Acalabrutinib for treating chronic lymphocytic leukaemia: A Single Technology Appraisal

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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

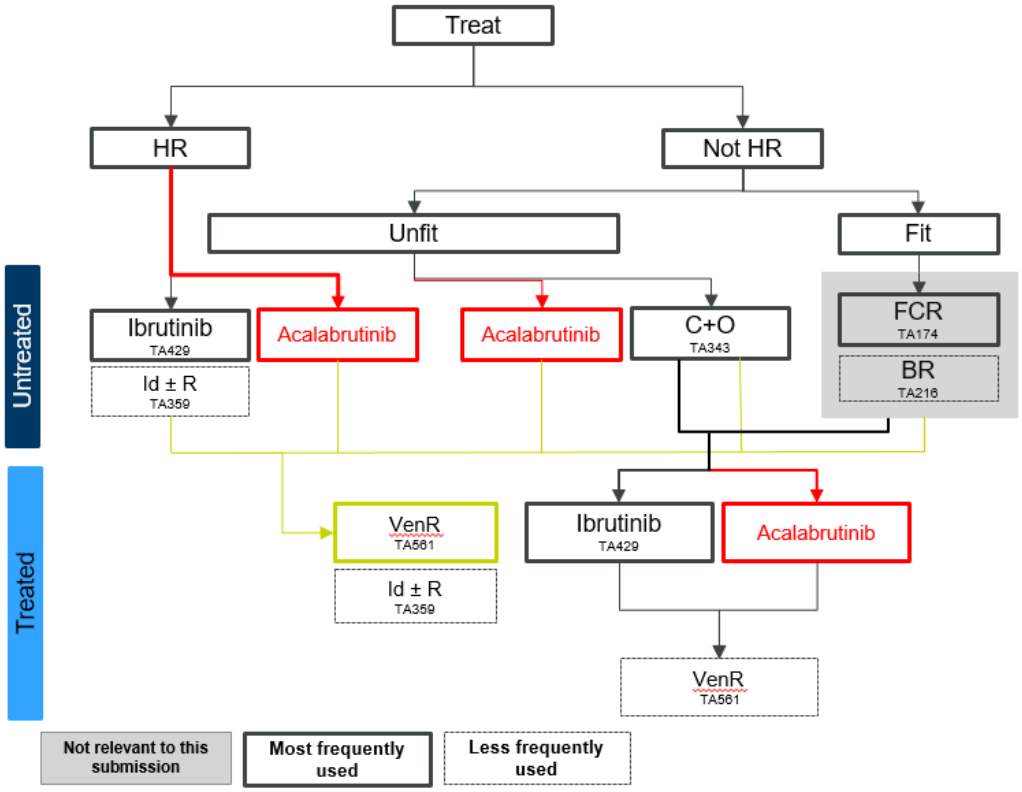
2.2 Critique of the company's overview of current service provision

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]

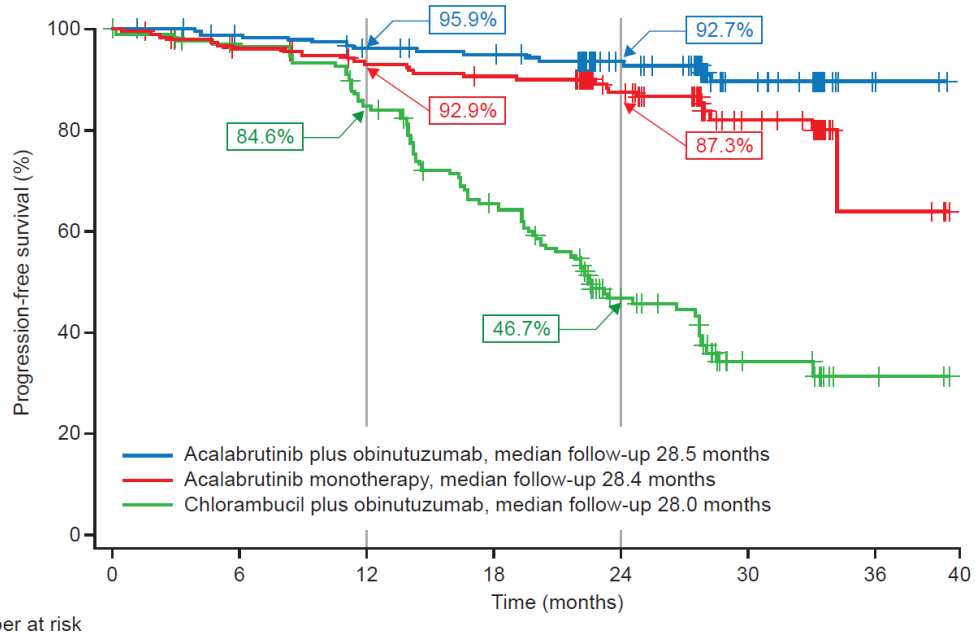
Median PFS for the acalabrutinib plus obinutuzumab group, and for the acalabrutinib monotherapy group, was not reached. Median PFS for the GClb group was 22.6 months.[1]

