chemoimmunotherapy, whilst idelalisib plus rituximab is associated with significant AEs.[5, 16] • Venetoclax with rituximab does not currently represent established NHS clinical practice as its utilisation is low, with only 1-7% patients currently treated with this regimen. UK clinicians advised that the 5-week ramp-up dosing regimen and the requirements for monitoring of TLS has resulted in clinicians typically preferring to use ibrutinib as second-line therapy, whilst venetoclax with rituximab is more often used subsequently[14] or in patients with a cardiac history who cannot tolerate ibrutinib. Further information is available in CS[1] Section B.1.1.1.

	Final scope issued by NICE	Decision problem addressed in CS	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Time to next treatment • Adverse effects of treatment • Health-related quality of life.	As per scope	N/a
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-minimisation analysis may be carried out. 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 perspective. The availability and cost of biosimilar products should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	• Cost-effectiveness of acalabrutinib versus obinutuzumab with chlorambucil in previously untreated patients with CLL: • Cost-minimisation analysis of acalabrutinib versus ibrutinib in previously untreated adults with CLL who have a 17p deletion or TP53 mutation: • Cost-minimisation analysis of acalabrutinib versus ibrutinib in adults with R/R CLL	N/a

	Final scope issued by NICE	Decision problem addressed in CS	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People with a 17p deletion or TP53 mutation • People untreated • People treated • People for whom fludarabine-based therapy is unsuitable • People for whom bendamustine-based therapy is unsuitable • People with IgHV unmutated disease	Subgroups considered: • People with a 17p deletion or TP 53 mutation • People untreated • People treated • People for whom fludarabine-based therapy is unsuitable • People for whom bendamustine-based therapy is unsuitable	The pharmacoeconomic evaluation of acalabrutinib is informed from the pivotal Phase 3 RCT evidence from the ELEVATE-TN and ASCEND trials, in patients either previously untreated or treated, respectively. Data from the ELEVATE-TN trial only includes patients in whom FCR-based therapy is unsuitable. A proxy for the comparative efficacy of high-risk patients, defined as having a 17p deletion or TP53 mutation, are considered using the ITT data from the ASCEND trial, and compared with the current standard of care, ibrutinib via a MAIC. As per the approach adopted in NICE TA429, in the absence of any direct head-to-head data in previously untreated patients with a 17p deletion of TP53 mutation, we have compared the efficacy and safety of acalabrutinib versus ibrutinib via a MAIC using data from previously treated patients in the ASCEND and RESONATE trials as a proxy for previously untreated patients.[5] In NICE TA429, the committee accepted that in the absence of any evidence, the data from previously treated patients could be taken into account and led to a positive recommendation in first line high-risk patients.[5]

AEs - adverse events; BR - bendamustine plus rituximab; BSH - British Society of Haematology; CLL - chronic lymphocytic leukaemia; FCR - fludarabine, cyclophosphamide and rituximab-based; IgHV - immunoglobulin heavy chain variable region; MAIC - matching-adjusted indirect comparison; QALY - quality-adjusted life year; RCT - randomised controlled trial; R/R -, relapsed or refractory; TLS - tumour lysis syndrome; ITT – intention-to-treat

3.1 Population

The patient population in the CS[1] relates to people with CLL, including patients who are treatment-naïve and patients who have received prior treatment. Within the previously untreated CLL population, the CS specifically focusses on patients for whom aggressive treatments such as FCR or BR are unsuitable, based on the characteristics of the population enrolled in the ELEVATE-TN trial. The company's economic analyses are presented for three populations:

1. Patients with untreated CLL without high-risk cytogenetic features (del(17p)/TP53 mutations) for whom treatment with FCR/BR is unsuitable. This population is hereafter referred to as the "untreated CLL population."
2. Patients with untreated CLL with high-risk cytogenetic features (del(17p)/TP53 mutations). This population is hereafter referred to as the "high-risk CLL population."
3. Patients with previously treated CLL. This population is hereafter referred to as the "R/R CLL population."

This is in line with the population defined in the final NICE scope.[13] However, the company's decision to focus on the FCR/BR ineligible population means that the population considered in the CS is narrower than the anticipated marketing authorisation set out in the draft Summary of Product Characteristics (SmPC)[19] for acalabrutinib, which states the following indications for acalabrutinib:

[redacted]

The CS does not present any clinical or economic evidence to support the use of acalabrutinib in fit patients for whom treatment with FCR or BR would be suitable. The company is not seeking reimbursement in this population.

The ELEVATE-TN trial,[20] the pivotal study of acalabrutinib in the untreated CLL population (which includes a proportion of patients with del(17p) and TP53 mutations), was conducted in 142 sites including Europe, North America, South America and Australasia. Of these, [redacted] trial sites were based in the UK with [redacted] UK patients enrolled in total. The ASCEND trial,[21] the pivotal study of acalabrutinib in patients with previously treated (R/R) CLL, was conducted in 102 sites including Europe, North America, Asia and Australasia. Of these, [redacted] trial site was based in the UK, with [redacted] UK patients enrolled. The clinical advisors to the ERG were satisfied that the populations recruited into ELEVATE-TN and ASCEND broadly reflect the populations of patients who would be eligible for treatment with acalabrutinib in England.

As acalabrutinib has not yet received a European/UK marketing authorisation, it is not yet clear whether certain medical conditions or patient groups may be contraindicated for treatment. [redacted]

3.2 Intervention

The intervention considered in the CS[1] is 100mg acalabrutinib twice daily (2 x 100mg tablets). Acalabrutinib (ACP-196, Calquence®) is a selective small-molecule inhibitor of Bruton's tyrosine kinase (BTK) which is manufactured by Astra Zenecca Ltd. Acalabrutinib was granted an orphan designation (EU/3/16/1624) in March 2016. In July 2020, the Committee for Medicinal Products for Human Use (CHMP) granted a positive opinion, recommending the granting of a marketing authorisation for acalabrutinib for the indications set out in Section 3.1. According to the CS, the company anticipated that a decision would be made in [redacted].

At the time of submission, the list price for acalabrutinib had not been confirmed. The anticipated list price per pack of 60 x 100mg acalabrutinib tablets (30 days' supply) is [redacted].[1] The company has proposed a Patient Access Scheme (PAS) which takes the form of a simple price discount of [redacted]; the discounted cost per pack of acalabrutinib is [redacted].

[redacted]

[redacted]

the CS[1] focusses only on the use of acalabrutinib as monotherapy. According to the CS, this decision was taken based on clinical advice relating to the comparative adverse event (AE) profiles of acalabrutinib in combination therapy and as monotherapy, and based on the feasibility of supporting claims regarding the cost-effectiveness of acalabrutinib.

3.3 Comparators

The final NICE scope[13] lists seven comparators in the untreated CLL population and five comparators in the previously treated (R/R) CLL population.

For the untreated CLL population, the NICE scope[13] includes: (i) ibrutinib (del(17p) or TP53 mutation); (ii) idelalisib with rituximab (IR; del(17p) or TP53 mutation); (iii) chlorambucil with or without rituximab; (iv) obinutuzumab plus chlorambucil (GClb); (v) bendamustine with or without rituximab; (vi) rituximab with fludarabine and cyclophosphamide (FCR) and (vii) venetoclax with obinutuzumab.

For the previously treated (R/R) CLL population, the NICE scope[13] includes: (i) bendamustine with or without rituximab; (ii) VenR; (iii) ibrutinib; (iv) FCR, and (v) IR.

In each of the three economic analyses presented in the CS,[1] the company considers a single comparator. In the untreated CLL population (without high-risk cytogenetic features), this is assumed to be obinutuzumab plus chlorambucil (GClb), whilst in the high-risk CLL and previously-treated (R/R) CLL populations, the comparator is assumed to be ibrutinib.

With respect to the untreated CLL population (without high-risk cytogenetic features), the CS[1] argues that:

- FCR and BR are not appropriate comparators as these treatments are considered unsuitable for "unfit" patients, noting that the population recruited into ELEVATE-TN[20] excludes those patients who would be suitable for FCR
- Chlorambucil with or without rituximab is not routinely used in UK clinical practice and NICE has not issued a positive recommendation for this therapy, therefore it does not represent NHS standard care
- Venetoclax plus obinutuzumab is the subject of an ongoing NICE appraisal[17] and currently does not reflect standard care in the UK
- GClb is the standard of care for patients with untreated newly diagnosed CLL who are considered unfit for chemo-immunotherapy (e.g. FCR). The CS notes that this is in line with the recommendations from the BSH and was supported by nine haematologists who attended the UK CLL advisory board meeting held by the company.[14]

With respect to the untreated high-risk CLL population with del(17)p/TP53 mutations, the CS[1] argues that:

- IR is not routinely used in clinical practice and its use has been superseded by ibrutinib due to the higher risk of infection and death associated with IR.
- Ibrutinib has become established NHS care for this patient population.

With respect to the R/R setting, the CS[1] argues that:

- Ibrutinib is established NHS practice and is therefore a relevant comparator. This view was supported by the haematologists who attended the company's UK CLL advisory board[14]

- FCR is not commonly used in patients with R/R CLL patients and therefore this regimen does not represent established NHS practice
- IR is not commonly used because it has a more intensive dosing regimen than ibrutinib and is associated with an increased risk of infection and toxicity
- Whilst VenR was recommended by NICE (TA561),[10] only a small proportion of patients currently receive treatment with this regimen after first relapse.

Within the untreated CLL population (without high-risk cytogenetic features), GClb reflects the comparator regimen included in the ELEVATE-TN trial.[20] In the high-risk CLL and R/R CLL populations, no head-to-head evidence is available to compare acalabrutinib versus ibrutinib; hence, an indirect comparison was required. The company's indirect comparison is detailed and critiqued in Sections 4.3 and 4.4.

The clinical advisors to the ERG agreed that GClb reflects the current standard of care for patients with untreated CLL (without high-risk cytogenetic features) who are unsuitable for treatment with FCR or BR. Within the untreated high-risk CLL population, they also agreed that the comparator should be ibrutinib, as IR is not commonly used due to its comparatively worse toxicity profile and risk of infection and death. In the previously treated (R/R) CLL population, the ERG's clinical advisors agreed that ibrutinib is commonly used following chemotherapy in this patient group, but noted that other options are also recommended as treatment options by NICE, including: VenR (given for a maximum of 2 years); venetoclax monotherapy (no maximum treatment duration, available through the CDF), and IR (again, the clinical advisors noted that this is not commonly used due to its toxicity profile). The ERG notes that the results of the company's matching adjusted indirect comparison (MAIC) and cost-minimisation analysis (CMA) for the R/R population are relevant only to patients who would otherwise be treated with ibrutinib; the CS does not present comparisons of acalabrutinib against other currently used second-line treatments e.g. VenR.

The ERG notes that comparator Patient Access Scheme (cPAS) discounts are available for obinutuzumab, chlorambucil, and ibrutinib. In addition, cPAS discounts are available for venetoclax and rituximab, which are assumed to be given as second-line treatments following progression on acalabrutinib in the company's economic analysis in the untreated CLL population (Model 1, see Section 5.2.2). These discounts are confidential and cannot be reported here. The impact of these price discounts on the cost-effectiveness of acalabrutinib is presented in a separate confidential appendix to this ERG report.

3.4 Outcomes

Outcomes listed in the final NICE scope[13] include:

- Progression-free survival (PFS)
- Overall survival (OS)
- Time to next treatment (TTNT)
- Adverse effects of treatment (AEs)
- Health-related quality of life (HRQoL).

The CS[1] reports clinical results from ELEVATE-TN[20] for PFS, OS, TTNT and AEs. Limited data on HRQoL were presented within the CS, but additional evidence was provided as part of the company's response to clarification questions from the ERG.[22] The company's MAIC for the R/R CLL population, which compares acalabrutinib versus ibrutinib using data from ASCEND[21] and RESONATE,[23] includes PFS, OS and AEs; no comparative data are available for TTNT or HRQoL. The company's economic models each include data relating to progression, death and AEs (see Section 5.2). HRQoL is included in the company's cost-utility analysis for the untreated CLL population (Model 1), but it not explicitly included in the economic analyses for the untreated high-risk CLL population (Model 2) or the R/R CLL population (Model 3) as these analyses adopt a cost-minimisation approach.

3.5 Other relevant factors

The CS[1] states that no significant equality considerations are associated with this appraisal. The CS does not present an argument that acalabrutinib should be considered as an end-of-life treatment.

4. CLINICAL EFFECTIVENESS

This chapter summarises the evidence for the clinical effectiveness of acalabrutinib from the CS,[1] including the company's systematic literature review (SLR) and MAIC, and provides a critique of the methods used to identify and synthesise this evidence.

4.1 Critique of the methods of review

4.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical effectiveness and safety studies of acalabrutinib or comparator treatments for adult patients with CLL in the previously untreated and the relapsed/refractory (R/R) settings.

The company's searches are detailed in CS Appendix D.1.[24] The company searched several electronic bibliographic databases in August 2019: MEDLINE (via Embase.com); MEDLINE in Process (via PubMed.com); EMBASE (via Embase.com), and the Cochrane Central Register of Controlled Trials (via Wiley). During the clarification stage, the ERG requested that the company update their search as it had been undertaken more than 12 months prior to the data of submission (see clarification response,[22] question A5). The company updated the search from the 19th August until the 10th February 2020 and confirmed that one additional randomised controlled trial (RCT) publication was identified (ELEVATE-TN - Sharman *et al*[15]); however, this study had already been described in the CS[1] based on information from the Clinical Study Report (CSR) for this trial.

The company searched key conference abstract websites in the last three years (2016-2019): the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the American Society of Hematology (ASH), the International Conference on Malignant Lymphoma (ICML) and the Academy of Managed Care Pharmacy (AMCP).

During the clarification process (see clarification response,[22] question A6), the ERG sought further information regarding whether the company had searched clinical trials registries such as clinictrials.gov and/or the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). The company's response confirmed that only the Cochrane Central Register of Controlled Trials (CENTRAL) was searched for ongoing trials; however, the company did not provide a reason for not searching both clinicaltrials.gov and WHO ICTRP. Since April 2019, both clinicaltrials.gov and WHO ICTRP records have been indexed in CENTRAL. However, a recent cross-sectional study by Banno *et al*[25] compared the coverage of the two trials registry records versus CENTRAL and concluded that both clinicaltrials.gov and ICTRP should be searched together with CENTRAL to identify unpublished trials.

Despite this limitation, the ERG considers that the company's search is free from significant errors and that the terms used were comprehensive. As such, the ERG believes that it is unlikely that relevant studies have been missed.

4.1.2 Inclusion criteria

The company conducted an SLR to identify clinical effectiveness and safety evidence relevant to the final NICE scope.[13] Evidence for acalabrutinib in patients with untreated CLL and patients with previously treated (R/R) CLL is presented in CS Sections B.2a and B.2b,[1] respectively.

The company undertook a broad review, which was then narrowed for inclusion in the CS. Inclusion criteria for the company's original systematic review, from which comparator studies for the CS were selected, are presented in CS Appendix D.1.2.[24] Following the review, further restrictions were placed on the inclusion criteria for comparators and study designs. Study design was restricted to randomised controlled trials (RCTs; see clarification response,[22] question A17). The ERG considers this to be generally appropriate given that RCTs represent a higher quality of evidence than other study types. However, the ERG notes that unanchored MAICs, the approach used to estimate the relative effectiveness of acalabrutinib versus ibrutinib in patients with R/R CLL (see Sections 4.3 and 4.4), do not require included studies to have adopted an RCT design.

The included population for the review comprised two sub-populations of adult patients with CLL irrespective of gender, race, and/or ethnicity: (1) patients with previously untreated CLL; and (2) patients with previously treated (R/R) CLL. All included studies defined adults as individuals who were aged 18 years or older.[22] The population reflected in the inclusion criteria for the company's SLR[24] were consistent with the decision problem set out in the final NICE scope.[13]

The included intervention was acalabrutinib as monotherapy or in combination with obinutuzumab for the untreated CLL population, and acalabrutinib monotherapy for previously treated CLL. The company's searches did not restrict the interventions or comparators by dose (see clarification response,[22] question A19). However, in included trials, the intervention of acalabrutinib [redacted] was consistent with the decision problem set out in the final NICE scope:[13] (i) acalabrutinib as monotherapy or in combination with obinutuzumab for treatment-naïve CLL, and (ii) acalabrutinib as monotherapy for previously treated CLL.

The outcomes specified in the final NICE scope[13] included: PFS; OS; TTNT; adverse effects of treatment (AEs); and HRQoL. For acalabrutinib, the CS[1] reports on PFS, OS, TTNT and AEs from the included studies (the ELEVATE-TN[20] and ASCEND[21] RCTs). HRQoL results from ELEVATE-TN were described briefly in the CS. Further information on HRQoL outcomes for both ELEVATE-TN

and ASCEND were provided following a request for clarification from the ERG (see clarification response,[22] questions A14 and A15).

The company's original review included a broad range of comparators. However, the inclusion criteria for comparators used in the CS were restricted to: either GClb or ibrutinib for untreated CLL, and ibrutinib only for previously treated CLL (clarification response,[22] question A17). This was more restrictive than the set of comparators listed in the final NICE scope.[13] The CS[1] argues that other comparators from the NICE scope are not routinely used in usual clinical practice, are not suitable for "unfit" patients, or are associated with a higher risk of infection and death (see Section 3.3, CS[1] Section B.1.1.1 and clarification response,[22] question A20). Whilst the ERG's clinical advisors agreed with some of these arguments, they commented that whilst ibrutinib is most commonly used for R/R CLL, other treatment options are also available, including VenR, venetoclax monotherapy (via the CDF) and IR.

Study selection was conducted by two reviewers and differences were discussed with a third reviewer, as is good practice in systematic reviews (CS Appendix D.1.3[24]).

ELEVATE-TN,[20] the key study of acalabrutinib in patients with untreated CLL, was not identified by the company's search, as it was published after the search date (19th August 2019), but was included in the CS.[1] ASCEND,[21] the key study of acalabrutinib in patients with previously treated CLL, was identified from the company's original systematic review (see clarification response,[22] question A21).

4.1.3 Critique of data extraction

Data in the CS[1] were extracted by one reviewer and checked by another, as is good practice in systematic reviews (CS Appendix D.1.3[24]). Data in the CS were checked by the ERG against trial publications and the CSRs for ELEVATE-TN and ASCEND and were found to be accurate.[20, 21]

4.1.4 Quality assessment

The studies of acalabrutinib included in the CS[1] were quality assessed by one reviewer (see clarification response,[22] question A22). The ERG notes that it would be good practice for the quality assessment to be checked by another reviewer. Quality items assessed by the company (presented in CS Appendix D.4[24]) were taken from the Centre for Reviews and Dissemination (CRD) guidelines for undertaking reviews in health care.[26] These are standard and appropriate criteria for assessing the risk of bias in RCTs. Quality assessment was checked by the ERG against information provided in the CSRs for ELEVATE-TN[20] and ASCEND[21] and trial publications[15 27] . The company's assessment of the quality of the ELEVATE-TN and ASCEND RCTs is summarised in Table 8 and Table 9, respectively.

Table 8: Quality assessment - ELEVATE-TN

Question	CS assessment How is the question addressed?	CS assessment Grade (yes/ no/ unclear/ N/a)	ERG assessment
Was randomisation carried out appropriately?	Patients were randomly assigned (1:1:1) via a centralised interactive voice and web response system	Yes	Yes Stratified randomisation by interactive voice and web response system (Sharman *et al*, 2020;[15] ELEVATE-TN CSR[20])
Was the concealment of treatment allocation adequate?	Open-label study	No	Yes Randomly assigned via a centralised interactive voice and web response system (Sharman *et al*, 2020[15]).
Were the groups similar at the outset of the study in terms of prognostic factors?	Baseline demographic and disease characteristics were similar between groups	Yes	Yes (Sharman *et al*, 2020[15]).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Patients and investigators were not masked to treatment. A masked IRC assessed progression and response data.	No	Patients and physicians – No. PFS outcome assessors – Yes (Sharman *et al*, 2020[15]).
Were there any unexpected imbalances in drop-outs between groups?	See CS[1] Section B.2a.3.4	No	No (Sharman *et al*, 2020[15]).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR[20]	No	N/a Study ongoing, not all outcomes complete or published (Sharman *et al*, 2020[15]).
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes (Sharman *et al*, 2020[15]).

CS – company's submission; CSR – Clinical Study Report; IRC - Independent Review Committee; N/a – not applicable

Table 9: Quality assessment - ASCEND

Question	CS assessment How is the question addressed?	CS assessment Grade (yes/ no/ unclear/ N/a)	ERG assessment
Was randomisation carried out appropriately?	Patients were randomly assigned via a centralised procedure in a 1:1 ratio to receive acalabrutinib monotherapy or investigator's choice.	Yes	Yes Stratified randomisation by interactive voice and web response system (ASCEND CSR[21]).
Was the concealment of treatment allocation adequate?	Open-label study – this study compared an oral monotherapy with (one of two) combination therapies.	N/a	Yes Randomly assigned via a centrally interactive voice and web response system (ASCEND CSR[21]).
Were the groups similar at the outset of the study in terms of prognostic factors?	See CS[1] Table 31	Yes	Yes (Ghia *et al*, 2020[27])
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants were unblinded to treatment allocation. Progression and responses were assessed centrally by the IRC, which was blinded to treatment-group assignments.	No	Patients and physicians – No. PFS outcome assessors – Yes (Ghia *et al*, 2020[27])
Were there any unexpected imbalances in drop-outs between groups?	See CS[1] Table 31	No	No (Ghia *et al*, 2020[27])
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The pre-specified outcomes are reported in the CSR[21]	No	N/a Study ongoing, not all outcomes complete or published (Ghia *et al*, 2020[27])
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes (Ghia *et al*, 2020[27])

CS – company's submission; CSR – Clinical Study Report; IRC - Independent Review Committee; N/a – not applicable

ELEVATE-TN

For the ELEVATE-TN RCT[20] (see Table 8), randomised sequence generation and allocation concealment were by a centralised interactive voice and web response system.[1, 15] Randomisation was stratified according to: the presence or absence of del(17p); European Cooperative Oncology Group

(ECOG) performance score (PS) score (0–1 *vs* 2); and geographic region (North America, Western Europe, or other).[1, 15]

[redacted]

There was also a low risk of bias with respect to balance between groups, as baseline characteristics appeared similar and there were no unexpected imbalances in drop-outs between groups.[1, 15]

An intention-to-treat (ITT) analysis was presented for the effectiveness analyses.[1, 20] ITT analyses were also conducted for patient-reported outcomes (PROs; reported separately in the ELEVATE-TN PRO CSR[28]). Assessments for outcomes of disease-related symptoms and AEs were frequent and the same for all treatment groups, thus reducing risk of bias in measuring time-related outcomes (see clarification response,[22] question A16 and ELEVATE-TN protocol[29]).

The ELEVATE-TN trial[20] used an open-label design. Lack of blinding can lead to a high risk of performance and detection bias. PRO measures are more likely to be biased than objective measures such as OS.[26] Blinded outcome assessment by Independent Review Committee (IRC) was conducted for the measure of PFS,[1] which reduces the risk of detection bias. Given differences between the intervention and comparator in administration, blinding would require a double-dummy trial design. This would reduce bias for objective measures, but would disguise potential benefits to HRQoL resulting from mode of administration.

The ELEVATE-TN trial[20] is ongoing and therefore final results have not yet been published, so it cannot be assessed if the authors measured more outcomes than they published. However, data from the clinical cut-off date (8th February 2019) for outcomes of relevance to this review were provided by the company in the CS[1] and accompanying documents.[20, 21, 28-30]

ASCEND

For the ASCEND RCT[21] (see Table 9), randomised sequence generation and allocation concealment were by a centralised interactive voice and web response system.[1, 27]

Randomisation was stratified according to: the presence or absence of del(17p); ECOG PS score (0–1 *vs* 2); and lines of prior therapy received (1-3 versus ≥ 4).[1, 27]

[redacted]

There was also a low risk of bias with respect to balance between groups, as baseline characteristics appeared similar and there were no unexpected imbalances in drop-outs between groups.[1, 27]

An ITT analysis was presented for analyses of effectiveness measures.[1, 21] ITT analyses were also conducted for PROs (presented separately in the ASCEND PRO CSR[28]). Assessments for outcomes of disease-related symptoms and AEs were frequent and the same for all treatment groups, thus reducing risk of bias in measuring time-related outcomes.[21]

As was the case for ELEVATE-TN,[20] the ASCEND trial[21] adopted an open-label design; however, there was blinded outcome assessment by IRC for the measure of PFS.[1]

The ASCEND trial[21] is ongoing and therefore final results have not yet been published, so it cannot be assessed if the authors measured more outcomes than they published. However, data from the clinical cut-off date (15th January 2019) for outcomes of relevance to this review were provided by the company in the CS[1] and accompanying documents. [20, 21, 28-30]

4.2 Trials of interest identified

The CS includes two RCTs of acalabrutinib which were relevant to the decision problem: ELEVATE-TN[20] and ASCEND[21] (see Table 10). As RCTs of acalabrutinib were available, these formed the key evidence for clinical effectiveness within the CS. The ERG does not believe that any relevant published RCTs of acalabrutinib that could have provided effectiveness data have been missed or omitted from the CS. The trials were both of good methodological quality, apart from being open-label. Blinded outcome assessment was available for the primary outcome measure of PFS for both trials.

Table 10: Publications of included acalabrutinib trials (adapted from clarification response question A4)

Trial	Trial registration	Publications - full text	Publications - abstract	CSR
ELEVATE-TN NCT02475681 ACE-CL-007	https://clinicaltrials.gov/ct2/show/NCT02475681	Sharman JP, Egyed M, Jurczak W, *et al*. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): A randomised, controlled, phase 3 trial. *Lancet.* 2020;395(10232):1278-1291.	Sharman J, Banerji V, Fogliatto LM *et al.* ELEVATE-TN: Phase 3 study of acalabrutinib combined with obinutuzumab (O) or alone vs O plus chlorambucil (Clb) in patients (pts) with treatment-naïve chronic lymphocytic lukaemia (CLL). *Blood* 2019;134(Suppl 1):31.	Provided with CS Acerta Pharma. ELEVATE-TN (ACE-CL-007) Clinical Study Report. 2019.
ASCEND NCT02970318 ACE-CL-309	https://clinicaltrials.gov/ct2/show/NCT02970318	Ghia P, Pluta A, Wach M, *et al*. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology*. 2020:JCO1903355. doi: 10.1200/JCO.19.03355	Ghia, P., Pluta, A., Wach, M *et al.* ASCEND phase 3 study of acalabrutinib vs. investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic lukemia. *European Hematology Association Library*. 16 June 2019; 273529; LB2606 Ghia, P., Pluta, A., Wach, M *et al.* Acalabrutinib (Acala) versus idelalisib plus rituximab (IdR) or bendamustine plus rituximab (BR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): ASCEND final results. *Journal of Clinical Oncology* 2020; 38(Suppl):Abstr 8015.	Provided with CS AstraZeneca. ASCEND (ACE-CL-309) Clinical Study Report. 2019

CSR – Clinical Study Report; CS – company's submission

At the time of writing, both the ELEVATE-TN[20] and ASCEND[21] trials were ongoing. For ELEVATE-TN, data were available from the interim analysis (data cut-off 8th February 2019).[1] The final analyses for ELEVATE-TN are expected in 2021. For ASCEND, data were available from the interim analysis (data cut-off 15th January 2019).[1] The final analyses for ASCEND are expected in 2020.

Other ongoing studies

The company identified 21 ongoing clinical studies of acalabrutinib in CLL (see clarification response,[22] question A7). Of these, six studies have an estimated primary completion date before September 2021 (see Table 11).

Table 11: Ongoing studies of acalabrutinib

Trial name	Treatments	Expected primary completion date
Ace-Cl-208 A Study of ACP-196 (Acalabrutinib) in Subjects With Relapsed/Refractory CLL and Intolerant of Ibrutinib Therapy. https://www.clinicaltrials.gov/ct2/show/NCT02717611. Accessed September 2020.	• Acalabrutinib	February 2020
Ace-Cl-002 Acalabrutinib in Combination With ACP-319, for Treatment of Chronic Lymphocytic Leukemia. https://clinicaltrials.gov/ct2/show/NCT02157324. Accessed September 2020.	• Acalabrutinib followed by ACP-319 • ACP-319 followed by acalabrutinib	July 2020
Ace-Cl-001 ACP-196 (Acalabrutinib), a Novel Bruton Tyrosine Kinase (Btk) Inhibitor, for Treatment of Chronic Lymphocytic Leukemia. https://clinicaltrials.gov/ct2/show/NCT02029443. Accessed September 2020	• Acalabrutinib	January 2021
Ace-Cl-006 ClinicalTrials.gov. Study of Acalabrutinib (ACP-196) Versus Ibrutinib in Previously Treated Subjects With High Risk CLL. Available at: https://clinicaltrials.gov/ct2/show/NCT02477696?term=NCT02477696&draw=2&rank=1 (accessed July 2020).	• Acalabrutinib • Ibrutinib	March 2021
CLL2-BAAG Sequential Regimen of Bendamustin-Debulking Followed by Obinutuzumab, Acalabrutinib and Venetoclax in Patients With Relapsed/Refractory CLL (CLL2-BAAG). https://clinicaltrials.gov/ct2/show/NCT03787264. Accessed September 2020.	• Bendamustine followed by obinutuzumab, acalabrutinib and venetoclax	May 2021
NCT02337829 Acalabrutinib in Patients With Relapsed/Refractory and Treatment naïve Deletion 17p CLL/SLL. https://www.clinicaltrials.gov/ct2/show/NCT02337829. Accessed September 2020.	• Acalabrutinib	July 2021

Source: Clarification response,[22] question A7

4.2.1 Treatment-naïve CLL - critique of trial of the technology of interest

4.2.1.1 ELEVATE-TN trial characteristics

ELEVATE-TN (see Table 12) is a three-arm, multicentre, international open-label RCT with centres in Asia, Australasia, Europe, and North and South America (CS,[1] Section B.2a). It includes [redacted] from the UK (see clarification response,[22] question A8).

Table 12: ELEVATE-TN - study characteristics

Study	Population	Interventions (N randomised)	Comparator (N randomised)	Primary outcomes
ELEVATE-TN	Adults with CLL, not previously treated: Age ≥ 65 years; or age 19–64 years with a creatinine clearance of 30–69 mL/min and/or a score > 6 on the Cumulative Illness Rating Scale-Geriatric	Acalabrutinib monotherapy (N=179) Acalabrutinib plus obinutuzumab (N=179)	Chlorambucil plus obinutuzumab (N=177)	Primary endpoint: PFS (IRC), acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab. Key secondary endpoint: PFS (IRC), acalabrutinib monotherapy vs chlorambucil plus obinutuzumab

N – number; CLL – chronic lymphocytic leukaemia; IRC – Independent Review Committee; PFS – progression-free survival

Key study eligibility criteria are shown in Table 13. Eligible participants were patients with previously untreated CLL who were either: age ≥ 65 years; or age 19–64 years with creatinine clearance CrCl) 30–69 mL/min and/or a score >6 on the Cumulative Illness Rating Scale-Geriatric.[1] Trial patients selected were thus considered ineligible for FCR therapy.

Table 13: Eligibility criteria for ELEVATE-TN (reproduced from CS Table 17)

Key inclusion criteria
• Age ≥65 years, or age 19–64 years with a CrCl of 30–69 mL/min and/or a score >6 on the Cumulative Illness Rating Scale-Geriatric • ECOG PS 0–2 • Diagnosis of CD20-positive CLL that meets published diagnostic criteria • Active disease meeting ≥ 1 of the iwCLL 2008 criteria for requiring treatment • Laboratory parameters: ANC ≥ 0.75 × 10^9/L;[a] platelet count ≥ 50 × 10^9/L;[b] AST and ALT ≤ 3.0 × ULN; total bilirubin ≤ 1.5 × ULN; estimated creatinine clearance of ≥ 30 mL/min
Key exclusion criteria
• Any previous systemic treatment for CLL • Significant cardiovascular disease • Required or received anticoagulation therapy with warfarin or other equivalent other vitamin K antagonists within 7 days of first dose of study drug

[a] ≥ 0.50 × 109/L in patients with bone marrow involvement.
[b] ≥ 30 × 109/L in patients with bone marrow involvement.
ALT - alanine aminotransferase; ANC - absolute neutrophil count; AST - aspartate aminotransferase; CLL - chronic lymphocytic leukaemia; ECOG - Eastern Cooperative Oncology Group; PS – performance score; iwCLL - International Workshop on Chronic Lymphocytic Leukemia; ULN - upper limit of normal.

Patients were randomised to one of three groups: chlorambucil plus obinutuzumab (GClb; N=177); acalabrutinib plus obinutuzumab (N=179) or acalabrutinib monotherapy (N=179). Randomisation was stratified by: presence versus absence of del(17p); ECOG PS (0, 1 versus 2); geographic region (North America and Western Europe versus other). Baseline characteristics were balanced between groups (see CS,[1] Table 19). Clinical advisors to the ERG considered that the population in the ELEVATE-TN RCT was broadly representative of a UK population of FCR/BR-ineligible patients with untreated CLL. GClb was prescribed for 6 four-week cycles; oral chlorambucil 0.5mg/kg on days 1 and 15 of each cycle; intravenous (IV) obinutuzumab 100mg on day 1 of cycle 1, 900mg on day 2 of cycle 1, 1,000mg on days 8 and 15 of cycle 1 and 1,000 mg on day 1 of cycles 2–6.[1] Oral acalabrutinib was prescribed at 100mg twice daily until disease progression or unacceptable toxicity. Participants allocated to GClb who experienced IRC-confirmed disease progression were allowed to cross over to acalabrutinib monotherapy, until disease progression or unacceptable toxicity. Forty-five patients (25.4%) crossed over to receive acalabrutinib.[1] The primary outcome was PFS. Definitions of the outcomes measured in the trial are detailed in Table 14.

The following concomitant medications were allowed: antiemetics; standard supportive care medications; hematopoietic growth factors; short course use of steroids for premedication use, or to manage obinutuzumab infusion-related reactions or to manage other inflammatory reactions (see clarification response,[22] question A8).

[redacted]

Table 14: ELEVATE-TN - outcome definitions

Outcome	Definition	Measured by
PFS	PFS measured according to iwCLL criteria. Defined as time from the date of randomisation to the date of first IRC-assessed disease progression or death due to any cause, whichever occurred first	IRC Investigator-assessed
OS	The time from date of randomisation to death due to any cause	-
ORR	ORR measured according to iwCLL criteria. The proportion of patients (assessed) by IRC of CR, CRi, nPR or PR at or before initiation of subsequent anti-cancer therapy	IRC
TTNT	The time from date of randomisation to date of start of non-protocol-specified subsequent anti-cancer treatment for CLL or death due to any cause, whichever occurred first	-
Safety	Safety and tolerability of acalabrutinib	Coded using the MedDRA reporting system (version 21.1) and graded according to the NCI CTCAE (version 4.03)
HRQoL	Change from baseline in HRQoL	FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D scores

PFS – progression-free survival; OS – overall survival; TTNT – time to next treatment; HRQoL – health-related quality of life; iwCLL – international workshop on chronic lymphocytic leukaemia; IRC – Independent Review Committee; CLL – chronic lymphocytic leukaemia; ORR – overall response rate; CR – complete response; CRi – complete response with incomplete bone marrow recovery; nPR – nodular partial remission; PR – partial response; NCI – National Cancer Institute; CTCAE - Common Terminology Criteria for Adverse Events; FACIT - The Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Core Quality of Life; EQ-5D – Euroqol 5-Dimensions
Source: CS,[1] Section B.2a.3.3

At the time of writing, data were available for the clinical cut-off date 8th February 2019, with acalabrutinib treatment ongoing for some patients (see Table 15). Median follow-up was 28.5 months in the acalabrutinib plus obinutuzumab group, 28.4 months in the acalabrutinib monotherapy group, and 28.0 months in the GClb group.[1]

Table 15: ELEVATE-TN - discontinuations at data cut-off date (8th February 2019)

		Acalabrutinib plus obinutuzumab N	Acalabrutinib monotherapy N	GClb N
Randomised		179	179	177
ITT analysis		179	179	177
Received at least one allocated study treatment		178	178	169
Safety analysis		178	179*	169
Treatment status	Ongoing	142	142	N/a
	Completed treatment course	N/a	N/a	137
	Cross-over to acalabrutinib monotherapy	N/a	N/a	45
	Withdrawn from treatment	37	36	32
Withdrawn from treatment reason	Death	2 died	3 died	1 died
	Adverse events	20 AEs	16 AEs	25 AEs
	Progressive disease	6 disease progression	7 disease progression	3 disease progression
	Richter transformation (disease progression)	0	1 Richter transformation	0
	Physician decision	4	5	1
	Withdrawal by subject	1 withdrew consent	1 withdrew consent	1 withdrew consent
	Lost to follow-up	-	1 lost to follow-up	1 lost to follow-up
	Patient decision	1 patient decision	1 patient decision	-
	Dose interruption	2 dose interruptions longer than 28 days	1 dose interruption longer than 28 days	-
	Risk of bleeding	1 risk of bleeding	-	-

GClb – obinutuzumab plus chlorambucil ; ITT – intention-to-treat; AE – adverse event; N/a – not applicable
**includes one patient from acalabrutinib plus obinutuzumab group who received acalabrutinib only)*
Source: CS,[1] Section B.2a.4.3

4.2.1.2 ELEVATE-TN effectiveness - PFS

Results presented in this section include all three trial arms; however, only data relating to the comparative effectiveness of acalabrutinib monotherapy versus GClb are used in the company's economic analyses (see Section 5.2).

IRC-assessed PFS events (disease progression or death due to any cause, whichever occurred first) occurred in 14 patients (7.8%) in the acalabrutinib plus obinutuzumab group, 26 patients (14.5%) in the acalabrutinib monotherapy group, and 93 patients (52.5%) of the GClb group (see

Table 16).[1]

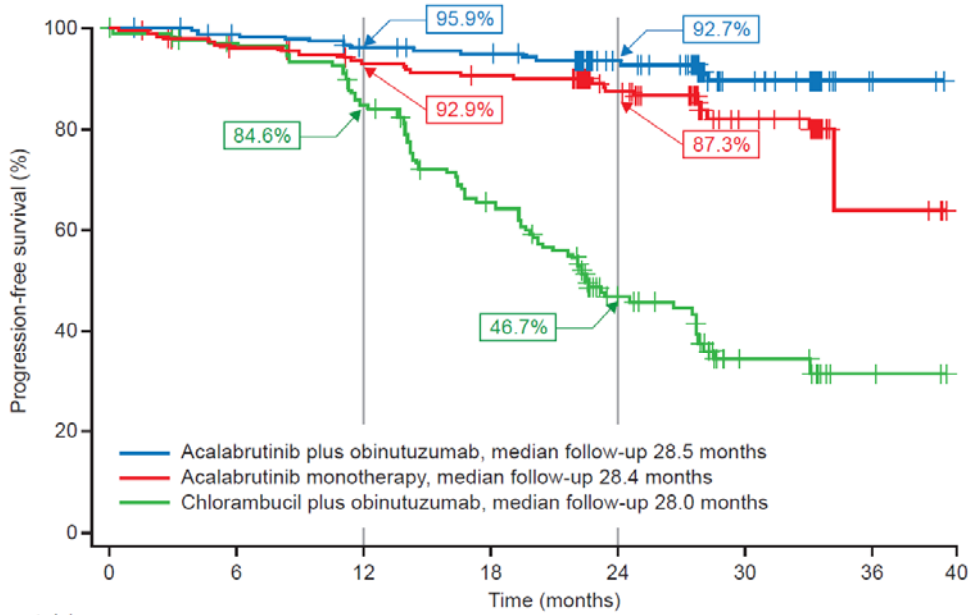
Median PFS for the acalabrutinib plus obinutuzumab group, and for the acalabrutinib monotherapy group, was not reached. Median PFS for the GClb group was 22.6 months.[1]

Kaplan-Meier PFS estimates are shown in Figure 2. The Kaplan-Meier estimate of PFS at 12 months was 95.9% (95% confidence interval [CI]: 91.7–98.0%) for acalabrutinib plus obinutuzumab, 92.9% (95% CI: 87.8–95.9%) for acalabrutinib monotherapy, and 84.6% (95% CI: 78.0–89.3%) for GClb.[1]

The primary endpoint of IRC-assessed PFS, acalabrutinib plus obinutuzumab versus GClb, significantly favoured acalabrutinib plus obinutuzumab (hazard ratio (HR) [redacted] 0.10, 95% CI: 0.6–0.17; $p<0.0001$).[1, 20] The unstratified HR was similar (see CS,[1] Figure 6; HR = 0.10, 95% CI: 0.6–0.18; $p<0.0001$).

The key secondary endpoint of IRC-assessed PFS, acalabrutinib monotherapy versus GClb, significantly favoured acalabrutinib monotherapy (HR [redacted] 0.20, 95% CI: 0.13–0.30; $p<0.0001$).[1]

Figure 2: Kaplan- Meier plot for IRC-assessed PFS, ELEVATE-TN (reproduced from CS Figure 5)



Number at risk

Acalabrutinib plus obinutuzumab	179	176	170	168	163	160	159	155	109	104	46	41	4	2
Acalabrutinib monotherapy	179	166	161	157	153	150	148	147	103	94	43	40	4	3
Chlorambucil plus obinutuzumab	177	162	157	151	136	113	102	86	46	41	13	13	3	2

IRC - Independent Review Committee; PFS - progression-free survival

Table 16: ELEVATE-TN - PFS (adapted from CS Tables 22 and 23)

Outcome	Acalabrutinib plus obinutuzumab (N=179)	Acalabrutinib monotherapy (N=179)	GClb (N=177)
IRC-assessed PFS			
Events, n (%)			
Events	14 (7.8)	26 (14.5)	93 (52.5)
Death	5 (2.8)	6 (3.4)	11 (6.2)
Disease progression	9 (5.0)	20 (11.2)	82 (46.3)
KM-estimated PFS, % (95% CI)			
6-month PFS	98.9 (95.5–99.7)	95.9 (91.6–98.0)	97.0 (92.9–98.7)
12-month PFS	95.9 (91.7–98.0)	92.9 (87.8–95.9)	84.6 (78.0–89.3)
18-month PFS	94.8 (90.2–97.2)	90.5 (84.9–94.1)	65.6 (57.7–72.4)
24-month PFS	92.7 (87.4–95.8)	87.3 (80.9–91.7)	46.7 (38.5–54.6)
30-month PFS	89.6 (82.0–94.1)	81.9 (73.3–88.0)	34.2 (25.3–43.2)
36-month PFS	89.6 (82.0–94.1)	63.9 (29.4–84.9)	31.3 (21.8–41.3)
Hazard ratio			
HR vs arm A (95% CI)	0.10 (0.06–0.17) $p<0.0001$	0.20 (0.13–0.30) $p<0.0001$	N/a

GClb – obinutuzumab plus chlorambucil; IRC – Independent Review Committee; N – number; PFS – progression-free survival; CI – confidence interval; HR – hazard ratio; N/a - not applicable

The CS[1] reports that the PFS analysis consistently favoured acalabrutinib plus obinutuzumab and acalabrutinib monotherapy over GClb across all pre-specified subgroups (CS, Section B.2a.7). Prespecified subgroups comprised: del(17p), del(11q), TP53 mutation, unmutated immunoglobulin heavy-chain variable (IgHV), Rai stage III-IV, B2–microglobin >3.5 mg/L at baseline, bulky disease ≥5 cm, sex and age group (<65 years or ≥65 years).

4.2.1.3 ELEVATE-TN effectiveness - OS

At the clinical cut-off date (8th February 2019), median OS had not been reached in any of the three treatment arms. Deaths from any cause (ITT population) occurred in [redacted] in the acalabrutinib plus obinutuzumab group, [redacted] in the acalabrutinib monotherapy group, and [redacted] in the GClb group (see Table 17).[1]

Kaplan-Meier plots for OS were not provided in the CS[1] or the ELEVATE-TN CSR;[20] however, numerical values were provided in the CS. Kaplan-Meier OS estimates were also available from the company's executable model: these are presented in Section 5.2. The Kaplan-Meier estimate of OS at 12 months was 96.1% (95% CI: 91.9–98.1%) for acalabrutinib plus obinutuzumab, 98.3% (95% CI 94.8–99.4%) for acalabrutinib monotherapy and 96.5% (95% CI: 92.4–98.4%) for GClb.[1] There was a trend towards an advantage in OS for acalabrutinib plus obinutuzumab compared with GClb; HR [redacted] 0.47, 95% CI: 0.21–1.06; $p=0.0577$). The HR [redacted] for acalabrutinib monotherapy versus GClb was 0.60 (95% CI: 0.28–1.27; $p=0.1556$).[1, 20]

Table 17: ELEVATE-TN - OS, ITT population (reproduced from CS Table 24)

Outcome	Acalabrutinib plus obinutuzumab (N=179)	Acalabrutinib monotherapy (N=179)	GClb (N=177)
Events[a]	[redacted]	[redacted]	[redacted]
KM estimated OS[b], % (95% CI)			
6 months	98.3 (94.9–99.5)	98.9 (95.5–99.7)	97.1 (93.2–98.8)
12 months	96.1 (91.9–98.1)	98.3 (94.8–99.4)	96.5 (92.4–98.4)
18 months	94.9 (90.5–97.3)	97.1 (93.2–98.8)	94.7 (90.1–97.2)
24 months	94.9 (90.5–97.3)	94.7 (90.2–97.2)	91.7 (86.3–95.0)
30 months	94.9 (90.5–97.3)	93.5 (88.6–96.3)	89.9 (83.9–93.7)
36 months	94.9 (90.5–97.3)	93.5 (88.6–96.3)	88.1 (80.7–92.8)

GClb – obinutuzumab plus chlorambucil; N – number; KM – Kaplan-Meier; OS – overall survival; CI – confidence interval
[a] Included all deaths on study, including deaths after crossover for obinutuzumab plus chlorambucil subjects who crossed over
[b] KM estimate of proportion subjects who were alive at the timepoint.