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]

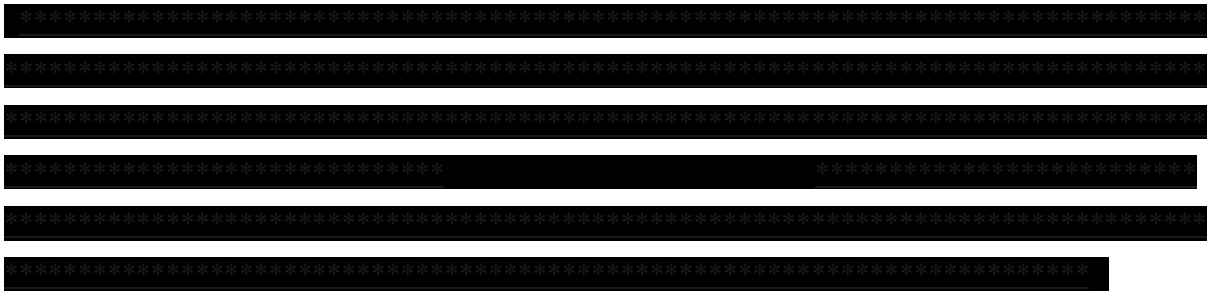


Table 21: ELEVATE-TN - HRQoL change from baseline

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]

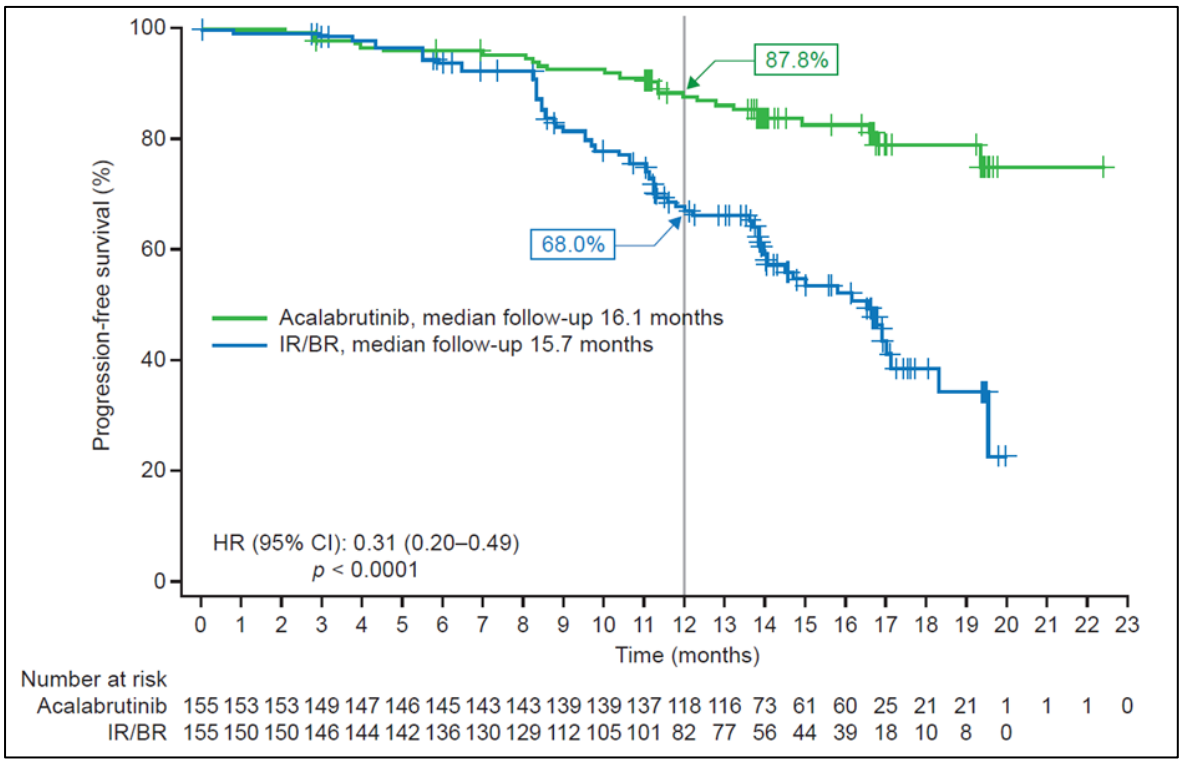
Kaplan-Meier PFS estimates are shown in Figure 3. The Kaplan-Meier estimated PFS probability at 12 months was 87.8% (95% CI: 81.3–92.1%) for acalabrutinib monotherapy, and 68.0 % (95% CI: 59.4–75.1%) for IR/BR. IRC-assessed PFS significantly favoured acalabrutinib monotherapy over IR/BR (HR 0.31, 95% 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	variables not included	ESS	PFS		OS	
				Naïve	MAIC	Naïve	MAIC
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Base case	12	Binet score					
S1	12	Rai stage					
S2	11	Complex karyotype, IgHV unmutated					
S3	13						
S4	12	Complex karyotype					
S5	12	IgHV unmutated					

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 , ibrutinib 42.0%; $p<0.05$), incidence of grade 3/4 diarrhoea (acalabrutinib , 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.