4.2.1.4 ELEVATE-TN effectiveness - TTNT

TTNT events (start of non-protocol-specified subsequent anti-cancer treatment for CLL, crossover to acalabrutinib monotherapy, or death due to any cause, whichever occurred first) occurred in [redacted] in the acalabrutinib plus obinutuzumab group, [redacted] in the acalabrutinib monotherapy group, and [redacted] in the GClb group (see Table 18).[1]

Compared with GClb, TTNT was significantly longer for both acalabrutinib plus obinutuzumab (HR [redacted]) and acalabrutinib monotherapy (HR [redacted].[1]

Table 18: ELEVATE-TN – TTNT (adapted from CS Table 22)

Outcome	Acalabrutinib plus obinutuzumab (N=179)	Acalabrutinib monotherapy (N=179	GClb (N=177)
Events	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Crossed over to acalabrutinib monotherapy	[redacted]	[redacted]	[redacted]
Subsequent anti-cancer therapy	[redacted]	[redacted]	[redacted]
Patients alive with no crossover or subsequent anti-cancer therapy, N (%)	[redacted]	[redacted]	[redacted]
HR vs chlorambucil + obinutuzumab (95% CI)	[redacted]	[redacted]	[redacted]

N – number; HR – hazard ratio; CI – confidence interval; N/a – not applicable

4.2.1.5 ELEVATE-TN - adverse effects of treatment

AEs were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03). AEs of any grade were experienced by 171 patients (96.1%) in the acalabrutinib plus obinutuzumab group, 170 patients (95.0%) in the acalabrutinib monotherapy group, and 167 patients (98.8%) in the GClb group (see Table 19).[1, 15] Grade ≥3 AEs were experienced by 125 patients (70.2%) in the acalabrutinib plus obinutuzumab group, 89 patients (49.7%) in the acalabrutinib monotherapy group, and 118 patients (69.8%) in the GClb group.[1, 15]

The most common grade ≥3 AEs were as follows. In the acalabrutinib plus obinutuzumab group: neutropenia (29.8%); thrombocytopenia (8.4%); anaemia (5.6%), and pneumonia (5.6%). In the acalabrutinib monotherapy group: neutropenia (9.5%); anaemia (6.7%), and thrombocytopenia (2.8%). In the GClb group: neutropenia (41.4%); thrombocytopenia (11.8%), and tumour lysis syndrome (TLS) (7.7%).[1]

Grade ≥3 infection occurred in 21% patients in the acalabrutinib plus obinutuzumab group, 14% patients in the acalabrutinib monotherapy group, and 8% patients in the GClb group.[15]

Deaths from AEs occurred in [redacted] in the acalabrutinib plus obinutuzumab group, [redacted] in the acalabrutinib monotherapy group, and [redacted] in the GClb group (see Table 20) (clarification response,[22] question A12), with one additional death in the GClb group following the randomisation period.[15]

Table 19: ELEVATE-TN - AE overview, safety population (adapted from CS Table 26 and clarification response question A12)

Event	Number (%) of patients		
	Acalabrutinib plus obinutuzumab (N=178)	**Acalabrutinib monotherapy (N=179)**	**GClb (N=169)**
Median time on treatment	Acalabrutinib 27.7 months (range: 0.7–40.3 months) obinutuzumab: 5.5 months (range: 0.8—7.1)	Acalabrutinib 27.7 months (range: 0.3–40.2 months).	chlorambucil: 5.5 months (range: 0.5–7.2 months) obinutuzumab: 5.6 months (range: 0.9—7.4)
Any grade AE	171 (96.1)	170 (95.0)	167 (98.8)
Grade 1	7 (3.9)	14 (7.8)	4 (2.4)
Grade 2	39 (21.9)	67 (37.4)	45 (26.6)
Grade ≥ 3	125 (70.2)	89 (49.7)	118 (69.8)
SAEs	69 (38.8)	57 (31.8)	37 (21.9)
Death from AE	[redacted]	[redacted]	[redacted]
AE leading to discontinuation of acalabrutinib	[redacted]	[redacted]	[redacted]
AE leading to discontinuation of obinutuzumab	[redacted]	[redacted]	[redacted]
AE leading to discontinuation of chlorambucil	[redacted]	[redacted]	[redacted]

GClb – obinutuzumab plus chlorambucil; AE – adverse event; SAE – serious adverse event; N – number; N/a – not applicable

Table 20: ELEVATE-TN discontinuations due to AEs (data cut-off 8th February 2019)

		Acalabrutinib plus obinutuzumab N	**Acalabrutinib monotherapy N**	**GClb N**
Randomised		179	179	177
Safety analysis		178	179*	169
Withdrawn from treatment reason	Death	2 died	3 died	1 died
	AE	20 AEs	16 AEs	25 AEs

GClb – obinutuzumab plus chlorambucil; AE – adverse event; N – number
**includes one patient from acalabrutinib plus obinutuzumab group who received acalabrutinib only*

4.2.1.6 ELEVATE-TN – HRQoL outcomes

No statistically significant treatment group differences were observed between acalabrutinib plus obinutuzumab or acalabrutinib monotherapy and GClb, for the EuroQol 5-dimensions questionnaire (EQ-5D-3L), the European Organisation for Research and Treatment of Cancer Core Quality of Life (EORTC QLQ-C30) global health status (GHS) domain, or the Functional Assessment of Cancer Therapy (FACIT)-Fatigue questionnaire.[1] All treatment arms improved from baseline in FACIT-F global fatigue score (GFS). Across treatment groups, improvements were greater in patients who had severe fatigue at baseline (FACIT-Fatigue score ≤ 34 at baseline; see Table 21).[1, 22]

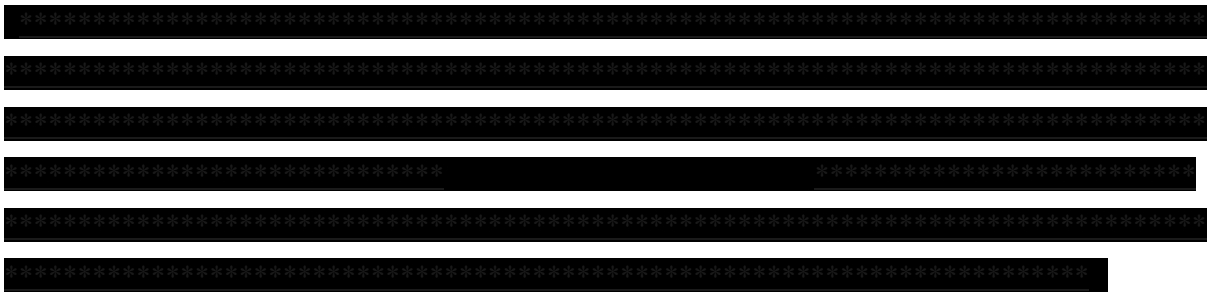


Table 21: ELEVATE-TN - HRQoL change from baseline

Instrument	Acalabrutinib plus obinutuzumab ITT (N=179)	Acalabrutinib plus obinutuzumab Severe fatigue population [redacted]	Acalabrutinib monotherapy ITT (N=179)	Acalabrutinib monotherapy Severe fatigue population [redacted]	GClb ITT (N=177)*	GClb Severe fatigue population [redacted]*
FACIT-Fatigue Global Fatigue Scale (GFS) (scale 0-52) Fatigue change from baseline over 96 weeks	3.77	9.98	4.66	11.79	[redacted]	[redacted]
EORTC QLQ-C30 Global Health Status) GHS Overall HRQoL 0–100 scale over 96 weeks	5.88	14.50	7.72	12.83	[redacted]	[redacted]

GClb – obinutuzumab plus chlorambucil; ITT – intention-to-treat; N - number; FACIT - Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Core Quality of Life
Sources: clarification response question A14;[22] ELEVATE-TN PRO CSR[28]

[redacted]

4.2.1 Previously treated CLL - Critique of trial of the technology of interest

4.2.2.1 ASCEND trial characteristics

ASCEND is a two-arm, multicentre, international open-label RCT with centres in Asia, Australasia, Europe, and North America (see Table 22). It includes [redacted] from the UK (see clarification response,[22] question A9).

Table 22: ASCEND - study characteristics

Study	Population	Intervention (N randomised)	Comparator (N randomised)	Primary outcomes
ASCEND	Adults with CLL, ≥1 previous systemic therapy for CLL (excluding single-agent steroids or localised radiation)	Acalabrutinib monotherapy (N=153)	Investigator choice (N=153): Either idelalisib plus rituximab (IR) Or bendamustine plus rituximab (BR)	Primary endpoint: PFS (IRC)

CLL – chronic lymphocytic leukaemia; N - number; PFS – progression-free survival; IRC – Independent Review Committee

Key study eligibility criteria are summarised in Table 23. Eligible patients were aged ≥18 years, had previously treated CLL (≥1 previous systemic therapy for CLL, excluding single-agent steroids or localized radiation), a diagnosis of CLL that meets published diagnostic criteria, documented CD20-positive CLL, active disease meeting ≥ 1 of the iwCLL 2008 criteria for requiring treatment, laboratory parameters: ANC ≥ 0.75 × 109/L; platelet count ≥ 50 × 109/L; AST and ALT ≤ 2.0 × ULN; total bilirubin ≤ 1.5 × ULN; estimated CrCl of ≥ 30 mL/min, and ECOG PS 0–2.[1]

Table 23: ASCEND eligibility criteria (adapted from CS Table 31)

Trial	ASCEND (NCT02970318)
Eligibility criteria for participants	**Key inclusion criteria:** • Age ≥18 years • ECOG PS 0–2 • Diagnosis of CLL that meets published diagnostic criteria • Documented CD20-positive CLL • Active disease meeting ≥ 1 of the iwCLL 2008 criteria for requiring treatment • Laboratory parameters: ANC ≥ 0.75 × 109/L; platelet count ≥ 50 × 109/L; AST and ALT ≤ 2.0 × ULN; total bilirubin ≤ 1.5 × ULN; estimated creatinine clearance of ≥ 30 mL/min • ≥ 1 previous systemic therapy for CLL (excluding single-agent steroids or localized radiation)
	Key exclusion criteria: • Previous exposure to a BCL-2 inhibitor or a BCR inhibitor • Significant cardiovascular disease • Required or received anticoagulation therapy with warfarin or other equivalent other vitamin K antagonists within 7 days of first dose of study drug

ECOG – Eastern Cooperative Oncology Group; PS – performance status; CLL – chronic lymphocytic leukaemia; iwCLL – International Workshop on CLL; AST - aspartate transaminase; ALT - alanine transaminase; ULN – upper limit of normal; BCR – B cell receptor

Patients were randomised to one of two groups: (1) acalabrutinib monotherapy (oral, 100mg twice per day until an unacceptable drug-related toxicity occurs or until disease progression, N=155), or (2) investigator's choice of therapy (N=155) - either: IR - idelalisib (oral 150mg twice daily) until disease progression or unacceptable toxicity + ≥8 IV infusions of rituximab; or BR - bendamustine 70mg/m² IV (day 1 and 2 of each cycle) plus 375mg/m²/500mg/m² IV rituximab on day 1 of each cycle for up to 6 cycles.[1] Randomisation was stratified by: del(17p); ECOG PS (0 or 1 versus 2) and number of prior therapies (1, 2 or 3 versus ≥4). Crossover from IR/BR to acalabrutinib monotherapy was permitted following confirmed disease progression: [redacted] (clarification response,[22] question A10). Treatment groups were balanced at baseline (see CS,[1] Table 33). Clinical advisors to the ERG considered that the population in the ASCEND RCT was broadly representative of the population with previously treated CLL who would be eligible for treatment with acalabrutinib in England. The primary outcome was PFS assessed by IRC. Definitions of outcomes measured in ASCEND are detailed in Table 24. The ERG notes that the IR/BR arm is not used in the company's economic analysis for the R/R population (Model 3, see Section 5.2).

The following concomitant medications were allowed: anti-emetics; standard supportive care medications, including hematopoietic growth factors; if at risk of TLS, appropriate hydration and allopurinol or rasburicase; if at risk of pneumonitis, anti-infectious prevention was considered; antibiotic prophylaxis against pneumocystis infection; prophylaxis with intravenous immunoglobulin (IVIG), if low immunoglobulin levels; if at risk of infections, bacterial/viral/fungal prophylaxis; steroids; localised, short courses of radiotherapy were allowed for the treatment of lesions unrelated to the disease under study (see clarification response,[22] question A9).

[redacted]

Table 24: ASCEND - outcome definitions

Outcome	Definition	Measured by
PFS	Time from date of randomisation to the date of first IRC-assessed disease progression or death due to any cause, whichever comes first. Kaplan-Meier curves were used to estimate the distribution of PFS.	IRC the iwCLL 2008 criteria
OS	The time from date of randomisation to death due to any cause.	-
TTNT	The time from date of randomisation to date of institution of non-protocol specified treatment for CLL (or first dose date of acalabrutinib for Arm B (IR/BR) subjects who crossed over to receive acalabrutinib) or death due to any cause, whichever occurred first.	-
DoR	DOR determined by IRC and by investigators was analysed in the same fashion as PFS, as described above	IRC / Investigators
ORR	Best overall response as assessed by investigators/IRC on or before the initiation of subsequent anticancer therapy	IRC / Investigators
Safety	Safety and tolerability of acalabrutinib	Graded according to the NCI CTCAE (version 4.03)
HRQoL	Change from baseline in PROs	FACIT-Fatigue , EORTC QLQ-C30, EQ-5D-5L VAS

PFS – progression-free survival; OS - overall survival; TTNT – time to next treatment; HRQoL – health-related quality of life; DoR – duration of response; ORR – overall response rate; IRC – Independent Review Committee; iwCLL – international workshop on chronic lymphocytic lymphoma; FACIT - Functional Assessment of Chronic Illness Therapy-Fatigue; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Core Quality of Life; EQ-5D-5L – Euroqol 5-Dimensions (5-level); VAS – visual analogue scale. Source: CS[1] Section B.2b.3.3 CS Table 32, and clarification response, question A10)

Table 25: ASCEND - discontinuations at data cut-off date ITT population (15th January 2019)

		Acalabrutinib monotherapy N	Investigator choice N			
			IR		BR	
Randomised		155	119		36	
ITT analysis		155	119		36	
Received at least one allocated study treatment		154	118		35	
Safety analysis		154	118		35	
Treatment status	Ongoing	124	I 42	R N/a	N/a	
	Completed treatment course	N/a	I N/a	R 95 (79.8)	B 30 (83.3)	R 28 (77.8)
	Cross-over to acalabrutinib mono	N/a	N/a		35 (22.6)	
	Withdrawn from treatment	30 (19.4)	I 76 (63.9)	R 95 (75.8)	B 5 (13.9)	R 7 (19.4)
Withdrawn from treatment reason	Death	1 (0.6)	I	R	B	R
	Adverse event	17 (11.4)	I 58 (48.7)	R 14 (11.8)	B 4 (11.1)	R 6 (16.7)
	Progressive disease	10 (6.5)	I 11 (9.2)	R 1 (0.8)	B 1 (2.8)	R 1 (2.8)
	Other	2 (1.2)	I 7 (5.9)	R 8 (6.7)	B 0	R 0
Exited study		18 (11.6)	21 (17.6)		7 (19.4)	

IR – idelalisib plus rituximab; BR – bendamustine plus rituximab; ITT – intention-to-treat; N/a - not applicable; Source: CS,[1] Section B.2b.3

ASCEND was ongoing at the time of writing; data were available for the clinical cut-off date of the 15th January 2019. Median follow-up was 16.1 months in the acalabrutinib monotherapy arm, and 15.7 months in the IR/BR arm.[1]

4.2.2.2 ASCEND effectiveness - PFS

IRC-assessed PFS events (disease progression or death due to any cause, whichever occurred first) occurred in 27 patients (17.4%) in the acalabrutinib monotherapy arm, and 68 patients (43.9%) in the IR/BR arm (see Table 26). Median PFS was not reached in either study arm.[1]

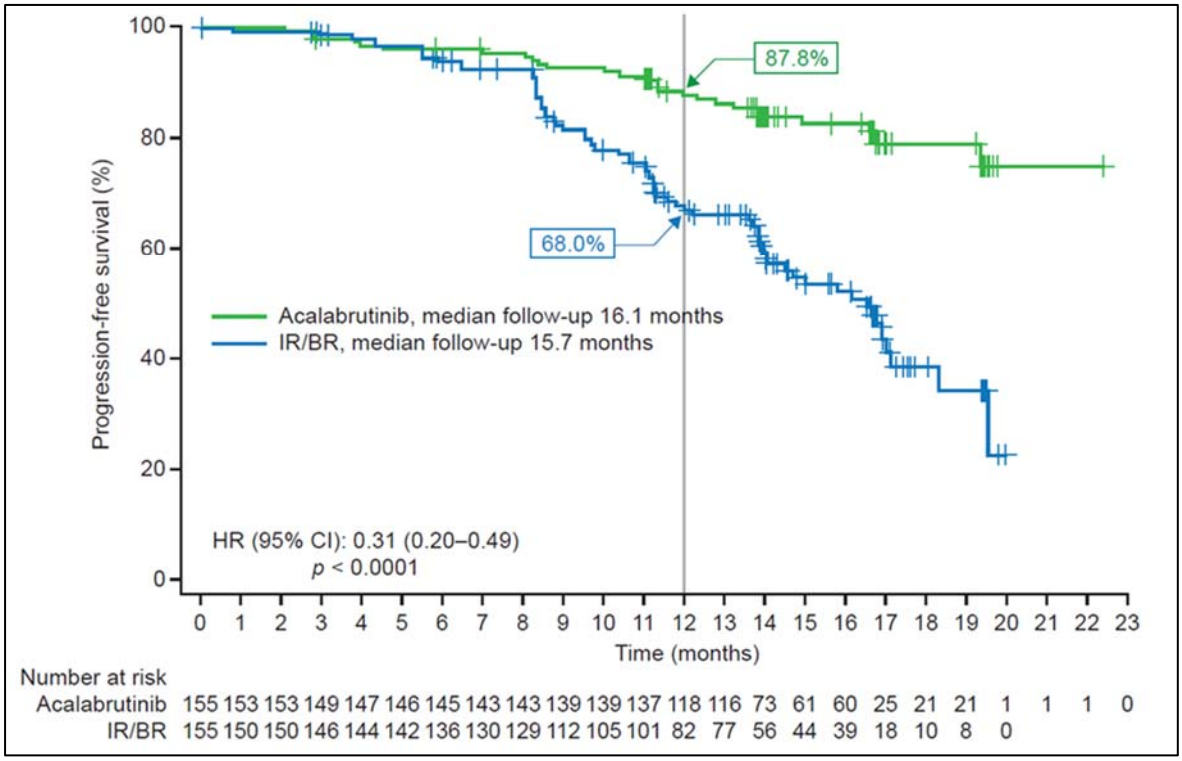
Kaplan-Meier PFS estimates are shown in Figure 3. The Kaplan-Meier estimated PFS probability at 12 months was 87.8% (95% CI: 81.3–92.1%) for acalabrutinib monotherapy, and 68.0 % (95% CI: 59.4–75.1%) for IR/BR. IRC-assessed PFS significantly favoured acalabrutinib monotherapy over IR/BR (HR 0.31, 95% CI: 0.20–0.49; $p<0.0001$).[1]

Table 26: ASCEND - IRC-assessed PFS (reproduced from CS Table 39)

	Arm A: Acalabrutinib (N=155)	**Arm B: IR/BR (N=155)**
Events, n (%)		
Death	8 (5.2)	9 (5.8)
Disease progression	19 (12.3)	59 (38.1)
KM-estimated PFS, % (95% CI)		
6-month PFS	96.1 (91.5–98.2)	93.9 (88.6–96.8)
9-month PFS	92.7 (87.3–95.9)	82.4 (75.0–87.7)
12-month PFS	87.8 (81.3–92.1)	68.0 (59.4–75.1)

IR - idelalisib plus rituximab; BR - bendamustine plus rituximab; CI - confidence interval; IRC - Independent Review Committee; KM - Kaplan–Meier; PFS - progression-free survival

Figure 3: Kaplan- Meier plot for IRC-assessed PFS, ASCEND (reproduced from CS Figure 12)



IRC – independent review committee; PFS – progression-free survival; IR – idelalisib plus rituximab; BR – bendamustine plus rituximab; HR – hazard ratio

4.2.2.3 ASCEND effectiveness - OS

At the clinical cut-off date (15th January 2019), median OS had not been reached in either treatment arm. Deaths from any cause occurred 15 patients (9.7%) in the acalabrutinib monotherapy arm, and 18 patients (11.6%) in the IR/BR arm (see Table 27).[1]

Kaplan-Meier plots for OS were not provided in the CS[1] or the ASCEND CSR;[21] however, numerical values were provided. The Kaplan-Meier estimated OS at 12 months was 94.1% (95% CI: 89.0–96.9%) for the acalabrutinib monotherapy arm, and 90.6% (95% CI: 84.6–94.3%) for the IR/BR arm. At data cut-off, there was no significant treatment group difference in OS for acalabrutinib monotherapy compared against IR/BR (stratified HR 0.84, 95% CI: 0.42–1.66; p=0.6089).[1]

Table 27: ASCEND - OS

	[redacted]	[redacted]
Events	15 (9.7%)	18 (11.6%)
KM estimated OS, % (95% CI)		
[redacted]	[redacted]	[redacted]
12 months	94.1 (89.0, 96.9)	90.6 (84.6, 94.3)
[redacted]	[redacted]	[redacted]

IR – idelalisib plus rituximab; BR – bendamustine plus rituximab; KM – Kaplan-Meier; OS – overall survival; CI – confidence interval; N - number

4.2.2.4 ASCEND effectiveness - TTNT

TTNT events (start of non-protocol-specified subsequent anti-cancer treatment for CLL, crossover to acalabrutinib monotherapy, or death due to any cause, whichever occurred first) occurred in [redacted] in the acalabrutinib monotherapy group, and [redacted] in the IR/BR group (see Table 28). [redacted]

Table 28: ASCEND - TTNT outcomes (reproduced from CS Table 41)

Outcome	Acalabrutinib (N=155)	IR/BR (N=155)
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Crossed over to acalabrutinib monotherapy	[redacted]	[redacted]
Subsequent anti-cancer therapy	[redacted]	[redacted]
Patients alive with no crossover or subsequent anti-cancer therapy, N (%)	[redacted]	[redacted]

IR – idelalisib plus rituximab; BR – bendamustine plus rituximab; N - number

4.2.2.5 ASCEND - adverse effects of treatment

AEs of any grade were experienced by 144 acalabrutinib-treated patients (93.5%), 117 (99.2%) IR-treated patients, and 28 (80.0%) BR-treated patients (see Table 29). Grade ≥3 AEs were experienced by 76 patients (49.4%) in the acalabrutinib monotherapy group, 106 IR-treated patients (89.8%), and 17 BR-treated patients (48.6%).[1]

The most common grade ≥3 AEs were as follows. Acalabrutinib monotherapy group: neutropenia (15.6%); anaemia (11.7%); pneumonia (5.2%); and thrombocytopenia (3.9%). IR-treated patients: neutropenia (39.8%); diarrhoea (23.7%); pneumonia (8.5%); alanine aminotransferase increased (8.5%); thrombocytopenia (7.6%); neutrophil count decreased (7.6%). BR treated patients: neutropenia (31.4%); and anaemia (8.6%).[1]

Deaths from AEs occurred in 8 patients (5.2%) in the acalabrutinib monotherapy group [redacted], 9 (7.6%) IR-treated patients [redacted] and 4 (11.4%) BR-treated patients (clarification response,[22] question A13).

Table 29: ASCEND - AE overview (safety population, adapted from CS Table 48 and clarification response question A13)

Event	Number (%) of patients		
	Acalabrutinib (N=154)	**IR (N=118)**	**BR (N=35)**
Median time on treatment (months)	Acalabrutinib - 15.7	Idelalisib - 11.5 Rituximab - 5.5	Bendamustine - 5.6 Rituximab - 5.5
Any grade AE	144 (93.5)	117 (99.2)	28 (80.0)
Grade ≥3	76 (49.4)	106 (89.8)	17 (48.6)
Grade 5	6 (3.9)	5 (4.2)	2 (5.7)
Serious AEs	28.6%	55.9%	25.7%
Death from AE	8 (5.2%)*	9 (7.6%)	4 (11.4%)
AE leading to discontinuation	[redacted]	[redacted]	[redacted]

IR – idelalisib plus rituximab; BR – bendamustine plus rituximab; AE – adverse event

*[redacted]

Serious AE defined as an AE that resulted in death, was life threatening, required or prolonged hospitalisation, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product, or was considered a significant medical event by the investigator

4.2.2.6 ASCEND – HRQoL outcomes

Patients in both treatment groups showed clinically meaningful improvements in fatigue (FACIT-Fatigue GFS) over 48 weeks, with a greater improvement shown by those with severe fatigue at baseline [redacted] (clarification response,[22] question A15).[30] In the ITT population (N=155 in both groups) at Week 48, the [redacted] change from baseline for GFS was 3.61 for acalabrutinib monotherapy [redacted] (clarification response,[22] question A15).[30] In the severe fatigue population at Week 48, the [redacted] change from baseline for GFS was 10.32 for acalabrutinib monotherapy [redacted] (clarification response,[22] question A15).[30]

There was an improvement in overall HRQoL (measured by the EORTC QLQ-C30 GHS) for acalabrutinib monotherapy, with increased scores of 7.21 points in the ITT population and 14.74 points in the severe fatigue population over 48 weeks (clarification response,22 question A15). In the IR/BR group, [redacted]

4.3 Critique of trials identified and included in the company's indirect comparison

The company did not undertake an indirect comparison of acalabrutinib versus any other therapy in the untreated high-risk CLL population. For previously treated (R/R) CLL, the company undertook an indirect comparison of acalabrutinib versus ibrutinib using data from ASCEND[21] and RESONATE (NCT01578707).[31]

The company's SLR identified four other studies of ibrutinib which were not included in the company's indirect comparison. The company's clarification response[22] (question A23) states that the company considered these studies to be unsuitable for the following reasons: De Jong (2015)[32] - single-arm study,

no effectiveness outcomes; Sharman (2017)[33] - no PFS or OS reported; Huang (2018)[34] - 85.6% patients were Asian; Burger (2019)[35] - Phase II study not considered as relevant as RESONATE. One of the ERG's clinical advisors considered that Huang *et al* may potentially have been relevant. In addition, the ERG notes that given the company's use of an unanchored MAIC to compare acalabrutinib against ibrutinib in patients with R/R CLL, there is no requirement for either study included in the comparison to adopt an RCT design. It is unclear from the CS[1] whether other non-randomised studies of acalabrutinib or ibrutinib could have been used to inform the comparison as only RCTs were included the company's SLR.

RESONATE was a Phase 3, multicentre, open-label, RCT that compared ibrutinib (420mg orally once daily until disease progression or unacceptable adverse effects, N=195) and ofatumumab (300mg IV week 1, 2000mg weekly for 7 weeks and then every 4 weeks for 16 weeks, N=196).[31] Randomisation was stratified by resistance to purine analogue chemoimmunotherapy and del(17p). Crossover to ibrutinib was allowed for patients in the ofatumumab arm after confirmed disease progression; however, data for this treatment group are not used in the company's indirect comparison. The primary outcome was IRC-assessed PFS.

RESONATE was at low risk of bias, apart from being open-label (Table 30); however, blinded outcome assessment was conducted for the primary outcome of PFS.[1]

Table 30: Quality assessment - RESONATE

Question	CS assessment How is the question addressed?	CS assessment Grade (yes/ no/ unclear/ N/a)	ERG assessment
Was randomisation carried out appropriately?	Details not provided in paper.	Unclear	Yes *"Randomisation was via an interactive web response system (IWRS). Two randomisation schemes were generated: one for each geographical region (US vs. non-US)"* (NICE TA429 ERG report[36])
Was the concealment of treatment allocation adequate?	Open-label study – all patients and clinicians were aware of the treatment received.	No	Yes *"Randomisation was via an interactive web response system (IWRS)."* (NICE TA429 ERG report[36])
Were the groups similar at the outset of the study in terms of prognostic factors?	See Table 31	Yes	Yes (Byrd *et al*, 2014[31]).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants were unblinded to treatment allocation. Primary outcome was PFS assessed by independent committee.	No	Patients and physicians – No. PFS outcome assessors – Yes (Byrd *et al,* 2014[31])
Were there any unexpected imbalances in drop-outs between groups?	See Table 31	No	No (Byrd et al 2014[31])
Is there any evidence to suggest that the authors measured more outcomes than they reported?	From assessment of the publications and NICE guidance available.	No	No (protocol available https://clinicaltrials.gov/ct2/show/study/NCT01578707)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes (Byrd *et al,* 2014[31]).

CS – company's submission; ERG – Evidence Review Group; NICE – National Institute for Health and Care Excellence; TA – technology appraisal; PFS – progression-free survival; N/a – not applicable

Eligibility criteria for RESONATE included: diagnosis of CLL that meets published diagnostic criteria (CLL or small lymphocytic leukaemia (SLL) diagnosis); ≥1 previous systemic therapy for CLL/SLL, and ECOG PS 0–1.[1] Both RESONATE and ASCEND included patients with previously treated CLL. The median age of patients in both RESONATE and ASCEND was 67 years. Unlike ASCEND, which did not include SLL patients, RESONATE did include SLL patients, although these were few in number (5.13% of the ibrutinib group). Unlike RESONATE, ASCEND included patients with ECOG PS 2.

Baseline characteristics for the acalabrutinib arm of ASCEND and the ibrutinib arm of RESONATE are given in Table 31. ASCEND had a significantly higher proportion of patients with only one prior therapy ([redacted] versus 18.0%, $p<0.0001$) and significantly lower proportions of patients with tumour bulk <5cm ([redacted] versus 64.0%, $p=0.02$), 17p deletions ([redacted] versus 32.0%, $p=0.01$) and Rai stage 3-4 ([redacted] versus 56.0%, $p=0.01$), than RESONATE (CS,[1] Section B.2b.9).

The median follow-up duration for patients in RESONATE was 9.4 months. Median IRC-assessed PFS was not reached in the ibrutinib arm. At 12 months, the OS rate was 90% in the ibrutinib arm. Median time on treatment was 8.6 months for ibrutinib. AEs were experienced by 99% of patients in the ibrutinib arm. Grade ≥3 AEs were experienced by 51% of the ibrutinib group.[31]

4.4 Critique of the company's indirect comparison

4.4.1 Methods for the ITC

In the absence of head-to-head evidence comparing acalabrutinib and ibrutinib in patients with R/R CLL, the company conducted an unanchored MAIC. The company considered that a network meta-analysis (NMA) would be unreliable as the evidence provided a disconnected network (unless an assumption of equal efficacy was made for certain interventions) and due to differences in the patient populations of ASCEND[21] and RESONATE[31] which may lead to an imbalance in treatment effect modifiers. The ERG considers that the company's decision to perform a MAIC was appropriate.

MAIC is a population adjustment method that makes use of the available individual patient data (IPD) to adjust for between-trial imbalances in the distribution of observed covariates. Individuals in the IPD population (the acalabrutinib arm of ASCEND) are weighted to balance the covariate distribution with that of the target aggregate population (the ibrutinib arm of RESONATE) with the intention of allowing meaningful comparisons to be derived. In order to make unanchored comparisons, MAICs rely on the assumption of conditional constancy of *absolute* effects. This is a much stronger assumption than that made for anchored comparisons, which require only conditional constancy of *relative* effects. MAICs therefore require that all effect modifiers and prognostic variables are known and accounted for in the adjustment model and this is known to be difficult to achieve in practice.[37]

Data contributing to MAIC

Aggregate baseline characteristics were extracted for RESONATE. Kaplan-Meier PFS and OS estimates were digitised using Engauge Digitizer (http://markummitchell.github.io/engauge-digitizer/) and IPD were reconstructed using the algorithm reported by Guyot *et al*.[38]

Selection of baseline covariates

The company selected baseline characteristics to be included in the MAIC based on data availability and input from clinical experts. A total of 13 categorical variables were considered in the analyses: age (>70 years), sex, presence of bulky disease ≥5cm, presence of del(17p), ECOG PS (0 or 1), beta-2 microglobulin >3.5 mg/L, Rai stage (1/2/0-2 or 3/4), Binet score, number of prior lines of therapy (1, 2, ≥ 3), CrCl < 60 mL/min, presence of del(11q), complex karyotype, and IgHV mutation status. For the last three of these variables, complete data were not available from RESONATE.

The base case analysis used by the company included all of these covariates, except for Binet score. Five sensitivity analyses were conducted including different sets of covariates in the logistic propensity score model (see Table 32). All models included the following 9 variables: age (>70 years), sex, presence of bulky disease ≥5cm, presence of del(17p), ECOG PS (0 or 1), beta-2 microglobulin >3.5 mg/L, number of prior lines of therapy (1, 2, ≥ 3), CrCl <60 mL/min, and presence of del(11q). The sensitivity analyses differed according to whether the remaining four variables were included: Rai stage (1/2/0-2 or 3/4), Binet score, complex karyotype and IgHV mutation status. The base case model was preferred by the company as the variables aligned with the CLL International Prognostic Index (CLL IPI)[39] and the effective sample size (ESS) was larger than that for the sensitivity analyses.

The clinical advisors to the ERG considered that the company's base case model contained all key prognostic variables and treatment effect modifiers, with presence of del(17p) and complex karyotype deemed as being particularly important.

Estimation of weights

ASCEND included 155 patients in the acalabrutinib arm; however, only 132 patients were included in the MAIC. Patients in ASCEND who had ECOG PS 2 at baseline (N=19) were excluded from the dataset due to lack of overlap with RESONATE, which was restricted to patients with ECOG PS 0 or 1. A further four patients were removed due to missing baseline characteristics.

In line with the methods described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) Number 18,[37] patients in the acalabrutinib arm of ASCEND were allocated a weight to ensure that baseline characteristics match those of the ibrutinib arm of RESONATE. Table 31 presents the baseline characteristics before and after matching for the base case MAIC.

The ESS was 44 (28% of the original sample size). A small ESS indicates that weights are highly variable due to a lack of population overlap and that the resulting estimate may be unstable.[37] In response to a request for clarification from the ERG[22] (question A29), the company provided further details of the distribution of estimated weights. The mean and median of the weights were 0.49 and 0.19 respectively, which indicates that half of the population were assigned small weights (<0.2) and have little impact on the resulting analyses. The provided histogram of the weights indicated that [redacted] individuals were assigned weights of $w \leq 1$, $1 < w \leq 2$, $2 < w \leq 3, w > 3$. However, the large bin width prevents an assessment of the number of individuals with weight close to zero.

Table 31: Baseline characteristics from RESONATE and ASCEND before and after application of weights from MAIC (adapted from CS Table 44)

Characteristic	Baseline characteristics in trial			MAIC weighted
	Ibrutinib	Acalabrutinib	*p*-value	Acalabrutinib
	N=195	N=132		ESS=44
Age ≥70 years	78 (40.0%)	[redacted]	0.58	[redacted]
Male	129 (66.0%)	[redacted]	0.38	[redacted]
Bulky disease <5 cm	124 (64.0%)	[redacted]	< 0.05	[redacted]
17p deletion	63 (32.0%)	[redacted]	< 0.01	[redacted]
11q deletion	63 (32.0%)	[redacted]	0.09	[redacted]
ECOG PS 0	79 (41.0%)	[redacted]	0.78	[redacted]
ECOG PS 1	116 (59.0%)	[redacted]	0.93	[redacted]
β2-microglobulin	153 (78.0%)	[redacted]	0.48	[redacted]
Rai stage 3-4	109 (56.0%)	[redacted]	< 0.01	[redacted]
Prior 1	35 (18.0%)	[redacted]	< 0.0001	[redacted]
Prior 2	57 (29.0%)	[redacted]	0.83	[redacted]
Prior ≥ 3	103 (53.0%)	[redacted]	< 0.0001	[redacted]
Complex karyotype	49 (25.0%)	[redacted]	0.35	[redacted]
IgHV unmutated	142 (73.0%)	[redacted]	0.29	[redacted]
CrCl <60	62 (32.0%)	[redacted]	0.35	[redacted]

MAIC – matching adjusted indirect comparison; ECOG – Eastern Cooperative Oncology Group; IgHV - immunoglobulin heavy chain variable; CrCI - creatinine clearance; N - number; ESS – effective sample size

4.4.2 Results of the MAIC

Weighted Kaplan-Meier estimates for PFS and OS for the base case MAIC were provided as part of the company's clarification response[22] (question A29); these are presented in Figure 4 and

Figure 5, respectively. The application of the weights results in reduced PFS and OS probabilities for the acalabrutinib arm and the resulting Kaplan-Meier estimates appear to be similar for both interventions.

Treatment effects were summarised as HRs for acalabrutinib versus ibrutinib using a weighted Cox proportional hazards (PH) model. Naïve comparisons using a standard Cox model (without application of weights) were also provided for comparison. The PH assumption was assessed statistically using tests based on Schoenfeld residuals. There was no evidence that the PH assumption was violated; however, the ERG notes that absence of statistical evidence for non-proportional hazards does not guarantee that the PH assumption holds and that relevance for the extrapolated period should also be considered. HRs for the MAIC base case and sensitivity analyses are provided in Table 32. Point estimates for the MAIC-adjusted HRs vary from [redacted] to [redacted] for PFS and [redacted] to [redacted] for OS, illustrating sensitivity to the choice of adjustment variables. Adjusted treatment effects were not statistically significant for either PFS or OS for any of the analyses.

The company concludes that the results of the MAIC demonstrate that the efficacy of acalabrutinib in PFS and OS in patients with R/R CLL is equivalent to that of ibrutinib. The primary use of the MAIC is to justify this assumption and the MAIC-weighted results are not applied directly in the company's economic analyses (see Section 5.2). Given the small ESS in the MAIC-weighted acalabrutinib population, the similarity of the weighted Kaplan-Meier curves for acalabrutinib and ibrutinib and the

variability in the treatment effects observed over the sensitivity analyses, the ERG considers that this is a reasonable conclusion.

Figure 4: Kaplan Meier PFS estimates before and after application of MAIC weights (reproduced from clarification response Figure 3)

Figure 5: Kaplan Meier OS estimates before and after application of MAIC weights (reproduced from clarification response Figure 4)

Table 32: Estimated HRs for MAIC sensitivity analyses (adapted from CS Table 47 and clarification response question A29)

Scenario	NV		ESS	PFS	OS

		variables not included		Naïve HR (95% CI)	MAIC HR (95% CI)	Naïve HR (95% CI)	MAIC HR (95% CI)
Base case	12	Binet score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1	12	Rai stage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S2	11	Complex karyotype, IgHV unmutated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3	13		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4	12	Complex karyotype	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5	12	IgHV unmutated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ESS – effective sample size; PFS – progression-free survival; OS – overall survival; HR – hazard ratio; CI – confidence interval; IgHV - immunoglobulin heavy chain variable; NV – number of variables

The company also used the MAIC to evaluate AE outcomes, with treatment effects calculated as mean differences and odds ratios (ORs). Full results are presented in Table 51 of the CS.[1] The incidence of AEs (any grade and grade 3/4) was generally lower with acalabrutinib than with ibrutinib. Acalabrutinib was associated with statistically significantly fewer serious adverse events (SAEs; acalabrutinib [redacted], ibrutinib 42.0%; $p<0.05$), incidence of grade 3/4 diarrhoea (acalabrutinib [redacted], ibrutinib 4.6%; $p<0.01$), infections (acalabrutinib [redacted], ibrutinib 21.0%; $p<0.05$), fatigue (acalabrutinib [redacted], ibrutinib 3.6%; $p<0.05$) and hypertension (acalabrutinib [redacted], ibrutinib 6.0%; $p<0.01$). However, acalabrutinib had a statistically significantly higher incidence of grade 3/4 anaemia (acalabrutinib [redacted], ibrutinib 6.0%; $p<0.05$).

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The ERG believes that all RCTs with currently available data on the clinical effectiveness of acalabrutinib in adults with CLL were included in the CS.

The key evidence of the clinical effectiveness and safety of acalabrutinib was from the ELEVATE-TN RCT[20] in untreated CLL (N=535), and the ASCEND RCT[21] in previously treated CLL (N=310), both of which were ongoing at time of writing. Both were open-label trials, but were otherwise at a low risk of bias. Both ELEVATE-TN and ASCEND included masked outcome assessment for the primary outcome of PFS. Clinical advisors to the ERG considered that the population in ELEVATE-TN was broadly representative of the population of FCR/BR-ineligible patients with untreated CLL in England,

and the population in ASCEND was broadly representative of the population with previously treated (R/R) CLL who would be eligible for treatment with acalabrutinib in England.

Untreated CLL (treatment-naïve population)

ELEVATE-TN[20] reported a statistically significant treatment group difference for PFS favouring acalabrutinib plus obinutuzumab over GClb (HR 0.10, 95% CI: 0.6–0.17; $p<0.0001$). There was also a statistically significant treatment group difference for PFS favouring acalabrutinib monotherapy over GClb (HR 0.20, 95% CI: 0.13–0.30, $p<0.0001$). At data cut-off, median PFS for the acalabrutinib plus obinutuzumab and the acalabrutinib monotherapy groups had not been reached; median PFS for GClb was 22.6 months.

The Kaplan-Meier estimated OS suggested a trend toward an advantage in OS for acalabrutinib plus obinutuzumab compared against GClb (HR=0.47, 95% CI: 0.21–1.06; $p=0.0577$). There was no significant treatment group difference between acalabrutinib monotherapy and GClb (HR=0.60, 95% CI: 0.28–1.27; $p=0.1556$). At data cut-off, median OS had not been reached in any of the three treatment arms.

The most common NCI-CTCAE grade ≥3 AEs experienced in the acalabrutinib plus obinutuzumab group were neutropenia (29.8%) and thrombocytopenia (8.4%). In the acalabrutinib monotherapy group, the most common grade ≥3 AEs were neutropenia (9.5%) and anaemia (6.7%). The most common grade ≥3 AEs in the GClb group were neutropenia (41.4%), thrombocytopenia (11.8%) and TLS (7.7%).

Previously treated (R/R) CLL

ASCEND[21] reported a statistically significant treatment group difference for PFS favouring acalabrutinib monotherapy over IR/BR (HR=0.31, 95% CI: 0.20–0.49; $p<0.0001$). At data cut-off, median PFS had not been reached in either study arm.

At data cut-off, there was no significant treatment group difference in OS for acalabrutinib monotherapy compared against IR/BR (HR=0.84, 95% CI: 0.42–1.66; $p=0.6089$) and median OS had not been reached in either study arm.

The most common grade ≥3 AEs in the acalabrutinib monotherapy group were neutropenia (15.6%) and anaemia (11.7%). In IR-treated patients, the most common grade ≥3 AEs were: neutropenia (39.8%); diarrhoea (23.7%); pneumonia (8.5%); ALT increased (8.5%); thrombocytopenia (7.6%); and neutrophil count decreased (7.6%). The most common grade ≥3 AEs in BR-treated patients were neutropenia (31.4%) and anaemia (8.6%).

As noted in Section 3.3, the company considers ibrutinib to be the relevant comparator in patients with R/R. In the absence of head-to-head evidence comparing acalabrutinib and ibrutinib, an unanchored MAIC was conducted using the ASCEND[21] and RESONATE[40] RCTs. RESONATE compared ibrutinib (N=195) versus ofatumumab (N=196). Median PFS was not reached in the ibrutinib group. Weights were applied to IPD from the acalabrutinib arm of ASCEND to balance the covariate distribution with that of the ibrutinib arm of RESONATE. Twelve covariates were included in the base-case MAIC and the ESS was 44. HRs for acalabrutinib versus ibrutinib from a weighted Cox PH model were [redacted] and [redacted] for PFS and OS. The results of the MAIC were used to justify an assumption of equivalent efficacy between acalabrutinib and ibrutinib; this assumption of equivalence underpins the cost-minisation approach employed in the company's economic analyses for the high-risk CLL and R/R CLL populations (See Section 5.2). Given the similarity in the weighted Kaplan-Meier curves for acalabrutinib and ibrutinib, the small ESS in the MAIC-weighted acalabrutinib population, and variability in the treatment effects observed over the sensitivity analyses, the ERG considers that this is a reasonable conclusion. The MAIC was also used to evaluate AE outcomes and demonstrated that the incidence of AEs (any grade and grade 3/4) was generally lower for acalabrutinib than ibrutinib. Acalabrutinib was also associated with statistically significantly fewer SAEs than ibrutinib ($p<0.05$).