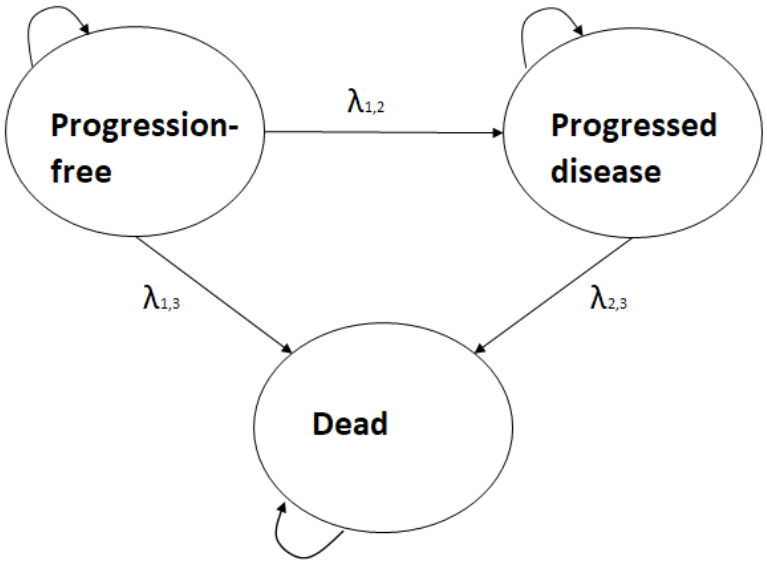
5.2.2 Model 1: Acalabrutinib versus GClb in patients with untreated CLL

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, [redacted]. 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

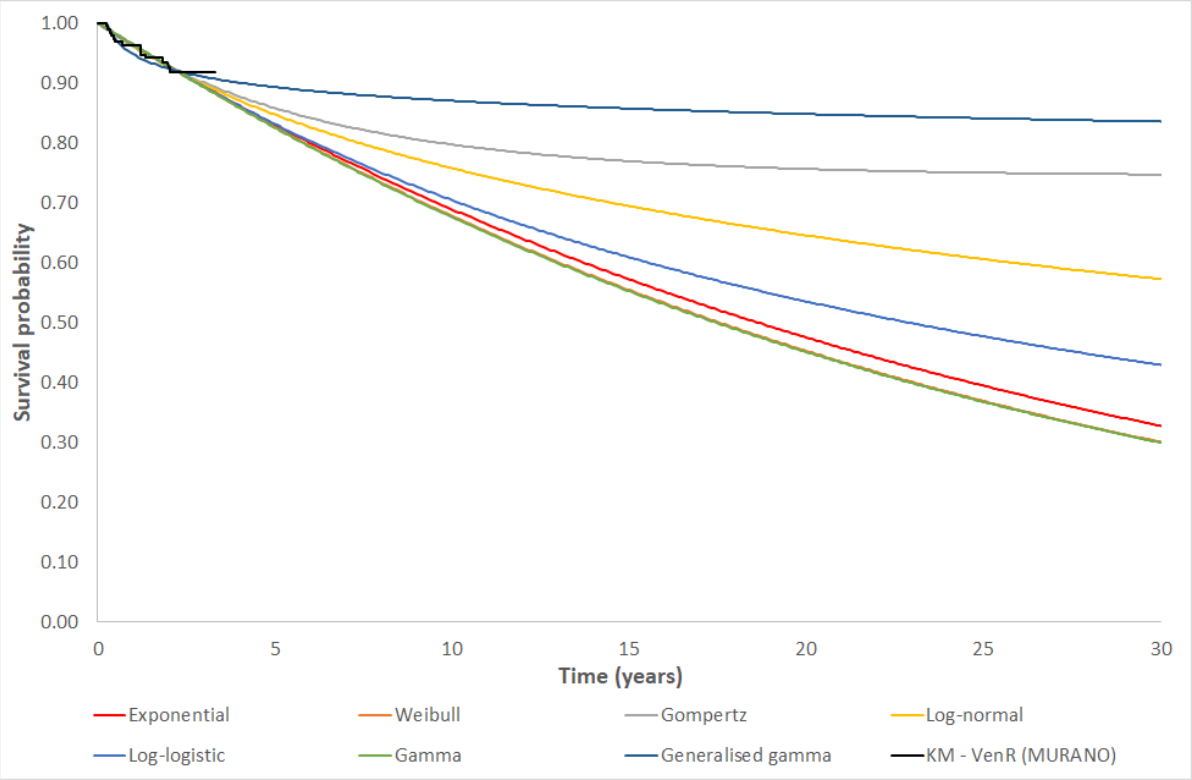
MURANO. Figure 13 presents the observed Kaplan-Meier plots and modelled OS functions for each of the candidate models for the ibrutinib arm of RESONATE.