The ERG notes that given the company's decision to perform an unanchored MAIC comparing acalabrutinib versus ibrutinib, their decision to restrict the eligibility criteria for the SLR to RCTs only was not necessary and it is unclear whether the MAIC could have been informed by other single-arm studies of acalabrutinib and/or ibrutinib. In addition, the ERG notes that the CS does not present any direct or indirect comparison of acalabrutinib versus ibrutinib specifically in the untreated high-risk CLL population (patients with del(17p)/TP53 mutations).

5. COST EFFECTIVENESS

This chapter provides a summary and critique of the company's economic analyses of acalabrutinib for the treatment of CLL. The chapter also presents the methods and results of additional exploratory analyses undertaken by the ERG using the company's models.

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 *Summary and critique of the company's search strategy*

The company performed systematic literature searches for: (i) published cost-effectiveness studies of treatments for people with CLL (CS Appendix G[24]); (ii) HRQoL studies in CLL (CS Appendix H[24]) and (iii) cost and resource use studies in CLL (CS Appendix I[24]). All three searches were undertaken in March 2018, followed by updates in June 2019 and February 2020.

The search strategies used to identify published cost-effectiveness studies and cost and resource use studies used one single search, and included the following sources: MEDLINE (via Embase.com), MEDLINE In-Process (via PubMed), Embase (via Embase.com), the Cochrane Central Register of Controlled Trials (via Wiley), the Health Technology Assessment (HTA) database (via Wiley), the Database of Abstracts of Reviews of Effects (DARE; via Wiley), the NHS Economic Evaluation Database (via Wiley) and EconLit (via AEAweb.org) in February 2020. The ERG does not have access to MEDLINE or Embase via the Embase.com host platform. The NHS EED, HTA and DARE databases are no longer accessible via Cochrane Library (since 2018), but remain accessible via the NIHR CRD website. The search strategies are comprehensive and the ERG did not identify any important errors.

The company searched several key conference abstract websites in the last three years via Embase.com, including: the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); ASCO; ESMO; ASH; ICML and AMCP. The ERG considers that the search should have been complemented by conference website searching,[41] especially for the most recent conference abstracts that are not immediately indexed in Embase (for example the ISPOR Presentations database at https://www.ispor.org/heor-resources/presentations-database/search).

In the HRQoL studies search, fewer databases were searched: MEDLINE (via Embase.com), MEDLINE In-Process (via PubMed), Embase (via Embase.com), and the Cochrane Central Register of Controlled Trials (via Wiley) in February 2020. There were no errors in the search and the ERG considers that the search is comprehensive and it is unlikely that relevant studies have been missed.

5.1.2 Summary of company's review findings

The company's searches identified 12 NICE appraisals and 52 economic evaluations in CLL. Of these, 25 studies were available as full texts, whilst 27 were available only as conference abstracts. The CS[1] (Section B.1.17) presents a table of 20 studies undertaken from a UK setting. Twelve of these UK analyses relate to the first-line treatment setting whilst the remaining eight studies relate to patients with previously treated (R/R) CLL. The identified studies adopted a range of economic modelling approaches including conventional state transition models, multi-state models and partitioned survival models.

Of particular note, one study (Vreman *et al*[42]) reported the methods and results of an early cost-utility analysis of acalabrutinib versus ibrutinib in patients with R/R CLL, based on an indirect comparison between the RESONATE study (ibrutinib versus ofatumumab) and a single-arm study of acalabrutinib (NCT02029443). This analysis suggested that acalabrutinib is effective and more expensive than ibrutinib. This contrasts with the company's cost-minimisation analysis (CMA) of acalabrutinib for patients with R/R CLL presented in the CS[1] (detailed in Section 5.2) which estimates cost-savings for acalabrutinib compared with ibrutinib, based on the assumption of clinically equivalent outcomes between the two treatments. In their clarification response[22] (question B26), the company stated that the assumptions regarding the relative efficacy of acalabrutinib and ibrutinib which underpin the analysis by Vremen *et al* do not represent the company's view. The company further stated that based on the results of the MAIC (see Section 4.4) and expert clinical opinion obtained by the company, acalabrutinib and ibrutinib have similar clinical efficacy, hence a CMA approach is appropriate.

As none of the other identified studies related to acalabrutinib, the company developed *de novo* models to inform the appraisal. Previous NICE technology appraisals (TAs) in CLL were used to justify the key features of the *de novo* model for acalabrutinib, including the modelling approach, the time horizon, the cycle length and the source of utility values (see CS,[1] Table 42).

5.2 Summary of the company's submitted economic evaluations

5.2.1 Scope of the company's economic analyses

As part of their submission to NICE,[1] the company submitted three model-based economic analyses of acalabrutinib. The models were programmed in Microsoft Excel.®

- **Model 1 (untreated CLL)** – This model compares acalabrutinib versus GClb for patients with untreated CLL. This is a model-based cost-utility analysis which uses a semi-Markov approach, based on data from ELEVATE-TN[20] as well as external sources (RESONATE[23] and MURANO[43]).

- **Model 2 (high-risk CLL)** – This model compares acalabrutinib versus ibrutinib for patients with untreated CLL with high-risk cytogenetic factors (del(17p) and TP53 mutations). This is a CMA which is based on the modelled clinical outcomes for the intervention group in the untreated CLL analysis (Model 1).
- **Model 3 (relapsed/refractory CLL)** – This model compares acalabrutinib versus ibrutinib for patients with R/R CLL. This is a CMA which uses a partitioned survival modelling approach based on PFS and OS data from RESONATE.[23] This analysis is distinct from Models 1 and 2, although some of the model parameter values are shared (e.g. treatment and health state costs).

The scope of the three economic analyses is summarised in Table 33.

Table 33: Scope of the company's economic analyses

Population	Model 1: Untreated CLL	Model 2: High-risk CLL (del(17p) and TP53 mutations)	Model 3: R/R CLL
Time horizon	30 years		
Intervention	Acalabrutinib		
Comparator	Obinutuzumab plus chlorambucil (GClb)	Ibrutinib	
Economic analysis approach	Cost-utility analysis	Cost-minimisation analysis	
Outcome	Incremental cost per QALY gained	Cost difference assuming clinically equivalent PFS and OS outcomes	
Perspective	NHS and PSS		
Discount rate	3.5%	Not applied in base case	
Price year	2017/18		

CLL - chronic lymphocytic leukaemia; del(17p) - 17p deletion; TP53 - tumour protein p53; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

All three economic analyses were undertaken from the perspective of the NHS and Personal Social Services (PSS) over a 30-year (lifetime) horizon. For the untreated CLL population (Model 1), cost-effectiveness is assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained for acalabrutinib (followed on progression by second-line VenR) versus GClb (followed on progression by second-line ibrutinib). The analyses in the high-risk CLL and R/R CLL populations (Models 2 and 3, respectively) estimate the differences in costs between acalabrutinib and ibrutinib, assuming clinically equivalent outcomes between the competing options; subsequent-line treatments given after disease progression are not included in either of these CMAs. For all three analyses, unit costs are valued at 2017/18 prices, except for drugs which are valued at current prices. For the untreated CLL population (Model 1), health outcomes and costs are discounted at a rate of 3.5% per annum. Discounting is not included in the base case analyses of the high risk CLL or R/R CLL populations (Models 2 and 3, respectively).

Populations

The company's economic analyses are intended to reflect three populations: (i) patients with untreated CLL, without high-risk cytogenetic features, and for whom FCR/BR are unsuitable, based on the characteristics of patients enrolled into the ELEVATE-TN trial;[20] (ii) patients with untreated CLL with high-risk cytogenetic factors (del(17p) and TP53 mutations), based on the characteristics of patients in the acalabrutinib arm of ELEVATE-TN,[20] and (iii) patients with R/R CLL, based on the characteristics of patients in the ASCEND trial.[21]

In the untreated CLL analyses (Models 1 and 2), patients are assumed to have a mean age of 70 years at model entry and 38% of patients are assumed to be female.[20] In the R/R CLL model (Model 3), patients are assumed to have a mean age of 67 years at model entry and 33% of patients are assumed to be female.[21]

Intervention

The intervention evaluated within the company's economic analyses is acalabrutinib administered orally at a dose of 100mg twice daily. [redacted] the model does not include a formal stopping rule for acalabrutinib; patients are assumed to continue treatment until disease progression or death, whichever occurs first.

In the untreated CLL population, the model assumes that following progression, patients initially treated with acalabrutinib will go on to receive second-line treatment with VenR for a maximum of 26 cycles (26 cycles of 400mg venetoclax daily, and 6 cycles of rituximab [first dose 375mg/m^2 once in the first 28-day cycle, subsequent doses 500mg/m^2 once per 28-day cycle]). In the high-risk untreated CLL population (Model 2) and the R/R CLL population (Model 3), no explicit assumption is made regarding which post-progression treatment regimens are used and the associated costs of these are excluded from the analysis, as these are expected to be the same between the two treatment groups.

Comparators

Each of the company's three analyses include a single comparator. In the untreated CLL population (Model 1), the comparator is assumed to be GClb. Patients are assumed to receive three doses of 1,000mg obinutuzumab given intravenously (IV) in the first 4-week period, followed by one dose of 1,000 mg IV obinutuzumab every 4 weeks thereafter. Chlorambucil is assumed to be administered orally at a dose of 0.5mg/kg once every 2 weeks. Treatment is capped at a maximum of 6 cycles. Following disease progression, the model assumes that these patients will go on to receive 420mg ibrutinib (oral) daily as second-line therapy until death or a maximum of 130 cycles. The ERG notes that in contrast to the model, which applies costs to all surviving patients following progression, the

SmPC for ibrutinib[44] states that treatment should be discontinued following progression. This issue is discussed further in Section 5.3.4.

In the high-risk untreated CLL population (Model 2) and the R/R CLL population (Model 3), the comparator is assumed to be ibrutinib taken orally at a dose of 420mg per day. Patients are assumed to continue to receive treatment until disease progression or death. As with the intervention group in these analyses, no second-line treatments are explicitly assumed and no costs are included.

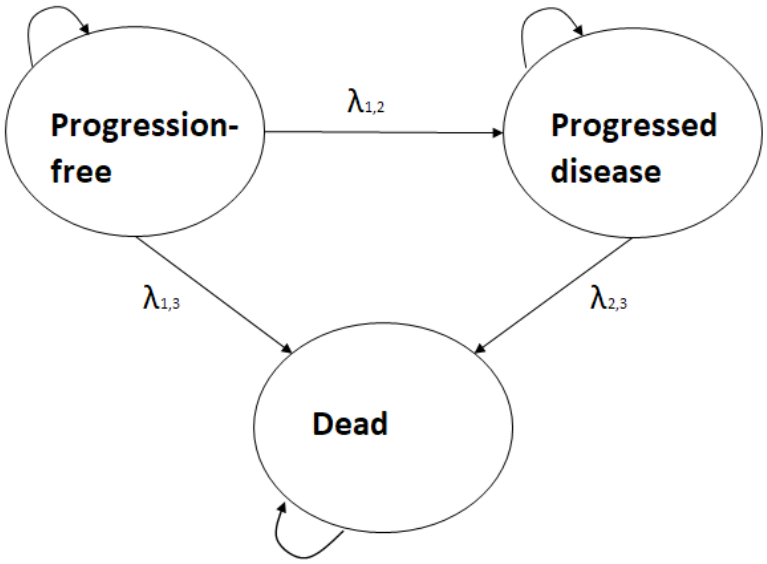
5.2.2 Model 1: Acalabrutinib versus GClb in patients with untreated CLL

This section describes the methods and results of the company's economic analysis of acalabrutinib in the untreated CLL population. The company's economic analysis of acalabrutinib in the high-risk CLL population is detailed in Section 5.2.3. The company's economic analysis of acalabrutinib in the R/R CLL population is detailed in Section 5.2.4. The key issues arising from the ERG's critical appraisal of these models are presented in Sections 5.3.4 and 5.3.5.

5.2.2.1 Model structure and logic

The company's economic analysis of acalabrutinib in the untreated CLL population adopts a semi-Markov structure comprised of three health states: (i) progression-free; (ii) progressed disease, and (iii) dead (see Figure 6).

Figure 6: Company's semi-Markov model structure, untreated CLL population



Where: $\lambda_{1,2}$ is governed by time to progression (TTP); $\lambda_{1,3}$ is governed by pre-progression mortality (PPM), and $\lambda_{2,3}$ is governed by post-progression survival (PPS)

The model logic operates as follows. Patients enter the model in the progression-free state and receive treatment with either acalabrutinib or GClb. Patients in the acalabrutinib group are assumed to continue

to receive treatment until disease progression or pre-progression death (whichever occurs first). Patients in the GClb group are assumed to receive treatment for up to six cycles, or until disease progression or pre-progression death (whichever occurs first). Following disease progression, patients in the acalabrutinib group are assumed to receive second-line treatment with VenR for up to 26 cycles, whilst patients in the GClb group are assumed to receive second-line treatment with ibrutinib for a maximum of 130 cycles (approximately 10 years). The model includes an assumed delay between progression and initiation of second-line therapy of [redacted] cycles for all patients ([redacted] years).

The model includes three permitted transitions:

(i) The transition from progression-free to progressed disease (denoted $\lambda_{1,2}$ in Figure 6) – the event rate for this transition is informed by an analysis of data on time to progression (TTP) from ELEVATE-TN[20] (PFS censored for pre-progression deaths)

(ii) The transition from progression-free to death (denoted $\lambda_{1,3}$ in Figure 6) – the event rate for this transition is informed by an analysis of data on pre-progression mortality (PPM) from ELEVATE-TN[20] (PFS censored for progression events)

(iii) The transition from progressed disease to death (denoted $\lambda_{2,3}$ in Figure 6) – the event rate for this transition (post-progression survival; PPS) is informed by an analysis of data on OS from external studies of patients with previously treated CLL – the VenR arm of the MURANO trial[43] (applied to patients who progress on first-line acalabrutinib) and the ibrutinib arm of the RESONATE trial[23] (applied to patients who progress on first-line GClb).

The two transitions for patients leaving the progression-free state ($\lambda_{1,2}$ and $\lambda_{1,3}$) are adjusted for competing risks; this adjustment involves multiplying the cause-specific hazard rates for TTP/PPM by the joint probability of progression or pre-progression death in each cycle. The two transitions into the dead state ($\lambda_{1,3}$ and $\lambda_{2,3}$) are each constrained by general population life tables[45] to ensure that the risk of death for patients with CLL is at least as high as the risk of death for the age- and sex-matched general population. Tunnel states are applied which allow mortality risk to be conditional on the time since entry into the intermediate (progressed disease) health state.

For any time *t*, health state occupancy is calculated as follows:

- The probability of being alive and progression-free in each cycle is calculated as 1 minus the probability of progressing or dying prior to disease progression.
- The cumulative probability of dying prior to progression in each cycle is calculated as the probability of dying in the previous cycles plus the probability of being alive and progression-free multiplied by the probability of PPM in the current cycle.

- The probability of entering the progressed disease state in a given cycle is given by the probability of being alive and progression-free multiplied by the probability of progression (based on TTP).
- The probability of being alive with progressed disease is calculated as the sum of patients who previously entered the progressed disease state minus those who leave the state. This is modelled using a series of tunnel states with a constant PPS probability.

HRQoL is assumed to be determined according to the presence/absence of disease progression (on first-line therapy): a higher utility value is applied to the progression-free state compared with the progressed disease state. Utilities are age-adjusted. The model also includes short-term QALY losses associated with AEs during the first model cycle.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration (GClb only); (iii) health state resource use; (iv) post-progression treatments (including a once-only monitoring cost for venetoclax); (v) the management of AEs, and (vi) end-of-life care.

The incremental health gains, costs and cost-effectiveness for acalabrutinib versus GClb are estimated over a 30-year time horizon using 28-day cycles. No subgroup analyses are presented using the full economic model for the untreated CLL population (although the CMA for the high-risk CLL population [Model 2] uses cost estimates derived from the intervention arm of the untreated CLL model; see Section 5.2.3).

5.2.2.2 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- Patients are assumed to be 70 years of age at model entry
- Patients who progress after receiving first-line acalabrutinib are assumed to receive second-line VenR. Patients who progress after receiving first-line GClb are assumed to receive second-line ibrutinib.
- The model does not explicitly include costs or outcomes associated with third- or subsequent-line therapies. In addition, the model includes only a single progression-free interval which relates to the period from initiation of treatment to disease progression on the first-line therapy.
- Within the acalabrutinib group, all three transitions (TTP, PPM and PPS) are assumed to follow exponential distributions.
- Within the GClb group, TTP and PPM are each assumed to follow log-normal distributions, whilst PPS is assumed to follow an exponential distribution.

- Transitions for patients without disease progression (TTP and PPM) are informed by ELEVATE-TN.[20] Owing to the immaturity of the OS data from ELEVATE-TN, PPS is informed by external sources (MURANO[43] and RESONATE[23]).
- Following disease progression on first-line treatment, patients are assumed to have a delay prior to commencing second-line treatment. All patients with progressed disease who remain alive after this delay are assumed to receive second-line treatment.
- HRQoL is assumed to be dependent on the presence/absence of disease progression. The same health state utility values are applied to each treatment group. Utilities are age-adjusted.
- First-line treatment is received until disease progression, pre-progression death or maximum treatment time (for GClb only – 6 cycles)
- Second-line treatment is given until death or maximum treatment time (VenR – 26 cycles, i.e. approximately 2 years; ibrutinib – 130 cycles, i.e. approximately 10 years).
- Only grade 3/4 AEs experienced by at least 1% of patients treated with acalabrutinib monotherapy or GClb in ELEVATE-TN are included in the model. These AEs are assumed to impact on both QALYs and costs.
- Monitoring costs for acalabrutinib are excluded as the CS states that additional monitoring will not be required. A once-only monitoring cost is included for patients initiating second-line VenR.
- Relative dose intensity (RDI) is assumed to be 100% for all drug regimen components.
- Wastage is not included for any therapy.

5.2.2.3 Evidence used to inform the company's model parameters

Table 34 summarises the evidence sources used to inform the model parameters in the company's base case analyses. These are discussed in detail in the subsequent sections.

Table 34: Summary of evidence used to inform the company's base case analyses, untreated CLL population

Parameter / group	Acalabrutinib	GClb
Patient characteristics	ELEVATE-TN[20]	
Time to progression (TTP) $\lambda_{1,2}$	Exponential model fitted to TTP data from ELEVATE-TN.[20] Adjusted for competing risks.	Log-normal model fitted to TTP data from ELEVATE-TN.[20] Adjusted for competing risks.
Pre-progression mortality (PPM) $\lambda_{1,3}$	Exponential model fitted to PPM data from ELEVATE-TN.[20] Adjusted for competing risks.	Log-normal model fitted to PPM data from ELEVATE-TN.[20] Adjusted for competing risks.
Post-progression survival (PPS) $\lambda_{2,3}$	Exponential model fitted to PPS estimated using OS data from the VenR arm of the MURANO trial.[43]	Exponential model fitted to PPS estimated using OS data from the ibrutinib arm of the RESONATE trial.[23]
General population mortality	UK life tables 2015-2017[45]	
Health state utility values	Utility value for progression-free state based on EQ-5D-3L data collected in ELEVATE-TN.[20] Utility value for progressed disease state reported to be based on Holzner *et al*[46] (see Section 5.3.4).	
General population utility	Ara and Brazier[47]	
Duration of interval between progression and initiation of second-line treatment	ELEVATE-TN[20] (estimated as the difference in median PFS and median TTNT in the GClb group)	
AE frequencies	ELEVATE-TN[20]	
AE disutilities	TA487,[11] NICE TA359[6] and Wehler *et al*[48]	
AE duration	NICE TA487,[11] NICE TA403[49] and assumptions	
Drug acquisition costs	CS[1] and BNF[50]	
Drug administration costs	NHS Reference Costs 2017/18[51] - relevant only to obinutuzumab (first-line) and rituximab (second-line)	
Health state costs	Taken from NICE TA561[10] (VenR for R/R CLL)	
Second-line treatment costs	Treatment durations and doses taken from SmPCs for ibrutinib, venetoclax and rituximab[44, 52, 53] and expert opinion. Acquisition costs taken from BNF[50]	
AE management costs	TA487,[11] TA561,[10] NHS Reference Costs 2017/18[51] and assumptions	
End-of-life care costs	Round *et al*[54]	

GClb – obinutuzumab plus chlorambucil; EQ-5D-3L – Euroqol 5-Dimensions (3-level); PFS – progression-free survival; TTNT – time to next treatment; CS – company's submission; BNF – British National Formulary; R/R – relapsed refractory; CLL – chronic lymphocytic leukaemia; NICE – National Institute for Health and Care Excellence; TA – technology appraisal; SmPC – Summary of Product Characteristics

5.2.2.3.1 Patient characteristics

Patient characteristics are based on ELEVATE-TN.[20] Patients are assumed to have a mean age of 70 years at model entry, a body mass of 79kg, a BSA of 1.93m^2 and 38% of patients are assumed to be female. Patient age and the proportion of patients who are female are used to determine general population mortality risks and utilities. Body mass is used only to determine the cost per dose of chlorambucil (given alongside obinutuzumab as the first-line treatment in the comparator group). BSA is used only to determine the cost per dose of rituximab (given alongside venetoclax as second-line treatment for patients in the acalabrutinib group).

5.2.2.3.2 Time-to-event parameters

The model uses separate data sources to model time-to-event outcomes for untreated CLL. Whilst TTP and PPM are informed using data from ELEVATE-TN,[20] PPS is informed using data from external sources. Patients receiving first-line acalabrutinib are assumed to receive VenR as second-line treatment, and their PPS is informed by OS data from the VenR arm of the MURANO trial[43] (patients with ≥1 prior CLL therapies). In contrast, patients receiving first-line GClb are assumed to receive ibrutinib as second-line treatment and PPS for this group is informed by OS data from a subset of the ibrutinib arm of the RESONATE trial[23] (patients with 1-2 prior CLL therapies). According to the CS[1] (Section B.3a.3.3), this approach was adopted due to immaturity of the OS data from ELEVATE-TN.

Time to progression (TTP) and pre-progression mortality (PPM)

Within the untreated CLL model population, TTP and PPM for acalabrutinib and GClb were modelled using available IPD for IRC-assessed PFS from ELEVATE-TN[20] (censored for death in the case of TTP and censored for progression in the case of PPM; acalabrutinib N=179; GClb N=177). The company fitted a range of standard parametric survival models to TTP and PPM data for each treatment group. These included exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma distributions. The parametric survival models were fitted independently without the inclusion of a treatment-indicating covariate.

The CS[1] states that the candidate models for each treatment group were assessed for inclusion in the base case analysis through consideration of: relative goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]); visual inspection of the fitted distributions; examination of log-cumulative hazard plots, and clinical plausibility (CS, page 126). The selection process also involved concurrently assessing the candidate functions for TTP and PPM in order to *"provide a better representation of PFS"* and checking the clinical plausibility of the composite PFS functions (CS, pages 134-136). The company made the *a priori* decision to select the same parametric function for both TTP and PPM.

The AIC and BIC statistics for TTP and PPM the candidate models for each treatment group are presented in Table 35. Kaplan-Meier plots and modelled TTP functions for the acalabrutinib and the GClb groups are presented in Figure 7 and

Figure 8, respectively. Kaplan-Meier plots and modelled PPM functions for the acalabrutinib and the GClb groups are presented in Figure 9 and

Figure 10, respectively.

Table 35: Summary of goodness-of-fit statistics for TTP (based on PFS assessed by IRC, censored for death) – untreated CLL patients in ELEVATE-TN

Distribution	Acalabrutinib		GClb	
	AIC	BIC	AIC	BIC
TTP				
Exponential	**256.80**	**259.98**	773.25	776.43
Weibull	260.10	266.48	716.25	722.61
Gompertz	258.65	265.02	736.32	742.67
Log-normal	257.99	264.37	702.05	708.40
Log-logistic	258.88	265.25	707.64	714.00
Gamma	258.68	265.05	708.21	714.56
Generalised gamma	260.42	269.98	**696.69**	**706.22**
PPM				
Exponential	**133.17**	**136.36**	164.01	**167.19**
Weibull	134.85	141.22	163.55	169.90
Gompertz	134.89	141.26	165.55	171.90
Log-normal	135.02	141.39	164.23	170.59
Log-logistic	134.85	141.22	163.62	169.97
Gamma	134.85	141.22	**163.50**	169.85
Generalised gamma	Not reported	Not reported	165.48	175.00

GClb – obinutuzumab plus chlorambucil; AIC - Akaike information criterion; BIC - Bayesian information criterion; IRC - Independent review committee; TTP - time to progression; PPM – pre-progression mortality
Bold indicates best-fitting model

Figure 7: Kaplan-Meier plot and modelled TTP (based on PFS assessed by IRC, censored for death) – untreated CLL patients in ELEVATE-TN, acalabrutinib

Note – models presented exclude general population mortality constraint

Figure 8: Kaplan-Meier plot and modelled TTP (based on PFS assessed by IRC, censored for death) – untreated CLL patients in ELEVATE-TN, GClb

Note – models presented exclude general population mortality constraint

Figure 9: Kaplan-Meier plot and modelled PPM (based on PFS assessed by IRC, censored for progression) – untreated CLL patients in ELEVATE-TN, acalabrutinib

Note – models presented exclude general population mortality constraint

Figure 10: Kaplan-Meier plot and modelled PPM (based on PFS assessed by IRC, censored for progression) – untreated CLL patients in ELEVATE-TN, GClb

Note – models presented exclude general population mortality constraint

Within the acalabrutinib group, the exponential model provided the best fit to TTP and PPM in terms of both AIC and BIC. The generalised gamma model was ruled out because it did not provide a good fit to the PPM data. The Gompertz model was ruled out as it provided a clinically implausible PFS projection, . The log-logistic and log-normal models were also ruled out as the PFS projections using these models were considered to be too optimistic. Following discussion with clinical experts, the company selected the exponential distribution for TTP and PPM as it provided a better fit compared with the remaining models (Weibull and gamma) and because it provided "*the most conservative estimates of cost-effectiveness"* (clarification response,[22] question B10). The company's scenario analyses explore the impact of applying the Weibull model for TTP and PPM in the acalabrutinib group (see Table 45).

Within the GClb group, for the outcome of TTP, the generalised gamma distribution was the best fitting model in terms of both AIC and BIC, whilst for PPM, the gamma model had the lowest AIC and the exponential model had the lowest BIC. The CS[1] notes that for TTP, the exponential model does not provide a good visual fit to the data during the observed period and that this model suggests a long tail which is not observed for the other models considered. For the outcome of PPM, all models represented the observed data well. The exponential, Weibull and Gompertz models were rejected on the basis of poor overall AIC and BIC values. The generalised gamma was rejected as the TTP model indicated a tail which was not considered clinically plausible. The gamma, log-normal and log-logistic distributions

produced similar PFS extrapolations. Of these three remaining models, the log-normal model was selected for inclusion in the base case analysis as it had the best fit to TTP. The company's sensitivity analyses explore the impact of applying the log-logistic model for TTP (and PPM) in the GClb group (see Table 45).

Within the company's economic model, TTP and PPM were adjusted for competing risks. The composite PFS functions used in the company's untreated CLL model are presented in Figure 11.

Figure 11: Observed versus predicted PFS, untreated CLL model, acalabrutinib TTP and PPM (exponential), GClb TTP and PPM (log-normal)

Note – models presented include general population mortality constraint

Post-progression survival

PPS for patients in the acalabrutinib group was modelled using observed OS data from the VenR arm of the MURANO trial (N=194).[43] The CS[1] states that data for patients with 1-2 prior treatments were used, however it appears that the available data reflect the ITT population, with 13% of patients having received three or more prior lines of treatment. PPS for patients in the GClb group was modelled using observed OS data from the subset of patients in the ibrutinib arm of the RESONATE trial who had received 1-2 prior treatments (N=68).[23] In both datasets, the company reconstructed the IPD from digitised Kaplan-Meier OS curves using the approach reported by Guyot *et al*.[38] The company then fitted seven standard parametric survival models to the replicated IPD. These included the exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma distributions. Table 36 presents the AIC and the BIC statistics for each treatment group. Figure 12 presents the observed

Kaplan-Meier plots and modelled OS functions for each of the candidate models for the VenR arm of MURANO.

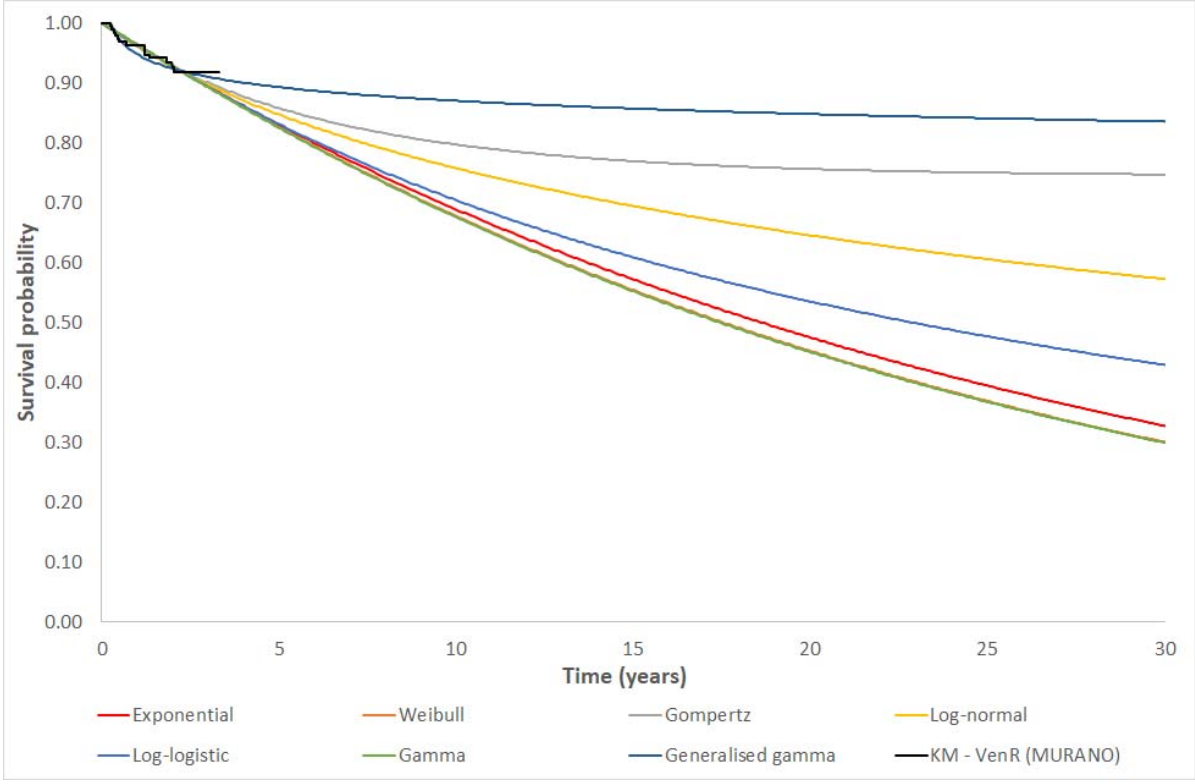
Figure 13 presents the observed Kaplan-Meier plots and modelled OS functions for each of the candidate models for the ibrutinib arm of RESONATE.

Table 36: Summary of goodness-of-fit statistics for PPS

Distribution	VenR (from MURANO[43])		Ibrutinib (from RESONATE[23])	
	AIC	BIC	AIC	BIC
Exponential	191.71	**194.98**	**175.57**	**177.786**
Weibull	193.70	200.23	177.28	181.72
Gompertz	193.59	200.12	177.19	181.63
Log-normal	192.74	199.28	178.00	182.44
Log-logistic	193.62	200.16	177.38	181.823
Gamma	193.69	200.23	177.30	181.74
Generalised gamma	**189.95**	199.75	179.20	185.86

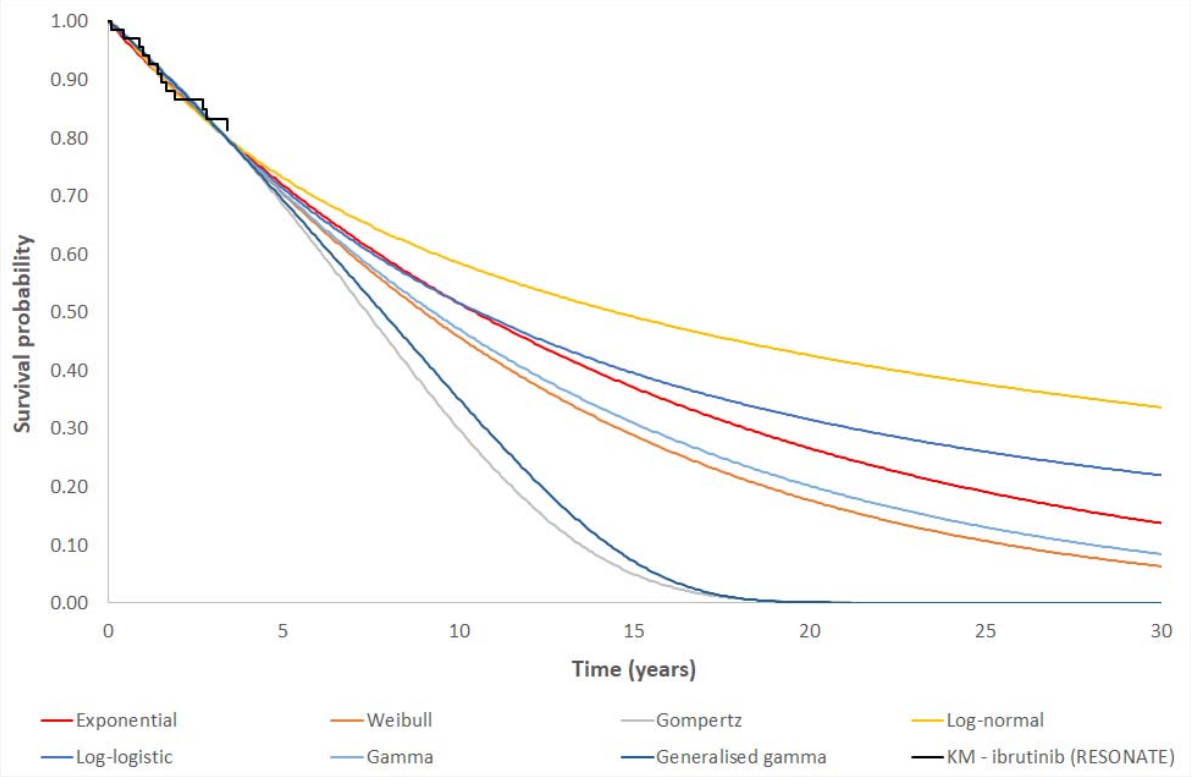
VenR – venetoclax plus rituximab; AIC - Akaike information criterion; BIC - Bayesian information criterion

Figure 12: Kaplan-Meier plot and modelled PPS – VenR arm of MURANO (ITT population), R/R CLL (re-drawn by the ERG)



Note – models presented exclude general population mortality constraint

Figure 13: Kaplan-Meier plot and modelled PPS – ibrutinib arm of RESONATE (1-2 prior lines of treatment), R/R CLL (re-drawn by the ERG)



Note – models presented exclude general population mortality constraint

In both treatment groups, the company selected the exponential model for PPS on the basis of relative goodness-of-fit statistics and visual inspection of the fitted distributions. The CS[1] argues that this is appropriate as there is no strong evidence of an increasing hazard of death prior to the general population mortality constraint taking effect within the model (see CS, pages 139 and 141). The ERG notes that the available OS data used to inform PPS are subject to high levels of censoring and the nature of the long-term hazard is uncertain.

Within the company's model, PPS is adjusted to ensure that the estimated event probabilities derived from the OS function in any given cycle are never lower than the overall risk of death in the general population.[45]

Figure 14 presents observed Kaplan-Meier plots for OS versus model-predicted OS for the acalabrutinib and GClb groups.

Figure 14: Observed and model-predicted OS, untreated CLL model, acalabrutinib versus GClb

Note – models presented includes general population mortality constraint

5.2.2.3.3 Health-related quality of life

ELEVATE-TN[20] includes the measurement of HRQoL using the EQ-5D-3L. [redacted]. EQ-5D-3L responses were valued using the UK value set.[55] Mean health utility values were reported to be [redacted] (95% CI: [redacted]; based on [redacted] observations) for patients who are progression-free and [redacted] (95% CI: [redacted]; based on [redacted] observations) for patients with progressed disease. No details are provided in the CS regarding how these estimates were generated or how repeated observations from the same patients were handled. The company's clarification response[22] (question B21) states that values were estimated as the mean values across all observations and across all patients.

The CS[1] notes that the EQ-5D-3L estimate for the progressed disease state is substantially higher than estimates used in economic models of treatments for progressed CLL and highlights that the sex-matched general population utility for patients age 65 to <70 years is 0.81, based on Ara and Brazier.[47] However, the ERG notes that as patients are assumed to already be 70 years old at model entry, the more relevant estimated general population utility value from Ara and Brazier is 0.78; this is lower than both the EQ-5D-3L estimates for patients with disease progression and for those who are progression-free in ELEVATE-TN.[20] The CS indicates that the implausibly high utility estimate for progressed patients is potentially due to the lack of available data for patients with progressed disease.[1] As such, the company used an alternative estimate for the progressed disease state of 0.60. According to the CS,

this estimate was sourced from Holzner *et al*.[46] This study reports on HRQoL measurements in 418 patients with cancer, including 81 patients with CLL, using the EORTC-QLQ-C30 and the FACT-G. However, the Holzner study does not map the results to the EQ-5D instrument, nor does it report any preference-based utility values. The original source of the estimate used in the company's model is therefore unclear from the CS, although as noted in the submission, this value has been used in several previous appraisals, including TA193,[12] TA359,[6] TA487[11] and TA561.[10] This issue is discussed further in Section 5.3.4.

The model also includes QALY losses associated with grade 3/4 AEs that occurred in at least 1% of patients treated with acalabrutinib monotherapy or GClb in ELEVATE-TN.[20] Disutilities for specific AEs were taken from previous NICE TAs[6, 11] and a poster presentation by Wehler *et al*[48] (based on a model of R/R acute myeloid leukaemia [AML] which, in turn, draws utility estimates from other literature). AE durations were based on previous NICE TAs[11, 49] and assumptions. AE frequencies, durations and disutilities included in the model are summarised in Table 37. QALY losses are applied as the sum of the product of these three factors in the first model cycle only.

Health utility estimates are adjusted for age using utility decrements based on sex-specific UK general population utilities reported by Ara and Brazier.[47] These are applied as a relative decrease from the mean utility for the population at model entry (70 years) and the multiplier is assumed to increase linearly with increasing age.

Table 37: Adverse event frequencies, durations and disutilities

AE	Frequency – acalabrutinib	Frequency – GClb	AE duration	AE disutility	Frequency source	Duration source	Disutility source
ALT/AST increased	0.56%	1.78%	20.99	-0.05	ELEVATE-TN[20]	TA487[11]	TA487[11]
Anaemia	6.70%	7.10%	23.21	-0.09	ELEVATE-TN[20]	TA487[11]	TA487[11]
Bleeding	1.70%	0.00%	14.00	-0.22	ELEVATE-TN[20]	Assumption	Wehler *et al*[48]
Diarrhoea	0.56%	1.78%	3.00	-0.20	ELEVATE-TN[20]	TA403[49]	TA359[6]
Febrile Neutropenia	1.12%	5.33%	4.00	-0.20	ELEVATE-TN[20]	TA403[49]	TA359[6]
Infections and infestations	14.00%	8.30%	14.00	-0.22	ELEVATE-TN[20]	Assumption	Wehler *et al*[48]
Infusion-related reaction	0.00%	5.33%	3.50	-0.20	ELEVATE-TN[20]	TA487[11]	TA487[11]
Neutropenia	9.50%	41.42%	15.09	-0.16	ELEVATE-TN[20]	TA487[11]	TA487[11]
Neutrophil count decreased	0.00%	2.96%	15.09	-0.16	ELEVATE-TN[20]	TA403[49]	TA487[11]
Thrombocytopenia	2.79%	11.83%	23.21	-0.11	ELEVATE-TN[20]	TA487[11]	TA487[11]
TLS	0.00%	7.69%	14.00	-0.22	ELEVATE-TN[20]	Assumption	Wehler *et al*[48]

GClb – obinutuzumab plus chlorambucil; AE - adverse event; ALT - alanine aminotransferase; AST- aspartate aminotransferase; TLS – tumour lysis syndrome; TA - technology appraisal

5.2.2.3.4 Resource use and unit costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration (GClb only); (iii) health state resource use; (iv) post-progression treatments; (v) the management of AEs, and (vi) end-of-life care. The costs applied in the company's model are summarised in Table 38; these are described in further detail below.

Table 38: Summary of model cost assumptions

Cost component	Acalabrutinib	GClb
First-line acquisition costs (per 28-day cycle)	Acalabrutinib [redacted]	Cycle 1 Obinutuzumab: £9,936.00; chlorambucil: £67.73 Cycles 2-6 Obinutuzumab: £3,312.00; chlorambucil: £67.73
First-line administration costs (per 28-day cycle)	N/a	Obinutuzumab only Cycle 1: £684.87 Cycles 2-6: £228.29
Second-line treatment costs (per 28-day cycle)	Venetoclax (maximum 26 cycles): £4,789.47 Rituximab (maximum 6 cycles): £1,683.57	Ibrutinib (maximum 130 cycles): £4,292.40
Health state costs – progression-free (per 28-day cycle)	£25.50	£25.50
Health state costs – progressed disease (per 28-day cycle)	£416.13	£416.13
AE management costs (once-only)	£410.28	£760.04
End-of-life care (once-only)	£6,975.00	£6,975.00

GClb – obinutuzumab plus chlorambucil; PAS – Patient Access Scheme; AE – adverse event; N/a – not applicable

Acquisition and administration costs

All drugs are costed according to a 28-day cycle length. The treatment options included in the first- and second-line settings are summarised in Table 39. It should be noted that a PAS is available for acalabrutinib; the impact of this PAS is included in all results presented in this ERG report. Comparator PAS (cPAS) discounts are also available for obinutuzumab, venetoclax, rituximab, ibrutinib and chlorambucil; the impact of these cPAS discounts on the cost-effectiveness of acalabrutinib is presented in a separate confidential appendix to this ERG report.

Table 39: Drug treatments included in company's model, includes PAS for acalabrutinib, excludes cPAS discounts for obinutuzumab, chlorambucil, venetoclax, rituximab and ibrutinib

Drug	Treatment line in model	Administration route	Stopping criteria used in company's model	Doses per 28 days	Drug cost per 28 days' supply (based on list prices)	Cost source
Acalabrutinib	First	Oral	Progression or pre-progression death	100mg twice daily	[redacted]	CS[1]
Obinutuzumab*	First	IV	Maximum 6 cycles (0.46 years), progression or pre-progression death	Cycle 1: 3 x 1,000mg Cycles 2-6: 1,000mg per cycle	Cycle 1: £9,936.00 Cycles 2-6: £3,312.00	BNF[50]
Chlorambucil	First	Oral	Maximum 6 cycles (0.46 years), progression or pre-progression death	2 x 0.5mg/Kg	£67.73	BNF[50]
Venetoclax	Second	Oral	Maximum 26 cycles (1.99 years) or death	400mg once daily	£4,789.47	BNF[50]
Rituximab	Second	IV	Maximum 6 cycles (0.46 years) or death	Cycle 1: 375mg/m^2 Cycles 2-6: 500mg/m^2	£1,454.58	BNF[50]
Ibrutinib	Second	Oral	Maximum 130 cycles (9.97 years) or death	420mg daily	£4,292.40	BNF[50]

IV – intravenous; PAS – Patient Access Scheme; BNF – British National Formulary; CS – company's submission

Based on its list price, the cost per pack of 60 x 100mg acalabrutinib tablets (30 days' supply) is [redacted]. The inclusion of the PAS for acalabrutinib leads to a discounted cost per pack of [redacted] treatment with acalabrutinib is assumed to continue until disease progression or death; the model does not include a stopping rule. Obinutuzumab is assumed to be given as three doses of 1,000mg obinutuzumab in the first 28-day cycle followed by one dose of 1,000mg obinutuzumab in cycles 2-6. The list price per 1,000mg dose of obinutuzumab is £3,312.00, taken from the British National Formulary (BNF).[50] Chlorambucil is assumed to be given at a dose of 0.5mg/kg every two weeks for a maximum of six cycles. The list price for 2mg chlorambucil is £42.87.[50]

Post-progression treatment costs

Second-line treatment costs are applied to the surviving cohort who progression event is not death and who survive for at least [redacted] cycles following disease progression ([redacted] years). This period reflects an assumption that patients experience a delay between disease progression and initiation of second-line treatment and is based on the difference in median PFS and median TTNT in patients in the GClb arm of ELEVATE-TN.[20] The same delay is applied to both treatment groups in the model.