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

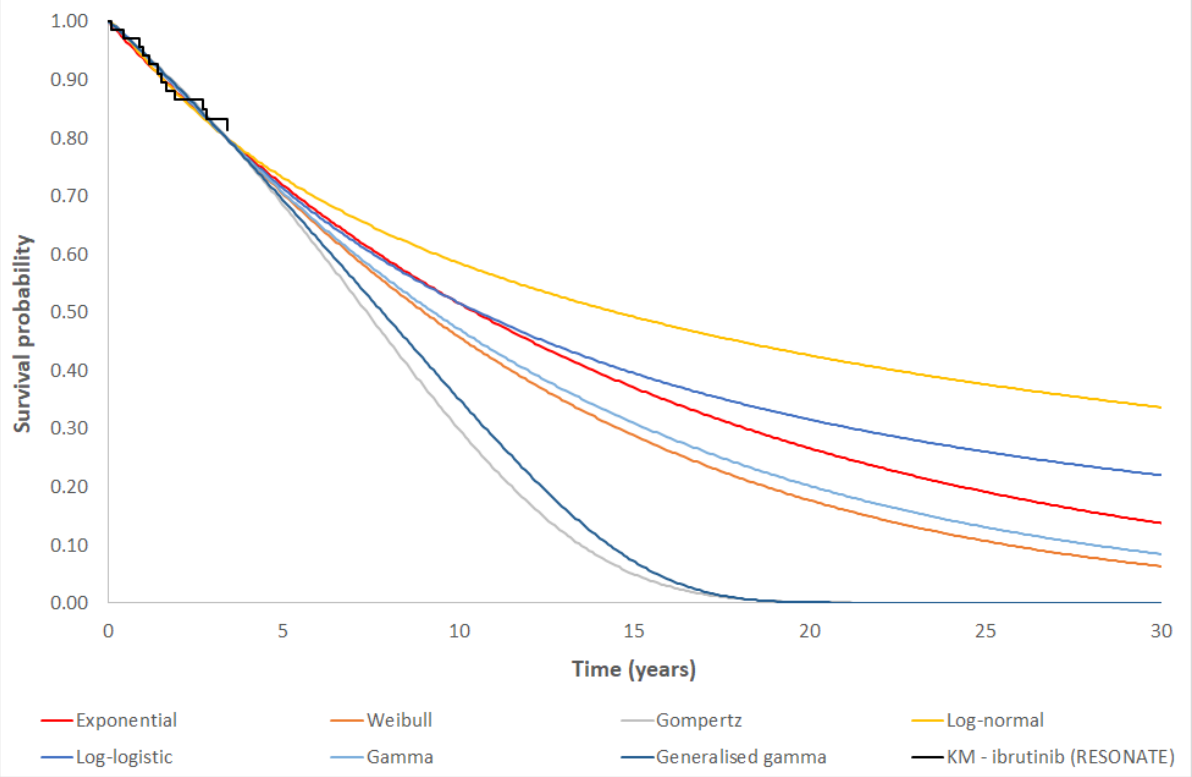
VenR – venetoclax plus rituximab; AIC - Akaike information criterion; BIC - Bayesian information criterion

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)

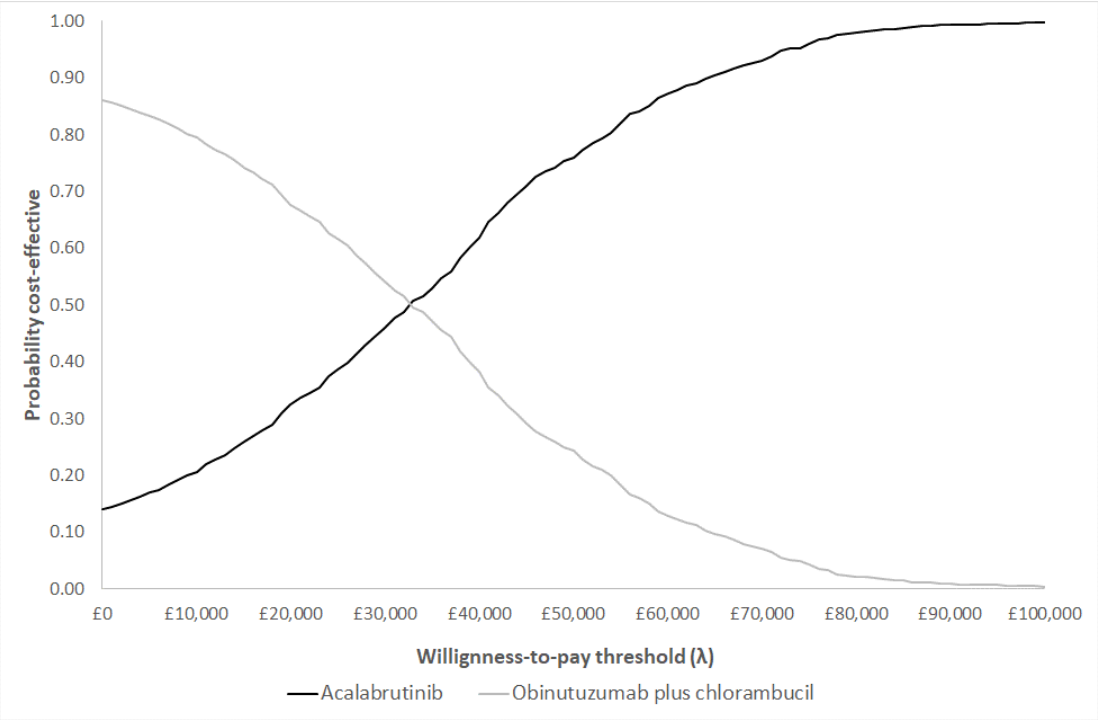
Figure 15 and Figure 16 present the cost-effectiveness plane and CEACs for acalabrutinib versus GClb within the untreated CLL population. Assuming willingness-to-pay (WTP) thresholds of £20,000 and