Following disease progression, patients who received acalabrutinib in the first-line setting are assumed to receive second-line VenR. The model assumes that patients receive 400mg venetoclax for up to 26 cycles (approximately 2 years) based on the list price of £4,789.47 per cycle[50] and 375mg/m^2 (cycle 1) or 500mg/m^2 (cycles 2-6) rituximab at an average cost of £1,454.58 per cycle.[50] The costs of VenR are applied to all surviving patients rather than those patients who are alive and progression-free; this is inconsistent with the SmPC for venetoclax.[52] After 26 cycles following initiation of second-line treatment, patients in the acalabrutinib group do not incur any further costs associated with active therapy. The model also includes a once-only cost for monitoring and TLS prophylaxis of £1,975.46 based on NICE TA561.[10]

Patients who received GClb in the first-line setting are assumed to receive second-line ibrutinib. The model assumes that patients receive 420mg ibrutinib once daily for a maximum of 130 cycles, based on a list price of £4,292.40 per 28 days.[50] Second-line ibrutinib treatment costs are applied to all surviving patients irrespective of progression status until the maximum treatment duration (130 cycles – approximately 10 years) or death; this is inconsistent with the SmPC for ibrutinib which advises that treatment should be discontinued upon progression.[44] This issue is further discussed in Section 5.3.4.

The cost calculations included in the model do not include wastage for any regimen. This issue is also discussed in Section 5.3.4.

The cost per administration of IV drugs (obinutuzumab and rituximab) was assumed to be £228.99, based on NHS Reference Costs 2017/18.[51]

Health state resource use

Table 40 presents the per-cycle costs assumed for the progression-free and progressed disease health states in the company's model. The numbers of each resource component required per cycle were taken from the previous NICE TA of VenR for untreated CLL (TA561).[10] Unit costs for each resource item were based on NHS Reference Costs 2017/18[51] Within the company's model, the same costs were applied to the health states for the acalabrutinib and the GClb groups.

Table 40: Health state resource use and costs applied in the company's model

Resource item	Frequency per 28-day cycle		Unit cost	Total cost per cycle	
	Progression-free	Post-progression		Progression-free	Post-progression
Full blood count	0.31	0.61	£2.51	£0.77	£1.54
LDH	0.23	-	£1.11	£0.26	-
Haematologist visit	0.15	0.46	£159.65	£24.48	£73.43
Chest X-ray	-	0.15	£77.48	-	£11.88
Bone marrow exam	-	0.08	£495.98	-	£38.02
Inpatient visit (Non-surgical)	-	0.31	£432.93	-	£132.75
Full blood transfusion	-	0.84	£187.97	-	£158.51
Total cost	-	-	-	**£25.50**	**£416.13**

LDH - lactate dehydrogenase

AE management costs

Table 41 summarises the unit costs associated with the management of AEs in the company's model. Costs were based on NHS Reference Costs 2017/18,[51] NICE TA487[11] (uplifted using Curtis *et al*[56]) and assumptions. All AE management costs are applied once-only during the first model cycle.

Table 41: Adverse event costs assumed in the company's model

AE	Frequency – acalabrutinib	Frequency – GClb	Unit cost	Frequency source	Unit cost source
ALT/AST increased	0.56%	1.78%	£0.00	ELEVATE-TN[20]	Assumption based on TA561[10]
Anaemia	6.70%	7.10%	£366.00	ELEVATE-TN[20]	NHS Reference Costs 2017/18[51]
Bleeding	1.70%	0.00%	£1,783.94	ELEVATE-TN[20]	NHS Reference Costs 2017/18[51] (assumed to be the same as infections)
Diarrhoea	0.56%	1.78%	£149.00	ELEVATE-TN[20]	NHS Reference Costs 2017/18[51]
Febrile Neutropenia	1.12%	5.33%	£6,623.14	ELEVATE-TN[20]	NICE TA487[11]
Infections and infestations	14.00%	8.30%	£1,783.94	ELEVATE-TN[20]	NHS Reference Costs 2017/18[51]
Infusion-related reaction	0.00%	5.33%	£0.00	ELEVATE-TN[20]	NICE TA487[11]
Neutropenia	9.50%	41.42%	£136.34	ELEVATE-TN[20]	NICE TA487[11]
Neutrophil count decreased	0.00%	2.96%	£136.34	ELEVATE-TN[20]	NICE TA487[11]
Thrombocytopenia	2.79%	11.83%	£640.09	ELEVATE-TN[20]	NHS Reference Costs 2017/18[11]
TLS	0.00%	7.69%	£1,226.80	ELEVATE-TN[20]	NICE TA487[11]

GClb – obinutuzumab plus chlorambucil; ALT – alanine aminotransferase; AST - aspartate aminotransferase; TLS - tumour lysis syndrome; TA – technology appraisal

End-of-life care costs

The cost of end-of-life care was estimated to be £6,975 based on Round *et al*[54] (including an uplift to current values). This is applied as a once-only cost to patients entering the dead health state.

5.2.2.4 Model evaluation methods

The CS[1] presents base case incremental cost-effectiveness ratios (ICERs) for acalabrutinib versus GClb. Results are presented using both the deterministic and probabilistic versions of the model; the probabilistic ICERs are based on 1,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). The CS also reports a number of deterministic sensitivity analyses (DSAs) and scenario analyses exploring alternative assumptions regarding: the model time horizon; discount rates; the utility value for the progression-free health state; the exclusion of age-adjustment of utilities, and a limited set of alternative parametric models for TTP and PPM. The distributions used in the company's PSA are presented in Table 42.

Table 42: Summary of distributions used in company's PSA

Parameter group	Distribution applied in PSA	ERG comment
Patient characteristics (start age, probability female, BSA, body mass)	Fixed	These parameters are subject to uncertainty
Time to progression (TTP)	Multivariate normal	-
Pre-progression mortality (PPM)	Multivariate normal	-
Post-progression survival (PPS)	Normal	Normal distribution applied as PPS is modelled using exponential distributions
AE frequencies	Beta	-
AE disutilities	Beta	-
Health utilities	Beta	-
Drug acquisition costs	Fixed	-
Drug administration costs	Fixed	This parameter is subject to uncertainty
Delay prior to initiating second-line treatment	Fixed	Fixed duration implemented as a structural assumption
Post-progression treatment costs	Gamma	Uncertainty relates to duration on second-line treatment rather than drug acquisition costs
AE duration	Gamma	-
Health state costs	Beta (applied to resource use frequency)	Selected distribution has an upper bound of 1.0 which may not be appropriate. Log-normal or gamma distributions would be more appropriate.
AE costs	Fixed	These parameters are subject to uncertainty. However, uncertainty is modelled in AE durations
End of life costs	Fixed	This parameter is subject to uncertainty but will have virtually no impact on the ICER

PSA – probabilistic sensitivity analysis; ERG – Evidence Review Group; BSA – body surface area; AE – adverse event; ICER – incremental cost-effectiveness ratio

5.2.2.5 Company's model validation and face validity check

Section B.3a.10.1 of the CS[1] describes a number of measures taken by the company to verify the executable model. These included: a review of the face validity of the model and verification of model calculations and data sources by third-party health economists employed by the company; comparison of model predictions against observed outcomes from ELEVATE-TN[20] and expert clinical opinion; extreme value testing and logic tests.

5.2.2.6 Compnay's model results – Untreated CLL (Model 1)

5.2.2.6.1 Central estimates of cost-effectiveness – Untreated CLL (Model 1)

Table 43 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of acalabrutinib versus GClb within the untreated CLL population. The probabilistic version of the company's model suggests that acalabrutinib is expected to generate an additional [redacted]

QALYs at an additional cost of [redacted] per patient compared with GClb; the corresponding ICER is £31,227 per QALY gained. The deterministic version of the model produces a lower ICER of £30,001 per QALY gained.

Table 43: Central estimates of cost-effectiveness, untreated CLL (Model 1), acalabrutinib versus GClb

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,227**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,001**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-

GClb – obinutuzumab plus chlorambucil; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio
** Undiscounted*

Table 43 presents a breakdown of costs and health outcomes for each treatment group. As shown in the table, the model suggests that patients treated with acalabrutinib spend longer in the PFS state and more time alive compared with patients in the GClb group. Mean OS in the acalabrutinib group is estimated to be [redacted] years. It is also evident that the majority of the total costs for the GClb group are attributable to second-line treatment with ibrutinib.

Table 44: Cost and QALY breakdown, untreated CLL (Model 1), acalabrutinib versus GClb, deterministic model

Component	Acalabrutinib	GClb
LYGs* – progression-free	[redacted]	[redacted]
LYGs* – post-progression	[redacted]	[redacted]
LYGs – total*	[redacted]	[redacted]
QALYs – progression-free	[redacted]	[redacted]
QALYs – post-progression	[redacted]	[redacted]
QALY loss - AEs	[redacted]	[redacted]
QALYs loss - age decrement	[redacted]	[redacted]
QALYs - total	[redacted]	[redacted]
Costs first-line treatment	[redacted]	[redacted]
Costs second-line treatment	[redacted]	[redacted]
Costs – other	[redacted]	[redacted]
Costs - total	[redacted]	[redacted]

GClb – obinutuzumab plus chlorambucil; LYG – life year gained; QALY – quality-adjusted life year
**Undiscounted*

5.2.2.6.2 Company's PSA results – Untreated CLL (Model 1)

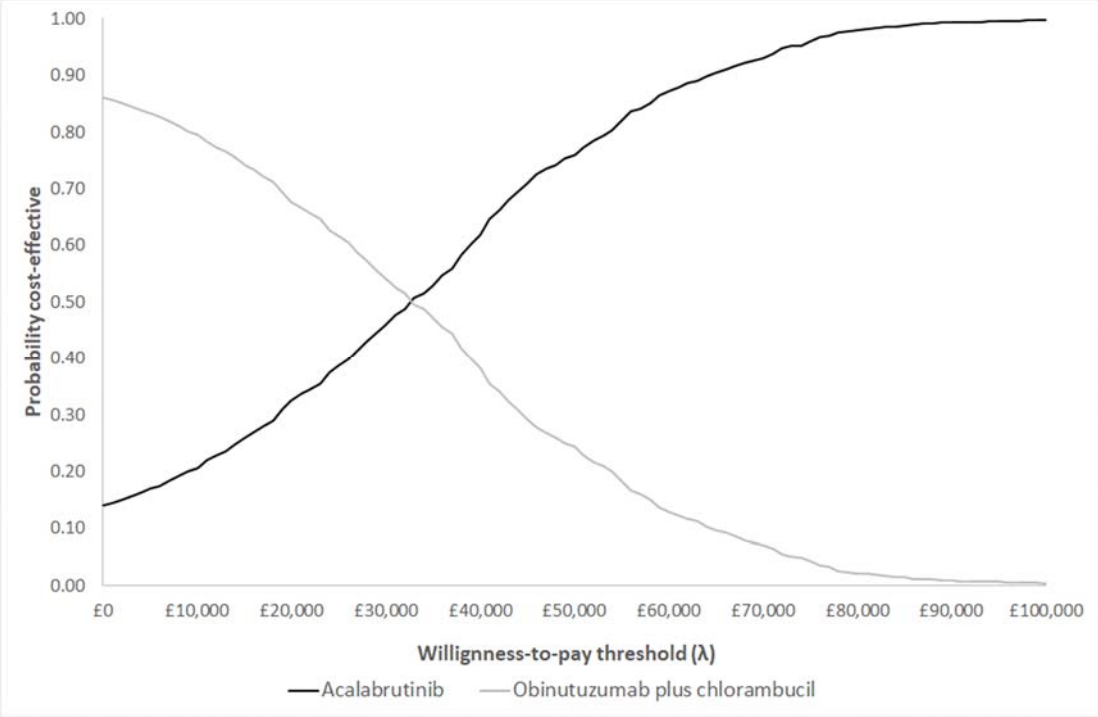
Figure 15 and Figure 16 present the cost-effectiveness plane and CEACs for acalabrutinib versus GClb within the untreated CLL population. Assuming willingness-to-pay (WTP) thresholds of £20,000 and

£30,000 per QALY gained, the probability that acalabrutinib generates more net benefit than GClb is estimated to be 032 and 0.46, respectively.

Figure 15: Cost-effectiveness plane, untreated CLL (Model 1), acalabrutinib versus GClb (re-drawn by the ERG)

[redacted]

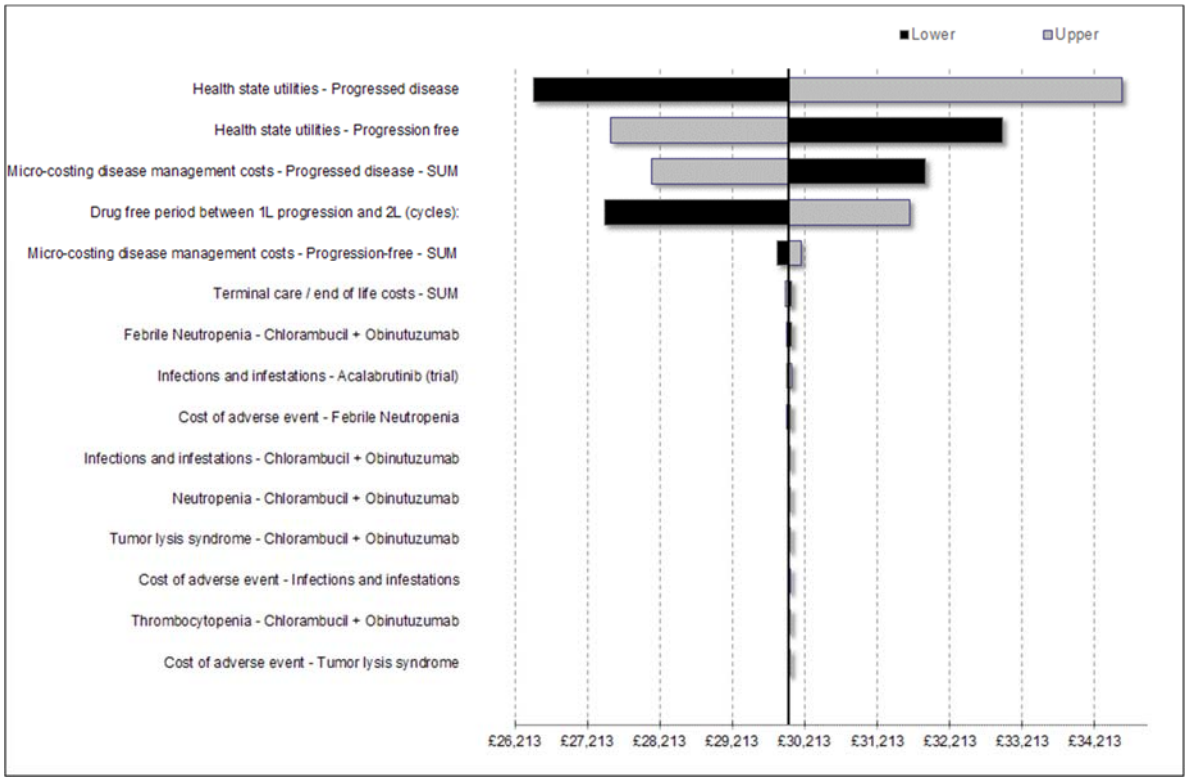
Figure 16: Cost-effectiveness acceptability curves, untreated CLL (Model 1), acalabrutinib versus GClb (re-drawn by the ERG)



5.2.2.6.3 Company's deterministic sensitivity analysis – Untreated CLL (Model 1)

Figure 17 presents a tornado plot summarising the results of the company's DSAs for the untreated CLL population. Across the range of parameters included in the DSA, the plot indicates that the ICER for acalabrutinib versus GClb is most sensitive to the health state utility values, the health state costs following disease progression and the duration of the lag between disease progression and the initiation of second-line therapy.

Figure 17: Tornado plot, untreated CLL (Model 1), acalabrutinib versus GClb (adapted by the ERG)



5.2.2.6.4 Company's scenario analyses – Untreated CLL (Model 1)

The results of the company's scenario analyses for the untreated CLL population are summarised in Table 45. Across all of the scenarios considered, the ICER for acalabrutinib versus GClb ranges from £26,337 per QALY gained (acalabrutinib TTP and PPM modelled using Weibull distributions) to £33,896 per QALY gained (discount rates for QALYs and costs = 6% per annum).

Table 45: Company's scenario analysis results, untreated CLL (Model 1), acalabrutinib versus GClb

Scenario	Inc. QALYs	Inc. Costs	ICER
Base case	[redacted]	[redacted]	**£30,001**
Time horizon = 25 years	[redacted]	[redacted]	**£29,658**
Time horizon = 20 years	[redacted]	[redacted]	**£27,518**
Discount rates for QALYs and costs = 6%	[redacted]	[redacted]	**£33,896**
Discount rates for QALYs and costs = 0%	[redacted]	[redacted]	**£27,036**
PF utility value equal to general population utility age 65 to <70 years (utility=0.81)	[redacted]	[redacted]	**£30,691**
No utility age adjustment	[redacted]	[redacted]	**£28,035**
Acalabrutinib TTP and PPM modelled using Weibull distributions	[redacted]	[redacted]	**£26,337**
GClb TTP and PPM modelled using log-logistic distributions	[redacted]	[redacted]	**£30,512**

GClb – obinutuzumab plus chlorambucil; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; TTP – time to progression; PPM – pre-progression mortality

5.2.3 Model 2: Acalabrutinib versus ibrutinib in patients with untreated high-risk CLL (del(17p) and TP53 mutations)

5.2.3.1 Methods

The company's CMA in the high-risk CLL population uses the semi-Markov model developed to assess acalabrutinib in the untreated CLL population (Model 1), with the following amendments:

- The comparator is assumed to be ibrutinib given at a dose of 420mg daily.
- PFS and OS outcomes for the ibrutinib group are assumed to be equivalent to those for the acalabrutinib group, based on the results of the company's MAIC of these two options in the R/R CLL population (see Section 4.4).
- As with acalabrutinib, ibrutinib is assumed to be given until disease progression. The cost of ibrutinib was taken from the BNF.[50]
- Post-progression treatment costs are excluded, based on the assumption that patients in both groups would receive the same second-line treatment.
- AE management costs for the ibrutinib group are based on the frequency of AEs in the intervention group of the RESONATE-2 trial of ibrutinib versus chlorambucil in patients with untreated CLL[57] (see Table 46).
- Discounting is excluded from the analysis. A scenario analysis was undertaken in which costs were discounted at a rate of 3.5% per annum.

All other aspects of the analysis for the high-risk CLL population are the same as Model 1 (untreated CLL). With the exception of the AE frequencies shown in Table 46, the model does not contain any additional evidence over and above that used in Model 1 (described previously in Table 34).

Table 46: AE frequencies included in high-risk CLL model, from ELEVATE-TN and RESONATE-2 (adapted from CS Table 109)

AE	Acalabrutinib	Ibrutinib
Abdominal pain	0.00%	2.96%
Anaemia	6.70%	5.93%
Atrial fibrillation	0.00%	4.00%
Bleeding	1.70%	6.00%
Diarrhoea	0.56%	3.70%
Febrile neutropenia	1.12%	2.22%
Hypo/ hypertension	0.00%	4.44%
Infections and infestations	14.00%	25.00%
Neutropenia	9.50%	10.37%
Platelet count decreased	0.00%	2.96%
Rash	0.00%	2.96%
Thrombocytopenia	2.79%	2.22%

AE – adverse event

5.2.3.2 Company's model results - High-risk CLL (Model 2)

The results of the company's CMA for the untreated high-risk CLL population are presented in Table 47. This analysis assumes that health state occupancy is equivalent between acalabrutinib and ibrutinib, hence life years gained (LYGs), health state costs and end-of-life care costs are the same for both treatment groups. Based on the list price for ibrutinib, the analysis suggests that acalabrutinib generates undiscounted cost savings of [redacted] per patient compared with ibrutinib. As shown in the table, almost all of these estimated cost savings are attributable to the estimated differences in drug acquisition costs between the two treatment options. When costs are discounted, the estimated cost savings are reduced to [redacted] per patient. Probabilistic results are not presented in the CS.[1]

Table 47: Company's CMA results, high-risk CLL (Model 2), acalabrutinib versus ibrutinib

Option	LYGs*	Drug acquisition costs	PF health state costs	PD health state costs	End of life care costs	AE costs	Total cost
Company's base case (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
Company's base case (costs discounted at 3.5%)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]

LYG – life year gained; PF – progression-free; PD – progressed disease; AE – adverse event

5.2.4 Model 3: Acalabrutinib versus ibrutinib in patients with R/R CLL

5.2.4.1 Methods

The company's economic analysis for the R/R CLL population also adopts a CMA approach, assuming clinical equivalence between acalabrutinib and ibrutinib. The model uses a partitioned survival approach using the same three health states as the untreated CLL analyses (shown previously in Figure 6). Unlike the semi-Markov model, transitions between health states are not explicitly modelled; instead, health state occupancy is estimated directly from parametric survival models fitted to data on PFS and OS from the ibrutinib arm of the RESONATE trial.[23]

Table 48 summarises the evidence sources used to inform the model's parameters in the company's base case analysis; these are discussed in further detail in the subsequent sections.

Table 48: Summary of evidence used to inform base case analysis for R/R CLL population

Parameter group	Acalabrutinib	Ibrutinib
Patient characteristics	ASCEND[21]	
General population mortality	UK life tables 2016-2018[45]	
OS	Clinical equivalence between acalabrutinib and ibrutinib assumed based on results of company's MAIC (see Section 4.4)	Exponential model fitted to observed OS data from the ibrutinib arm of RESONATE[40]
PFS		Weibull model fitted to observed PFS data from the ibrutinib arm of RESONATE[40]
Drug acquisition costs	CS[1]	BNF[50]
Dosing schedules and RDIs	Dosing schedules from ASCEND.[21] RDI assumed to be 100%	Dosing schedules from RESONATE,[31] RDI assumed to be 100%
Health state costs	Same as untreated CLL model (Model 1, see Section 5.2.2)	
End-of-life costs	Same as untreated CLL model (Model 1, see Section 5.2.2)	
AEs frequencies	ASCEND[21]	RESONATE[40]
AEs costs	NHS Reference Costs 2017/18[51] and NICE TA487[11]	

CLL – chronic lymphocytic leukaemia; R/R – relapsed/refractory; AE - adverse event; MAIC - matching adjusted indirect comparison; OS - overall survival; PFS - progression-free survival; RDI - relative dose intensity; CS – company's submission

The CMA for the R/R CLL population includes the following features:

- Patient characteristics are based on ASCEND.[21] At model entry, patients are assumed to have a mean age of 67 years, and 33% of patients are assumed to be female.
- The comparator is assumed to be ibrutinib given at a dose of 420mg daily.
- The company's model adopts a partitioned survival approach whereby the probability of being alive and progression-free is given by the cumulative probability of PFS, the probability of being alive is given by the cumulative probability of OS, and the probability of being alive following disease progression is given by the cumulative probability of OS minus the cumulative probability of PFS.

- Within each treatment group, the model applies two constraints: PFS must be less than or equal to OS, and OS risk must be at least as high as the mortality risk for the age- and sex-matched general population
- PFS and OS outcomes for the acalabrutinib group are assumed to be equivalent to those for the ibrutinib group, based on the company's MAIC for the R/R CLL population (see Section 4.4). PFS is assumed to follow a Weibull distribution, whilst OS is assumed to follow an exponential distribution. The parameters of these distributions were estimated using reconstructed IPD from digitised PFS and OS data from RESONATE.[23]
- Both acalabrutinib and ibrutinib are assumed to be given until disease progression
- The acquisition cost of ibrutinib was taken from the BNF[50]
- Post-progression treatment costs are excluded for both treatment groups
- Only grade ≥3 AEs experienced by 1% of patients in the ASCEND and RESONATE trials are included in the analysis; the company assumes that most AEs occur and are resolved during the first 28-day cycle.
- Discounting is excluded from the analysis. A scenario analysis was undertaken in which costs were discounted at a rate of 3.5% per year.

All other model parameters are the same as those used in Model 1 (untreated CLL). The following sections provide further detail on the company's survival modelling and estimates of AEs included in the CMA for the R/R CLL population.

5.2.4.1.1. Time-to-event model parameters

Survival functions were estimated for PFS and OS in order to inform cost outcomes in the CMA for the R/R CLL population. Clinical equivalence was assumed between acalabrutinib and ibrutinib, based on the results of the company's MAIC (see Section 4.4). The company elected to use the RESONATE study as the baseline model for PFS and OS as it had longer follow-up than ASCEND (CS,[1] Section B.3b.2.2). The company reconstructed IPD from digitised Kaplan-Meier curves for PFS and OS from the ibrutinib arm of RESONATE (N=195)[40] using the algorithm reported by Guyot *et al*.[38] The company fitted six standard parametric models to the available data on PFS and OS. These included the exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma distributions. The 2-parameter gamma model was not fitted to the data.

Overall survival

The company selected the exponential model for inclusion in the base case analysis through consideration of relative goodness-of-fit statistics (AIC and BIC) and visual inspection of the fitted distributions. The CS is unclear with respect to whether other information was used to inform the choice of parametric model for OS, for example, examination of hazard functions or consideration of clinical

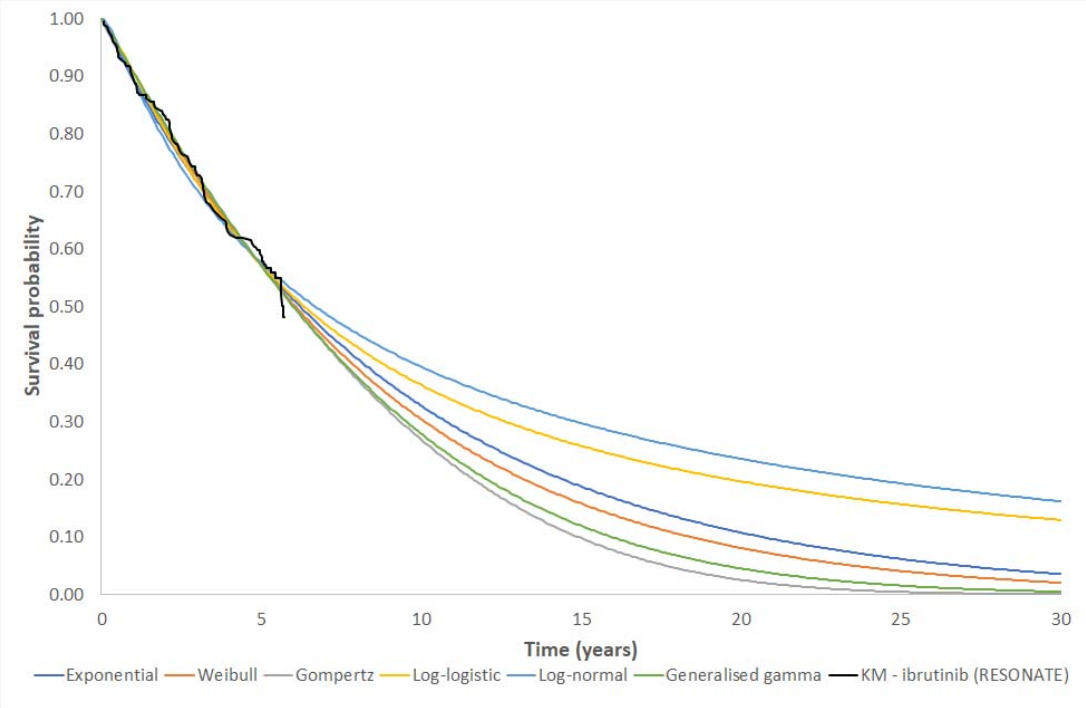
plausibility. AIC and BIC statistics for each of the candidate models are presented in Table 49. The Kaplan-Meier plot for the ibrutinib arm of RESONATE and the modelled OS functions are presented in Figure 18.

Table 49: Goodness-of-fit statistics for OS – R/R CLL population, RESONATE ibrutinib arm, ITT population (reproduced from CS Table 95)

Distribution	Ibrutinib OS (RESONATE; ITT population)	
	AIC	BIC
Exponential	**978.40**	**981.68**
Gompertz	979.64	986.19
Weibull	979.79	986.34
Log-logistic	981.08	987.63
Generalised gamma	981.72	991.54
Lognormal	983.84	990.38

AIC - Akaike information criterion; BIC - Bayesian information criterion; ITT – intention-to-treat; OS - overall survival

Figure 18: Kaplan-Meier plot and modelled OS – R/R CLL population, RESONATE ibrutinib arm, ITT population (re-drawn by the ERG)



KM - Kaplan-Meier; OS - overall survival
Note – models presented exclude general population mortality constraint

Within each treatment group, the model applies two constraints: (i) PFS must be less than or equal to OS, and (ii) OS risks must be at least as high as the mortality risk for the age- and sex-matched general population. No alternative OS models were considered in the company's sensitivity analyses.

Progression-free survival

The company selected the Weibull model to represent PFS on the basis of statistical goodness-of-fit (AIC and BIC), visual comparison with empirical Kaplan-Meier survival functions and the clinical

plausibility of the projected survival functions. It is unclear from the CS[1] whether other information such as the hazard plots were used to inform model selection. The AIC and the BIC statistics for each of the candidate models are presented in Table 50. The Kaplan-Meier plot for the ibrutinib arm of RESONATE and the modelled PFS functions are presented Figure 19.

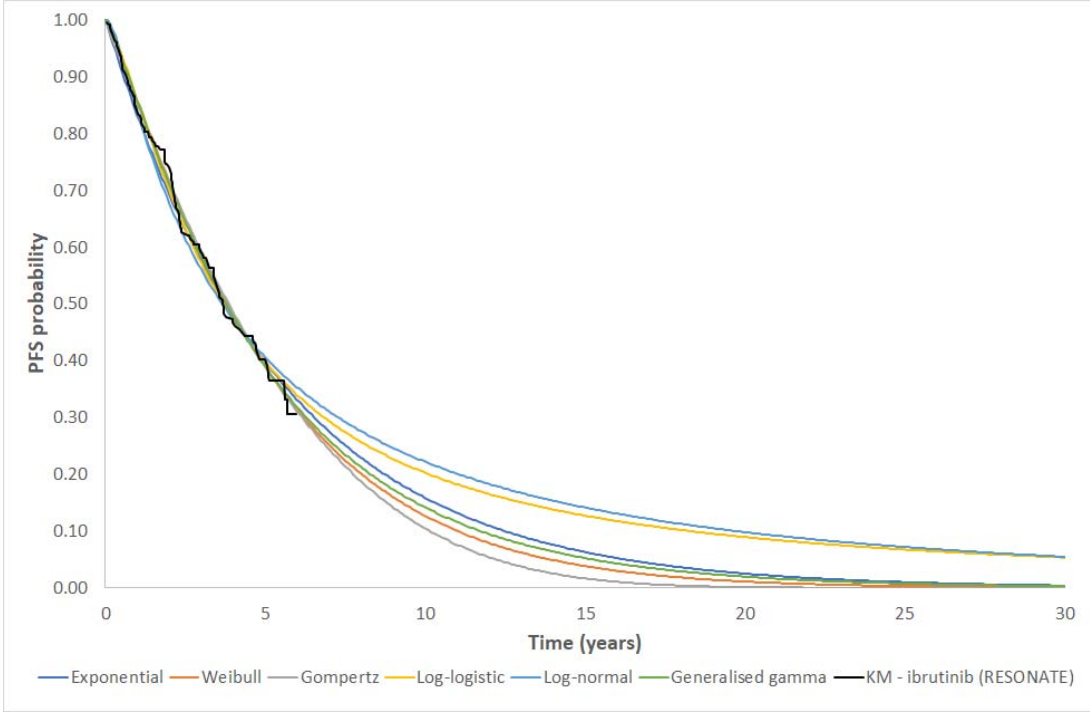
Clinical advice received by the company suggested that the log-logistic and log-normal models resulted in overly optimistic survival estimates, whilst estimates from the Gompertz model were considered to be overly pessimistic (CS,[1] Section B.3b.2.2). No alternative PFS models were explored in the company's sensitivity analyses.

Table 50: Goodness-of-fit statistics for PFS – R/R CLL population, RESONATE ibrutinib arm, ITT population (reproduced from CS Table 94)

Distribution	Ibrutinib PFS (RESONATE; ITT population)	
	AIC	BIC
Exponential	**1233.71**	**1236.99**
Weibull	1233.62	1240.16
Gompertz	1234.40	1240.95
Log-logistic	1235.30	1241.84
Lognormal	1239.650	1246.19
Generalised gamma	1235.46	1248.28

AIC - Akaike information criterion; BIC - Bayesian information criterion; ITT – intention-to-treat

Figure 19: Kaplan-Meier plot and modelled PFS – R/R CLL population, RESONATE ibrutinib arm, ITT population (re-drawn by the ERG)



KM - Kaplan-Meier; PFS - progression-free survival

5.2.4.1.2 AE management costs

Costs related to the management of AEs are applied as once-only costs during the first model cycle, based on the frequency of individual grade 3/4 AEs in ASCEND[21] and RESONATE[31] and unit costs from previous NICE appraisals (TA487[11] and TA359[6]) and NHS Reference Costs 2017/18. Unit costs from NICE TAs were uplifted to 2019 prices using the Hospital and Community Health Services (HCHS) index.[56] Only AEs with an incidence of ≥1% in either treatment group were included, with an assumed duration of four weeks. The AE frequencies and costs used in the base-case analysis are summarised in Table 51. The AE incidence rates obtained from the MAIC (see Section 4.4) were included in a scenario analysis.

Table 51: Frequency of grade 3/4 AEs and associated costs, R/R CLL population, base-case analysis

AE	AE frequency		Unit cost	Total costs	
	Acalabrutinib	Ibrutinib		Acalabrutinib	Ibrutinib
Anaemia	11.7%	4.6%	£366.00	£42.82	£16.91
Diarrhoea	1.3%	4.1%	£149.00	£1.94	£6.11
Fatigue	0.0%	2.1%	£636.67	£0.00	£13.05
Febrile neutropenia	0.6%	0.0%	£6,623.14	£43.01	£0.00
Infections and infestations	14.9%	24.0%	£1,783.94	£265.81	£428.15
Neutropenia	15.6%	16.4%	£136.34	£21.25	£22.37
Neutrophil count decreased	1.3%	0.0%	£136.34	£1.77	£0.00
Atrial fibrillation	1.3%	3.0%	£1,783.94	£23.19	£53.52
Thrombocytopenia	3.9%	5.6%	£640.09	£24.94	£36.10
Bleeding	1.9%	1.0%	£1,783.94	£33.89	£17.84
Total				**£458.61**	**£594.05**

AE – adverse event

5.2.4.2 Company's model results – R/R CLL (Model 3)

Table 52 presents the results of the company's CMA for the R/R CLL population. This analysis assumes that health state occupancy is equivalent between acalabrutinib and ibrutinib, hence LYGs, health state costs and end-of-life care costs are the same for both treatment groups. Based on ibrutinib list price, the deterministic version of the model suggests that acalabrutinib generates cost savings of [redacted] per patient compared with ibrutinib. The results of the scenario analysis around AE rates are similar to the base case analysis (AE scenario analysis cost savings = [redacted]). The inclusion of discounting leads to a smaller cost saving of [redacted]. Probabilistic results are not presented in the CS.

Table 52: Company's CMA results, R/R CLL (Model 3), acalabrutinib versus ibrutinib

Option	LYGs*	Drug acquisition costs	PF health state costs	PD health state costs	End of life care costs	AE costs	Total Costs
Company's base case (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
Scenario analysis (AE incidence rates taken from MAIC)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
Scenario analysis (discount rate=3.5%)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]

LYGs – life years gained; PF –progression-free; PD - progressed disease; MAIC – matching adjusted indirect comparison
**undiscounted*

5.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic models upon which these are based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[58, 59]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's models to fully assess the logic of the model structures, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the models reported in the CS[1] and the company's executable models.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS.
- Where possible, checking of key parameter values used in the company's models against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the models.

5.3.1 Model verification by the ERG

Table 53 presents a comparison of the results of the company's models and the ERG's double-programmed models for the untreated CLL population, high-risk CLL population and R/R CLL population. As shown in the table, the ERG's results are very similar to those generated using the

company's model. However, the ERG's double-programming exercise revealed some minor implementation errors in all three models, as well as a more significant structural limitation relating to subsequent-line treatment costs in the untreated CLL analysis (Model 1). These issues are discussed in detail in Section 5.3.4 and are addressed as part of the ERG's exploratory analyses in Section 5.4.

Table 53: Comparison of company's original models and ERG's double-programmed models, untreated CLL, high-risk CLL and R/R CLL populations, excludes correction of errors

	Company's model				ERG's model			
Model 1 - Untreated CLL								
Option	**LYGs***	**QALYs**	**Costs**	**ICER**	**LYGs***	**QALYs**	**Costs**	**ICER**
Acalabrutinib	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-
GClb	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	[redacted]	**£30,001**	[redacted]	[redacted]	[redacted]	**£30,003**
Model 2 - High-risk CLL (del(17p)/TP53 mutations)								
Option	**LYGs***	**QALYs**	**Costs**	**ICER**	**LYGs***	**QALYs**	**Costs**	**ICER**
Acalabrutinib	[redacted]	N/a	[redacted]	-	[redacted]	N/a	[redacted]	-
Ibrutinib	[redacted]	N/a	[redacted]	-	[redacted]	N/a	[redacted]	-
Incremental	0.00	N/a	[redacted]	N/a	0.00	N/a	[redacted]	N/a
Model 3 - R/R CLL								
Option	**LYGs***	**QALYs**	**Costs**	**ICER**	**LYGs***	**QALYs**	**Costs**	**ICER**
Acalabrutinib	[redacted]	N/a	[redacted]	-	[redacted]	N/a	[redacted]	-
Ibrutinib	[redacted]	N/a	[redacted]	-	[redacted]	N/a	[redacted]	-
Incremental	0.00	N/a	[redacted]	N/a	0.00	N/a	[redacted]	N/a

CLL – chronic lymphcytic leukaemia; GClb – obinutuzumab plus chlorambucil; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; ERG – Evidence Review Group; N/a – not applicable
** Undiscounted*

5.3.2 Correspondence of the model inputs and the original sources of parameter values

Where possible, the ERG checked the model input values against their original sources, although many of these were based on analyses of actual/replicated IPD from ELEVATE-TN,[20] RESONATE[23] and MURANO.[43] The ERG did not have access to these IPD.

The ERG identified a likely transcription error relating to health state resource use estimates taken from NICE TA561.[60] In addition, the life tables used to inform general population mortality rates and unit costs applied in all three models were outdated. These issues are discussed in Section 5.3.4. The other model parameters appear to be consistent with their original sources.

5.3.3 Adherence of the company's model to the NICE Reference Case

The extent to which the company's economic analyses adhere to the NICE Reference Case[61] is summarised in Table 54. The company's analyses are generally in line with the NICE Reference Case; the main deviations relate to the narrower set of comparators included in the models compared with those listed in the final NICE scope.[13]

Table 54: Adherence of the company's model to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analyses are generally in line with the final NICE scope.[13] Three separate economic analyses are presented: • Model 1 – acalabrutinib versus GClb in patients with untreated CLL • Model 2 – acalabrutinib versus ibrutinib in patients with untreated CLL with high-risk cytogenetic features (del(17p)/TP53 mutations) • Model 3 – acalabrutinib versus ibrutinib in patients with R/R CLL
Comparator(s)	As listed in the scope developed by NICE	The final NICE scope[13] includes seven comparators for the untreated CLL population (with/without high-risk features) and five comparators for the R/R CLL population. The company's three models each includes a single comparator (GClb in the untreated CLL population [Model 1] and ibrutinib in the high-risk CLL and R/R CLL populations [Models 2 and 3]).
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health outcomes are explicitly included in Model 1 (untreated CLL) in terms of QALYs. Health outcomes are not explicitly estimated for Model 2 (high-risk CLL) or Model 3 (R/R CLL).
Perspective on costs	NHS and PSS	The company's economic analyses adopt an NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Model 1 (untreated CLL) adopts a cost-utility approach; ICERs are reported in terms of the incremental cost per QALY gained for acalabrutinib versus GClb. Model 2 (high-risk CLL) and Model 3 (R/R CLL) adopt a CMA approach; results are reported in terms of differences in cost between acalabrutinib and ibrutinib, based on the assumption of clinically equivalent outcomes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	All three models adopt a lifetime horizon (30 years).
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review to identify RCTs of treatments for CLL in the first-line and R/R treatment settings (see Chapter 4).

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Within Model 1 (untreated CLL), the health utility value for the progression-free state was measured and valued using EQ-5D-3L data collected in ELEVATE-TN.[20] The health utility value for the post-progression state was reported to be based on the literature (Holzner *et al*[46]) but does not appear to reflect a preference-based estimate of HRQoL and does not appear in the cited publication. Model 2 (high-risk CLL) and Model 3 (R/R CLL) adopt a CMA approach and do not include the explicit quantification of health outcomes.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
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 costs include those relevant to the NHS and PSS. Unit costs were valued at 2017/18 prices, except for drug prices which are based on current list prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

NICE – National Institute for Health and Care Excellence; ERG – Evidence Review Group; CLL – chronic lymphocytic leukaemia; R/R – relapsed/refractory; CMA – cost-minimisation analysis; QALY – quality-adjusted life year; HRQoL – health-related quality of life; ICER – incremental cost-effectiveness ratio; PSS – Personal Social Services; EQ-5D – Euroqol 5-Dimensions

5.3.4 Key issues identified from the ERG's critical appraisal – Untreated CLL and high-risk CLL populations (Models 1 and 2)

This section presents a discussion of the main issues identified from the ERG's critical appraisal of the company's economic analyses for the untreated CLL population (Model 1) and the high-risk CLL population (Model 2). The critical appraisal of these two models is presented together, as they both employ the same semi-Markov model structure; the CMA for the high-risk population (Model 2) is based on the intervention group outcomes estimated within the untreated CLL population (Model 1). A discussion of the main issues identified from the critical appraisal of the company's CMA for R/R CLL (Model 3) is presented separately in Section 5.3.5, as this uses a different modelling approach (partitioned survival) and different evidence sources compared with the untreated CLL models.

The main issues identified in the ERG's critical appraisal of Models 1 and 2 are summarised in Box 1. These are described in further detail in the subsequent sections.

Box 1: Main issues identified from ERG's critical appraisal – untreated CLL and high-risk CLL (Models 1 and 2)

(1) Model errors and inappropriate data sources
(2) Inclusion of patients with high-risk cytogenetic features in untreated CLL analysis (Model 1)
(3) Issues relating to comparators and sequences of therapy
(4) Model structure
(5) Concerns regarding the company's survival modelling
(6) Issues relating to health utilities
(7) Issues relating to costs
(8) Additional concerns regarding the company's economic analyses in the high-risk CLL population (Model 2)

(1) Model errors and inappropriate data sources

The ERG identified a number of errors in the company's models; each of these is described in turn below. As most of these errors were identified during the early stages of the appraisal process, the company presented an updated base case analysis as part of their clarification response which addresses some of these errors. The impact of each individual error and the company's updated base case ICERs are summarised in Table 55 and Table 56.

(i) *Error in the application of half-cycle correction*

The company's models apply half-cycle correction to account for patients transitioning part-way through each discrete time cycle. However, the approach taken by the company erroneously double-

counts QALYs and costs in the first model cycle. During the clarification process, the ERG asked the company to further investigate these issues (see clarification response,[22] questions B17 and B18). In their response, the company acknowledged that their original model was subject to errors. Their response noted that the errors had little impact on estimated QALYs, but did have a more pronounced impact on costs. The company provided updated versions of the model which included the correction of these errors (see Table 55 and Table 56). Correcting these errors reduce the ICER for acalabrutinib in the untreated CLL population from £30,001 per QALY gained to £23,809 per QALY gained, whilst in the high-risk CLL population, the estimated cost-savings for acalabrutinib are increased from [redacted] to [redacted] per patient.

(ii) Use of outdated NHS Reference Costs

The company's model uses unit costs sourced from NHS Reference Costs 2017/18;[51] however, a newer tariff for the years 2018/19 is available.[62] In response to a request for clarification from the ERG[22] (question B1), the company provided updated models which use up-to-date unit costs. This issue has only a minor impact on the model results (see Table 55 and Table 56).

(iii) Incorrect estimation of general population mortality risk

The general population mortality constraints applied in the company's models are based on UK life tables for the period 2015 to 2017.[45] The ERG believes that it would be more appropriate to use life tables for England for the period 2016 to 2018.[63] In addition, the ERG notes that the company's untreated CLL and high-risk CLL models estimate mortality rates for women and men separately and apply a constant proportionate split for men and women across all ages based on the initial distribution of men and women at baseline in ELEVATE-TN.[20] The models also incorrectly apply mortality rates as probabilities. As part of their clarification response[22] (question B15), the company applied UK life tables for period 2016 to 2018 and corrected the error relating to the inappropriate use of rates. The use of more recent life tables and the correction of the error have a negligible impact on the model results (see Table 55 and Table 56).

The company's clarification response[22] (question B16) comments that the assumption of a constant proportionate split of men and women was intentionally applied to avoid further complexities in the model. The company's response also notes the anticipated minimal impact on the cost-effectiveness results. The ERG would have preferred an analysis which estimates general population mortality conditional on the proportionate split of men and women at model entry (age 70 years), and which applies life tables for England rather than the UK. These amendments are included as part of the ERG's exploratory analyses (see Section 5.4).

Table 55: Impact of errors and company's updated base case, untreated CLL population (Model 1)

Error/issue	Acalabrutinib		GClb		Incremental (acalabrutinib versus GClb)		
	QALYs	Costs	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Company's original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,001**
Half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,809**
Updated NHS Reference Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,592**
Updated life tables and rate conversion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,223**
Company's updated base case (post-clarification)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,679**

GClb – obinutuzumab plus chlorambucil; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 56: Impact of errors and company's updated base case, high-risk CLL population (Model 2)

Error/issue	Acalabrutinib cost	Ibrutinib cost	Incremental cost
Original base case	[redacted]	[redacted]	[redacted]
Half-cycle correction	[redacted]	[redacted]	[redacted]
Updated NHS Reference Costs	[redacted]	[redacted]	[redacted]
Updated life tables and rate conversion	[redacted]	[redacted]	[redacted]
Company's updated base case (post-clarification)	[redacted]	[redacted]	[redacted]

Following the clarification round, the ERG identified two further errors in the company's model.