£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]

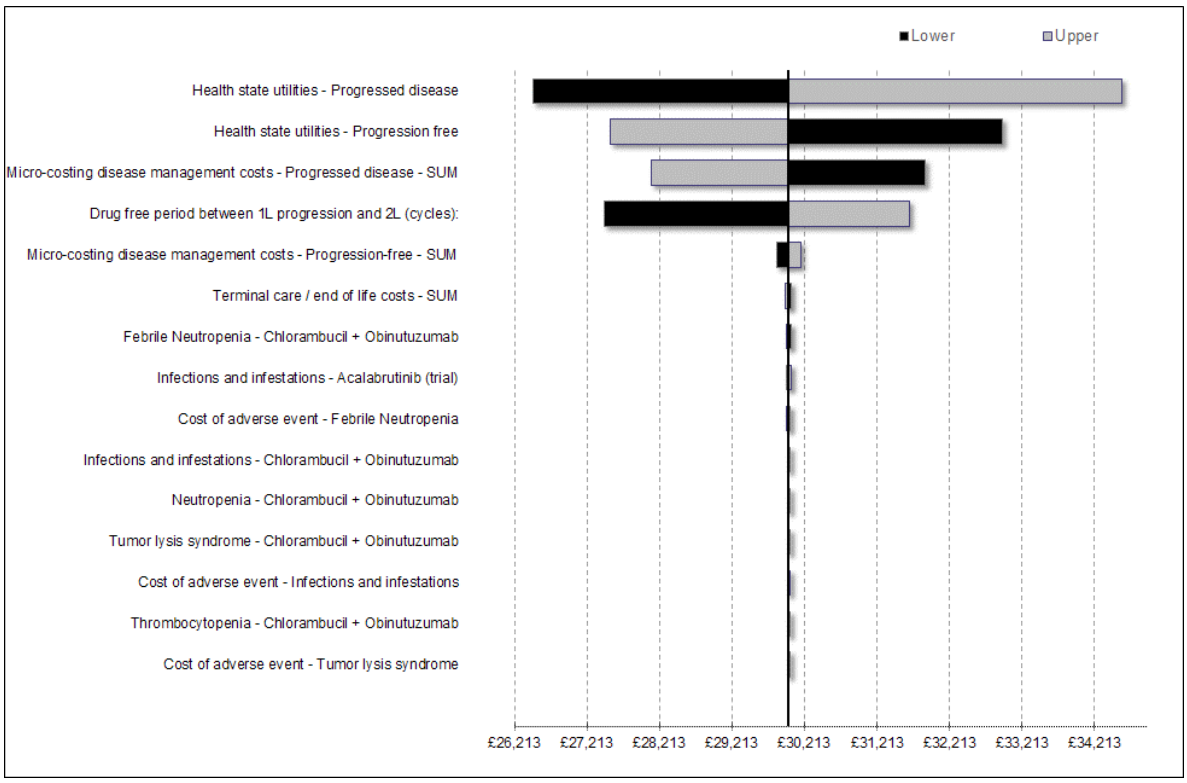
Figure 16: Cost-effectiveness acceptability curves, untreated CLL (Model 1), acalabrutinib versus GClb (re-drawn by the ERG)