(iv) Error in the transcription of health state resource use

According to the CS,[1] health state resource use estimates were taken from NICE TA561.[60] The model includes an assumption that patients who are progression-free undergo 3 LDH monitoring tests each year (0.23 tests every 28 days). However, the committee papers for TA561[60] report a value of 2 tests each year (0.15 tests every 28 days). The ERG believes that this is a transcription error. All other frequencies for interventions and tests used to estimate disease management costs are correctly reported in the models. This issue has a negligible impact on the model results.

(v) *Incorrect application of second-line treatment costs associated with VenR and ibrutinib*

As noted in Section 5.2.2.6, the costs of second-line treatments are an important driver of the ICER for acalabrutinib. In the company's model for the untreated CLL population, all patients who progress and survive an additional [redacted] years ([redacted] model cycles) are assumed to receive second-line VenR (following first-line acalabrutinib) or second-line ibrutinib (following first-line GClb). These costs are applied in

the model on a cyclical basis to all patients who remain alive in the post-progression state, irrespective of whether they are still progression-free (from the point of initiating second-line therapy). However, the SmPCs for venetoclax, rituximab and ibrutinib[44, 52, 53] each indicate that these treatments should be discontinued at the point of disease progression. As such, the company's model overestimates second-line treatment costs in both groups; the magnitude of the error is greater for second-line ibrutinib as this is given over a long time frame than second-line VenR. This problem is partly driven by the structural limitations of the model, which does not include a separate state to track progression status after initiating second-line treatment (see critical appraisal point [4]).

Following the clarification process, the ERG highlighted this issue with the company and suggested an alternative approach in which the full lifetime cost of second-line ibrutinib, calculated using mean PFS time from RESONATE,[23] is applied as a once-only cost for patients who initiate second-line treatment. The company submitted an updated model together with an additional document[64] explaining the company's attempt to reflect the ERG's requested analysis. In the updated untreated CLL model, the estimated ibrutinib costs were substantially higher than those estimated in their original model (second-line ibrutinib costs: new model - [redacted]; original model - [redacted]), which resulted in a situation in which acalabrutinib dominated GClb (see company's additional analysis document, Tables 3, 5, 7 and 9). This is counter-intuitive, as restricting second-line treatment to patients who have not yet progressed, rather than applying second-line treatment costs to all surviving patients irrespective of progression status, should lead to a reduction in estimated second-line treatment costs. The ERG scrutinised the company's updated model and identified four reasons which contribute to the company's counterintuitive findings: (i) PFS time was not constrained by general population mortality risk; (ii) in contrast to the original untreated CLL model, ibrutinib treatment duration was no longer restricted to a maximum of 130 cycles (10 years), (iii) discounting was not handled appropriately, and (iv) ibrutinib costs were applied to all patients who leave the progression state, rather than being limited to those patients who survive for an additional [redacted] years following disease progression. As such, the ERG believes the company's updated analyses are incorrect and should be disregarded. The impact of rectifying this problem is included as part of the ERG's exploratory analyses (see Section 5.4).

(2) Inclusion of patients with high-risk cytogenetic features in untreated CLL analysis (Model 1)

The company's economic analysis of acalabrutinib in the untreated CLL population (Model 1) is based on the ITT population of ELEVATE-TN,[20] with external evidence used to inform PPS.[23, 43] The company's economic analysis of acalabrutinib in the high-risk CLL population with del(17p)/TP53 mutations (Model 2) is based on the intervention arm of Model 1. This has two implications:

(i) The untreated CLL analysis (Model 1) uses data which includes a subset of patients with high-risk cytogenetic features (del(17p) and TP53 mutations) who are not relevant to this population and for whom the CS[1] argues would otherwise be treated with ibrutinib rather than GClb.

(ii) The time-to-event data used to inform the high-risk CLL analysis (Model 2) reflect a population in whom the majority (80.45%) of patients do not have del(17p) or TP53 mutations. It should also be noted that the HRs obtained from the company's MAIC, which are used to justify the use of a CMA approach, also relate to the R/R CLL population, rather than patients with untreated high-risk CLL (see Section 4.4).

In response to a request for clarification from the ERG (see clarification response,[22] question B6), the company stated that patients with del(17p) and TP53 mutations comprised only a small proportion of the ITT population enrolled in ELEVATE-TN (35 of 179 [19.55%] patients in the acalabrutinib group and 37 of 177 [20.90%] patients in the GClb group). The company explained that they considered it more appropriate that the analysis is informed by the overall ITT population*, "rather than a small post-hoc subgroup representing ~10% of the ELEVATE-TN study"* (note - the ERG believes the quoted value should be ~20%). The company's clarification response also indicates that the HRs for PFS were similar in the group with a del(17p) or TP53 mutation and in the group without these mutations (HR 0.23, 95% CI: 0.09-0.61 versus HR 0.19, 95% CI: 0.11-0.31, respectively). However, the company notes that the data are currently immature.

The ERG considers that the relevance of the results of the untreated CLL economic analysis are contaminated by the inclusion of high-risk CLL patients in the time-to-event data used to inform the model. However, in ELEVATE-TN randomisation was stratified according to del(17p) but not TP53 mutations, hence excluding these patients may also introduce bias and confounding into the economic analysis for the untreated CLL population. The extent of this potential confounding is unclear as the company did not present an analysis for the untreated CLL population (Model 1) which excludes high-risk patients. In the high-risk CLL analysis (Model 2), less than 20% of the patients in the datasets used to inform TTP and PPM have high-risk cytogenetic features, and the evidence used to justify equivalent outcomes relates to patients with R/R CLL rather than high-risk CLL; as such, neither the data sources used to inform the baseline model nor the relative treatment effects relate specifically to patients with del(17p) and TP53 mutations. It is unclear whether the company could have undertaken a reliable indirect comparison using the 35 patients with del(17p) and TP53 mutations in the acalabrutinib arm of ELEVATE-TN, or whether an equivalent dataset exists for high-risk CLL patients treated with ibrutinib.

(3) Issues relating to comparators and sequences of therapy

The final NICE scope[13] lists five comparators in people with untreated CLL without high-risk features: (i) chlorambucil with or without rituximab; (ii) GClb; (iii) bendamustine with or without rituximab; (iv) FCR, and (v) venetoclax with obinutuzumab. For previously treated patients, the NICE scope lists five comparators: (i) bendamustine with or without rituximab; (ii) VenR; (iii) ibrutinib; (iv) FCR and (v) IR.

The CS[1] argues that GClb is the standard of care for patients with untreated newly diagnosed CLL who are considered unfit for chemo-immunotherapy (e.g. FCR). The CS states that this is in line with the recommendations from the BSH[16] and that this view was supported by the haematologists consulted by the company at their UK advisory board meeting.[14] For previously treated (R/R) CLL patients, the CS argues that ibrutinib is established NHS practice and therefore this represents the relevant comparator; this view was also supported by the company's UK advisory board. The company therefore assumes that the comparator sequence for patients with untreated CLL (Model 1) is first-line GClb followed by second-line ibrutinib. The CS argues that patients receiving a BTK inhibitor (i.e. acalabrutinib) as first-line therapy would typically be ineligible for a BTK inhibitor (i.e. ibrutinib) at second-line; hence the sequence assumed in the intervention group is first-line acalabrutinib followed by second-line VenR.

Assumptions about subsequent-line treatments are particularly important drivers of the cost-effectiveness of acalabrutinib in the untreated CLL population. As previously shown in the breakdown of costs and QALYs in Table 44, more than 78% of the total treatment costs in the GClb group are attributable to the use of second-line ibrutinib. This is driven by: (a) the cost of ibrutinib per cycle (£4,292.40 every 28 days); (b) the company's model predictions which suggest that patients spend a long time alive after progressing on GClb ([redacted] years), and (c) the error in which second-line ibrutinib costs are applied to all surviving patients for up to 130 cycles, rather than being restricted to patients who have not yet progressed (critical appraisal point [1]). In contrast, subsequent-line treatment costs are lower in the acalabrutinib group because: (a) patients spend comparatively less time alive after progression ([redacted] years), and (b) whilst the cost of VenR is broadly similar to that for ibrutinib in the cycles in which treatment is given, time on treatment with VenR is limited to 2 years.

The ERG has a number of concerns regarding the comparison of the treatment sequences included in the untreated CLL model. These are described below.

(a) Assumed fixed sequences are inconsistent with available data from ELEVATE-TN

Generally speaking, the ERG believes that it is important that the costs and health outcomes included in an economic model should be aligned: that is, costs should reflect those resources used to generate the modelled health outcomes. Both costs and outcomes would usually be estimated using information obtained from the same clinical trial. Owing to the immaturity of the data on OS from ELEVATE-TN,[20] the model uses PPS data for second-line VenR (from MURANO[43]) and ibrutinib (from RESONATE[23]). Data on post-progression treatments from ELEVATE-TN are also immature, with only [redacted] of 356 patients in the acalabrutinib or GClb groups receiving subsequent treatment. However, the limited available data already indicate that the sequences assumed in the company's untreated CLL model do not reflect the subsequent-line regimens received in the trial (see Table 57).

Table 57: Subsequent treatments received in ELEVATE-TN (reproduced from clarification response, question B14)

Subsequent treatment	Acalabrutinib (N=[redacted])	GClb (N=[redacted])
Bendamustine	[redacted]	[redacted]
Anti-CD20	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]
Venetoclax	[redacted]	[redacted]
RCHOP	[redacted]	[redacted]
FCR	[redacted]	[redacted]
CVP	[redacted]	[redacted]
Steroids	[redacted]	[redacted]
GClb	[redacted]	[redacted]
PI3K	[redacted]	[redacted]

GClb – obinutuzumab plus chlorambucil; CVP - cyclophosphamide vincristine sulphate prednisone; FCR - fludarabine, cyclophosphamide and rituximab; PI3K - phosphoinositide 3-kinase; RCHOP – rituximab, cyclophosphamide, hydroxydaunomycin, oncovin and prednisone

(b) Absence of empirical studies to estimate OS for sequences included in company's model

There are no randomised trials which directly compare the specific sequences of treatments included in the model. The only RCT of acalabrutinib for untreated CLL, ELEVATE-TN,[20] will not provide evidence on patients receiving acalabrutinib followed exclusively by second-line VenR, or on GClb followed exclusively by second-line ibrutinib. Later data-cuts from the ELEVATE-TN will not help to resolve this uncertainty.

(c) The assumed sequences automatically disadvantage the GClb group

The company's untreated CLL model generates predictions of OS for each fixed treatment sequence using PPS data relating to the second-line treatment from MURANO[43] and RESONATE.[23] The model assumes that second-line VenR is more effective than second-line ibrutinib in terms of OS (see critical appraisal point [6]). In addition, as noted above, second-line ibrutinib is considerably more expensive than VenR per patient treated. The joint consequence of these two factors is that for patients with progressed disease, the company's model is predisposed to assume that second-line ibrutinib is dominated by second-line VenR. This automatically disadvantages the GClb group and reduces the ICER for acalabrutinib. The CS does not present any head-to-head evidence to suggest that second-line VenR is more effective than ibrutinib, or *vice versa*. In response to a request for clarification from the ERG[22] (question B12), the company stated that they undertook an additional analysis in which both treatment groups receive second-line ibrutinib and that the impact on the ICER is minimal, with the company's updated ICER increasing from £22,679 to £22,882 per QALY gained. However, the ERG notes that this analysis applied the PPS function from RESONATE in both treatment groups, but retained the costs of second-line VenR in the acalabrutinib group. The ERG considers this to be misleading. The ERG's exploratory analyses indicate that applying the same PPS function and the same

costs of second-line VenR in both treatment groups increases the ICER for acalabrutinib substantially (see Section 5.4).

(d) Clinical advisors' views on comparators and subsequent-line therapies

The ERG's clinical advisors suggested the following:

- Within the first-line setting, the relevant comparator for patients who are unsuitable for FCR and BR is GClb. In the second-line setting, ibrutinib reflects the most appropriate comparator for patients who have previously been treated with chemotherapy.
- In accordance with the CS,[1] the advisors stated that would not give a BTK inhibitor in the second-line setting to a patient who had received BTK inhibitor in the first-line setting.
- Patients treated with VenR in the second-line setting might go on to be re-challenged with ibrutinib in the third-line setting. This possibility is not included in the company's model.
- Ibrutinib is not the only NICE-approved second-line treatment option for patients who have been previously treated with chemotherapy. Patients could also receive: (i) VenR; (ii) IR, or (iii) venetoclax monotherapy (via the CDF). The clinical advisors suggested that IR is not commonly used due to toxicity associated with this regimen, specifically, increased risks of infection and toxicity.
- One clinical advisor stated that in clinical practice, there is a general preference for the use of second-line ibrutinib over VenR, with more than 80% of patients receiving ibrutinib and less than 20% of patients receiving VenR. They suggested that the use of VenR was unlikely to change in the next few years and that this preferential use of ibrutinib was because there is no need for ramping up dosage or monitoring for TLS with ibrutinib and fewer hospital attendances are required. The second clinical advisor largely agreed with the first advisor's view, and noted that whilst the COVID-19 pandemic continues, there would be a continued preference towards ibrutinib rather than VenR as patients do not need to attend hospital as frequently. They also noted that a number of units have developed outpatient-based dose escalation for VenR, hence they would use this regimen as well. The advisor further commented that emerging data suggest that ibrutinib works well in patients who have had VenR without a prior BTK inhibitor, which may lead to an increase in the use of VenR in the future.
- Both clinical advisors noted that patient choice is an important factor. Some patients may prefer to receive ibrutinib to avoid the complex dosing associated with VenR, whilst others may prefer VenR as this regimen is given over a fixed duration (2 years) whereas ibrutinib is not.

The ERG understands that patient choice is an important factor in determining appropriate treatments for patients with CLL. However, it is clear from the company's model that the choice of second-line therapy has a marked impact on the cost-effectiveness of acalabrutinib in the first-line setting. If the

proportion of patients receiving second-line VenR increases, this will result in a less favourable cost-effectiveness profile for first-line acalabrutinib. As such, the ERG believes it would be prudent to consider the cost-effectiveness of acalabrutinib separately in: (a) patients who would receive ibrutinib following GClb, and (b) patients who would receive VenR following GClb.

(4) Issues surrounding model structure

The company's analyses in the untreated CLL population (Models 1 and 2) adopt a semi-Markov approach. The CS[1] justifies the use of a state transition modelling approach due to *"challenges in independently extrapolating PFS and OS."* The CS notes that a similar approach has been adopted in previous CLL appraisals, including TA487,[11] TA343,[7] and TA359.[6] The CS (Section B.3a.2) also notes that the semi-Markov approach, which includes tunnel states for progressed disease states, allows for greater flexibility in modelling PPS and *"more nuanced estimation of treatment costs."*

The ERG believes that the company's decision to adopt a state transition approach for the untreated CLL population is reasonable. Whilst it would have been possible to implement the model using a partitioned survival approach, very few deaths were observed in ELEVATE-TN:[20] [redacted] deaths occurred in the GClb group and [redacted] deaths occurred in the acalabrutinib group. As such, the available data are very immature. It is unlikely that fitting parametric survival models directly to these data would have produced reliable estimates of long-term survival. However, the ERG notes that the OS data from MURANO[43] and RESONATE[23] used to inform PPS are also subject to high levels of censoring (see Figure 12 and

Figure 13). Irrespective of whether a state transition or partitioned survival model approach is used, the resulting estimates of modelled OS will inevitably be subject to considerable uncertainty.

The ERG notes that whilst the company's semi-Markov approach allows for event risks in the intermediate state (progressed disease) to be conditioned on the time since entry into that state, the company's base case model assumes that PPS in each group follows an exponential distribution (with a constant hazard rate). As such, the flexibility of the semi-Markov approach is not utilised in the estimation of OS in the company's base case analysis; however, this flexibility does allow for alternative parametric PPS functions with time-varying hazard rates to be explored in sensitivity analyses. The main purpose of the tunnel states in the model is to incorporate the assumed time lag between disease progression and initiation of second-line therapy.

The company's model includes an adjustment for competing risks. The company's general approach of multiplying the cause-specific hazard rates for TTP/PPM by the joint probability of progression or pre-progression death in each cycle appears to be broadly in line with the approach described in the tutorial on multi-state models and competing risks analysis by Putter *et al*.[65] The ERG notes that removing this aspect of the model has a negligible impact on the model results.

The ERG believes that the company's model is subject to four structural limitations:

(i) The model is limited to two lines of treatment. The clinical advisors to the ERG noted that some patients may receive three (or more) lines of treatment, although they commented that these treatments tend to be experimental and may not be required with the advent of newer effective second-line treatments such as ibrutinib. In their clarification response[22] (question B13), the company commented that the nine clinical experts who attended their UK advisory board meeting agreed that a minority of patients would require or be suitable for third-line treatment.[14] The company also highlighted gaps relating to the evidence supporting the effectiveness of subsequent-line treatments, noting that *"there is a distinct lack of sequencing data available."* The ERG notes however that this same criticism applies to estimating OS benefits for the fixed sequences which are assumed in the company's untreated CLL model.

(ii) The model includes a single progression event (on first-line therapy) which determines whether the patient is in the progression-free or the progressed disease health state. This has two implications:

   a) Additional HRQoL benefits associated with being progression-free on second-line therapy (VenR or ibrutinib) are excluded from the model.

   b) As noted in critical appraisal point [1], second-line treatment costs are applied on a cyclical basis to all surviving patients, rather than those who are alive and progression-

free. This leads to the overestimation of the treatment costs, particularly for second-line ibrutinib as this is given over a longer time period than VenR.

(iii) The model assumes that there is a fixed time lag between the time at which a patient progresses and the time at which they initiate second-line therapy ([redacted] cycles, [redacted] years). Whilst the company's clarification response[22] (question B20) notes that this assumption was required due to limited data from ELEVATE-TN,[20] in reality, this interval would follow a distribution.

(iv) The model assumes that all patients who progress (and who survive an additional [redacted] years) will receive second-line therapy. The company's clarification response[22] (question B20) acknowledges that an estimated 7-10% of patients would not receive second-line treatment. The ERG's clinical advisors broadly agreed with this estimate. As such, the costs and benefits of second-line treatment are likely to be overestimated in both treatment groups.

(5) Concerns regarding the company's survival modelling

Within the acalabrutinib group, the company selected the exponential distributions for all three transitions (TTP, PPM and PPS). Within the GClb group, the company selected the log-normal distributions for TTP and PPM and the exponential distribution for PPS. A general population mortality constraint is included for PPM and PPS. In each treatment group, OS is modelled as a function of all three transitions.

The ERG has five main concerns with the company's approach: (i) the company's selected PFS models appear to be inconsistent with the views of their UK CLL advisory board; (ii) there is limited evidence to support the assumption of a survival advantage for acalabrutinib; (iii) the company's selected models for death endpoints are rapidly superseded by general population mortality risks; (iv) the assumption of different PPS between second-line VenR and ibrutinib may be confounded by other factors, and (v) the company's modelled OS projection for the acalabrutinib group is very similar to that of the general population without CLL. These issues are discussed in detail below.

(i) Selected PFS models inconsistent with views of company's UK CLL advisory board

The minutes of the company's UK CLL advisory board meeting[14] state the following: *"In predicted long-term PFS curves for Chl-G and acala, it was hypothesised that the generalised gamma model would most likely reflect clinical outcomes in UK clinical practice."* However, the company did not use the generalised gamma models for TTP or PPM in either treatment group: in the acalabrutinib group, the generalised gamma distribution was rejected due to problems in fitting the model to PPM, whilst in the GClb group, the company rejected the generalised gamma model because *"the tail of the extrapolation was not observed in any of the other fitted curves of TTP data for chlorambucil plus obinutuzumab and lacked clinical validity."* (CS,[1] page 137). The ERG agrees that the generalised gamma model may not be appropriate for the acalabrutinib group because of the model-fitting problems

encountered by the company. However, the company's justification for selecting a different model for the GClb group from that preferred by their experts is unclear, and the ERG believes that the company's selected log-normal distribution may be pessimistic. The log-normal and generalised gamma PFS models for the GClb group are shown in Figure 20. As shown in the figure, there is a marked difference in estimated PFS at 5-years, with the generalised gamma suggesting a longer tail beyond the observed period of ELEVATE-TN. The ERG notes that long-term follow-up from the CLL11 trial[66] indicates a 5-year PFS probability for the GClb group of around 0.23 (median follow-up 59.4 months, with 54 patients still at risk at 5-years). This is considerably higher than the estimate derived from the company's log-normal model (5-year PFS probability = [redacted]). Whilst PFS is expected to vary across patient populations, this suggests that the company's selected log-normal models are likely to underestimate the PFS benefits of GClb.

Figure 20: Modelled PFS, GClb – log-normal and generalised gamma models

PFS – progression-free survival; GClb – obinutuzumab plus chlorambucil

(ii) Limited evidence to support the assumption of a survival advantage for acalabrutinib

Whilst the CS reports an HR for OS for acalabrutinib versus GClb of 0.60 (95% CI 0.28, 1.27; *p*=0.16), the available OS data from ELEVATE-TN[20] are immature. For this reason, PPS data were sourced from other trials (OS data from trials in R/R CLL). However, these external data are also immature (see Figure 12 and

Figure 13). Further uncertainty is introduced as the company's model evalutes fixed sequences of therapies for which no randomised OS data exist.

The company's updated base case untreated CLL model predicts an undiscounted OS gain for acalabrutinib of [redacted] years compared with GClb. Given the limited OS data available, the ERG considers that the company's estimate of additional OS gain for acalabrutinib versus GClb, and the company's base case ICER, should be considered highly uncertain.

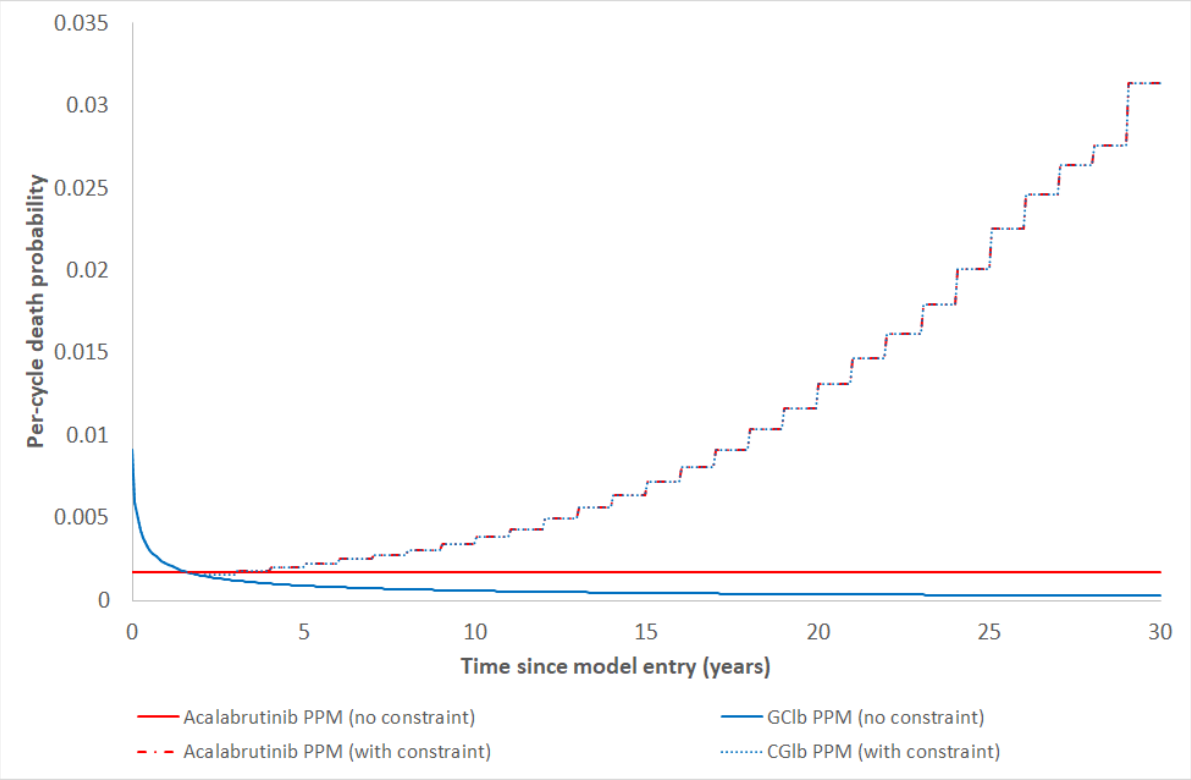
(iii) Strong influence of general population mortality risks

The company fitted seven standard parametric models to the available time-to-event data. The model selection process followed by the company is broadly in line with the recommendations set out in NICE TSD 14.[67] Justification for each selected model is described in Section 5.2.2.3. The model includes a general population mortality constraint which is applied to both death transitions (PPM and PPS) and which ensures that the risk of death in the modelled CLL population is at least as high as the mortality risk for the age- and sex-matched general population. This approach is conventional for economic models. However, in this instance, the general population mortality constraints quickly override the predicted hazard rates obtained from the parametric survival functions for PPM and PPS and have a substantial influence on predicted OS.

Figure 21 shows the predicted 28-day risk of death in patients without disease progression with and without the general population mortality constraint. As shown in the figure, the constraint takes effect within 3 years for both groups. After this timepoint, mortality risk in patients who are progression-free is governed entirely by the life tables.

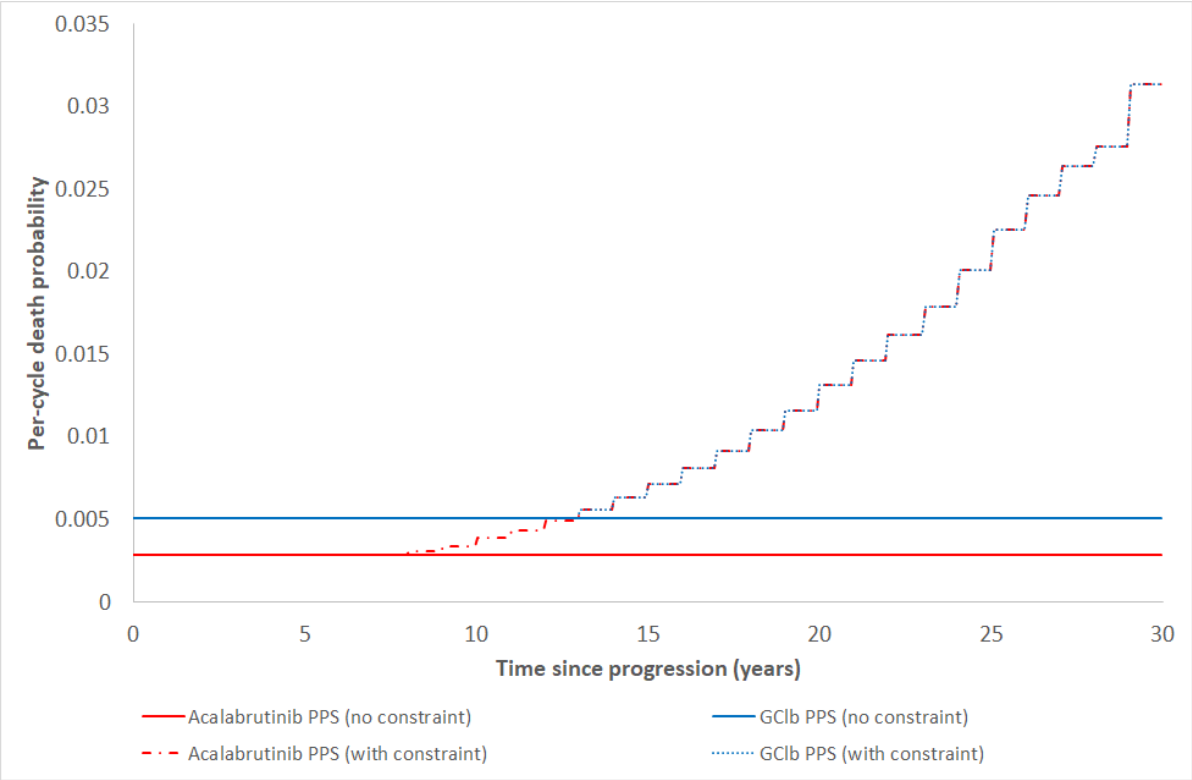
Figure 22 shows the equivalent plot for the 28-day risk of death for patients following progression (from age 70); this shows that the general population mortality constraint overrides the parametric survival model predictions within 8 years in the acalabrutinib group and within 13 years in the GClb group. Whilst not described as such in the CS,[1] this reflects an implicit assumption of cure for these patients. Figure 23 presents a comparison of modelled OS with and without the general population mortality constraints. As shown in the figure, the overall influence of the constraint on the survival projection is considerable in both treatment groups.

Figure 21: Per-cycle death probability for progression-free patients with/without general population mortality constraint



GClb – obinutuzumab plus chlorambucil; PPM – pre-progression mortality

Figure 22: Per-cycle death probability for progressed patients with/without general population mortality constraint



GClb – obinutuzumab plus chlorambucil; PPS – post-progression survival

Figure 23: Company's OS model projections including/excluding general population mortality constraint

[redacted]

GClb – obinutuzumab plus chlorambucil; OS – overall survival

(iv) Differences in PPS for VenR versus ibrutinib may be confounded by other factors

As shown in

Figure 22, prior to the general population mortality constraint taking effect, the assumed monthly risk of death for patients who have progressed after receiving acalabrutinib (solid red line) is assumed to be lower than the monthly risk of death for patients who progressed after receiving GClb (solid blue line). The company's approach to estimating PPS involved unadjusted arm-based analyses of OS data from the ibrutinib arm of RESONATE[23] and the VenR arm of MURANO.[43] The CS[1] does not explicitly state whether this difference in PPS risk is intended to reflect improved overall effectiveness of second-line VenR over second-line ibrutinib in progressed patients irrespective of prior treatment, or a residual ongoing benefit associated with patients who have received acalabrutinib in the first-line setting and have then progressed. Within NICE TA561,[10] there was uncertainty regarding whether VenR was more or less effective than ibrutinib in R/R CLL and the Appraisal Committee was unable to resolve this uncertainty.

In their clarification response[22] (question B12), the company argues that earlier treatment with effective therapies is likely to translate into improvements in response to subsequent therapies, but acknowledges that there may be *a degree of residual confounding between the two studies [RESONATE and MURANO]"*. The company's clarification response also comments that because IPD were not available from either study, it was not possible to adjust for potential confounding. Overall, the ERG believes that the company's assumption of improved PPS for VenR versus ibrutinib should be interpreted with caution.

(v) Optimistic OS projection for acalabrutinib

As a consequence of the factors described above, the ERG has concerns regarding the clinical plausibility of the company's modelled OS function. Based on the combination of the company's parametric survival modelling and the general population mortality constraint, the model suggests a highly favourable OS projection for patients treated with acalabrutinib.

Figure 24 shows the company's modelled OS functions for acalabrutinib (solid red line) and GClb (solid blue line); the plot also shows the OS projection for the age- and sex-matched general population (solid black line). As shown in the plot, OS in the acalabrutinib group is very similar to OS for the general population. Mean undiscounted OS for the acalabrutinib group is estimated to be [redacted] years; this is only slightly lower than mean undiscounted OS in the general population (15.56 years). The vertical dashed lines in the plot show the point at which the overall death risk (based on all transitions) fully converges on the general population mortality rate; these suggest that at least [redacted] of patients receiving acalabrutinib are cured.

Figure 24: Company's modelled OS compared with general population OS

GClb – obinutuzumab plus chlorambucil; OS – overall survival

Table 58 summarises the expected survival duration, the timepoint at which the modelled death risk is driven solely by general population mortality risk (denoted "cure" time) and the proportion of patients alive at this timepoint (denoted "cure" proportion) for all combinations of TTP/PPM and PPS models. As shown in the table, the majority of combinations of models exhibit similar behaviour, whereby a large proportion of acalabrutinib-treated patients are implicitly assumed to be cured. The only exceptions are when TTP/PPM is modelled using the Gompertz distribution and where PPS is modelled using the generalised gamma distribution.

Table 58: Survival, "cure" time and "cure" proportion for all combinations of TTP/PPM and PPS (company's base case shown in grey shading), generated using the company's updated model

PPS model	TTP&PPM model	Acalabrutinib			GClb		
		LYGs*	Cure prop	Cure time	LYGs*	Cure prop	Cure time
Exponential	Exponential	[redacted]	[redacted]	8.43	[redacted]	[redacted]	13.11
	Weibull	[redacted]	[redacted]	8.28	[redacted]	[redacted]	13.11
	Gompertz	[redacted]	[redacted]	19.55	[redacted]	[redacted]	13.03
	Log-normal	[redacted]	[redacted]	8.20	[redacted]	[redacted]	13.19
	Log-logistic	[redacted]	[redacted]	8.05	[redacted]	[redacted]	13.11
	Gamma	[redacted]	[redacted]	8.51	[redacted]	[redacted]	13.11
	Gen gamma	[redacted]	[redacted]	8.20	[redacted]	[redacted]	13.19
Weibull	Exponential	[redacted]	[redacted]	8.82	[redacted]	[redacted]	16.41
	Weibull	[redacted]	[redacted]	8.66	[redacted]	[redacted]	16.25
	Gompertz	[redacted]	[redacted]	19.78	[redacted]	[redacted]	16.25
	Log-normal	[redacted]	[redacted]	8.36	[redacted]	[redacted]	16.10
	Log-logistic	[redacted]	[redacted]	8.13	[redacted]	[redacted]	16.10
	Gamma	[redacted]	[redacted]	8.13	[redacted]	[redacted]	16.25
	Gen gamma	[redacted]	[redacted]	8.13	[redacted]	[redacted]	16.02
Gompertz	Exponential	[redacted]	[redacted]	9.35	[redacted]	N/a	N/a
	Weibull	[redacted]	[redacted]	9.43	[redacted]	N/a	N/a
	Gompertz	[redacted]	[redacted]	19.78	[redacted]	N/a	N/a
	Log-normal	[redacted]	[redacted]	9.66	[redacted]	N/a	N/a
	Log-logistic	[redacted]	[redacted]	9.20	[redacted]	N/a	N/a
	Gamma	[redacted]	[redacted]	9.20	[redacted]	N/a	N/a
	Gen gamma	[redacted]	[redacted]	9.20	[redacted]	N/a	N/a
Log-normal	Exponential	[redacted]	[redacted]	9.12	[redacted]	[redacted]	14.03
	Weibull	[redacted]	[redacted]	9.05	[redacted]	[redacted]	13.42
	Gompertz	[redacted]	[redacted]	19.62	[redacted]	[redacted]	11.04
	Log-normal	[redacted]	[redacted]	9.05	[redacted]	[redacted]	14.41
	Log-logistic	[redacted]	[redacted]	9.05	[redacted]	[redacted]	14.18
	Gamma	[redacted]	[redacted]	9.35	[redacted]	[redacted]	14.11
	Gen gamma	[redacted]	[redacted]	9.89	[redacted]	[redacted]	14.26
Log-logistic	Exponential	[redacted]	[redacted]	8.82	[redacted]	[redacted]	14.57
	Weibull	[redacted]	[redacted]	8.20	[redacted]	[redacted]	13.34
	Gompertz	[redacted]	[redacted]	19.62	[redacted]	[redacted]	13.03
	Log-normal	[redacted]	[redacted]	8.59	[redacted]	[redacted]	14.26
	Log-logistic	[redacted]	[redacted]	8.20	[redacted]	[redacted]	14.34
	Gamma	[redacted]	[redacted]	8.28	[redacted]	[redacted]	14.34
	Gen gamma	[redacted]	[redacted]	8.05	[redacted]	[redacted]	14.11
Gamma	Exponential	[redacted]	[redacted]	9.12	[redacted]	[redacted]	15.26
	Weibull	[redacted]	[redacted]	9.20	[redacted]	[redacted]	15.03
	Gompertz	[redacted]	[redacted]	19.70	[redacted]	[redacted]	16.33
	Log-normal	[redacted]	[redacted]	9.05	[redacted]	[redacted]	15.10
	Log-logistic	[redacted]	[redacted]	9.05	[redacted]	[redacted]	15.03
	Gamma	[redacted]	[redacted]	9.05	[redacted]	[redacted]	15.18
	Gen gamma	[redacted]	[redacted]	9.05	[redacted]	[redacted]	15.10
Gen gamma	Exponential	[redacted]	[redacted]	18.02	[redacted]	N/a	N/a
	Weibull	[redacted]	[redacted]	18.02	[redacted]	N/a	N/a
	Gompertz	[redacted]	[redacted]	19.47	[redacted]	N/a	N/a
	Log-normal	[redacted]	[redacted]	18.02	[redacted]	N/a	N/a
	Log-logistic	[redacted]	[redacted]	18.09	[redacted]	N/a	N/a
	Gamma	[redacted]	[redacted]	18.17	[redacted]	N/a	N/a
	Gen gamma	[redacted]	[redacted]	18.25	[redacted]	N/a	N/a
Minimum		[redacted]	[redacted]	8.05	[redacted]	[redacted]	11.04
Maximum		[redacted]	[redacted]	19.78	[redacted]	[redacted]	16.41

LYGs – life years gained; TTP – time to progression; PPM – pre-progression mortality; PPS – post-progression survival
** Undiscounted. Note: "Cure" time and "cure" proportion reflect the timepoint and proportion of patients alive at which the risk of death from both model health states fully switches to the general population risk. This does not have the same interpretation as a cure fraction estimated using a mixture-cure model.*

The ERG notes the following:

- The ERG's clinical advisors commented that the company's OS projections for acalabrutinib were likely to optimistic and noted that the available OS data from ELEVATE-TN[20] are limited and do not show a statistically significant survival advantage for acalabrutinib over GClb. Whilst they suggested that a survival benefit may be expected due to significant improvements in PFS, they considered the company's OS projection to be premature and speculative.
- The ERG considers the minimal loss of life expectancy for acalabrutinib-treated CLL patients implied by the comparison of modelled OS and general population OS to be clinically unlikely (general population expected survival = 15.56 years; acalabrutinib modelled survival = [redacted] years).
- The company's model implicitly assumes that a large proportion of patients are cured; however, the company has not attempted to model cure statistically (e.g. estimating cure fractions using mixture-cure models).
- The majority of combinations of standard parametric models fitted to PPM/TTP and PPS produce highly optimistic OS estimates for the acalabrutinib group. It is unclear whether the use of more flexible models, for example restricted cubic splines, might improve the plausibility of the model predictions.

Given the limited OS data available from ELEVATE-TN,[20] the ERG believes that the results obtained from the company's untreated CLL model should be interpreted with caution.

(6) Issues relating to health utilities

The ERG has concerns regarding the utility values applied to the progression-free and progressed disease health states in the model.

(a) Utility value for the progression-free health state

In the untreated CLL population (Model 1), patients in the progression-free health state are assigned a utility value of [redacted], based on the mean EQ-5D-3L estimate for patients who were progression-free in ELEVATE-TN (data pooled across both groups).[20] This value is higher than the age- and sex-matched EQ-5D value for the general population for individuals at model entry based on Ara and Brazier[47] (aged 70 years, 38% female - estimated utility = 0.78). The CS[1] recognises this issue and presents a scenario analysis in which the utility value for the progression-free state was set equal to EQ-5D value for the general population (see Table 45); this scenario analysis suggested an increase in the company's original base case ICER of around £690. However, the utility value applied in this scenario relates to a population aged ≥65 to <70 years, whilst the modelled population are already aged 70 at entry into the model. Therefore, the ERG considers this scenario analysis to be inappropriate.

In response to a request for clarification from the ERG[22] (question B21), the company states that *"it is not uncommon for patients to achieve a 'functional cure' when receiving treatment for CLL and therefore will reach their normal life expectancy and will die from causes unrelated to CLL"* and that *"with the introduction of more efficacious treatment options in the front-line setting, it is not implausible for patients to at least achieve a utility estimate equivalent to the age- and sex-matched general population"*. Furthermore, the company notes that the Health Survey for England (HSE) data used to inform the analysis by Ara and Brazier[47] are at least 14 years old and may no longer reflect HRQoL in the current UK general population.

The ERG considers it unlikely that patients with CLL enjoy a better level of HRQoL compared with the general population and notes that Ara and Brazier[47] remains the most recent and appropriate source of general population EQ-5D. As such, the ERG believes that the utility value for the progression-free state should be set equal to the value for the general population.

(b) Utility value for the progressed disease health state

A mean health utility value of [redacted] was reported for patients with progressed disease in ELEVATE-TN.[20] This value is also higher than general population utility. The company attributes this finding to the limited number of observations for these patients (n=[redacted]). Within the model, the company sourced the utility value for the progressed disease state from the literature. The ERG agrees that that the estimate from ELEVATE-TN may not be representative of patients with progressed CLL and that it is appropriate to instead derive estimates from other sources.

The model applies a value of [redacted] for patient utility in the progressed disease state. According to the CS,[1] this value was based on Holzner *et al*.[46] This study included the measurement of the EORTC QLQ-C30 and the FACIT-General in cancer patients, some of whom had CLL. According to the CS (page 148), *"The data were then used to give a general indication of reasonable utility values for CLL."* The ERG notes that this is not a preference-based utility study, no information is provided on how the value of 0.60 was estimated, and the Holzner *et al* paper does not report this value. Despite this, the ERG notes that this same value and source are quoted in a number of previous NICE appraisals (including TA561,[10] TA487,[11] TA359[6] and TA193[12]). Despite these precedents, the ERG is unclear whether this value presents a reasonable reflection of the level of HRQoL in patients with progressed disease.

The ERG notes that health utility may be higher for patients who are progression-free on second-line treatment compared with that for patients whose disease has subsequently progressed. As discussed in critical appraisal point [4], the model structure includes only one progression event and does not explicitly include benefits resulting from further time without disease progression after the initiation of second-line treatment.

(7) Issues relating to costs

The ERG believes that two relevant factors are missing from the company's modelled cost estimates: (a) drug wastage, and (b) imperfect RDI.

(a) Drug wastage

The company's models do not include drug wastage costs. However, drug wastage may be relevant if vial sharing is not permitted for IV drugs (rituximab and chlorambucil, which are dosed according to BSA and body mass, respectively), or if a patient does not complete a prescribed course of oral medicine, for example due to death (acalabrutinib, venetoclax and ibrutinib). Excluding wastage will underestimate costs. In response to a request for clarification on this issue[22] (question B19), the company stated: *"There is no clinical justification to assume wastage of oral treatments in first- or second-line treatment. Pharmacists often follow clear dispensing protocols to ensure that there is no wastage of oral cytotoxic medications, with dispensing of subsequent prescriptions limited until the existing supply is exhausted… As the treatment cycles are continuous, in practice, patients receiving oral treatment would only incur the full cost of a pack of medication once the previous pack has been fully consumed. It is unrealistic to assume that a patient receiving a pack of medication sufficient for 30 days treatment would discard 2 days' worth of medication following completion of a 28-day cycle."*

The ERG considers the company's response to be insufficient as it fails to acknowledge that patients who die without completing their full course of oral treatment will inevitably lead to some degree of wastage. One of the ERG's clinical advisors suggested that, on average, wastage for oral treatments might be around half a pack per patient.

(b) Imperfect RDI

The company's model assumes an RDI of 100% for all drug treatments. In their clarification response[22] (question B4), the company stated that this assumption was made on basis that *"…relative dose intensity (RDI) for acalabrutinib, chlorambucil plus obinutuzumab and the subsequent treatments were high and consistently above 94%"*. In addition, the company provided a summary of the mean/median RDI for each first-/second-line treatment regimen from ELEVATE-TN,[20] RESONATE,[23] and MURANO[43] (see Table 59). The data provided by the company show that RDI was not 100% in any study. Consequently, drug acquisition costs included in the model are overestimated.

Table 59: Mean relative dose intensity for acalabrutinib and comparators (adapted from clarification response, Table 14)

Treatment	Mean RDI	Source
Acalabrutinib	96.8%	ELEVATE-TN CSR[20]
GClb	93.8%	ELEVATE-TN CSR[20]
Ibrutinib (RESONATE)	94.8%	NICE TA429 committee papers[68]
VenR (MURANO)	97% (median; mean not reported)	NICE TA561 committee papers[60]

GClb – obinutuzumab plus chlorambucil; VenR – venetoclax plus rituximab; CSR - Clinical Study Report; RDI - relative dose intensity

(8) Additional concerns regarding the company's economic analyses in the high-risk CLL population (Model 2)

The company's CMA for the high-risk population (Model 2) indicates that acalabrutinib produces cost savings of [redacted] per patient compared with ibrutinib (see Table 56). The ERG has some concerns regarding the reliability of this finding. Within the company's original CMA,[1] the baseline models for TTP and PPM are based on the acalabrutinib arm of the ITT population from ELEVATE-TN,[20] whilst the MAIC, which is used to support the assumption of clinical equivalence, is based on data from the overall R/R CLL populations recruited into RESONATE[40] and ASCEND.[21] Neither the baseline model for the CMA nor the studies used to estimate relative treatment effects in the MAIC relate specifically to a population of CLL patients with del(17p) or TP53 mutations. The company's CMA for the high-risk CLL population therefore relies on two assumptions: (i) that the estimated relative treatment effects from the MAIC in patients with untreated CLL are transportable to patients with high-risk CLL, and (ii) that the baseline outcomes for acalabrutinib in patients with untreated CLL also reflect expected outcomes for patients with high-risk CLL. In the absence of a comparison of outcomes relating to this specific population, it is unclear whether either of these assumptions is reasonable or whether the direction and/or magnitude of the incremental costs estimated using the model are robust. The ERG notes that data are available for 35 patients with del(17p)/TP53 mutations in the acalabrutinib arm of ELEVATE-TN; however, it is unclear whether similar external data exist for high-risk CLL patients treated with ibrutinib.