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

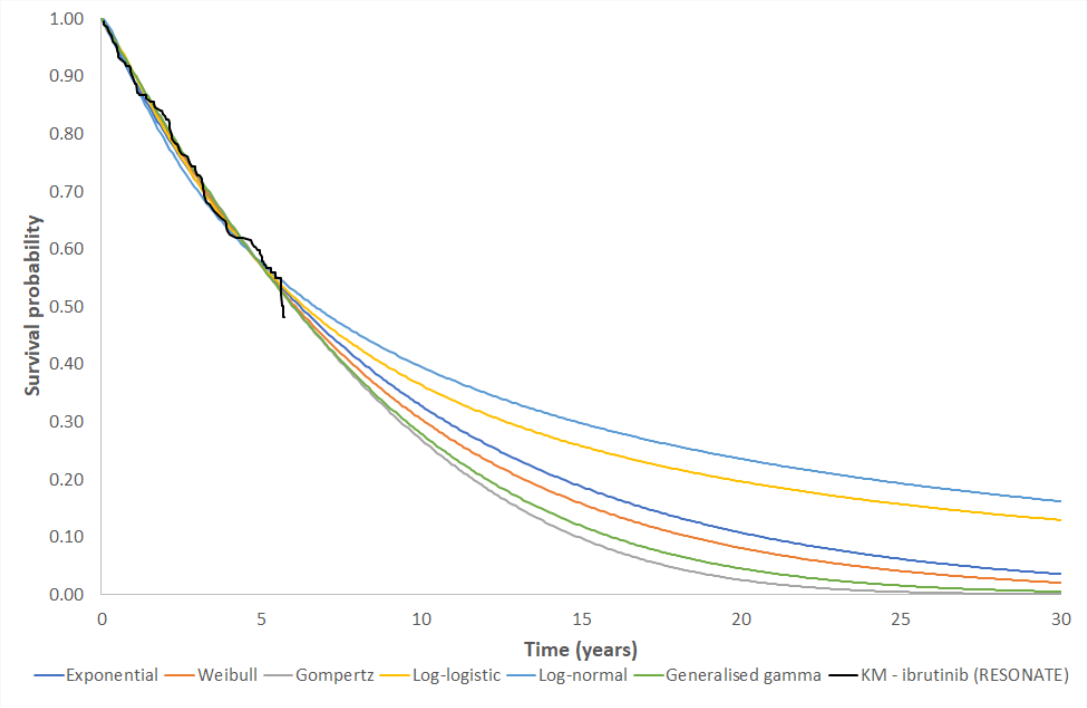
plausibility. AIC and BIC statistics for each of the candidate models are presented in Table 49. The Kaplan-Meier plot for the ibrutinib arm of RESONATE and the modelled OS functions are presented in Figure 18.

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.

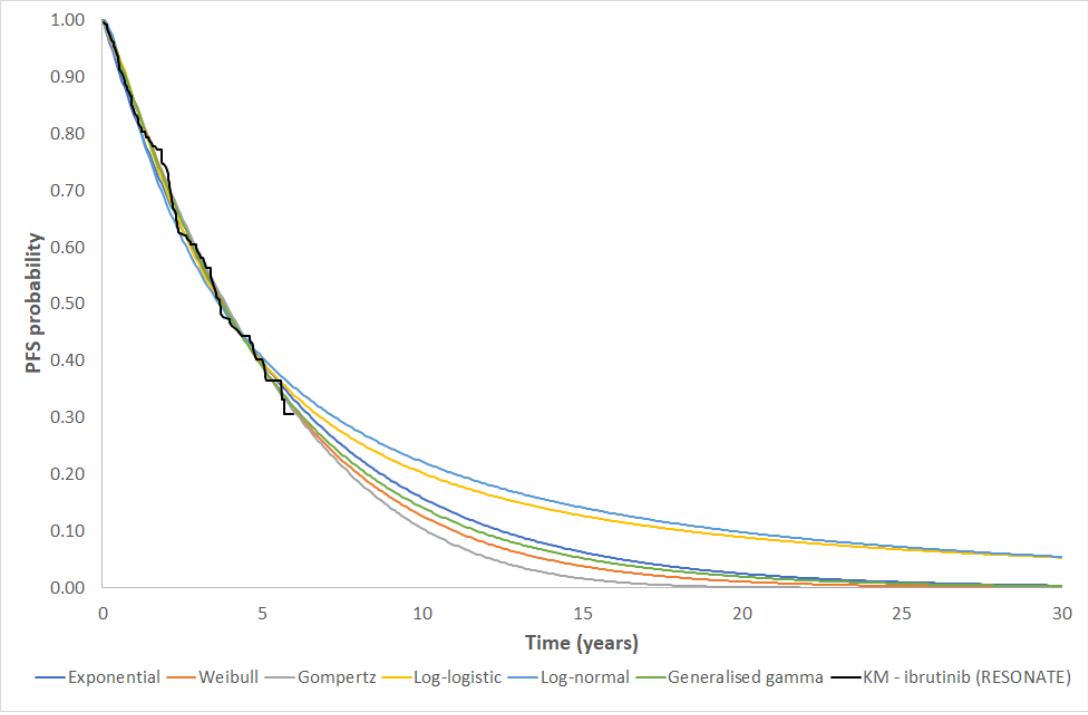
Clinical advice received by the company suggested that the log-logistic and log-normal models resulted in overly optimistic survival estimates, whilst estimates from the Gompertz model were considered to be overly pessimistic (CS,[1] Section B.3b.2.2). No alternative PFS models were explored in the company's 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.