During the clarification process, the ERG requested that the company undertake a full cost-utility analysis using parametric models fitted to the MAIC-weighted time-to-event data, thereby avoiding *a priori* assumptions of clinical equivalence (see clarification response,[22] question C1). The ERG requested that this analysis should avoid assumptions of proportional hazards. As part of their clarification response, the company undertook a full economic analysis by extending their original CMA for the high-risk CLL population (Model 2). The methods and results of the company's additional analysis are presented in detail in the company's clarification response[22] (questions B23 and C1).

Briefly, this additional analysis involved applying the following amendments to the company's original CMA for the high-risk CLL population:

- A further MAIC was undertaken which used IPD from ELEVATE-TN[20] and aggregate data from RESONATE-2.[69] This MAIC produced an estimated HR for PFS of [redacted] (standard error [redacted]).
- The company's selected parametric survival models for TTP, PPM and PPS in the acalabrutinib group were refitted using an alternative PFS endpoint to align with the data used to inform the MAIC.
- The HR from the MAIC was applied to both the TTP and PPM distributions in the acalabrutinib group.
- Health state utility values were based on the values used in the economic analysis for the untreated CLL population (Model 1).
- QALY losses associated with AEs were included.
- All patients who progress were assumed to receive second-line VenR.
- Cost-effectiveness results were presented using both the deterministic and probabilistic versions of the model.
- Health outcomes and costs were discounted at a rate of 3.5% per annum.
- All other aspects of the model remain the same as the original CMA.

The probabilistic version of the company's full cost-utility analysis suggests that acalabrutinib dominates ibrutinib, producing [redacted] additional QALYs and cost savings of [redacted] per patient.

The ERG considers the company's full cost-utility analysis for the high-risk CLL population to be problematic for several reasons. As with the original CMA, the cost-utility model does not relate to patients with del(17p) or TP53 mutations. As noted in the company's clarification response[22] (question B23), RESONATE-2 specifically excluded patients with del(17p) and included only 12 patients with a TP53 mutation. The relevance of this additional MAIC to the high-risk CLL population is thus questionable. Furthermore, contrary to the ERG's request, the company's full model assumes PH: given the state transition model structure, the PH assumption, together with an estimated lower cost per cycle and equal treatment duration between the treatment groups, this inevitably leads to a situation whereby acalabrutinib dominates ibrutinib.

The ERG's clinical advisors suggest that it is likely that acalabrutinib and ibrutinib are similarly effective in patients with del(17p) and TP53 mutations. However, neither the CS[1] nor the company's clarification response[22] provide any comparative clinical data for acalabrutinib versus ibrutinib in patients with these high-risk features to support this finding.

5.3.5 Key issues identified from the ERG's critical appraisal – R/R CLL (Model 3)

This section presents a discussion of the main issues identified from the critical appraisal of the company's economic analyses for the R/R CLL population (Model 3).

Within the company's original CMA,[1] clinical equivalence is assumed between acalabrutinib and ibrutinib, based on the results of the company's MAIC using data from RESONATE[40] and ASCEND[21] (see Section 4.4). PFS and OS were estimated using parametric survival models fitted to data from the ibrutinib arm of the ITT population of RESONATE. The company's updated CMA for this population (Model 3), which includes the correction of minor errors, suggests that acalabrutinib produces cost savings of [redacted] per patient compared with ibrutinib.[22]

Owing to concerns regarding the company's MAIC, during the clarification process, the ERG requested that the company undertake a full cost-utility analysis using parametric models fitted to the MAIC-weighted time-to-event data, thereby avoiding *a priori* assumptions of clinical equivalence (see clarification response,[22] question C2). The ERG requested that this analysis should avoid assumptions of proportional hazards. As part of their clarification response, the company undertook a full economic analysis by extending their original CMA.

Briefly, this additional analysis involved applying the following amendments to the company's original CMA for the R/R CLL population:

- The results of the MAIC for the R/R CLL population were used; estimated HRs of [redacted] (SE [redacted]) for PFS and [redacted] (SE [redacted]) for OS were applied to the PFS and OS models used in the ibrutinib treatment group.
- The company's selected parametric survival models for PFS and OS in the ibrutinib group remained unchanged (Weibull for PFS and exponential for OS).
- Health utilities were based on EQ-5D-3L data collected in ASCEND[21] and previous NICE TAs (progression-free utility=[redacted] [standard error [redacted]]; progressed disease utility=0.60 [standard error 0.06]).
- The model included QALY losses resulting from AEs, based on durations and disutilities from various sources (NICE TA487,[11] TA359,[6] TA403,[49] Wehler *et al*[48] 2018 and assumptions[22]).
- All patients who progress were assumed to receive second-line VenR, using the same cost assumptions as those applied in Model 1 (see Section 5.2.2).
- Health outcomes and costs were discounted at a rate of 3.5% per annum.
- Cost-effectiveness results were presented using both the deterministic and probabilistic versions of the model.
- All other aspects of the model remain the same as the original CMA.

The full description of the methods and results of the company's additional analysis are presented in detail in the company's clarification response[22] (question C2). The probabilistic version of the company's cost-utility analysis suggests that acalabrutinib dominates ibrutinib, with acalabrutinib generating an additional [redacted] QALYs and cost savings of [redacted] per patient.

As described in the ERG's critique of the company's MAIC (see Section 4.4), the ERG considers that on the basis of the analyses presented in the CS[1] and additional information provided in response to the ERG's clarification questions[22] (question A29), the company's conclusion of equivalent efficacy in PFS and OS between acalabrutinib and ibrutinib in patients with R/R CLL is likely to be reasonable. Furthermore, the ERG's clinical advisors supported this conclusion. For these reasons, the ERG considers the company's CMA for the R/R population to be reasonable. The ERG notes that the original CMA model is subject to several issues which also apply to the other models; with the exception of issue (vi) below, these issues have been described previously in Section 5.3.4:

(i) Use of outdated NHS Reference Costs
(ii) Incorrect estimation of general population mortality risk
(iii) Error in the transcription of health state resource use
(iv) Costs of drug wastage are not included
(v) RDI is assumed to be 100% for acalabrutinib and ibrutinib
(vi) Error in the transcription of AEs.

In their clarification response[22] (question B30), the company highlighted that they had erroneously included AEs which occurred in less than 1% of patients treated with either acalabrutinib or ibrutinib in the R/R CLL model. The company provided a summary of the AEs used in the updated cost-utility model for R/R CLL patients as part of their clarification response (see Table 60).

All of these issues are addressed in the ERG's exploratory analyses (see Section 5.4).

Table 60: Frequency of grade 3/4 AEs and associated costs, R/R CLL population updated base-case analysis (adapted from clarification response, question B30)

AE	AE incidence	
	Acalabrutinib	**Ibrutinib**
Anaemia	11.70%	4.62%
Diarrhoea	1.30%	4.10%
Dyspnoea	0.00%	2.05%
Fatigue	0.00%	2.05%
Infections and infestations	14.90%	24.00%
Neutropenia	15.58%	16.41%
Neutrophil count decreased	1.3%	0%
Atrial fibrillation	1.30%	3.00%
Thrombocytopenia	3.90%	5.64%
Bleeding	1.9%	1.0%

AE – adverse event

5.4 Exploratory analyses undertaken by the ERG

5.4.1 ERG exploratory analysis – methods

The ERG undertook exploratory analyses within all three CLL models (untreated CLL, high-risk CLL and R/R CLL). These exploratory analyses differ between the three models. The ERG's analyses include correcting model errors, applying alternative assumptions and exploring the impact of other areas of uncertainty in which evidence is lacking. All analyses were undertaken using the deterministic versions of the company's original models.

The exploratory analyses were implemented by two modellers to ensure that they are free from errors.

5.4.1.1 ERG exploratory analysis methods: Model 1 - untreated CLL population

ERG exploratory analysis 1: Correction of model errors and use of up-to-date data sources

As detailed in Section 5.3.4 (critical appraisal point [1]), the ERG identified several errors and out-of-date data sources in the company's original model for the untreated CLL population. The company's updated model which was provided as part of their clarification response included the correction of some, but not all, of these issues. Five model amendments were applied within this exploratory analysis.

(1a) Half cycle correction

The error in the company's half cycle correction of QALYs and costs was corrected such that costs and QALYs for each cycle were counted only once in the model calculations.

(1b) Use of current NHS Reference Costs

Unit costs associated with health state resource use were updated using NHS Reference Costs 2018/19.[62]

(1c) Use of relevant general population life tables and mortality model corrections

The model was amended to include life tables for England 2016-2018.[63] The probability of all-cause mortality in each model cycle was modelled as being conditional on the male:female ratio of the modelled cohort at model entry (age 70 years).

(1d) Correction of health state transcription error

For consistency with the values reported in the NICE TA561 committee papers,[60] the model was amended to assume that patients undergo 0.15 LDH monitoring tests every 28 days.

(1e) Correction of second-line treatment durations

The company's model does not have the functionality to estimate subsequent-line treatment costs according to progression status. Attempts made by the company and the ERG to estimate these costs following the clarification process were unsatisfactory. In response to criticisms raised by the company within their factual accuracy check, the ERG developed a separate model to estimate the costs associated with second-line treatments based on second-line PFS rather than OS. The ERG reconstructed the IPD for PFS for ibrutinib-treated patients with 1-2 prior lines of therapy from RESONATE[23] and fitted six standard parametric survival models to these data (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). A general population mortality constraint was applied to the PFS models, with an initial age of 70 years. In addition, the PFS risk was constrained by the PPS probability from the ibrutinib arm of the company's model (based on RESONATE). The Weibull distribution was selected to represent PFS in the ERG's preferred analysis, as this was the company's preferred model in TA561[60] and because, unlike the exponential, log-normal, log-logistic and generalised gamma models, it was not strongly influenced by the PPS mortality constraint. The per cycle cost of second-line treatment was then estimated as the cumulative PFS probability multiplied by the RDI and the drug cost for the regimen. Per cycle costs were calculated for each model cycle for patients starting at age 70 years.

Importantly, the maximum number of remaining cycles of second-line treatment, the general population mortality risk and the appropriate initial discount multiplier for costs are dependent on the time at which a patient progresses on first-line treatment. For example, for a patient who progresses on first-line treatment at age 70, maximum remaining treatment time is 30 years, the general population mortality risk is low and the initial discount multiplier in the first treatment cycle is 1/(1.035^0). In contrast, for a patient who progresses on first-line treatment at age 90, maximum remaining treatment time is 10 years, general population mortality risk is comparatively higher and the initial discount multiplier in the first treatment cycle is 1/(1.035^20). In order to account for these factors, discounted lifetime second-line costs were calculated for every possible progression tine (i.e. every 28-day cycle), with remaining treatment time, age-related mortality risk and discount multipliers conditioned on the time of

progression. The resulting vector of discounted lifetime second-line treatment costs conditional on the time of progression was then multiplied by the proportion of patients who progress and survive [redacted] additional cycles in the company's model in each cycle. The sumproduct of these two vectors gives the expected lifetime discounted second-line treatment cost in each arm. The same approach was used for ibrutinib (no maximum duration), venetoclax (maximum 26 cycles) and rituximab (maximum 6 cycles). The once-only monitoring cost was included for venetoclax. No half cycle correction was applied and the same second-line PFS function was applied to each treatment group. The expected post-progression costs estimated within the company model were then replaced with the estimates from the ERG's.costing model The ERG notes that this approach is essentially the same as the company's original approach, except that expected costs are driven by second-line PFS rather than OS. A summary of the ERG's survival model outputs is presented in Appendix 1.

All other exploratory analyses for the untreated CLL population undertaken by the ERG include these model corrections.

ERG exploratory analysis 2: Use of generalised gamma models for TTP and PPM in the GClb group

Within this analysis, the generalised gamma models for TTP and PPM were applied in the GClb group.

ERG exploratory analysis 3: Use of PPS exponential model from RESONATE in both treatment groups

Within this analysis, the exponential model fitted to PPS data from RESONATE[23] was applied within both the acalabrutinib and GClb groups. This source was selected instead of MURANO[43] as it leads to comparatively less favourable estimates of OS for the acalabrutinib group. The ERG notes that PPS trajectories for patients receiving second-line VenR (following acalabrutinib) and for patients receiving second-line ibrutinib (following GClb) are uncertain and other studies not included in the CS may be more appropriate than RESONATE.

ERG exploratory analysis 4: PF utility based on general population utility (age 70 years)

Within this analysis, health utility for the progression-free state was assumed to be 0.78, based on the estimated EQ-5D value for the age- and sex-matched general population from Ara and Brazier.[47]

ERG exploratory analysis 5: Inclusion of RDI for all treatments

Within this analysis, all treatment cost calculations were amended to include estimates of mean RDI provided by the company within their clarification response (shown previously in Table 59).

ERG exploratory analysis 6: Inclusion of costs of drug wastage

Based on clinical advice received by the ERG, the model was amended to include costs associated with 14 days of wastage for all oral drugs (acalabrutinib, venetoclax and ibrutinib). This cost was applied to patients who die prior to progression. Wastage costs were not included for IV drugs (obinutuzumab and rituximab).

ERG exploratory analysis 7: Inclusion of VenR as second-line treatment for [redacted] of patients

Based on additional evidence provided by the company within their factual accuracy response document, the model cost calculations were amended to assume that for patients who receive GClb in the first-line setting, [redacted] receive ibrutinib and [redacted] receive VenR in the second-line setting.

ERG exploratory analysis 8: ERG-preferred analysis

The ERG's preferred analysis for the untreated CLL population combines ERG exploratory analyses 1-7.

Three additional sensitivity analyses were undertaken using the ERG's preferred analysis for the untreated CLL population.

ERG additional sensitivity analysis 1: Fully incremental analysis of acalabrutinib followed by VenR versus GClb followed by ibrutinib versus GClb followed by VenR

Within this sensitivity analysis, three options were evaluated within a fully incremental analysis: (i) acalabrutinib followed by VenR; (ii) GClb followed by ibrutinib, and (iii) GClb followed by VenR.

ERG additional sensitivity analysis 2: Alternative scenarios surrounding survival gains

Within this sensitivity analysis, the hazard rate for PPS in the acalabrutinib group was amended to explore the following scenarios: (a) undiscounted incremental OS gain for acalabrutinib versus GClb assumed to be equal to 50% of that predicted within the ERG preferred analysis; (b) zero incremental OS gain for acalabrutinib versus GClb. The ERG notes that given the observed improvement in PFS in ELEVATE-TN, the latter analysis is particularly pessimistic.

ERG additional sensitivity analysis 3: Alternative second-line PFS models

Within this sensitivity analysis, alternative parametric models were used to represent second-line PFS. This influences the duration of second-line therapy (particularly for ibrutinib). The Gompertz and log-normal models were selected as they represent the shortest and second-longest PFS durations, respectively (note – the generalised gamma model, which had the longest PFS duration, was disregarded as it was heavily constrained by OS even at the earliest age of progression).

5.4.1.2 ERG exploratory analysis methods: Model 2 – high-risk CLL population

Several of the issues identified in the company's model for the untreated CLL population (described in Section 5.4.1.1) also apply to the model for the high-risk CLL population (Model 2). The ERG applied the following amendments to the company's original version of the high-risk CLL model.

- ERG exploratory analysis 1: Correction of model errors (exploratory analyses 1(a) to 1(d))
- ERG exploratory analysis 3: Use of the PPS exponential model fitted to data from RESONATE in both treatment groups
- ERG exploratory analysis 5: Inclusion of RDI for all treatments
- ERG exploratory analysis 6: Inclusion of costs of drug wastage.

The ERG's preferred analysis combines all of these model amendments. Given the company's use of a CMA in this population, ERG exploratory analyses 1(e), 2, 4 and 7, as described in Section 5.4.1.1, are not relevant to this analysis. No additional sensitivity analyses were undertaken in this population.

5.4.1.3 ERG exploratory analysis methods: Model 3 – R/R CLL population

Several of the issues identified in the company's model for the untreated CLL population (see Section 5.4.1.1) also apply to the model for the R/R CLL population (Model 3). The ERG applied the following amendments to the company's original CMA for this population.

- ERG exploratory analysis 1: Correction of model errors (amendments 1(b) to 1(d) and 1(f)).
  This model includes an additional error whereby the company erroneously included some AEs which occurred in less than 1% of either treatment group. This was corrected by the company in their clarification response[22] (corrected values are shown in Table 60).
- ERG exploratory analysis 5: Inclusion of RDI for all treatments
- ERG exploratory analysis 6: Inclusion of costs of drug wastage

The ERG's preferred analysis combines all of these model amendments. ERG exploratory analyses 1(a), 1(e), 2, 3, 4 and 7, as described in Section 5.4.1.1, are not relevant to this analysis. No additional sensitivity analyses were undertaken in this population.

The ERG's exploratory analyses for all three models are summarised in Table 61. Full details regarding the implementation of the ERG's exploratory analyses are provided in Appendix 2.

Table 61: Summary of ERG exploratory analyses

ERG analysis	Included?		
	Model 1 – untreated CLL	**Model 2 – high-risk CLL**	**Model 3 – R/R CLL**
EA1(a): Half-cycle correction	✓	✓	✗
EA1(b):Updated NHS Reference Costs	✓	✓	✓
EA1(c): Updated life tables and mortality model correction	✓	✓	✓
EA1(d): LDH transcription error	✓	✓	✓
EA1(e): Second-line treatment durations corrected	✓	✗	✗
EA1(f):AE error	✗	✗	✓
EA2: Use of generalised gamma TTP and PPM for GClb group	✓	✗	✗
EA3: Use of RESONATE PPS in both groups	✓	✓	✗
EA4: PF utility from Ara and Brazier	✓	✗	✗
EA5: Inclusion of RDI	✓	✓	✓
EA6: Inclusion of drug wastage	✓	✓	✓
EA7: Second-line treatment mix for comparator ([redacted] VenR;[redacted] ibrutinib)	✓	✗	✗
ERG's preferred analysis	All items marked "✓" above	All items marked "✓" above	All items marked "✓" above
ASA1: Fully incremental analysis - acalabrutinib followed by VenR versus GClb followed by ibrutinib versus GClb followed by VenR	✓	✗	✗
ASA2: OS scenarios	✓	✗	✗
ASA3: Alternative second-line PFS models	✓	✗	✗

GClb – obinutuzumab plus chlorambucil; VenR – venetoclax plus rituximab; ERG – Evidence Review Group; CLL – chronic lymphocytic leukaemia; EA – exploratory analysis; ASA – additional exploratory analysis; LDH - lactate dehydrogenase; TTP – time to progression; PPM – pre-progression mortality; PPS – post-progression survival; RDI – relative dose intensity; OS – overall survival

5.4.2 Exploratory analysis results

This section presents the results of the ERG's exploratory analyses. These results include the PAS for acalabrutinib. The results of the analyses including the cPAS discounts for obinutuzumab, venetoclax, rituximab, ibrutinib and chlorambucil are presented in a confidential appendix to this report.

5.4.2.1 ERG exploratory analysis results: Model 1 - untreated CLL population

Table 62 presents the results of the ERG's exploratory analyses for the untreated CLL population (Model 1). As shown in the table, the correction of errors and use of updated data sources increases the company's original base case ICER from £30,001 to £32,298 per QALY gained. With the exception of the inclusion of RDI estimates (EA5), all other exploratory analyses increase the ICER for acalabrutinib relative to the company's base case. The ERG's preferred analysis, which includes all of the individual

analyses shown in Table 62, results in an ICER for acalabrutinib versus GClb of £61,702 per QALY gained. It is likely that the probabilistic ICER for this scenario would be slightly higher than this value.

Table 62: ERG's preferred analysis – Model 1, untreated CLL, acalabrutinib versus GClb

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's base case (deterministic)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,001**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA1: Correction of errors and outdated data sources							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,298**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA2: Generalised gamma TTP and PPM for GClb							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,921**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA3: Use of RESONATE PPS in both groups							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,112**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA4: PF utility from Ara and Brazier							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,153**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA5: Inclusion of RDI							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,448**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA6: Inclusion of wastage							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,641**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA7: Second-line treatment mix for comparator ([redacted] VenR; [redacted] ibrutinib)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,653**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
EA8: ERG's preferred analysis							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£61,702**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-

GClb – obinutuzumab plus chlorambucil; VenR – venetoclax plus rituximab; LYGs – life years gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; TTP – time to progression; PPM – pre-progression mortality; PPS – post-progression survival; RDI – relative dose intensity; EA – exploratory anlaysis
Note – EA2 to EA8 all include the correction of errors included in EA1

Table 63 presents the results of the ERG's additional sensitivity analysis which includes first-line GClb followed by second-line VenR as an additional comparator within a fully incremental analysis. Within this analysis, GClb followed by ibrutinib is ruled out of the analysis as it is strongly dominated by GClb followed by VenR. The ICER for acalabrutinib followed by VenR versus GClb followed by VenR is estimated to be £141,889 per QALY gained.

Table 63: Additional sensitivity analysis 1 – Model 1, untreated CLL, fully incremental analysis of acalabrutinib followed by VenR versus GClb followed by ibrutinib versus GClb followed by VenR

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Acalabrutinib →VenR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£141,889**
GClb →VenR	[redacted]	[redacted]	[redacted]	-	-	-	**-**
GClb →ibrutinib	[redacted]	[redacted]	[redacted]	-	-	-	**Dominated**

GClb – obinutuzumab plus chlorambucil; VenR – venetoclax plus rituximab; LYGs – life years gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 64 presents the results of the ERG's additional analysis around the incremental survival gain for acalabrutinib versus GClb. As expected, this analysis indicates that applying less optimistic assumptions regarding survival (PPS) for acalabrutinib increases the ICER. Adjusting PPS in the acalabrutinib group such that the incremental undiscounted OS gain is half that estimated in the ERG's preferred analysis increases the ICER to £73,535 per QALY gained. Under the highly pessimistic assumption of zero incremental survival gain between acalabrutinib versus GClb, the ICER is increased to £92,985 per QALY gained.

Table 64: Additional sensitivity analysis 2 – Model 1, untreated CLL, alternative scenarios surrounding survival gains, acalabrutinib versus GClb

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
ERG's preferred analysis							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£61,702**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	**-**
50% survival gain relative to EA7 (PPS rate = RESONATE * 1.63)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£73,535**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	**-**
Zero survival gain (PPS rate = RESONATE * 2.44)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£92,985**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	**-**

GClb – obinutuzumab plus chlorambucil; PPS – post-progression survival; LYGs – life years gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 65 presents the results of the ERG's preferred analysis assuming alternative survival models for second-line PFS. Applying the Gompertz model, which leads to the shortest second-line PFS duration, increases the ICER for acalabrutinib versus GClb to £65,572 per QALY gained. Applying the log-normal model, which leads to the longest second-line PFS duration, reduces the ICER for acalabrutinib versus GClb to £40,935 per QALY gained. The ERG notes that the log-normal model is more heavily constrained by the OS constraints compared with the Weibull and Gompertz models (see Appendix 1, Table 69).

Table 65: Additional sensitivity analysis 3 – Model 1, untreated CLL, alternative second-line PFS models, acalabrutinib versus GClb

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
ERG's preferred analysis							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£61,702**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
Second-line PFS = Gompertz (shortest treatment duration for ibrutinib)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,572**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-
Second-line PFS = Log-normal (second-longest treatment duration for ibrutinib)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,935**
GClb	[redacted]	[redacted]	[redacted]	-	-	-	-

5.4.2.2 ERG exploratory analysis results: Model 2 – high-risk CLL population

Table 66 presents the results of the ERG's exploratory analyses within the high-risk CLL population (Model 2). None of the ERG's exploratory analyses have a substantial impact on the estimated cost-savings associated with acalabrutinib. The ERG's preferred analysis suggests cost savings for acalabrutinib of [redacted] per patient compared with ibrutinib. As noted in Section 5.3.4 (critical appraisal point [8]), these results should be interpreted with caution as none of the evidence used to inform this analysis specifically relates to patients with del(17p)/TP53 mutations.

Table 66: ERG's preferred analysis – Model 2, high-risk CLL, acalabrutinib versus ibrutinib

Option	LYGs*	Drug acquisition costs	PF health state costs	PD health state costs	End of life care costs	AE costs	Total cost
Company's base case (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA1: Correction of errors and outdated data sources							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA3: Use of RESONATE PPS in both groups							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA5: Inclusion of RDI							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA6: Inclusion of wastage							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]

Option	LYGs*	Drug acquisition costs	PF health state costs	PD health state costs	End of life care costs	AE costs	Total cost
EA8: ERG's preferred analysis							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]

LYGs – life years gained; PF – progression-free; PD – progressed disease; AE – adverse event; PPS – post-progression survival; RDI – relative dose intensity; EA – exploratory analysis
** Undiscounted*

5.4.2.3 ERG exploratory analysis results: Model 3 – R/R CLL population

Table 67 presents the results of the ERG's exploratory analyses for the R/R CLL population (Model 3). As shown in the table, none of the changes proposed by the ERG had a marked impact on the magnitude of estimated cost-savings for acalabrutinib. The ERG's preferred analysis suggests cost savings for acalabrutinib of [redacted] per patient compared with ibrutinib.

Table 67: ERG's preferred analysis – Model 3, R/R CLL, acalabrutinib versus ibrutinib

Option	LYGs*	Drug acquisition costs	PF health state costs	PD health state costs	End of life care costs	AE costs	Total cost
Company's base case (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA1: Correction of errors and outdated data sources (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA5: Inclusion of RDI (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
EA6: Inclusion of wastage (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]
ERG's preferred analysis (undiscounted)							
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	0.00	[redacted]	£0	£0	£0	[redacted]	[redacted]

LYGs – life years gained; PF – progression-free; PD – progressed disease; AE – adverse event; PPS – post-progression survival; RDI – relative dose intensity; EA – exploratory analysis
** Undiscounted*

5.5 Discussion

The company's systematic review of published economic evaluations identified one study of acalabrutinib versus ibrutinib in patients with R/R CLL. The company stated that the findings of this

study did not reflect their view of the relative efficacy of acalabrutinib compared to ibrutinib. No published economic analyses of acalabrutinib were identified in patients with untreated CLL.

The CS[1] presents the methods and results of three economic analyses of acalabrutinib for CLL. The company developed a semi-Markov model to assess the cost-effectiveness of acalabrutinib versus GClb for patients with untreated CLL (Model 1). This model assumes fixed sequences of treatment, whereby patients who progress on first-line acalabrutinib are assumed to receive second-line VenR, whilst patients who progress on first-line GClb receive second-line ibrutinib. Model health states are defined in terms of progression and survival status. The cost-effectiveness of acalabrutinib was evaluated over a 30-year time horizon from the perspective of the NHS and PSS. The model uses data on TTP and PPM from ELEVATE-TN,[20] with PPS drawn from external sources (MURANO[43] and RESONATE[23]). A general population mortality constraint[45] is applied to ensure that the mortality rate predicted by the parametric survival models never falls below that of the general population. Health state utility values were based on estimates derived from ELEVATE-TN[20] and other sources.[46, 47] Information on the frequency of AEs was taken from ELEVATE-TN; associated disutilities and AE durations were taken from the literature,[48] previous NICE TAs.[6, 11, 49] and assumptions. Costs were taken from the BNF,[50] previous NICE TAs[10, 11] and NHS Reference Costs.[51]

The company used the acalabrutinib arm of the semi-Markov model to present a CMA comparing acalabrutinib against ibrutinib in patients with high-risk CLL ((del17p)/TP53 mutations – Model 2). This model assumes clinical equivalence between the two treatment options based on the findings of the company's MAIC for R/R CLL.

The CS also presents a separate CMA which compares acalabrutinib against ibrutinib in patients with R/R CLL (Model 3). This model adopts a partitioned survival approach, assuming clinical equivalence between the treatment options based on the company's MAIC for R/R CLL. Parametric survival models were fitted to PFS and OS data from the ibrutinib arm of the RESONATE trial.[40]

The company has proposed a PAS for acalabrutinib which takes the form of a simple price discount; this is included in the analyses of all three models. Price discounts also exist for obinutuzumab, chlorambucil and ibrutinib (the included comparators) and for venetoclax and rituximab (which are assumed to reflect second-line treatment following acalabrutinib in Model 1). The impact of including these cPAS discounts on the cost-effectiveness of acalabrutinib is presented as a separate appendix to this report.

The deterministic version of the company's updated model for untreated CLL (Model 1) provided following the clarification process suggests that the ICER for acalabrutinib versus GClb is £22,679 per

QALY gained. The company's updated CMA for the high-risk CLL population (Model 2) suggests that acalabrutinib produces cost-savings of [redacted] per patient compared with ibrutinib. The company's updated CMA for the R/R CLL population (Model 3) suggests that acalabrutinib produces cost-savings of [redacted] per patient compared with ibrutinib.

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic versions of the company's original models for each population. The ERG's critical appraisal identified several issues relating to the company's models and the evidence used to inform their parameters. Within the untreated CLL population (Model 1), these include: (i) the presence of programming errors and use of outdated data sources; (ii) restrictive structural assumptions which lead to the overestimation of second-line treatment costs in the comparator group; (iii) the inappropriate assumption that all patients who progress on GClb will receive second-line ibrutinib (iv) highly optimistic estimates of survival for the acalabrutinib group despite immature OS data; (v) pessimistic assumptions regarding PFS for GClb; (vi) the use of health utility values which are higher than those for people without CLL, and (vii) the omission of RDI and wastage from the cost calculations. Several of the programming errors identified in the untreated CLL population also applied to the high-risk and R/R CLL populations. Within the R/R population (Model 3), the ERG considers the assumption of clinical equivalence to be reasonable, based on the company's MAIC and clinical input received by the ERG. Given the assumption of equivalent first-line treatment duration, equivalent subsequent-line treatments, and a lower price per cycle between the options, this inevitably leads to estimated cost-savings for acalabrutinib versus ibrutinib. The ERG notes that within the high-risk CLL population (Model 2), neither the sources used to inform baseline event rates (TTP, PPM and PPS) nor the studies included in the MAIC to justify the assumption of equivalence between acalabrutinib and ibrutinib specifically relate to the high-risk CLL population.

The ERG undertook exploratory analyses using all three models. Within the untreated CLL population (Model 1), these included: correcting errors and updating data sources; using PPS rates from RESONATE in both treatment groups; using the generalised gamma PFS model for the GClb group; using an alternative utility value for the progression-free health state; including RDI and wastage in the model cost calculations, and assuming a different mix of second-line treatments for patients who progress on first-line GClb. The ERG's preferred analysis, which includes all of these amendments, suggests that the deterministic ICER for acalabrutinib versus GClb is £61,702 per QALY gained. Additional sensitivity analyses undertaken using the ERG's preferred model indicate that the ICER may be markedly higher when patients in the comparator group are assumed to receive second-line VenR rather than ibrutinib, and/or if less optimistic assumptions are made regarding the relative survival benefit for acalabrutinib versus GClb. The ERG's results are also sensitive to the choice of parametric

model used to estimate second-line PFS; the use of the Gompertz model increases the ICER, whilst the log-normal model decreases the ICER.

The ERG's exploratory analyses within the high-risk CLL population (Model 2) did not have a marked impact on the estimated cost-savings for acalabrutinib versus ibrutinib; the ERG's preferred estimate of undiscounted cost-savings is [redacted] per patient. However, the ERG advises caution regarding the findings of this analysis due to the absence of comparative evidence relating to this specific population.

The ERG's exploratory analyses within the R/R CLL population (Model 3) also did not have a marked impact on the estimated cost-savings for acalabrutinib versus ibrutinib; the ERG's preferred estimate of undiscounted cost-savings for acalabrutinib is [redacted] per patient compared with ibrutinib.

6. END OF LIFE

The CS does not make a case for acalabrutinib to be considered as a life extending therapy given at the end of life.

7. OVERALL CONCLUSIONS

Clinical effectiveness conclusions

The key evidence of the clinical effectiveness and safety of acalabrutinib was from the ELEVATE-TN RCT in untreated CLL (N=535), and the ASCEND RCT in previously treated CLL (N=310), both of which were ongoing at time of writing. Clinical advisors to the ERG considered that the populations in the ELEVATE-TN and ASCEND RCTs were broadly representative of the populations who would be eligible for treatment with acalabrutinib in England.

In the untreated CLL population, ELEVATE-TN reported a statistically significant advantage in PFS for acalabrutinib plus obinutuzumab over GClb, HR 0.10 (95% CI: 0.6–0.17; $p<0.0001$), and also for acalabrutinib monotherapy over GClb, HR 0.20 (95% CI: 0.13–0.30; $p<0.0001$). OS data were immature and neither acalabrutinib group demonstrated a significant advantage over GClb ($p>0.05$). The most common grade ≥3 AEs experienced in the acalabrutinib plus obinutuzumab group were neutropenia (29.8%) and thrombocytopenia (8.4%). In the acalabrutinib monotherapy group, the most common grade ≥3 AEs were neutropenia (9.5%) and anaemia (6.7%). The most common grade ≥3 AEs in the GClb group were neutropenia (41.4%); thrombocytopenia (11.8%); and TLS (7.7%).

In the previously treated (R/R) CLL population, ASCEND reported a statistically significant treatment group difference for PFS favouring acalabrutinib monotherapy over IR/BR, HR 0.31 (95% CI: 0.20–0.49; $p<0.0001$). The most common grade ≥3 AEs in the acalabrutinib monotherapy group were neutropenia (15.6%) and anaemia (11.7%). The most common grade ≥3 AEs were neutropenia (39.8%) and diarrhoea (23.7%) in IR-treated patients, and neutropenia (31.4%); and anaemia (8.6%) in BR-treated patients.

In the absence of head-to-head evidence comparing acalabrutinib and ibrutinib, the company conducted an unanchored MAIC using data from the ASCEND and RESONATE RCTs. The HRs for acalabrutinib versus ibrutinib from a weighted Cox proportional hazards model were [redacted] for PFS and [redacted] for OS. The results of the MAIC were used to justify the assumption of equal efficacy between acalabrutinib and ibrutinib in the company's economic analyses in the high-risk CLL population (Model 2) and the R/R CLL population (Model 3).

Cost-effectiveness conclusions

Within the untreated CLL population (Model 1), the ERG's preferred deterministic ICER for acalabrutinib versus GClb is £61,702 per QALY gained. This is considerably higher than the company's updated base case ICER of £22,069 per QALY gained. The ERG's preferred analysis leads to a higher ICER as it includes a less favourable OS projection for acalabrutinib, a more favourable PFS

distribution for GClb and lower second-line treatment costs following progression on GClb. The ERG's preferred ICER is increased further if a greater proportion of patients in the GClb group are assumed to receive second-line VenR rather than ibrutinib, and/or if less optimistic assumptions are made regarding the relative OS benefit for acalabrutinib versus GClb. The ERG's results are also sensitive to the choice of parametric model used to estimate second-line PFS. Within the high-risk CLL population (Model 2) and the R/R CLL population (Model 3), the company's CMAs suggest that acalabrutinib is cost-saving compared with ibrutinib. Within the R/R population, the ERG believes that the company's assumption of clinical equivalence between acalabrutinib and ibrutinib, based on their MAIC in R/R CLL, is likely to be reasonable; given equivalent clinical outcomes and treatment duration between the groups, acalabrutinib is expected to generate cost-savings over ibrutinib. However, the ERG advises caution regarding the results of the CMA for the high-risk CLL population, as the CS does not present any direct or indirect comparison between acalabrutinib and ibrutinib in this population and the evidence used to inform this economic analysis does not specifically relate to patients with high-risk CLL.

8. REFERENCES

1. AstraZeneca. Acalabrutinib for untreated and treated chronic lymphocytic leukaemia (ID1613). Document B - company's evidence submission to NICE. Cambridge, UK; 2020.
2. Cancer Research UK. Chronic lymphocytic leukaemia (CLL): Incidence statistics.; 2020.
3. Pflug N, Bahlo J, Shanafelt TD, Eichhorst BF, Bergmann MA, Elter T*, et al.* Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. *Blood* 2014;124:49-62.
4. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M*, et al.* Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015;26 v78-v84.
5. National Institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. Technology Appraisal Guidance [TA429]. London; 2017.
6. National Institute for Health and Care Excellence. Idelalisib for treating chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA359]. London; 2015.
7. National Institute for Health and Care Excellence. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA343]. London; 2015.
8. National Institute for Health and Care Excellence. Rituximab for the first-line treatment of chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA174]. London; 2009.
9. National Institute for Health and Care Excellence. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA216]. London; 2011.
10. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA561]. London; 2019.
11. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA487]. London; 2017.
12. National Institute for Health and Care Excellence. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia. Technology Appraisal Guidance [TA193]. London; 2010.
13. National institute for Health and Care Excellence. Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]. Final scope. London, UK; 2020.
14. Astrazeneca. AstraZeneca UK CLL Advisory Board. Cambridge, UK; 2020.
15. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW*, et al.* Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. 2020;395:1278-91.
16. Schuh AH, Parry-Jones N, Appleby N, Bloor A, Dearden CE, Fegan C*, et al.* Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. 2018;182:344-59.
17. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. Technology Appraisal [ID1402]. London; 2020.
18. Electronic Medicines Compendium. SmPC: Zydelig 150 mg Film-coated Tablets. 2019.
19. European Medicines Agency. Calquence - Summary of Product Characteristics (draft). London; 2020.
20. Acerta Pharma. ELEVATE-TN (ACE-CL-007) Clinical Study Report. Springfield; 2019.
21. Acerta Pharma. ASCEND (ACE-CL-309) Clinical Study Report. Springfield; 2019.

22. AstraZeneca. Acalabrutinib for untreated and treated chronic lymphocytic leukaemia (ID1613). Company's response to clarification questions from the ERG. Cambridge, UK; 2020.

23. O'Brien SM, Byrd JC, Hillmen P, Coutre S, Brown JR, Barr PM*, et al.* Outcomes with ibrutinib by line of therapy and post-ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. 2019;94:554-62.

24. AstraZeneca. Acalabrutinib for untreated and treated chronic lymphocytic leukaemia (ID1613). Document B - company's evidence submission to NICE. Appendices. Cambridge, UK; 2020.

25. Banno M, Y T, Y K. Using the Cochrane Central Register of Controlled Trials to identify clinical trial registration is insufficient: a cross-sectional study. *BMC Medical Research Methodology* 2020;20.

26. (CRD). CfRaD. CRD's Guidance for Undertaking Reviews in Health Care.; 2010.

27. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M*, et al.* ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology* 2020;38:2849-61.

28. Acerta Pharma. Integrated Patient Experience Report for ACE-CL-007. Springfield; 2019.

29. Acerta Pharma. ELEVATE-TN (ACE-CL-007) Protocol. Springfield; 2016.

30. Acerta Pharma. Patient-Reported Outcome (PRO) Analysis of Data Collected in ACE-CL-309. Springfield; 2019.

31. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM*, et al.* Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. 2014;371:213-23.

32. de Jong J, Sukbuntherng J, Skee D, Murphy J, O'Brien S, Byrd JC*, et al.* The effect of food on the pharmacokinetics of oral ibrutinib in healthy participants and patients with chronic lymphocytic leukemia. . *Cancer Chemotherapy and Pharmacology* 2015;75:907-16.

33. Sharman JP, Brander DM, Mato AR, Kambhampati S, Burke JM, Lansigan F. Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: Results of the GENUINE phase 3 study. Journal of Clinical Oncology 2017;35(1):7504-7504. *Journal of Clinical Oncology* 2017;35:7504.

34. Huang X, Qiu L, Jin J, Zhou D, Chen X, Hou M*, et al.* Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. . *Cancer Medicine* 2018;7:1043-55.

35. Burger JA, Sivina M, Jain N, Kim E, Kadia T, Estrov Z*, et al.* Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. . *Blood* 2019;133:1011-9.

36. Cummins E, Culligan D, Cooper D, Fraser C, Robertson C, Ramsay C. Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID 749]. Evidence Review Group report. Aberdeen, UK; 2016.

37. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Medical Decision Making* 2018;38:200-11.

38. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology* 2012;12.

39. Muñoz-Novas C, Poza-Santaella M, González-Gascón Y Marín I, Hernández-Sánchez M, Rodríguez-Vicente AE, Infante MS*, et al.* The international prognostic index for patients with chronic lymphocytic leukemia has the higher value in predicting overall outcome compared with the Barcelona-Brno Biomarkers Only prognostic model and the MD Anderson Cancer Center Prognostic Index. *Biomedical Research International* 2018;15.

40. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM*, et al.* Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *American Journal of Hematology* 2019;94:1353-63.

41. Wong R. Conference abstract searching In National Institute for Health and Care Excellence health technology appraisals (abstract OP89). *International Journal of Technology Assessment in Health Care* 2019;35:23.

42. Vreman RA, Geenen JW, Hovels AM, Goettsch WG, Leufkens HGM, Al MJ. Phase I/II clinical trial-based early economic evaluation of acalabrutinib for relapsed chronic lymphocytic leukaemia. *Applied Health Economics and Health Policy* 2019;17:883-93.

43. Kater AP, Seymour JF, Hillmen P, Eichhorst B, Langerak AW, Owen C*, et al.* Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: Post-treatment follow-up of the MURANO Phase III study. *Journal of Clinical Oncology* 2019;37:269-77.

44. European Medicines Agency. Imbruvica - Summary of Product Characteristics. London; 2020.

45. Office for National Statistics. National life tables: UK, 2015-2017. London; 2019.

46. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *European Journal of Haematology* 2004;72:381-9.

47. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;13:509-18.

48. Wehler E, Storm M, Kowal S, Caresse C, Boscoe B. A health state utility model estimating the impact of ivosidenib on quality of life in patients with relapsed/refractory acute myeloid leukemia. *EHA Library* 2018;06/16/18, 215730; PS1442.

49. National institute for Health and Care Excellence. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer: Technology Appraisal Guidance [TA403]. London; 2016.

50. Joint Formulary Committee. British National Formulary. London; 2020.

51. NHS Improvement. NHS Reference Costs 2017/18. London; 2018.

52. European Medicines Agency. Venclyxto - Summary of Product Characteristics. London; 2020.

53. European Medicines Agency. Mabthera - Summary of Product Characteristics. London; 2020.

54. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliative Medicine* 2015;29:899-907.

55. Dolan P. Modeling valuations for EuroQol health states. *Medical Care* 1997;35:1095-108.

56. Curtis, A L, Burns, Amanda. Unit Costs of Health and Social Care 2018. Unit Costs of Health and Social Care . PSSRU, Kent, UK, 176 pp. ISBN 978-1-911353-10-2. 2018.

57. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P*, et al.* Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *New England Journal of Medicine* 2015;373:2425-37.

58. Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Claxton KP. Methods for the economic evaluation of health care programmes (4th edition). New York: Oxford University Press; 2015.

59. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C*, et al.* Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value in Health* 2003;6:9-17.

60. National institute for Health and Care Excellence. Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]. TA561 committee papers London,; 2018.

61. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London; 2013.

62. NHS Improvement. NHS Reference Costs 2018/19. London; 2020.

63. Office for National Statistics. National life tables: England 2016 to 2018. London; 2019.

64. AstraZeneca. Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]. Company's response to ERG additional information request. Cambridge, UK; 2020.

65. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Statistics in Medicine* 2006;26:2389-430.

66. Goede C, Fischer K, Dyer MJS, Müller L, Smolej L, Di Bernardo MC*, et al.* Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study. *EHA Learning Center* 2018;15:215923.

67. Latimer N. NICE DSU TSD 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Sheffield; 2011.

68. National institute for Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation. TA429 Committee papers London; 2017.

69. Burger JA, Barr PM, Robak T, Owen C, Ghia P, Tedeschi A*, et al.* 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* 2020;34:787-98.