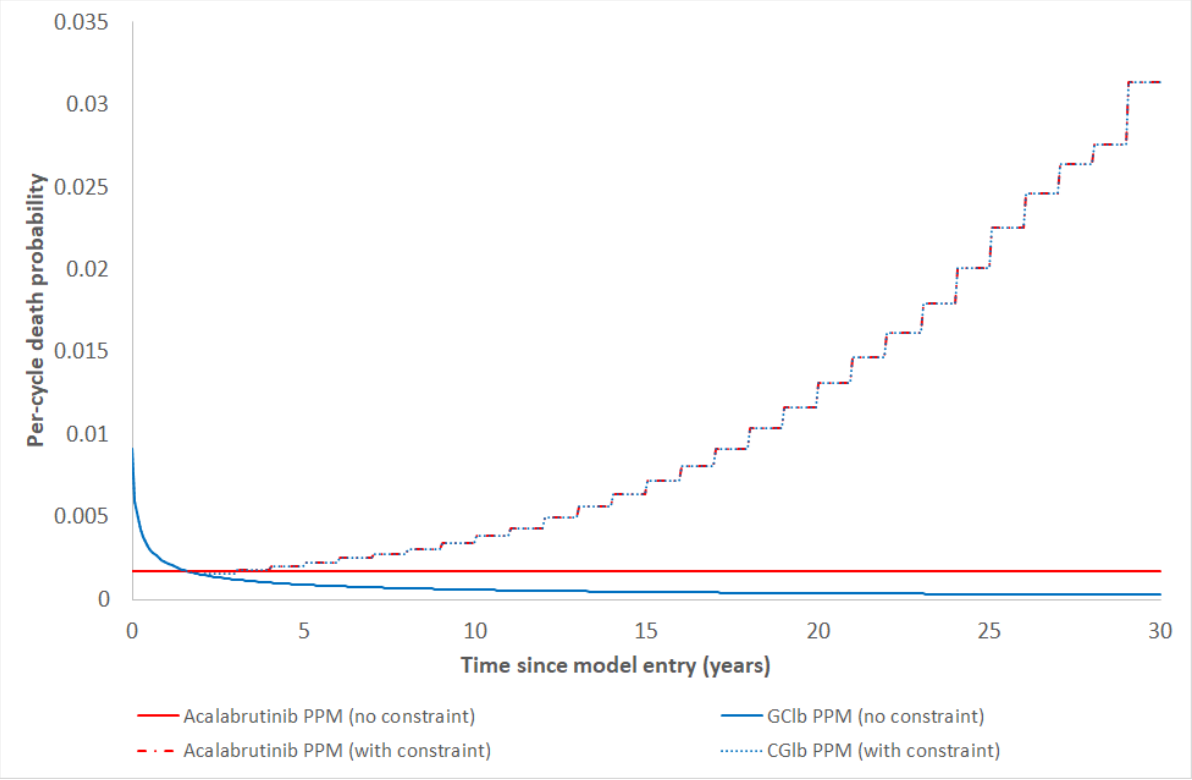
(iii) Strong influence of general population mortality risks

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.