9. APPENDICES

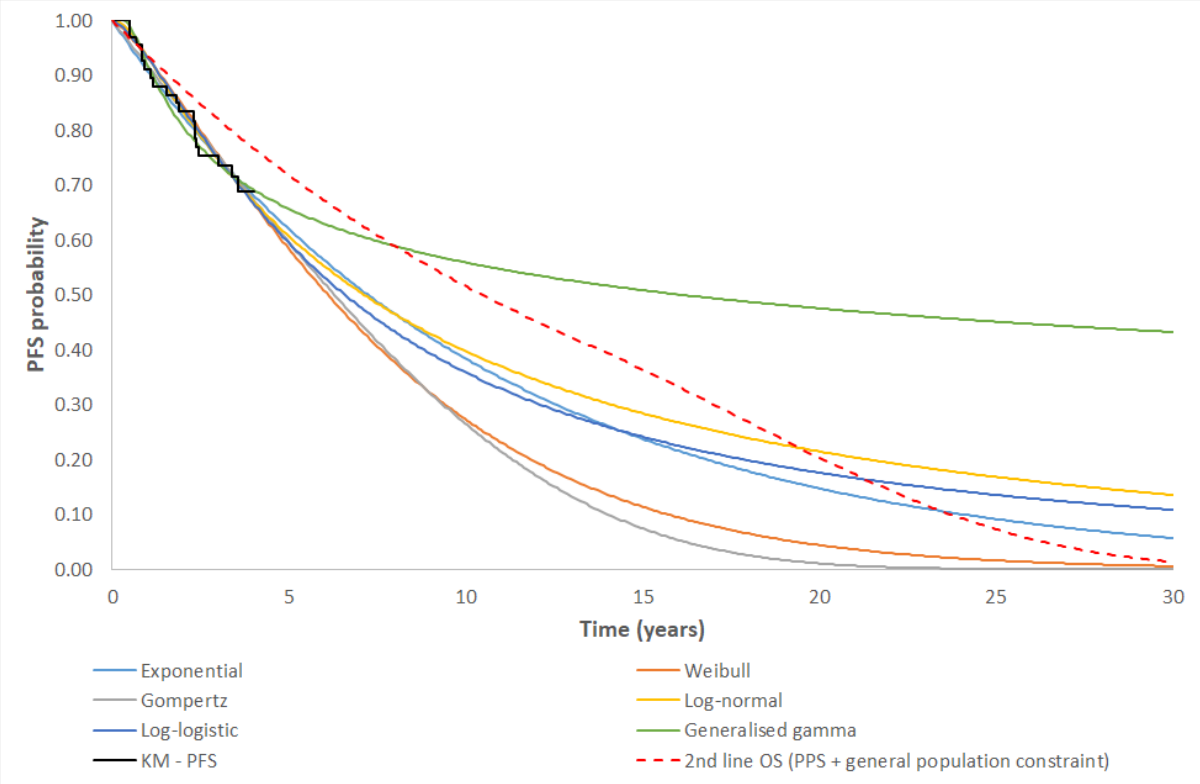
Appendix 1: Summary outputs from survival modelling for ibrutinib-treated patients with 1-2 prior lines of treatment in RESONATE

Table 68: Goodness of fit statistics, PFS, ibrutinib-treated patients with 1-2 prior lines of therapy, RESONATE, ERG-fitted models

Model	AIC	BIC
Exponential	114.01	**116.23**
Weibull	114.88	119.32
Gompertz	115.84	120.28
Log-normal	**113.02**	117.46
Log-logistic	114.36	118.78
Generalised gamma	113.21	119.87

PFS – progression-free survival; AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion
** Bold indicates best fitting model*

Figure 25: Kaplan-Meier plot and PFS models, ibrutinib-treated patients with 1-2 prior lines of therapy, RESONATE, ERG-fitted models



PFS – progression-free survival; AUC – area under the curve
PFS models presented exclude CLL-related mortality and general population mortality constraints. PPS model presented includes general population mortality constraint, age 70 years

Table 69: Mean AUC time over 30-year horizon, PFS, ibrutinib-treated patients with 1-2 prior lines of therapy, RESONATE, ERG-fitted models

Model	Mean AUC, 30-year horizon (unconstrained)	Mean AUC 30-year horizon (constrained, ibrutinib PPS risk from company's model and general population mortality risk at age 70)
Exponential	9.84	9.43
Weibull	7.53	7.48
Gompertz	7.05	7.05
Log-normal	11.06	9.72
Log-logistic	10.17	9.20
Generalised gamma	16.64	10.49

PFS – progression-free survival; PPS – post-progression survival; AUC – area under the curve

**Notes: Estimates of mean AUC with OS constraints depend on the patient's age at the time of progression. Values shown in this table will be more heavily constrained at older ages as general population mortality risk increases. The CLL-related OS constraint applied in the right-hand column is based on 28-day PPS probability from company's untreated CLL model (exponential distribution, 28-day probability = 0.0051), whilst the general population mortality constraint is based on life tables for England 2016-2018*

Appendix 2: Technical appendix detailing the implementation of the ERG's exploratory analyses

This appendix details how to implement the ERG's exploratory analyses. Note that all exploratory analyses presented in the report are based on the deterministic version of the original models.

Model 1 - untreated CLL population

Exploratory analysis 1: Correction of model errors and use of up-to-date data sources

1a) Half cycle correction

In worksheets 'Cost_calcs' and 'Outcome_calcs', replace the value in cell A14 with value '2'. Replace the value in cell A15 with formula '=A14+1'. Drag each formula down until row 537.

1b) Use of current NHS Reference costs

In worksheet 'Country_data', replace the values in cells E57:E68 with the values in Table 70.

Table 70: Unit costs – Disease management costs – progression-free state

Management costs	Unit Cost (£)
Full blood count	2.787325961
LDH	1.098871722
Blood glucose	0
Lymphocyte counts	0
Chest X-Ray	0
Bone marrow exam	0
Hematologist visit	166.512025
Inpatient visit (Non-surgical)	0
Nurse Home visit	0
Full blood transfusion	0
Platet transfusion	0
Biopsy	0

Replace the values in cells E70:E81 with the values in Table 71.

Table 71: Unit costs – Disease management costs – post-progression state

Management costs	Unit Cost (£)
Full blood count	2.787325961
LDH	0
Blood glucose	0
Lymphocyte counts	0
Chest X-Ray	71.91751831
Bone marrow exam	558.1593589
Hematologist visit	166.512025
Inpatient visit (Non-surgical)	433.1728658
Nurse Home visit	0
Full blood transfusion	253.1275052
Platet transfusion	0
Biopsy	0

Replace the values in cells C262:C279 with the values in Table 72.

Table 72: Unit costs – AEs

AEs	Unit Costs (£)
Abdominal Pain	802.83
ALT/AST increased	0.00
Anemia	341.86
Atrial fibrilation	1770.38
Bleeding	1770.38
Diarrhea	140.89
Febrile Neutropenia	6623.14
Hyperglycemia	1253.14
Hypo/Hypertension	598.58
Infections and infestations	1770.38
Infusion-related reaction	0.00
Leucopenia	0.00
Neutropenia	136.34
Neutrophil Count Decreased	136.34
Platet count decreased	0.00
Rash	0.00
Thrombocytopenia	674.07
Tumor lysis syndrome	1226.80

Update the value in cell C129 with the '£241.06'.

1c) Use of relevant general population life tables and mortality model corrections

In worksheet 'Surv_calcs_MM', copy the respective values in the table below to cells AE26:AE418. Delete the values in cells AE419:AE549.

Table 73: Mortality risk based on national life tables for England, 2016-2018

Age	Mortality risk in cycle
70	0.001223635
70.07666	0.001223582
70.15332	0.00122353
70.22998	0.001223477
70.30664	0.001223424
70.3833	0.001223371
70.45996	0.001223318
70.53662	0.001223266
70.61328	0.001223213
70.68994	0.00122316
70.7666	0.001223107
70.84326	0.001223054
70.91992	0.001223001
70.99658	0.001222949
71.07324	0.001359123
71.1499	0.001359056
71.22656	0.001358988
71.30322	0.00135892
71.37988	0.001358853
71.45654	0.001358785
71.5332	0.001358718
71.60986	0.00135865
71.68652	0.001358582
71.76318	0.001358515
71.83984	0.001358447
71.9165	0.001358379
71.99316	0.001358311
72.06982	0.00152812
72.14648	0.001528051
72.22313	0.001527981
72.29979	0.001527912
72.37645	0.001527842
72.45311	0.001527773
72.52977	0.001527703
72.60643	0.001527634
72.68309	0.001527564
72.75975	0.001527495
72.83641	0.001527425
72.91307	0.001527356
72.98973	0.001527286
73.06639	0.001711141
73.14305	0.001711041
73.21971	0.001710942
73.29637	0.001710843
73.37303	0.001710743
73.44969	0.001710644
73.52635	0.001710544
73.60301	0.001710445
73.67967	0.001710346
73.75633	0.001710246
73.83299	0.001710147
73.90965	0.001710047
73.98631	0.001709948
74.06297	0.001880248
74.13963	0.001880128
74.21629	0.001880007
74.29295	0.001879887
74.36961	0.001879766
74.44627	0.001879646
74.52293	0.001879525
74.59959	0.001879405
74.67625	0.001879284
74.75291	0.001879163
74.82957	0.001879043
74.90623	0.001878922
74.98289	0.001878801
75.05955	0.002132706
75.13621	0.00213256
75.21287	0.002132414
75.28953	0.002132269
75.36619	0.002132123
75.44285	0.002131977
75.51951	0.002131832
75.59617	0.002131686
75.67283	0.00213154
75.74949	0.002131394
75.82615	0.002131249
75.90281	0.002131103
75.97947	0.002130957
76.05613	0.00239234
76.13279	0.00239217
76.20945	0.002392
76.28611	0.002391831
76.36277	0.002391661
76.43943	0.002391491
76.51608	0.002391321
76.59274	0.00239115
76.6694	0.00239098
76.74606	0.00239081
76.82272	0.00239064
76.89938	0.00239047
76.97604	0.0023903
77.0527	0.002671052
77.12936	0.002670832
77.20602	0.002670612
77.28268	0.002670391
77.35934	0.002670171
77.436	0.00266995
77.51266	0.002669729
77.58932	0.002669509
77.66598	0.002669288
77.74264	0.002669067
77.8193	0.002668847
77.89596	0.002668626
77.97262	0.002668405
78.04928	0.002962941
78.12594	0.002962699
78.2026	0.002962458
78.27926	0.002962216
78.35592	0.002961973
78.43258	0.002961731
78.50924	0.002961489
78.5859	0.002961247
78.66256	0.002961005
78.73922	0.002960762
78.81588	0.00296052
78.89254	0.002960278
78.9692	0.002960035
79.04586	0.0032743
79.12252	0.003274004
79.19918	0.003273708
79.27584	0.003273413
79.3525	0.003273117
79.42916	0.003272821
79.50582	0.003272525
79.58248	0.003272229
79.65914	0.003271933
79.7358	0.003271637
79.81246	0.003271341
79.88912	0.003271045
79.96578	0.003270749
80.04244	0.003694637
80.1191	0.003694267
80.19576	0.003693898

80.27242	0.003693528
80.34908	0.003693158
80.42574	0.003692789
80.5024	0.003692419
80.57906	0.003692049
80.65572	0.003691679
80.73238	0.003691308
80.80903	0.003690938
80.88569	0.003690568
80.96235	0.003690197
81.03901	0.004155339
81.11567	0.0041549
81.19233	0.004154461
81.26899	0.004154021
81.34565	0.004153582
81.42231	0.004153142
81.49897	0.004152702
81.57563	0.004152262
81.65229	0.004151822
81.72895	0.004151382
81.80561	0.004150942
81.88227	0.004150501
81.95893	0.004150061
82.03559	0.004662654
82.11225	0.004662168
82.18891	0.004661682
82.26557	0.004661195
82.34223	0.004660709
82.41889	0.004660222
82.49555	0.004659735
82.57221	0.004659248
82.64887	0.004658761
82.72553	0.004658274
82.80219	0.004657787
82.87885	0.004657299
82.95551	0.004656812
83.03217	0.005344994
83.10883	0.005344417
83.18549	0.005343841
83.26215	0.005343265
83.33881	0.005342688
83.41547	0.005342111
83.49213	0.005341534
83.56879	0.005340957
83.64545	0.00534038
83.72211	0.005339802
83.79877	0.005339225
83.87543	0.005338647
83.95209	0.005338069
84.02875	0.006049015
84.10541	0.006048251
84.18207	0.006047487
84.25873	0.006046723
84.33539	0.006045959
84.41205	0.006045194
84.48871	0.006044429
84.56537	0.006043664
84.64203	0.006042899
84.71869	0.006042134
84.79535	0.006041368
84.87201	0.006040602
84.94867	0.006039836
85.02533	0.006819197
85.10198	0.006818368
85.17864	0.006817538
85.2553	0.006816708
85.33196	0.006815878
85.40862	0.006815047
85.48528	0.006814217
85.56194	0.006813386
85.6386	0.006812555
85.71526	0.006811724
85.79192	0.006810892
85.86858	0.006810061
85.94524	0.006809229
86.0219	0.007751384
86.09856	0.007750374
86.17522	0.007749365
86.25188	0.007748355
86.32854	0.007747345
86.4052	0.007746334
86.48186	0.007745324
86.55852	0.007744313
86.63518	0.007743301
86.71184	0.00774229
86.7885	0.007741278
86.86516	0.007740266
86.94182	0.007739254
87.01848	0.008764152
87.09514	0.008762978
87.1718	0.008761804
87.24846	0.00876063
87.32512	0.008759455
87.40178	0.008758281
87.47844	0.008757105
87.5551	0.00875593
87.63176	0.008754754
87.70842	0.008753578
87.78508	0.008752401
87.86174	0.008751225
87.9384	0.008750048
88.01506	0.009915088
88.09172	0.009913757
88.16838	0.009912427
88.24504	0.009911096
88.3217	0.009909765
88.39836	0.009908433
88.47502	0.009907102
88.55168	0.009905769
88.62834	0.009904437
88.705	0.009903104
88.78166	0.009901771
88.85832	0.009900438
88.93498	0.009899104
89.01164	0.011178083
89.0883	0.011176364
89.16496	0.011174645
89.24162	0.011172925
89.31828	0.011171205
89.39493	0.011169484
89.47159	0.011167763
89.54825	0.011166041
89.62491	0.01116432
89.70157	0.011162597
89.77823	0.011160875
89.85489	0.011159152
89.93155	0.011157429
90.00821	0.012395128
90.08487	0.012393663
90.16153	0.012392199
90.23819	0.012390733
90.31485	0.012389268
90.39151	0.012387802
90.46817	0.012386337
90.54483	0.012384871
90.62149	0.012383404
90.69815	0.012381938
90.77481	0.012380471
90.85147	0.012379004
90.92813	0.012377537
91.00479	0.013818199

91.08145	0.013816649
91.15811	0.013815098
91.23477	0.013813547
91.31143	0.013811996
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91.46475	0.013808894
91.54141	0.013807342
91.61807	0.01380579
91.69473	0.013804238
91.77139	0.013802686
91.84805	0.013801133
91.92471	0.013799581
92.00137	0.015469405
92.07803	0.015467364
92.15469	0.015465322
92.23135	0.01546328
92.30801	0.015461237
92.38467	0.015459195
92.46133	0.015457152
92.53799	0.015455109
92.61465	0.015453066
92.69131	0.015451023
92.76797	0.015448979
92.84463	0.015446935
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92.99795	0.015442847
93.07461	0.01719082
93.15127	0.017188265
93.22793	0.017185709
93.30459	0.017183154
93.38125	0.017180598
93.45791	0.017178042
93.53457	0.017175486
93.61123	0.017172929
93.68789	0.017170373
93.76454	0.017167817
93.8412	0.01716526
93.91786	0.017162703
93.99452	0.017160147
94.07118	0.018972915
94.14784	0.018970357
94.2245	0.018967798
94.30116	0.018965239
94.37782	0.018962681
94.45448	0.018960122
94.53114	0.018957564
94.6078	0.018955005
94.68446	0.018952447
94.76112	0.018949889
94.83778	0.01894733
94.91444	0.018944772
94.9911	0.018942214
95.06776	0.021361966
95.14442	0.021359039
95.22108	0.021356112
95.29774	0.021353186
95.3744	0.02135026
95.45106	0.021347334
95.52772	0.021344408
95.60438	0.021341483
95.68104	0.021338558
95.7577	0.021335633
95.83436	0.021332709
95.91102	0.021329785
95.98768	0.021326862
96.06434	0.023422651
96.141	0.023418759
96.21766	0.023414868
96.29432	0.023410977
96.37098	0.023407087
96.44764	0.023403198
96.5243	0.02339931
96.60096	0.023395422
96.67762	0.023391535
96.75428	0.023387649
96.83094	0.023383764
96.9076	0.023379881
96.98426	0.023375998
97.06092	0.0256019
97.13758	0.025597668
97.21424	0.025593438
97.2909	0.025589209
97.36756	0.025584981
97.44422	0.025580755
97.52088	0.025576529
97.59754	0.025572306
97.6742	0.025568084
97.75086	0.025563863
97.82752	0.025559643
97.90418	0.025555426
97.98084	0.02555121
98.05749	0.027398765
98.13415	0.027395389
98.21081	0.027392014
98.28747	0.027388641
98.36413	0.027385269
98.44079	0.027381898
98.51745	0.027378528
98.59411	0.02737516
98.67077	0.027371793
98.74743	0.027368427
98.82409	0.027365063
98.90075	0.0273617
98.97741	0.027358339
99.05407	0.030953318
99.13073	0.030945715
99.20739	0.030938118
99.28405	0.030930525
99.36071	0.030922939
99.43737	0.030915357
99.51403	0.030907781
99.59069	0.030900211
99.66735	0.030892647
99.74401	0.030885089
99.82067	0.030877537
99.89733	0.030869992
99.97399	0.030862452
100.0507	1

1d) Correction of health state transcription error

In worksheet ‘Country_data’, amend the value in cell G58 to “2”.

1e) Correction of second-line treatment durations

Copy the values in additional ERG file 'ERG2ndLineCosts', worksheet "Regimens" cells G15:H406 to a new worksheet in the company's model; use the same name of the file for the spreadsheet.

In worksheet 'Results':

(i) Replace the formula in cell O43 with the formula '=SUMPRODUCT(ERG2ndLineCosts!H15:H406,Flow_Acala!AR26:AR417)';

(ii) Replace the formula in cell O45 with the formula '=SUMPRODUCT(ERG2ndLineCosts!G15:G406,Flow_Tx3!AR26:AR417)'.

Note that the RDI estimates for acalabrutinib, obinutuzumab and chlorambucil are included later in exploratory analysis 5.

All other exploratory analyses undertaken by the ERG include these corrections of errors. Apply all changes described above before running the following analyses.

Exploratory analysis 2: Use of generalised gamma models for TTP and PPM in the GClb group

In worksheet 'Survival', select 'Gen gamma' from the dropdown menu in cell L188.

Exploratory analysis 3: Use of PPS exponential model from RESONATE in both treatment groups

In worksheet 'Clinical_data', replace the value in cell C1193 with the formula '=C1063'.

Exploratory analysis 4: PF utility based on general population utility (age 70 years)

In Spreadsheet 'Country_data', replace the value in cell C33 with the formula '=0.9508566+0.0212126*(1-female_prop)-0.0002587*(start_age) - 0.0000332*(start_age)^2'.

Exploratory analysis 5: Inclusion of RDI for all treatments

In Spreadsheet 'Country_data', replace the values:

(i) in cell I93 with the value '0.968';

(ii) in cells I96 and I97 with '0.938';

(iii) in cells I98 and I115 with '0.948';

(iv) in cells I120 and I121 with '0.97'.

Exploratory analysis 6: Inclusion of costs of drug wastage

Go to worksheet 'Results.' Include the term '+((Costs_Tx!Z16/2)*SUM(Flow_Acala!Z26:Z549))' at the end of the formulae in cell K43. Include the term '+((Costs_Tx!Z19/2)*SUM(Flow_Tx3!Z27:Z32))' at the end of the formulae in cell K45.

Exploratory analysis 7: Inclusion of VenR as second-line treatment for [redacted] of patients

In worksheet 'Results', replace the formula in cell O45 with the formula '=((SUMPRODUCT(ERG2ndLineCosts!G15:G406,Flow_Tx3!AR26:AR417))*[redacted])+((SUMPRODUCT(ERG2ndLineCosts!H15:H406,Flow_Tx3!AR26:AR417))*[redacted]).

Exploratory analysis 8: ERG preferred analysis

The ERG's preferred analysis includes ERG exploratory analysis 1 to 7; therefore, apply all the changes listed above.

All additional sensitivity analyses undertaken by the ERG were applied separately, using the ERG's preferred model as a starting point.

Additional sensitivity analysis 1: Fully incremental analysis of acalabrutinib followed by VenR versus GClb followed by ibrutinib versus GClb followed by VenR

Store the total LYGs (undiscounted), total QALYs and total costs for the acalabrutinib group from the ERG's preferred analysis.

Calculate total LYGs (undiscounted), total QALYs and total costs for the two GClb comparators by setting the second-line cost in worksheet 'Results' equal to:
(a) the cost for 100% VenR by replacing the formula in cell O45 with the formula '=SUMPRODUCT(ERG2ndLineCosts!H15:H406,Flow_Tx3!AR26:AR417',and
(b) the cost for 100% ibrutinib by replacing the formula in cell O45 with the formula '=SUMPRODUCT(ERG2ndLineCosts!G15:G406,Flow_Tx3!AR26:AR417'.

Perform a full incremental analysis using the results obtained for the three sequences.

Additional sensitivity analysis 2: Alternative scenarios surrounding survival gains

(a) 50% survival gain relative to EA8 (PPS rate = RESONATE * 1.63)

In Spreadsheet 'Clinical_data', include the term '*1.63' at the end of the formulae in cell C1193.

(b) Zero survival gain relative to EA8 (PPS rate = RESONATE * 2.44)

In Spreadsheet 'Clinical_data', include the term '*2.44' at the end of the formulae in cell C1193.

Additional sensitivity analysis 3: Alternative second-line PFS models

Open the ERG's additional second-line costing model. Replace the cumulative PFS probabilities in column K with the relevant cumulative PFS probabilities for the Gompertz/log-normal models. Re-run the macro for each drug. Store the estimated per cycle cost vector in worksheet "regimens" columns C, D and E. Copy cells G15:H406. Go to the ERG's preferred model and paste the new cost vector in worksheet "ERG_2ndlinecosts" cell G15:H406. Repeat this process for each parametric model.

Model 2 – high-risk CLL population

As described in Section 5.4.1.2, several of the ERG's exploratory analyses identified for the untreated CLL model also apply to the high-risk CLL analysis. Therefore, the ERG has applied the following amendments to the original version of the company's high-risk CLL model (see the corresponding description for each item for Model 1, as described above).

- **Exploratory analysis 1: Correction of model errors (exploratory analyses 1(a) to 1(d))**
- **Exploratory analysis 3: Use of the PPS exponential model fitted to data from RESONATE in both treatment groups**
- **Exploratory analysis 5: Inclusion of RDI for all treatments**
- **Exploratory analysis 6: Inclusion of costs of drug wastage**

Please note that for the inclusion of wastage for the acalabrutinib group, the formula used will be the same as that for Model 1. For the ibrutinib treatment group, go to worksheet 'Results' and include the term '+((Costs_Tx!Z21/2)*SUM(Flow_Tx3!Z26:Z549))' at the end of the formulae in cell K45.

Exploratory analysis 8: ERG preferred analyses

The ERG's preferred base case for the high-risk CLL population model includes ERG exploratory analysis 1, 3, 5 and 6.

Please note that given the company's use of a CMA in this population, ERG exploratory analyses 1(e), 2, 4 and 7, as described for the untreated CLL population, are not relevant to this analysis.

No additional sensitivity analyses were performed in this population.

Model 3 – R/R CLL population

As described in Section 5.4.1.3, several of the exploratory analyses identified for the untreated CLL population also apply to the model for the R/R CLL population. Therefore, the ERG has applied the following amendments to the company's original version of the CMA model for the R/R CLL population (see the corresponding description for each item for Model 1, as described above).

Exploratory analysis 1: Correction of model errors (amendments 1(b) to 1(d))

For analysis 1(b), update the unit costs for disease management states the same way as for the untreated CLL population (Model 1). For the AE unit costs, in worksheet 'Country_data', replace cells C260:C279 with the values in Table 74.

Table 74: Unit costs – AEs

AEs	Unit costs (£)
ALT/AST increased	0.00
Anemia	341.86
Diarrhea	140.89
Dyspnea	0.00
Fatigue	603.34
Febrile Neutropenia	0.00
Hyperglycemia	0.00
Hypogammaglobulinemia	0.00
Infections and infestations	1770.38
Infusion-related reaction	0.00
Neutropenia	136.34
Neutrophil Count Decreased	136.34
Atrial fibrillation	1770.38
Pyrexia	0.00
Rash	0.00
Thrombocytopenia	674.07
Transaminases Increased	0.00
Tumor lysis syndrome	0.00
Bleeding	1770.38
Urinary tract infection	0.00

Note that the updated administration cost for 'Deliver Simple Parenteral Chemotherapy at First Attendance' does not apply in this analysis.

For analysis 1c (Use of relevant general population life tables and mortality model corrections), the start age and proportion of females are different from Model 1. Therefore, in worksheet 'Surv_calcs_MM', copy the respective values in the table below to cells BG26:AE418. Delete the values in BG419:AE549.

Table 75: Mortality risk based on National Life tables for England, 2016-2018

Age	Mortality risk in cycle
67	0.00096
67.07666	0.00096
67.15332	0.00096
67.22998	0.00096
67.30664	0.00096
67.3833	0.00096
67.45996	0.00096
67.53662	0.00096
67.61328	0.00096
67.68994	0.00096
67.7666	0.00096
67.84326	0.00096
67.91992	0.00096
67.99658	0.00096
68.07324	0.001059
68.1499	0.001059
68.22656	0.001059
68.30322	0.001059
68.37988	0.001059
68.45654	0.001059
68.5332	0.001059
68.60986	0.001059
68.68652	0.001059
68.76318	0.001059
68.83984	0.001059
68.9165	0.001059
68.99316	0.001058
69.06982	0.001142
69.14648	0.001142
69.22313	0.001142
69.29979	0.001141
69.37645	0.001141
69.45311	0.001141
69.52977	0.001141
69.60643	0.001141
69.68309	0.001141
69.75975	0.001141
69.83641	0.001141
69.91307	0.001141
69.98973	0.001141
70.06639	0.001246
70.14305	0.001246
70.21971	0.001246
70.29637	0.001246
70.37303	0.001246
70.44969	0.001246
70.52635	0.001246
70.60301	0.001246
70.67967	0.001246
70.75633	0.001246
70.83299	0.001246
70.90965	0.001245
70.98631	0.001245
71.06297	0.001385
71.13963	0.001384
71.21629	0.001384
71.29295	0.001384
71.36961	0.001384
71.44627	0.001384
71.52293	0.001384
71.59959	0.001384
71.67625	0.001384
71.75291	0.001384
71.82957	0.001384
71.90623	0.001384
71.98289	0.001384
72.05955	0.001554
72.13621	0.001554
72.21287	0.001554
72.28953	0.001554
72.36619	0.001554
72.44285	0.001554
72.51951	0.001554
72.59617	0.001553
72.67283	0.001553
72.74949	0.001553
72.82615	0.001553
72.90281	0.001553
72.97947	0.001553
73.05613	0.001742
73.13279	0.001742
73.20945	0.001742
73.28611	0.001742
73.36277	0.001742
73.43943	0.001742
73.51608	0.001741
73.59274	0.001741
73.6694	0.001741
73.74606	0.001741
73.82272	0.001741
73.89938	0.001741
73.97604	0.001741
74.0527	0.001914
74.12936	0.001914
74.20602	0.001914
74.28268	0.001914
74.35934	0.001914
74.436	0.001914
74.51266	0.001914
74.58932	0.001913
74.66598	0.001913
74.74264	0.001913
74.8193	0.001913
74.89596	0.001913
74.97262	0.001913
75.04928	0.00217
75.12594	0.00217
75.2026	0.00217
75.27926	0.00217
75.35592	0.00217
75.43258	0.002169
75.50924	0.002169
75.5859	0.002169
75.66256	0.002169
75.73922	0.002169
75.81588	0.002169
75.89254	0.002169
75.9692	0.002169
76.04586	0.002433
76.12252	0.002433
76.19918	0.002433
76.27584	0.002432
76.3525	0.002432
76.42916	0.002432
76.50582	0.002432
76.58248	0.002432
76.65914	0.002432
76.7358	0.002431
76.81246	0.002431
76.88912	0.002431
76.96578	0.002431
77.04244	0.002717
77.1191	0.002717

77.19576	0.002717
77.27242	0.002717
77.34908	0.002716
77.42574	0.002716
77.5024	0.002716
77.57906	0.002716
77.65572	0.002716
77.73238	0.002715
77.80903	0.002715
77.88569	0.002715
77.96235	0.002715
78.03901	0.003011
78.11567	0.003011
78.19233	0.003011
78.26899	0.003011
78.34565	0.003011
78.42231	0.00301
78.49897	0.00301
78.57563	0.00301
78.65229	0.00301
78.72895	0.003009
78.80561	0.003009
78.88227	0.003009
78.95893	0.003009
79.03559	0.003328
79.11225	0.003328
79.18891	0.003327
79.26557	0.003327
79.34223	0.003327
79.41889	0.003327
79.49555	0.003326
79.57221	0.003326
79.64887	0.003326
79.72553	0.003326
79.80219	0.003325
79.87885	0.003325
79.95551	0.003325
80.03217	0.003755
80.10883	0.003755
80.18549	0.003754
80.26215	0.003754
80.33881	0.003753
80.41547	0.003753
80.49213	0.003753
80.56879	0.003752
80.64545	0.003752
80.72211	0.003752
80.79877	0.003751
80.87543	0.003751
80.95209	0.003751
81.02875	0.004221
81.10541	0.004221
81.18207	0.00422
81.25873	0.00422
81.33539	0.004219
81.41205	0.004219
81.48871	0.004219
81.56537	0.004218
81.64203	0.004218
81.71869	0.004217
81.79535	0.004217
81.87201	0.004217
81.94867	0.004216
82.02533	0.004732
82.10198	0.004732
82.17864	0.004731
82.2553	0.004731
82.33196	0.00473
82.40862	0.00473
82.48528	0.004729
82.56194	0.004729
82.6386	0.004728
82.71526	0.004728
82.79192	0.004727
82.86858	0.004727
82.94524	0.004726
83.0219	0.005421
83.09856	0.00542
83.17522	0.00542
83.25188	0.005419
83.32854	0.005418
83.4052	0.005418
83.48186	0.005417
83.55852	0.005417
83.63518	0.005416
83.71184	0.005416
83.7885	0.005415
83.86516	0.005415
83.94182	0.005414
84.01848	0.006136
84.09514	0.006136
84.1718	0.006135
84.24846	0.006134
84.32512	0.006133
84.40178	0.006133
84.47844	0.006132
84.5551	0.006131
84.63176	0.00613
84.70842	0.00613
84.78508	0.006129
84.86174	0.006128
84.9384	0.006128
85.01506	0.00691
85.09172	0.00691
85.16838	0.006909
85.24504	0.006908
85.3217	0.006907
85.39836	0.006906
85.47502	0.006906
85.55168	0.006905
85.62834	0.006904
85.705	0.006903
85.78166	0.006902
85.85832	0.006902
85.93498	0.006901
86.01164	0.007852
86.0883	0.007851
86.16496	0.00785
86.24162	0.007849
86.31828	0.007848
86.39493	0.007847
86.47159	0.007846
86.54825	0.007845
86.62491	0.007844
86.70157	0.007844
86.77823	0.007843
86.85489	0.007842
86.93155	0.007841
87.00821	0.008873
87.08487	0.008872
87.16153	0.008871
87.23819	0.00887
87.31485	0.008869
87.39151	0.008868
87.46817	0.008866
87.54483	0.008865
87.62149	0.008864
87.69815	0.008863
87.77481	0.008862
87.85147	0.008861
87.92813	0.00886

88.00479	0.010031
88.08145	0.01003
88.15811	0.010029
88.23477	0.010028
88.31143	0.010026
88.38809	0.010025
88.46475	0.010024
88.54141	0.010022
88.61807	0.010021
88.69473	0.01002
88.77139	0.010019
88.84805	0.010017
88.92471	0.010016
89.00137	0.011311
89.07803	0.011309
89.15469	0.011307
89.23135	0.011306
89.30801	0.011304
89.38467	0.011302
89.46133	0.011301
89.53799	0.011299
89.61465	0.011297
89.69131	0.011296
89.76797	0.011294
89.84463	0.011292
89.92129	0.011291
89.99795	0.011289
90.07461	0.012516
90.15127	0.012515
90.22793	0.012513
90.30459	0.012512
90.38125	0.012511
90.45791	0.012509
90.53457	0.012508
90.61123	0.012506
90.68789	0.012505
90.76454	0.012503
90.8412	0.012502
90.91786	0.012501
90.99452	0.012499
91.07118	0.013943
91.14784	0.013942
91.2245	0.01394
91.30116	0.013939
91.37782	0.013937
91.45448	0.013936
91.53114	0.013934
91.6078	0.013933
91.68446	0.013931
91.76112	0.013929
91.83778	0.013928
91.91444	0.013926
91.9911	0.013925
92.06776	0.015613
92.14442	0.015611
92.22108	0.015609
92.29774	0.015607
92.3744	0.015605
92.45106	0.015603
92.52772	0.015601
92.60438	0.015599
92.68104	0.015597
92.7577	0.015595
92.83436	0.015593
92.91102	0.015591
92.98768	0.015589
93.06434	0.017354
93.141	0.017352
93.21766	0.017349
93.29432	0.017346
93.37098	0.017344
93.44764	0.017341
93.5243	0.017339
93.60096	0.017336
93.67762	0.017334
93.75428	0.017331
93.83094	0.017329
93.9076	0.017326
93.98426	0.017324
94.06092	0.019136
94.13758	0.019134
94.21424	0.019131
94.2909	0.019129
94.36756	0.019126
94.44422	0.019124
94.52088	0.019121
94.59754	0.019119
94.6742	0.019116
94.75086	0.019114
94.82752	0.019111
94.90418	0.019109
94.98084	0.019106
95.05749	0.021537
95.13415	0.021534
95.21081	0.021531
95.28747	0.021528
95.36413	0.021525
95.44079	0.021523
95.51745	0.02152
95.59411	0.021517
95.67077	0.021514
95.74743	0.021511
95.82409	0.021508
95.90075	0.021505
95.97741	0.021502
96.05407	0.023625
96.13073	0.023621
96.20739	0.023617
96.28405	0.023613
96.36071	0.023609
96.43737	0.023605
96.51403	0.023601
96.59069	0.023597
96.66735	0.023594
96.74401	0.02359
96.82067	0.023586
96.89733	0.023582
96.97399	0.023578
97.05065	1

The changes required for exploratory analysis 1(d) are applied the same way as for the untreated CLL population model.

Exploratory analysis 1: Correction of model errors (amendment 1(f))

In Model 3, spreadsheet 'Safety', copy the values in the table below to, respectively, columns F and R.

Table 76: Adverse event rates – R/R CLL population model

AE type	Acalabrutinib	Ibrutinib
ALT/AST increased	[redacted]	[redacted]
Anemia	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Febrile Neutropenia	[redacted]	[redacted]
Hyperglycemia	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil Count Decreased	[redacted]	[redacted]
Atrial fibrilation	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Transaminases Increased	[redacted]	[redacted]
Tumor lysis syndrome	[redacted]	[redacted]
Bleeding	[redacted]	[redacted]

Exploratory analysis 5: Inclusion of RDI for all treatments

In Spreadsheet 'Country_data', replace the values:

(i) in cell I93 with the value '0.968';

(ii) in cell I98 with the value '0.948'.

Exploratory analysis 6: Inclusion of costs of drug wastage

For the inclusion of wastage for the acalabrutinib treatment group, in the spreadsheet 'Results' include the term '+(Costs_Tx!Z16/2)' at the end of the formulae in cell K44. For the inclusion of wastage for 'ibrutinib, include the term '+(Costs_Tx!Z21/2)' at the end of the formulae in cell K45.

Exploratory analysis 8: ERG preferred analyses

The ERG's preferred base case for the R/R CLL population model includes ERG exploratory analysis 1(b) to 1(d), 1(f), 5 and 6; therefore, apply all the corresponding changes.

Please note that given the company's use of a CMA in this population, ERG exploratory analyses, 1(a), 1(e), 2, 3, 4 and 7, as described for the untreated CLL population, are not relevant to this analysis.

No additional sensitivity analyses were performed in this population.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the midday **15 October,** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Company response to draft ERG report	ERG Response
The Company would like to thank NICE and the ERG for the opportunity to review the draft ERG report. Issues identified by the Company are presented in this document. The key considerations are as follows: • The Company accept the proposed correction of errors put forward by the ERG in *"EA1: Correction of errors and outdated data sources",* **with the exception of the duration of ibrutinib subsequent treatment following first-line C+O treatment**. The rationale provided by the Company is presented in Company Issue 4. • The Company also accept the ERG's exploratory analyses: EA2, EA4, EA5 and EA6. • The Company disagree with scenario *EA3: Use of RESONATE PPS in both groups*, as it does not align with the expected treatment pathway for patients in the UK for both costs and outcomes (see Company Issue 4). • The Company have presented an alternative scenario for *EA7: Second-line treatment mix for comparator (20% VenR; 80% ibrutinib)*, in which RWE collected by the Company is used to inform the split between V+R and ibrutinib as subsequent treatments following C+O (see Company Issue 4). • The Company accept the ERG revised CMA for the high-risk CLL population (Model 2) and for the R/R CLL population (Model 3), and note that the updates implemented by the ERG did not have a marked impact on the estimated cost-savings for acalabrutinib versus ibrutinib presented by the Company. In light of this, the Company present a revised version of Table 2 (Section 1.6, page 17 of the ERG report), in which the ERG's exploratory scenario analyses have been re-run with a more clinically plausible range of treatment durations for ibrutinib subsequent treatment (7.26 – 8.57 years) (**Error! Not a valid result for table.**), based on the estimated mean PFS from patients who have previously received 1-2 prior lines of treatment (capped by OS with ibrutinib from Model 3), and is therefore more reflective of the patients population modelled. The Company request that the ERG reconsider their exploratory and preferred analyses for Model 1 based on the evidence provided in this response document	The ERG does not agree with all of the company's suggestions and believes that the company's new ICERs should be disregarded. Please refer to detailed responses from the ERG below. Updated ICERs are presented for Model 1 in the post-factual check version of the ERG report.

Table 1. Company's revised "ERG report Table 2"

Exploratory analysis*	Mean duration of subsequent ibrutinib = 7.26 years			Mean duration of subsequent ibrutinib = 8.57 years		
	Incremental QALYs	Incremental cost (£)	ICER (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
Company's base case in response to ERG clarification questions	[redacted]	[redacted]	£22,679	[redacted]	[redacted]	£22,679
EA1: Correction of errors and outdated data sources*	[redacted]	[redacted]	11,526	[redacted]	[redacted]	Dominating
EA2: Generalised gamma TTP and TTD for C+O	[redacted]	[redacted]	24,091	[redacted]	[redacted]	Dominating
EA4: Progression-free utility from Ara and Brazier	[redacted]	[redacted]	12,545	[redacted]	[redacted]	Dominating
EA5: Inclusion of RDI	[redacted]	[redacted]	7,676	[redacted]	[redacted]	Dominating
EA6: Inclusion of wastage	[redacted]	[redacted]	11,869	[redacted]	[redacted]	Dominating
EA7: Second-line treatment mix for comparator ([redacted] % VenR; [redacted] % ibrutinib)	[redacted]	[redacted]	23,440	[redacted]	[redacted]	2,261
Company's revised base following response to ERG report**	[redacted]	[redacted]	35,378	[redacted]	[redacted]	11,454

Abbreviations: EA, exploratory analysis; ERG, Evidence Review Group; PPS, post-progression survival; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; RDI, relatively dose intensity; TTD, time to death preprogression VenR, venetoclax plus rituximab. *Ibrutinib subsequent treatment duration changed from 4.88 years to 7.26 or 8.57 years.**The Company's revised base-case following response to the ERG includes all changes listed in the table above.

Table 2. Abbreviations

AIC	Academic in confidence
ASA	Additional sensitivity analyses
BTKi	Bruton's tyrosine kinase inhibitor
C+O	Chlorambucil plus obinutuzumab
CIC	Commercial in confidence
CLL	Chronic lymphocytic leukaemia
CR	Complete response
Cri	Complete response with incomplete bone marrow recovery
CS	Company submission
DOR	Duration of response
EA	Exploratory analyses
ECOG	Eastern Cooperative Oncology Group
ERG	Evidence Review Group
GClb	Chlorambucil plus obinutuzumab
HR	Hazard ratio
HRQoL	Health-related quality-of-life
ICER	Incremental cost-effectiveness ratio
IRC	Independent review committee
ITT	Intention-to-treat
KM	Kaplan-Meier
MAIC	Matched adjusted indirect comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nPR	Nodular partial response
ORR	Overall response rate
OS	Overall survival

PFS	Progression-free survival
PPS	Post-progression survival
PR	Partial response
PS	Performance status
QALY	Quality adjusted life year
R/R	Relapsed and refractory
RWE	Real world evidence
RDI	Relative dose intensity
TSL	Tumour lysis syndrome
TTD	Time to pre-progression death
TTNT	Time to next treatment
TTP	Time to progression
UK	United Kingdom
V+R	Venetoclax plus rituximab
VenR	Venetoclax plus rituximab

Company Issue 1 Restricted populations and comparators: Untreated CLL analyses restricted to patients in whom FCR/BR would be unsuitable. R/R CLL analyses restricted to patients who would otherwise be treated with ibrutinib (ERG issue 1)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 3.1, Page 30: With respect to the untreated CLL population: "The CS does not present any clinical or economic evidence to support the use of acalabrutinib in fit patients for whom treatment with FCR or BR would be suitable." **Section 3.2, Page 33:** With respect to the R/R setting: "the CS does not present comparisons of acalabrutinib against other currently used second-line treatments e.g. VenR."	The Company requests that the text is updated as follows: "The CS does not present any clinical or economic evidence to support the use of acalabrutinib in fit patients for whom treatment with FCR or BR would be suitable. The Company is not seeking reimbursement in this population." The Company requests that the text is updated as follows: "the CS justified not presenting comparisons of acalabrutinib against other second-line treatments available but not commonly used in patients with R/R CLL patients in the UK (e.g. VenR)."	The Company would like to clarify that they are not seeking reimbursement in fit patients for whom treatment with FCR or BR would be suitable. Clinicians agreed that the population in the ELEVATE-TN trial is generally aligned with patients who would be considered unfit for FCR therapy. The Company acknowledge that a relatively small proporation of patients in the R/R setting may receive treatment with V+R. However, clinical experts advised that ibrutinib represents the main-stay treatment option for patients in the R/R setting and particularly in whom have only received one prior line of treatment. This position was also confirmed by clinical advisors to the ERG. In particular, clinicians report that the intensive dosing regimen and risk of TLS as the main reasons for	The ERG believes that both of the statements cited from the ERG report are already factually accurate. For the sake of clarity, the text in Section 3.1 (page 30) has been amended as follows: *"The CS does not present any clinical or economic evidence to support the use of acalabrutinib in fit patients for whom treatment with FCR or BR would be suitable. The company is not seeking reimbursement in this population"* The text in Section 3.2 (page 33) has not been amended as it is factually correct. The CS justifies not presenting comparisons against other second-line treatments, but the company's fact check

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
		preferring ibrutinib use. In general, clinicians believe that patients are often treated with a BTKi, followed by V+R. Nonetheless, the Company does recognise that V+R is used in a small proportion of patients in the R/R setting. These patients are often those with a cardiac history and in patients who cannot tolerate treatment with ibrutinib. A Chart review study reviews that approximately [redacted] % of BTKi naïve patients are prescribed a venetoclax-containing regimen, with approximately [redacted] % of these receiving venetoclax monotherapy, which is in the CDF and therefore is not a relevant comparator. Therefore, the Company believe that [redacted] % of patients in the R/R setting receive treatment with V+R.	comments and the ERG report both highlight that a proportion of patients with R/R CLL do not receive ibrutinib. The issue with respect to this point is that the company's CMA for R/R CLL relates only to a population in whom ibrutinib would otherwise be used. No comparison is presented against other treatments for R/R CLL (e.g. VenR). This is stated in Issue 1 of the Executive Summary and in Section 3.3 of the ERG report; the text has not been amended.