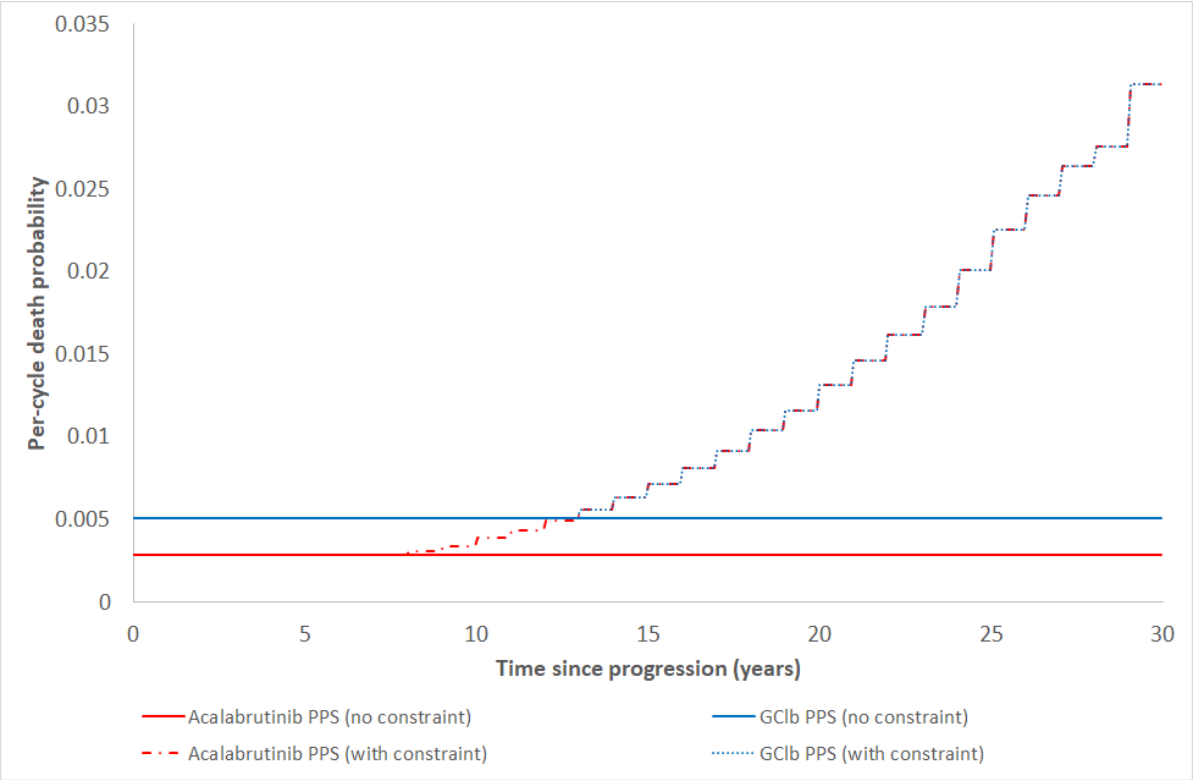
Figure 21 shows the predicted 28-day risk of death in patients without disease progression with and without the general population mortality constraint. As shown in the figure, the constraint takes effect within 3 years for both groups. After this timepoint, mortality risk in patients who are progression-free 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

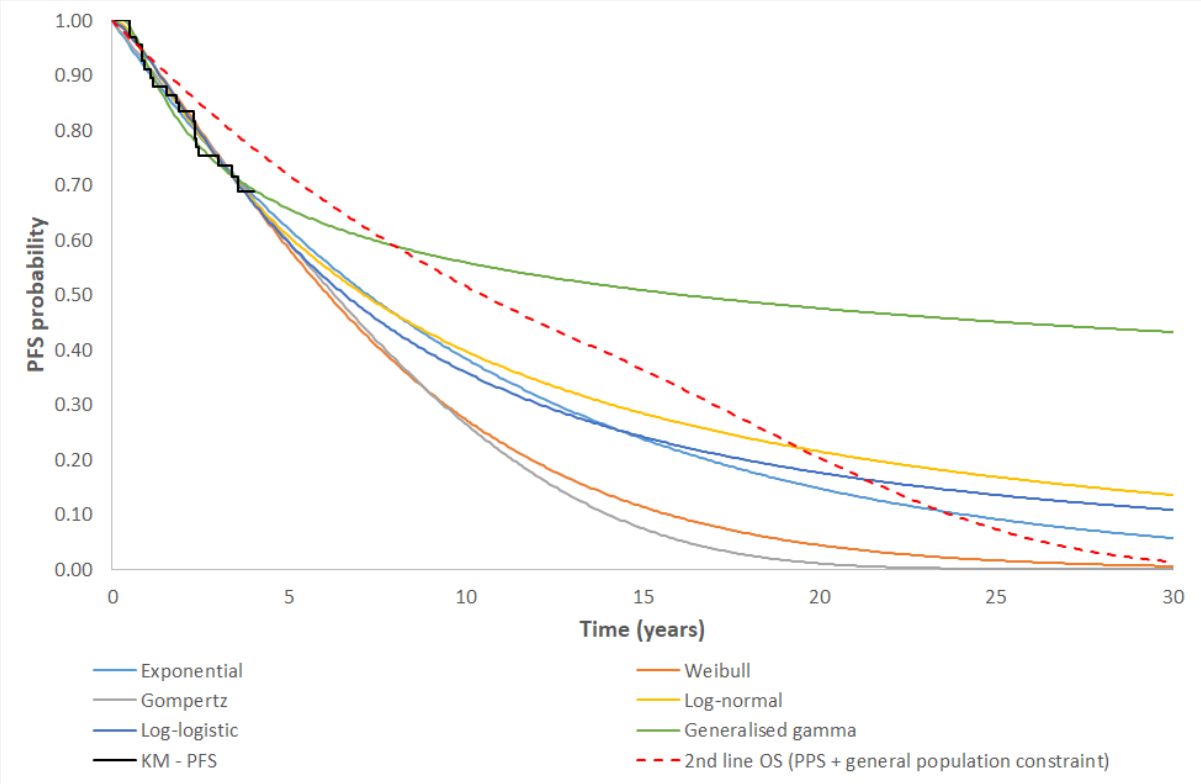
Appendix 1: Summary outputs from survival modelling for ibrutinib-treated patients with 1-2 prior lines of treatment in RESONATE

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
91.38809	0.013810445
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
92.92129	0.015444891
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.