Company Issue 2 Uncertainty surrounding clinical equivalence of acalabrutinib and ibrutinib in R/R CLL and high-risk CLL (ERG issue 2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3, Page 62: "The company did not undertake an indirect comparison of acalabrutinib versus any other therapy in the untreated CLL population." **Section 4.6, Page 71:** "[…] the ERG notes that the CS does not present any direct or indirect comparison of acalabrutinib versus ibrutinib specifically in the untreated high-risk CLL population (patients with del(17p)/TP53 mutations)." **Section 5.3.4, Page 115:** "[...] the HRs obtained from the company's MAIC, which are used to justify the use of a CMA approach, also relate to the R/R CLL population, rather than	The Company ask that the ERG rephases these statements given that results for a MAIC for acalabrutinib versus ibrutinib in the untreated CLL population were submitted during clarification questions. The results and conclusions were consistent with those made from the MAIC between ASCEND and RESONATE in R/R CLL. The Company would also like to reiterate that there is insufficient data to conduct a formal comparison of acalabrutinib versus ibrutinib specifically in the untreated high-risk CLL population (patients with del(17p)/TP53 mutations). However clinical evidence, UK expert opinion and NICE precedent reimbursement decisions in this population, support the assumption of clinical	**NICE has previously accepted evidence in R/R CLL as a proxy to support reimbursement decisions in high-risk untreated CLL** In appraisal TA429, NICE assessed ibrutinib for the treatment of untreated and previously treated patients with CLL, with evidence for ibrutinib based on the RESONATE study. The RESONATE trial was conducted in patients with previously treated CLL, and therefore did not contain any evidence of efficacy in the first-line setting. Despite this, the committee accepted that in the absence of any evidence, data from previously treated patients could be taken into account and NICE recommended ibrutinib as an option for treated CLL in people who have had at least one prior therapy as well as in patients who have a 17p deletion or TP53	The text extract in Section 4.3, page 62 has been amended to read "The company did not undertake an indirect comparison of acalabrutinib versus any other therapy in the untreated high-risk CLL population" The other statements in Section 4.6 (page 71) and 5.4.3 (page 115) are already factually accurate and have not been amended. The additional MAIC presented by the company following the clarification round was not a comparison of acalabrutinib versus ibrutinib in high-risk CLL patients – this is discussed in Section 5.3.4. In addition, the ERG considers that the approach taken by the Appraisal Committee in TA429 is unrelated to the accuracy of the ERG's statements that the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
patients with untreated high-risk CLL." "It is unclear whether the company could have undertaken a reliable indirect comparison using the 35 patients with del(17p) and TP53 mutations in the acalabrutinib arm of ELEVATE-TN […]"	equivalence in the untreated high-risk CLL population.	mutation and in whom chemo-immunotherapy is unsuitable. **Data from high-risk patients in untreated and R/R CLL support the assumption of clinical equivalence in the untreated high-risk CLL population** Evidence from the ASCEND trial (in previously treated patients with CLL) and a MAIC (demonstrating equivalence with ibrutinib), can be generalised to the high-risk untreated setting. Data from the ASCEND trial is deemed to be the most relevant as a proxy for high-risk patients in the untreated setting, as the trial includes approximately 40% patients with a 17p and/or TP53 mutation, compared with approximately 20% in the ELEVATE-TN study. Since the recommendation for ibrutinib (TA429), data in the front-line setting has become available from the RESONATE-2 trial.[1] This trial however excluded patients with 17p deletion and only included 12 patients with a	has not presented any evidence to compare acalabrutinib versus ibrutinib specifically in the high-risk CLL population. In the absence of any evidence, the ERG believes it is unclear whether the findings from the MAIC in the R/R population can be generalised to the high-risk population. In addition, as discussed in Section 4.6 of the ERG report, the company used an unanchored MAIC to compare acalabrutinib versus ibrutinib (in R/R CLL) but restricted their SLR criteria to RCTs only. Unanchored MAICs do not require the studies informing them to have adopted an RCT design. It is unclear from the evidence presented in the CS whether it would have been possible to conduct an indirect comparison using data for untreated high-risk CLL patients using the 35 high-risk patients in ELEVATE-TN and high-risk CLL patients treated with ibrutinib using some other source (e.g. a

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		TP53 mutation. Therefore, it is not possible to conduct a MAIC vs the high-risk patients in the RESONATE-2 trial due to the small sample size. However, a MAIC in the ITT population between the ELEVATE-TN and RESONATE-2 trials demonstrated a consistent response and conclusion to those made from the MAIC between ASCEND and RESONATE in R/R CLL.	single-arm study). Despite the absence of comparative evidence presented in the CS, the ERG's advisors considered it likely that acalabrutinib and ibrutinib are similarly effective in high-risk CLL. These points are already made in the ERG report and no further amendment is required.

Company Issue 3 Inclusion of high-risk patients in untreated CLL model (ERG issue 3)

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
Section 5.3.4, Page 115: "The ERG considers that the relevance of the results of the untreated CLL economic analysis are contaminated by the inclusion of high-risk CLL patients in the time-to-event data used to inform the model." **Section 5.3.4, Page 132:** "The ERG's clinical advisors suggest that it is likely that acalabrutinib and ibrutinib are similarly effective in patients with del(17p) and TP53 mutations. However, neither the CS nor the company's clarification response provide any comparative clinical data in patients with these high-risk features to support this finding."	The Company ask that the statement about the CS not providing comparative clinical data in patients with high-risk disease is removed. Evidence for acalabrutinib vs C+O is provided in Figure 7 of CS (section B.2a.7) and Figures 10 and 11 of the clarification response (question B23). The evidence shows consistency of treatment effect and thus the use of the word 'contaminated' is potentially misleading. As mentioned in response to Issue 2, it is not possible to generate comparative clinical data relative to ibrutinib in high-risk CLL patients.	**Clinical data and expert opinion given by ERG's clinical advisors support the argument that acalabrutinib and ibrutinib are similarly effective in high-risk and non high-risk patients.** The KM curves in ELEVATE-TN were not derived specifically for the high-risk subgroups due to the relatively small number of patients with del(17p) and/or TP53 mutations in either the acalabrutinib monotherapy or chlorambucil-obinutuzumab treatment arms (n=23 [12.8%] and 25 [14.1%], respectively). Data from the ELEVATE-TN trial demonstrates that the PFS response is robust and consistent across all subgroups, irrespective of cytogenetic status (HR: 0.23; 95% CI: 0.09, 0.61 and HR: 0.19; 95% CI: 0.11, 0.31 for patients with and without a del(17p) and/or TP53 mutation, respectively). Furthermore, although the inclusion of high-risk	This is not a factual inaccuracy. However, the ERG has amended the report slightly for clarity. The text extract in Section 5.3.4 (page 115) has not been amended as the company's fact check comment agrees that *"the inclusion of high-risk patients may contaminate the population included in the untreated CLL [model]".* The text extract in Section 5.3.4 (page 132) has been amended to read: *"The ERG's clinical advisors suggest that it is likely that acalabrutinib and ibrutinib are similarly effective in patients with del(17p) and TP53 mutations. However, neither the CS nor the company's clarification response provide any comparative clinical data <u>for acalabrutinib versus ibrutinib</u> in patients with these*

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
		patients may 'contaminate' the population included in the untreated CLL, the HRs and CIs suggest that the bias would be detrimental to the overall treatment effect of acalabrutinib as patients with high-risk CLL experienced a smaller benefit than patients without such risk factors. KM curves derived excluding patients with a del(17p) and/or TP53 mutation are consistent with those from the ITT population further supporting the conclusion that, although the data is relatively immature for acalabrutinib, response to acalabrutinib is consistent across subgroups.	*high-risk features to support this finding."* The ERG notes that whilst subgroup analyses are presented in the CS for high-risk patients in ELEVATE-TN, these analyses are comparing acalabrutinib versus GClb and so are not relevant to either the untreated CLL population without high-risk features (because patients in the ELEVATE-TN subgroup have high-risk features) or the untreated CLL population with high-risk features (because the comparator in the ELEVATE-TN subgroup analysis is GClb, not ibrutinib or some other currently used therapy e.g. VenR). The ERG also notes that the company's statement that *"it is not possible to generate comparative clinical data relative to ibrutinib in high-risk CLL patients"* is not adequately demonstrated within the CS as non-RCT evidence was excluded from the company's SLR and no attempt was made to present an indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
			using specifically high-risk patients in ELEVATE-TN. In addition, the number of patients with del(17p)/TP53 mutations in ELEVATE-TN quoted in the company's fact check comments appears to be incorrect – according to Table 19 of the CS, 35 patients had del(17p)/TP53 mutations in the acalabrutinib monotherapy arm (not 23 patients quoted in the company's fact check comments).

Company Issue 4 Post-progression survival, treatment sequencing and subsequent treatment costs (ERG issues 4, 5 and 7)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Costs of post-progression treatments overestimated			
Section 1.6, Page 17, Table 2, row 3: "EA1: **Correction of errors** and outdated data sources" **Section 5.3.4, Page 113:** **"(v) *Incorrect*** *application of second-line treatment costs associated with VenR and ibrutinib …..* As such, the company's model overestimates second-line treatment costs in both groups; the magnitude of the error is greater for second-line ibrutinib as this is given over a long time frame than second-line VenR. This problem is partly driven by the structural limitations of the model, which does not include a separate state to track progression status after	The Company ask that the ERG reconsider the assumption that mean ibrutinib treatment duration (modelled for subsequent treatment in the C+O) is equivalent to 4.88 years. Given the justification presented in the *"Justification for amendments"* column, the Company disagree with the use of 4.88 years for mean second-line ibrutinib treatment in the C+O treatment arm. The Company would also like to highlight that they do not consider their original assumptions surrounding subsequent ibrutinib treatment duration as **errors** and would respectively request that the ERG do not refer to this change as an error or include	**<u>Incorrect assumption</u>** **The input value of 4.88 years is incorrect** The ERG sourced the value of 4.88 years from the CS for TA561 (V+R R/R appraisal). The value was derived through an unanchored MAIC for V+R (MURANO ITT population, May 2017 data cut) versus ibrutinib (RESONATE ITT population), in which an adjusted HR was applied to MURANO baseline curves to predict ibrutinib curves.[3] During the appraisal, more mature MURANO data became available (May 2018 data cut). The MAIC was subsequently re-ran, and the estimated mean treatment duration of ibrutinib increased to 5.181 years.[3]	*(a) Second-line treatment costs* The company's original model applies second-line treatment costs to all patients who are alive rather than those who are alive and progression-free. As described in the ERG report (Section 5.3.4), this is not in line with the SmPCs for ibrutinib, venetoclax or rituximab. This is incorrect and leads to incorrect model results. As such, the ERG disagrees with the company's view and believes that it is reasonable to label this as an unequivocal "error". The text describing the issue and the structure of the ERG's exploratory analyses have therefore not been changed.However, the ERG's exploratory analyses have been revisited (see below). The ERG notes the following points:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
initiating second-line treatment (see critical appraisal point [4]).” **Section 5.3.4, Page 116:** “(c) the error in which second-line ibrutinib costs are applied to all surviving patients for up to 130 cycles, rather than being restricted to patients who have not yet progressed (critical appraisal point [1]).” **Section 5.4.1.1, Page 136:** “(1e) Correction of second-line treatment durations The model was amended to apply a once-only treatment cost for second-line VenR and ibrutinib, based on mean treatment durations assumed in NICE TA561.[2] Based on reported values for the non-del(17p)/TP53 population, mean time on treatment was assumed to be **4.88** years for ibrutinib and 1.87 years for VenR. In line with	this change within their “**correction of errors”** analysis (Page 17, 113 and 144). The Company request that if the ERG would like to change the assumptions surrounding ibrutinib treatment duration they do so in a separate scenario analyses and make it clear that this is not a correction of an error.	**RESONATE population used to inform the MAIC in TA561 is not appropriate to this decision problem population** The full ITT population from RESONATE was used to inform the MAIC versus V+R in TA561.[3] This population includes patients who have received a median of 3 prior lines of treatment.[4] For the purpose of this appraisal, the more relevant patient population is patients who have received 1-2 lines of prior therapy (PFS data for this subgroup of patients is available from O’Brien et al. 2019).[4] The Company have consistently utilised these data to inform post subsequent treatment duration of ibrutinib for the C+O treatment arm, and post-progression survival for C+O. **RESONATE data used to inform the MAIC in TA561 is outdated** The RESONATE data used to inform the MAIC versus V+R in	• Whilst the CS states that MURANO is also based on patients with 1-2 prior lines, this does not appear to be the case as the Kaplan-Meier plot reported in Figure 28 of the CS relates to the ITT population. • As discussed above, the ERG considers the company’s original approach to deriving second-line costs to be incorrect because it applies costs to all patients who are alive rather than those who are alive and progression-free. • The ERG considers the company’s additional analyses provided following clarification to be incorrect because 2nd line treatment time was not constrained by mortality risk and 2nd line treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the company's original model, these costs were applied only to those patients who survive progression on first-line treatment and who initiate second-line treatment [redacted] years later." **Section 5.4.2.1, Page 139:** "As shown in the table, the correction of errors and use of updated data sources increases the company's original base case ICER from £30,001 to £56,049 per QALY gained; **the main contributor to this higher ICER is the use of second-line treatment durations from NICE TA561**" **Section 5.4.2.1, Page 140, Table 62. row 5-7:** "EA1: **Correction of errors** and outdated data sources"		TA561 is sourced from Byrd et al. 2017.[3,5] This publication reports PFS data for a median follow-up of 9.4 months, with 86% of patients still receiving ibrutinib at the time of the analysis. Since the publication of TA561, 6 year long-term follow-up data is available for RESONATE.[4,5] Long-term data from O'Brien et al. 2019 demonstrates that approximately 70% of the 1-2 prior lines ibrutinib cohort remains progression-free at 51 months. Number of prior line of treatment has been shown to have a large impact on PFS. In Munir et al.[6] 2019, PFS split by 1, 2 and 3 prior lines demonstrates that median PFS is longer in patients who have had fewer prior lines, with the median in patients who have only received 1 prior line not reached. In addition, 5 year data for ibrutininb in R/R patients provides further evidence to support the impact of prior lines of treatment on PFS (O'Brien 2018, Figure 5A).[7] Throughout this appraisal the Company have	costs were applied to all patients leaving the progression-free state, rather than those who progress and survive the delay prior to starting second-line treatment. There was also a problem with discounting. • The ERG agrees with the company's fack check comments that the values used in the ERG's exploratory analyses should ideally relate to time on treatment for patients with 1-2 prior therapies and that PFS appears to be better for this group compared with the ITT population in RESONATE. The ERG therefore agrees that values from the MAIC presented in TA561 used in the ERG's original exploratory analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix 1, Page 158: **"1e) Correction of second-line treatment durations** In worksheet 'Cost_calcs', apply the once-only costs estimated by the ERG in the table below as follows:"		utilitised the mature RESONATE data to inform post subsequent treatment duration of ibrutinib for the C+O treatment arm, as opposed to the original datacut. Utilising the original RESONATE datacut to inform ibrutinib treatment duration underestimates the time on treatment with ibrutinib. **The restricted mean PFS KM from long-term RESONATE data is expected to mature beyond 4.88 years** The restricted KM mean for RESONATE PFS for ibrutinib was calculated from O'Brien et al. 2019 for patients who had received 1-2 prior lines of therapy (the patient population relevant to this decision problem).[4] The estimate suggests that even without extrapolation methods, ibrutinib mean PFS is approximately 3.42 years. This value is only 1.6 years shorter than the ERG's estimate of 4.88 years. Approximately 70% of patients remain progression-free after 51	should be replaced with more appropriate estimates of time on treatment. • The ERG considers that the company's updated second-line treatment costing approach presented in this fact check form is incorrect as it does not account for the fact that patients who progress later will have less remaining treatment time and higher mortality risks, and because discounting is not handled appropriately. All of these issues lead to the cost of second-line treatment (particularly ibrutinib) being overestimated. The ERG considers that the company's updated ICERs presented in this fact-check document should therefore be disregarded.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		months, which indicates that the mature mean PFS estimate is expected to be longer than 4.88 years. When the KM data for patients who have only received 1-2 prior lines of therapy is extrapolated (please refer to Company's response to additional ERG question 15th October 2020) the mean PFS over 30 years for ibrutinib ranges between 87.16 months (7.26 years) and 102.79 months (8.57 years), after capping for OS with ibrutinib from Model 3. This highlights that the ERG's approach lacks clinical validity and, by ignoring long-term evidence available, it highly underestimates time on treatment with ibrutinib. It is imperative that the mean PFS are estimated based on mature data which is more reflective of the patient population relevant to the decision problem (i.e. extrapolated estimates based on patients who have received 1-2 prior lines of therapy only rather than using the	• In response to the company's concerns raised in this fact check, the ERG has implemented a separate costing model which takes essentially the same approach as the company's original model, but which estimates costs based on time in second-line PFS rather than PPS. The ERG's updated exploratory analyses are presented in Section 5.4 of the updated post-fact check version of the ERG report. The ERG's costing model will be made available to the company for scrutiny. Sensitivity analyses have been presented around the choice of 2nd line PFS model. The ERG believes that this updated approach provides a sufficient approximation of second-

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		full ITT population). Data from the full ITT population is confounded by patients who have more advanced disease and have therefore received additional lines of therapy. For example, mature data from the RESONATE study reports a median PFS of 44.1 months for patients who received 3 prior lines of therapy compated with 67.3 months for patients who received 2 prior lines of therapy. Median PFS was not reached in patients who received just 1 prior line of therapy.[6] **In conclusion, the Company believe that the ERG's decision to model 4.88 years for mean ibrutinib treatment duration is incorrect. The Company believe that treatment duration for subsequent ibrutinib in the C+O treatment should be informed by the long-term evidence available for ibrutinib in the relevant patient population (RESONATE 1-2 prior lines, O'Brien et al. 2019). The Company acknowledges that some level of**	line treatment costs and that this issue should now be considered resolved. Further details are available in Section 5.4 and Appendix 1 of the updated ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		uncertainty remains and has presented a range of clinically plausible values for ibrutinib subsequent treatment duration based on the extrapolation of the data from patients who received 1-2 prior lines of treatment.	
Assumptions regarding fixed sequences of first- and second-line therapies for CLL			
Section 1.5, Page 13: **"**An additional ERG sensitivity analysis is presented in which all progressed patients who receive first-line acalabrutinib or GClb receive second-line VenR." **Section 1.5, Page 13:** **"**If all progressed patients in both groups receive second-line VenR, the ICER increases to £140,568 per QALY gained."	The Company request that the ERG remove the exploratory analyses in which 100% of patients across both treatment arms receive subsequent V+R treatment. These are discussed on pages 13, 116, 119, 137 and 140-1, and presented in Table 63 of the ERG report. The Company believe this scenario is not representative of the treatment pathway for CLL in the UK.	**<u>Incorrect assumption</u>** **Assuming 100% of acalabrutininb and C+O patients transition onto V+R is not aligned with UK clinical practice** As highlighted in the CS and supported by the ERG's clinical advisors (page 118 of the ERG report), the majority of patients in the C+O arm are expected to receive ibrutinib as subsequent treatment. This is supported by recent market share data collected by the Company, in which it is estimated that [redacted] % of BTKi naïve patients received second-line treatment with a venetoclax-containing regiment, and of which,	*(b) Assumptions regarding fixed sequences of second-line therapies for CLL* The ERG report includes a fully incremental analysis in which two comparator sequences are considered: (1) first-line GClb followed by second-line ibrutinib and (2) first-line GClb followed by second-line VenR. The company's fact check comments criticise this as an *"incorrect assumption"* and argue that it is *"not aligned with UK clinical practice."* The ERG highlights that this analysis was not intended to reflect UK clinical practice – the issue is that the company's submitted model is predisposed to disadvantage the comparator group because the

Section 5.3.4, Page 116: **"**However, the limited available data already indicate that the sequences assumed in the company's untreated CLL model do not reflect the subsequent-line regimens received in the trial." **Section 5.3.4, Page 117 and 118:** "The ERG's exploratory analyses indicate that applying the same PPS function and the same costs of second-line VenR in both treatment groups increases the ICER for acalabrutinib substantially (see Section 5.4)." **Section 5.3.4, Page 119:** "As such, the ERG believes it would be prudent to consider the cost-effectiveness of acalabrutinib separately in: (a) patients who would receive ibrutinib following GClb, and (b)		[redacted]% receive V+R; resulting in [redacted]% patients receiving treatment with V+R in second-line. The "ERG additional sensitivity analysis 1", which assumes that 100% of all patients across either treatment arm will receive second-line V+R is not clinically appropriate and is **not** reflective of the treatment pathway in the UK. Both of the ERG's clinical advisors agreed that the majority of patients in the C+O arm will receive subsequent ibrutinib. This treatment pathway is particularly relevant in the current COVID-19 pandemic, as it reduces the number of patients who would need to attend the hospital for treatment. The Company believe that the "ERG additional sensitivity analysis 1" is misleading, does not reflect the CLL treatment pathway in the UK and is therefore not relevant to the decision problem.	assumed second-line treatment following GClb (ibrutinib) is assumed to be more expensive and less effective than the second-line treatment in the acalabrutinib group (VenR). Given that the company's model assumes that second-line VenR dominates second-line ibrutinib, the ERG's fully incremental analysis was presented to highlight that clinical practice is not aligned with the assumptions underpinning the company's model i.e. the NHS is predominantly using second-line ibrutinib but the company's model suggests that the NHS should be using second-line VenR because it is more cost-effective. This has implications for the interpretation of any cost-effectiveness estimates for acalabrutinib. As discussed in the ERG report (Section 5.3.4), reduced hospital attendance is only one factor influencing patient choice e.g. some patients may prefer fixed dose therapy. The ERG's fully incremental analysis does not form part of the ERG's preferred analysis – it is an additional

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
patients who would receive VenR following GClb." **Section 5.4, Page 137:** "ERG additional sensitivity analysis 1: Fully incremental analysis of acalabrutinib followed by VenR versus GClb followed by ibrutinib versus GClb followed by VenR Within this sensitivity analysis, three options were evaluated within a fully incremental analysis: (i) acalabrutinib followed by VenR; (ii) GClb followed by ibrutinib, and (iii) GClb followed by VenR." **Section 5.4, Page 140 – 141, Table 63:** "Table 63 presents the results of the ERG's additional sensitivity analysis which includes first-line GClb followed by second-line VenR as an additional comparator within a fully			sensitivity analysis which demonstrates the importance of the sequences assumed in the model.No amendment has been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
incremental analysis. Within this analysis, GClb followed by ibrutinib is ruled out of the analysis as it is strongly dominated by GClb followed by VenR. The ICER for acalabrutinib followed by VenR versus GClb followed by VenR is estimated to be £140,568 per QALY gained."			
Section 1.6, Page 17, Table 2, Row 8 **"**EA7: Second-line treatment mix for comparator (20% VenR; 80% ibrutinib)" **Section 5.4.1.1, Page 137:** **ERG exploratory analysis 7: Inclusion of VenR as second-line treatment for 20% of patients.** **"**Based on clinical advice received by the ERG, the model cost calculations were amended to assume that for patients who receive GClb in the first-line	In light of the evidence presented in the 'Justifications to amendments' column the Company request that this scenario analyses be re-run using RWE provided by the Company.	**RWE collected by the Company in patients treated with CLL within the UK supports a lower proportion of venetoclax regimens for subsequent treatments in patients who are BTKi naïve.** A clinician survey of n=215 UK clinicians suggested that approximately [redacted] % of second-line treatment regimens for patients who are BTKi naive will be venetoclax based regimens. The remaining patients were estimated to be receiving treatment with ibrutinib.	*(c) Use of second-line ibrutinib and VenR* The company's fact check comments include additional data on the proportionate use of second-line ibrutinib and VenR in CLL. These data have not been previously presented in the CS. Whilst the ERG believes that the fact check is not an ideal timepoint for the company to present new evidence, the UK IQVIA prescription data have been incorporated into the ERG's exploratory analyses, including the ERG's preferred analysis ([redacted] VenR; [redacted] ibrutinib).

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
setting, 80% receive ibrutinib and 20% receive VenR in the second-line setting." **Section 5.4.1.3, page 139, Table 61, row 13:** "EA7: Second-line treatment mix for comparator (20% VenR; 80% ibrutinib)"		UK prescription data from IQVIA, collected from a chart review of n=148 patients, estimates that [redacted] % and [redacted] % of second-line regimens will constitute of venetoclax based regimens and ibrutinib treatment, respectively. Of the [redacted] % of venetoclax-based regimens an estimated [redacted] % are expected to be venetoclax monotherapy, which is outside the scope of this appraisal. As such based-on prescription data from IQVIA, the split of second-line treatment treatments for BTKi naïve patients in the UK is estimated to be [redacted] %:[redacted] % for V+R relative to ibrutinib. This is further supported by the clinical advisor contacted by the ERG, who stated that they expected "more than 80% of patients receiving ibrutinib and less than 20% of patients receiving V+R". Furthermore, the clinical advisor did not expect this split to change in the 'next few years'. As such, the scenario presented by	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		the ERG represents the most extreme case possible. **The Company request that the ERG exploratory analysis 7 is updated to reflect the RWE collected by the Company. The Company have included the estimate, of [redacted] %:[redacted] % split for V+R to ibrutinib following C+O as a scenario analyses in their revised base-case analysis (**Error! Not a valid result for table.**).**	
Highly optimistic assumptions regarding overall survival benefit for acalabrutinib			
Section 1.4, Page 8: "There was no significant treatment group difference between acalabrutinib monotherapy and GClb for OS (HR 0.60, 95% CI: 0.28–1.27; p=0.1556)." **Section 1.5, Page 15:** "Assuming zero incremental survival gain for acalabrutinib	The Company request that additional context on the maturity of the ELEVATE-TN trial data is added to balance the ERG's statements on page 8 and 128. The Company request that the ERG reconsider the scenarios in which acalabrutininb provides no OS benefit compared to C+O. The Company requests that the ERG reconsider the	**ELEVATE-TN OS data is highly immature** The Company acknowledge that OS data from ELEVATE-TN is immature. Only [redacted] ([redacted]%) and [redacted] ([redacted]%) of events have occurred in the acalabrutininb and C+O treatment arms, respectively. As such the Company request that statements regarding the observed OS benefit to date are balanced with the caveat of data immaturity.	(d) *Highly optimistic assumptions regarding overall survival benefit for acalabrutinib* The company's requested amendments regarding additional context on the maturity of the OS data are unclear. The reported text in Section 1.4 (page 8) is factually accurate and the subsequent sentence highlights that median OS was not reached in any arm. The ERG is not disputing the company's argument that increased PFS may to lead to

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
versus GClb increases the ICER to £144,529 per QALY gained." **Section 5.3.4, Page 117:** "The model assumes that second-line VenR is more effective than second-line ibrutinib in terms of OS (see critical appraisal point [6])." **Section 5.3.4, Page 122:** "Given the limited OS data available, the ERG considers that the company's estimate of additional OS gain for acalabrutinib versus GClb, and the company's base case ICER, should be considered highly uncertain." **Section 5.3.4, Page 125:** "As shown in the plot, OS in the acalabrutinib group is very similar to OS for the general population. Mean undiscounted	assumption of RESONATE PPS for both treatment arms as a scenario analysis. This assumption does not align with the expected treatment pathway for patients with CLL in the UK.	**Effective treatments in CLL have demonstrated an improved OS for patients** The Company acknowledge the long-term uncertainty surrounding the OS data from ELEVATE-TN. Acalabrutininb has demonstrated significant improvements in PFS compared to C+O within the ELEVATE-TN trial (HR: 0.20; 95% CI: 0.13, 0.30; p<0.0001). As highlighted within the Company's response to ERG clarification B12, evidence from other novel agents, such as ibrutinib and V+R clearly demonstrate that the early PFS benefit does indeed translate into long-term survival benefit.[8,9] Given the vast improvement in PFS within ELEVATE-TN, the historical evidence from other novel agents and the evidence and clinical support for the use of more efficacious treatment regimens used as front-line therapy translating into improved outcomes, it is clinically plausible	an OS gain for acalabrutinib. This point is already made in Section 5.3.4 (page 136) with respect to the views of the ERG's clinical advisors and this extract of text is included in the company's fact check comments. However, ELEVATE-TN does not provide substantive evidence to support this assumption, the sequences included in the model do not reflect the experience of the RCT, and the model (which uses external PPS data from MURANO) generates highly optimistic estimates of OS. No amendment has been made with respect to this point. As discussed in the ERG's critical appraisal (see ERG report, Section 5.3.4), the ERG believes that the company's estimates of OS are highly optimistic, as they suggest only a minimal loss of expected OS for acalabrutinib-treated patients compared with the age- and sex-matched general population (modelled acalabrutinib OS = [redacted] years; general

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
OS for the acalabrutinib group is estimated to be [redacted] years; this is only slightly lower than mean undiscounted OS in the general population (15.56 years)." **Section 5.3.4, Page 128:** "… and noted that the available OS data from ELEVATE-TN are limited and do not show a statistically significant survival advantage for acalabrutinib over GClb." **Section 5.3.4, Page 136:** "Whilst they suggested that a survival benefit may be expected due to significant improvements in PFS, they considered the company's OS projection to be premature and speculative." **Section 5.4, Page 137:**		for acalabrutinib to result in improved survival as more mature data becomes available. **Clinical experts support the opportunity of a 'functional cure' in patients with CLL** As highlighted in the Company's response to ERG clarification question B17, UK clinicians support the possibility of patients with CLL achieving a 'functional cure', meaning that patients can achieve their natural life expectancy and die from causes unrelated to CLL. UK clinicians felt that by providing a non-DNA damaging agent such as acalabrutinib in the front-line setting, the disease is likely to be more clinically stable in the longer-term, and therefore result in improved outcomes. **The Company's model is not driven by PPS survival**	population OS = 15.56 years). This is a consequence of the model assumptions regarding all three transitions, and the use of external data on PPS from MURANO. Given the uncertainty around modelled OS, the ERG believes it is reasonable to explore the impact of assuming lower OS gains for acalabrutinib. The sensitivity analysis in which zero additional OS gain is assumed does not form part of the ERG's preferred analysis – as noted in Section 5.4.4.1 of the ERG report, this analysis is described as being *"particularly pessimistic"*. This sensitivity analysis has not been removed; however, the text has been amended to read *"The ERG notes that given the observed improvement in PFS in ELEVATE-TN, the latter analysis is particularly pessimistic."* The company's fact check also requests that the ERG's preferred analysis be amended to remove the amendment in which PPS is

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG additional sensitivity analysis 2: Alternative scenarios surrounding survival gains. "Within this sensitivity analysis, the hazard rate for PPS in the acalabrutinib group was amended to explore the following scenarios: (a) undiscounted incremental OS gain for acalabrutinib versus GClb assumed to be equal to 50% of that predicted within the ERG preferred analysis; (b) zero incremental OS gain for acalabrutinib versus GClb. The ERG notes that the latter analysis is particularly pessimistic."		The Company would like to highlight that the economic analysis for non-high risk previously untreated patients is not driven by PPS estimates. The increase in survival compared to C+O is driven by an extension in the time patients remain progression-free, as opposed to extending time in the progressed disease state. PPS data sources selected by the Company were chosen to accurately reflect the treatment pathway and align with subsequent treatment costs. As highlighted by the ERG's clinical advisor, the majority of patients in the C+O would receive ibrutinib subsequent treatment, whilst patients who progress on the acalabrutininb arm would receive V+R subsequent treatment. In order to align costs with outcomes, the Company informed PPS estimates with data from RESONATE (1-2 prior lines of therapy) and MURANO for C+O	modelled using RESONATE in both groups. As noted above, the company's base case model (using MURANO) results in OS estimates which are very similar to the general population life expectancy. The company's proposed approach (using MURANO for the acalabrutinib group and RESONATE for the GClb group) may be subject to confounding due to differences between the trials (see ERG report, Section 5.3.4). This aspect of the analysis has not been changed, and the ERG report already highlights that other data besides RESONATE may be more appropriate. Overall, this aspect of the model remains highly uncertain and the ERG believes that the analyses presented in the ERG report provides a useful exploration of the impact of this uncertainty on the cost-effectiveness of acalabrutinib.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		and acalabrutininb PPS, respectively. However, the Company do acknowledge the uncertainty around long-term OS and accept that the ERG's decision to explore modelling RESONATE PPS for both treatment arms could be an appropriate scenario analysis. However, the Company do not agree that it is appropriate for the base-case analysis as it does not align subsequent treatment costs and outcomes with the treatment pathway for patients with CLL in the UK.	

Company Issue 5 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive summary, Page 15: "The ERG believes that it would be more appropriate to use the utility value of 0.78 from Ara and Brazier for patients who are progression-free. Given earlier 4.81.8…"	To update the text as follows: "The ERG believes that it would be more appropriate to use the utility value of 0.78 from Ara and Brazier for patients who are progression-free. ~~Given earlier 4.81.8~~…"	Typographical error – remove phrase or add in potentially missing information.	This apparent error does not appear in the ERG's version of the report. No amendment has been made.
Executive summary, Page 17, Table 2: Errors in the incremental costs reported for the the following: - EA8: [redacted] - ASA1: [redacted] - ASA2a: [redacted] - ASA2b: [redacted]	Update incremental costs to the following: - EA8: [redacted] - ASA2a: [redacted] - ASA2b: [redacted]	Typographical error - numerical	The ERG agrees that these were minor errors. However, in light of Issue 4 (see above), the ERG's exploratory analysis results have been updated using a more appropriate costing approach. Consequently, these errors no longer apply.
Section 2.2, Page 21: "For patients with R/R CLL, the clinical advisors noted that whilst ibrutinib is most commonly used, other treatment options are also available…".	To update the text as follows: "For patients with R/R CLL, the clinical advisors noted that whilst ibrutinib is most commonly used (except for patients with a history of cardiac	Missing information – Based on expert opinion, ibrutinib is not often used in patients with a history of cardiac co-morbidities.	This is not a factual inaccuracy. The ERG does not believe that the information the company suggests is missing changes the point being made. The report has not been amended.

	co-morbidities), other treatments options are also available…"		
Section 3.1, Page 30: "Within the previously untreated CLL population, the CS specifically focusses on patients for whom aggressive treatments such as FCR or BR are unstuiable…"	To update the text as follows: "Within the previously untreated CLL population, the CS specifically focusses on patients for whom aggressive treatments such as FCR or BR are ~~unstuiable~~ unsuitable…"	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 3.5, Page 34: "The CS1 states that no significant equality considerations associated with this appraisal."	To update the text as follows: "The CS1 states that no significant equality considerations **are** associated with this appraisal."	Typographical error – grammar.	The ERG agrees. The text has been amended.
Section 4.1.1, Page 36: "As such, thre ERG believes that it is unlikely that relevant studies have been missed."	To update the text as follows: "As such, ~~thre~~ the ERG believes that it is unlikely that relevant studies have been missed."	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 4.2.1.1, Page 44: "ELEVATE-TN (see Table 12) is a three-arm, multicentre, international open-label RCT with centres in Asia, Australasia, Canada, Europe, and North and South America (CS,1 Section B.2a)."	Remove "Canada" from the list of regions.	It is not necessary to include both Canada and North America.	The ERG agrees. The text has been amended.

Section 4.2.1, Page 46, Table 14: Table 14 contains primary and secondary outcome definitions, but the secondary outcome of overall response rate (ORR) IRC is missing from this list.	The company request adding the following description of ORR taken from table 18 of the CS: "ORR measured according to iwCLL criteria. The proportion of patients (assessed) by IRC of complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular partial remission (nPR) or partial response (PR) at or before initiation of subsequent anti-cancer therapy. "	Missing information – As the secondary outcomes of OS, TTNT, and safety are listed in Table 14, we believe ORR (IRC) should be included as well.	The ERG agrees. The table has been amended.
Section 4.2.1, Page 57, Table 24: Table contains primary and second outcome definitions, but the secondary outcomes of Investigator-assessed DOR, and Investigator and IRC-assessed ORR are missing from this list.	The company request adding the following definitions taken from table 32 of the CS: "Investigator-assessed DOR: DOR determined by IRC and by investigators was analysed in the same fashion as PFS described above. Investigator and IRC-assessed ORR: Best overall response was defined as the best response as assessed by the investigator or IRC on or before the initiation of subsequent anticancer therapy."	Missing information – As the secondary outcomes of OS, TTNT, Safety and HRQoL are listed in Table 24, we believe Investigator-assessed DOR, and Investigator and IRC-assessed ORR should be on this list too.	The ERG agrees. The table has been amended.

Section 4.4.2, Page 65: "A total of 13 categorical variables were considered in the analyses: age (>70 years), sex, presence of bulky disease ≥5cm, presence of del(17p), ECOG PS (0 or 1), beta-2 microglobulin >3.5 mg/L, Rai stage (1/2/0-2 or 3/4), Binit score…" "The base case analysis used by the company included all of these covariates, except for Binit score... The sensitivity analyses differed according to whether the remaining four variables were included: Rai stage (1/2/0-2 or 3/4), Binit score…"	To update the text as follows: "A total of 13 categorical variables were considered in the analyses: age (>70 years), sex, presence of bulky disease ≥5cm, presence of del(17p), ECOG PS (0 or 1), beta-2 microglobulin >3.5 mg/L, Rai stage (1/2/0-2 or 3/4), ~~Binit~~ Binet score …" "The base case analysis used by the company included all of these covariates, except for Binit score... The sensitivity analyses differed according to whether the remaining four variables were included: Rai stage (1/2/0-2 or 3/4), ~~Binit~~ Binet score …"	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 4.4.2, Page 68, Table 32: "Binit score"	To update the text as follows: "~~Binit~~ Binet score"	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 5.2.1, Page 75: **"…**(ii) patients with untreated CLL with high-risk cytogenetic factors ((del)7p and TP53 mutations)"	To update the text as follows: **"…**(ii) patients with untreated CLL with high-risk cytogenetic factors ((del)**1**7p and TP53 mutations)"	Typographical error – spelling.	The ERG agrees this was a typo. The text has been amended to "del(17p)".

Section 5.2.2.2, Page 79: "Second-line treatment is given until death or maximum treatment time (VenR – 24 cycles, i.e. approximately 2 years; ibrutinib – 130 cycles, i.e. approximately 10 years)."	To update the text as follows: "Second-line treatment is given until death or maximum treatment time (VenR – 2**6** cycles, i.e. approximately 2 years; ibrutinib – 130 cycles, i.e. approximately 10 years)."	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 5.2.2.3.1, Page 80: "Patients are assumed to have a mean age of 70 years at model entry, a body mass of 79kg, a BSA of 1.91m^2"	To update the text as follows: "Patients are assumed to have a mean age of 70 years at model entry, a body mass of 79kg, a BSA of 1.9**3**m^2"	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 5.2.2.3.2, Page 81: "…(patients with ≥1 prior CLL therapies)."	To update the text as follows: "…(patients with 1-2 prior CLL therapies)."	Consistency of language error.	The ERG believes that the company's comment is inaccurate. The text is referring to the MURANO trial. Whilst the CS states that data for patients with 1-2 prior therapies were included, the Kaplan-Meier plot provided in Figure 28 of the CS relates to the ITT population of MURANO (i.e. patients with ≥1 prior CLL therapies, from Kater *et al*). The text has not been amended. Unless different data were digitised (in which case, the CS would be subject to an

			error), the ERG believes that the report is already correct.
Section 5.2.2.3.1, Page 87, Figure 13: "Kaplan-Meier plot and modelled PSS – ibrutinib arm of RESONATE (1-2 prior lines of treatment), R/R CLL (re-drawn by the ERG)"	To update the text as follows: "Kaplan-Meier plot and modelled ~~PSS~~ PPS – ibrutinib arm of RESONATE (1-2 prior lines of treatment), R/R CLL (re-drawn by the ERG)"	Typographical error – spelling.	The ERG agrees. The text has been amended.
Section 5.2.2.3.4, Page 92, Table 39: **"**Cycle 1: 3 x 1,000mg. Cycles 2-5: 1,000mg per cycle" "Cycle 1: £9,936.00. Cycles 2-5: £3,312,00"	To update the text as follows: **"**Cycle 0: 3 x 1,000mg. Cycles 1-5: 1,000mg per cycle" "Cycle 0: £9,936.00. Cycles 1-5: £3,312,00"	Typographical error – numerical.	The ERG has amended the dosing to refer to "cycle 1" and then "cycles 2-6".
Section 5.2.2.3.4, Page 93: **"**Obinutuzumab is assumed to be given as three doses of 1,000mg obinutuzumab in the first 28-day cycle followed by one dose of 1,000mg obinutuzumab in cycles 2-6"	To update the text as follows: **"**Obinutuzumab is assumed to be given as three doses of 1,000mg obinutuzumab in the first 28-day cycle followed by one dose of 1,000mg obinutuzumab in cycles 1-5"	Typographical error – numerical.	The ERG disagrees. The text is consistent with the amendments described in the ERG's previous response.
Section 5.2.4.1, Page 102: "UK life tables 2015-2017"	To update the text as follows: "UK life tables 2016-2018"	Typographical error – numerical.	The ERG agrees. The text has been amended.

Section 5.2.4.1, Page 103: "Only grade 3/4 AEs experienced by 1% of patients in the ASCEND and RESONATE trials are included in the analysis; the company assumes that most AEs occur and are resolved during the first 28-day cycle"	To update the text as follows: "Only grade ≥3 AEs experienced by 1% of patients in the ASCEND and RESONATE trials are included in the analysis; the company assumes that most AEs occur and are resolved during the first 28-day cycle"	Consistency of language error.	The ERG agrees. The text has been amended.
Section 5.2.4, Page 114: "original model - [redacted]), which resulted in a situation in which acalabrutinib dominated GClb (see company's additional analysis document, Tables 3, 5, 7 and 9)"	To update the text as follows: "original model - [redacted]), which resulted in a situation in which acalabrutinib dominated GClb (see company's additional analysis document, Tables 3, 5, 7 and 9)"	Typographical error – numerical.	The correct value should be [redacted] (from the company's original submitted model, worksheet "Results", cell O45). The text has been amended.
Section 5.3.4, Page 121: "In each treatment group, OS is modelled as a function of all three transitions."	To update the text as follows: "In each treatment group, OS is modelled as a function of ~~all three transitions~~ **PPM and PPS."**	TTP does not directly inform OS.	The company's comment is not accurate. The model uses a state transition approach whereby OS is modelled as a function of all three transitions, not just PPM and PPS. If the parameter value(s) for the TTP model changes, OS also changes. The text has not been amended.

Section 5.3.5, Page 132: "The company's full cost-utility analysis suggests that acalabrutinib dominates ibrutinib, producing [redacted] additional QALYs and cost savings of [redacted] per patient."	The company's full cost-utility analysis suggests that, **in probabilisitic analysis**, acalabrutinib dominates ibrutinib, producing v[redacted] additional QALYs and cost savings of [redacted] per patient.	A probabilistic analyses were conducted for the cost-utility versus ibruntinib.	The ERG agrees. The text has been amended.
Section 5.3.5, Page 132: "The ERG considers the company's full cost-utility analysis for the high-risk CLL population to be problematic several reasons."	To update the text as follows: "The ERG considers the company's full cost-utility analysis for the high-risk CLL population to be problematic **for** several reasons."	Typographical error – grammar.	The ERG agrees. The text has been amended.
Section 5.3.4, Page 132: "The company's selected parametric survival models for TTP, PPM and PPS in the acalabrutinib group remained unchanged (i.e. the same as the models used for the untreated CLL population)."	To update the text as follows: "The company's selected parametric survival models for TTP, PPM and PPS in the acalabrutinib group **were refitted using an alternative PFS endpoint to align with the data used to inform the MAIC."**	Despite both the ELEVATE-TN and RESONATE-2 trial for acalabrutinib and ibrutinib defining IRC PFS as their primary endpoints, INV PFS was used in the MAIC to allow long-term data from ibrutinib to be captured. The data cut from Barr 2018[10] matched the scheduled follow-up in ELEVATE-TN study and only reported INV-assessed PFS. As the hazard ratio was generated using the INV PFS endpoint, this endpoint was also used for the acalabrutinib monotherapy	The ERG agrees. The text has been amended.

		extrapolations to provide a fair comparison. Models were fitted independently for the INV endpoint.	
Section 5.3.5, Page 133: "The company's updated CMA for this population (Model 3), which includes the correction of minor errors, suggests that acalabrutinib produces cost savings of [redacted] per patient compared with ibrutinib"	To update the text as follows: "The company's updated CMA for this population (Model 3), which includes the correction of minor errors, suggests that acalabrutinib produces cost savings of [redacted] per patient compared with ibrutinib"	Typographical error – numerical.	The ERG agrees. The text has been amended.
Section 5.3.5, Page 134: "The company's cost-utility analysis suggests that acalabrutinib dominates ibrutinib, with acalabrutinib generating an additional [redacted] QALYs and cost savings of [redacted] per patient."	To update the text as follows: "The company's cost-utility analysis suggests that **in probabilistic analysis** acalabrutinib dominates ibrutinib, with acalabrutinib generating an additional [redacted] QALYs and cost savings of [redacted] per patient."	Clarification required – these results are probabilistic.	The ERG agrees. The text has been amended.
Section 5.3.5, Page 134: "(1e) Correction of second-line treatment durations"	To update the text as follows: "(1e) ~~Correction~~ Amendment of second-line treatment durations"	Clarification required – this is not a correction just and alternative way of modelling subsequent treatment costs.	The ERG disagrees (please refer to ERG response to Issue 4 above). The model applies second-line costs to patients who are alive. The ERG considers this to be incorrect and that it therefore represents

			an error. The text has not been amended.
Appendix 1, page 158, Table 71 Rituimab mean time (years): 168	Rituimab mean time (years): 0.460	Typographical error – numerical.	This was an error in the original ERG report. However, the table has now been removed from the updated ERG report, as the 2nd line costing approach has been amended.

References

1. Burger JA, Barr PM, Robak T, et al. 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.* 2020;34(3):787-798.
2. National institute for Health and Care Excellence. *Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]. TA561 committee papers* London,2018.
3. National Institute for Health and Care Excellence. TA561 Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. 2019. Available at: https://www.nice.org.uk/search?q=Venetoclax+with+rituximab+for+previously+treated+chronic+lymphocytic+leukaemia (accessed February 2020). In.
4. O'Brien SM, Byrd JC, Hillmen P, et al. Outcomes with ibrutinib by line of therapy and post-ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. *Am J Hematol.* 2019;94(5):554-562.
5. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.
6. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94(12):1353-1363.
7. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood.* 2018;131(17):1910-1919.
8. Paul M Barr, Talha Munir, Jennifer R Brown, et al. Final Analysis From RESONATE: 6-Year Follow-Up in Patients With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma on Ibrutinib. Poster #264. Presented at the 2019 ASCO Annual Meeting; May 31 - June 4, 2019; Chicago, IL, USA. Published 2019. Accessed.
9. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med.* 2018;378(12):1107-1120.
10. Barr PM, Robak T, Owen C, et al. 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.* 2018;103(9):1502-1510.